Impact of smoking on cardiovascular outcomes in patients with stable coronary artery disease

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Abstract

Aims: Smoking is a major preventable risk factor for cardiovascular disease and mortality. However, the 'smoker's paradox' suggests that it is associated with better survival after acute myocardial infarction. We aimed to investigate the impact of smoking on mortality and cardiovascular outcomes in patients with stable coronary artery disease.

Methods: The international CLARIFY registry included 32,703 patients with stable coronary artery disease between 2009 and 2010. Among the 32,378 patients included in the present analysis, Cox proportional hazards models (adjusted for age, sex, geographic region, prior myocardial infarction, and revascularization status) were used to estimate associations between smoking status and outcomes. Patients were stratified as follows: 41.3% of patients never smoked, 12.5% were current smokers and 46.2% were former smokers.

Results: Current smokers were younger than never-smokers and former smokers (59 vs. 66 and 64 years old, respectively, $p<0.0001$). There were more men among current or former smokers compared with never-smokers. Compared with never-smokers, both current and former smokers were at higher risk of all-cause death (hazard ratio.1.96 and 1.37) and cardiovascular death (hazard ratio.1.92 and 1.38) within five years (all $p<0.05$). Similarly graded and increased risks were present for myocardial infarction and the composite of cardiovascular death, myocardial infarction and stroke (all $p<0.05$).

Conclusion: In contrast to the 'smoker's paradox', current smokers with stable coronary artery disease have a greatly increased risk of future cardiovascular events, including mortality, compared with never-smokers. In former smokers, cardiovascular risk remains elevated albeit at an intermediate level between that of current and never-smokers, reinforcing the importance of smoking cessation. (ISRCTN43070564).

Keywords: Smoking, coronary artery disease, outcomes, mortality.

Introduction

Tobacco remains the leading cause of preventable death in Western countries. It is responsible for 700,000 deaths a year in Europe,1 and it accounts for substantial increases in preventable cardiovascular mortality and disability.2–7 Therefore, reduction of tobacco use is an important health priority. However, the extent to which its use and cessation impacts morbidity and mortality in patients with stable coronary artery disease (CAD) receiving contemporary medical therapy warrants further study. Indeed, confusing data regarding the so-called 'smoker's paradox',8 which refers to the seemingly better survival of smokers early after an acute myocardial infarction, may have to some extent limited the effectiveness of secondary prevention.8–10

The prospeCtive observational LongitudinAl RegIstry oF patients with stable coronary arterY disease (CLARIFY) registry aims to improve knowledge on the contemporary management and outcomes of both symptomatic and asymptomatic patients with stable CAD.11 This large international registry provides detailed information on clinical and biological characteristics, medications and yearly outcomes, up to five years.11 In the present analysis, we aimed to assess the contemporary impact of smoking status at baseline on cardiovascular outcomes in patients with stable CAD receiving contemporary treatment.

Methods

Study design and population

CLARIFY is an international registry which included outpatients with stable CAD receiving contemporary treatment and followed up yearly for up to five years. The rationale and design of the study have been previously described.11 A total of 32,703 patients were enrolled in 45 countries in Africa, Asia, Australia, Europe, the Middle East, and North, Central and South Americas. All patients gave written informed consent, and ethics approval was obtained in all participating countries in accordance to local regulations.

Patient demographics, clinical profile, ongoing therapies and clinical outcomes were prospectively collected in order to provide reliable information with regard to the contemporary management of stable CAD worldwide. Physicians, including cardiologists, general practitioners, internists and hospital-based physicians, were selected in order to provide a representative distribution of healthcare providers in each country. This selection process was validated by the study executive committee, and physicians were instructed to manage their patients according to usual practice regardless of their enrolment in the present registry.11

Inclusion and exclusion criteria have been detailed previously.11,12 Briefly, patients were recruited between November 2009 and July 2010 if they had stable CAD defined according to the presence of at least one of the following: (a) documented myocardial infarction (MI) at least three months before enrolment; (b) angiographic demonstration of coronary artery stenosis of at least 50% in at least one vessel; (c) history of chest pain with evidence of myocardial ischaemia proven by either stress electrocardiogram, stress echocardiography or stress myocardial perfusion imaging; (d) coronary artery bypass graft (CABG) surgery or percutaneous coronary intervention (PCI) at least three months before enrolment. Patients were excluded if they had a history of hospitalization for cardiovascular disease within the past three months (including revascularization), planned myocardial revascularization or any condition hampering follow-up, including any severe cardiovascular and non-cardiovascular conditions potentially interfering with life expectancy (e.g. cancer or advanced heart failure) within the following five years.

Outcomes

Clinical events were collected as reported by investigators without central adjudication.11 The main outcomes included mortality and cardiovascular morbidity data. Cardiovascular deaths were categorized into fatal MI, fatal stroke and other cardiovascular deaths (including sudden cardiac death and deaths from unknown cause). Non-cardiovascular deaths were any deaths that were not classified as related to a cardiovascular cause. Non-fatal events included non-fatal MI, non-fatal

stroke and coronary revascularization (PCI and CABG). Non-fatal events collected were mostly non-fatal MI, unstable angina, new-onset or worsening heart failure requiring hospitalization, coronary revascularization, non-fatal stroke or transient ischaemic attack and major bleeding.

Statistical analysis

Data were centrally analyzed by an academic statistics center (Robertson Centre for Biostatistics, University of Glasgow, UK). Baseline characteristics are summarized using counts and percentages for categorical variables and mean +/- standard deviation (SD) or median (interquartile range (IQR)) for continuous variables. Comparisons were made according to smoking status at baseline: current smokers were defined as subjects who had smoked during the month before the visit; former smokers had stopped smoking more than one month before enrolment; and never-smokers had never smoked. Comparisons were made using chi-square tests, one-way analysis of variance or Kruskal–Wallis tests, as appropriate. The effects of smoking status on clinical outcomes were determined using Cox proportional hazards models adjusted solely for age as well as for major clinical variables known to be associated with prognosis; including cardiovascular risk factors, geographic region, prior MI, and revascularization status (PCI and CABG). Data were analyzed as recorded, without imputation for missing data. Unadjusted hazard ratios and corresponding 95% confidence intervals are not provided owing to the confounding association between smoking information and other baseline characteristics. Hazard ratios and 95% confidence intervals were determined, and p-values calculated from the Wald statistic. p-values <0.05 were considered to be statistically significant. The analysis for this paper was generated using SAS software version 9.3.

Results

Baseline characteristics

Of the total of 32,703 patients enrolled in the CLARIFY registry, 32,378 patients had available information on smoking status and were included in the present analysis. Patients were distributed as follows: 41.3 never smoked, 12.5% were current smokers and 46.2% were former smokers. The median (IQR) duration from CAD diagnosis to year of enrolment in the study is 5.0 (2.0; 9.0) years. Overall, patients were predominantly males (78%) with a mean age of 64 years and multiple cardiovascular risk factors; 71% were treated for hypertension, 29% had diabetes and 75% dyslipidaemia; 60% of patients had prior MI and 75% had a history of myocardial revascularization (either CABG or PCI). Patients were mostly asymptomatic, 85% had no heart failure and 78% had no angina, while patients were under well-conducted medical therapy in general (88% were treated with aspirin, 75% had beta-blockers and 92% lipid-lowering drugs; Table 1).

Baseline characteristics according to smoking status

Current smokers were younger than both never smokers and former smokers (59 vs. 66 and 64 years respectively, $p<0.0001$; Table 1). There were more men among current or former smokers compared with never-smokers (87% and 90% vs. 61%, $p<0.0001$). Current and former smokers had a higher prevalence of previous MI in comparison with their never-smoker counterparts. Notably, patients with recent smoking cessation (<5 years) had the highest revascularization rates (either PCI or CABG) in comparison with other groups (according to timing of smoking cessation and daily tobacco consumption; Supplemental Material online, Table S-1).

Rates of clinical events according to smoking status

After a median follow-up (IQR) of 5.0 (4.4; 5.1) years, 7.1% of patients who never smoked, 8.1% of current smokers and 8.5% of former smokers died from all causes. Cardiovascular death occurred in 4.5%, 5.1% and 5.4% of never-smokers, current and former smokers, respectively. Rates of fatal or non-fatal MI were 2.8, 4.3 and 3.7% respectively in the three groups. The composite of cardiovascular death or MI occurred in 6.3% of never-smokers, 8.3% of current smokers and 7.8%

of former smokers, while the composite of cardiovascular death, MI or stroke was observed in 7.8, 9.7 and 9.2%, respectively. The composite of cardiovascular death, MI, coronary revascularization or stroke occurred in 13.5%, 15.6 and 15.2% of patients (online Supplemental Table S-1).

Rates of clinical events according to duration of smoking cessation and cigarettes daily consumption

Clinical events according to time of smoking cessation for former smokers and daily tobacco consumption for current smokers are provided in online Supplemental Table S-1. All-cause death occurred in 10.3%, 7.7% and 6.2% of former smokers who had quit smoking >9 years, 5–9 years and <5 years ago; cardiovascular death in 6.6%, 5.1% and 3.8% and non-cardiovascular death in 3.8%, 2.6% and 2.4% respectively. Regarding the daily cigarette consumption (>10 cigarettes smoked per day vs. 1–10), all-cause deaths occurred in 7.6% vs. 8.5%, respectively; cardiovascular deaths in 4.8% vs. 5.4% respectively, and the rates of MI (fatal or nonfatal) were 4.2% vs. 4.4%, respectively.

Clinical outcomes according to smoking status

The associations between smoking status and clinical outcomes are shown in Table 2, adjustments being made for age, sex, geographic region, prior MI, and revascularization status. Compared with never smokers, both current and former smokers were at higher risk of all-cause death (adjusted hazard ratio = 1.96 and 1.37, respectively, $p<0.0001$) and cardiovascular death (adjusted hazard ratio = 1.92 and 1.38, respectively, $p<0.0001$). Similarly graded and increased risks were present for MI and composite endpoints (all $p<0.05$). The risk of fatal or non-fatal MI was increased in current smokers (adjusted hazard ratio = 1.69) and former smokers (adjusted hazard ratio = 1.28). The risk of the composite endpoint of cardiovascular death or MI was raised in both current (adjusted hazard ratio¼1.86) and former smokers (adjusted hazard ratio = 1.34), while that of the composite of cardiovascular death, MI or stroke was also higher (adjusted hazard ratio = 1.73 and

1.28 respectively) compared with never-smokers. Finally, the risk of the composite of cardiovascular death, MI, coronary revascularization or stroke was significantly increased in both current smokers (adjusted hazard ratio = 1.36) and former smokers (adjusted hazard ratio = 1.17). These associations remained significant when adjusting for age only (online Supplemental Table S-2).

Clinical outcomes according to duration of smoking cessation and cigarette daily consumption

Regarding duration of smoking cessation, patients with <5 years, 5–9 years or >9 years of smoking cessation remained at higher risks of all-cause deaths (adjusted hazard ratio = 1.51, 1.41 and 1.30, respectively), cardiovascular deaths (adjusted hazard ratio = 1.42, 1.46 and 1.35, respectively), and non-cardiovascular deaths (adjusted hazard ratio = 1.69, 1.33 and 1.23, respectively) when compared with non-smokers (Table 3). When compared with non-smokers, active smoking was consistently associated with graded worse outcomes in CLARIFY, regardless of the amount of smoked cigarettes per day (>10 or <10 cigarettes per day; Table 3), with a significant association with all-cause mortality (adjusted hazard ratio = 2.14 and 1.88, respectively), cardiovascular-mortality (adjusted hazard ratio = 2.07 and 1.83, respectively), non-cardiovascular mortality (adjusted hazard ratio = 2.29 and 1.97, respectively) and fatal or non-fatal MI (adjusted hazard ratio = 1.71 and 1.66. respectively).

Discussion

This is the largest cohort analysis of the impact of smoking status on cardiovascular outcomes in patients with stable CAD receiving contemporary treatment who were included in the CLARIFY registry. The main observations from the present analysis are that: (a) active smoking remains strongly associated with poor cardiovascular outcomes; (b) although former smokers are at lower risk than active smokers, they remain at higher risk for major clinical outcomes when compared with patients who never smoked; (c) the adjusted hazard ratio for the composite of cardiovascular death, MI and stroke was 1.73 (1.53; 1.96) for current smokers compared with never smokers (after

adjusting for age, sex, geographic region, prior MI, prior PCI and prior CABG), indicating that the potential harm associated with continued smoking vastly exceeds the benefits related to evidence-based therapies in this population.

Impact of smoking status on major outcomes

In this study, we demonstrate that active smoking remains a major determinant of both all-cause and cardiovascular mortality in a contemporary cohort of relatively young patients with CAD and no other major comorbidity. In the Coronary Artery Surgery Study cohort,13 survival was significantly better in never smokers when compared with current smokers (80% and 77%, respectively). In a post-hoc analysis of the Treating to New Targets study14 and the Incremental Decrease in End Points Through Aggressive Lipid Lowering study, smoking cessation in patients with stable CAD was demonstrated to provide an absolute decrease of 4.5% in the occurrence of the composite end-point of cardiac death, myocardial infarction, stroke or resuscitated cardiac arrest.15,16 As such, the number needed to treat to prevent one major cardiovascular event was shown to be as low as 22 among patients also receiving intensive statin therapy,16 and the protective effect associated with smoking cessation was demonstrated to exceed that achieved by conventional medical treatments in various settings, including patients with chronic cardiovascular disease.17 The harmful effects of smoking were shown to be additive to those of other cardiovascular risk factors.18 In CLARIFY, up to 25% of current smokers also suffered from diabetes, 64% had hypertension and 73% dyslipidaemia. Although the combined effects of current smoking and other risk factors were not analyzed in CLARIFY, a recent meta-analysis of 89 cohort studies demonstrated that smoking was associated with nearly half of the increase in cardiovascular deaths and all-cause mortality among diabetic patients.19

Clinical outcomes according to the duration of smoking cessation

In the present study, we demonstrate that although at lower risk in comparison with active smokers, former smokers remain at higher risk for major outcomes regardless of the timing of smoking cessation within the duration of smoking cessation that was examined in this work. As such, patients in CLARIFY who have stopped smoking for>9 years are still at high risk for cardiovascular deaths with adjusted hazard ratio 1.35 (1.18; 1.54), comparison being made with non-smokers. Although previous studies have provided evidence that smoking cessation yields a significant benefit that may manifest rapidly after quitting,17 with a 50% decrease in cardiovascular risk reported after one year of smoking cessation,20,21 our results highlight the long-lasting effects of smoking on cardiovascular outcomes for longer periods of smoking cessation. Our results are in line with the most recent cohort analysis where the risk related to smoking lasted for>20 years for coronary heart disease in patients from the Atherosclerosis Risk In Communities study without baseline atherosclerotic disease.22

Clinical outcomes according to cigarettes daily consumption

In this study, we observed that active smoking is consistently associated with poor outcomes among a contemporary cohort of patients with stable CAD, even in light smokers. Risks associated with light smoking have also been shown by others, with light smokers being at higher risk for cardiovascular mortality as well as all-cause mortality in comparison with non-smoking individuals. 23–25 This association between cardiovascular outcomes and light smoking is all the more important in terms of counselling and healthcare prevention policies, as it highlights the harmful impact of any level of smoking on cardiovascular outcomes. As such, smoking cessation rather than smoking reduction should always be strongly encouraged in patients with stable CAD.

Clinical perspectives

This study provides important insights with regard to cardiovascular outcomes according to smoking status in patients with stable CAD. Although cardiovascular risk significantly declined

after smoking cessation in comparison with current smokers, former smokers still demonstrate a significantly higher risk of poor cardiovascular outcomes, even for long durations of smoking cessation, when compared with their never smoked counterparts. These results further highlight the need for more aggressive smoking prevention policies.

Study limitations

The present study has limitations. Smoking status was determined at one time point (baseline) and then reassessed yearly during follow-up. Smoking relapse during follow-up was not analyzed, due to the small numbers of patients changing in the groups of interest. There was no central adjudication of the clinical events that were reported by the local investigators. Yet, the associations observed between baseline smoking status and adverse cardiovascular outcomes were robust and consistent throughout the entire range of events, including all-cause mortality (where adjudication is immaterial). This being said, this is the largest cohort analysis regarding the contemporary impacts of smoking status on cardiovascular outcomes in well-treated patients with stable CAD (in contrast to most prior analyses, in which the use of antiplatelet therapy and statins was low).23

Conclusion

In contrast to the 'smoker's paradox' reported after acute MI, and despite high rates of use of evidence-based preventive therapies, current smokers with stable CAD have a greatly increased risk of future cardiovascular events compared with never-smokers. Cardiovascular risk remains elevated in former smokers, albeit at an intermediate level between that of current and never-smokers, reinforcing the importance of smoking cessation in patients receiving contemporary management for stable CAD.

Author contribution

NB, IF, RF, NG, NM, DPN, PGS, JCT and MT and contributed to the conception or design of the work. NB, IF, NG, NM, PGS, JCT and MT contributed to the acquisition, analysis, or interpretation of data for the work. NB, NM and JCT drafted the manuscript. NB, IF, KMF, RF, NG, CH, NM, DPN, PGS, JCT and MT critically revised the manuscript. All gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

Declaration of conflicting interests

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