Chapter 25

# Impact of Renal Dysfunction and Peripheral Arterial Disease on Post-Operative Outcomes After Coronary Artery Bypass Grafting

Muhammad A. Chaudhry, Zainab Omar and Faisal Latif

Additional information is available at the end of the chapter

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## 1. Introduction

In-hospital and long-term outcomes after Coronary artery Bypass grafting (CABG) are impacted by various factors including age, gender and various co-morbidities including chronic obstructive pulmonary disease, hypertension, diabetes Mellitus, dyslipidemia, chronic kidney disease (CKD), Peripheral arterial disease (PAD) and even connective tissue disorders such as systemic lupus erythematosus, and rheumatoid arthritis.

Both CKD and PAD have been considered a major risk factor for morbidity and mortality post-CABG [1]. Therefore, both are always considered as a variable when calculating risk for perioperative mortality in patients undergoing CABG in the popular EUROSCORE and society of Society of Thoracic Surgeons National Cardiac Surgery Database scoring system [1,2].

We will discuss the degree of importance of these co-morbidities along with the epidemiology, underlying proposed pathogenetic mechanisms, significant associated co-factors, and also highlight the pertinent existing data on these parameters.

## 2. CKD and its impact on outcomes after CABG

Chronic kidney disease is defined as derangement in renal function for a period of at least six months. It is broadly divided into five stages based on creatinine clearance or glomerular filtration rate (GFR) obtained from either Cockcroft-Gault or modification of diet in renal disease (MDRD) equations [3,4]:

Cockcroft-Gault equation: Creatinine Clearance (ml/min) = [([140 − age] × weight [kg])/72 × serum creatinine (mg/dl)] (× 0.85 for women),

MDRD equation: GFR (mL/min/1.73 $m^2$) = 175 × (serum creatinine)$^{-1.154}$ × (Age)$^{-0.203}$ × (0.742 if female) × (1.212 if African American) (conventional units)

Creatinine clearance or glomerular filtration rate (GFR) represents renal function. Declining values represent a decline in renal function. Stage 1 refers to glomerular filtration rate (GFR) >90 ml/min and is generally asymptomatic. GFR between 60-90 ml/min is stage 2 CKD. Stage 3 is GFR between 30 and 60 ml/min and is further subdivided into Stage 3A (GFR 45-60 ml/min) and Stage 3B (GFR 30-45 ml/min). Stage 4 is defined by GFR between 15-30 ml/min while GFR <15 ml/min signifies Stage 5 and is considered an indication for renal replacement therapy i.e. dialysis. The most common etiological factors for CKD include diabetes mellitus and hypertension resulting in diabetic nephropathy and hypertensive nephrosclerosis, respectively.

The presence of CKD is considered a major independent predictor for development of coronary artery disease (CAD). An analysis from the atherosclerosis risk in communities (ARIC) study, Manjunath et al demonstrated that in 15,350 subjects with a mean follow up of over 6 years, there was a significant increase in acute coronary syndrome events in patients with stage 3 and 4 CKD (14.2%) compared with 5.5% in patients with stage 1 CKD (HR 1.38 (1.02, 1.87). Additionally, with every 10 ml/min/1.73 $m^2$ decline in GFR, there was a progressive increase in the incidence of cardiac events [5].

### 2.1. Proposed pathogenic mechanisms

Many factors contribute in the mechanisms associated in the renal contribution to increased risk of cardiovascular events. We briefly discuss a few here: Impaired renal function is associated with reduced erythropoietin synthesis and consequent anemia, which has been associated with cardiovascular disease [6]. Reduced 1, 25 (OH) vitamin D synthesis is associated with increased parathyroid hormone levels and higher prevalence of vascular calcification and arteriosclerosis [7].

Abnormal calcium phosphate metabolism is a consequence of renal dysfunction and it has a strong association with increased adverse cardiovascular events. Hyperphosphatemia and hypercalcemia are distinctly independent risk factors leading to a greater occurrence of cardiovascular events in patients with CKD and additionally, are also associated with poor surgical outcomes in patients undergoing CABG. Increased calcium-phosphate product greater than 55 and hyperphosphatemia escalates the development of secondary hyperparathyroidism which has been linked to increased osteoclastic activity and enhanced calcium-phosphate precipitation in the vasculature. There is also increase in the number of protein receptors in vessel cell membrane which increases deposition of calcium. In patients with CKD, vitamin D deficiency is also present even in the early stages. Vitamin D levels have a pivotal role in calcium-phosphorus homeostasis, regulation of parathyroid hormone (PTH), and bone metabolism and turnover. Three plausible mechanisms have been suggested in the protective effects of vitamin D against cardiovascular disease mortality are that vitamin D can inhibit various foci of inflam-

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mation which is a key pathogenic mechanism in atherosclerosis; vitamin D also has an anti-proliferative effect on myocardial cell hypertrophy and proliferation and prevents remodeling which underlies the pathogenesis of congestive heart failure and vitamin D acts as an inhibitory endocrine regulator for the renin-angiotensin system, which triggers the cascade of hypertension and decompensated heart failure[8]. Thus, with low 1,25 hydroxy cholecalciferol levels, this effect is pronounced causing even further increase in cardiovascular risk.

We will discuss the outcomes of patients with CKD with the two modes of revascularization namely percutaneous and then, surgical. Additionally, we will take into account the impact of various comorbidities such as diabetes, dyslipidemias with respect to lipoprotein levels as well as the role of oxidative stress in this patient population.

Although long-term mortality may improve with surgical revascularization in dialysis patients with coronary artery disease, perioperative mortality continues to remain higher among patients with end-stage renal disease (ESRD) requiring CABG. Various studies have compared the outcomes of percutaneous coronary intervention (PCI) versus CABG and showed that mortality is not different [9-11]. However, these studies were from the 1990s and percutaneous techniques have been refined since then with improved outcomes. Newer studies are required to compare outcomes of percutaneous versus surgical revascularization.

### 2.2. Outcomes with percutaneous coronary intervention

In hemodialysis dependent patients (CKD stage 5), clinical outcomes of PCI are especially poor. Before the advent of coronary stents 20 years ago, when percutaneous revascularization was performed with balloon angioplasty alone, it was found that patients with ESRD experience a higher rate of coronary restenosis and recurrent angina, when compared to patients without ESRD [12]. In another case control study of twenty patients with ESRD and 20 age and sex matched controls without renal disease, it was shown that the rate of restenosis was 60% in ESRD patients, as compared to 35% in patients without renal disease. Restenosis was found to be dependent on size of vessel dilated and there was increased prothrombotic risk secondary to increased fibrinogen concentrations [13].

Many patients with ESRD experience silent ischemia. The possible mechanism being uremic polyneuropathy and therefore, may not experience typical ischemic symptoms.

In a prospective study of 5327 patients undergoing percutaneous coronary intervention (PCI) with a follow up of over five years, rate of death or myocardial infarction at one year was 1.5% in CKD patients with creatinine clearance >70 ml/min, 3.6% in patients with creatinine clearance between 50-70 ml/min, 7.8% between 30 and 49 ml/min and 18.1% with creatinine clearance less than 30ml/min. This study showed a progressive increase in adverse outcomes with worsening renal function. CKD was a strong predictor of adverse cardiovascular events including death and MI [14].

### 2.3. CABG in patients with renal dysfunction

Even though conflicting studies exist, a large study has shown that although there is increased risk of mortality in patients with ESRD undergoing CABG when compared to pa-

tients without significant renal disease, it still portends a better outcome in terms of mortality when compared to percutaneous revascularization in this patient population [15].

### 2.4. Hard endpoints after CABG

It has been shown that the lower the GFR, the worse the mortality after CABG. In a study of 2067 patients, it was found that estimated GFR was a powerful and independent predictor of mortality in multivariate analysis. Estimated average GFR in patients who died was 57.9+/-17.6 mL/min per 1.73 $m^2$ mg/dl, as compared to 64.7 +/- 13.8 mL/min per 1.73 $m^2$ in those who survived at an average follow-up for 2.3 years [16].

In a database review of 483,914 CABG patients over a three year period, it was shown that the post-operative mortality rates for stage 2, stage 3, and stage 4 CKD patients were 1.8%, 4.3% and 9.3 % respectively. Also, there was a higher incidence of stroke, need for re-operation, sternal infection, prolonged mechanical ventilation greater than 48 hours and a hospital stay of longer than two weeks [17]. In a prospective study of 15,500 CABG patients over a five year period, it was shown that dialysis dependent patients with CABG had higher risk of in-hospital mortality as compared to non- dialysis dependent CABG patients (12.2% as compared to 3.1%) and also significantly higher risk of mediastinitis (3.6 vs. 1.2%) [18].

One of the largest initial studies on CABG outcomes in ESRD patients 13 years ago was a retrospective study on 82 patients in which patients had a mean follow-up of 3 years. 18.5 % of the patients had left ventricular ejection fraction (LVEF) <0.45 and the aortic cross clamp time was fairly good at 50 ± 3 minutes [10]. Mean number of grafts was 2.3. Sixty-two percent of patients received left internal mammary grafts. In this study, 30-day mortality rate was 14.6%, and the mean survival rate at one, three and five years was 71%, 56% and 39% respectively. Thirty day mortality was 14.6% due to a variety of causes including myocardial infarction, cardiac arrest or cardiac tamponade. This study showed that although there was high peri and post- operative as well as long term mortality in ESRD patients undergoing CABG, there was a significant improvement in functional status as a result of CABG. The use of internal mammary artery grafts was related with less in-hospital mortality as well. Perioperative atrial fibrillation occurred in 12.1 % of patients within the first thirty days. With patients having preoperative Newyork Heart Association (NYHA) class III or class IV symptoms, LVEF less than 45% and age greater than 60 years, there was higher long term mortality. The incidence of post- operative bleeding and sternal infection was 3.6% which was higher when compared to patients not on dialysis.

Patients with CKD have a poor baroreceptor reflex. Therefore, they do not adjust very well in conditions like post-operative hypotension. Therefore, poor cardiac output can be more symptomatic in this group of patients [19].

In a study of 2438 CKD patients undergoing CABG over a three year period, operative mortality was 4.8% in individuals with stage 3 CKD and 7.1% in individuals with stage 4–5 CKD while it was 2.2% in those without significant CKD [20]. CKD was associated with increased post-operative blood transfusion requirement, acute kidney injury superimposed on CKD,

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myocardial injury and cardiac arrest. Use of blood transfusions and acute kidney injury were strongly associated with in-hospital death in CKD patients.

### 2.5. Impact of mode of dialysis on outcomes after CABG

The mode of dialysis is equally important in influencing CABG outcomes, namely peritoneal (PD) and hemo-dialysis (HD). Peritoneal dialysis has been associated with worse outcomes when compared with hemodialysis [21,22]. Following CABG, diaphragmatic splinting, atelectasis and hypoxemia can occur after early post-operative initiation of PD. In a retrospective analysis of 105 patients, among whom 40 were on PD, and 65 on HD and all patients had been on dialysis for at least 2 months prior to CABG, it was demonstrated that the incidence of post- operative dialysate leak and peritonitis was 10% and 12.5% respectively in patients on PD. On the other hand, incidence of arterio-venous access thrombosis was 4.6% in patients on HD. Besides older age, PD was an independent risk factor of high operative mortality (adjusted OR for in hospital mortality in PD patients was 22.58). Actual causes of mortality included sepsis, cardiac arrest, pneumonia and gastrointestinal bleed. Chief infective organisms in septic patients were Staphylococcus aureus (coagulase negative), Pseudomonas aeruginosa, and Enterococcus faecalis [21]. Risk of peritonitis is higher if gastroepiploic artery is harvested for CABG as it requires diaphragmatic incision [22].

### 2.6. Impact of comorbidities in patients with CKD undergoing CABG

Diabetes and hypertension are the most common causes of CKD and they are also the major risk factors for coronary artery disease, therefore, the incidence of CAD is higher in these patients.

#### *2.6.1. Diabetes*

Diabetes is present in almost one third of CKD patients undergoing CABG and is considered a strong predictor of mortality in this patient group [23,24].

Szabo et al showed in a study of 2779 CABG patients that in 19.4% of patients with diabetes, the cross-clamp and cardiopulmonary bypass times as well as the need for inotropic support, transfusion of blood products and progression of renal failure were all higher in patients with CKD. Additionally, the incidence of post-operative stroke was greater in diabetic patients (4.3% vs. 1.7%). Five year survival rate was 84.4% in diabetic group while it was 91.3% in the non- diabetic group [25]. Another study showed that diabetes was an independent major predictor of morbidity and mortality in CABG patients. In 12,198 patients, it was observed that the diabetic group had higher rates of post-operative mortality (3.9% vs. 1.6%) and stroke (2.9% vs. 1.4%). The five and ten year survival rates were 78% and 50% among patients with diabetes as compared to 88 and 71% in the non-diabetic group [26]. Morris et al demonstrated in a study of 5654 patients undergoing CABG that the five year survival rate for diabetic patients was 80% as compared to 91% for non- diabetics [27]. Outcomes of CABG are improved in diabetic patients who undergo grafting of internal mammary arteries, with two being better than one. In a retrospective analysis of 4382 patients undergoing CABG, it was shown at 10 year follow-up that bilateral internal mammary ar-

tery grafting in addition to SVGs in diabetic patients improved survival and decreased need for revascularization compared with single internal mammary artery grafting along with SVGs [28]. The strong correlation between diabetes and cardiovascular outcomes including survival and myocardial infarction is due to the diffusely extensive and rapidly progressive nature of atherosclerotic coronary artery disease (CAD) in this group of patients. Various other factors such as oxidized low-density lipoproteins (LDL), hyperglycemia causing adverse metabolic shifts, deranged fibrinolysis, increased coagulability, and advanced renovascular hypertension resulting in change in vessel architecture also contribute to the progressive nature of CAD in diabetics. There is increased tendency for LDL induced atherosclerotic plaque formation and there is greater predisposition to thrombosis due to increased blood viscosity secondary to high plasma protein levels. There is also platelet and endothelial dysfunction and increased production of thromboxane A2 and von- willebrand factor along with decreased production of prostacyclins which creates a procoagulant state. Coronary vasodilation is impaired as a result of loss of the hyperpolarizing mechanics normally present in endothelial cells. Autonomic neuropathy in diabetes increases cardiac chrontropic workload and subsequently leads to greater oxygen demand even at rest. There is enhanced vascular tone in the coronary atherosclerotic plaque area leading to further reduction in blood flow, producing orthostatic changes which leads to reduction in coronary perfusion pressure and mitigates warning signs of ischemia such as angina [27,29-32].

*2.6.2. Hypertension*

Hypertension has also been associated with worse post CABG outcomes. In a multi centre study of 2417 patients among whom patients were categorized into patients with normal preoperative blood pressure, isolated systolic hypertension (systolic blood pressure >140 mm Hg), diastolic hypertension (diastolic blood pressure >90 mm Hg), or a combination of systolic and diastolic hypertension. It was found that isolated systolic hypertension was associated with a 40% greater risk of adverse outcomes such as stroke, renal failure, congestive heart failure and all cause mortality after CABG. Even after correction for confounding risk factor adjustment, the increased risk of adverse outcomes was significantly more pronounced in hypertensive patients [33].

*2.6.3. Impact of other risk factors*

In a study of 936 hemodialysis patients to elucidate correlation of recognized risk factors in CKD patients, it was found that correlation with diabetes, smoking, African-American race and increasing age of above fifty- five years was strong. It is suspected that non-traditional risk factors like uremic environment and hemodialysis procedure using arteriovenous fistulae and high output state associated with these fistulae also impact the outcomes after CABG adversely [34].

Dyslipidemia with a high LDL is a classic risk factor for development of CAD in the general population. However, it is likely not a major risk factor in patients with advanced renal disease. In a study of 210 dialysis dependent patients compared with 223 control subjects with normal renal function, it was found that high density lipoprotein (HDL) levels were low

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while intermediate and very low density lipoprotein (IDL and VLDL) levels as well as triglyceride levels were higher in dialysis patients while there was no significant difference in LDL levels [35]. In part, the role of decreased renal metabolism of lipids leads to a decreased level of LDL is likely the cause.

Atherosclerosis is regarded as an inflammatory process [36]. It has also been shown that in dialysis-dependent patients, oxidative stress is increased resulting in a pro-inflammatory environment. As a result, incidence of cardiovascular events is increased. In a comparison study of 28 healthy subjects and 31 patients with renal disease, it was discovered that glutathione peroxidase and superoxide dismutase activities were increased in patients on HD while total glutathione and glutathione reductase activity is reduced resulting in increased oxidative stress [37].

#### *2.6.4. Impact of renal artery stenosis on CABG*

Renal artery stenosis (RAS) can lead to refractory hypertension and gradual deterioration in kidney function. The presence of underlying RAS and its effect on CABG outcomes has been studied and variable results have been obtained. In a study of 798 patients undergoing isolated CABG with 18.7% having renal artery stenosis (>50% stenosis), acute renal failure developed in 10.2% of patients post procedure. The mortality rate was 14% in patients who developed acute renal failure (ARF) post operatively, while it was 0.2% in patients who did not develop ARF. However, presence of RAS was not associated with development of ARF post-operatively [38].

In a series of eighteen patients undergoing CABG who also had varying degrees of RAS with mean serum creatinine of 2.6±2.7 mg/dl, RAS was not associated with adverse outcomes post-operatively [39].

### 2.7. Post-CABG complications in patients with CKD

Besides relatively increased short-term mortality in patients with CKD undergoing CABG, they also encounter increased morbidity from infections, blood transfusions, and stroke. In a retrospective analysis of 3954 patients where 82.7% patients had creatinine <1.5 mg/dl, and 16% had a serum creatinine level between 1.5 and 3.0 mg/dl, it was demonstrated that patients with a serum creatinine level >1.5 mg/dl had a mortality of 7% compared to 3% in patients with serum creatinine <1.5 mg/dl. Additionally, patients with a higher serum creatinine level had a higher incidence of requiring prolonged mechanical ventilation (15% vs. 8%), risk of stroke (7% vs. 2%), and bleeding complications (8% vs. 3%). Three infectious complications (mediastinitis, graft harvest site infection, and chest wound infections) were not different among these groups, whereas the occurrence of pneumonia and endocarditis was significantly higher in patients with a higher serum creatinine [40].

#### *2.7.1. Prolonged mechanical ventilation*

It is believed that the prolonged mechanical ventilation and the need for re-intubation after CABG in patients with renal dysfunction are due to a compromised ability to eliminate fluid

volume, thereby predisposing patients to impaired alveolar gas exchange. Additionally, renal failure would result in decreased metabolism and elimination of sedative, anxiolytic and analgesic drugs leading to impairment of respiratory drive.

A study showed that ventilatory complications such as need for greater than 48 hours of mechanical ventilation and re- intubation is high in patients with significant renal dysfunction undergoing CABG, when compared to patients with normal or mild renal dysfunction [40]. Another study showed a stepwise increase in need for prolonged mechanical ventilation as the renal function deteriorates. In this study, the ventilator dependence rate greater than 24 hours was 8.6%, 14.7%, and 20.2%, as the stage of CKD increased [20].

*2.7.2. Bleeding complications post CABG*

Platelet dysfunction is a consequence of uremia in patients with CKD and they are more prone to bleeding complications requiring blood transfusion. A study showed that significant renal dysfunction (serum creatinine of 1.5 to 3.0 mg/dl) significantly increases bleeding complications such as disseminated intravascular coagulation, gastrointestinal hemorrhage, or thoracic hemorrhage sufficient to require reoperation, or result in cardiac complications such as cardiac arrest and low cardiac output [40].

The association of transfusion with mortality is particularly interesting. CKD impairs erythropoiesis in the bone marrow due to reduced synthesis of erythropoietin, and is associated with pre-operative anemia of chronic disease and also leads to increased risk of bleeding after CABG [41]. Strategies to optimize preoperative hemoglobin and to minimize post-operative transfusion could possibly improve operative outcomes in patients with CKD. Transfusion needs are also increased as a result of uremia induced platelet dysfunction which can cause an increase in bleeding tendency in these patients.

*2.7.3. Other post-CABG complications in CKD*

Interestingly, occurrence of post-operative atrial fibrillation has been shown to increase with worsening renal function as well. In a study, the occurrence of atrial fibrillation was 22.2%. 19.2% and 16.5% in severe, moderate and mild CKD patients respectively [20].

Different studies have demonstrated the increased incidence of stroke in patients with CKD. In an analysis on 2438 patients undergoing CABG, the incidence of stroke was 3%, 2.7% and 1.7% in severe, moderate and mild CKD groups [20].

Infectious complications occur more commonly in patients with CKD undergoing CABG as well. A study showed that deep sternal infection, pneumonia, septicemia, infection involving a leg vein and overall infection rate was higher as the CKD stage increased (9.0%, 5.1%, and 3.5% in severe, moderate and mild CKD respectively) [20].

### 2.8. Impact of aortic cross clamp time in CABG

Aortic cross clamping time is the period during which an occlusive clamp is placed on the ascending aorta close to the innominate artery as a part of achieving cardioplegia before proceed-

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ing with coronary bypass grafting. The mechanism of induction of cardioplegia involves prevention of repolarization of myocardial cell membrane due to the high potassium concentration of the cardioplegic fluid causing inactivation of the sodium channels which initiate the action potential. The hypothermic fluid of cardioplegia induces asystole. When the solution is administered in the aortic root it is termed antegrade and when administered in the coronary sinus, it is called retrograde. Myocardial protection with cardioplegia decreases the energy demands of the heart by arrest of the contractile apparatus. This is considered to be an extension of ischemia tolerance which is considered to minimize the deleterious effects of induced cardiac arrest. However, it still is desirable to keep duration of cardioplegia at a minimum as the aortic cross-clamp time is an important factor in predicting mortality in cardiac surgery and the lesser it is, the better the outcomes. The metabolic processes resulting from cardiac ischemia include sudden cessation of normal aerobic cardiac metabolic events, reduction in creatine phosphate, initiation of anaerobic glycolysis, and build-up of lactate and alpha glycerol phosphate as well as nucleotide metabolites. This is associated with contractile impairment and electrical pathway alterations consistent with typical EKG changes. The myocardial demand for high energy phosphate substrates is increased when the availability of adenosine triphosphate decreases. The predominant mode of energy derivation is switched to anaerobic glycolysis in the ischemic tissue. With early ischemic component, contractile activity and later on ion transport utilizes available adenosine triphosphate but gradually with the increase in ischemic time period, the metabolic demands undergo a compensatory reduction to prevent further ischemic damage. Irreversible injury in cardiac muscle is highlighted by very low levels of adenosine triphosphate, lack of energy production even by anaerobic mode, progressive accumulation of hydrogen ions, adenosine monophosphate, and lactic acid with a consequently high osmotic load, mitochondrial swelling and amorphous densities in matrix, and loss of integrity of the sarcolemmal membrane. The precise mechanism of pathogenesis is still elusive. In animal models, severe ischemia causes irreversible cell injury and death in one hour while with less severe ischemia in the mid and sub-epicardial myocardium, survival is possible up to six hours. Irreversible injury and cell death after six hours is inevitable. The ischemic injury changes reverse to a certain degree after reperfusion but how quickly and completely this transformation occurs is highly variable ranging from minutes to days. Aerobic metabolism is restored early while adenine nucleotide pool and stunning resolve slowly [42].

Systolic dysfunction with reduction in LVEF <0.40 is also an indicator of poor prognosis in CKD patients undergoing CABG. In a comparison study of aortic cross clamp times in patients with normal versus reduced ejection fraction in 27,215 patients in which 99.8 % received antegrade, retrograde or combined cardioplegia, it was found that prolonged aortic cross clamp time was an independent predictor of mortality [43]. It was shown that a combination of reduced LVEF and prolonged aortic cross clamp time especially with CKD compounds the ischemic effects and increases overall risk of perioperative mortality. In this study, the mean aortic cross clamp time was 68± 20 minutes, number of distal grafts was 3.1± 1.4 and 68.7% of patients underwent grafting of the left internal mammary artery. The incidence of pulmonary complications was 12.2% and stroke was 2.27%. Fifty-two percent of the patients had baseline hypertension, 29% had diabetes and 7% were dialysis dependent.

It has been shown that patients undergoing CABG with off pump or beating heart technique experience improved post-operative outcomes and less perioperative mortality. In a study

of 638 patients with acute coronary syndrome undergoing emergency CABG out of which 240 were operated off pump and 398 had standard on-pump CABG. 14.5% of patients were in cardiogenic shock along with serum creatinine greater than 1.8 mg /dl. Follow-up was up to 5 years. The results showed that in the off pump CABG group, in-hospital outcomes were significantly better. With off-pump CABG, skin incision to culprit lesion revascularization time was significantly reduced. There was less requirement for prolonged mechanical ventilation, less need for inotropic support, less incidence of atrial fibrillation, lower stroke rate (2.5 % vs. 6.7%), shorter intensive care unit stay and less sternal wound healing complications (2.5% vs. 3.5%). The overall hospital mortality rate was also reduced (5.7%) as compared to those on cardiopulmonary bypass (8.6%) [44].

## 2.9. Conclusion

As we have discussed, numerous studies have shown that patients with CKD have worse outcomes including an increased mortality and other complications after undergoing CABG, when compared to patients without CKD. However, an increasing number of patients with ESRD continue to undergo CABG and additionally, these patients are getting more complex a higher presence of comorbidities including diabetes, hypertension and obesity [Figure 1]. However, fortunately, in-hospital mortality rates have declined remarkably from over 31% to 5.4% in patients with ESRD (versus 4.7% to 1.8% among patients without ESRD) [45]. However, the mortality in ESRD patients remains 3-fold higher which indicates the need of continued work to improve outcomes in these patients [Figure 2].

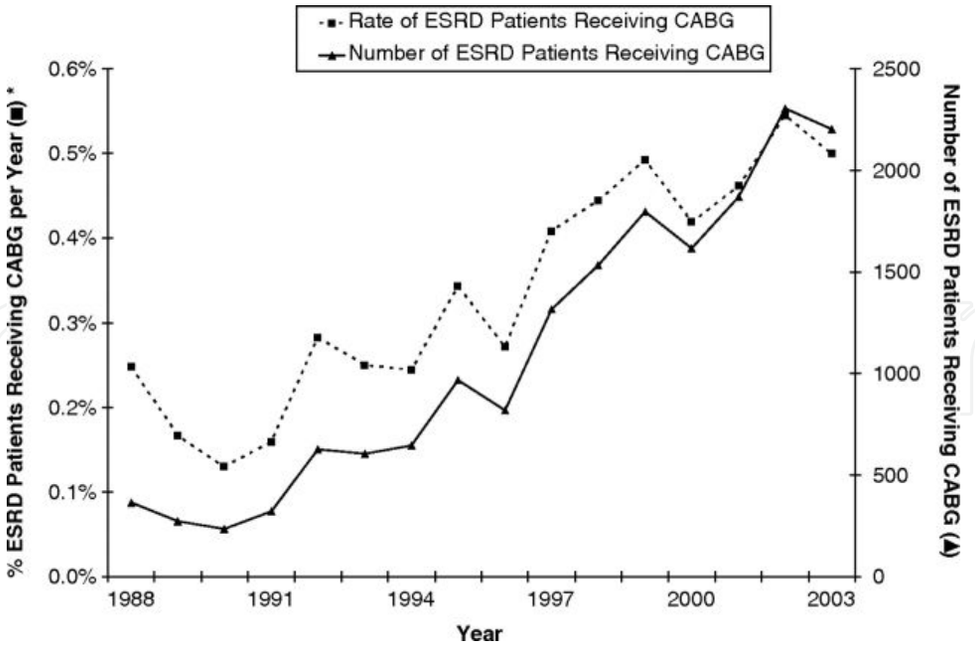


**Figure 1.** Graph depicting the increasing trend in the number of patients with end-stage renal disease (ESRD) undergoing coronary artery bypass grafting (CABG) over a 15-year period (Data from Parikh DS, Swaminathan M, Archer LE, et al. Perioperative outcomes among patients with end-stage renal disease following coronary artery bypass surgery in the USA. Nephrol. Dial. Transpl 2010; 25(7):2275-2283).

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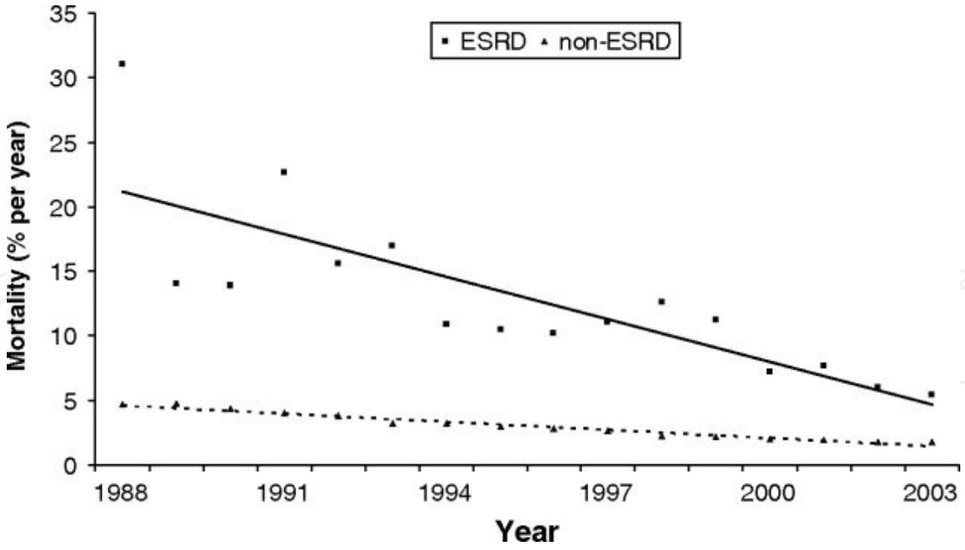


**Figure 2.** Graph depicting the constantly decreasing trend in mortality of patients with end-stage renal disease (ESRD) undergoing coronary artery bypass grafting (CABG) compared to patients without ESRD, over a 15-year period (Data from Parikh DS, Swaminathan M, Archer LE, et al. Perioperative outcomes among patients with end-stage renal disease following coronary artery bypass surgery in the USA. Nephrol. Dial. Transpl 2010; 25(7):2275-2283)..

Studies have shown that cardiovascular risk modification using ACC/AHA guideline recommended therapies for CAD, such as aspirin, beta blockers, hydroxymethyl coenzyme A (HMG-Co A inhibitors popularly known as statins) and angiotensin converting enzyme (ACE) inhibitors are used less frequently in patients with CKD when compared to patients without CKD [14,46-48]. These medications have been shown to decrease the risk of cardiovascular events across the population at risk. However, it is also true that many of those trials excluded patients with significant renal disease, which therefore poses a questions mark on their efficacy in patients with advanced CKD. Randomized trials to evaluate efficacy of these medications in patients with advanced renal dysfunction are warranted.

## 3. Peripheral arterial disease and CABG outcomes

The presence of peripheral arterial disease (PAD) plays a significant role in the potential morbidity and mortality of patients undergoing CABG. Coexisting CAD and PAD significantly influences long term survival adversely [49,50]. In the Coronary Artery Surgery Study (CASS), PAD was found to carry a higher risk of mortality even when compared to patients who had previously experienced myocardial infarction and angina [51].PAD is included as a major risk factor when calculating risk of mortality in patients undergoing CABG [1,2]. Non-invasive diagnostic testing for PAD includes segmental pressure measurement, treadmill stress, and Doppler ultrasound with the most significant information provided by the ankle-brachial index (ABI). Normally it is greater than 1.0 while <0.9 is considered abnormal. In patients with critical limb ischemia, the ABI is commonly <0.4. It is suspected that in PAD patients, poor surgical outcomes after CABG could be related to rapid progression of atherosclerotic coronary artery disease and more extensive small vessel

CAD with poor target foci for intervention resulting in higher mortality rates. Also the highly variable rates of CAD progression in patients with and without PAD leads to poor outcomes as well [52].

In comparison with PCI, CABG has been shown to improve mortality significantly more in patients with PAD. Data from 1305 consecutive patients undergoing coronary revascularization (PCI, n = 341; CABG, n = 964) between 1994 and 1996 showed that patients with PAD undergoing CABG had better survival at 3 years when compared to PCI (hazard ratio 0.68; 95% CI 0.46-1.00; p = 0.05) [53].

In a retrospective analysis on 1,164 consecutive patients who underwent CABG (370 with PAD), it was shown that PAD did not impact 30-day mortality. However, multivariable analysis showed that patients with PAD had a significantly worse 9-year survival rate compared to patients without PAD (72.9% vs. 82.8%; adjusted hazard ratio, 1.7; p = 0.004) [54]. Trachiotis et al studied long-term survival in 11,830 CABG patients, 744 of whom had LVEF <0.35. Among all patients, regardless of ventricular function, diabetes was linked with a 59% increase in the relative risk of death [55]. It was shown by Birkmeyer et al that patients undergoing CABG with history of PAD had a 20% five-year mortality rate as compared to 8% for those without known PAD [56,57]. Kaul et al showed that after risk factor adjustment, patients with PAD had mortality rates twice as high as patients without PAD [58]. Loponen et al showed in a multicenter study on 3000 patients that patients with PAD undergoing CABG had a 71% greater in-hospital mortality rate than those without PAD [59].

In a ten year prospective study of 8000 patients with PAD undergoing CABG, it was seen that they had a higher incidence of various intra- and post-operative complications including arrhythmias, stroke, pulmonary complications, low cardiac output state, longer hospital stay, infections, and acute renal failure. These results have been borne out by other studies as well [60-63].

The anatomic diversity of obstructive atherosclerotic disease process is particularly interesting. Patient can have isolated cerebrovascular disease involving carotid arteries, or lower extremity arterial disease or a combination thereof. It has been shown that as the number of involved arterial beds increases, the mortality increases. In a study on 2817 patients undergoing CABG, it was demonstrated that when compared to patients with CAD alone, the mortality was 1.6 times, 2.5 times, and 2.8 times higher for patients with concomitant cerebrovascular disease, lower extremity arterial disease and both cerebrovascular and lower extremity arterial disease, respectively [64]. Another study found that in patients younger than 40 years, the most common pattern of lower extremity arterial disease is aortoiliac disease while in patients older than 40 years, femoro-popliteal disease is predominant and causes intermittent claudication in 65% of these patients [65].

Commonly, patients with iliac disease have hemodynamically significant stenoses, while majority of patients with femoral disease have total occlusions characteristically involving long segments of the superficial femoral artery. Consequently, percutaneous revascularization of the femoral arterial segments is technically difficult as compared to iliac endovascular repair. The risk factors associated with PAD are similar to those for CAD, with diabetes

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and smoking being the major ones. Diabetes is a major predictor of outcomes of CABG in patients with PAD. It is associated with more than 50% of major amputations in patients with PAD. In a study of 261 patients by Jonason et al (47 diabetic and 224 non diabetic), at six year follow up, showed an incidence of gangrene in 31% of diabetics as compared to 5% in non-diabetics [66]. Also hypertension, strong family history of premature atherosclerotic vascular disease, and hyperlipidemia are also contributory. Progression to severe ischemia or amputation in symptomatic patients with intermittent claudication occurs at 1.4% per year with poor prognosis in patients with diabetes and smoking [66,67].

The rate of all-cause mortality in patients with large-vessel PAD compared with the normal population is three times greater, while the risk of cardiovascular mortality is six-fold more, with the most common etiology being myocardial infarction or stroke [67]. In an analysis of 900 patients with LVEF of 0.35 or less, among whom 38% were diabetics, all-cause mortality was 26% in diabetics and 24% in non-diabetics ($p>0.05$). However, 4 -year re-hospitalization rates were 85% in diabetics and 69% in non-diabetics ($p = 0.0001$). The incidence of superficial sternal wound infection was 3.3 times higher and of renal failure was 2.2 times greater in diabetic patients as compared to non- diabetics [68].

Finally, a combination of CKD and PAD is even worse for the overall outcomes of patients undergoing CABG. In a prospective study of 36,641 CABG patients over a ten year period, long term survival rates of patient groups stratified as non- diabetic, diabetic with PAD and CKD, and diabetics without PAD and CKD were determined. The follow up was equivalent to 154,140 person-years. Annual mortality rates for non-diabetic and diabetic groups were 3.1 deaths per 100 person-years and 4.4 deaths per 100 person-years, respectively. The annual mortality rate for diabetic subjects with CKD, PAD, or both was significantly higher at 9.4 deaths per 100 person-years. Thus, patients undergoing CABG who are diabetic along with having PAD and CKD are at highest mortality risk over long term follow up of 10 years [69].

### 3.1. Impact of cerebrovascular disease on outcomes of CABG

Carotid artery stenosis is an important risk factor in determining post CABG outcomes such as stroke and additionally, has a direct impact on perioperative mortality [70,71]. Duplex ultrasonography or contrast-based techniques can be utilized pre-operatively in high risk patients with age greater than 65 years and multiple risk factors such as diabetes mellitus, hypertension, and previous transient ischemic attacks or stroke. In case of severe carotid disease, surgical planning might need to include carotid endarterectomy along with CABG simultaneously versus consideration for endovascular repair of carotid disease pre-operatively.

In a study of 582 patients undergoing CABG, preoperative carotid artery duplex scans were performed to assess the presence of asymptomatic carotid artery stenosis. >50% uni- or bilateral stenosis was present in 22% while >80% uni- or bilateral stenosis was present in 12% of patients. The post-operative hemispheric stroke rate in patients with carotid stenosis >50% was 3.8% as compared to 0.34% in patients without carotid

stenosis (p = 0.0072). Also the risk of hemispheric stroke was 5.3% in patients with unilateral 80% to 99% stenosis, or bilateral 50% to 99% stenosis, or unilateral occlusion with contralateral 50% or greater stenosis. Patients with a unilateral 50% to 79% stenosis did not suffer a stroke in this study [70].

In a study of 3344 patients undergoing CABG who were followed over a three year period to assess the effect of carotid artery stenosis on perioperative stroke and mortality, it was found that the clinical outcomes were directly related to the degree of carotid stenosis. Patients with carotid stenosis <60% had a significantly less risk of suffering perioperative stroke and mortality when compared to patients with >60% stenosis, especially patients with a totally occluded carotid artery [71].

These studies signify carotid artery disease as an important subset of patients with PAD which can adversely affect post CABG outcomes in terms of incidence of stroke and mortality rates.

### 3.2. Impact of microvascular disease on CABG

Microvascular disease, such as that which occurs in diabetic patients has also been shown to adversely affect outcomes after CABG. These complications generally stem from a cumulative poor glycemic control. In a study on 223 patients with diabetic retinopathy followed 11 years post-CABG, it was found that diabetic retinopathy was a strong independent predictor of overall mortality (relative risk [RR], 4.0), and repeat revascularization (RR, 3.0) [72].

### 3.3. Use of LIMA and SVG grafts

Use of internal mammary artery (IMA) grafts in patients undergoing CABG have been associated with improved short and long-term survival, increased patency and decreased perioperative mortality. However, in patients with significant PAD, it could be the major source of collateral flow to the lower extremities in patients with aorto-iliac disease. The finding that the mammary artery collateralized the iliac artery led to major treatment changes in all patients undergoing CABG [73]. Therefore, it is advisable to perform angiography of this conduit before referral for CABG in patients with PAD.

In a study on 21,873 patients among whom 87% underwent grafting of left IMA, and were followed for 7 years, there was a significantly decreased risk of mortality in all subgroups. Additionally, the incidence of stroke, repeat intervention, bleeding complications, mediastinitis or sternal dehiscence requiring surgery was less with use of IMA grafts. The adjusted mortality rate was 2.2% vs. 4.9%, and rate of stroke was 1.6% vs. 1.9% in patients undergoing IMA versus no IMA grafting, respectively. Infective mediastinitis or sternal dehiscence was seen in 1.1% of the LIMA group and 1.3% of the non-LIMA group [74].

It has been shown that use of LIMA grafts is even associated with lower in hospital mortality even in patients with a higher number of risk factors such as age greater than 70 years, elevated left ventricular end-diastolic pressure, left ventricular ejection

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fraction less than 40%, small body mass index, or clinical presentation in acute or emergency setting. So, there is a proven consistent trend of protective LIMA effect in high risk groups as well [75].

### 3.4. Impact of PAD on graft failure in CABG

A major cause of short-term mortality post CABG and therefore, poor surgical outcome is graft failure. In 1972, Lesperance et al reported that out of a total of 105 saphenous vein grafts (SVG) used during CABG, 20% had early occlusion [76]. In a review of SVG disease, Motwani and Topol showed an early SVG occlusion rate of 15% and elucidated the diverse etiology of SVG closure [77]. At one month post CABG, the major cause of graft failure is thrombosis. From a month to one year post CABG, intimal hyperplasia is the chief contributor while after one year, atherosclerotic changes have been primarily implicated. They also demonstrated that arterial runoff was the single most important determinant of short-term graft survival. Occluded vessels distal to the SVG anastomosis resulted in thrombosis and graft failures.

The internal diameter of the mid-LAD is approximately1.7 mm, while that of the saphenous vein is 4-5 mm. This difference leads to variable flow rates and slow flow velocity in the SVG as compared to mid-LAD. The sluggish flow causes red blood cell sledging and consequent thrombosis. The internal diameter of the IMA is almost equivalent the mid-LAD, and thus there is decreased risk of graft thrombosis. They also highlighted that LIMA graft in addition to matching favorable dimensions of native LAD, lacks valves, has less endothelial fenestrations, and has a greater resistance to trauma while it is being harvested [78]. Other advantageous physiological characteristics of the IMA include higher flow reserve and shear stress, greater nitric oxide and prostacyclin production leading to vasodilation and inhibition of platelet aggregation, appropriate relaxation response to thrombin, less vasoconstrictor sensitivity and high vasodilator sensitivity along with decreased number of fibroblast growth factor receptors thus reducing plaque formation [78].

In a patent population in whom both radial artery and SVG grafts were used for CABG, it was found that radial artery grafts fared worse than SVGs in patients with PAD [79].

### 3.5. Off pump CABG and standard CABG

Off pump CABG (OPCAB) is referred to as CABG without use of cardiopulmonary bypass or cardioplegia while on pump CABG is referred to the use of cardiopulmonary bypass and cardioplegia. There have been various studies which generally show benefits of OPCAB as compared to standard CABG. Benefits include less bleeding complications, stroke and renal failure after OPCAB.

In a retrospective analysis of 68,000 patients by Ractz et al, 9000 OPCAB revascularizations were performed with this group comprising many high-risk patients including those with >60 years of age, female gender, low LVEF, previous history of CABG, stroke, PAD, conges-

tive heart failure, calcified aortic disease, and renal failure. It was seen that the standard CABG group as compared to OPCAB group had higher rates of stroke (2.0% vs. 1.6%), higher bleeding complications (2.2% vs. 1.6%), and prolonged hospital stay by one day. At 3-year follow-up, the need for repeat revascularization was also greater in standard CABG versus the OPCAB group [80].

In another retrospective study by Mack et al in which 17401 patients were reviewed and 7283 received OPCAB, it was found that even in patients with PAD among other risk factors, patients undergoing OPCAB had improved mortality when compared to patients undergoing on-pump CABG (1.9% vs. 3.5%). The rate of complications including major bleeding, wound infection, atrial fibrillation, permanent stroke, gastrointestinal and respiratory complications, renal failure, myocardial infarction, and multiorgan failure was higher in standard CABG group [81].

In another study comprising 214 patients at high risk (high EuroSCORE) with >50% of patients with significant PAD, it was found that off-pump CABG was safer and was associated with less early post-operative complications including multi-organ failure [82].

Patients with PAD are likely to have complex atheromatous plaques in the arch of aorta which poses a risk for peri-operative stroke during manipulation for on-pump CABG surgery An analysis of 422 patients demonstrated that there was a significant reduction in post-operative stroke in patients who had OPCAB when compared to patients undergoing on-pump surgery (0.9% vs. 5.7%, p=0.007) [83]. Therefore, for patients with PAD needing CABG, OPCAB would help avoid manipulation of aorta and in turn, decrease post-operative cerebrovascular complications.

Over a period of time, an increasing body of evidence has indicated that OPCAB is better than on-pump CABG, especially in high-risk groups. This includes a significant benefit of OPCAB in patients with PAD as it reduces the risk of postoperative stroke. As it has been shown in the SYNTAX trial, which is the largest contemporary trial comparing PCI versus CABG, showed that the major risk with CABG appears to be the increased risk of stroke from it [84]. OPCAB can, at least reduce that chance which might improve the overall benefit of CABG in patients with advanced CAD.

## 4. Conclusion

Based on current data, there is sufficient evidence to suggest that diabetes, peripheral arterial disease, CKD, on-pump CABG, increased aortic cross clamp and cardiopulmonary bypass duration, lack of use of IMA graft are strongly associated with poor in hospital, short term and long term outcomes after CABG. Rigorous modification of these risk factors to the maximum possible extent preoperatively can result in further improvement of surgical outcomes following CABG.

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## Author details

Muhammad A. Chaudhry[1], Zainab Omar[2] and Faisal Latif[3]

*Address all correspondence to: faisal-latif@ouhsc.edu

1 Scripps Green Hospital, La Jolla, California, USA

2 King Edward Medical College, Lahore, Pakistan

3 University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma, USA

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