

## Review Article

# Predictors of Early Adverse Events after Isolated Coronary Artery Bypass Grafting: Current Status

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## Abstract

The most serious early adverse events after Coronary Artery Bypass Grafting (CABG) include in-hospital mortality, low cardiac output, perioperative myocardial infarction, renal dysfunction, stroke, atrial fibrillation and sternal wound infection. Prediction of outcome after CABG has a considerable importance which constitutes guidance for proper perioperative care and improved postoperative outcome. Establishment of risk stratification models results in identification of many significant predictors of outcome after CABG including in particular older age, female gender, low ejection fraction, urgency of surgery, neurological dysfunction, renal impairment, perioperative myocardial infarction and severity of angina. Advances in anesthesia and surgical techniques play a role in enrollment of patients with higher risk for CABG which indicates periodic updating of the traditional predictors of outcome. This review tries to highlight the current status of the important preoperative predictors of early mortality and morbidity after CABG.

**Keywords:** Coronary artery bypass grafting; Outcome; Predictors

## Abbreviations

AF: Atrial Fibrillation; BMI: Body Mass Index; CABG: Coronary Artery Bypass Grafting; CAD: Coronary Artery Disease; CCS: Canadian Cardiovascular Society; COPD: Chronic Obstructive Pulmonary Disease; CPB: Cardiopulmonary Bypass; CrCl: Creatinine Clearance; cTn: cardiac troponin; DM: Diabetes Mellitus; EuroSCORE: European System for Cardiac Operative Risk valuation; HbA1c: Haemoglobin A1c; IABP: Intra-Aortic Balloon Pump; LCOS: Low cardiac output syndrome; LMS: Left Main Stem; LVD: Left Ventricular Dysfunction; LVEF: Left Ventricular Ejection Fraction; NSTEMI: Non-ST Elevation Myocardial Infarction; PMI: Perioperative Myocardial Infarction; POAF: Postoperative Atrial Fibrillation; PVD: Peripheral Vascular Disease; SBP: Systolic Blood Pressure; SWI: Sternal Wound Infection

## Introduction

Awareness of perioperative risk factors associated with mortality and morbidity after cardiac surgery is an important issue that may provide valuable insights on areas to focus for better outcome and improved quality of care [1].

Research for perioperative predictors of outcome results in establishment of multiple risk stratification models, of which European System For Cardiac Operative Risk Evaluation (EuroSCORE) and Parsonnet score (Table 1) are the most frequently used models [2,3].

In the recent years more complex preoperative patient profile had been referred for Coronary Artery Bypass (CABG) including older patients, more advanced and diffuse coronary artery disease, impaired left ventricular function, failed previous percutaneous manipulations, more serious comorbidities, and multiple reoperations [4].

The increasing complexity and disability of patients is an important reason for periodic update of the perioperative predictors

to account for the changes in patient characteristics and contemporary surgical techniques [5,6]. The aim of this review is to highlight the current status of the established preoperative predictors of adverse outcome after CABG.

## Early Adverse Events after Coronary Artery Bypass Grafting

### Early mortality

The 30-day mortality after CABG has greatly improved with 40% reduction over the last decade [7]. In large trials, the early 30 days mortality after CABG ranged from 1.7% to 3.5% [8,9]. The goal to achieve  $\leq 1\%$  operative mortality for primary isolated CABG appears feasible in appropriately selected patients in the modern surgical era [10].

The perioperative risk factors that result in increased early mortality after primary CABG include older age, diffuse Coronary Artery Disease (CAD), Left Ventricular Dysfunction (LVD), failure of multiple previous percutaneous manipulations, more serious comorbidities and greater number of reoperations [4].

### Low cardiac output syndrome

Low Cardiac Output Syndrome (LCOS) is still the most common and the most serious complication after CABG and other cardiac surgeries with increased risk for morbidity, mortality, and healthcare resource utilization [11].

Risk factors associated with LCOS include age  $>65$  years, female gender, diabetes mellitus, left main and triple-vessel CAD, Left Ventricular Ejection Fraction (LVEF)  $<50\%$ , redo or emergency surgery, recent Myocardial Infarction (MI), incomplete revascularization, long Cardio Pulmonary Bypass (CPB) time, and poor intraoperative myocardial protection [12].

**Table 1:** The established predictors of mortality after cardiac surgery as determined in EuroSCORE and Parsonnet score models for risk stratification. Modified from references [2,3].

| <i>EuroSCORE</i>   |       | <i>Parsonnet Score</i>   |       |
|--|-------|--|-------|
| Risk factors   | Score | Risk factors   | Score |
| <b>Patient related factors:</b>  |       |  |       |
| Age:   |       | Age:   |       |
| Per each 5 years above 60 years  | 1     | <70 years  | 7     |
|  |       | 71-74 years  | 12    |
|  |       | ≥75 years  | 20    |
| Female gender  | 1     | Female gender  | 1     |
| Serum creatinine >2.3 mg preoperatively  | 2     | Dialysis dependency  | 10    |
| Critical preoperative state (ventricular tachycardia or fibrillation, aborted sudden death, or preoperative heart massage, ventilation, inotropic support or IABP)               | 3     | Catastrophic states (acute structural defect, cardiogenic shock, acute renal failure or similar conditions)    | 10-50 |
| Neurological dysfunction affecting walking or daily activities   | 2     | Other rare circumstances (paraplegia, pacemaker dependency, severe asthma, congenital heart disease in adults) | 2-10  |
| Extracardiac arteriopathy: claudication or obstruction >50% of carotid arteries or previous or planned intervention for abdominal aorta, carotid arteries or peripheral arteries | 2     | Preoperative IABP  | 20    |
| Active endocarditis patient still under antibiotic treatment for endocarditis at the time of surgery   | 1     | Morbid obesity (≥ 1.5 of ideal weight)   | 3     |
| Chronic pulmonary disease  | 3     | Diabetes   | 3     |
|  |       | Hypertension (Systolic blood pressure > 140 mmHg)  | 3     |
| <b>Cardiac related factors:</b>  |       |  |       |
| Ejection fraction:   |       | Ejection fraction:   |       |
| 30-50%   | 1     | 30-49%   | 2     |
| <30%   | 3     | <30%   | 4     |
| Pulmonary hypertension: Systolic pressure of pulmonary artery > 60 mmHg  |       |  |       |
| Unstable angina requiring use of nitrates before arrival to operating room   | 2     |  |       |
| Recent MI < 90 days  | 2     |  |       |
| <b>Procedure related factors:</b>  |       |  |       |
| Emergency within 24 hours  | 2     | Catheter lab emergency   | 10    |
| Reoperation:   |       | Reoperation:   |       |
| Requiring opening of the pericardium   | 3     | First  | 5     |
|  |       | Second   | 10    |
| Another heart procedure at the same time as CABG   | 2     | CABG at time of valve surgery  | 2     |
| Surgery on thoracic aorta for disorder of ascending, arch or descending aorta  | 3     | Aortic surgery   | 5     |
| Post-infarction VSD  | 4     | LV aneurysm  | 5     |
|  |       | Aortic surgery and aortic gradient ≥120 mmHg   | 7     |
|  |       | Mitral surgery   | 5     |
|  |       | Mitral surgery and PA pressure ≥60 mmHg  | 8     |

### Perioperative myocardial infarction

Perioperative Myocardial Infarction (PMI) occurs in 2% to 30% after CABG and it is associated with high morbidity and mortality [9,13]. The causes of PMI include graft-related problems such as kinking and overstretching of the grafts, acute occlusion, technical anastomotic stenosis, or conduit spasm. Other causes may be related to the native coronary circulation including inadequate myocardial protection, incomplete revascularization, and coronary embolization [14].

### Re-exploration for bleeding

Re-exploration for bleeding occurs in 2% to 6% of CABG

cases and carries more than 4-fold higher risk of mortality [15,16]. Predisposing factors for postoperative bleeding and excessive blood transfusion after CABG include advanced age, female gender, lower body weight, preoperative cardiogenic shock, anemia, renal dysfunction (especially dialysis-dependent patients), Peripheral Vascular Disease (PVD), poor nutritional status, recent thrombolytic therapy, urgent surgery, repeat operations, longer CPB times and individual surgeon performance [16,17].

### Neurological complications

Stroke is a devastating type I neurological complication after CABG with a risk peaks 40 hours after surgery [18]. Type II deficits

(confusion, agitation, memory deficit or seizure) are more difficult to detect and characterize than type I. Delirium occurs in 3% to 50% of patients after CABG [19].

The mechanisms of neurological complications after CABG are believed to arise primarily from cerebral emboli, hypoperfusion, or inflammation related to the use of CPB [20].

### Renal dysfunction

Postoperative renal dysfunction is associated with high mortality and increased rates of cardiovascular events including the long-term risk of heart failure [21]. Risk factors for renal dysfunction after CABG include: older age, preoperative serum creatinine > 1.2 mg/dL, duration of CPB > 90 min, use of Intra-Aortic Balloon Pump (IABP), need for inotropic drugs, increased catecholamine level, non-pulsatile flow, hypothermia, renal hypoperfusion, and the induction of inflammatory mediators [22,23].

### Atrial fibrillation

Postoperative Atrial Fibrillation (POAF) develops in 20% to 40% of patients undergoing CABG, with a peak incidence on the second and third postoperative days [24]. Risk factors for POAF include advanced age, male sex, smoking, prolonged cross-clamp time, Chronic Obstructive Pulmonary Disease (COPD), chronic renal disease, valvular heart disease, atrial enlargement, obesity, prior pericarditis, and withdrawal of beta blockers [25,26].

### Sternal wound infection

The overall incidence of Sternal Wound Infection (SWI) after CABG ranged from 0.47% to 8.0% with an incidence of 0.25% to 4% for deep SWI (bone infection and mediastinitis) [27-29].

Reported risk factors for deep SWI include advanced age, male sex, COPD, obesity, diabetes mellitus, smoking history, steroid use, renal insufficiency, non-elective surgery, repeat operations, long operative times, re-exploration for bleeding, use of bone wax, perioperative transfusion, prolonged hospital stay (>5 days), and the number of internal thoracic arteries [29,30].

## Predictors of Early Outcome after CABG

### Age at surgery

Respecting more extensive coronary atherosclerosis, older age has been recognized as an independent predictor of short- and long-term mortality and adverse outcome after CABG [31,32].

Although age of 60 years is traditionally considered as a cut-off value for worse outcome after CABG, other values of 65, 70, 75 or 80 years has been recognized, mostly due to the decline in operation risks thanks to the advances of technology, methods and proper selection of patients [33,34].

### Female gender

Female gender is well recognized as an independent predictor of short- and long-term mortality and adverse events after CABG [35,36]. The gender-specific differences in outcome may be aggravated by older age, advanced symptoms, urgency, coronary artery diameters, as well as higher incidence of comorbidities such as diabetes, arterial hypertension and hypercholesterolemia [37].

### Obesity

Obesity defined as Body Mass Index (BMI)  $\geq 30$  kg/m<sup>2</sup> has been reported to be associated with increased pulmonary morbidity [38] and severe obesity (BMI  $\geq 40$  kg/m<sup>2</sup>) has been determined as an independent risk factor for longer length of stay after CABG [39].

The impact of obesity on early mortality after CABG remains uncertain [40]. Obesity has not been associated with increased in-hospital or 3 months mortality [41], while morbid obesity was recognized as an independent predictor for late mortality after CABG [42].

Compared to non-obese patients, overweight and obese individuals have similar early mortality rate following CABG which can substantiate the presence of obesity paradox only in terms that elevated BMI patients have comparable outcome with non-obese [43].

### Diabetes mellitus

Patients with diabetes and CAD often have more extensive and complicated atherosclerosis, thus they are at higher risk of developing major adverse events and death after CABG with prolonged hospital stay and greater hospital costs than are patients without diabetes [44].

Diabetes on insulin treatment is considered as a predictor of outcome after cardiac surgery [45]. Patients with insulin treated DM have a significantly higher rate of mortality and major adverse events compared to patients with non-insulin treated DM patients after CABG [46].

Elevated preoperative Haemoglobin A1c (HbA1c) is debated as a predictor of mortality and morbidity irrespective of previous diabetic status. In particular, the mortality risk for CABG is quadrupled at HbA1c levels >8.6% [47]. In a recent study preoperative HbA1c was the only diabetic variable to independently predict operative mortality after CABG [48].

### Hypertension

Isolated Systolic Hypertension (systolic blood pressure (SBP) >140 mmHg) only was reported to be associated with adverse outcomes after CABG, causing a 40% increase in the likelihood of postoperative morbidity [49]. Recent studies reported hypertension among risk factors associated with early mortality in haemodialysis patients undergoing CABG [50], and it has been considered with other demographic risk factors among predictors of AF after CABG [51].

### Chronic obstructive pulmonary disease

Chronic Obstructive Pulmonary Disease (COPD) is traditionally established as a predictor of postoperative morbidity and mortality after CABG surgery, especially in patients older than 75 years with severe COPD and receiving steroids [52].

The known postoperative complications of COPD include respiratory failure, re-intubation, sternal dehiscence, prolonged mechanical ventilation, rhythm disturbances and prolonged hospital stays [53]. A recent study reported that COPD does not necessarily lead to mortality, readmission, or AMI after CABG, and the major respiratory complications associated with CABG in patients with COPD were pneumonia and acute respiratory failure [54].

### Extra-cardiac arteriopathy

Evidence from recent studies suggests that Peripheral Vascular Disease (PVD) still adversely affects the short- and long-term outcomes after CABG [55]. However, diversity of symptoms as well as the severity and location of occluded vessels may influence outcome [56].

Carotid artery disease is considered as an epiphenomenon that serves as a marker for diffuse systemic atherosclerotic disease [57]. Extracranial Carotid Artery Stenosis (CAS) is a risk factor for perioperative stroke in patients undergoing CABG surgery [58]. In patients with 50% to 80% stenosis of the carotid arteries, the incidence of stroke after CABG ranged from 3% to 10%, and approached 22% in patients with >80% stenosis [59].

### Neurological dysfunction

Preoperative neurological events are determined as risk factors for postoperative neurologic events and in-hospital mortality particularly with cardiopulmonary bypass [60].

Preoperative stroke was reported to be associated with mortality, increased risk of early and late postoperative stroke, and prolonged length of stay [61]. However, optimal time interval between stroke and surgery has a debate, as there is no contemporary evidence that more recent preoperative stroke predisposed patients undergoing CABG to have adverse perioperative outcomes [62].

### Chronic renal impairment

Preoperative renal impairment is a well-established predictor of adverse events in after CABG [21]. However, when compared with expected survival, only advanced renal impairment led to worse outcome, and patients with moderate renal impairment had an outcome similar to that expected [63].

Serum creatinine is a main predicting factor in the scoring systems for risk estimation with a significant impact on surgical outcome after cardiac surgery [64]. For a better estimate of kidney failure degree, current risk scores, such as EuroSCORE II, have included Creatinine Clearance (CrCl) calculation rather than serum creatinine to predict mortality after cardiac surgery [65,66].

Cystatin C which is less affected by dietary protein intake has been shown to have a greater predictive power than serum creatinine for overall mortality after elective CABG [67].

### Left main stem disease

A significant Left Main Stem (LMS) disease, defined as stenosis of  $\geq 50\%$  of the vessel diameter, is an important predictor of cardiopulmonary morbidity and mortality after CABG [68]. Multiple clinical variables have been shown as prognostic factors in LMS lesion, including: cardiogenic shock, ST-elevation MI, reduced LVEF, older age, multi-vessel disease, and diabetes mellitus [69].

### Severity of angina

High Canadian Cardiovascular Society (CCS) class of angina before CABG is still determined as an independent predictor of adverse outcome and quality of life after CABG [70].

Acute coronary syndrome (unstable angina and non-ST-segment elevation myocardial infarction) is determined as an independent predictor of early mortality, however the long-term outcomes after

CABG are similar between patients with acute coronary syndrome and stable angina [71].

### Perioperative myocardial infarction

Perioperative Myocardial Infarction (PMI) is a well-known cause of morbidity and mortality after CABG surgery [72]. Ninety days threshold is traditionally accepted as minimal time interval between MI and CABG [45]. However, a recent study showed that patients operated on 1 to 2 days and 3 to 7 days after MI had a similar mortality rate [73].

It has been suggested that CABG may be safely performed in non-ST elevation myocardial infarction (NSTEMI) patients at any time after the first 6 hours of the event in patients with cardiac troponin I (cTnI)  $< 0.15$  ng/ml [74]. The contemporary findings show that it is safe to wait until cTnT levels decrease to the 1 ng/ml threshold value in cTnT positive patients having a stable course [75].

### Urgency of CABG

Urgency of CABG (urgent, emergent or salvage operation) was determined as a significant predictor of outcome after CABG in Euroscore II risk model [45]. Urgency is associated with significantly higher adverse outcomes, including death, when compared with elective CABG [76].

Early mortality in patients undergoing emergent and salvage CABG is substantial, especially in salvage patients. Long-term survival is acceptable in both emergent and salvage patients [77].

### Low left ventricular ejection fraction (LVEF)

Preoperative low LVEF is still an important predictor of mortality and morbidity after CABG [78-80]. However, surgery had been shown to be superior to medical therapy alone in patients with low LVEF [81,82]. The current literature suggests that CABG remains a viable option in selected patients with low EF, particularly in those with myocardial viability [79,83].

## Conclusions

Predicting outcome after CABG is multifactorial. In the current literature, traditional predictors of adverse outcome are subjected to isolated or combined revision and validation. The cut-off value of age as a predictor of worse outcome does not stand at 60 years. The predictive value of female gender is further investigated in respecting of gender difference in preoperative comorbidities. A debate exists regarding the impact of obesity on early outcome after CABG. Not only suffering from DM, but also elevation of preoperative HbA1c has a useful predictive value. The role of COPD in predicting outcome is related to presence of other risk factors especially older age and steroid therapy. Carotid artery stenosis  $> 50\%$  remains a significant predictor of postoperative stroke. The optimal time interval between preoperative stroke and CABG is still under debate. The predictive role of serum creatinine is questionable in comparison to creatinine clearance and Cystatin C. Left main stem disease  $\geq 50\%$ , severity of angina, perioperative MI, urgency of surgery and low preoperative LVEF are still recognized as important predictors of adverse outcome after CABG. Timing between NSTEMI and CABG is related to reduction of the level of cardiac troponin. In patients with low LVEF, proper selection of patients for surgery and myocardial viability still has a great influence on outcome after CABG. Searching for more

predictors related to the current practical era and updating the established risk models of adverse outcome after CABG is highly recommended.

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