

# The Unrecognized Patient and Economic Burdens of Post Coronary Artery Bypass Grafting Surgery Morbidities: Could Contemporary Medical Therapy Play a Bigger Role?

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## Abstract

**Background:** The recognition of the impact of new medications and the synergic effect of new drug combinations is absent in studies comparing coronary artery bypass grafting surgery (CABG) with medical therapy. There are limited review data regarding the contribution of morbidities after CABG on outcomes.

**Methods:** Full texts and data were collected from Mayo Clinic library, PubMed, and Google Scholar sources. We reviewed all pertinent article texts and study designs and identified relevant studies. Because we intended to include all morbidity results, we gathered all systematic reviews relating to specific morbidities and provided a comprehensive explanation of results. Published articles were assessed from 1994 up to the present time considering contemporary studies regarding morbidities.

**Results:** The impact of morbidities and economic costs after CABG go unrecognized in the decision process to pursue CABG while the beneficial effects of newer medications on managing ischemia and cardiovascular outcomes are potentially undervalued.

**Conclusions:** Considering new medications in the light of the deleterious impact of morbidities and costs following CABG should prompt needed studies to evaluate in a more comprehensive manner the impact of coronary surgical revascularization vs. contemporary medical therapy.

**Condensed Abstract:** The impact of morbidities and costs after CABG is significant. New studies comparing CABG with MT based on advances in contemporary medications relative to the morbidities and costs following CABG are needed.

**Keywords:** Complication; Coronary revascularization; Follow-up studies; Long-term outcome; Medications

## ABBREVIATIONS

AF: Atrial Fibrillation

BARI 2D: the Bypass Angioplasty Revascularization Investigation 2 Diabetes

CABG: Coronary Artery Bypass Grafting

CASS: Coronary Artery Surgery Study

DALYs: Disability Adjusted Life Years

MASS II: the second Medical, Angioplasty, or Surgery Study

MT: Medical Therapy

STICH: Surgical Treatment for Ischemic Heart Failure

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SYNTAX: the SYnergy between percutaneous coronary intervention with TAXus and surgery

US: United States

### **INTRODUCTION**

Coronary artery bypass grafting (CABG) surgery is one of the most common major surgeries in the world(1-3), with 156,931 CABG-only surgeries performed in the United States (US) alone in 2016 (54% of total cardiac surgeries)(1). The costs of CABG and its morbidities have a large effect on health systems, patients, and families (4-7). Morbidities after CABG are common (40% to 50%)(2,3,8-14) and some are very serious (3,11,12,15-19). If we count disability adjusted life years (DALYs) including years of life lost and years lived with disability associated with each morbidity, we encounter a larger burden which has not been considered in previous studies comparing CABG with medical therapy (MT)(20-24). For example, atrial fibrillation (AF) after CABG is associated with 53.6 years of life lost for one thousand patients during twenty years of follow-up (8). Another very important issue is that studies which compared CABG with MT are not contemporary (20-24) and with new medications and synergic effect of modern combination of drugs in ischemic heart disease, heart failure, diabetes mellitus, hypertension, dyslipidemia, and renal failure(25-37), new evaluations of CABG versus MT are needed. The aims of our review are to highlight the detrimental impact of morbidities after CABG and their associated patient and economic burdens and the necessity of new studies comparing CABG with MT based on new medications and combinations of the drugs. The impact of CABG-related morbidities on patients, their families, and the economic costs to our health care system are consequential.

### **METHODS**

Data were collected from three online data bases: Mayo Clinic library, PubMed, and Google Scholar. The research terms used were “CABG”, “CABG versus MT”, “morbidity after CABG”, “names of morbidities and complications after CABG in detail”, and “new medications and “combination of drugs for each cardiovascular risk factor”. The reference lists of the selected articles yielded via electronic database search were completely examined to find potential relevant articles. The research articles were assessed from 1994 up to the present time. Decision about inclusion of the studies was made independently and was based on the rigor of the study design, longer follow-up durations, effect of study limitations, and contemporary studies especially regarding morbidities. Because we intended to include all morbidity results, we gathered all systematic reviews relating to specific morbidities and provided a comprehensive explanation of results. We included all relevant studies which compared CABG with MT and discussed study results. We referenced new medications which have been proven to be effective at decreasing ischemia and improving cardiovascular outcomes in multiple studies and/or large multicenter randomized control trials. The full reports of articles were reviewed and considered for all relevant data including study designs, clinical validity, statistical analysis, primary and secondary outcomes, and follow-up time periods; and studies with high risk of bias were not included. Randomized controlled trials with high risk of bias as evaluated by the Cochrane Risk of Bias Tool (Higgins and Green, 2011) were excluded(38).

### **RESULTS**

#### **Mortality**

Many of the studies which compared CABG with MT demonstrated more increases in event free survival in CABG groups (20-24), but in the Surgical Treatment for Ischemic Heart Failure (STICH) trial CABG versus MT did not decrease all-cause mortality in older patients. In the second Medical, Angioplasty, or Surgery Study (MASS II) trial overall mortality rates were similar in CABG group and MT group, and the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) trial did not show significant differences in major cardiovascular events and death between the revascularization group and MT group (20,21,39).

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### **Angina**

Previous studies have shown better freedom from angina in CABG group comparing with MT group (21,23). In MASS II trial, the free from angina rates were 64% in CABG group and 43% in MT group(21), although a review of three former large trials showed no differences in the Class 3 and 4 angina during the follow-up of patients between MT group and CABG group(23).

### **Pain**

The most common symptom of patients who seek medical care is chronic pain and surgery is the most common cause of this problem (13) with CABG-related sternotomy or thoracotomy pain(40,41). Various prospective studies of cardiac surgery patients demonstrated that the incidence of chronic pain after sternotomy is 17% to 56%(42-44); and meta-analyses of prospective studies showed that the incidence of chronic pain after thoracotomy is 57% at three months and 47% at six months (13,45). These patients have worse quality of life, reduced physical activity, and sleep disturbances(46,47). A systematic review of 29 studies revealed that pre-operative anxiety plays an important role in development of chronic pain after surgery(48).

### **Depression and Anxiety**

Substantial numbers of cardiac surgery patients are subject to depression (14-47%) and anxiety (15-52%) (12,49-51). Significant depressive symptoms documented in one fifth of CABG patients one year after the operation and it was associated with high level of inflammation after CABG (10,52-54). Depressive disorders remarkably increase mortality and morbidities after cardiac surgery(12,49-51,55,56). The morbidities include persistent post-surgical pain, low adherence to medication, poor physical activity, new coronary events, suppression of immune system and progression of malignant tumors, and increased incidence of infection (49-51,55-57). A meta-analysis of 54 prospective cohort studies showed that there is a significant relationship between depression and risk of coronary artery disease, although the results of this study were limited because of heterogeneity of results in primary studies(57). A systematic review of pre-op predictors of depression and anxiety following CABG explained that a history of depression, neuroticism, female gender, and younger age might be risk factors of post-CABG depression(58).

### **Inflammation**

A significant inflammatory condition commonly occurs after cardiac surgery and it was diagnosed by high detected levels of inflammatory cytokines such as C-reactive protein, interleukin 6, and interleukin 8 (10,16,52,54,59,60). The main factors which cause the inflammation are surgical trauma, cardiopulmonary bypass, and ischemia-reperfusion injury subsequent to ischemic cardioplegic arrest (10,16,54,59). Inflammation after CABG would contribute to myocardial cell apoptosis and contractile dysfunction, AF, cerebral infarction, cognitive impairment, depression, respiratory dysfunction, renal failure, gastrointestinal problems, shoulder disorders, and pericarditis and post-pericardiotomy syndrome.(2,3,10,18,52,53,59,61-67) A systematic review of 63 studies including 27,363 cardiac surgery patients demonstrated that post-op inflammatory response, reflected mostly via an increased white blood cell blood levels, is associated with the risk of developing post-op atrial fibrillation (60). A similar systematic review of 42 studies involving 8398 cardiac surgery patients showed that post-op levels of inflammatory biomarkers encompassing C-reactive protein, interleukin 6, interleukin 8, and interleukin 10 are significantly related to post-op AF(10).

### **Atrial Fibrillation**

Post-operative AF is a very common problem after CABG, affecting up to half of the patients after CABG alone and over 60% of the patients after combined valvular surgery and CABG (10,59,68). It increases short-term mortality and predicts long-term mortality independently (68-70). It is associated with many adverse sequelae

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such as stroke, myocardial infarction, and organ failure among others (6,10,59,70) and it prolongs hospital stay two to five days (6,60). A systemic review about assessment of quality of life in AF patients revealed that quality of life is significantly poorer in AF patients compared to general population and coronary artery disease patients(71). Many reasons are suggested as the pathogenesis of the AF such as inflammation, ischemia from cardiopulmonary bypass, and surgical trauma (6,10,59,60).

### **Infection**

One of twenty patients (5%) after cardiac surgery experiences a major infection (72,73) and the infection substantially increases mortality and morbidity (72,74,75). Some of the risk factors are blood transfusion (increased risk with more transfusions), open saphenous vein graft approach, using bilateral internal mammary artery grafts, prolonged ventilation, and post-surgery vasopressor support (72-76). Pneumonia is the most common infection after CABG, involving 3% of patients (73,74,77). Surgical site infection has the incidence of 1% to 4% after CABG and it is related to significant morbidity and cost (72,75,78). A meta-analysis of 15 randomized controlled trials comparing conventional vein harvesting versus minimally invasive vein harvesting in patients undergoing CABG showed that the rate of leg wound infection is 13% and 3%, respectively(78). Mediastinitis is an uncommon infection (0.4-4%), but it carries a high rate of mortality (10-47%)(17). Prophylactic antibiotics are common after CABG and they are a crucial risk factor of Clostridium difficile infection(79). Recent cases of disseminated infection with Mycobacterium chimaera is a new long term challenge after cardiac surgery(80).

### **Cerebral Infarction**

Post-CABG stroke is a devastating morbidity which associates with high mortality (acute mortality is up to 38%)(15,61,81,82). A meta-analysis of 57 reports ( the analysis was done on 80314 patients) including MASS II trial and the SYnergy between percutaneous coronary intervention with TAXus and surgery (SYNTAX) trial demonstrated that the risk of stroke after CABG is significant and there is a persistent risk of accumulative stroke during five years after procedure(83). In MASS II trial the risk of stroke was 8.4% in CABG group and 6.9% in MT group at ten years of follow-up; and in SYNTAX trial the risk of stroke was 4.3% in left main disease group after CABG and 3.7% in three vessels disease and left main disease groups after CABG at five years of follow-up (21,84,85). Most of perioperative strokes happen 24 hours after the procedure, although those which happen during first 24 hours are much more lethal (15,82). Some of pathogenic factors of post-CABG stroke are manipulation of atherosclerotic aortic arch, utilization of cardiopulmonary bypass, systemic inflammatory reaction, and AF (61,81,82,86). A meta-analysis of 11,398 off-pump CABG cases observed that aortic manipulation significantly increase the risk of neurologic complications after the surgery(86). Studies with magnetic resonance imaging showed that brain infarcts are substantially more common than clinically visible strokes (61).

### **Cognitive Impairment, Delirium, and Dementia**

Cognitive impairment after CABG is common, involving about 50% of patients at time of discharge and approximately 42% after five years of surgery(2,64,87) and it has an enormous effect on the patients' life and their families (2,87,88). The most popular explanatory factors are systemic inflammatory reaction, cerebral hypoperfusion, microemboli, general anesthesia, and specific patient characteristics (2,64). Delirium commonly occurs after cardiac surgery (7.6-67%)(14,89). Lingehall et al. found an association between delirium after cardiac surgery and late dementia within five years of follow-up(89). A prospective study on 326 CABG patients showed that dementia is significantly higher in these patients at 7.5 years of follow-up. This study also showed an association between post-operative cognitive impairment and mortality(90). Crocker and his colleagues did a systematic review on 14,824 cardiac surgery patients to examine long-term (up to 10 years) outcomes

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of post-op delirium. They found that post-op delirium is firmly associated with functional decline, decreased cognition, lower health-related quality of life, hospital readmission, and death(14).

### **Respiratory Problems**

Following CABG, pulmonary complications were described as a major cause of mortality and morbidity (3,91-93). Patients often experience atelectasis and substantial decrease in pulmonary volumes and oxygenation (3,93,94) and almost all the patients have hypoxemia (91,92,94). A systematic review of 18 trials involving 1457 cardiac surgery patients demonstrated that the incidence of atelectasis is 15% to 98% and the incidence of pneumonia is 0% to 20% after cardiac surgery(95). Westerdahl et al. followed their patients for four months and they observed a significant restrictive pulmonary dysfunction remaining up to four months(94). Some of the pulmonary dysfunction mechanisms are general anesthesia, median sternotomy, utilization of cardiopulmonary bypass, topical cooling for protection of myocardium, dissection of internal thoracic artery, lung injury related to blood transfusion, diaphragmatic dysfunction, phrenic nerve injury, and muscle wasting due to inflammation(3,7,92-94). Large diminution in pulmonary function was observed in patients who have more post-operative increment in blood cortisol and C-reactive protein levels (3).

### **Renal Failure**

Acute renal failure is a common and debilitating morbidity after cardiac surgery which affects 30% to 50% of patients (11,62,65,66,96). Even slight increase in serum creatinine level (less than 0.3 milligrams per deciliter or 26 micromoles per liter) was associated with significant increase in long term mortality and chance of end stage renal disease in large population studies(97,98). About 0.6% to 5% of patients immediately after cardiac surgery require dialysis (11,62,98). These patients have really elevated mortality rate (approximately 25%) and substantial risk of chronic dialysis(98). A cohort study in the US using the Society of Thoracic Surgeons national database observed that 24% of patients undergoing CABG have moderate renal failure (glomerular filtration rate = 30-60 milliliter/minutes/1.73 square meters)(99). Sajja and his colleagues studied 116 CABG patients who had pre-op non-dialysis dependent renal failure (glomerular filtration rate  $\leq$  60 milliliter/minutes/1.73 square meter). They showed that the rate of acute renal failure is significantly higher in on-pump CABG versus off-pump CABG (62% versus 30%)(96). Likewise, a systematic review of six randomized controlled trials and sixteen observational studies (including 27,806 CABG patients) demonstrated a substantial decrease in post-op acute renal failure with off-pump CABG than conventional CABG(100). Pathogenesis of renal failure after CABG is multifactorial such as platelet activity, inflammation, emboli, hypothermia, non-pulsatile blood flow and renal hypoperfusion during cardiopulmonary bypass, and drugs (11,62,65,66). About half of CABG patients receive red blood cell products(73,74) and it adversely limits the patients access to kidney transplantation if needed in the future(101).

### **DISCUSSION**

CABG surgery is among the most frequent major surgeries performed in both the US and Europe (1-3). The mean hospital cost of a CABG surgery is \$40,424 in the US.(4)In addition, costs for morbidities following CABG are high. For example, expenditures related to post-operative AF are one to two billion dollars per year in the US (6,59). Expenditures related to mediastinitis are more than fifty-eight thousand dollars per episode(5).

Many previous studies comparing CABG with medical treatment showed better improvement in event free survival and angina in CABG group than MT group, but these studies have not been updated from the perspective of contemporary medication therapy(20-24). New medications and synergic effect of modern combinations of drugs in ischemic heart disease, heart failure, diabetes mellitus, hypertension, dyslipidemia, and renal failure have shown a better effect on decreasing ischemia, treatment of significant risk factors, cardiovascular

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outcomes, and survival (25-37). STICH trial was the last study comparing CABG with MT in 1212 heart failure patients starting in 2002, and therefore patients were not receiving optimal therapy by current standards. Moreover, every patients had reduced ejection fraction (< 35%), and hence the result is not attributable to all ischemic heart disease patients. The follow-up duration was 9.8 years and we do not know about the mortality beyond that time frame. The follow-up duration in Coronary Artery Surgery Study (CASS) registry was 15 years and it showed increased mortality rate after 8 to 10 years in CABG group and similar survival for medically and surgically managed patients at 15 years (20,24). STICH trail demonstrated that CABG does not decrease all-cause mortality in older patients. In this trail the number of patients was relatively small in the women's group (12%) and in the group of patients older than 75 years (7%); therefore, the CABG outcome was not well supported in these groups (20). BARI 2D trail enrolled 2368 diabetic patients with coronary artery disease. This trial began in 2001 and followed the patients for approximately 5 years and demonstrated that the rates of major cardiovascular events and death were not significantly different in revascularization group and MT group(39). MASS II trial of 611 patients who had multi-vessel coronary artery disease was initiated in 1995 with a follow-up duration of about 10 years. In this study event free survival rates were 74.9% in CABG group and 69% in MT group, however overall mortality rates were similar in both groups. Freedom-from-angina rates were 64% in CABG group and 43% in MT group (21).

The studies which compared CABG with MT did not account for the years of life lost from post-op morbidities (20-24,39) and unfortunately these morbidities are common following CABG (2,3,8-13). Geulayov and colleagues undertook a prospective study on 1125 CABG patients with 11 years of follow-up. They demonstrated that postoperative depression (especially one year after operation) is related to elevated long term mortality and postoperative anxiety is related to increased long term mortality in women (12). Al-Shaar and colleagues studied 7610 CABG patients for prediction of postoperative AF long term mortality. They showed postoperative AF is related to increased mortality at 18 years and this association was without the confounding effect of other postoperative complications(68). Ryden et al. studied 29330 isolated CABG patients for long term consequences of postoperative acute renal failure and followed the patients for 4.3 ±2.4 years. They showed that even small increase in serum creatinine level is related to significant increased risk of end stage renal disease and it predicts long term mortality(98).

Years of life lost and years lived with disability following the post-op development of morbidities have not been addressed in previous studies comparing CABG with MT. Costs of CABG and the morbidities are very high. The place of contemporary medications is undefined at the present time. In current guidelines(102)which are based on the above citedstudies, CABG is the Class 1 recommendation for many patients with ischemic heart disease, therefore new studies based on contemporary medical therapy and considering the post-CABG morbidities and costs are essential.

### **STUDY LIMITATIONS**

We did not discuss infrequent or more minorpost-CABG morbidities such assurgical re-exploration(19), gastrointestinal problems(18), orthopedic (shoulder) disorders(63), and pericarditis(67) but these are also significant patient concerns.

### **CONCLUSIONS**

Considering newer and contemporary medications, the burden of morbidities, and the substantial costs of CABG and morbidities following CABG strongly suggests that new era studies comparing in a more comprehensive manner to include longer term post-op morbidities CABG with contemporary MT should be a high value clinical research target.

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