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OFF-PUMP CORONARY ARTERY BYPASS GRAFTING: LITERATURE REVIEW

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Coronary artery bypass grafting (CABG) is a commonly used revascularization technique for coronary artery disease. In addition to traditional on-pump CABG (ONCABG) with cardiopulmonary bypass (CPB), the operation can be performed on a beating heart without CPB and with no need for cardiac arrest, a procedure often called off-pump coronary artery bypass grafting (OPCABG).

Extracorporeal circulation, aortic cross-clamping and cardiac arrest in ONCABG predispose the body to inflammatory response, global myocardial damage, coagulation defects and ischemia-reperfusion injury. These are associated with low blood pressure, thrombosis, hyperthermia, tachycardia, leukocytosis and tissue edema which all have detrimental effects on the outcome of the surgery. In OPCABG, these complications were initially thought to be reduced.

Especially high-risk patients seem to benefit from OPCABG when compared to conventional ONCABG as it decreases the risk for mortality and morbidity shortly after discharging. On the other hand, the risk of incomplete revascularization and poor graft patency are higher in OPCABG procedures and reoperation is more often needed. Thus, in the long term, the benefit of OPCABG is not as significant. In low- and mid-risk population undergoing OPCABG no significant benefit has been reported.

In addition to mortality, the choice between the two is an issue of financial aspect, total hospital stay, risk of complications and the experience of the surgeon. Significant superiority to each other is yet to be proven. The choice between the two methods has still to be made individually for each patient undergoing CABG.

The purpose of this review is to search and gather literature and articles related to OPCABG, shortly discuss the role of it in cardiothoracic surgery, consider financial and healthcare aspects, compare short- and long-term outcomes and list some of the major complications of the procedure. Finally, there is a summary of the pros and cons, and the literature-based conclusions.

Articles related to OPCABG were searched on PubMed using search keywords myocardial revascularization or myocardial revascularization [Mesh] in combination with OPCAB or OPCABG or off-pump coronary artery bypass or coronary artery bypass, off-pump [Mesh]. Also, some basic information such as explanations of procedures, have been cited from organization websites and published articles related to cardiothoracic surgery.

Key words: myocardial revascularization, off-pump coronary artery bypass grafting, OPCABG

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ABBREVIATIONS

AF	atrial fibrillation
AKI	acute kidney injury
CABG	coronary artery bypass grafting
CAD	coronary artery disease
CPB	cardiopulmonary bypass
CVD	cardiovascular disease
ECG	electrocardiography
EF	ejection fraction
EuroSCORE	European System for Cardiac Operative Risk Evaluation
IABP	intra-aortic balloon pump
LAD	left anterior descending coronary artery
LIMA	left internal mammary artery (left internal thoracic artery)
LMCA	left main coronary artery
LVD	left ventricular dysfunction
LVEF	left ventricular ejection fraction
MI	myocardial infarction
ON- BHCABG	on-pump beating heart coronary artery bypass grafting
ONCABG	on-pump coronary artery bypass grafting
OPCABG	off-pump coronary artery bypass grafting
PCI	percutaneous coronary intervention
POAF	postoperative atrial fibrillation
POCD	postoperative cognitive dysfunction
RCT	randomized controlled trial
SIRS	systemic inflammatory response syndrome

1. INTRODUCTION

Cardiovascular disease (CVD) is the number one cause of death in the world. Three out of four CVD deaths occur in low- or middle-income countries. In 2016, an estimated 17,9 million people died because of CVDs which makes up to 31% of all deaths globally. In 85% of these deaths, the immediate cause was heart attack or stroke. (Cardiovascular diseases. WHO.) Coronary artery disease (CAD) is the most common underlying cause of death in developed countries (Caliscan et al. 2019). As a result, CVDs have a huge impact not only in healthcare but also in socioeconomics (Emelia et al. 2019).

Coronary artery bypass surgery or coronary artery bypass grafting (CABG) together with coronary angioplasty (PCI for percutaneous coronary intervention) are the most common clinical procedures for myocardial revascularization (Kowalewski et al. 2016). CABG was first time used as myocardial infarction (MI) intervention in 1960 by Robert Goetz and Michael Rohman in the United States (Goetz et al. 1960). A few years later PCI was invented and then performed on a human almost ten years later (Mehta and Khan 2002). Both CABG and PCI are still used, although for the past years PCI has become more common and often used due to improved procedural technique and advanced stent design. Nevertheless, CABG is a rather safe revascularization technique that is associated with a risk of 1-2% for intraoperative mortality among elective patients (Halkos et al. 2008). Emergency operations increase the risk for in-hospital and early mortality. On the other hand, emergency and salvage CABG is often needed in cases where PCI is not suitable or unsuccessful. Survival rate in emergency and salvage patients is acceptable except for patients who received cardiac massage during the surgery. (Axelsson et al. 2016.)

In CABG, the stenotic coronary artery or arteries are revascularized by blood vessels harvested from other parts of the body, known as grafts. Both veins and arteries can be used and have their advantages and disadvantages. Grafts are sutured to the target coronary arteries (surgical anastomoses) distally in relation to the occlusions and the normal flow of the blood is restored. The most common anastomosis is the left internal mammary artery (LIMA) to the left anterior descending artery (LAD) with supplemental grafts. (Montalescot et al. 2013). The superiority and safety of bilateral internal mammary artery (BIMA) compared to single internal mammary artery (SIMA) grafting in terms of long-term survival was reported in a large meta-analysis of observational studies conducted in 2016. Although BIMA grafting was associated with bigger risk for deep sternal wound infection, the long-term survival benefit outweighs this short-term risk. (Buttar et al. 2017.) The radial artery has been proposed to be used instead of a second internal mammary artery. The long-term graft patency of arteries is generally thought to be superior compared with vein grafts. Despite of the superiority of the radial artery, saphenous veins remain the most used grafts in CABG. (Montalescot et al. 2013.)

The conventional way of performing CABG is on-pump CABG (ONCABG) with cardiopulmonary bypass (CPB). In ONCABG the patient is connected to extracorporeal circulation (heart-lung machine), the aorta is clamped and the beating heart is arrested with cardioplegia solution.

Another form of CABG is off-pump coronary artery bypass grafting (OPCABG) in which the surgeon operates on a beating heart without extracorporeal circulation and the clamping of the aorta can be avoided (Buffolo et al. 1985). Target coronary artery is stabilized and blood flow is stopped while the anastomosis is being sutured (Calafiore et al. 1998). Also, quite often a shunt is placed inside the target coronary artery for a better view (Yeatman et al. 2002).

When comparing OPCABG and ONCABG solely on a technical aspect, the most important advantages of OPCABG are the avoidance of CBP and aortic manipulation since they are both usually followed by severe comorbidities such as renal failure, stroke, coagulation defects and systemic inflammatory response. These comorbidities were thought to be minimized by avoiding cardiac arrest, aortic cross-clamping and extracorporeal circulation. High expectations were set for off-pump method but its superiority compared to other surgical techniques remains unproven to this day. The operating technique and the difficulty to access the posterolateral wall of the heart are possibly the main technical disadvantages of OPCABG (Arom et al. 1999). A more detailed comparison between these two techniques is done in this review in terms of perioperative complications, short- and long-term outcomes, financial aspect and the role of surgeon and hospital experience.

2. RISK EVALUATION

The European Society of Cardiology (ESC) published guidelines on the management of stable coronary artery disease in 2013 and then later in 2018 guidelines on myocardial revascularization together with the European Association for Cardio-Thoracic Surgery (EACTS). Guidelines suggest that basic examination including laboratory tests, electrocardiography (ECG) and echocardiography at rest, cardiac magnetic resonance imaging (MRI) and ambulatory ECG known as Holter, should be tested when CAD is first suspected. After the patient has been diagnosed with CAD, it is essential to assess ischemia and the condition of the coronary arteries to identify lesions that require or are likely to benefit from revascularization. In addition, assessment helps finding the optimal drug therapy. Evaluation of the severity and stability of CAD includes both non-invasive and invasive examination. Non-invasive examination is recommended as the first-line testing. Invasive tests are recommended to carry out when findings in non-invasive examination are not enough or signs of severe stenosis are found. (Montalescot et al. 2013, Neumann et al. 2019.)

Although the specificity of stress ECG in assessing the extent of ischemia is up to 90%, it is not recommended as the first-line test because of its poor sensitivity of 45-50%. Non-invasive computed tomography (CT) angiography is recommended as the first-line test due to its high sensitivity (95-99%) and specificity (64-83%). Assessment of myocardial viability can be achieved with several imaging techniques including myocardial contrast echocardiography, single-photon emission CT and positron emission tomography (PET). Assessment of ischemia is more critical in patients with mild to moderate CAD but viability assessment is more essential in patients with severe CAD. The condition of stenotic arteries can be examined by either fractional flow reserve (FFR) or with invasive CT-imaging. (Neumann et al. 2019.)

The individual cardiac and extracardiac characteristics must be taken into account when choosing a compatible revascularization technique. These include, for example, anatomy of the heart and the coronary arteries, calcification of the aorta and other comorbidities. The choice has to be made in a multidisciplinary heart team which includes clinical cardiologists, cardiothoracic surgeons, interventional cardiologists and anaesthetists. Also, patient's preferences must be taken into account. Different characteristics favouring either PCI or CABG are listed in Table 1. (Neumann et al. 2019.)

Favours PCI	Favours CABG
Severe comorbidities	Diabetes
Advanced age and reduced life expectancy	Left ventricular dysfunction
Estimation of poor rehabilitation	Contraindication to antiplatelet therapy
Anatomy that likely results in incomplete revascularization with CABG	Anatomy that likely results in incomplete revascularization with PCI
Severe chest deformation	Severely calcified coronary artery lesions
Porcelain aorta	Need for concomitant interventions such as valve replacement or intervention of pathologic ascending aorta

Table 1. Different characteristics favouring either PCI or CABG.

When the decision of CABG has been made, the risk for operational complications has to be carefully assessed. A number of evaluation methods are globally used to calculate the risk of mortality for patients undergoing CABG. In Europe, European System for Cardiac Operative Risk Evaluation (EuroSCORE) calculator was invented in 1999 based on a dataset collected of 13 302 patients that underwent CABG before 1995 (Nashef et al. 1999). In 2011, the EuroSCORE calculator was updated and calibrated to EuroSCORE II (Table 2) to better match improved cardiothoracic surgery outcomes since the old EuroSCORE calculator overpredicted mortality. A new EuroSCORE II dataset was collected over a three-month period from May to July in 2010 and consisted of 22 381 patients from 43 different countries and 154 units all around the world to whom cardiac surgery was performed. Of these, 10 448 underwent an isolated CABG. Using EuroSCORE II to assess mortality risk in cardiac surgery is highly recommended. (Nashef et al. 2012.)

Patient related factors		
Age (years)	1-95	
Sex	Male/female	
Renal impairment	Normal (CC>85ml/min) Moderate (CC 50-85ml/min) Severe (CC<50ml/min) Dialysis (regardless of CC)	Cockroft-Gault creatinine clearance (CC) calculator based on plasma creatinine, age, weight and sex. CC = (140-age (years)) x weight (kg) x (0.85 if female) / [72 x plasma creatinine (mg/dl)]
Extracardiac arteriopathy	No/Yes	Claudication, carotid occlusion or >50% stenosis, amputation for arterial disease, previous or planned intervention on the abdominal aorta, limb arteries or carotids
Poor mobility	No/Yes	Severe impairment of mobility secondary to musculoskeletal or neurological dysfunction
Previous cardiac surgery	No/Yes	
Chronic lung disease	No/Yes	Long term use of bronchodilators or steroids for lung disease
Active endocarditis	No/Yes	Patient still on antibiotic treatment for endocarditis at time of surgery
Critical preoperative state	No/Yes	Ventricular tachycardia or ventricular fibrillation or aborted sudden death, preoperative cardiac massage, preoperative ventilation before anaesthetic room, preoperative inotropes or IABP, preoperative acute renal failure (anuria or oliguria <10ml/h)
Diabetes on insulin	No/Yes	
Cardiac related factors		
NYHA functional classification	I-IV	
CCS grade IV angina	No/Yes	Angina at rest
LV function	Good (LVEF>50%) Moderate (LVEF 31-50%) Poor (LVEF 21-30%) Very poor (LVEF ≤ 20%)	
Recent MI	No/Yes	Myocardial infarction within 90 days
Pulmonary hypertension	No Moderate (31-55mmHg) Severe (>55mmHg)	Systolic pulmonary artery pressure
Operation related factors		
Urgency	Elective Urgent Emergency Salvage	Elective (routine admission for operation) Urgent (patients who have not been electively admitted for operation but who require intervention or surgery on the current admission for medical reasons. These patients cannot be sent home without a definitive procedure) Emergency (operation before the beginning of the next working day after decision to operate) Salvage (patients requiring cardiopulmonary resuscitation (external cardiac massage) en route to the operating theatre or prior to induction of anaesthesia. This does not include cardiopulmonary resuscitation following induction of anaesthesia)
Weight of the intervention	Isolated CABG Single non-CABG 2 procedures 3 procedures	Include major interventions on the heart such as CABG, valve repair or replacement, replacement of part of the aorta, repair of a structural defect, maze procedure, resection of a cardiac tumour
Surgery on thoracic aorta	No/Yes	

Table 2. Modified EuroSCORE II calculator showing different characteristics used to assess the operative risks based on patient related, cardiac related and operation related factors. (Original EuroSCORE II calculator available online at http://euroscore.org/index.htm)
CC=creatinine clearance, CCS= Canadian Cardiovascular Society, IABP=intra-aortic balloon pump, LV=left ventricular, LVEF=left ventricular ejection fraction, MI=myocardial infarction, NYHA=New York Heart Association.

The New York Heart Association (NYHA) Functional Classification (Table 3) and Canadian Cardiovascular Society grading scale (CCS scale) (Table 4) describe the state of heart failure based on the symptoms and limitations during physical activities together with objective assessment.

Class	Patient symptoms
I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea (shortness of breath)
II	Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea (shortness of breath).
III	Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, or dyspnea.
IV	Unable to carry on any physical activity without discomfort. Symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases.
Class	**Objective assessment**
I	No objective evidence of cardiovascular disease. No symptoms and no limitation in ordinary physical activity.
II	Objective evidence of minimal cardiovascular disease. Mild symptoms and slight limitation during ordinary activity. Comfortable at rest.
III	Objective evidence of moderately severe cardiovascular disease. Marked limitation in activity due to symptoms, even during less-than-ordinary activity. Comfortable only at rest.
IV	Objective evidence of severe cardiovascular disease. Severe limitations. Experiences symptoms even while at rest.

Table 3. NYHA functional classification.

The New York Heart Association (NYHA) Functional Classification describe the state of patient's heart failure based on symptoms and limitations during physical activities together with objective assessment.

Grade	Description
I	Ordinary physical activity does not cause angina, such as walking and climbing stairs. Angina with strenuous or rapid or prolonged exertion at work or recreation.
II	Slight limitation of ordinary activity. Walking or climbing stairs rapidly, walking uphill, walking or stair climbing after meals, or in cold, or in wind, or under emotional stress, or only during the few hours after awakening. Walking more than two blocks on the level and climbing more than one flight of ordinary stairs at a normal pace and in normal conditions
III	Marked limitation of ordinary physical activity. Walking one or two blocks on the level and climbing one flight of stairs in normal conditions and at normal pace.
IV	Inability to carry on any physical activity without discomfort, anginal syndrome may be present at rest.

Table 4. CCS grading scale.

Canadian Cardiovascular Society (CCS) grading scale is used together with NYHA classification to describe the state of heart failure based on symptoms and limitations during physical activities.

EuroSCORE is categorized into three different categories based on the points given by the calculator. Patients getting score 0-2 are in low risk, 3-5 in medium risk and over 6 in high risk profile. (Nashef et al. 1999.)

In the USA, The Society of Thoracic Surgery Risk Score (STS risk score) is preferred over EuroSCORE II since in addition to mortality, it predicts other severe complications and prolonged total hospital stay. STS risk score has also its updated version published in 2018. (Shahian et al. 2018.)

3. OPCABG TARGET GROUP

3.1 High risk patients

The risk profile of an OPCABG patient comprises many factors. Of these, the most remarkable ones are left ventricular dysfunction (LVD), highly calcified vessels, advanced age, diabetes mellitus, renal dysfunction, reoperations, chronic pulmonary disease, and EuroSCORE II greater than 5. (Kowalewski et al. 2016). In the USA, Society of Thoracic Surgeons Predicted Risk of Mortality (PROM) was developed to predict risk-adjusted outcomes for patients undergoing cardiothoracic surgery. It consists of 30 risk factors, of which most are the same as in EuroSCORE II calculator. The PROM score is divided into four quartiles so that the higher risk profiles are placed in the upper quartiles. A total of 14 766 CABG patients between 1997 and 2007 were studied in the USA. Of these, 7083 (48,0%) underwent OPCAB and 7683 (52,0%) CPB-assisted CABG. In the lower two quartiles, no intraoperative difference was observed between the two techniques. In the highest quartile, the death rates were 3,2% and 6,7% for OPCABG and ONCABG, respectively. (Puskas et al. 2009).

3.2 Left ventricular dysfunction

Ultrasound measured ejection fraction (EF) is a common measurement for left ventricular function (LVF). EF describes the ratio of the stroke volume to end-diastolic volume and 50-70% is considered normal. EF less than 50% may correlate to left ventricular dysfunction. (Kettunen 2014.)

EuroSCORE II classification divides left ventricular ejection fraction (LVEF) into four different categories: good (LVEF 51% or more); moderate (LVEF 31-50%); poor (LVEF 21–30%) and very poor (LVEF 20% or less) (Nashef 2012). Patients with LVEF less than 30% undergoing primary and nonemergent coronary artery revascularization without CPB are associated with decreased early mortality and morbidity and better short-term outcomes when compared to ONCABG (Keeling et al. 2013, Ueki et al. 2016). Systematic literature reviews and meta-analyses have shown that mid- and long-term benefit is uncertain due to higher risk of incomplete revascularization in patients undergoing OPCABG. The need for reoperations predisposes to severe complications and increases the mortality rates in the long term (Jarral et al. 2011).

3.3 Female sex

Female sex is associated with smaller target vessels, more comorbidities and higher age at the time of CABG. These factors put women in higher risk for mortality and peri- and postoperative complications. Whether or not female gender is an independent risk factor has been a subject for numerous studies. (Attaran et al. 2014.) In EuroSCORE II calculator, female gender is one of the 17 independent risk factors that increase the risk for mortality (Nashef 2012). Women carry a significantly higher risk for operative mortality in all categories except in very high-risk patients (Edwards et al. 1998). Women undergoing CABG have a 1,76 times higher risk for in-hospital mortality than men before adjusted to other risk factors. Even after adjusting the two sexes for the presence of other risk factors, mortality rates were still higher for women (4,45%) than men (3,33%). (Hannan et al. 1992.) OPCABG narrows the early mortality rate gap between the two sexes and decreases the risk for severe complications in women when compared to traditional ONCABG (Puskas et al. 2007).

3.4 Age

Advanced age is a known risk in cardiac surgery (Nashef et al. 2012). Patients with greater age are usually associated with poor condition and concomitant cardiopulmonary diseases which understandably increase the risk for peri- and postoperative complications. In terms of in-hospital mortality (pooled odds ratio (OR) = 0,64; 95% confidence interval (CI) = 0.44 - 0.93; p = 0.02) and stroke (pooled OR = 0.61; 95% CI 0= 0.48 – 0.76; p<0.001), OPCABG provides a significantly safer option for conventional CABG in over 80-year-old patients. This was studied in a large observational meta-analysis where literature was searched from 1966 to 2016. 16 studies were included with 18 685 ONCABG and 8938 OPCABG patients. (Khan et al. 2017.) Risk for postoperative stroke for patients over 80 years was decreased (OR = 0.70; 95% CI= 0.52–0.93, p = 0.02) also in a comprehensive propensity analysis of 83 914 high-risk patients when compared with on-pump (Cavallaro et al. 2014). However, conflicting results have also been obtained. The German off-pump coronary artery bypass grafting in elderly patients (GOPCABE) was a randomized controlled trial of 2539 patients over 75 years old conducted in 12 German institutions between 2008 and 2011. The effect of the surgeon was minimized by including only very experienced CABG surgeons. The average surgery number for off-pump surgeons was 514 and 1378 for on-pump surgeons. No significant difference between the two groups was found when mortality, stroke, MI, repeat revascularization or renal replacement therapy at 30 days and 12 months were set as end points. (Diegeler et al. 2013.) Similar results were reported in a Danish on-pump versus off-pump randomization study (DOORS), a randomized controlled trial of patients over 70 years of age, and also in a recent retrospective cohort analysis conducted in 2019 (Houlind et al. 2012, Parmeshwar et al. 2019).

Off-pump technique in the elderly seems to pay off especially in the long term. Short-term outcomes of OPCABG are not as clear and the benefits seem to be clearer in terms of cost-effectiveness, resource use and hospital stay. As age remains a significant risk factor for mortality from 60 years onward, choosing off-pump surgery for the elderly could possibly decrease stroke and mortality and ease the economic burden (Nashef et al. 2012, Khan et al. 2017).

4. COMPLICATIONS

4.1 Cardiovascular complications

Atrial fibrillation (AF) and atrial flutter are the most common postoperative complications in cardiac surgery that require intervention or prolong intensive care (ICU) and total hospital stay. The incidence of postoperative atrial fibrillation (POAF) is approximately 30% in patients undergoing an isolated CABG and 50% in those having a combination of valve replacement and CABG. The peak for tachyarrhythmias is between the second and fourth postoperative day and 94% of the incidents happen during the first week after the operation. (Mitchell 2011.) Preoperative factors that might predict POAF include previous AFs, advanced age, chronic renal insufficiency, the use of vein grafts and withdrawal of β-blocker therapy. A concomitant valve replacement, high number of grafts, duration of aortic cross-clamp and total procedure duration also increase the risk POAF. (Mitchell 2011, Vidotti et al. 2019.) CPB use does not correlate to peri- or postoperative AF and the occurrence of POAF is similar between OPCABG and ONCABG (Mitchell 2011).

Most of the incidences are transient and symptoms vary from mild discomfort and anxiety to chest pain and cognitive impairment. However, AF might have detrimental consequences especially in a subgroup of high-risk patients. It might predispose to more adverse arrhythmias, hemodynamic instability and heart failure in addition to thromboembolic events including stroke. (Mitchell 2011, Vidotti et al. 2019.)

According to Canadian cardiovascular society (CCS) guidelines, the prevention of POAF can be best obtained by continuing β-blocker therapy among those who have used them before the operation. For those who have not received prior β-blockers, therapy should be initiated just before or immediately after bypass surgery. Amiodarone therapy should be used for patients having β-blocker contraindications. (Mitchell 2011.)

Although POAF treatment does not differ remarkably from the treatment of a normal AF, some differences in therapeutic strategies are recommended. Slowing of ventricular response should be treated with β-blockers and arrhythmia should be converted to sinus rhythm with cardioversion or drug therapy. Antithrombotic drug therapy should be initiated carefully for patients with prolonged AF of over 72 hours and continued for at least six weeks. Anticoagulation therapy initiated too soon after the occurrence of POAF might predispose to pericardial bleeding and cardiac tamponade. (Kokkonen and Majahalme 2003, Mitchell 2011.)

Myocardial damage that leads to heart failure occurs in 1-2% of CABG patients. Other cardiac complications associated with CABG include pathologic changes in ECG and bundle branch blocks. Cardiac enzymes, such as creatine kinase myocardial band (CK-MB) and troponin I and T (TnI and TnT), are commonly used tests to assess myocardial damage. However, these enzyme levels do not always correlate to the extent of the damage since the release of the enzymes is relatively small in cardiac arrest. (Ihlberg 2016.)

4.2 Neurological risk

Stroke is defined as an abrupt neurologic deficiency caused by cerebral blood supply disturbance that does not resolve within 24 hours. While stroke requires intervention, transient ischemic attack (TIA) is defined as a loss of neurologic function caused by cerebral blood flow disturbance that resolves spontaneously within 24 hours. (Halkos et al. 2008.) TIA is associated with complete return of normal brain function with no brain damage whereas stroke usually causes permanent neurological dysfunction.

Stroke and TIA occurring after CABG constitute a major share of adverse outcomes that lead to morbidity and mortality (Mishra et al. 2006). While non-complicated CABG is considered as a safe revascularization method with a 1-2% risk for intraoperative mortality (Halkos et al. 2008, Ihlberg 2016), stroke and TIA increase the risk remarkably. Overall incidence for stroke and TIA, or the composite of the two, after CABG was around 2% in a retrospective cohort study of 14 278 patients conducted between 1996 and 2006. Of these 274 incidents, 13,5% led to in-hospital death. Moreover, previous stroke or TIA further increase the risk for mortality. In addition to death and postoperative neurological complications, stroke and TIA patients are at higher risk for postoperative AF, renal failure and prolonged ventilation. (Halkos et al. 2008.)

When compared with ONCABG, OPCABG benefits patients in terms of postoperative neurological events. Microembolization, inflammatory response and inconstant perfusion flow are considered to be the main reasons for postoperative neurological events caused by CPB. These complications can be minimized by avoiding the use of CPB. (Halkos et al. 2008.)
Atheromatous aorta is the main origin of both micro- and macro-sized emboli that cause stroke and TIA. The condition of the aorta is an important part of clinical examination of patients undergoing cardiac surgery and should be carefully assessed since severely calcified aorta could be a

contraindication for cross-clamping required in ONCABG. Most often, the location of atheromatous aorta is either in the ascending aorta or in the arch of aorta. Depending of the location, several surgical techniques have been invented to minimize the risk of plaque rupture resulting in stroke. Such techniques include no-touch technique of the ascending aorta, intra-aortic occlusion using balloon, long aortic cannula, prior or concomitant endarterectomy and graft replacement of the aorta. Moreover, intra-aortic filtration was invented to capture emboli of the atheromatous aorta. Although it is an effective way of capturing solid emboli with a rate of up to 97%, its role in preventing a stroke is minimal especially in low-risk patients. (Banbury et al. 2003). The benefit might be more distinct in high-risk patients. Gaseous emboli associated with open-heart surgery might be an explanation for adverse neurological outcomes despite the high capture rate of intra-aortic filters. (Wimmer-Greinecker 2003.) Routine intraoperative evaluation of the aorta, such as transesophageal and epiaortic echocardiography, is helpful in identifying atheromatous aorta and could help when choosing a proper surgical technique (Mishra et al. 2004, Sharony et al. 2004, Mishra et al. 2006). Several studies have shown the association of OPCABG with reduced risk for postoperative stroke (Mishra et al. 2006, Halkos et al. 2008).

Patients with severe carotid stenosis undergoing cardiac surgery are a subgroup of high-risk patients. 8 to 14% of CABG patients have a severe carotid artery disease and 40-50% of carotid endarterectomy patients have coronary artery disease. Not surprisingly, concomitant endarterectomy and CABG has been an interest of many cardiac surgeons. OPCABG and ONCABG both seem to be equally effective and safe techniques when performed together with carotid endarterectomy with a mortality rate of 1,6%. (Mishra et al. 2004.)

In addition to stroke and TIA, patients undergoing cardiac surgery carry a higher risk for postoperative cognitive dysfunction (POCD) when compared to patients undergoing a non-cardiac surgery. Among cardiac patients, CABG is the most common cause of POCD (Kozora et al. 2010.) Postoperative neurological dysfunction is characterized by impairment of attention, concentration and memory. A large literature review of 28 relevant prospective and retrospective studies including 3373 patients reported contradictory results of superiority between OPCABG and ONCABG with regard to POCD. While early POCD occurred more often in OPCABG patients compared to ONCABG (50% and 31%, respectively), late outcomes were contrary (9,4% and 26,4%, respectively). (Yuan and Lin 2019.) The incidence of delirium requiring pharmacological treatment is also decreased in OPCABG when compared to ONCABG (Dominici et al. 2019).

Phrenic nerve paralysis and paresis of the left recurrent laryngeal nerve or the left plexus brachial are rare and usually transient complications followed by surgical trauma or compression caused by retractors used in sternotomy (Ihlberg 2016).

4.3 Acute kidney injury

Chronic renal dysfunction is a common comorbidity in patients undergoing CABG (Ueki et al. 2018). It is also a well-known risk factor for mortality as described in EuroSCORE II calculator (Nashef et al. 2012). Although weight and serum creatinine levels are not independent risk factors, they affect total creatinine clearance (CC) which in turn is an independent risk factor. Renal function is divided into four categories based on the CC levels. A CC level of over 85ml/min is considered normal, 50-85ml/min moderate and less than 50ml/min severe. Renal dysfunction requiring dialysis is also a sign of severely impaired renal function regardless of plasma creatinine levels. (Nashef et al. 2012.)

Acute kidney injury (AKI) is defined by an abrupt decrease in kidney function. AKI includes, but is not limited to, acute renal failure. AKI leads to changes in urine output and blood chemistry which can have serious clinical consequences. In addition to AKI being an emergent complication on its own, it can also cause severe complications in other organs resulting in multiple organ failure, coma and death if not treated rapidly. Several factors predispose to peri- and postoperative AKI. Such risk factors are, for example, sepsis, a severe illness, circulatory shock and major surgeries including CABG. There are several diagnostic criteria for AKI. KDIGO (Kidney disease: improving global outcomes) is probably the most used classification globally and is based on either serum creatinine or urine output as listed below in Table 5. KDIGO is a global organization founded by the National Kidney Foundation that provides evidence based clinical practice guidelines for kidney diseases (KDIGO Clinical Practice Guideline for Acute Kidney Injury.)

Stage	Serum creatinine	Urine output
1	1,5-1,9 times baseline OR > 0,3mg/dl (26,5µmol/l) increase within 7 days	<0,5ml/kg/h for 6-12 hours
2	2,0-2,9 times baseline	<0,5ml/kg/h for over 12 hours
3	3,0 times baseline OR increase to > 4,0mg/dl (353,65µmol/l) OR renal replacement therapy OR estimated glomerular filtration rate (eGFR) <35ml/min per 1,73m^2	<0,5ml/kg/h for over 24 hours OR anuria for over 12 hours

Table 5. KDIGO classification of AKI.
Acute kidney injury (AKI) can be classified into three stages based on serum creatinine and urine output. KDIGO (kidney injury: improving global outcomes) is a global, non-profit organization founded by National Kidney Foundation to provide guidelines for kidney diseases.

AKI associated with cardiac surgery occur approximately in 8-30% of the cases. In CABG, the overall rates have been reported to be between 1,4% and 19,5% (Di Mauro et al. 2007). Preoperative renal dysfunction, hypertension and the duration of surgery are all independent risk factors for postoperative AKI. Chronic low glomerular filtration rate (GFR) is a sign of impaired renal function and is the most significant risk factor for AKI. (Zhiwei et al. 2019.) The benefit of off-pump surgery in terms of AKI has been studied in patients with normal and abnormal preoperative kidney function. A study of 1724 patients (862 OPCABG and 862 ONCABG) with normal preoperative renal function reported significantly higher 30-day AKI incidence in ONCABG arm (7,9% and 2,9%, p<0,0001). Interestingly, no benefit of OPCABG was reported in patients with abnormal preoperative kidney function. (Di Mauro et al. 2007.) On the other hand, a more recent and larger Japanese study published in 2018 showed clear association between the stage of preoperative renal dysfunction and incidence of postoperative renal damage requiring dialysis. Same study also demonstrated significant benefit of OPCABG over ONCABG regardless of the stage of preoperative renal dysfunction. (Ueki et al. 2018.) Since CPB seems to cause renal damage, shorter extracorporeal circulation time could be beneficial. In isolated ONCABG surgeries, an optimal cut-off time has been reported to be between 66min and 94min (Di Mauro et al. 2007, Zhiwei et al. 2019).

4.4 Other complications

According to a single-centre study of 7606 patients, intestinal ischemia is a rare but critical complication of CABG with an incidence of 0,4%. Acute mesenteric ischemia and its complications made up 7,1% of all deaths associated with CABG. The rates of acute mesenteric ischemia in ONCABG and OPCABG are 1,07% and 0,28%, respectively. Survival rates were 61,1% in OPCABG surgery and only 7,1% in ONCABG. (Soylu et al. 2019). This implicates that intestinal

ischemia is more pronounced when CPB is used and survival after acute mesenteric ischemia is very unlikely.
Another rare complication of CABG, as well as other cardiac surgery, is chylothorax (Weber et al. 1981). Chylothorax is defined as leakage of chyle into pleural cavity. Chylothorax can have various etiologies including congestion, trauma and obstruction or it can happen spontaneously (Pêgo-Fernandes et. al 1999). Its incidence in cardiovascular surgery performed through thoracotomy has been reported to be between 0,25 and 0,50% (Weber et al. 1981).

The rarity of chylothorax in cardiovascular surgery can be explained by the normal anatomic position of the thoracic duct in the upper mediastinum. It lies on the left side of the esophagus posterior to the arch or aorta. In the neck it ascends laterally and then turns left to descend and enter the left subclavian-jugular venous junction. Because of its relatively distant location to the heart, damage of the thoracic duct should rarely occur. However, due to anatomic variations, two or more tributaries occur in 40-60% of people. These branches are usually in close proximity to the origin of the LIMA. (Weber et al. 1981). Thus, in intrapericardial surgery, harvesting the LIMA for CABG through median sternotomy is the most common cause of chylothorax (Waikar et al. 2018).

Surgical intervention has been recommended if the drainage exceeds 1000ml/day for several consecutive days (Cerfolio et al. 1996). If untreated, chylothorax can lead to severe morbidities due to malnutrition and immunosuppression through loss of lymphocytes. (Shah et al. 2012).

5. SYSTEMIC INFLAMMATORY RESPONSE SYNDROME

Systemic inflammatory response syndrome (SIRS) is a broad and complex pathophysiological inflammatory reaction to various insults, such as trauma, burn or foreign particles (Balk 2014). SIRS was defined in Critical Care Medicine Consensus Conference in the USA in 1991 to separate the infectious and non-infectious inflammatory reactions from each other. SIRS is manifested by two or more of the following conditions:

- temperature >38°C or <36°C
- heart rate >90 beats per minute
- respiratory rate >20 breaths per minute or PaCO2 <32 mm Hg
- white blood cell count > 12,000/ mm^3 or <4,000/ mm^3, or >10% immature (band) forms

For long, sepsis was defined as microbial infection with at least two of the conditions above. (Bone et al 1992.) This definition was in large use worldwide and remained unchanged despite the advances made in pathobiology, management and epidemiology during the past few decades. In 2016, sepsis was redefined by the European Society of Intensive Care Medicine and the Society of Critical Care Medicine to meet the changes. Nowadays, sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection. (Singer et al. 2016.)

Surgical trauma per se is a potential trigger of inflammatory response. This is caused by tissue injury and foreign particles. Median sternotomy is associated with increased inflammatory response when compared to smaller incision made in anterolateral thoracotomy. Thus, more extensive tissue injury is associated with increased inflammatory response. Median sternotomy is the most common incision made in both OPCABG and ONCABG. Off-pump surgery eliminates the use of CPB, aortic cross-clamping and cardiac arrest which predispose the body to inflammatory response, global myocardial damage, platelet and coagulation activation and ischemia-reperfusion injury. Whether or not these eliminations decrease the inflammatory reactions has been controversial or at least the mechanisms have stayed unclear. (Gu et al. 1999.)

Cytokines are polypeptides secreted by leukocytes and other cells that act on hematopoietic cells and activate and regulate immune and inflammatory responses (O'Shea et al. 2013). The use of CPB is associated with SIRS, activation of complement system and cytokine release. This can be seen in increased complement protein synthesis and increased release of inflammatory mediators by circulating leukocytes intra- and postoperatively. (Czerny et al. 2000, Wan et al. 2014, Greilich et al. 2008.) Interleukins (IL) are a wide group of proinflammatory cytokines that have an important role in inflammatory response, as they act on white cell proliferation, activation, growth and differentiation in addition to platelet and endothelium activation (O'Shea et al. 2013).

C-reactive protein (CRP) is an acute-phase protein synthesized by the liver and its concentration rises rapidly in inflammatory states. Although its use in diagnosing the cause of inflammation is rather unspecific, it can be used as a tool to assess early and late mortality in coronary artery bypass surgery. It has been shown that elevated preoperative CRP is an independent risk factor of mortality for patients undergoing CABG. High concentration of CRP might be an indication of an underlying infectious disease or inflammatory response that might stay hidden in clinical examination. High preoperative CRP in elective patients should be a reason for postponement whenever it is possible. (van Straten et al. 2009.) Behaviour of ultrasensitive CRP (US-CRP) was studied between 2012 and 2014 in a prospective, non-randomized clinical study. Surprising results were obtained since no difference could be shown between OPCABG and ONCABG groups with respect to elevated US-CRP concentration. US-CRP was higher postoperatively when compared with preoperative concentrations in both groups but no statistically significant difference was found between the two groups. Thus, the concentration of US-CRP is not a valid tool for assessing independent proinflammatory effect of CPB. (Abrantes et al. 2018.)

In CABG, serum concentration of IL-6, IL-8 and IL-10 are commonly used markers for inflammation, together with CRP and tumor necrosis factor alpha (TNF-α). Levels of these markers are elevated in both surgeries due to surgical trauma, contact with foreign surfaces and myocardial damage but is more significant in ONCABG which might implicate that CPB has a proinflammatory effect. (Czerny et al. 2000, Wan et al. 2004, Nesher et al. 2006, Meng et al. 2017.)

In addition to cytokines and complement proteins, there are other markers to evaluate the inflammatory and injurious state related to CABG. High concentration of creatine kinase myocardial band (CK-MB) and troponin I (TnI) in blood specifically indicate myocardial injury. These markers start to increase soon after the induction of anaesthesia and sternotomy but remain similar in the beginning of CABG regardless of surgery technique. From the end of ischemia, the levels of CK-MB and TnI are significantly more increased in ONCABG patients up to 24 hours postoperatively when compared to OPCABG. Significantly increased levels of CK-MB and TnI associated with CPB is a sign of considerable myocardial damage. (Nesher et al. 2006.)

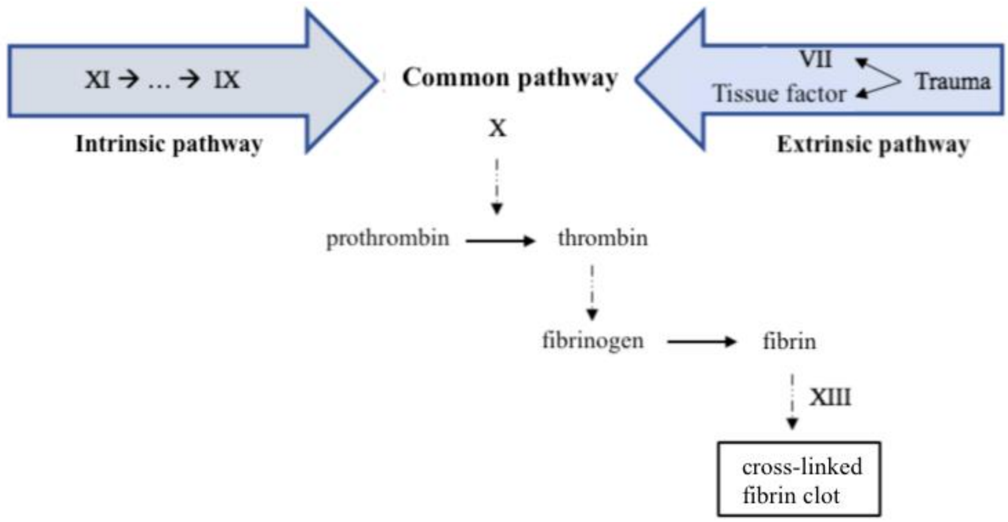
Whether or not CPB is an independent risk factor for inflammatory response has been rarely studied. Wan et al. set up a randomized and prospective study in 2003 to elucidate the isolated effect of CBP on inflammation response by categorizing patients into two groups. Other group consisted of OPCABG and the other one of on-pump beating heart coronary artery bypass grafting (ON-BHCABG) patients, a hybrid technique accepted as a trade-off for subgroup of high-risk patients. They reported significant elevation of proinflammatory mediators in ON-BHCABG group suggesting that the use of CBP is the major triggering factor of inflammatory response. (Wan et al. 2004.)

6. COAGULATION AND PLATELET ACTIVATION

Surgical trauma per se is a potential activator of several molecular pathways, such as inflammation, hemostasis and endothelial function. The effect of these pathways is multidirectional: activation of one pathway triggers the activation of the others and vice versa. For example, thrombin, prothrombin, factor X and tissue factor all stimulate the synthesis of IL-6 and IL-8. (Parolari et al. 2016.) OPCABG does not eliminate these responses and whether or not these reactions are decreased in off-pump surgery is still debatable. In this review, biochemical properties are considered less, and the focus is more on clinical approach.

It was long thought that the use of CPB was the main reason for the activation of previously described molecular pathways. However, similar responses are activated in operations which do not include extracorporeal circulation, such as orthopedic and neurological surgery. This finding suggests that surgical trauma and operation themselves elicit endocrine and vascular stress, coagulation as well as pro- and anti-inflammatory responses. (Parolari et al. 2016.)

Hemostatic response begins initially at the time of incision due to contact of blood with surgical wound and then continues when blood is circulated in a nonendothelial CPB or cell saver. Coagulation happens in two interrelated but separate pathways of plasmatic and cellular mechanisms. (Parolari et al. 2016.) A complex pathway of plasmatic activation including several coagulation factors in intrinsic and extrinsic pathways lead to a common coagulation pathway resulting in a cross-linked fibrin clot formation and thus to coagulation (Graph 1).



Graph 1. Two different coagulation pathways lead to a common pathway resulting in fibrin clot formation. Coagulation factors shortened in roman numbers.

Platelets play a key role in the cellular coagulation mechanism. Platelets normally travel to the location of vascular damage where they initially start the clotting process by aggregating and attaching to von Willebrand factor of endothelium and cross-linked fibrin clot with other blood cells. Soon after, more platelets from circulating blood are recruited by several mediators, such as adenosine diphosphate (ADP), thrombin and thromboxane A_2 (TXA_2). (Davi and Patrono 2007.) Vascular damage is not the only mechanism that triggers platelet activation. Similar to the molecular pathways of hemostasis, platelets are activated when in contact with the nonendothelial surface of CPB. Activation of platelets leads to a decreased formation of new platelets and platelet dysfunction in existing platelets. (Parolari et al. 2016.)

Besides extracorporeal circulation, removal of aortic-cross clamp and administration of protamine right after the surgery might have pro-thrombotic affect due to possible ischemia-reperfusion injury and complement system activation, respectively. Such hemostatic activation bursts especially during the surgery and few first hours after closing of the incision. (Parolari et al. 2016.) It is well known that CPB triggers the coagulation pathways. Whether or not this happens solely due to use of CPB is unlikely. The link between CPB avoidance and reduced hemostatic response is contradictory and off-pump surgery could only provide limited benefit. (Parolari et al. 2016, Gaudino et al. 2018.)

Antithrombotic drugs can be classified into two different groups by their mechanism. The first group targets the clotting factors of the plasma and inhibit the gamma carboxylation thus preventing their attachment to aggregating platelets. The other group targets the platelets by inhibiting the enzymatic action of cyclooxygenase and thus, prevents the synthesis of TXA_2 which stimulates the formation and recruitment of new platelets. The balance between physiologic coagulation and antithrombosis after a surgery should be obtained by proper medication. The excess use of antithrombotic drugs predisposes to bleeding. On the other hand, medication is necessary to prevent formation of fatal thrombi.

Oral acetylsalicylic acid (aspirin) is a commonly used peri- and postoperative antithrombotic drug for CABG patients. The pharmacodynamic effects of antiplatelet drugs have been examined by administrating low-dose aspirin either once or twice a day, both in vivo and ex vivo. (Zimmermann et al. 2005, Cavalca et al. 2017, Ivert et al. 2017, Paikin et al. 2017.) Unfortunately, ex vivo studies provide unreliable results since the behaviour of platelets differs significantly when compared to in vivo. The capacity of platelets to excrete thromboxane A_2 is up to 5000 higher in vitro when compared with in vivo, and hence only the latter should be taken in consideration on clinical implications (Davì and Patrono 2007).

It seems higher doses or alternatively more frequent dosing of aspirin is associated with more suppressed synthesis of platelet mediators (Paikin et al. 2017). 100mg twice a day versus 100 mg or 200mg once a day decreased the synthesis of TXA_2 in vivo in a randomized trial conducted in 2016 (Cavalca et al. 2017). Similarly, 75mg twice a day or 160mg once a day were both equally more effective when compared to a once-a-day dosing of 75mg (Ivert et al. 2017).

The number of circulating platelets after ONCABG slightly decreases postoperatively and rapidly increases few days after. The increased formation of new platelets seems to compensate the inhibiting effect of aspirin. Within the dosing intervals, increased number of platelets are competent to the formation of thromboxane. Thus, CPB is associated with a phenomenon called aspirin resistance. (Zimmermann et al. 2005.) Although such resistance is not usually connected with OPCABG, the turnover of platelets is usually higher in the long run when compared to ONCABG. This might be associated with impaired graft patency in the long run.

7. SHORT-TERM OUTCOMES

Until this day, a few large randomized controlled trials (RCT) have been conducted to compare early outcomes of on- and off-pump surgery. Randomized on/off bypass (ROOBY) trial was an American study of 2203 patients conducted at 18 Veterans affair centres in 2009. (Shroyer et al. 2009.) No significant difference could be obtained between OPCABG and ONCABG in early primary end points including death, reoperation, new mechanical support, cardiac arrest, coma, stroke and renal failure (7,0% and 5,6%, respectively, p=0,19). A few years later a larger study was carried out. The CABG off- or on-pump revascularization study (CORONARY) was an international RCT including participants from 79 different centres in 19 countries. (Lamy et al. 2012, Lamy et al. 2013.) Whereas high risk patients in ROOBY were excluded, CORONARY trial only included patients with at least one of the following risk factors: advanced age, peripheral arterial disease, cerebrovascular disease, carotid stenosis of 70% or more, renal insufficiency and LVD. In addition, surgeons had more experience than in ROOBY to minimize the impact of inexperience. The purpose of the trial was to study the 30-day and twelve-month outcomes exclusively in high-risk population undergoing CABG. Similar results were reported. Primary early outcomes (similar to those in ROOBY) at 30 days (9,8% for OPCABG and 10,3% for ONCABG, p=0,59) and at twelve months (12,1% for OPCABG and 13,3% for ONCABG, p=0,24) did not differ significantly. Third RCT in Germany only included first-time CABG patients over 75 years of age. 2539 patients were included in GOBGABE (The German off-pump coronary artery bypass grafting in elderly patients) study. (Diegeler et al. 2013.) Similar 30-day end point (composite of death, stroke, MI, repeat revascularization or new renal replacement therapy) was set for the trial. Despite the age of the patients, GOBGABE also failed to show any difference between the two techniques with respect to early adverse outcomes. Another follow-up was done after 12 months but the differences remained insignificant.

Although randomized controlled trials have failed to show any difference in early outcomes in terms of mortality and adverse complications, some meta-analyses seem to favour off-pump technique when short-term outcomes are observed. A systematic review of 42 RCTs and 31 observational studies with more than 1,2 million patients showed significant reductions (OR 0,81) in off-pump patients in the odds of 30-day mortality (Filardo et al. 2018). Another, smaller meta-analysis of 35 propensity analyses and 123 137 patients also showed the short-term superiority of OPCABG. OR for mortality was 0,69 (p<0,0001), for stroke 0,42 (p<0,0001), for renal failure 0,60 (p<0,0001) and for wound infection 0,69 (p<0,001) (Kuss et al. 2010). A reduction of 28% in the odds of 30-day postoperative stroke was showed in a meta-analysis of 100 studies reviewed in 2016 (Kowalewski et al. 2016).

8. LONG-TERM OUTCOMES

Late outcomes of CABG have been studied far less than those occurring shortly after the operation. Existing studies suggest that better short-term outcomes of OPCABG come at the expense of poorer long-term survival. While some studies show no difference between the two techniques with respect to late mortality, others show that there is a clear and significant correlation between on-pump surgery and long-term survival.

Large RCTs could not show any significant short-term effectiveness of OPCABG. Just a few years ago the five-year outcomes of ROOBY and CORONARY were finally published. In December 2016, CORONARY reported no difference in primary composite outcome of death, nonfatal MI, nonfatal new renal failure requiring dialysis or repeat revascularization when ONCABG and OPCABG were compared. (Lamy et al. 2016.) While the long-term outcomes of CORONARY study were similar to the short-term outcomes, ROOBY showed significant difference in primary outcomes (death and major adverse cardiovascular event (MACE) with death) favouring ONCABG. On the other hand, no significant difference was observed with respect to secondary outcomes. (Shroyer et al. 2017.) The five-year outcomes of CORONARY and ROOBY are listed in more details in Table 6 and Table 7, respectively.

Five-year outcomes of CORONARY study				
Outcome	**OPCABG (n=2375)**	**ONCABG (n=2377)**	**Hazard ratio (HR) (95% CI)**	**p-value**
[a] Second co primary outcome, n (%)	548 (23,1)	560 (23,6)	0,98 (0,87 – 1,10)	0,72*
Death	346 (14,6)	322 (13,5)	1,08 (0,93 – 1,26)	0,30*
MI	178 (7,5)	194 (8,2)	0,92 (0,75 – 1,13)	0,41*
Stroke	55 (2,3)	66 (2,8)	0,83 (0,58 – 1,19)	0,32*
New renal failure requiring dialysis	40 (1,7)	45 (1,9)	0,89 (0,58 – 1,37)	0,60*
Repeat revascularization	66 (2,8)	55 (2,3)	1,21 (0,85 – 1,73)	0,29*

Table 6. **Five-year outcomes of CABG off- or on-pump revascularization (CORONARY) study.**

[a] Second co primary outcome = composite of death, nonfatal stroke, nonfatal myocardial infarction (MI), nonfatal new renal failure requiring dialysis, or repeat coronary revascularization ***statistically not significant.**

Five-year outcomes of ROOBY study				
Outcome	**OPCABG (n=1104)**	**ONCABG (n=1099)**	**Relative risk (RR) (95% CI)**	**p-value**
Primary outcomes				
Death	168 (15,2)	131 (11,9)	1,28 (1,03 – 1,58)	0,02
[a] Composite MACE with death	342 (31,0)	298 (27,1)	1,14 (1,00 – 1,30)	0,046
Secondary outcomes				
Death from cardiac cause	70 (6,3)	58 (5,3)	1,20 (0,86 – 1,68)	0,29*
Acute MI (nonfatal)	134 (12,1)	105 (9,6)	1,27 (1,00 – 1,62)	0,05*
Repeat revascularization	145 (13,1)	131 (11,9)	1,10 (0,88 – 1,37)	0,39*
[b] Composite MACE outcome with death	270 (24,5)	234 (21,3)	1,15 (0,98 – 1,34)	0,08*

Table 7. Five-year outcomes of Randomized on/off bypass (ROOBY) study.

[a] Death from any cause, acute MI or repeat revascularization. [b] Death from cardiac causes, acute MI or repeat revascularization. ***statistically not significant**

So far, two large meta-analysis of long-term effectiveness of OPCABG have been conducted. First ever large RCT-only meta-analysis considering long-term (over four-year follow-up) clinical effects including 8145 patients showed significantly increased mortality incidence (OR 1,16; p=0,03) in OPCABG population when compared to ONCABG. Surprisingly, the same meta-analysis found no significant difference when MI, angina pectoris, repeat revascularization and stroke were studied. (Smart et al. 2018.) A second, larger meta-analysis was published soon after. A study of three RCTs, five observational studies and 60 405 patients were included in a five-year follow-up. A risk ratio (RR) of 1,10 (95% CI 1,05 – 1,10) favoured on-pump technique. At ten-year follow-up, only one observational study was found. OPCABG was associated with an increase of 14% in terms of all-cause mortality. (Filardo et al. 2018.)

A few retrospective, single-centre observational studies showed no difference in late survival between the CABG procedures (Lattouf et al. 2008, Kirmani et al. 2016). Interestingly, it has been proposed that long-term mortality is associated with incompleteness of revascularization rather than operation technique or number of grafts. The index of completeness of revascularization (ICOR) is the division of grafts performed by the number of diseased vessels and could predict long-term mortality. (Lattouf et al. 2008.) Thus, higher ICOR score predicts better long-term survival.

Just like short-term outcomes, RCTs fail to show the difference or show contradictory results between OPCABG and ONCABG in regard to long-term outcomes. Meta-analysis of observational and retrospective studies on the other hand show strong correlation between ONCABG and long-term survival. Mortality among OPCABG population is associated with incompleteness of revascularization.

9. FINANCIAL ASPECT AND HOSPITAL STAY

In 2008, the direct and indirect costs of CVDs were $171,7 billion and are projected to increase to $275,8 billion by 2030, meaning a 61% increase in just 20 years in the USA alone. In 2009, 416 000 inpatients underwent bypass surgery in the USA. (Roger et al. 2012.) The average cost of a single CABG procedure is $36 580 with no complications. Each complication related to CABG increase the total costs exponentially. Of these complications, prolonged ventilation of over 24 hours (estimated cost $33 840), reoperation ($35 239) and renal failure ($33 847) increase expenses the most. For the past ten years, 36 588 patients underwent CABG in 18 centres in Virginia alone. Complications increased the medical costs by $78,6 million with prolonged ventilation being the highest at $59,1 million. (Mehaffey et al. 2018.)
In comparison, between 1994 and 2013, the number of first-ever CABG patients in Finland was 74 338 (Kiviniemi et al. 2016). As might be expected, bypass surgery is a huge expense in healthcare especially when funding is being lowered and at the same time the number of patients is rapidly increasing.

The total cost of a single CABG is difficult to define and depends on many factors. In addition to the procedure itself, pre- and perioperative together with postoperative costs make up the total price. The ICU and cardiac ward stay make up most of the total costs. (Lamy et al. 2006.) Most of the studies have been conducted only nationwide and international comparison between the prices is missing since the healthcare systems differ considerably. Only one international study that consisted of 19 different countries was found with the search strategy used in this literature review (Lamy et al. 2014).

Cost-effectiveness of OPCABG has been shown in several studies. The benefit of OPCABG with respect to total costs at discharge is considerably high and could be up to 30% (Ascione et al. 1999). Increased costs were found only in one study (Chu et al. 2009). Financial benefit from discharge to one-year follow-up also seem to favour OPCABG over ONCABG (Table 8).

Within OPCABG population, advanced age, prolonged anaesthesia, use of intra-aortic balloon pump (IABP) and the length of preoperative hospital stay increased the medical costs due to increased resource use (Lamy et al. 2014, Shinjo et al. 2015). Renal failure, LVD, high EuroSCORE II and cerebrovascular diseases are the most expensive comorbidities (Lamy et al. 2014). Surprisingly, diabetes and peptic ulcer disease without bleeding seem to decrease the costs

(Lamy et al. 2014, Shinjo et al. 2015). From a financial point of view, low EF is the most important factor when choosing between OPCABG and ONCABG. Avoidance of CPB in this subgroup of patients could be up to 2,3 times more expensive ($8325 and $19 242 for ONCABG and OPCABG, respectively). (Lamy et al. 2014.)

In high-risk patients, such as patients with diabetes, chronic obstructive pulmonary disease (COPD), peripheral vascular disease, cerebrovascular disease, renal dysfunction, EF < 35% or age of over 70 years, there is no statistically significant difference with respect to total costs at 5 years and the choice between OPCABG and ONCABG should be rather made based on clinical risks and surgeon experience (Lamy et al. 2014, Wagner et al. 2019). Nevertheless, reliable studies on long-term cost-effectiveness of OPCABG compared to ONCABG are still needed.

Length of stay for CABG patients consists of pre-, peri- and postoperative stay in addition to follow-ups. Total hospital stay depends highly on the patient characteristic and preoperative risk factors, such as age, sex and severity of other comorbidities. Although operation times are usually longer in OPCABG (Arom et al. 1999, Nathoe et al. 2003), length of stay in ICU, cardiac ward and total hospital stay are shorter for OPCABG patients (Table 8) (Boyd et al. 1999, Scott et al. 2005, Chu et al. 2009). This applies also when there is no statistical difference in the two groups regarding to age, BMI, body weight, EF, IABP use, previous MIs, left main coronary artery (LMCA) disease, COPD, hypertension, chronic heart or renal failure and risk-adjusted mortality estimation (Scott et al. 2005).

Author(s)	Country	Study design	Patient number OPCABG vs. ONCABG	Total benefit of OPCABG	Total postoperative length of stay OPCABG vs ONCABG
Arom et al. 1999	USA	Retrospective review	62 vs 243	discharge: 21% decreased costs	
Ascione et al. 1999	UK	Prospective, total hospital costs	100 vs 100	discharge: 30% decreased costs	
Boyd et al. 1999	Canada	Retrospective, based on a database	30 vs 60	discharge:14% decreased costs	6,3 vs 7,7
Chu et al. 2009	USA	Retrospective, based on a database	14 389 v 48,658	discharge: 2,6% increased costs	10,24 vs 9,90
Houlind et al. 2013	Denmark	Randomized, controlled trial	450 vs 450	6 months: 6,9% decreased costs	
Lamy et al. 2006	Canada	Propensity score matching	1233 vs 1233	discharge: 14% decreased costs 1 year: 15 decreased costs	7,24 vs 8,73
Lamy et al. 2014	International (19 countries)	Multicentre, prospective, randomized	4752 altogether	discharge: 0,69% increased costs 6 months: 1,0% increased costs 1 year: 0,70% increased costs	
Nathoe et al. 2003	Netherlands	Multicentre, randomized trial	142 vs 139	discharge: 14% decreased costs 1 year: 12% decreased costs	
Puskas et al. 2014	USA	Randomized, controlled trial	100 vs 100	discharge: 11% decreased costs 1 year: 7,9 decreased costs	
Scott et al. 2005	USA	Observational	865 vs 881		8,8 vs 9,7
Wagner et al. 2013	USA	Randomized controlled trial	1104 vs 1099	discharge: 1,4% increased costs 1 year: 6,4 increased costs	11,1 vs 10,6*

Table 8. The differences between OPCABG and ONCABG in terms of total hospital costs at discharge, at six-month and at one-year follow-up in addition to total postoperative length of stay. *** statistically not significant**

10. SURGEON AND HOSPITAL EXPERIENCE

The operation technique on a beating heart is usually considered more demanding than in cardiac arrest. Surgeon experience and its effect on statistical outcomes, such as mortality, financial costs and length of stay, has been a subject for numerous studies. (Glance et al. 2005, Lapar et al. 2012, Lamy et al. 2014, Benedetto et al. 2018a, Chikwe et al. 2018.) The relative use of OPCABG has fluctuated for the past 20 years worldwide. In the USA, the highest peak of 21% was in 2008 before it declined to 17% in 2012. Ever since it has been used less frequently while PCI has gained more popularity. Same declining trend in the number of OPCABG procedures can be seen in high- and intermediate-volume centres and among high- and intermediate-volume surgeons. The use has been more constant in low-volume centres and among low-volume surgeons with a share of slightly less than 10% of all CABGs. (Bakaeen et al. 2014.)

Surgeon and hospital experience play an important role in OPCABG outcomes and seem to be more significant when compared to conventional CABG with CBP (Lapar et al. 2012, Benedetto et al. 2018a). A linear correlation exists between decreased mortality rates and surgeon experience. It has been recommended that 50 to 75 procedures are needed to acquire expertise in OPCABG (Patel et al. 2010). For surgeons operating more than 48 OPCABG procedures a year, the in-hospital mortality rates were significantly lower when compared to ONCABG (Lapar et al. 2012, Benedetto et al. 2018a). In a retrospective study including 999 hospitals in 44 states, 2 094 094 patients in the USA were reviewed from 2003 to 2011. OPCABG performed in low-volume hospitals (less than 29 procedures a year) or by low-volume surgeons (less than 6 procedures a year) increased the risk-adjusted mortality significantly when compared to ONCABG. Contrary, a lower risk-adjusted mortality was associated with high-volume centres (over 164 procedures a year) and high-volume surgeons (over 48 procedures a year). (Benedetto et al. 2018a.) Although surgeon experience seems to be an important factor for in-hospital survival, no similar connection can be seen in the long run. Even high surgeon experience does not seem to improve the well-known and poor long-term outcomes of OPCABG. Among surgeons that had a history of over 100 OPCABG cases, a ten-year follow-up in terms of mortality (29,6% vs 33,4%), incomplete revascularization (8,8% vs 15,7%) and repeat revascularization (14,0% vs 15,4%) seems to favour the use of CPB. (Chikwe et al. 2018.)

Many studies have showed the importance of experience and volume in OPCABG with respect to mortality and severe complications and suggest that OPCABG should only be performed by experienced surgeons. Surprisingly, the vast majority (86%) of American cardiac surgeons are considered low-volume OPCABG surgeons performing less than 20 procedures a year. One third perform no OPCABG procedures at all and only one percent are in the highest third with annual rate of over 100 procedures. (Bakaeen et al. 2014.)

Intraoperative conversion from OPCABG to ONCABG is possible and either used intendedly as part of the operation or unintendedly in case of an emergency. Such emergencies are usually arrhythmias or severe hypotension after commencement of coronary anastomoses. (Mukherjee et al. 2012.) Overall conversion rates, undifferentiated between emergency and elective, are usually between 2% and 6% (Mukherjee et al. 2012, Bakaeen et al. 2014, Benedetto et al. 2018b). Conversion between the two techniques, especially unintended conversions, are associated with more adverse outcomes and increased mortality. In a trial of 1260 patients with 29 conversions (2,3%), the mortality rates for OPCABG converted to ONCABG compared to non-converted OPCABGs were 10,7% and 0,7% ($P<0,001$), respectively (Benedetto et al. 2018b). Similar results were observed in another, larger meta-analysis that included 17 studies and a total of 18 870 patients with a conversion rate of 4,9%. Overall conversion to ONCABG increased in-hospital mortality by an OR of 6,18. Furthermore, emergency conversion raised the OR to 6,99. (Mukherjee et al. 2012.)

Conversion from a beating heart to the use of CPB is more frequently used among less experienced surgeons. For surgeons who had experience of over 60 cases, the conversion rate was only 1,0% while for unexperienced surgeons with a history of one to five procedures the rate was as high as 12,9%. (Mukherjee et al. 2012.) Given the fact that conversion is more common among unexperienced surgeons and the poor in-hospital outcomes that follow a conversion, OPCABG should be operated by experienced surgeons and unnecessary conversions should definitely be avoided.

OPCABG procedures in high- and intermediate-volume hospitals decreased between 2008-2012 while in low-volume hospitals the rates remained constant (Bakaeen et al. 2014). This is controversial since mortality, medical costs and hospital stay are significantly higher in low-volume centres. (Bakaeen et al. 2014, Shinjo et al. 2015, Benedetto et al. 2018a.) The benefit of hospital volume, together with surgeon experience, implicate that OPCABG should be performed in hospitals specialized in off-pump surgery. This is, of course, highly dependent on the health care system in different countries. In addition to total survival rates and financial aspect, hospital organizational structure and its influence on short- and long-term outcomes should be studied in more details.

11. CONCLUSION

Although there are numerous different calculators for assessing the risk for mortality, morbidities and other severe complications, clinical examination stays as the most important way of predicting a suitable operation technique for an individual. Very high-risk patients seem to gain most benefit of OPCABG. Such population consists of females, especially of great age. Other comorbidities including left ventricular dysfunction, diabetes, renal insufficiency, preoperative heart failure and concomitant pulmonary disease could favour OPCABG technique.

Myocardial damage, atrial fibrillation, neurological complications including stroke and TIA and acute kidney injury are the most common and detrimental complications of coronary artery surgery. Although they cannot fully be eliminated by avoiding on-pump surgery, off-pump technique clearly diminishes some of these hazardous consequences, especially in patients with preoperative morbidities.

In addition to previous complications, systemic inflammatory response syndrome, hypercoagulation and excess platelet activation are associated with CPB in numerous reports. OPCABG was initially invented to prevent these complications and the effect of off-pump technique on inflammation, hypercoagulation and platelet activation is not as clear as in ONCABG. Thus, elective bypass surgery should be postponed among patients with infectious or inflammatory disease and should rather be performed without CPB whenever surgery is urgently needed.

OPCABG offers better perioperative and short-postoperative results when compared to ONCABG but seems to come at the expense of higher late mortality at five- and ten-year follow-up. In addition to operation technique, incompleteness of revascularization increases the risk for adverse late-term outcomes.

Cardiovascular diseases and coronary artery disease are the most common cause of death in low-income and developed countries, respectively. In general, they are a cause of huge economic burden and in the near future the expenses are expected to increase. The cost-effectiveness of OPCABG has been shown in almost every study available. In addition to lower hourly theatre costs, it is associated with shorter total hospital stay and lesser resource use.

While surgeon and hospital experience seem to be beneficial for OPCABG patients, it still plays a minor role when choosing between the two techniques. Although the benefit of experience in terms of medical costs and resource use is inevitable, risk factors and comorbidities play a more crucial role when it comes to complications and mortality. Thus, the choice between OPCABG and ONCABG on a single patient should be made on medical basis rather than financial.

Increased mortality and severe complications are associated with low-volume hospitals and low-volume surgeons. At the same time, the number of experienced surgeons is alarmingly decreasing. Conversion from OPCABG to ONCABG increases the risk for morbidities and mortality. Nevertheless, conversion is more frequent among inexperienced surgeons. These facts implicate that OPCABG should be centralized in high-volume hospitals with experienced off-pump surgeons and conversion from OPCABG to ONCABG should be avoided whenever it is possible.

The debate between the two methods and their superiority compared to each other has been going on for decades and there seems to be no final outcome. Both techniques have their advantages and disadvantages. Overall, CABG is a rather safe revascularization procedure with low mortality, given that sternotomy is major surgery and heart is one of the most vital organs of the human body.

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