Title:

# Smoking Status and Mortality Outcomes Following Percutaneous Coronary Intervention

Study Design:

Retrospective analysis of prospectively collected data

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Ethics:

The study received Caldicott guardianship approval from Freeman Hospital and Aberdeen royal Infirmary.

Funding and Sponsors:

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

**Word count**

Structured Abstract - 250

Manuscript (main text, tables, figures and references) - word count 3981

**Structured Abstract** (Word count- 250)

**Objective:** To assess the impact of smoking on short (30 day) and intermediate (30-day to 6-month) mortality following PCI.

**Background:** Effect of smoking on mortality post-PCI is lacking in the modern PCI era.

**Methods:** Retrospective analysis of prospectively collected data comparing short and intermediate term mortality amongst smokers, ex-smokers and non-smokers.

**Results:** The study cohort consisted of 12,656 patients: never-smokers (n=4288), ex-smokers (n=4806) and current smokers (n=3562). Mean age (±SD) was 57(±11) years in current smokers compared to 67(±11) in ex-smokers and 67 (±12) in never-smokers; *P* < 0.0001. PCI was performed for ACS in 84.1% of current smokers, 57% of ex-smokers and 62.9% in never-smokers; *P* < 0.0001. In a logistic regression model correct, the adjusted odds ratios (95% confidence intervals [CI]) for 30-day mortality were 1.60 (1.10 - 2.32) in current smokers and 0.98 (0.70 - 1.38) in ex-smokers compared to never-smokers. In the Cox proportional hazard model, the adjusted hazard ratios (95% CI) for mortality between 30 days and 6 months were 1.03 (0.65 - 1.65) in current smokers and 1.19 (0.84 - 1.67) in ex-smokers compared to never-smokers.

**Conclusion:** This large observational study of non-selected patients demonstrates that ex-smokers and never-smokers are of similar age at first presentation to PCI, and there is no short and intermediate term mortality difference between them following PCI. Current smokers undergo PCI at younger age, more often for ACS, and have higher short-term mortality. These findings underscore the public message on benefits of smoking cessation and harmful effects of smoking.

**Key words:** Smoking; Percutaneous Coronary Intervention; PCI outcome; Smoking mortality; Smoking and PCI; PCI mortality; smokers' outcome; heart attack and smoking; stents in smokers

**Abbreviations list**

PCI-Percutaneous Coronary Intervention

ACS-Acute Coronary Syndrome

CAD-Coronary Artery Disease

MI-Myocardial Infarction

CVA-Cerebro Vascular Accident

CABG-Coronary Artery Bypass Grafting

PVD-Peripheral Vascular Disease

Main text - word count 3981 (main text, tables, figures and references)

# Smoking Status and Mortality Outcomes Following Percutaneous Coronary Intervention

## Introduction

Smoking is a major risk factor for cardiovascular disease and sudden cardiac death [1, 2], with the benefits of quitting well-documented [3].

Prior studies have confirmed that smokers have reduced life expectancy compared to non-smokers [4]. However, data from the pre-thrombolytic, thrombolytic, and early percutaneous coronary intervention (PCI) eras have yielded conflicting results on the survival of smokers following myocardial infarction [5-7]. Such data are lacking in the modern PCI era; with advances in PCI technology, new anti-platelet therapy and widespread use of secondary prevention, which may differentially influence survival in smokers versus non-smokers.

The aim of this study is to compare the short and intermediate-term mortality of smokers and ex-smokers versus never-smokers following PCI.

## Methods

*Study Population:*

The study population consisted of all patients undergoing PCI between March 2008 and December 2011 at two regional cardiac centres in the UK - Freeman Hospital, Newcastle-upon-Tyne, and Aberdeen Royal Infirmary, Aberdeen.

*Study Design:*

This was a retrospective analysis of prospectively collected data on all PCI procedures during the study period. The primary sources of data were the local Coronary Artery Disease (CAD) databases, which hold information on every PCI procedure performed at each centre. Baseline demographics, procedure details, and clinical data were prospectively entered into these databases at the time of the procedure and updated on discharge.

*Outcome Measures:*

The main outcome measure was all-cause mortality assessed at 30 days (30-day mortality) and between 30 days and 6-months (intermediate-term mortality) post PCI. Mortality data were provided by the Office of National Statistics (ONS) and Grampian Health Intelligence and were linked to our databases using National Health Service (NHS) or Community Health Identifier (CHI) patient-unique identification numbers. Mortality was assessed up to the 2nd February 2012, and patient follow-up was censored upon death.

*Smoking Status and Procedure Setting:*

Patients were classified into three groups according to their smoking status at time of index PCI: 1) "Never smokers" have never smoked cigarettes; 2) "Ex-smokers" stopped smoking at any point prior to their index PCI procedure; and 3) "Current smokers" continued to smoke. These definitions were used by cardiologists, who collected and recorded the history and performed PCI.

PCI was classified according to the clinical setting: 'elective' PCI for patients presenting with stable coronary artery disease (CAD) and 'acute' PCI for patients with acute coronary syndrome (unstable angina, non-ST elevation and ST elevation myocardial infarction).

All patients presenting with acute coronary syndrome were seen by the cardiac rehabilitation team during their hospital stay or contacted soon following their discharge and offered a referral to smoking cessation services. Elective patients were advised regarding smoking and offered a referral to smoking cessation team at the time of their cardiology clinic visit or by their general practitioners.

*Statistical analysis:*

Data are presented as percentages for categorical variables and as means ± standard deviations (SD) or medians and interquartile ranges (25th to 75th) for continuous variables. Comparisons between groups were made using chi-squared test for categorical variables and one-way ANOVA for continuous variables. Multiple logistic regression analysis was used to test for the impact of smoking on 30-day mortality and to correct for confounders. For the longitudinal analysis for intermediate-term mortality, Kaplan-

Meier survival curves were generated, and the log-rank test was used to assess for differences in survival. Cox proportional hazards regression was used to assess the impact of smoking status on intermediate-term mortality following adjustment for confounders. P value <0.05 (2-sided) was considered statistically significant. All analysis was performed using SPSS (SPSS version 19, SPSS, Inc., Chicago).

## Results

A total of 13041 patients underwent PCI during the study period. Data on smoking status were missing in 385 patients. The remaining 12656 patients were included in this analysis and their smoking status was recorded as follows: never-smokers (n=4288, 33.9%), ex-smokers (n=4806, 38.0%) and current smokers (n=3562, 28.1%).

Baseline characteristics are detailed in Table 1.

*Table 1: Baseline patient characteristics*

Abbreviations: SD-Standard Deviation; MI-Myocardial Infarction; CVA-Cerebro-Vascular Accident; TIA-Transient Ischemic Attack; PVD-Peripheral Vascular Disease;

Current smokers were 10 years younger compared to other groups (p<0.001), while never-smokers and ex-smokers were of similar age. The never- and ex-smoker cohorts were more likely to have suffered a previous myocardial infarction (MI), cerebro-vascular accident (CVA) and to have undergone previous PCI compared to the current smoker group. Current smokers were less likely to have pre-existing hypertension and/or diabetes compared to other groups. Peripheral vascular disease (PVD) and airway disease were more prevalent in current and ex-smokers compared to never-smokers, Table 1.The percentage of patients undergoing PCI for ACS was highest in current smokers (84.1%) compared to ex-smokers (57.0%) and never-smokers (62.9%); $P < 0.0001$ (table 2). Among smokers, 30% had multi vessel disease and 1.3% had left main stem disease compared to 37.5% and 2.6% for ex-smokers and 36.3% and 2.0% for the never-smokers, respectively.

*Table 2: Indication for PCI*

Abbreviations: ACS-Acute coronary syndrome

After excluding patients with any previous coronary revascularisation (PCI or CABG) and analysing only those in whom the study index PCI procedure was their first ever coronary revascularisation (n=10612), current smokers were still significantly younger and more likely to have PCI for ACS compared to other groups, Table 3.

*Table 3: First presentation for PCI*

Abbreviations: PCI-Percutaneous Coronary Intervention; ACS-Acute Coronary Syndrome

At discharge, 94.8% of patients were on dual anti-platelet therapy, 94.6% on a statin, 84.8% on a beta blocker and 84.9% on an angiotensin converting enzyme inhibitor or an angiotensin receptor blocker.

*Thirty-day mortality outcome:*

Overall 30-day mortality rate was 1.8%. The respective figures in the never-smokers, ex-smokers and current smokers groups were 1.7%, 1.7% and 1.9%. In a logistic regression model corrected for Age, gender, PCI setting, diabetes, airway disease, history of previous MI, history of other vascular disease and the presence of left main stem/multivessel disease, the adjusted odds ratios (95% confidence intervals [CI]) for 30-day mortality were 0.98 (0.70 - 1.38) in ex-smokers and 1.60 (1.10 - 2.32) in current smokers compared to never-smokers. See table 4, Figure 1.

***Figure 1: Thirty-day mortality among the three groups- the adjusted odds ratios (95% confidence intervals [CI]) for 30-day mortality were 0.98 (0.70 - 1.38) in ex-smokers and 1.60 (1.10 - 2.32) in current smokers compared to never-smokers***

*Table 4: Crude and adjusted mortality among the groups*

Abbreviations: CI- Confidence Interval

*Six-month mortality outcome:*

Overall 30-day to 6-month mortality rate was 1.5%. In the Cox proportional hazard model adjusted for age, gender, PCI setting, diabetes, airway disease, history of previous MI, history of other vascular disease and the presence of left main stem/multi-vessel disease the adjusted hazard ratios (95% CI) for mortality between 30 days and 6 months were 1.03 (0.65 - 1.65) in current smokers and 1.19 (0.84 - 1.67) in ex-smokers compared to never-smokers (Figure 2).

***Figure 2: 30-day to 6-month mortality among the three groups- the adjusted hazard ratios (95% CI) for mortality between 30 days and 6 months were 1.03 (0.65 - 1.65) in current smokers and 1.19 (0.84 - 1.67) in ex-smokers compared to never-smokers***

## Discussion

There are three main findings from this large observational study of unselected, all-comers PCI cohort. Firstly, smokers undergo PCI at a much younger age and more frequently for an ACS presentation. Secondly, smoking is associated with a higher 30-day mortality compared to never-smokers. Thirdly, ex-smokers have similar presentation age for PCI and mortality outcomes to never-smokers. To our knowledge, this is the first study to demonstrate such favourable findings in ex-smokers compared to current smokers in the modern PCI era.

Smoking is a risk factor for coronary thrombosis and myocardial infarction [8]. The risk of acute myocardial infarction in young smokers is almost three times that of never-smokers and it diminishes to baseline if they quit smoking for more than two years [9]. There is also a clear dose response relationship between smoking and cardiovascular risk with no safe lower limit [10].

In our study, smokers underwent PCI at a considerably younger age (10 years younger) compared to ex- and never-smokers; despite having the lowest rates of other cardiovascular risk factors such as hypertension and diabetes. A similar observation was noted in

previous observational studies from different eras and across different ACS presentations [11, 12]. This confirms the impact of smoking as a major risk factor for coronary artery disease. In our study, the age difference remained equally significant even when we only looked at patients in whom the index PCI procedure was their first ever coronary revascularisation. Interestingly, there was no age difference between never- and ex-smokers. From a public health point of view, the message from this study is that smokers presented with accelerated coronary artery disease and intrusive symptoms at a younger age and importantly quitting smoking eliminates this age difference at first presentation.

When looking at gender differences, women appear to be more prone to the deleterious effects of smoking with female smokers having higher risk of developing acute myocardial infarction compared to male smokers [13]. It has been shown that women metabolise nicotine faster due to oestrogen [14], which may explain their higher risk.

In our study, smokers had PCI more commonly for acute coronary syndromes compared to never-smokers and ex-smokers. Studies have shown that smokers have endothelial dysfunction [15] and higher platelet aggregability [16]. Newby et al demonstrated impairment of smokers' endothelium to release tissue-plasminogen activator, probably causing impaired endogenous fibrinolysis [17]. As a result, otherwise subclinical micro-thrombus could propagate to an occlusive thrombus. Furthermore, denudation of endothelium and micro-thrombi are common on the surface of atheromatous plaques [18] and the fact that smokers benefit from dual anti-platelet therapy significantly more than never-smokers is suggestive of an altered rheology among smokers [19]. Burke et al demonstrated that among men who suffered sudden cardiac death due to acute thrombosis, 75% were smokers [20]. He further showed that in women suffering sudden cardiac death, smoking was a risk factor for both plaque erosion and rupture [21]. Smoking causes endothelial injury, atherogenesis, inflammation and impaired vasomotor function, all of which predispose to atheromatous plaque formation [22, 23].

Our study highlights some angiographic differences between groups including higher prevalence of multi-vessel and left main stem disease among ex- and never-smokers compared to smokers. This observation closely resembles the data from TRANSFER-AMI trail [24]. A higher prevalence of acute presentation despite relatively mild underly-

ing coronary disease further supports the hypothesis that smoking expedites plaque instability, and in some cases leads to thrombus formation and/or impaired endogenous thrombolysis.

Surprisingly, studies from the pre-thrombolytic, thrombolytic and old PCI eras suggested a similar or even better survival among smokers compared to never-smokers post myocardial infarction [5-7]. Barbash et al found never smoking to be associated with an increased in-hospital complication rates and early mortality post thrombolysis even after correcting for differences in baseline clinical characteristics [6]. The TIMI-II study showed that the risk of death and fatal and non-fatal MI at 42 days was highest among never smokers [25]. This conundrum was termed the "smoker's paradox", although no plausible mechanistic explanation has ever been postulated [11].

The ACUITY trial showed smoking to be an independent risk factor for 1-year mortality in patients presenting with non-ST elevation acute coronary syndrome patients [11]. The life expectancy after AMI was less among elderly (≥65) smokers than never-smokers, leading to significant loss of life years [26]. In those with coronary artery disease, smoking cessation has been shown to reduce mortality irrespective of age, sex, index cardiac event or nationality[27, 28]. Hasdai et al followed up 5,450 patients undergoing PCI at Mayo clinic between 1979 and 1995 over a mean of 4.5 years [7]. The crude mortality was lower in smokers but the mortality adjusted for baseline variables was higher in smokers than never-smokers, ex-smokers and quitters. In addition, the adjusted risk for need for future revascularisation was lower in the smoking group. It has been shown that younger patients with ST-elevation myocardial infarction (STEMI) treated by primary PCI have a better survival than older patients (>45 years), likely due to differences in baseline comorbidities [29]. It is probable that younger age and associated favourable profile are to be credited for better outcomes among smokers in some past studies.

There has been considerable advancement in the management of patients undergoing PCI. The use of secondary prevention and dual antiplatelet therapy is now well-established in this population and newer antiplatelet agents [30, 31] have also contributed to improved post PCI outcomes. As a result, there has been significant reduction in cardiovascular deaths driven by a reduction in fatal myocardial infarction and sudden cardiac death in patients undergoing PCI [32]. Our study population was a well-treated cohort, with high use of dual anti-platelet therapy, statins and other cardiovascular drugs.

In our study, 30-day mortality among smokers was higher, despite a significantly younger age and better clinical profile at presentation. Meanwhile, 30-day to 6-month mortality rates were similar in the three groups. We obtained only a snapshot smoking history at the time of presentation to PCI but no data for subsequent smoking habits were recorded. Hence, we believed a focus on short mortality will be a true reflection of the effects of smoking in our cohort. Furthermore, the deleterious effect of smoking on endothelial function and thrombosis in patients undergoing PCI is most likely to have the biggest impact on short term outcomes; particularly given the high cardiovascular event rate in this period. Importantly, ex-smokers exhibited no difference in either short or intermediate term mortality compared to never-smokers. The inference from this is that giving up smoking can reduce the risk of death after PCI to never-smokers' levels.

Primary care-based health checks have been shown to improve the management of cardiovascular risk factors such as hypertension, hypercholesterolemia and high body mass index [33]. However, smokers are less likely to participate in such health checks [34], which underscores the complex interaction between cardiovascular risk factors and preventative strategies.

Increasing public awareness, government policies, media campaigns and counselling have resulted in a positive trend in smoking cessation. In the United States, the prevalence of smoking among adults has decreased from 42.4% to 19.3% from 1965 to 2010 and the number of ex-smokers exceeding that of current smokers in 2002 [35]. Furthermore, in Scotland, Finland and Switzerland, prohibition of smoking in public indoor spaces has led to significant reduction in hospital admissions with acute coronary syndrome [36-38].

*Limitation and strength:*

Data on smoking intensity and duration of smoking cessation in ex-smokers were not collected. We also did not collect data on the proportion of patients who attended cardiac rehabilitation or smoking cessation services and no follow-up on the smoking status was made. Consequently, only short term and intermediate term mortality data were analysed. Nevertheless, the current study examines post PCI outcomes in a large cohort.

## Conclusion

This large observational study of unselected patients treated with PCI in the modern era demonstrates that smokers undergo PCI at a much younger age and more commonly for acute coronary syndrome compared to never-smokers. In addition, current smoking was associated with increased 30-day mortality. This age difference and survival disadvantage was not seen in ex-smokers. Our findings reinforce the public message of the harmful effect of smoking and the benefits of smoking cessation.

Authorship:

AN, AZ, JA, RE, RD, DG, IP contributed to the conception or design of the work. AN, SP, ME, AB, PB and DG contributed to the acquisition, analysis, or interpretation of data for the work.

SP and AN drafted the manuscript. JA, RE, IP and RD critically revised the manuscript.

All gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

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Table 1: Baseline patient characteristics

| Descriptive 12656 | Never-smokers 4288 (32.9%) | Ex-smokers 4806 (36.9%) | Current smokers 3562 (27.3%) | Significance |
|---|---|---|---|---|
| Age (mean ± SD) years | 67±12 | 67±11 | 57±11 | P<0.001 |
| Male gender (72.3%) | 67.1% | 77% | 72.2% | P<0.001 |
| Hypertension 49.6% | 50.5% | 57.2% | 38.3% | P<0.001 |
| Hypercholesterolemia 33.9% | 32.6% | 35.1% | 34% | P=0.043 |
| Diabetes 16.9% | 17.7% | 20% | 11.7% | P<0.001 |
| Previous MI 22.9% | 19% | 30.2% | 17.8% | P<0.001 |
| Previous coronary revas-cularisation | 14.5% | 22.3% | 9.8% | P<0.001 |
| CVA/TIA 5.7% | 5.4% | 6.6% | 4.7% | P=0.001 |
| Family History 44.2% | 37.3% | 47.1% | 48.7% | P<0.001 |
| Peripheral vascular dis-ease 4.9% | 2.8% | 6.9% | 4.6% | P<0.001 |
| Airway disease 11.4% | 7.2% | 14.6% | 12.2% | P<0.001 |

Abbreviations: SD-Standard Deviation; MI-Myocardial Infarction; CVA-Cerebro-Vascular Accident; TIA-Transient Ischemic Attack; PVD-Peripheral Vascular Disease

Table 2: Indication for PCI

| Descriptive | Non-smokers | Ex-smokers | Current smokers | Significance |
|---|---|---|---|---|
| Elective | | (43) | (15.9) | p<0.001 |
| ACS | (62.9) | (57) | (84.1) | p<0.001 |

Table 3: First presentation for PCI

| | Never-smokers | Ex-smokers | Current smokers | P-value |
|---|---|---|---|---|
| Elective, % | 35 | 39.3 | 14.1 | < 0.001 |
| Mean age ± SD, years | 67±12 | 68±11 | 57±11 | < 0.001 |
| ACS, % | 65 | 60.7 | 85.9 | < 0.001 |
| Mean age ± SD, years | 66±11 | 66±9 | 58±10 | < 0.001 |

Abbreviations: PCI-Percutaneous Coronary Intervention; ACS-Acute Coronary Syndrome

Table 4: Crude and adjusted mortality among the groups

| | Crude 30-day mortality n (%) | Adjusted 30-day mortality odds ratio (95% CI) | Crude 30 day to 6-month mortality n (%) | Adjusted 30 day to 6-month mortality Hazard ratio (95% CI) |
|---|---|---|---|---|
| Non-smokers (n=4288) | 74 (1.7) | 1.00 | 64 (1.5) | 1.00 |
| Ex-smokers (n=4807) | 82 (1.7) | 0.98 (0.7-1.38) | 91 (1.9) | 1.19 (0.84-1.67) |
| Current Smokers (n=3563) | 68 (1.9) | 1.60 (1.1-2.32) | 32 (0.9) | 1.03 (0.65-1.65) |

Abbreviations: CI- Confidence Interval

Figure 1: Thirty-day mortality among the three groups- the adjusted odds ratios (95% confidence intervals [CI]) for 30-day mortality were 0.98 (0.70 - 1.38) in ex-smokers and 1.60 (1.10 - 2.32) in current smokers compared to never-smokers

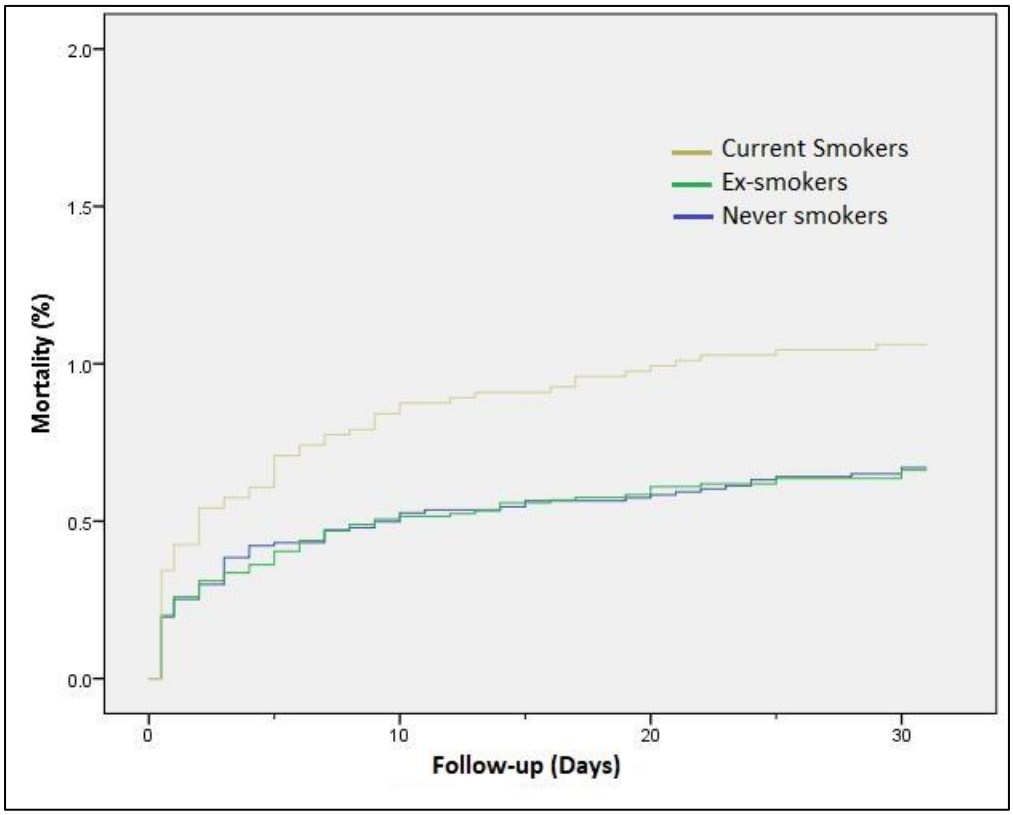

Figure 2: 30-day to 6-month mortality among the three groups- the adjusted hazard ratios (95% CI) for mortality between 30 days and 6 months were 1.03 (0.65 - 1.65) in current smokers and 1.19 (0.84 - 1.67) in ex-smokers compared to never-smokers