Smoking cessation before coronary artery bypass grafting improves operative outcomes

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Background: The detrimental effect of active smoking on operative outcome after coronary artery bypass grafting (CABG) is still debated and smoking cessation programs are usually deferred until after surgery. The potential benefit from smoking cessation on postoperative outcomes is investigated in this study.

Methods: A retrospective analysis on a large cohort of patients who underwent CABG at a single institution was performed. Generalized boosted regression modeling was used to estimate the multinominal propensity scores for smoking status categories and the average treatment effect on the treated was calculated for all outcomes of interest.

Results: A total of 6113 patients who underwent isolated CABG for the first time were included. At baseline, there were 640 (10.4%) current smokers, 3309 (54.1%) ex-smokers, and 2164 (35.3%) nonsmokers. Multilevel propensity score weighted analysis showed a beneficial effect of smoking cessation compared with current smoking, which increased the risk for all major pulmonary complications (odds ratio [OR], 1.54; 95% confidence interval [CI], 1.13-2.10; $P = .006$), including reintubation (OR, 1.95; 95% CI, 1.17-3.25; $P = .01$), full tracheostomy (OR, 3.04; 95% CI, 1.49-6.18; $P = .002$), lung infection/consolidation (OR, 1.44; 95% CI, 1.02-2.02; $P = .03$). Although smoking cessation did not significantly improve other outcomes, it was associated with a nonsignificant trend toward a decreased risk for in-hospital mortality (OR, 1.83; 95% CI, 0.85-3.91; $P = .1$).

Conclusions: This study showed that smoking cessation before CABG reduced the risk of serious pulmonary complications. The present findings indicate that embarking on a smoking cessation program should not be deferred until after surgery. (J Thorac Cardiovasc Surg 2014;148:468-74)

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Tobacco smoking remains the leading cause of preventable morbidity and mortality in the world[1] and smoking cessation is associated with important benefits.[2] In addition to the general health risks associated with smoking, it has been shown that smokers are more likely to have postoperative complications including delayed wound healing, pulmonary complications, and mortality.[3]

Smoking cessation has been consistently shown to offer important benefits in reducing complications in patients undergoing noncardiac surgery.[3]

Cigarette smoking is a major contributor to the risk of coronary heart disease[4] and a large number of active smokers are referred for coronary artery bypass grafting (CABG) worldwide. Although smoking cessation after CABG has been found to improve late outcomes,[5,6] cardiac surgeons continue to debate whether patients who have stopped smoking should wait for a definite period of time before undergoing surgery.[7] Few limited studies have investigated the effect of active smoking on CABG operative outcomes and discordant results have been reported.[8-12]

The main risk scoring systems in cardiac surgery such as EuroSCORE and STS score failed to investigate the effect of active smoking on operative mortality.[13] As a consequence, active smoking at the time of surgery is not commonly perceived as a main risk factor for operative morbidity and mortality, and smoking cessation programs are usually deferred until after surgery.

Therefore, we investigated the potential benefit of smoking cessation on operative outcomes after CABG by conducting a detailed analysis on a large cohort of patients from a single institution.

PATIENTS AND METHODS

Study Population

The study was conducted in accordance with the principles of the Declaration of Helsinki.

Prospectively collected data from the institutional surgical database (PATS; Dendrite Clinical Systems, Ltd, Oxford, UK) were analyzed

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Abbreviations and Acronyms

- ATT = average treatment effect on the treated
- CABG = coronary artery bypass grafting
- CI = confidence interval
- GBM = generalized boosted regression modeling
- IR = incomplete revascularization
- NYHA = New York Heart Association
- POAF = postoperative atrial fibrillation
- SWI = sternal wound infection

retrospectively. The PATS database captures detailed information on a wide range of preoperative, intraoperative, and hospital postoperative variables (including complications and mortality) for all patients undergoing cardiac surgery in our institution. The data are collected and reported in accordance with the Society for Cardiothoracic Surgery in Great Britain & Ireland database criteria. The database is maintained by a team of full-time clinical information analysts, who are responsible for continuous prospective data collection as part of a continuous audit process. Data collection is validated regularly. Patients undergoing isolated first-time CABG from April 2001 to May 2013 were included in the present analysis.

Patients were scheduled for surgery according to internal guidelines for the scheduling of patients on the waiting list: emergency (within 24 hours), very urgent (0-4 weeks), urgent (4-8 weeks), soon (8-12 weeks), and routine (18 weeks from referral to surgery). Patients on the waiting list complaining of worsening of symptoms were reviewed in the clinic by the allocated consultant or given a theatre slot with the first available consultant as appropriate.

Patients were queried about their smoking habits at index admission. The study population was divided into 3 groups based on smoking habits: (1) never smoked, defined as patients who had never smoked cigarettes regularly; (2) ex-smokers, defined as those who had quit smoking at least 4 weeks before the index procedure; and (3) current smokers, defined as those who smoked within 4 weeks before the index procedure. Four weeks was chosen as the smoking cessation cut-off according to a previous meta-analysis of randomized controlled trials enrolling patients undergoing noncardiac surgery demonstrating that trials of at least 4 weeks' smoking cessation had significantly larger treatment effects on postoperative complications than shorter trials.[3]

Smoking cessation services were provided for all prospective surgical candidates and brief intervention counseling was offered during surgical preadmission checks. All smokers and ex-smokers (within 5 years) had preoperative pulmonary function testing. When an airflow obstruction (defined as an FEV_1/FVC ratio <0.7, where FEV_1 is forced expiratory volume in the first second of expiration and FVC is forced vital capacity, and a predicted FEV_1 <80%) was demonstrated, bronchodilators were started before surgery. During the study period, no case was delayed to achieve a period of smoking cessation.

Outcomes

The following postoperative complications were investigated: major lung complications including full tracheostomy, reintubation, lung infection/consolidation; low cardiac output syndrome defined as the need for inotropes and/or an intra-aortic balloon pump after surgery, need for renal replacement therapy, a postoperative cerebrovascular accident, both transient or permanent, reexploration for bleeding, sternal rewiring for instability, sternal wound infection (SWI) either superficial or deep, postoperative atrial fibrillation (POAF), pleural effusion requiring drainage, prolonged postoperative hospital stay (defined as length of stay ≥75th percentile of postoperative stay length distribution), and in-hospital mortality.

Statistical Analysis

For baseline characteristics, variables were summarized as the mean ± standard deviation for continuous variables and number and percentage for categorical variables. The standardized mean difference was used to quantify differences in means or prevalence among groups using ex-smokers as reference; a value >0.10 represented meaningful imbalance in a given covariate.[14]

The following risk factors were investigated: age, gender, diabetes mellitus, body mass index (BMI) ≥30 kg/m^2, renal impairment defined as a baseline serum creatinine level ≥200 mmol/L, previous myocardial infarction, history of congestive heart failure, chronic obstructive pulmonary disease (defined as long-term use of bronchodilators or steroids for lung disease or evidence of airflow obstruction on preoperative pulmonary function testing), history of cerebrovascular accident, functional New York Heart Association (NYHA) class III or IV, reduced left ventricular ejection fraction (<50%), peripheral vascular disease, nonelective surgery, use of cardiopulmonary bypass, number of grafts, and incomplete revascularization.

The incidence of postoperative complications was compared among groups by means of the χ^2 test or analysis of variance for continuous variables. To separate the effect of smoking cessation on outcomes from observed confounding factors that influenced smoking status at the time of surgery, nonparsimonious, generalized boosted regression modeling (GBM) was implemented to estimate the multinominal propensity scores (number of interactions = 3000) for smoking status categories including all preoperative risk factors. This method relies on tree-based regression models that are built in an iterative fashion. As the iterations or number of regression trees added to the model increases, the model becomes more complex. However, at some point, more complex models typically result in worse balance and therefore are less useful in a propensity score weighting context. The key assumption that each unit had a nonzero probability of belonging to each group was assessed by the overlap of the empirical propensity score distributions. Balance among smoking status groups was assessed by means of comparisons of effect size standardized as the mean difference of the effect size before and after weighting.

The propensity score weights were used as case weights in a generalized linear logistic model to estimate the average treatment effect on the treated (ATT) for all outcomes of interest.[13] In brief, the ATT answers the question of how the average outcome would change if everyone who received surgery without smoking cessation had instead received surgery after a smoking cessation period. These models estimated the odds ratio (OR) and 95% confidence interval (CI) for each smoking status category using ex-smokers as the treatment group.

The following programs were used for the statistical analysis: R version 2.15.2 (R Foundation for Statistical Computing, Vienna, Austria; http://www.R-project.org/), twang (Toolkit for weighting and analysis of nonequivalent groups, R package version 1.3-18; http://CRAN.R-project.org/package=twang), and survey packages (Survey: analysis of complex survey samples, R package version 3.28-2; http://carn.r-project.org).

RESULTS

Baseline Characteristics

A total of 6113 patients who underwent isolated first-time CABG were included. At baseline, the were 640 (10.4%) current smokers, 3309 (54.1%) ex-smokers, and 2164 (35.3%) nonsmokers. Baseline characteristics stratified by smoking status are shown in Table 1. Eight of 16 variables were different among smoking status groups (standardized mean difference >0.1) including age, female gender, previous myocardial infarction, chronic obstructive pulmonary disease, reduced left ventricular ejection fraction, peripheral vascular disease, nonelective indication, and the use of cardiopulmonary bypass.

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TABLE 1. Baseline characteristics

	Ex-smokers (N = 3309)		Never smokers (N = 2164)		Current smokers (N = 640)		Standardized difference (never smokers vs ex-smokers)		Standardized difference (current smokers vs ex-smokers)	
	n	%	n	%	n	%	Before weighting	After weighting	Before weighting	After weighting
Age ≥70 y	1307	39.5	878	40.6	99	15.6	0.03	0.006	0.66	0.08
Female	112	3.4	151	7	16	2.6	0.19	0.005	0.05	0.01
Diabetes	787	23.8	545	25.2	131	20.5	0.03	0.005	0.09	0.02
BMI ≥30 kg/m^2	1012	30.6	566	26.2	183	28.6	0.09	0.02	0.017	0.02
Renal impairment	79	2.4	51	2.4	7	1.2	0.001	0.04	0.07	0.04
Previous MI	1393	42.1	757	35	280	43.9	0.14	0.027	0.03	0.007
CHF	231	7	123	5.7	42	6.7	0.04	0.03	0.03	0.06
COPD	347	10.5	142	6.6	92	14.5	0.13	0.05	0.08	0.02
Previous CVA	214	6.48	101	4.68	46	7.34	0.08	0.02	0.03	0
NYHA III-IV	956	28.9	605	28	190	29.8	0.02	0.02	0.006	0
LVEF <50%	698	21.1	359	16.6	144	22.5	0.11	0.03	0.014	0.01
PVD	322	9.74	103	4.76	77	12.1	0.15	0.06	0.069	0.007
LMD	906	27.4	551	25.5	173	27.1	0.03	0.02	0.023	0.006
Emergency or very urgent	916	27.7	629	29.1	197	30.9	0.05	0	0.1	0.02
CPB	1012	30.6	566	26.2	183	28.6	0.1	0.001	0.002	0.01
No. grafts/patient (mean, SD)	2.6	0.8	2.6	0.8	2.6	0.8	0.01	0.006	0.03	0.04
IR	635	19.2	408	18.9	110	17.2	0.01	0.01	0.05	0.04

BMI, Body mass index; *MI*, myocardial infarction; *CHF*, chronic heart failure; *COPD*, chronic obstructive pulmonary disease; *CVA*, cerebrovascular accident; *NYHA*, New York Heart Association; *LVEF*, left ventricular ejection fraction; *PVD*, peripheral vascular disease; *LMD*, left main disease; *CPB*, cardiopulmonary bypass; *IR*, incomplete revascularization; *SD*, standard deviation.

Operative Outcomes

The incidence of postoperative complications was as follows: major lung complication 847 (13%), including reintubation 265 (4.1%), full tracheostomy 102 (1.6%), and lung infection/consolidation 847 (13.8%); low output syndrome 1514 (24.7%); need for renal replacement therapy 278 (4.5%); perioperative cerebrovascular accident 72 (1.1%); reexploration for bleeding 253 (4.1%); sternal rewiring for instability 176 (2.8%), SWI 385 (6.2%); POAF 1271 (21.2%); pleural effusion requiring drainage 285 (4.6%); hospital death 129 (2.1%). Median postoperative length of stay was 7 days (interquartile range, 6-10). Prolonged hospital stay (≥10 days) occurred in 1604 patients (26.2%). The rate of postoperative complications stratified by smoking status is shown in Table 2. The crude incidence of postoperative complications did not differ significantly among smoking status groups apart from the incidence of POAF, which was decreased among current smokers. The rate of lung infection/consolidation was slightly increased among current smokers ($P = .047$) but not the incidence of reintubation ($P = .25$), full tracheostomy ($P = .1$), and overall incidence of major lung complication ($P = .1$).

Effect of Smoking on Operative Outcomes

To separate the effect of smoking cessation on outcomes from observed confounding factors, multinominal propensity scores were then calculated. Balance measures were optimized by GBM with substantially fewer than 3000 iterations (Figure 1). A total of 2280 iterations minimized the average effect size difference between current smokers and ex-smokers for the covariates (average difference before weighting, 0.08; after weighting, 0.02). A total of 2720 iterations minimized the average effect size difference between never smokers and ex-smokers (average difference before weighting, 0.07; after weighting, 0.02). All covariates were well balanced after weighting (Table 1) and there was good overlap for propensity scores among groups (Figure 2).

Multilevel propensity score weighted analysis for the ATT estimate (Table 3) showed a beneficial effect of smoking cessation compared with current smoking, which increased the risk for all major pulmonary complications (OR, 1.54; 95% CI, 1.13-2.10; $P = .006$) including reintubation (OR, 1.95; 95% CI, 1.17-3.25; $P = .01$), full tracheotomy (OR, 3.04; 95% CI, 1.49-6.18; $P = .002$), lung infection/consolidation (OR, 1.44; 95% CI, 1.02-2.02; $P = .03$). Smoking cessation did not significantly improve other outcomes, however it was associated with a nonsignificant trend toward a decreased risk for prolonged postoperative length of stay (OR, 1.35; 95% CI, 0.85-3.91; $P = .08$) and in-hospital mortality (OR, 1.83; 95% CI, 0.85-3.91; $P = .1$). On the other hand, patients who stopped smoking at least 4 weeks before surgery achieved results comparable with never smokers for all outcomes of interest (Table 3).

TABLE 2. Operative outcomes

	Ex-smokers (N = 3309)		Never smokers (N = 2164)		Current smokers (N = 640)		
	n	%	n	%	n	%	χ^2 *P* value
Reintubation	142	4.31	81	3.75	33	5.2	.25
Full tracheostomy	53	1.61	32	1.48	17	2.68	.1
Lung infection/consolidation	456	13.8	283	13.1	108	17	.047
Main pulmonary complications	545	16.5	341	15.8	124	19.4	.1
Low output syndrome	800	24.2	564	26.1	150	23.5	.22
Real replacement therapy	136	4.13	115	5.33	27	4.23	.1
New cerebrovascular accident	32	0.977	27	1.25	13	2.04	.07
Reexploration for bleeding	147	4.47	82	3.8	24	3.77	.4
Sternal rewiring for instability	99	3.01	58	2.69	19	2.99	.77
Sternal wound infection	212	6.42	133	6.17	40	6.3	.9
Postoperative atrial fibrillation	751	22.7	443	20.5	103	16.2	.0007
Pleural effusion drained	155	4.69	97	4.49	33	5.17	.7
Prolonged hospital stay (≥10 d)	877	26.5	569	26.3	152	23.7	.4
Hospital death	61	1.87	51	2.38	17	2.71	.25

The benefit of smoking cessation on pulmonary complications was confirmed when patients who could not be delayed at least 4 weeks (classified as emergency or very urgent cases) were excluded: all major pulmonary complications (OR, 1.50; 95% CI, 1.11-2.21; *P* = .009), reintubation (OR, 1.90; 95% CI, 1.13-3.35; *P* = .02), full tracheotomy (OR, 2.96; 95% CI, 1.23-6.78; *P* = .001), and lung infection/consolidation (OR, 1.41; 95% CI, 1.01-2.25; *P* = .04).

DISCUSSION

The main finding of the present study was that smoking cessation at least 4 weeks before CABG reduced the risk of major pulmonary complications including reintubation, full tracheotomy, and lung infection/consolidation.

In the United States, approximately 8 to 10 million procedures requiring surgery and anesthesia are performed on cigarette smokers.[15] It has been estimated that if all patients were offered a smoking cessation intervention before surgery, this could avoid 2 million complications, resulting in large savings for both patients and health services.[3]

The deleterious effect of smoking after CABG has been the subject of long-standing speculation.[7] The beneficial effect of smoking cessation after CABG has been clearly demonstrated.[5,6] However, the effect of smoking cessation before surgery on operative outcomes remains to be determined. Several reports have confirmed that current smoking has a deleterious effect on operative outcomes compared with no smoking, In a multivariate analysis of individuals more than 70 years old undergoing internal thoracic artery grafting, He and colleagues[8] reported a history of smoking (current and ex-smokers were compared with never smokers) as an independent predictor of in-patient mortality. Jones and colleagues[9] demonstrated that current smoking had the worst operative outcomes, including pulmonary complications and operative death, compared with never smokers in 275 patients aged more than 70 years. In a retrospective analysis of 2597 patients, Al-Sarraf and colleagues[10] reported that current smoking was associated with an increased risk of pulmonary complications but not operative mortality compared with never smoking. The investigators concluded that a smoking cessation period should be encouraged in smokers before surgery.

This recommendation cannot be extrapolated from the aforementioned studies as they demonstrated that current smoking increased operative morbidity compared with non-smokers, but the benefit from smoking cessation was not demonstrated. The benefit from a short period of smoking cessation on operative outcomes has only been shown by a small prospective study from Warner and colleagues.[11] On the other hand, Utley and colleagues[12] have rejected preoperative smoking as a predictor of outcomes in a large retrospective study with 2916 patients. In this analysis, however, patients were classified as either current smokers or nonsmokers. Given that smokers are more likely to quit around the time of surgery, the nonsmoking group is likely to have included several smokers who recently quit.

In the absence of stronger evidence, current smoking continues to be not perceived as a main risk factor by surgeons worldwide and smoking cessation programs are commonly delayed until after surgery.

To the best of our knowledge, the present investigation includes the largest sample size on the effect of smoking cessation on operative outcomes.

In the present study, the crude incidence of postoperative complications, including pulmonary complications, was not significantly increased in current smokers compared with ex-smokers and never smokers. This was partially because of their better risk profile mostly related to younger age (only 15% of current smokers were more than 70 years of age compared with 40% among ex-smokers and never

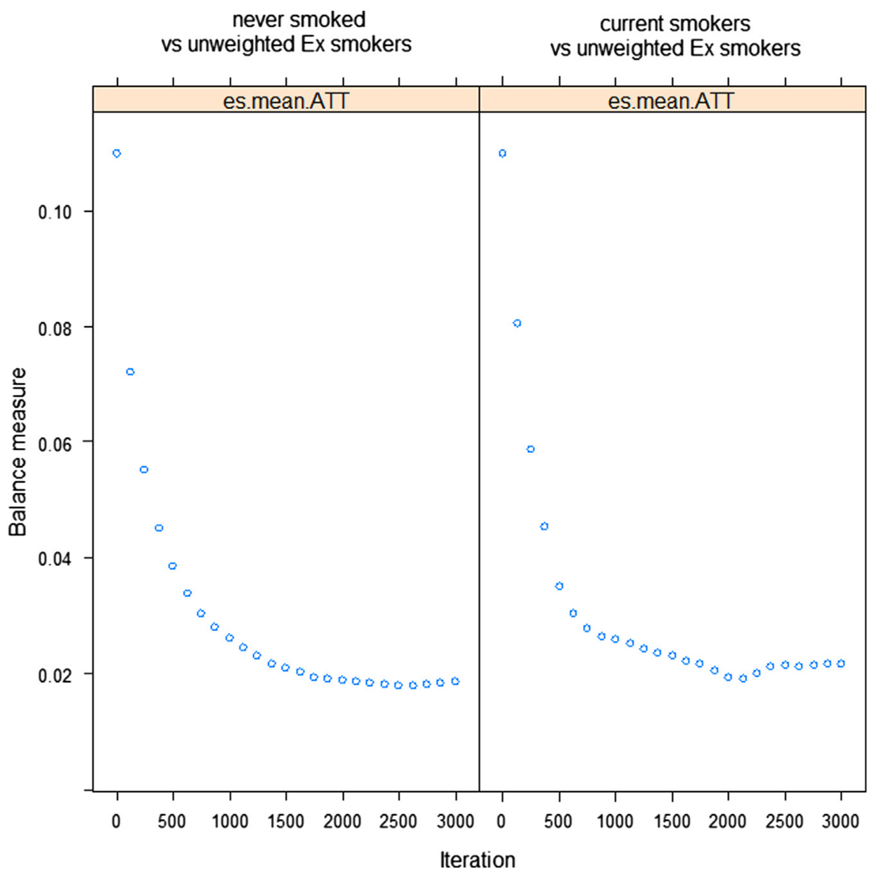

FIGURE 1. Relationship between balance measure and number of interaction in the generalized boosted regression modeling for propensity score. Balance measures were optimized with substantially fewer than 3000 iterations. *ATT*, Average treatment effect on the treated.

smokers). However, multinominal propensity score weighting analysis was able to demonstrate that smoking cessation reduced the risk for all major pulmonary complications (54% absolute risk decrease), including reintubation (2-fold risk decrease), full tracheostomy (3-fold risk decrease), and lung infection/consolidation (44% absolute risk decrease). In addition, smoking cessation was associated with a nonsignificant trend toward reduced risk of prolonged postoperative length of hospital stay (38% absolute risk decrease) and in-hospital mortality (83% absolute risk decrease). Smoking cessation did not reduce the risk of other operative complications such as pleural effusion requiring drainage, postoperative stroke, need for renal replacement therapy, POAF, sternal rewiring for instability, and SWI. On the other hand, the operative outcomes of patients who stopped smoking at least 4 weeks before surgery were comparable with the outcomes of patients who never smoked.

Although smoking cessation is an important health issue, information about the underlying mechanisms of the effects of smoking cessation on the lungs is surprisingly scarce. Smoking cessation can result in a decrease in postoperative pulmonary complications through physiologic improvement in ciliary action, macrophage activity, and small airway function as well as a decrease in sputum production.[16] In addition, an acute effect of smoking cessation on inflammation is expected to play a main role. Previous studies showed that macroscopic signs of chronic bronchitis (edema, erythema, and mucus) decreased within 3 months after smoking cessation, and totally disappeared after 6 months.[17] In addition, exhaled nitric oxide levels increased to almost normal values within 1 week of smoking cessation, suggesting that the smoke-induced inhibition of inducible nitric oxide synthase production by epithelial cells is reversible. A decrease in the number of macrophages in sputum and bronchoalveolar lavage fluid has been shown to be evident 1 to 2 months after smoking cessation. In addition, a decrease in proinflammatory mediator (soluble intercellular adhesion molecules and soluble CD44) levels has been reported.[18]

This study has some limitations. Despite the use of multinominal propensity weighting to minimize bias related to different risk profiles, this remains a retrospective analysis with known inherent limitations. Although smoking cessation has been shown to reduce wound-related complications, wound healing time, and bone fusion time in orthopedic surgery,[19,20] in the present study we were

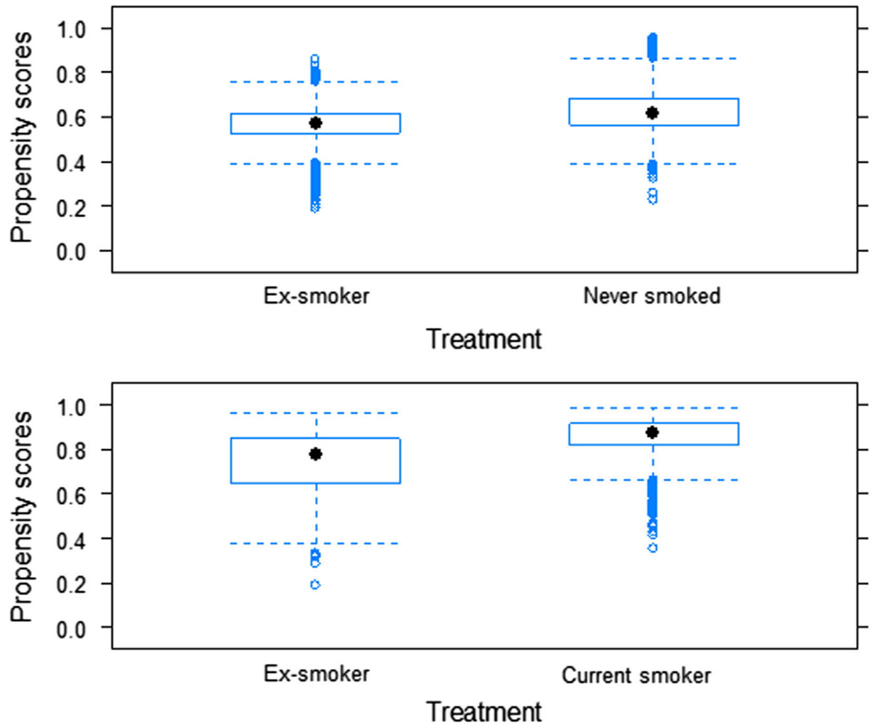

FIGURE 2. Propensity score distributions.

unable to demonstrate any impact on SWI or sternal rewiring for instability. We cannot exclude that smoking cessation duration longer than 4 weeks may improve sternal wound healing and prevent SWI. However, in the present retrospective analysis, we were unable to identify the optimum time to quit before surgery to achieve maximum benefit; some previously published research indicates a minimum of 6 to 8 weeks.[15]

The number of cigarette smoked per day or the number of pack-years smoked was not recorded in the present study, and the smoking status was determined from self-reports with no biochemical proof of the patients' smoking habits. However, self-reported smoking habits have been found to be accurate in other studies.[21]

Within these acceptable limitations, the findings of the present study strongly support the recommendation of at least 4 weeks' smoking cessation before nonurgent CABG to improve postoperative outcomes and in particular to reduce the risk of postoperative pulmonary complications.

However, all patients referred for CABG should be encouraged to stop smoking at any time before surgery because it is expected to be beneficial[3]; embarking on a

TABLE 3. Average treatment effect on the treated (ATT) with patients who stopped smoking at least 4 weeks before surgery as reference

	ATT for current smokers	95% CI	*P* value	ATT for never smokers	95% CI	*P* value
Reintubation	1.95	1.17-3.25	.01	0.88	0.62-1.25	.49
Full tracheostomy	3.04	1.49-6.18	.002	0.97	0.55-1.72	.9
Lung infection/consolidation	1.44	1.02-2.02	.03	1.06	0.86-1.30	.5
Main pulmonary complication	1.54	1.13-2.10	.006	1.04	0.86-1.26	.6
Low output syndrome	1.10	0.82-1.46	.5	1.15	0.99-1.35	.06
Real replacement therapy	1.28	0.72-2.29	.39	1.3	0.96-1.75	.08
New cerebrovascular accident	0.88	0.32-2.42	.8	1.02	0.55-1.90	.9
Reexploration for bleeding	0.89	0.47-1.69	.73	0.79	0.58-1.09	.16
Sternal rewiring for instability	1.25	0.68-2.28	.46	0.82	0.56-1.20	.3
Sternal wound infection	1.05	0.68-1.62	.8	0.86	0.66-1.10	.2
Postoperative atrial fibrillation	0.83	0.62-1.11	.2	0.88	0.76-1.03	.1
Pleural effusion drained	0.89	0.51-1.54	.68	0.99	0.75-1.35	.99
Prolonged hospital stay (≥10 d)	1.35	0.98-1.96	.08	0.99	0.85-1.14	.89
Hospital death	1.83	0.85-3.91	.1	1.16	0.74-1.83	.5

ATT, Average treatment effect on the treated; *CI*, confidence interval.

smoking cessation program should not be deferred until after surgery.[6]

Smoking cessation services, which are limited at the moment, should be developed to assist all prospective surgical candidates. These results should help to guide treatment and have the potential to improve outcomes and use of resources.

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