SAHLGRENSKA ACADEMY

Smoking and Postoperative Risk in Cardiac Surgery Patients

Degree Project in Medicine

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Innehåll

Abstract

Introduction: Smoking affects physiologic functions in various ways. The effects of smoking and cessation on postoperative outcomes have been studied in general and in orthopedic surgery. Regarding patients undergoing cardiac surgery, not many studies about how smoking affects surgical risk have been published.

Aim: Examine the association between smoking and time since smoking cessation on postoperative complications.

Methods: A retrospective register study was conducted including patients who had an isolated coronary artery bypass (CABG) surgery at Sahlgrenska University Hospital during January 2010-December 2020. Baseline- and outcome variables were collected from Swedish Cardiac Surgery Registry (SWEDEHEART) and smoking status was manually collected from patient records. Comparison of current and never-smokers was made, as well as univariate and multivariate logistic regression for time since smoking cessation.

Results: 5072 patients were included, 4645 had smoking status available (1438 never-smokers, 750 current smokers, 2457 previous smokers). Current smokers were younger with significantly higher risk of acute coronary syndrome prior to surgery and compared to patients that had never smoked. Smokers had significantly higher occurrence of pulmonary complications (12.0% vs 5.1%), including pneumonia and prolonged ventilation, as well as higher incidence of post-operative stroke (1.9% vs 0.6%) and infections requiring antibiotics (18.2% vs 7.2%). These complications were statistically significant also after propensity score matching. Both univariate and multivariate logistic regression analysis showed a significant decrease in risk of pulmonary complications and infections with longer time since smoking

cessation. In our data, patients with short smoking abstinence before surgery (up to six months) had no statistically significant difference in occurrence of pulmonary complications compared to smokers.

Conclusion: Smoking seems to be associated with pulmonary complications and infections after CABG surgery and we found an association between abstinent time from smoking and reduced complications. Improved smoking-prevention and intervention might reduce morbidity in cardiac surgery patients.

1. Introduction

Today's leading cause of death is ischemic heart disease, responsible for 16% of total deaths in the world (1). The pathophysiology behind ischemic heart disease is most often atherosclerosis and formation of plaques in the coronary arteries leading to a reduced blood supply to the heart (2)

The process of atherosclerosis begins early in life, and exposure to risk factors will contribute to a more rapid plaque formation. Some of these risk factors are non-modifiable, such as age, gender, and genetics. Other factors that can be modified include hyperlipidemia, diabetes, hypertension, and cigarette smoking (2). Reduction of these risk factors can decrease the risk of mortality (3).

Treatment for ischemic heart disease include lifestyle changes and medical therapy, including antiplatelet drugs to reduce the risk for future thrombotic events. Furthermore, some patients are applicable for revascularization, either in form of percutaneous coronary intervention (PCI) or coronary artery bypass graft surgery (CABG) (4, 5).

CABG is a surgical procedure indicated for relief of symptoms and prolongation of life in coronary artery disease patients. Generally, patients with excessive stenosis in the left main artery, the left anterior descending artery (LAD) or patients with three-vessel disease are considered candidates for CABG (6).

Today approximately 2500 isolated CABG operations are performed each year in Sweden. 30-day mortality of all CABG procedures performed in Sweden in 2019 was 0.7%, but about 5% of CABG patients suffer one or more major complications related to their operation (7).

CABG surgery comprises unique challenges including access through a median sternotomy, harvesting of the internal mammary artery, high doses of systemic heparin and the use of extra-corporeal circulation. These challenges have been shown to induce a high inflammatory response and reduce respiratory function which might delay recovery (8, 9). The already strenuous condition of the surgery makes it important to decrease other risk-factors influencing the outcome of surgery.

Smoking has been shown to affect the outcome of many non-cardiac surgeries, such as general and orthopedic procedures. Studies demonstrate an increase in pulmonary complications, such as postoperative pneumonia and reintubation (10), as well as wound healing complications in smokers compared to non-smokers (11). One study of patients undergoing CABG surgery showed that continued smoking after the procedure increases both long-term mortality as well as risk of future repeated revascularization (12).

In 2019, 9.2% of patients undergoing cardiac surgery in Sweden, were active smokers and another 32% were previous smokers (7). Smoking causes physiological changes in several of the body's systems, raising the risk for cardiovascular disease. This includes endothelial dysfunction, lipid abnormalities, systemic inflammation and increased coagulation (13). Regarding the respiratory system, smoking causes dysfunctional epithelium, ciliary clearance,

and modulated immune response leading to increased risk for pulmonary infections (14). Airway narrowing and loss of elasticity in the lungs are due to inflammation in the airways and lung parenchyma, leading to reduced ventilation (15).

At least some of the effects of smoking seem to be reversible. Significant difference in all-cause mortality is seen in people who quit smoking compared to continuous smokers. Smoking cessation before middle age results in a similar survival rate compared to those who never smoked (16). Smoking cessation prior to surgery reduces the risk of postoperative complications, including pulmonary and wound healing complications (17).

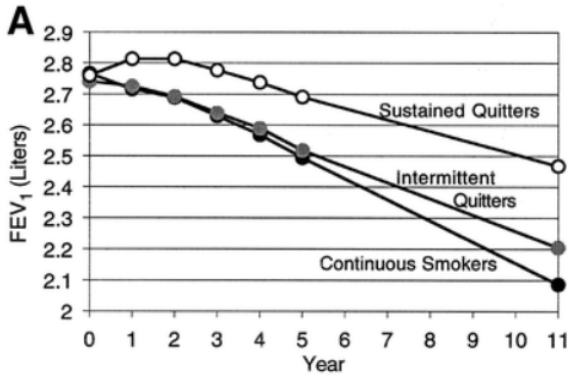

***Figure 2**. Lung function during eleven years of active smokers and quitters. Active smokers can be seen to have a steeper decline in FEV1. Figure 2 in original source (20).*

Some beneficial effects of smoking cessation are seen within weeks or months, though it may take many years for other benefits to be significant. Endothelial function improves already within 6 months of abstinence (18), and airway inflammation is noticeably reduced within the first year of cessation (19). Pulmonary ventilation measured with spirometry and forced expiratory volume during first second (FEV1) improves within the first year of cessation, then declines at half the rate of continuous smokers (figure 1) (20), and biochemical markers for

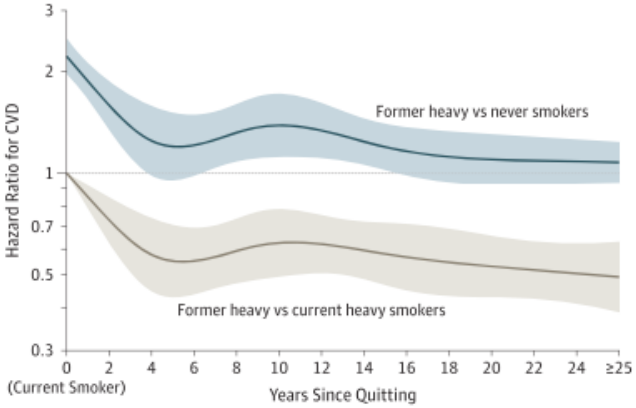

***Figure 1.** Risk of CVD in heavy ever smokers and never smokers. Figure 2 in original source (22).*

inflammation and coagulation also reduce within the first years but are still significantly elevated for more than a decade (21). Duncan, MS et al. also demonstrated a significant risk reduction for cardiovascular disease (CVD) within the first five years of cessation (figure 2) (22).

Regarding the effects of smoking cessation in CABG patients, there are a limited number of studies. Furthermore, the applicability of studies from other surgical patients may be limited due to the complexity of the CABG surgery. Some studies have demonstrated that smoking cessation before CABG surgery decrease the risk of pulmonary complications, including postoperative pneumonia (23, 24), reintubation and tracheostomy (25). Some studies also indicate a possible relation between smoking cessation and reduced duration of mechanical ventilation (26), a risk factor for pneumonia and lung injury (27, 28).

2. Aim

To investigate the occurrence of early postoperative complications in CABG patients depending on smoking status and to determine the association between time elapsed since smoking cessation and early complications after CABG surgery.

3. Methods

3.1 Study design

We conducted a retrospective cohort study. Patients were identified using the national Swedish Cardiac Surgery Registry (SCSR), which is part of the SWEDEHEART registry. The registry is mandatory and includes 100% of all cardiac surgery patients operated in Sweden during the study period. Background and outcome variables were collected from SCSR. Smoking status, including time between cessation and surgery in former smokers, was obtained from hospital medical records (Melior).

3.2 Study population

Patients undergoing an isolated coronary artery bypass grafting surgery (CABG) at Sahlgrenska University Hospital during a period of eleven years, between January 2010-December 2020, were included in the study. All patients were >18 years of age. Patients who underwent any other type of concomitant surgical procedure were excluded.

3.3 Data collection

The study population was identified from SCSR by sorting cardiac patients by type of procedure. Background variables as well as outcome variables were extracted from SCSR. Smoking status, including the year of smoking cessation, was obtained from the hospital patient records system (Melior). Smoking status was found either in the scanned health

declaration form answered by patients, or in the medical records documented by medical professionals.

All patients who quit smoking less than four weeks prior to surgery were classified as active smokers.

When the year of cessation was specified by a decade, the chosen year was in the middle of the decade. Similarly, for all mixed answers we chose the date in the middle of the ones mentioned. When the records of smoking status were contradictory, the answer containing most smoke exposure was chosen (i.e. stated active smoker and previous smoker, we chose to include the patient as an active smoker). So called “party-smokers” were viewed as smokers, either previous or current. Patients stating that they quit smoking in their youth were estimated to have quit at the age of 18.

3.4 Baseline characteristics

Background variables were displayed to demonstrate our patient sample based on smoking status. Age, gender, and BMI were reported, along with comorbidities and preoperative status (diabetes, hypertension, chronic lung disease, extracardiac arteriopathy, previous PCI, previous stroke, circulatory support preoperatively, serum-creatinine, preoperative dialysis, unstable angina, recent myocardial infarction, critical preoperative state, poor mobility, left ventricular function, pulmonary hypertension, NYHA, and logistic Euroscore II).

Chronic lung disease included patients with long term use of bronchodilators or steroids for lung disease. Extracardiac arteriopathy comprised of claudication, carotid occlusion or >50% stenosis, amputation for arterial disease as well as previous or planned intervention on the abdominal aorta, limb arteries or carotids.

Critical preoperative state was defined as ventricular arrythmia or aborted sudden cardiac death, preoperative cardiac massage or preoperative ventilation before anaesthetics, preoperative inotropes, the use of intra-aortic balloon pump or preoperative acute renal failure. EuroSCORE II were included in baseline characteristics to predict the risk of in-hospital mortality after major cardiac surgery. Acute coronary syndrome when mentioned are patients with either unstable angina or myocardial infarction.

Furthermore, we presented operative factors as urgency of surgery, type of graft used, number of peripheral and central anastomoses, duration for extracorporeal circulation (ECC) and aortic cross clamp (ACC).

3.5 Outcome variables

Outcome variables investigated were 30-day mortality and postoperative complications occurring during the hospital stay. Complications included pneumonia, patients requiring mechanical ventilation more than 48 hours, postoperative stroke, bleeding or mediastinitis/sternum insufficiency requiring re-operation, any infection requiring antibiotics, postoperative dialysis, mechanical circulatory support (use of ECMO or intra-aortic balloon pump), and atrial fibrillation.

Pneumonia and mechanical ventilation more than 48h were separately analyzed, as well as a composite endpoint (“pulmonary complications”) expressing the number of patients suffering from pulmonary complications.

3.6 Data analysis and statistical methods

To analyse the data, patients were categorized depending on their smoking status at the time of surgery. They were either current smokers (including patients who quit smoking <4 weeks before the operation), never-smokers or former smokers. Former smokers were categorized by how long they had been smoke-free at the time of surgery.

Patient characteristics, operative factors, and outcome variables were assessed and compiled into tables displaying descriptive statistics, organized by smoking status. A multiple propensity score matching was made to control for confounding factors.

Statistical analysis was conducted with the use of computer software IBM SPSS (IBM SPSS Statistics for Windows, Version 27.0) and R (https://www.R-project.org/). Normality tests were conducted for all continuous variables, using Shapiro-Wilks’s test of normality. Variables not normally distributed were presented by median with interquartile range or range. Categorical variables were displayed as frequency and percentage. Confidence intervals for proportions were displayed in graphs, and the method used to calculate the confidence intervals was the Wilson interval (29).

Hypothesis testing was conducted to test for significance, using Mann-Whitney U test for non-normally distributed, continuous data. For dichotomous categorical variables, a Chi-square test with continuity correction was used, or Fisher's exact test when sample size was small. For ordinal data, a Pearson's Chi square test was used. The level of significance chosen in our study was $p \leq 0.05$.

Comparison between smokers and never smokers was made both unadjusted and after propensity score matching. This was done using complete case analysis. Six variables which had large proportions (>20%) of missing data were not included in the analysis ((ECC time [58,7% missing], aortic occlusion time [58,7% missing], hypertension [59,3% missing], pulmonary hypertension [22,7% missing], poor left ventricular function [20,2% missing] and NYHA class [27,7% missing]).

In line with other studies (23, 30), our data showed a strong association between smoking and chronic lung disease and extracardiac arteriopathy. We chose to not include either of these variables in the PS matching. If included, the matching might be biased by excluding patients from the smoking group who were susceptible to negative consequences of smoking.

The following background variables were included in the propensity score matching: year of surgery, BMI, preoperative dialysis, previous PCI, previous stroke, diabetes, age, gender, reduced mobility, unstable angina, recent myocardial infarction, emergency operation and critical preoperative state. Patients with complete dataset in these background variables were eligible for matching (non-smokers, n=1250 [86.9%]; current smokers, n=580 [77.3%])

Matching was done using the R package MatchIt (https://www.jstatsoft.org/v42/i08/) using a 1:1 ration, a caliper of 0.2 and “nearest” method. Exact matching was required for the age variable.

The association between years since smoking cessation and the risk of postoperative complications was examined using univariate and multivariate logistic regression. The number of variables in the multivariate model was limited to aim for at least ten events for each variable (31). Multivariate logistic regression was done using the following nine clinically meaningful variables: time since smoking cessation, age, BMI, gender, diabetes, chronic pulmonary disease, reduced mobility and emergency operation.

The more advanced analyses were made with the help of the supervisor.

4. Ethics

This study was conducted in accordance with the Declaration of Helsinki. The study was considered a department follow-up study and the head of department of cardiothoracic surgery at Sahlgrenska University Hospital approved the implementation of the study. Patient records were accessed solely at the department of cardiothoracic surgery. Patients were treated anonymously when conducting statistical analysis and their identification number were kept in a separate datafile.

5. Results

5.1 Enrollment

We extracted 5276 patients from SCSR that met our inclusion criterias. After review of the dataset 196 patients were excluded because they were miscategorized and had undergone concomitant procedures in addition to CABG. Seven patients were removed because they were duplicates and one patient was excluded because he or she could not be found in the patient records. The remaining 5072 patients were included in our study and analysis.

Smoking status was available for 4645 patients, with the distribution of 1438 never-smokers, 2457 former smokers, and 750 current smokers. Smoking status could not be found in the medical records for 427 patients. For former smokers, the time of cessation was found for 2193 patients (89.3%).

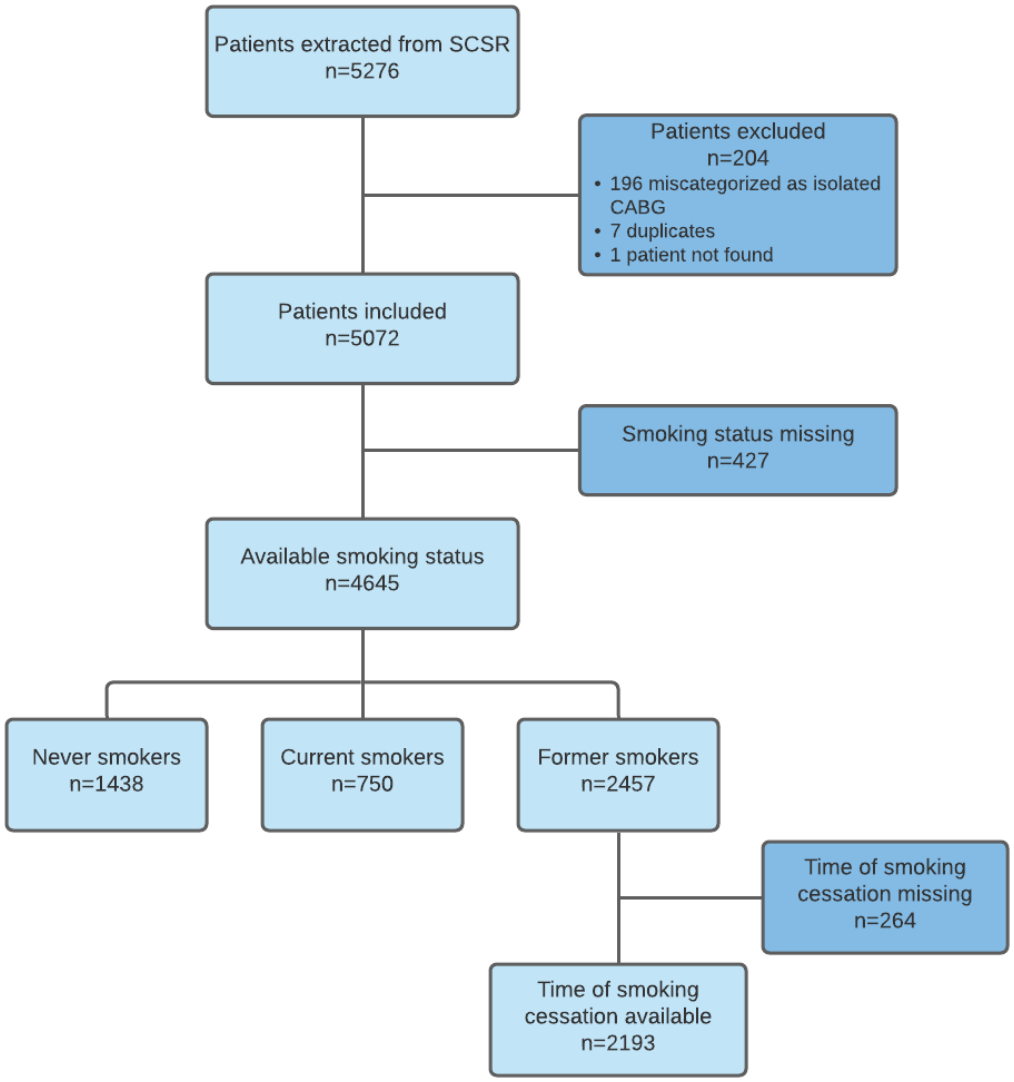

***Figure 3**. Flowcharts of the patients included in the study.*

5.2 Baseline characteristics in current and never-smokers

Table 1. *Preoperative characteristics for never-smokers, current smokers, and former smokers.*

Preoperative characteristics		Never smoker N=1438	Current smoker N=750	p-value[†]	Ex-smoker N=2457	p-value[†]
Age	Median (IQR)	69 (62-75)	64 (57-69)	<0.001	69 (63-74)	0,738
Gender	Women N (%)	255 (17.7%)	162(21.6%)	0.033	370 (15,1%)	0,032
BMI	Median (IQR)	26.4 (24.3-29.1)	26.6 (24.1-29.4)	0.759	27,4 (25,0-30,1)	<0,001
Diabetes	N (%)	341 (24.4%)	168 (23.7%)	0.778	692 (29,7%)	<0,001
Hypertension	N (%)	519 (76.0%)	226 (76.6%)	0.898	825 (80,2%)	0,045
Chronic lung disease	N (%)	57 (4.0%)	118 (15.8%)	<0.001	206 (8,4%)	<0,001
Extracardiac arteriopathy	N (%)	39 (2.7%)	83 (11.1%)	<0.001	218 (8,9%)	<0,001
Circulatory support preoperatively	N (%)	2 (0.1%)	2 (0.3%)	0.837	6 (0,3%)	0,718
Previous PCI	N (%)	216 (15.4%)	130 (18.4%)	0.092	506 (21,8%)	<0,001
Previous stroke	N (%)	99 (7.1%)	58 (8.2%)	0.412	209 (9,0%)	0,047
Serum-creatinine	Median (IQR)	84 (73-96)	79 (67-92)	<0.001	85 (74-99)	0,184
Dialysis preoperatively	N (%)	7 (0.5%)	5 (0.8%)	0.719	23 (1,0%)	0,146
Unstable angina	N (%)	200 (13.9%)	157 (20.9%)	<0.001	367 (14,9%)	0,413
Recent MI	N (%)	581 (40.4%)	436 (58.2%)	<0.001	1079 (44,0%)	0,033
Critical preoperative state	N (%)	12 (0.8%)	32 (4.3%)	<0.001	45 (1,8%)	0,018
Poor mobility	N (%)	39 (2.7%)	26 (3.5%)	0.398	82 (3,3%)	0,327
Left ventricular function[1]	Very poor N (%)	14 (1.1%)	17 (2.9%)	<0.001	29 (1,5%)	0,366
	Poor N (%)	53 (4.2%)	49 (8.3%)		84 (4,2%)	
	Moderate N (%)	257 (20.3%)	164 (27.8%)		445 (22,5%)	
	Normal N (%)	941 (74.4%)	359 (61.0%)		1420 (71,8%)	
Pulmonary hypertension[2]	Severe N (%)	7 (0.6%)	5 (0.9%)	0.281	11 (0,6%)	0,334
	Moderate N (%)	58 (4.7%)	35 (6.2%)		113 (5,9%)	
	Normal N (%)	1170 (94.7%)	526 (92.9%)		1784 (93,5%)	
NYHA	I N (%)	497 (42.9%)	194 (35.9%)	0.025	721 (40,6%)	0,554
	II N (%)	446 (38.5%)	231 (42.8%)		729 (41,0%)	
	III N (%)	181 (15.6%)	90 (16.7%)		273 (15,4%)	
	IV N (%)	34 (2.9%)	25 (4.6%)		54 (3,0%)	
Logistic Euroscore II (mortality %)	Median (IQR)	1.32 (0.91-2.14)	1.45 (0.98-2.45)	0.006	1,41 (0,94-2,23)	0,013

[1] Exact definitions of grading of left ventricular function: Very poor=LVEF ≤20%, Poor=LVEF 21% - 30%, Moderate=LVEF 31% - 50%, Normal=LVEF > 50%.

[2] Exact definitions of grading of pulmonary hypertension: Severe=PA systolic > 55 mmHg, Moderate=PA systolic 31-55 mmHg, Normal=PA systolic ≤ 30 mmHg

[†] p-value in comparison to never smokers

Table 2. *Intraoperative factors in never-smokers, current smokers, and former smokers.*

Intraoperative factors		Never smoker N=1438	Current smoker N=750	p-value[1]	Ex-smokers N=2457	p-value[1]
Urgency of surgery[1]	Emergency N (%)	70 (5.5%)	64 (10.9%)	<0.001	108 (5,5%)	0,771
	Urgent N (%)	630 (49.8%)	351 (59.7%)		1004 (50,8%)	
	Elective N (%)	566 (44.7%)	173 (29.4%)		863 (43,7%)	
	During HLR N (%)	0 (0.0%)	0 (0.0%)		2 (0,1%)	
Grafting material	Venous graft N (%)	1364 (96.5%)	716 (96.9%)	0.606	2348 (96,9%)	0,458
	IMA sin N (%)	1386 (98.0%)	711 (96.2%)	0.012	2354 (97,2%)	0,099
	IMA dx N (%)	22 (1.6%)	7 (0.9%)	0.245	25 (1,0%)	0,155
	Radial artery N (%)	22 (1.6%)	7 (0.9%)	0.245	41 (1,7%)	0,749
Number of peripheral anastomoses	Median (Range)	3 (1-6)	3 (1-6)	0.131	3 (1-6)	0,012
Number of central anastomoses	Median (Range)	1 (0-3)	1 (0-4)	0.074	1 (0-4)	0,285
ECC-time	Median (IQR)	70 (58-86)	70 (59-86)	0.967	72 (59-86)	0,738
Aortic clamping time	Median (IQR)	45 (37-56)	46 (37-57)	0.827	46 (37-57)	0,907

[1] p-value in comparison to never smokers.

[1] Exact definitions of urgency of surgery: Emergency=surgery required before the next working day after planning to operate. Urgent=not electively admitted but require surgery or intervention on the current admission, cannot be sent home without procedure. Elective=routine admission for operation.

Baseline characteristics for current and never-smokers can be seen in table 1 and table 2. Our population consisted mostly of men, with the current smokers having a significantly higher proportion of women compared to never-smokers (21.6% vs 17.7%, p=0.033). The median age varied depending on smoking status, with current smokers being on median five years younger than never-smokers at the time of surgery (median age 69 vs 64 years, p<0.001).

Furthermore, chronic lung disease and extracardiac arteriopathy were significantly more common in current smokers compared to never-smokers (see figure 4, p<0.001 for both conditions).

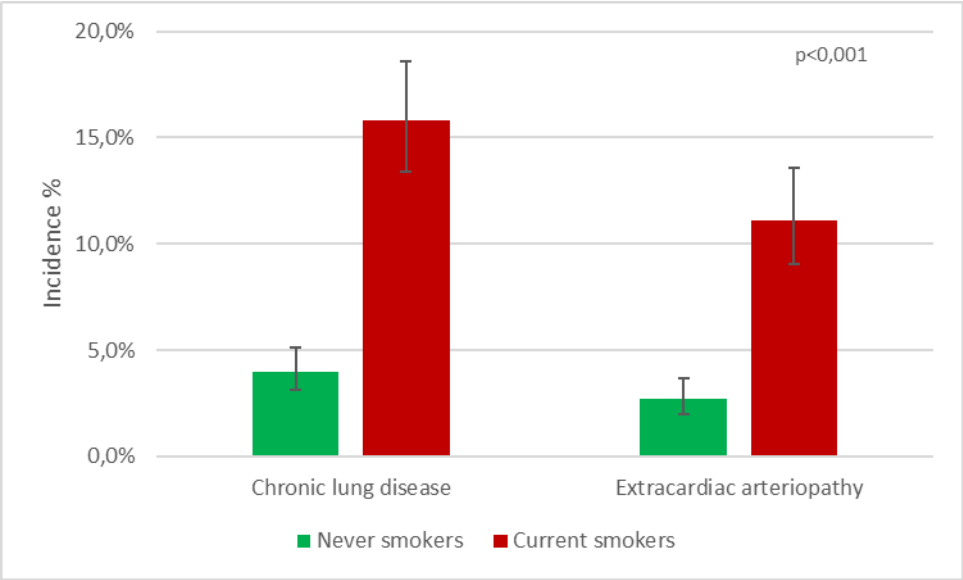

Figure 4. *Proportion of chronic pulmonary disease and extracardiac arterial disease depending on smoking status. Error bars display 95% confidence interval.*

Current smokers were observed to have more acute coronary syndromes and a larger number of patients in a critical condition (4.3% compared to never-smokers 0.8%, p<0.001) as well as higher EuroSCORE (1.45 compared to 1.32 in never-smokers, p=0.006).

The intraoperative factors did not differ significantly between the current smokers and never-smokers, except for more smokers requiring more acute/urgent and less elective surgery (figure 5).

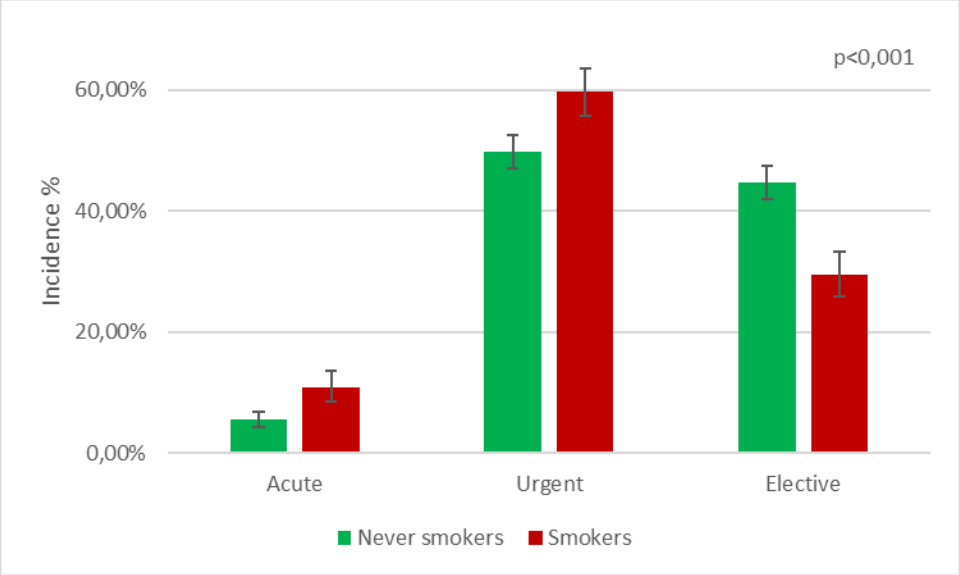

***Figure 5**. Distribution of urgency of surgery. See definition of urgency of surgery below table 2. Error bars display 95% confidence interval.*

5.3 Outcome after surgery

The outcomes after surgery for current and never-smokers are displayed in table 3.

Table 3. *Early outcomes after surgery for current and never-smokers. P-value comparing current- and never-smokers.*

Postoperative outcomes		Never smoker N=1438	Current smoker N=750	p-value
30-day mortality	**N (%)**	21 (1.5%)	19 (2.6%)	0.102
Pulmonary complications	**N (%)**	74 (5.1%)	90 (12.0%)	<0.001
Mechanical ventilation >48h	**N (%)**	27 (1.9%)	38 (5.1%)	<0.001
Pneumonia	**N (%)**	63 (4.4%)	73 (9.7%)	<0.001
Postoperative stroke	**N (%)**	9 (0.6%)	14 (1.9%)	0.013
Infection requiring antibiotics	**N (%)**	103 (7.2%)	136 (18.1%)	<0.001
Reoperation for sternuminsufficiency or mediastinitis	**N (%)**	4 (0.3%)	7 (0.9%)	0.054
Reoperation for bleeding within 24h	**N (%)**	52 (3.6%)	34 (4.5%)	0.353
Mechanical circulatory support postoperatively	**N (%)**	16 (1.1%)	16 (2.1%)	0.09
New atrial fibrillation	**N (%)**	473 (32.9%)	237 (31.6%)	0.565
New dialysis	**N (%)**	17 (1.2%)	16 (2.1%)	0.122

5.3.1 Postoperative complications depending on smoking status

There was a trend to a higher incidence of 30-day mortality in active smokers compared to never-smokers, though this finding was not statistically significant (2.6% vs 1.5%, p=0.102).

Pulmonary complications were more common in current smokers, both when comparing the composite endpoint (postoperative pneumonia or mechanical ventilation >48h: 12.0% vs 5.1%, p<0.001) and pneumonia and prolonged mechanical ventilation (>48h) analyzed

separately (postoperative pneumonia: 9.7% vs 4.4%, p<0.001; mechanical ventilation>48h: 5.1% vs 1.9%, p<0.001) (figure 6).

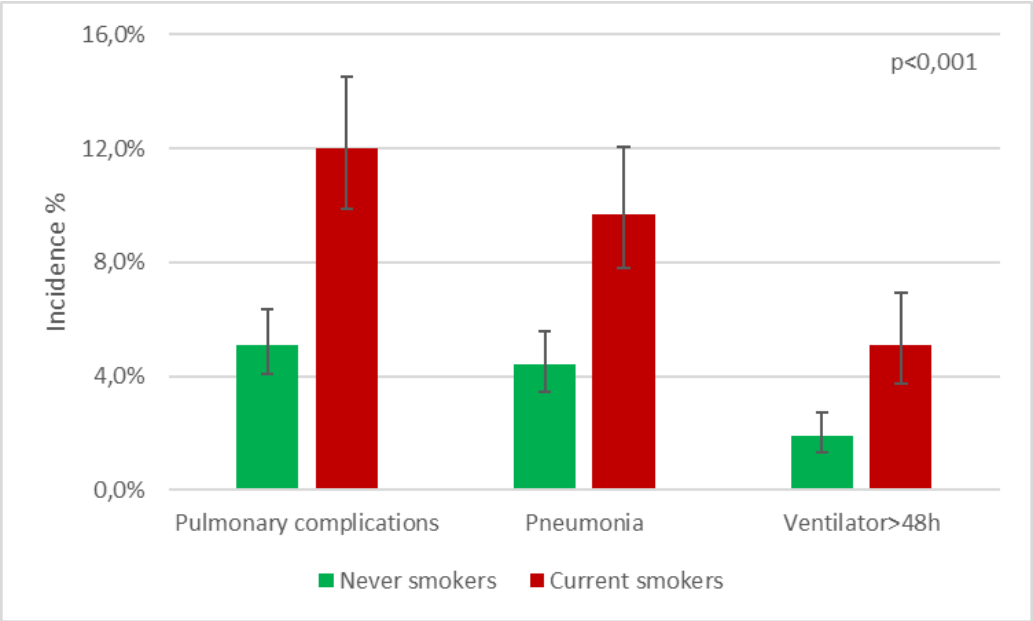

Figure 6. *Distribution of pulmonary complications, pneumonia and prolonged mechanical ventilation depending on smoking status.*

Furthermore, infections requiring antibiotics and postoperative stroke were also significantly more common in current smokers compared to never-smokers (infections: 18.1% vs 7.2%, p<0.001; postoperative stroke: 1.9% vs 0.6%, p=0.013).

Reoperation for bleeding, mediastinitis or insufficiency in sternum, postoperative dialysis, postoperative circulatory support, and atrial fibrillation was not statistically significantly different between the two groups.

5.3.2 Adjusted analysis

Propensity score matching was performed to adjust for differences in background variables in current and never-smokers. After matching, outcome variables of two new groups of 465 current smokers matched with 465 never-smokers were analyzed.

Current smokers still had a higher incidence of composite pulmonary complications, pneumonia, postoperative stroke, and infection requiring antibiotics (table 4). 30-day mortality showed a strong trend to be more common in current smokers in this adjusted analysis, though not statistically significant (2.4% vs 0.7%, p=0.059). After matching, mechanical ventilation >48h was not significantly different between the two groups, although there was a trend for a higher occurrence in current smokers (3.7% vs 1.8%, p=0.105). Atrial fibrillation was significantly more common in our current smokers after adjusted analysis (31.8% vs 25.2%, p=0.033).

***Table 4**. Early postoperative outcomes after propensity score matched analysis in never-smokers and current smokers. P-value comparing current- and never-smokers.*

Postoperative outcomes	Never smoker n=456	Current smoker n=456	p-value
30-day mortality	3 (0.7%)	11 (2.4%)	0.059
Pulmonary complications	25 (5.5%)	51 (11.2%)	0.003
Mechnical ventilation >48h	8 (1.8%)	17 (3.7%)	0.105
Pneumonia	23 (5.0%)	45 (9.9%)	0.008
Postoperative stroke	0 (0.0%)	9 (2.0%)	0.007
Infection requiring antibiotics	36 (7.9%)	73 (16.0%)	<0.001
Reoperation for sternuinsufficiency or mediastinitis	1 (0.2%)	4 (0.9%)	0.370
Reoperation for bleeding within 24h	15 (3.3%)	21 (4.6%)	0.395
Mechanical circulatory support postoperatively	3 (0.7%)	4 (0.9%)	1.000
New atrial fibrillation	115 (25.2%)	145 (31.8%)	0.033
New dialysis	3 (0.7%)	10 (2.2%)	0.094

5.4 Time since smoking cessation

5.4.1 Baseline characteristics

In table 1 and table 2, the baseline characteristics for ex-smokers can be viewed. Former smokers differed from never-smokers regarding BMI and several comorbidities, such as diabetes, hypertension and chronic lung disease. Recent myocardial infarction and critical preoperative state were also more common in former smokers, though not as prevalent as in current smokers.

5.4.2 Time between smoking cessation and surgery

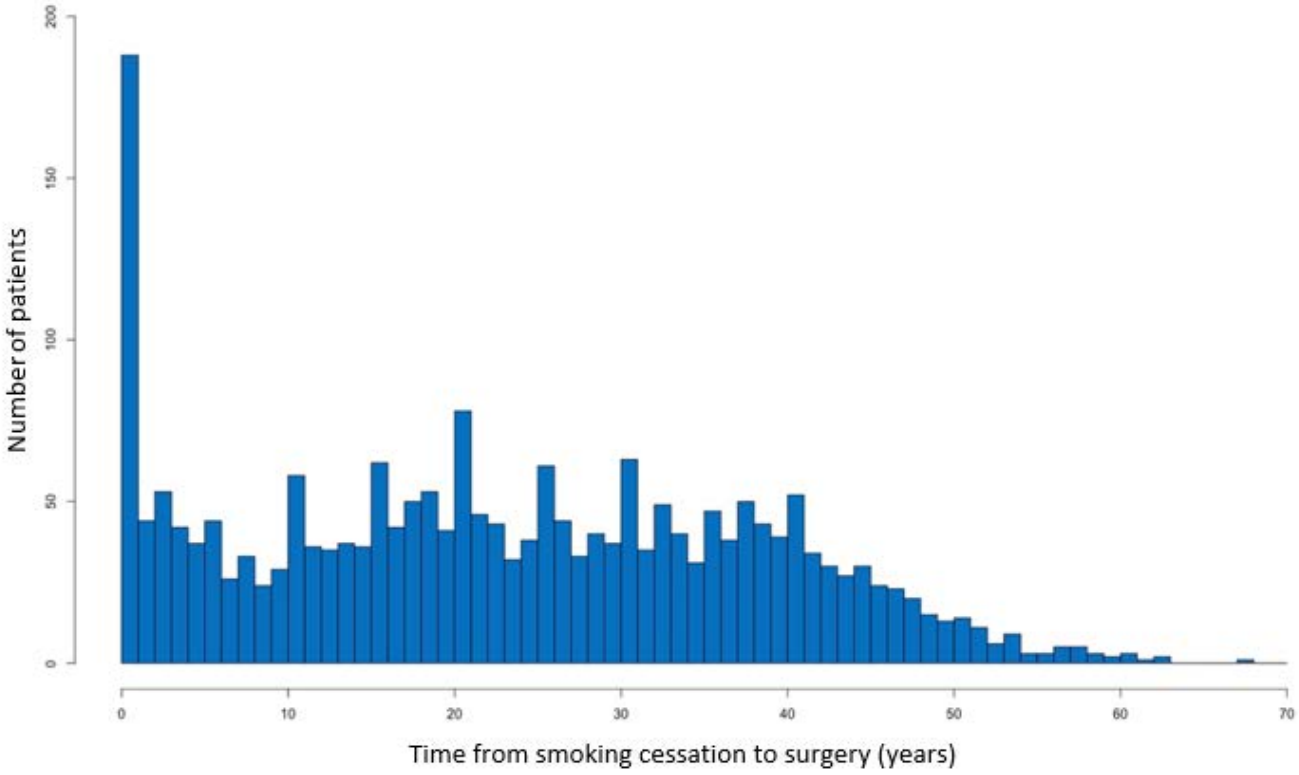

Figure 7. *Distribution of how many years former smokers had been smoke-free before surgery. n=2193 Each stack represents one year.*

The spread of time since smoking cessation is displayed in figure 7. A large proportion quit smoking less than a year before their operation (188 of 2193 patients [8.6%]). Apart from that

there was similar number of patients with smoke-free years between 2-40 years. Our study population had decreasing number of patients being smoke-free more than 40 years (figure 7).

188 patients quit within the first year before surgery (figure 8).

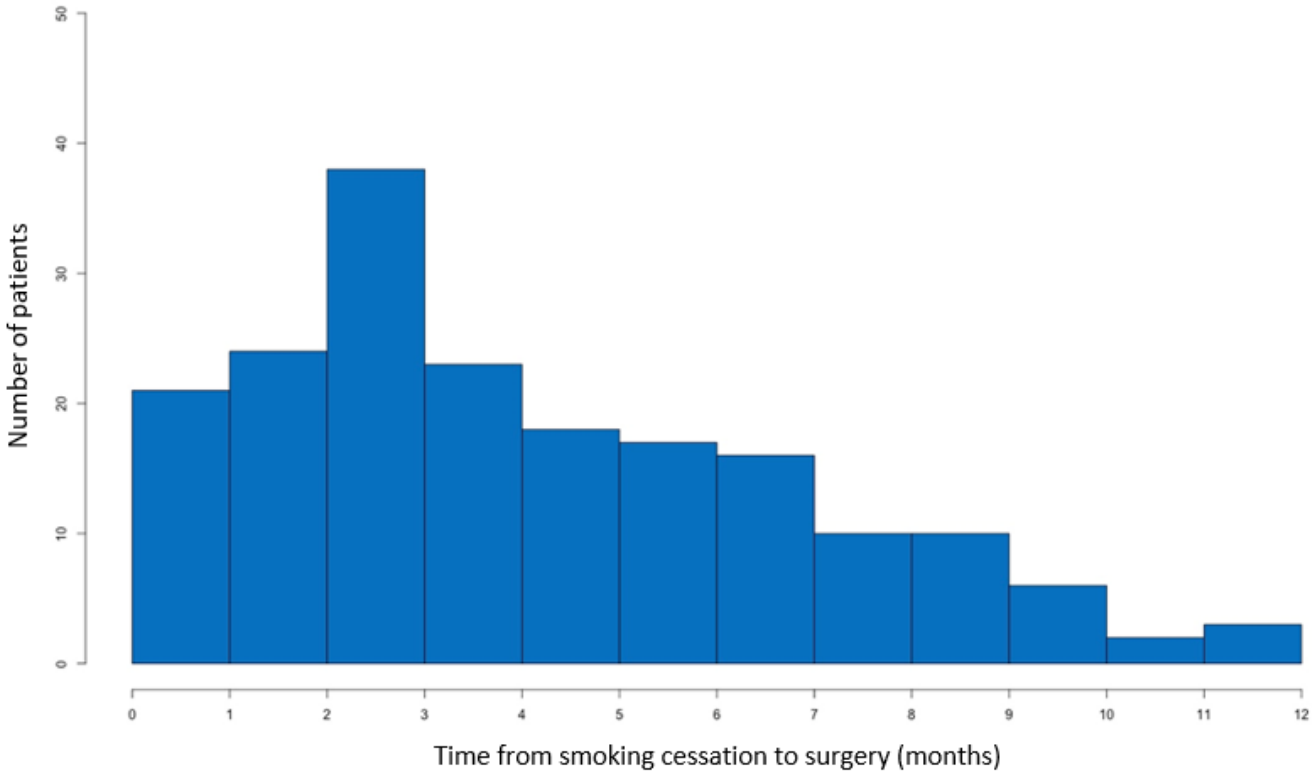

Figure 8. *Distribution of patients who stopped smoking within one year of surgery. n=188 One stack representing one month.*

5.4.3 Short term smoking abstinence

To examine short term smoking abstinence before surgery, we divided the former smokers in four intervals of smoke free duration: 1-3 months, 3-6 months, 6 months-1 year, and more than one year. The groups consisted of 82, 57, 84, and 1970 patients respectively.

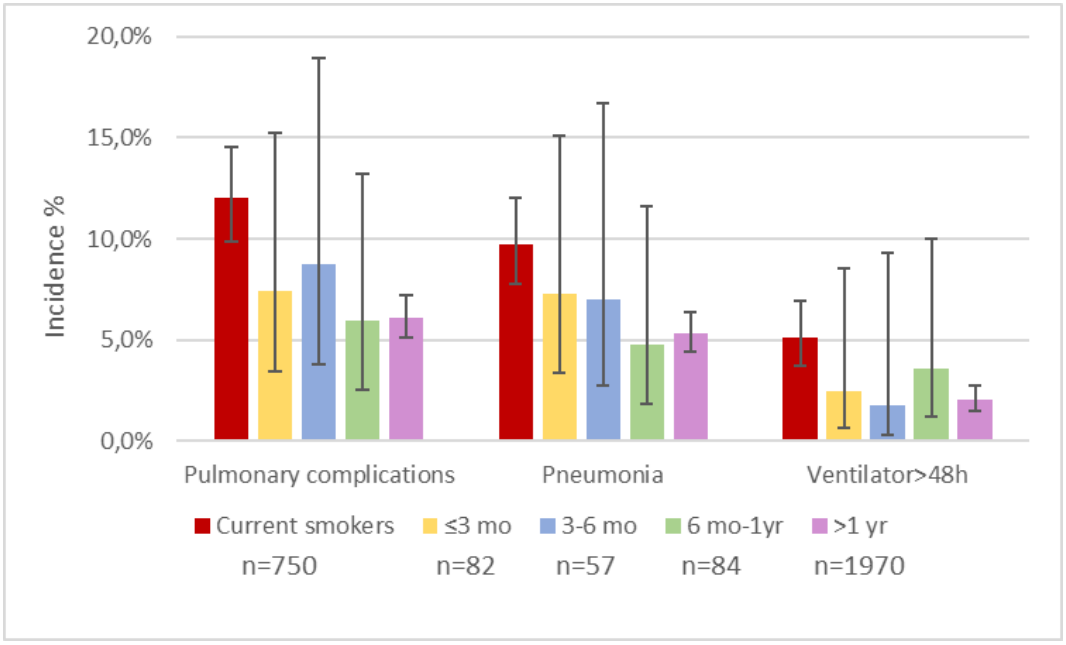

Figure 9. *Short term smoking abstinence and occurrence of composite pulmonary complications, pneumonia and mechanical ventilation >48h. Error bars display 95% confidence intervals.*

As we can see in figure 9, the proportion of patients with pulmonary complications in those who quit smoking was numerically smaller compared to active smokers. However, this difference was only statistically significant for patients with smoking cessation more than one year before surgery. Because of small number of patients in the other groups, the confidence intervals were large.

5.4.4 Postoperative complications depending on years of smoking abstinence

We analyzed if there was a time-dependent reduction of risk for adverse outcomes of those that were more common in current smokers compared to never-smokers in our unadjusted data (composite pulmonary complications, postoperative pneumonia, mechanical ventilation >48h, infections requiring antibiotics, postoperative stroke). Using univariate logistic regression we found an association between a reduced risk and increased time since smoking cessation in all these outcomes except for postoperative stroke. Graphs illustrate the decrease in risk over time for these variables in figure 10. The risk reduction seems to develop quite slowly in our data.

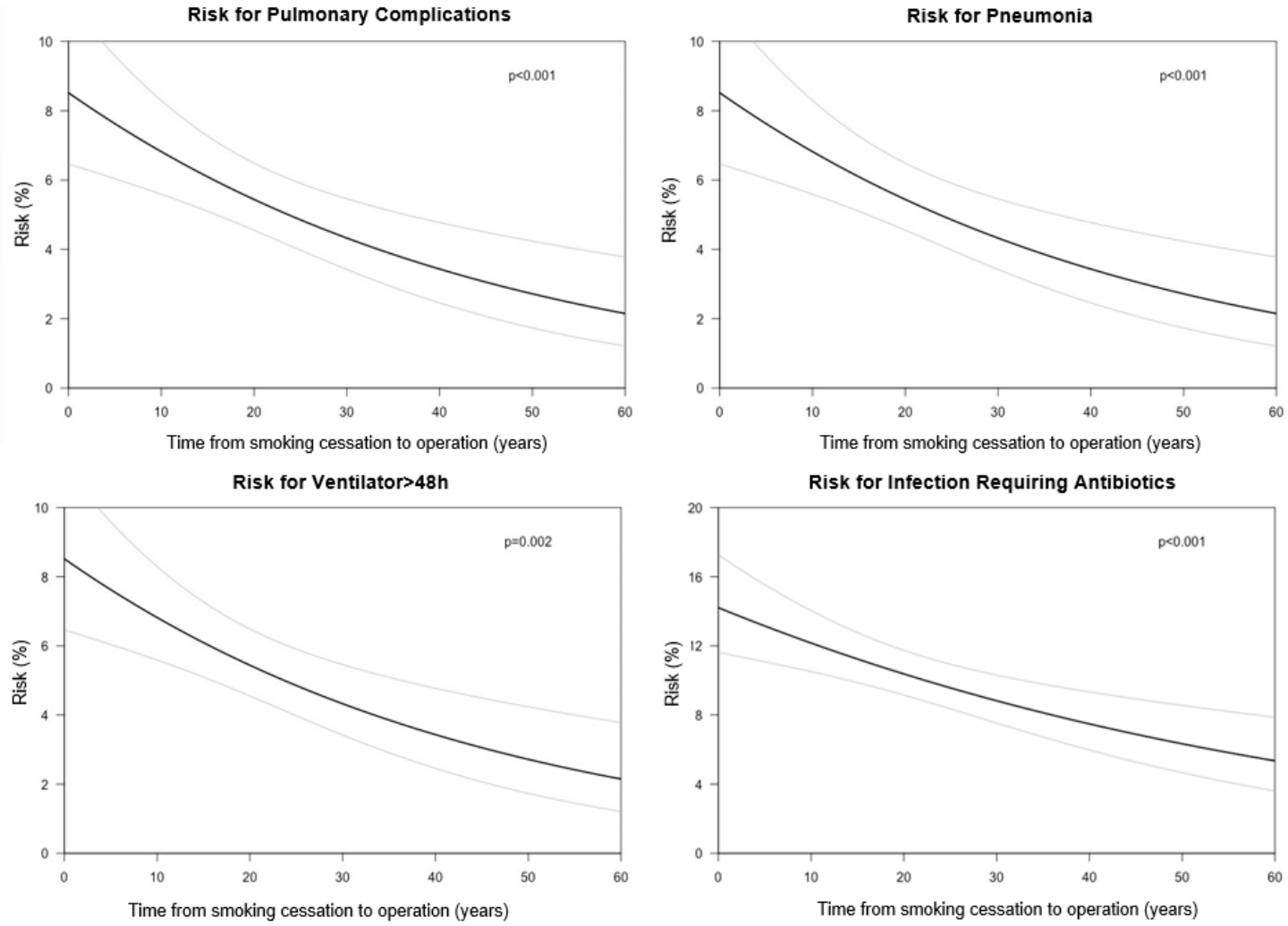

Figure 10. *The risk of composite pulmonary complications, pneumonia, mechanical ventilation >48h and infection requiring antibiotics in relation to time since smoking cessation.*
Area around the curve represents 95% confidence interval.

In multivariate logistic regression the following variables were included: time since smoking cessation, age, BMI, diabetes, gender, COPD, poor mobility, less acute operation and critical preoperative state. Also in these analyses, increased time from smoking cessation was associated with a significantly reduced risk of composite pulmonary complications, pneumonia, and prolonged ventilation. The odds ratio represents the decrease in risk per year for time since smoking cessation and age, and per unit of BMI. We could not see a significant association between postoperative stroke and time since smoking cessation in the multivariate logistic regression (odds ratio 1.03, p=0.11) (table 5 and table 6 in the appendix).

Table 5. *Multivariate analysis of predicting variables for pulmonary complications. For continuous variables (time since smoking cessation, age and BMI) the odds ratio is per unit increased.*

Predictors for pulmonary complication	Odds ratio (95% CI)	P-value
Time since smoking cessation	0.97 (0.96-0.99)	<0.01
Age	1.06 (1.03-1.09)	<0.01
BMI	1.05 (1.00-1.09)	0.044
Diabetes	1.61 (1.07-2.41)	0.021
Gender (male)	0.64 (0.41-1.03)	0.058
COPD	1.58 (0.90-2.66)	0.095
Poor mobility	1.62 (0.68-3.45)	0.24
Less acute operation	0.68 (0.49-0.95)	0.023
Critical preopertive state	3.04 (0.92-8.58)	0.047

In addition to time since smoking cessation, increased age, increased BMI, diabetes, urgent surgery, and a critical preoperative state were statistically significant risk factors associated with pulmonary complications in our analysis. Risk factors for pneumonia and prolonged

ventilation were quite similar to the composite endpoint (table 6). For postoperative stroke, we found no statistically significant risk factors (table 6).

6. Discussion

This study examined smoking and cessation and the association to early postoperative complications after CABG surgery. The key findings were that current smokers were on average five years younger when they required CABG surgery compared to non-smokers. Also, current smokers more often suffered an acute coronary syndrome as their indication for surgery requiring more urgent or emergency operations. Furthermore, we found a higher incidence of pulmonary complications, including pneumonia and mechanical ventilation >48h, and a higher occurrence of postoperative stroke, infections requiring antibiotics and atrial fibrillation in active smokers compared to never-smokers. In former smokers, we found an association between reduced risk of pulmonary complications as well as infections requiring antibiotics and longer cessation time before surgery.

6.1 Outcome depending on smoking status

Comparison of the findings with those of other studies confirms the association between smoking and increased occurrence of pulmonary complications (24-26). Regarding time in mechanical ventilation previous studies have been inconsistent. Al-Sarraf et al (24) showed no difference between smoking groups, while Saxena et al and Ji et al found current smoking to be associated with longer ventilation time (23, 26). Our study was consistent with Saxena

et al and Ji et al. Active smokers seem to possibly associate with longer time in ventilator, which also increases the risk for pneumonia (32). The higher frequency of pneumonia in active smokers might therefore be partly due to a longer time in ventilator.

Our study demonstrated a higher occurrence of postoperative stroke in smokers compared to never-smokers. This finding is contrary to previous studies (24-26) who did not find a statistically significant difference (24, 25). However, our results are in line with the physiologic changes that occur in smokers (i.e. atherosclerosis, endothelial dysfunction, altered coagulation) which may contribute to increased risk of stroke. Also, studies of the risk of stroke, not specifically in the perioperative setting, demonstrate a higher incidence of stroke in smokers than in never-smokers (33).

When analyzing 30-day mortality, we found no statistically significant difference between the current and never-smokers. This finding was in accordance with previous studies on CABG patients and postoperative outcome (24-26). In these studies, as well as in ours, there were quite few events of mortality. Larger studies may find significance in this outcome.

6.2 Adjusted comparisons of outcome depending on smoking status

The patient groups in our study differed in baseline characteristics, especially in age at surgery. Age is a strong risk factor for adverse outcomes, but despite current smokers being younger, they experienced more adverse outcomes.

After adjusting for age and other baseline factors with propensity score matching, smokers were still observed to have more occurrence of pulmonary complications and stroke. This suggests that it is not only the comorbidities that are the reasons for smokers' more frequent complications. Smoking itself seems to be associated with some postoperative complications, but not all. Mechanical ventilation >48h was not statistically different in our adjusted analysis, though the matching reduced the study cohorts thereby increasing confidence intervals.

After the adjusted analysis we found atrial fibrillation to be more common in active smokers compared to never-smokers. This finding is not previously reported by other studies on CABG-patients. For instance, Benedetto et al found a significantly lower occurrence of postoperative atrial fibrillation in smokers compared to never-smokers (25). To be considered is that they used other statistical methods compared to our study and had fewer active smokers (650 vs 750 in our study). We believe our findings are plausible and in line with other studies that demonstrate an increased risk of atrial fibrillation in smokers compared to non-smokers (34, 35).

6.3 Effects of smoking cessation

In our study population, former smokers had a higher BMI and prevalence of diabetes than current smokers and never-smokers. This corresponds to previous knowledge of smoking cessation and metabolic changes. Smoking cessation leads to weight gain, and because of this, type 2 diabetes and metabolic syndrome are more frequently occurring in those who quit smoking (36-38).

This study found a clear association between time since smoking cessation and reduced pulmonary complications. Our study suggests that there is perhaps a possibility to reduce an increased risk for pulmonary complications, pneumonia, and prolonged mechanical ventilation, caused by smoking, to the same level of never smokers, though the decrease of risk proceeds slowly. These results of a slow decrease of risk for pneumonia are in line with Nuorti et al that demonstrate an increased risk of pneumococcal disease for more than ten years after smoking cessation (39).

Multivariate logistic regression analysis confirmed that a longer time since smoking cessation was associated with a decrease of risk for pulmonary complications but failed to demonstrate significant reduction of risk of postoperative stroke. This is probable due to the rarity of this complication occurring only in 1.2% (27 of 2193) of former smokers in our data.

Our study found that several years of smoking cessation were needed to find a beneficial association regarding pulmonary complications. However, patients who had been abstinent from smoking for less than a year also had a lower frequency of pulmonary outcomes in our study, as could be seen in figure 9. This finding, though not statistically significant, is in accordance with Nakagawa et al who demonstrated a time dependent decrease in incidence of pulmonary complications during the first months of smoking cessation (40). Unfortunately, our study had small sample sizes in the subgrouped former smokers, and our confidence intervals were large, so no conclusions can be made on the preferable time of smoking cessation before surgery.

If there are benefits regarding pulmonary complications with quitting smoking only months before surgery, this might be an important consideration when planning elective surgeries. A study of Ailawadi et al found postoperative pneumonia in cardiac surgery patients to be associated with a higher incidence of early mortality (41). This shows the clinical importance of reducing these complications, and although no recommendations can be made regarding a specific time to stop smoking before surgery, the general health benefits of improved survival (16) and less morbidity (22, 33, 39) still supports cessation as early as possible.

6.4 Strengths and limitations

This study was a single center study, with one observer who went through all 5276 patient records. This means that smoking status was uniformly interpreted among all patients. Patients receiving surgery during a decade of time was included in our study, making it possible to enroll as much as 5000 patients. This still being a period where guidelines and treatment for ischemic heart disease at our institution did not change drastically. Additionally, not many other studies have examined the impact of time since smoking cessation on operative outcomes in cardiac surgery, therefore we contribute to more knowledge regarding this.

Limitations of our study include the lack of quantification of smoking. Studies have shown that effects of smoking on for instance risk of stroke and pulmonary complications depend on the quantity smoked (33, 42). Patients stating they only smoked at parties are also a difficult group, since we do not know how much they smoked or how often. Another aspect to bear in

mind may be the self-report of smoking habits, which might yield false categorization of smoking status. However, the accuracy of self-reports have been demonstrated as acceptable in a previous meta-analysis, though with great variances between studies (43).

Another limitation of this study was the small sample sizes in quitters within a year, making it difficult to draw any conclusions regarding short term smoking cessation on postoperative outcome. Similarly some outcomes had few events, such as 30-day mortality. For a better understanding and more preciseness, larger studies need to be performed to be able to accurately compare the risk of mortality and morbidity in those who quit smoking prior to surgery.

Since this was a retrospective study, it is difficult to control for possible confounders not included in the register. It is also difficult to handle missing or ambiguous data. For example, we had to assume all missing data in pneumonia to be equal to not having had pneumonia after surgery. This can produce some margins of error since we had to affect the data. We had to determine if we believe the missing data to be at random, so all patients were relatively equally represented, which in regard to pneumonia we examined the missing data and concluded it to be randomly distributed through the years.

7. Conclusion

In conclusion, we found smoking to be associated with a higher incidence of postoperative pulmonary complications, including pneumonia and ventilation >48h, as well as postoperative

stroke, infections and atrial fibrillation in patients undergoing CABG surgery. Our study demonstrates an association between the amount of time a patient has been abstinent from smoking and reduced occurrence of pulmonary complications and infections, increasing the support for better intervention and prevention of smoking. No conclusions could be made regarding shorter abstinence before surgery. Future studies with larger sample sizes are needed to determine shorter effects of smoking cessation.

8. Populärvetenskaplig sammanfattning

Rökning och risk för komplikationer efter kranskärlsoperation

Den vanligaste orsaken till död i världen idag är ischemisk hjärtsjukdom. Detta är en sjukdom som beror på att hjärtats kranskärl blir blockerade och inte kan ge hjärtat tillräckligt med syre. Kranskärlen blockeras successivt under åren, men en del saker gör att de blockeras snabbare.

En behandling mot blockerade kärl är en bypass-operation av hjärtats kranskärl, så kallad CABG operation. Detta är en komplicerad operation med flera moment som är tuffa för patienten. För att skapa bra förutsättningar för en lyckad operation, så är det viktigt att minska faktorer som kan öka risken för komplikationer. En sådan riskfaktor är rökning, vilket påverkar kroppen på många olika sätt.

Rökning påverkar både utvecklingen av ischemisk hjärtsjukdom och en del forskning har visat att de som är rökare när de behöver opereras har större risk att utveckla komplikationer efter operationen. Rökstopp minskar en del av dessa risker. Dock så är detta inte så välstuderat när det kommer till hjärtoperationer.

Vi ställde oss därför frågorna:

- Hur påverkar rökning risken för komplikationer efter en CABG operation?

- Finns det ett tidssamband mellan hur länge man varit rökfri och risken för komplikationer?

Detta försökte vi besvara genom att titta på 5000 patienter som gjort en CABG operation på Sahlgrenska mellan 2010 och 2020. Vi tittade på deras rökstatus och på hur det hade gått för alla patienter.

Det vi fann var att de som var rökare behövde opereras vid en yngre ålder, och att de oftare hade en svårare sjukdom. Rökare var associerade med en högre risk för att drabbas av lungkomplikationer, både lunginflammation och behövde ligga längre i respirator, samt att de drabbades oftare av stroke jämfört med de som aldrig hade rökt. Vi såg även att rökare eventuellt är associerade med en ökad risk för att dö inom första månaden efter operation, dock var det för få patienter för att kunna säga något säkert gällande detta.

Fortsättningsvis så kunde vi se att en längre tid sedan man slutat röka var associerat med en lägre risk för att utveckla lungkomplikationer. Dock så såg vi att det tar flera år för risken för lungkomplikationer att minska och man kan inte be patienter vänta i flera år på en kranskärlsoperation. När vi tittade på effekten av kortare rökstopp hade vi tyvärr inte tillräcklig mängd patienter som slutat röka så nära inpå operationen att vi kunde dra några slutsatser.

Det vi kan säga av vår studie är att rökning är associerat med en ökad risk för komplikationer i samband med en kranskärlsoperation, men att denna risk kan minskas om man slutar röka. Därför är det viktigt att samhället jobbar mot att man aldrig ska börja röka, och att hjälpa de som röker med att sluta. Vi kan också säga att det behövs fler och större studier på hur rökstopp påverkar hur det går efter operation för att bättre förstå effekterna av rökning och vad som är reversibelt.

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10. Figures and tables

***Table 1**. Multivariate analysis of predictors for pneumonia, ventilation>48h and postoperative stroke. For continuous variables (time since smoking cessation, age and BMI) the odds ratio is per unit increased.*

	Pneumonia		Ventilation>48h		Postoperative stroke	
Predictors	**Odds ratio (95% CI)**	**P**	**Odds ratio (95% CI)2**	**P**	**Odds ratio (95% CI)3**	**P**
Time since smoking cessation	0.97 (0.96-0.99)	<0.01	0.96 (0.93-0.99)	<0.01	1.03 (0.99-1.06)	0.11
Age	1.05 (1.02-1.09)	<0.01	1.08 (1.03-1.14)	<0.01	1.01 (0.94-1.09)	0.15
BMI	1.04 (0.99-1.09)	0.13	1.07 (0.99-1.16)	0.088	1.04 (0.93-1.16)	0.46
Diabetes	1.69 (1.11-2.57)	0.014	0.88 (0.39-1.89)	0.75	1.13 (0.37-3.17)	0.82
Gender (male)	0.78 (0.48-1.30)	0.32	0.32 (0.16-0.68)	<0.01	0.82 (0.25-3.69)	0.76
COPD	1.73 (0.97-2.93)	0.05	2.06 (0.80-4.78)	0.11	1.42 (0.22-5.46)	0.65
Poor mobility	1.89 (0.79-4.02)	0.12	0.49 (0.026-2.53)	0.50	1.79 (0.095-9.88)	0.59
Less acute operation	0.67 (0.47-0.95)	0.024	0.73 (0.40-1.31)	0.30	0.47 (0.20-1.10)	0.082
Critical preoperative state	2.51 (0.67-7.51)	0.13	12.9 (3.30-44.9)	<0.01	<0.01 (<0.01->100)	0.99