

# Effect of smoking on age at the time of coronary artery bypass graft surgery; baseline data results from the ROSETTA-CABG registry

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## ABSTRACT

**Background** Coronary artery disease (CAD) is a leading cause of death. The aetiology of this disease is not known, but many important risk factors have been recognised.

**Objective** To evaluate the effect of smoking on age at the time of coronary artery bypass graft surgery (CABG), and to examine this finding in the light of medical literature.

**Methods** The authors recruited patients immediately after CABG in a prospective, study in 16 centres and enrolled 408 patients, of which 395 were ultimately analysed.

**Results** Among the 395 patients analysed, there were 60 smokers and 335 non-smokers. The smokers were 8.4 years younger than non-smokers at the time of index CABG. The average age of smokers was 55.79.0 years, and that of non-smokers was 64.1±9.9 years ( $p<0.001$ ). Hyperlipidaemia was present in 76.7% of smokers and 74.6% of non-smokers ( $p=NS$ ). Hypertension was present in 58.3% of smokers and 63.9% of non-smokers ( $p=NS$ ). Diabetes mellitus was present in 21.3% of smokers and 29.3% of non smokers ( $p=NS$ ). Left ventricular ejection fraction was 53.0±10.5% in smokers and 53.3±13.8% in non-smokers ( $p=NS$ ). Myocardial infarction had occurred in 41.7% of smokers and 35.5% of non-smokers ( $p=NS$ ).

**Conclusion** Smoking accelerates atherosclerosis and coronary thrombosis resulting in severe form of CAD that cannot be managed by medications or PCI, and requires coronary artery bypass graft surgery (CABG) 8.4 years earlier than non-smokers.

## INTRODUCTION

Coronary artery disease (CAD) is a leading cause of death worldwide. The underlying aetiology is mainly coronary arterial atherosclerosis. Multiple risk factors play a role in the development and progression of atherosclerosis. The incidence of Acute Coronary syndrome (ACS) and acute myocardial infarction (AMI) internationally, especially in developed countries, is the same as observed in the US but there is two to three fold higher mortality in immigrant Asian Indians living in the developed world as compared to the native population.<sup>1</sup> where 20 million people have symptomatic atherosclerosis and are at risk of CAD, stroke and death. A coronary event occurs approximately every 29 s, causing the death of one person nearly every minute. There is

30% initial mortality and 6% morbidity of CAD in the affected population. CAD occurs during the most productive part of the lifespan of a person professionally and economically. Preventive measures and lifelong treatment of CAD impose enormous costs on society. While the search for the aetiology of CAD continues, some major and minor risk factors have been identified. Smoking, diabetes mellitus, hyperlipidaemia, hypertension, family history and obesity are the major risk factors. Smoking causes over 3 million deaths a year worldwide, and according to WHO projections, deaths will rise to 10 million in 2025 due to the continuous increase in smoking habits in the third world. A US National Health Interview Survey—2006 (NHIS) conducted to assess the progress of a national health objective to reduce prevalence of smoking among adults to below <12% by the year 2010 indicated that 20.8% of US adults were current smokers.<sup>2</sup> This prevalence has not decreased since 2004, revealing a plateau in decline of smoking in the last 7 years (1997–2004). The survey also showed that persons with smoking-related diseases smoke more, compared with those without such diseases. Rosengren *et al* have shown that a staggering 73% of smokers suffer from CAD before their 65th birthday, compared with 35% of non-smokers.<sup>3</sup> The treatment modalities of CAD like coronary artery bypass graft (CABG), percutaneous coronary intervention (PCI) and medicines are at best palliative. CABG is offered in failed medical treatment, in certain angiographic patterns of disease not suitable for PCI, such as left main stem stenosis, triple vessel and diffuse disease especially in patients with mildly impaired LV function. The benefit of CABG may not last long and can decrease or disappear with time because of occlusion of the grafts or progression of the disease in the native coronary arteries. It is, therefore, desirable to offer CABG as late in life as possible. Medical research has established that smoking causes premature CAD, but no study has shown that smokers require CABG 8.4 years earlier than non-smokers.

## METHODS

### Study population

We recruited patients immediately after CABG in 16 centres of six countries (Canada, France, Pakistan, USA, Belgium and UK) from 30 May 1999 to 30 May 2002. The study was approved by the ethics committees of each participating centre. The patients were enrolled after obtaining written informed consent.

## Baseline data

The baseline data consisted of clinical and procedural events. The clinical characteristics recorded included age, gender, smoking habits, hyperlipidaemia, diabetes mellitus, hypertension, left ventricular ejection fraction (LVEF) previous myocardial infarction, PCI or CABG. The smoker was a patient smoking tobacco in any fashion and in any quantity up to admission in hospital for index CABG; an ex-smoker was anyone who had been smoking in the past; hyperlipidaemia was diagnosed if triglycerides >200 mg/dl, total cholesterol >200 mg/dl and LDL >160 mg/dl (alone or in any combination). A patient was labelled diabetic or hypertensive if they were discharged from hospital on antidiabetic or antihypertensive treatment. Other demographic characteristics such as prior procedures, comorbid factors and medical treatment with success or otherwise and cardiac function scanned with Canadian Cardiac Society (CCS) class prior to index CABG were also recorded. The relevant biochemical tests were conducted at each centre. The left ventricular functions were studied with 2-D, M Mode trans-thoracic echocardiography and radionuclide cardiac scan. The procedural characteristics recorded include indications for the CABG such as unstable angina, stable angina, positive functional tests or recent myocardial infarction.

## STATISTICAL ANALYSIS

The clinical and procedural data collected at baseline were analysed for the role of major risk factors operating in these patients. The categorical variable data are presented as a percentage and compared with the  $\chi^2$  test. The continuous data were presented as a mean with two standard deviations and compared using the Student unpaired t test. Potential interactions between variables were also examined. All statistical tests were two-tailed, and a p value <0.05 was taken as significant.

## RESULTS

The total patient recruitment was 408; data of 13 patients was not available for final analysis, leaving 395 patients in the study. There were 60 smokers and 335 non-smokers. The smokers were 8.4 years younger than non-smokers at the time of index CABG. The average age of smokers was  $55.7 \pm 9.0$  years, and that of non-smokers was  $64.1 \pm 9.9$  years ( $p < 0.001$ ). Hyperlipidaemia was present in 76.7% of smokers and 74.6% of non-smokers ( $p = \text{NS}$ ). Hypertension was present in 58.3% of smokers and 63.9% of non-smokers ( $p = \text{NS}$ ). Diabetes mellitus was present in 21.3% of smokers and 29.3% of non-smokers ( $p = \text{NS}$ ). LVEF was  $53.0 \pm 10.5\%$  in smokers and  $53.3 \pm 13.8\%$  in non-smokers ( $p = \text{NS}$ ). Myocardial infarction had occurred in 41.7% of smokers and 35.5% of non-smokers ( $p = \text{NS}$ ). PCI was done in 18.3% of smokers and 16.7% of non-smokers ( $p = \text{NS}$ ) (table 1).

The clinical events (myocardial infarction, unstable angina, composite endpoint) and procedural events (cardiac catheterisation, PCI, repeat CABG, composite endpoint) were equal and non-significant in both groups (table 2).

There was no difference in the use of medications, clinical and procedural composite events in smokers and nonsmokers.

## DISCUSSION

The baseline data in this study have shown that smokers undergo CABG at an average age of  $55.7 \pm 9.0$  years as compared with a mean age of  $64.1 \pm 9.0$  years for non-smokers. There was a significant difference of 8.4 years between the two groups ( $p < 0.0001$ ). The other baseline characteristics were the same in both groups. There was no difference in the use of antiangina

**Table 1** Clinical and procedural characteristics of 395 patients

	Percentage smokers (n=60)	Percentage non-smokers (n=335)	p Value
<b>Clinical characteristics</b>			
Male gender	86.7	79.1	NS
Age (years $\pm$ SD)	$55.7 \pm 9.0$	$64.1 \pm 9.9$	<0.0001
Left ventricular ejection fraction (mean $\pm$ SD)	$53.0 \pm 10.5$	$53.3 \pm 13.8$	NS
Pre-coronary artery bypass graft surgery Canadian Cardiovascular Society Class III–IV	56.7	42.4	0.0404
Hyperlipidaemia	76.7	74.6	NS
Hypertension	58.3	63.9	NS
Diabetes mellitus	21.7	29.3	NS
Past smoker	60.0	55.2	NS
Prior myocardial infarction	41.7	35.5	NS
Prior percutaneous coronary intervention	18.3	16.7	NS
Prior coronary artery bypass graft surgery	0.0	2.4	NS
<b>Procedural characteristics</b>			
Primary indication for coronary artery bypass graft surgery			
Unstable angina	51.7	52.2	NS
Stable angina	15.0	17.9	NS
Positive functional test	8.3	13.7	NS
Recent myocardial infarction (<1 month)	20.0	10.7	0.0433
Other	5.0	5.5	NS
Multivessel bypass	88.3	94.6	0.0636
Grafts used			
Left interior mammary artery	91.7	94.0	NS
Saphenous vein graft	56.7	61.5	NS
Radial	16.7	13.4	NS
Right interior mammary artery	16.7	7.5	0.0209
Gastroepiploic	1.7	0.3	NS
Mean grafts/patient ( $\pm$ SD)	$3.2 \pm 1.2$	$3.6 \pm 1.3$	0.0174

medications, MACE or revascularisation procedures after the index CABG in both groups.

## Literature review

Tobacco smoke contains over 300 chemical compounds. Nicotine, an important component of tobacco smoke, stimulates aortic and carotid chemoreceptors to enhance the activity of the sympathetic nervous system. The stimulation of the autonomic nervous system and sensory receptors in the heart increase heart rate, blood pressure and cardiac output. The carbon monoxide (CO) in tobacco smoke decreases the oxygen ( $O_2$ )-carrying capacity of haemoglobin due to the high affinity of CO for haemoglobin compared with  $O_2$ . Furthermore, the high level of carboxyhaemoglobin (COHB) induced by smoking decreases the  $O_2$ -carrying capacity of haemoglobin. Goldsmith and Landaw had reported a median COHB level of 5.9% in heavy smokers (two packs of cigarettes a day) who inhale.<sup>4</sup> The cardiovascular system is susceptible to the adverse effects of COHB. COHB is directly toxic to the myocardium, reduces the effort tolerance of a patient, causes hypoxia of the myocardium and can precipitate angina and myocardial infarction in a patient of CAD.<sup>5,6</sup> Ayer *et al* proved in 1970 that at 6–12% of COHB, body metabolism shifts from aerobic to anaerobic.<sup>7</sup> While studying macaca trus monkeys, Thomsen produced experimental evidence that long-term exposure to CO can facilitate the development of atherosclerosis.<sup>8</sup> The ischaemic heart disease adversely affecting cardiac

**Table 2** Clinical outcomes at 12 months after coronary artery bypass graft surgery among the 395 patients

	Percentage smokers (n = 60)	Percentage non-smokers (n = 335)	P Value
<b>Clinical events</b>			
Death	0 (0.0)	5 (1.5)	NS
Myocardial infarction	1 (1.7)	5 (1.5)	NS
Unstable angina	3 (5.0)	15 (4.5)	NS
Composite endpoint	4 (6.7)	24 (7.2)	NS
<b>Procedural events</b>			
Catheterisation	4 (6.7)	20 (6.0)	NS
Percutaneous coronary intervention	3 (5.0)	11 (3.3)	NS
Repeat coronary artery bypass graft surgery	0 (0.0)	0 (0.0)	NS
Composite endpoint	4 (6.7)	20 (6.0)	NS

reserve renders the patients more vulnerable to the toxicity of CO, since they are unable to cope with extra stress imposed by the hypoxia and relative polycythaemia.<sup>9</sup> The overall risk of death from CAD increases twofold in smokers, the reason being acceleration in formation of atherosclerotic plaques, endothelial dysfunction, increase in plasma fatty acids, blood viscosity, platelet aggregability, altered prostaglandin, hypoxia, relative polycythaemia and reduced high-density lipoproteins promoted by smoking.<sup>10</sup>

It has also previously been reported that pharmacological stimulation of acute tissue-type plasminogen activator (t-PA) release in the peripheral and coronary arterial circulations is markedly attenuated in smokers.<sup>11–14</sup> It has been shown that t-PA activity during thrombus formation dissolves the thrombus more effectively than t-PA activity operating after thrombus formation.<sup>15</sup> Robinson *et al* have shown that acutely stimulated t-PA release predicts the future risk of cardiovascular events.<sup>16</sup> Ninian Lang *et al* have also shown recently in a comparison of forearm blood flow that thrombin-mediated vascular responses are impaired in smokers, with a substantial reduction in protease-activated receptors, PAR-1-mediated endothelial t-PA release. They have concluded that this impaired endothelial PAR-1 action increased atherothrombotic risk in smokers. This increases the incidence of atherothrombotic disorders including acute myocardial infarction and stroke.<sup>17</sup> Thrombin plays a critical part in atherothrombosis. It has an enzymatic role in the coagulation cascade and a direct cellular activating action on endothelium via PAR.<sup>18</sup> Lang *et al* have shown that thrombin has unique and contrasting effects in the human vasculature, including arterial dilation, venous constriction, platelet activation and t-PA release, which are attenuated in smokers resulting in CAD acceleration.<sup>19</sup> A specific genetic linkage of smoking interaction with calcified coronary atherosclerosis has been demonstrated by North *et al* in the NHLBI Family Heart Study (FHS).<sup>20</sup>

These studies support the hypothesis that smoking accelerates the blockage of coronary arteries. There are many ways that this acceleration takes place. There may be escalation of coronary atherosclerotic plaque formation, destabilisation of the plaque, enhancement of blood clotting or some other as yet unknown mechanism. Rosengren *et al* found that cigarette smokers were more likely to present with ST elevation ACS, while patients with hypertension and/or obesity were more likely to present with non-ST elevation ACS.<sup>3</sup> These findings are taken from a very broad-based registry of 10 253 patients with a discharge diagnosis of ACS, treated in 103 hospitals in 25 countries of Europe and the

Mediterranean basin; 43% of these ACS patients showed ST elevation, and among these patients, myocardial infarction was detected in 87%, compared with 33% of patients without ST elevation. The patients with ST elevation develop larger infarctions, have more in-hospital complications and have a higher short-term mortality than patients with non ST elevation.<sup>21</sup> ST segment elevation myocardial infarction occurs due to transmural ischaemia. Patients with ST elevation who progress to Q wave AMI have occlusive thrombus in most cases.<sup>22</sup> Smoking enhances coagulation and thrombosis on fissured or ruptured atheromatous plaque to cause total and prolonged occlusion of a major coronary artery.<sup>23–25</sup> The occlusive thrombus precipitated by increased concentrations of plasma fibrinogen and platelet activation associated with smoking superimposes itself upon fixed atherosclerotic narrowing as well.<sup>26</sup> Smokers have a better prognosis when thrombolysed for the ST elevation AMI than non-smokers.<sup>27–28</sup> This finding also proves that smoking is responsible for thrombosis. Teo *et al* have found that smoking tobacco increases the risk of non-fatal myocardial infarction as well, by as much as sevenfold.<sup>29</sup> Smoking-induced atherosclerosis and acute coronary thrombosis increase the incidence of myocardial infarction, which necessitates CABG at an early age.<sup>30–32</sup> Furthermore, smoking advances CAD to severe forms unresponsive to medical treatment and PCI requiring CABG 8.4 years earlier than non-smokers.

## CONCLUSION

Our study shows that smoking accelerates atherosclerosis and coronary thrombosis resulting in a severe form of CAD that cannot be managed by medications or PCI, and requires CABG 8.4 years earlier than non-smokers.

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**Competing interests** None.

**Patient consent** Obtained.

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