

## Coronary Artery Bypass Graft Surgery Outcomes Following 6.5 Years: A Nested Case-control Study

### Abstract

**Background:** Coronary artery disease (CAD) is the leading causes of mortality and morbidity in worldwide. This nested case-control study investigated the predictors of death in long-term follow-up after coronary artery bypass graft surgery (CABG). **Methods:** Cases were defined as CABG patients who died in the period of May 2006–March 2013. Controls were CABG patients who were alive in the same period. Cases and controls were derived from an existing cohort, Tehran Heart Center-Coronary Outcome Measurement. One hundred and fifty-nine patients in control group were randomly selected from 566 available patients in follow-up database. A series of simple and multiple logistic regressions was performed in the context of univariate and multivariate analyses, respectively, for computing unadjusted and adjusted odds ratios and their confidence intervals (CI). In the univariate analyses, demographic or cardiometabolic factors were entered separately, and for multivariate analysis, we got both significant risk factors from univariate analysis and the major risk factors. **Results:** The results of multivariate analyses showed that for age, the likelihood of mortality increases in CABG patients (95%CI: 1.1; 1.03–1.2;  $P < 0.005$ ). Other significant independent risk factors were peripheral vascular disease (PVD) (95%CI: 2.7; 1.06–6.8;  $P = 0.036$ ), diabetics (95%CI: 2.49; 0.9–6.3;  $P = 0.039$ ), smoking (95%CI: 4.38; 1.45–13.7;  $P = 0.011$ ), length of stay in hospital after CABG surgery (95%CI: 1.14; 1.0–1.24;  $P = 0.001$ ), total cholesterol (95%CI: 1.12; 1–1.2;  $P = 0.001$ ), and C-reactive protein (CRP) (95%CI: 1.12; 0.99–1.27;  $P = 0.049$ ) (all  $P < 0.05$ ). **Conclusions:** The study results indicated that age, diabetes, cigarette smoking, PVD, long length of stay in hospital, elevated triglycerides, total cholesterol, CRP, and high-density lipoprotein cholesterol were significant contributing to increased mortality after CABG. It seems that vulnerable older patients continue to be at high risk with poor outcomes.

**Keywords:** Cardiometabolic risk factors, coronary artery bypass graft surgery, mortality, outcome

### Introduction

Coronary artery disease (CAD) is the leading causes of mortality and morbidity as well as the major causes of disability worldwide. CAD is responsible for more than half of all the deaths annually.<sup>[1]</sup> CAD and its risk factors have become a major health problem globally. For nearly 50 years, coronary artery bypass graft (CABG) surgery has remained the predominant mode of revascularization and complete treatment for ischemic heart diseases.<sup>[2]</sup> The American Heart Association (AHA) and the American College of Cardiology (ACC) have outlined that the major risk factors for CAD are cigarette smoking, hypertension, elevated serum total cholesterol, low-density lipoprotein cholesterol (LDL-C), low serum high-density lipoprotein cholesterol

(HDL-C), diabetes mellitus, and advancing age. Other factors are associated with increased risk for CAD such as obesity, family history of CAD, inflammatory markers, elevated serum triglycerides (TGs), and ethnic characteristics.<sup>[3]</sup> A substantial number of studies have identified that these risk factors are associated with death among CABG patients. These risk factors are diabetes mellitus,<sup>[4]</sup> obesity,<sup>[5]</sup> age,<sup>[6]</sup> gender, family history of coronary heart disease (CHD), cigarette smoking, dyslipidemia, and hypertension.<sup>[5]</sup> Jones *et al.* demonstrated that elevated early postoperative glucose levels dramatically increase mortality rate after CABG.<sup>[6]</sup> The review study of cardiopulmonary outcomes by Thiessen *et al.* indicated that appropriate glycemic control during and after cardiac surgery prevents additional damage to CABG patients.<sup>[7]</sup> Similar study has demonstrated that patients with failure

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in diabetes management are more likely to experience increased risk of congestive heart failure, increased mortality rate.<sup>[8]</sup>

According to AHA and ACC statements, some characteristics of patient's lifestyle increased the risk for CAD.<sup>[3]</sup> Addiction and illicit drug abuse is contributed to potentially problematic and specific risky lifestyle among CABG patients<sup>[9]</sup> and is considered as a serious public health and social problem in Iran.<sup>[10]</sup> Furthermore, available evidence from Iran shows that the prevalence of addiction among cardiac surgery patients approaches to higher than 20% in men.<sup>[11]</sup>

The nested case-control study is a relatively new observational approach that increasingly being used to identify novel cardiac risk factors.<sup>[12]</sup> This design has the advantage of allowing for statistically efficient analysis of data from a cohort with substantial savings cost and time.<sup>[13]</sup> Case-control (cross-sectional) studies have evaluated the long-term outcomes of CABG patients.<sup>[14]</sup> However, an unselected study of risk factors for death among CABG patients in long term has not been previously performed in Iran. The aim of this nested case-control study on patients undergoing CABG surgery was investigated to determine potential risk factors associated with mortality risk.

## Methods

### Study design

This is a nested case-control study in a prospective cohort of patients undergoing CABG. Cases and controls were derived from an existing cohort, Tehran Heart Center (THC)-Coronary Outcome Measurement started in patients undergoing CABG in a tertiary level cardiac hospital, Tehran, Iran. Baseline data were collected as part of the large study started in May 2006, and 566 admitted patients to surgical ward were invited to participate in the study by their informed consent. All patients who underwent CABG were followed up until discharge and then in different time intervals until March 2013. In addition, hospital records were reviewed by a trained research assistant and initially enrolled patient's phone numbers extracted. Phone call interviews were conducted with patients or family members if died during the follow-up. Follow-up data were available for 566 patients. Figure 1 shows the flowchart of the study. The institutional review board of THC approved the study.

### Definition of cases and controls

Cases were defined as CABG patients who were died in the period between May 2006 and March 2013. Controls were CABG patients that were alive in the same period. The all 53 patients of the cohort, who died, selected as cases; for each case, two controls were randomly selected from the cohort data.<sup>[15]</sup> The randomly selection of controls was performed through STATA resampling command.<sup>[16]</sup>

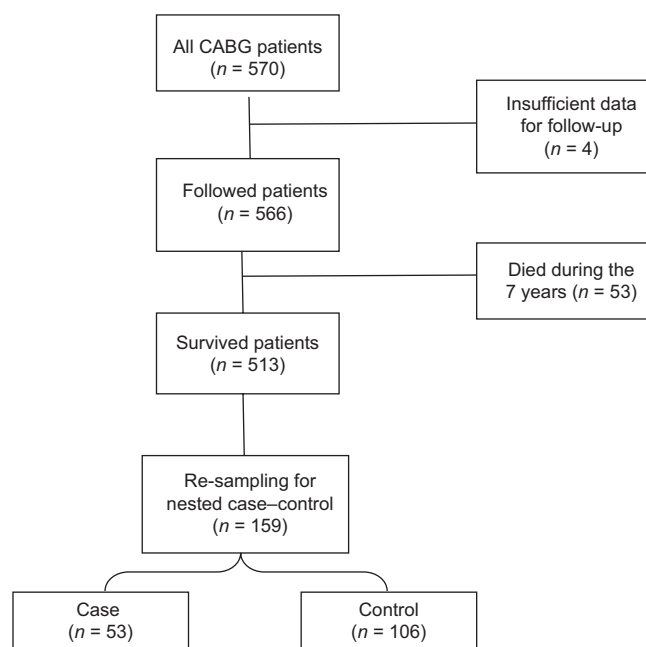


Figure 1: The study flowchart

### Data collection

Data collection was conducted through interviews, physical and clinical examinations. Demographics (gender, age, family history of CAD, cigarette smoking, alcohol consumption, opium addiction, history of myocardial infarction (MI), and having diabetes and hypertension), fasting blood sugar, total cholesterol, HDL-C, TGs, LDL-C, blood urea nitrogen (BUN), creatinine, hematocrit, lipoprotein (LP), C-reactive protein (CRP), peripheral vascular disease (PVD), ejection fraction (EF), and body mass index (BMI) were measured.

Measuring the baseline characteristics as preoperative risk factors including: current smoking history (patient regularly smokes a tobacco product/products one or more times per day or has smoked in 30 days before admission),<sup>[17]</sup> alcohol consumption (the use of alcohol in average 1/week despite recurrent adverse consequences),<sup>[18]</sup> opium dependence (according to the Diagnostic and Statistical Manual of Mental Disorders, 4<sup>th</sup> edition criteria for substance dependence, daily regular using of substances),<sup>[19]</sup> family history of CAD (first-degree relatives before the age of 55 in men and 65 years in women),<sup>[20]</sup> hypertension (blood pressure reading  $\geq 140/90$  mmHg, current use of antihypertensive medications),<sup>[21]</sup> diabetes mellitus (symptoms of diabetes plus at least one of the following: plasma glucose concentration = 200 mg/dl [11.1 mmol/L], fasting plasma glucose = 126 mg/dl [7.0 mmol/L], plasma glucose 2 h postprandial = 200 mg/dl [11.1 mmol/L]),<sup>[22]</sup> cerebrovascular disease, and PVD. Furthermore, EuroSCORE, number of grafts, and length of stay in hospital after CABG were extracted from the baseline database.

Based on AHA/ACC statement,<sup>[3]</sup> the cardiovascular risk factors were classified into the major risk factors including cigarette smoking, hypertension, total cholesterol, HDL, diabetes mellitus, and age and the other risk factors including drug addiction, alcohol use, BMI, LP, TG, family history of CAD, CRP, number of grafts, length of stay in hospital after CABG, and EuroSCORE. Because of the great association between opium addiction and cigarette smoking, we categorized into three subgroups as cigarette smoking, opium abuse, and concurrent cigarette smoking and opium abuse. Major risk factors and other risk factors were analyzed by two univariate and multiple logistic regression models separately.

### Statistical analysis

Statistical analysis was conducted using the STATA release 12.0 software (College Station, Texas, USA). Data were presented using frequency (percent) for categorical variables and mean (standard deviation [SD]) for numeric variables. Descriptive statistics were calculated for baseline characteristics to compare case and controls for each outcome. Between-group differences were measured using  $\chi^2$  or Student's *t*-tests, as appropriate. A series of simple and multiple logistic regressions was performed in the context of univariate and multivariate analyses, respectively, for computing unadjusted and adjusted odds ratios (ORs) and their confidence intervals (CIs). Mortality status considered as the dependent outcome of interest by coding one for dead and coding zero for live patients. In the univariate analyses, demographic or cardiometabolic factors were entered separately, and for multivariate analysis, we got both significant risk factors from univariate analysis and the major risk factors. *P* < 0.05 considered to be as significant.

### Results

Table 1 shows the baseline characteristics in cases and controls. In this prospective study of 566 CABG patients, 53 cases and 106 randomly selected controls were evaluated. Of these, 77.3% were men and 22.6% were women. The mean ages at baseline were 64.1 years (SD = 8.6) and 58.4 years (SD = 8.3) in cases and controls, respectively. The cases were approximately 6 years older than the controls. The mean values of BMI were 26.3 kg/m<sup>2</sup> (SD = 4.2) and 27 kg/m<sup>2</sup> (SD = 4.1) in cases and controls, respectively. There were significant differences between cases and controls for hypertension (47.2 vs. 39.5) (*P* < 0.05). Compared with controls, the cases had significantly higher rate of opium use (25.5% vs. 11.7%). In addition, there were significant differences between the cases and controls regarding the mean values of BUN (cases: 44.5 ± 16.1, controls 38.8 ± 11.1), PVD (41.5% vs. 23.8), and CRP (cases: 8.4 ± 6.2, controls: 5.9 ± 2.2) (*P* < 0.05 for all).

The results of the univariate and multivariate analyses based on logistic regression for unadjusted and adjusted ORs for

**Table 1: Demographic and cardiometabolic factors in two groups of the case and nested-control**

Variables	Case (n=53)	Control (n=106)	P
Dichotomous, n (%)			
Gender			
Men	43 (81.1)	80 (75.4)	0.421
Women	10 (18.9)	26 (24.5)	
Smoking	20 (37.8)	35 (33)	0.556
Alcohol drinking	6 (11.3)	15 (14.2)	0.604
Addiction	13 (25.5)	13 (11.7)	0.039
Diabetics	28 (52.8)	44 (41.5)	0.049
Hypertension	25 (47.2)	51 (39.5)	0.012
History of MI	32 (60.3)	54 (50.9)	0.42
PVD	22 (41.5)	21 (23.8)	0.004
Continues, mean (SD)			
Age (years)	64.1 (8.6)	58.4 (8.3)	<0.0001
BMI (kg/m <sup>2</sup> )	26.3 (4.2)	27 (4.1)	0.371
Total cholesterol (mg/dL)	165.1 (40.7)	148.1 (40)	0.015
LDL-C	92.3 (35.5)	75.8 (34.1)	0.006
HDL-C (mg/dL)			
Women	45.9 (11.8)	47.3 (10)	0.721
Men	41.9 (8.8)	38.5 (7.6)	0.030
TG (mg/dL)	144 (63.5)	165.3 (64.8)	0.049
FBS (mg/dL)	112.1 (47.7)	106.3 (34.5)	0.383
BUN	44.5 (16.1)	38.8 (11)	0.009
Creatinine	1.3 (0.26)	1.2 (0.29)	0.814
HCT	42.8 (3.8)	42.4 (4.1)	0.592
LP	37.9 (27.4)	34.5 (28.1)	0.4710
CRP	8.4 (6.2)	5.9 (2.2)	<0.0001
EF	37.9 (15.5)	43.3 (18.3)	0.066

MI=Myocardial infarction, PVD=Peripheral vascular disease, SD=Standard deviation, BMI=Body mass index, LDL-C=Low-density lipoprotein cholesterol, HDL-C=High-density lipoprotein cholesterol, TG=Triglycerides, FBS=Fasting blood sugar, BUN=Blood urea nitrogen, HCT=Hematocrit, LP=Lipoprotein, CRP=C-reactive protein, EF=Ejection fraction

participant characteristics to predict mortality are shown in Table 2. Age, gender, history of MI, diabetes, BMI, EF, smoking and opium addiction, alcohol use, number of grafts, length of stay in hospital after CABG, EuroSCORE, PVD, total cholesterol, CRP, BUN, LDL, TG, and HDL were included into simple logistic regression (unadjusted ORs). The results showed that for age, the likelihood of mortality increases in CABG patients (95%CI: 1.08; 1.03–1.2; *P* = 0.001). Other significant independent risk factors were length of stay in hospital after CABG surgery (95%CI: 1.14; 1.0–1.29; *P* = 0.04), PVD (95%CI: 2.8.01; 1.38–5.9; *P* = 0.004), total cholesterol (95%CI: 1.01; 1–1.2; *P* = 0.012), LDL-C (95%CI: 1.13; 1.0–1.23; *P* = 0.007), and CRP (95%CI: 1.2; 1.04–1.39; *P* = 0.009). Although participants with opium addiction and cigarette smoking had 60% and 2.57 times the odds of mortality than others, it did not achieve statistical significance.

**Table 2: Results of logistic regression for unadjusted and adjusted odds ratios for participant characteristics**

Variables	Unadjusted			Adjusted		
	OR	95% CI	P	OR	95% CI	P
Age	1.08	1.03-1.12	0.001	1.1	1.03-1.17	0.005
Gender						
Male	1.00			-	-	-
Female	0.71	0.31-1.6	0.42	-	-	-
History of MI	1.5	0.78-3	0.21	-	-	-
PVD	2.8	1.38-5.9	0.004	2.7	1.06-6.8	0.036
EF	0.98	96.5-1	0.061	-	-	-
Diabetics	1.58	0.81-3.07	0.179	2.49	0.9-6.3	0.039
BMI	0.96	0.88-1.04	0.36	-	-	-
Not smoker or opium addicted	1.000			-	-	-
Smoker	1.67	0.61-2.44	0.55	4.38	1.45-13.7	0.011
Opium addiction	2.57	0.98-5.4	0.05	-	-	-
Smoking plus opium addiction	2.01	0.79-5.1	0.147	-	-	-
Alcohol use	0.76	0.27-2.1	0.60	-	-	-
Hypertension	0.96	0.49-1.86	0.91	1.23	0.51-2.85	0.613
Graft number	1.20	0.74-1.37	0.07	-	-	-
Length of stay in hospital after CABG	1.14	1.00-1.29	0.04	1.14	1.05-1.24	0.001
EuroSCORE	0.99	0.99-1.00	0.59			-
TG	0.994	0.98-1	0.085	0.95	0.91-0.98	0.014
Total cholesterol	1.01	1-1.2	0.012	1-1.02	0.046	0.001
CRP	1.2	1.04-1.3	0.009	1.12	0.99-1.27	0.049
BUN	1.014	1-1.05	0.008	1	0.96-1.03	0.92
LDL	1.13	1.003-1.23	0.007	0.83	0.73-0.95	0.05
HDL	1.04	0.98-1.06	0.21	0.83	0.72-0.95	0.041

Hosmer and Lemeshow test showed an acceptable of model fit ( $\chi^2=11.43$ ,  $P=0.0.17$ ). A total of 79.75% of participants were correctly classified. CABG=Coronary artery bypass graft, OR=Odds ratio, CI=Confidence interval, MI=Myocardial infarction, PVD=Peripheral vascular disease, BMI=Body mass index, LDL=Low-density lipoprotein, HDL=High-density lipoprotein, TG=Triglycerides, BUN=Blood urea nitrogen, CRP=C-reactive protein, EF=Ejection fraction

The significant and the major risk factors including age, diabetes, cigarette smoking, hypertension, Length of stay in hospital after CABG, PVD, total cholesterol, LDL and HDL cholesterol, BUN, CRP, and TG were candidate as to enter in the multivariate analysis. Age, having diabetes, smoking, length of stay in hospital after CABG, PVD, TG, total cholesterol, and HDL-C were significantly related to mortality of CABG patients (All  $P < 0.05$ ).

## Discussion

This study investigated the associations of potential risk factors after CABG with death over around 6.5 years. The study indicated that age, diabetes, cigarette smoking, PVD, long length of stay in hospital, elevated TGs, total cholesterol, CRP, and HDL-C were significant contributing to increased mortality after CABG.

According to other studies, age is the most important predictor for death in long term among CABG candidates.<sup>[23]</sup> In our study, the case group was about 6.5 years older than control group because older patients generally are at higher risk of cardiac events than younger patients.<sup>[24]</sup> According to our results, an increase of age in 1 year in CABG patients increased odds of mortality by 8%. A large

proportion of older patients with CABG often discontinues or takes the drugs inappropriately. A study indicated that older people failed to take medications as prescribed. These caused vulnerable older patients continue to be at high risk with poor outcomes. The useful recommendation for the vulnerable older patients is to identify poor adherence to medications in older patients. This problem must be elucidated through a multidisciplinary team effort including physicians, pharmacists, and nurses as well as staff at community-based centers.<sup>[25]</sup>

The prevalence of opium addiction in CABG patients is relatively high.<sup>[26]</sup> Our previous study showed that patient with positive history of opium use significantly experienced lower EF, higher creatinine level, and higher prevalence of MI.<sup>[27]</sup> In the current paper, the opium consumption rate in cases (25.5) was significantly higher than control (11.7) group ( $P = 0.039$ ). Although the results of logistic regression for opium consumption showed relatively greater OR (2.57) to predict mortality, it was not statistically significant.

Our result suggests that patient with cigarette smoking had 1.67 times the odds of death than other CABG patients in 6.5-year period after surgery ( $P < 0.05$ ).

A study by Asgary *et al.* showed that opium consumption has deleterious effect on cardiovascular disease risk factors including HDL, HbA1c, and CRP.<sup>[28]</sup> Studies suggest that the high level of CRP that was seen in opium addicts increased the risk for heart attack or stroke. Our findings are in line with other studies that higher level of CRP as an inflammatory biomarker is associated with increased risk of death.<sup>[29]</sup> This study revealed that diabetes mellitus as a major health problem in Iran is a strong predictor of death among CABG patients during 7 years. It is estimated that over one third of CABG patients have high levels of blood glucose which are in accordance with diabetes mellitus definition. These patients are more likely to experience acute MI compared to nondiabetics.<sup>[30]</sup> Various studies from different populations confirmed that diabetes is a major risk factor for cardiovascular disease with 1.5–4-fold increased risk of death after CAD.<sup>[31]</sup> Previous studies have indicated significant positive association between elevated CRP levels and incident of diabetes. Some investigations have been shown an association between elevated glucose level and CRP. CRP is a marker of systemic inflammation that was found as additional risk factor for CHDs.<sup>[32]</sup> The cohort study by Jones *et al.* introduced CRP as a novel risk factor for CAD.<sup>[33]</sup>

Higher level of CRP as an inflammatory marker plays more important role in developing the risk of diabetes and its complication. Among CABG patients, inflammation is probably responsible for increased risk of death, especially in patients with diabetes.<sup>[34]</sup>

Our results showed that patients with a PVD history undergoing CABG had a mortality rate nearly 2.7 times as high as those without. The previous studies obtained similar findings found that CABG patients with a PVD history had about 20% 5 years.<sup>[35]</sup> Patients with a PVD history undergoing CABG had more coexistent risk factors.<sup>[36-38]</sup> The another study showed that these patients also exhibited higher rates of cardiac, systemic, and pulmonary complications.<sup>[36]</sup>

One possible limitation is that an important part of our cohort's questionnaire was dedicated to details of patients' medications. Then, we categorized their medication into four groups of nitrates, statins, beta-blockers, and angiotensin receptor blockers. However, most of our patients were under treatment with all these four groups. Outcome prediction was the focus of this paper with special emphasis on the mortality. Hence, we did not add them to our primary analysis assuming that they have not changed the outcome. The other limitation is the limited numbers of patients including into nested case-control study due to nature of methodological approach.

## Conclusions

The study results indicated that age, diabetes, cigarette smoking, PVD, long length of stay in hospital, elevated TGs, total cholesterol, CRP, and HDL-C were significant

contributing to increased mortality after CABG. It seems that vulnerable older patients continue to be at high risk with poor outcomes.

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## Conflicts of interest

There are no conflicts of interest.

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