Risks of Stroke After Coronary Artery Bypass Graft – Recent Insights and Perspectives

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Abstract

Stroke is one of the most devastating complications after coronary artery bypass graft (CABG) surgery, entailing permanent disability, a 3–6 fold increased risk of mortality, an incremental hospital resource consumption and a longer length of hospital stay. Notwithstanding advances in surgical, anaesthetic and medical management across the last 10 years, the risk of stroke after CABG has not significantly declined, likely because an older and sicker population is now deemed suitable to undergo CABG. The pathogenesis of stroke is multifactorial, but two variables are believed to play a major role – cerebral embolisation of atheromatous debris arising from the ascending aorta during surgical manipulation and hypoperfusion during surgery. Identification of vulnerable patients at increased risk of stroke before CABG is of paramount importance for the surgical decision-making approach and informed consent. Several models including demographic, clinical and procedural variables have been developed to risk-stratify the hazard of stroke in patients undergoing CABG, but identification of severe atherosclerosis of the ascending aorta and pre-existing cerebrovascular disease are key determinants for appropriate risk stratification and decision-making. Atherosclerotic disease of the ascending aorta can be identified before surgery using transoesophageal echocardiography, computed tomography and magnetic resonance imaging. However, intra-operative ultrasound scanning of the ascending aorta is the diagnostic tool with the best sensitivity and specificity for the detection of atheromatous debris in the ascending aorta. Although many investigators have advocated the use of off-pump CABG to minimise the risk of peri-operative stroke, results from randomised trials and meta-analyses have been inconsistent. Anaortic approaches, including total arterial revascularisation with *in situ* grafting of both mammary arteries, or the use of the HEARTSTRING® seal device avoid any manipulation of the aorta, thus potentially minimising the risk of stroke in high-risk patients. Assessment and treatment of severe carotid artery disease, and aggressive and prompt treatment of post-operative atrial fibrillation are other important strategies that should be routinely implemented to reduce the risk of stroke in patients undergoing CABG.

Keywords

Stroke, coronary artery bypass, atheroembolism, off-pump, aorta

Disclosure: The authors have no conflicts of interest to declare.

Received: 4 April 2014 **Accepted:** 22 April 2014 **Citation:** *Interventional Cardiology Review*, 2014;9(2):77–83

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Neurological dysfunction following coronary artery bypass graft (CABG) surgery can manifest as stroke, encephalopathy including delirium and post-operative cognitive dysfunction. Stroke is one of the most devastating complications after CABG surgery, entailing permanent disability and a 3–6 fold increased risk of death with a case-fatality rate up to 20 %.^{1,2} It is also associated with incremental hospital resource consumption and a longer length of hospital stay. It has been estimated among a population of 114,233 Medicare beneficiaries that the occurrence of stroke entails an incremental cost of US\$18,552 and an incremental length of hospital stay of seven days.³

The risk of stroke after CABG varies across studies ranging from 0.0 % to 5.2 %, ^{4,5} depending on study design, patient risk profile, operative techniques and the length of study follow-up. Although advances in surgical, anaesthetic and medical management have occurred across the last 10 years, the risk of stroke after CABG has not significantly

declined, likely because an older and sicker population is now deemed suitable to undergo CABG surgery.⁶

In addition, stroke represents a dismal point against CABG when deciding the optimal strategy of revascularisation between CABG and percutaneous coronary intervention (PCI) in patients with multivessel coronary artery disease. Specifically, in a recent meta-analysis including 19 randomised controlled trials with 10,944 patients, CABG was associated with significantly higher 30-day and one-year rates of stroke compared with PCI.⁷ Interestingly, the difference in the risk of stroke between the two strategies of revascularisation seemed more evident in patients with unprotected left main coronary artery disease or multivessel coronary artery disease than in patients with single vessel coronary artery disease.⁷ In addition, in a recently published meta-regression analysis including 20 randomised controlled trials comparing PCI versus CABG in patients with stable angina, a significant interaction

between female gender and stroke risk reduction with PCI was apparent.⁸

Pathogenesis

The pathogenesis of stroke is multifactorial, but two variables are believed to play a major role – cerebral embolism and hypoperfusion during surgery. Some studies suggested that panvasacular inflammation may also play a role, especially in the setting of acute coronary syndromes.⁹ Cerebral embolism is by far the most common cause of peri-operative stroke accounting for 50–75 % of cases. Cerebral emboli arise from either the ascending aorta during surgical manipulation or from the heart due to atrial fibrillation.

The prevalence of atherosclerotic disease in the ascending aorta varies across studies, depending on the patient population, the criteria used to define the disease, and the diagnostic tool implemented to detect the disease, with case rates up to 38 % in some studies.¹⁰ This prevalence has significantly increased in recent years, likely due to better diagnostic methods and an increasing population of elderly. Peripheral vascular disease, age, hypertension and diabetes have been reported to be independent predictors of atherosclerotic disease of the ascending aorta.¹¹

A high correlation between atherosclerosis of the ascending aorta and atheroembolism during CABG surgery has been established by several studies.^{5,12–14} In a prospective multicentre study including more than 2,000 patients, atherosclerosis of the ascending aorta was the strongest independent predictor of stroke associated with CABG.⁵ In the study by Bergman et al., extensive atherosclerotic disease of the ascending aorta was associated with a 31 % risk of post-operative stroke.¹² The risk depends on the presence, location and extent of disease when the aorta is surgically manipulated.¹⁵

Embolisation of atheromatous debris from the aorta is likely to occur at the time of cannulation of the aorta for establishing cardiopulmonary bypass, when the aortic clamp is applied or released, or when proximal graft anastomoses are performed using side-biting clamp. Cerebral emboli often co-exist with intra-operative hypoperfusion, which impairs the clearance of microemboli¹⁶ and may be responsible of bilateral watershed infarcts after CABG.¹⁷ Cerebral hypoperfusion may be exacerbated by the co-existence of carotid artery stenosis, which is another important risk factor for intra-operative stroke.¹⁸

Chronic atrial fibrillation is a risk factor for cerebral embolism, and in patients undergoing CABG the peri-operative period may be at increased risk of stroke due to the necessity to modulate anticoagulant therapy. In addition, recent studies have suggested that new onset atrial fibrillation in the peri-operative period is also a risk factor for post-CABG stroke.¹⁹ Atrial fibrillation develops in 15–30 % of patients undergoing CABG,^{20,21} and although initial reports suggested that it was a self-limited phenomenon with no relevant clinical sequelae, a recent study including 8,058 patients undergoing CABG, suggested that new onset atrial fibrillation was associated with significantly higher rates of stroke and long-term mortality.¹⁹

Risk Stratification

Identification of vulnerable patients at increased risk of stroke before CABG is of paramount importance for the surgical decision-making approach and informed consent. The risk of stroke before CABG has been extensively scrutinised leading to the identification of several

risk factors. Age, diabetes, hypertension, peripheral vascular disease, renal failure, left ventricular dysfunction and non-elective surgery have consistently been reported as risk factors of peri-operative stroke in patients undergoing CABG surgery.^{22,23} All these risk factors can be assessed before surgery, so the information can assist informed decision-making by patients, their family and their physicians. The combination of these variables has generated several risk stratification tools that can be implemented before surgery, to determine the individual probability of stroke in patients undergoing CABG.

In the Charlesworth score, generated from 33,000 consecutive patients undergoing isolated CABG, seven variables are integrated, including age, diabetes, left ventricular ejection fraction <40 %, female gender, priority of surgery, renal dysfunction and peripheral vascular disease.²² In the simpler model generated by McKhann et al. only three variables are considered: age, hypertension and history of stroke.⁶ More recently, Hornero et al. generated and validated a new risk model (Pack₂ score), including priority of surgery, peripheral vascular disease, preoperative cardiac failure/left ventricular ejection fraction <40 % and chronic kidney failure.²³ Interestingly, in patients with Pack₂ score ≥2, off-pump CABG significantly reduced the risk of stroke compared with on-pump CABG, whereas no difference was apparent between the two strategies of revascularisation in patients with Pack₂ score <2. Further studies should externally validate this score and assess whether it is useful in clinical practice to select the optimal strategy of revascularisation between on-pump and off-pump CABG in high-risk patients.

However, while these risk stratification tools are important because they factor the additive effect of several variables, they also share a major limitation in disregarding two important risk factors – atherosclerotic disease of the ascending aorta¹² and pre-existing cerebrovascular disease.⁶ As the impact of these two factors on the risk of post-operative stroke is substantial, they should always be scrutinised before deciding the optimal strategy of coronary revascularisation.

Severe atherosclerosis of the ascending aorta is often an unexpected intra-operative finding during CABG, when preoperative risk stratification has not been accurate. It represents a challenge for the surgeon, who may need to change the operative strategy. A variety of methods can be used before surgery to diagnose severe atherosclerosis in the ascending aorta, including computed tomography scanning, transoesophageal echocardiography or magnetic resonance imaging. Intra-operative ultrasonographic scanning of the aorta can also be used to detect atherosclerotic changes in the entire ascending aorta. It is a rapid, safe and sensitive method, and some studies have reported that it is more accurate than both transoesophageal echocardiography¹⁴ and computed tomography in detecting atheromatous debris in the ascending aorta.²⁴

Assessment of the neurological risk profile of patients before CABG is another essential step to make accurate risk stratification. The neurological profile of the patient should be carefully characterised, seeking for a history of stroke, the presence of initial neurocognitive disorders, or the presence of pre-existing cerebrovascular disease.⁶ Recent studies have also suggested that detection of cerebral ischaemia by magnetic resonance imaging before CABG is strongly associated with the risk of post-operative stroke.^{25,26} Screening of carotid artery disease with echo Doppler before CABG should also be performed, especially in high-risk patients.

The Value of Off-pump Coronary Artery Bypass Graft in Reducing the Risk of Stroke

The observation that atherosclerosis of the ascending aorta is a major determinant of stroke after CABG has led some investigators to advocate the use of off-pump CABG to reduce surgical manipulation of the aorta. Several studies have compared clinical outcomes of patients treated with on-pump versus off-pump CABG, and results have been controversial. In general, observational studies have consistently suggested an association between off-pump CABG and stroke reduction, but this association has not been confirmed in several randomised controlled trials (RCTs).

Specifically, in a propensity matched analysis involving more than 42,000 patients, there was a 35 % reduction in the risk of stroke in patients treated with off-pump CABG compared with those treated with on-pump CABG.²⁷ In sharp contrast, in the recently published CABG Off or On Pump Revascularization Study (CORONARY), no significant difference in stroke rates was apparent between patients treated with on-pump CABG versus those treated with off-pump CABG. Similar results were apparent in two other recently published RCTs: German Off-Pump Coronary Artery Bypass Grafting in Elderly Patients (GOPCABE)²⁸ trial and PRAGUE 6 trial.²⁹ Several other RCTs comparing off-pump versus on-pump CABG have been performed, and results are summarised in *Table 1*.

In order to clarify relative safety and efficacy of off-pump versus on-pump CABG, several meta-analyses have been performed, but results have been controversial too. In particular, in the meta-analysis by Afilalo et al.,³⁰ including 59 RCTs with 8,961 patients, there was a significantly lower 30-day risk of stroke with off-pump CABG compared with on-pump CABG. In sharp contrast, in the broader meta-analysis by Moller et al.,³¹ including 86 RCTs with 10,716 patients, there was no significant difference in the risk of stroke at long-term follow-up. Evaluation of different time-points, study selection and different methodology likely explain discrepancies. It should be noted that neither of these two meta-analyses included the CORONARY trial, which with 4,752 patients enrolled, is the largest RCT performed to date.

In the largest meta-analysis performed to date, including the CORONARY trial and analysing the risk of stroke in 22,279 patients, Palmerini et al. showed that patients treated with off-pump CABG had a significantly lower 30-day risk of stroke than patients treated with on-pump CABG. However, when the analyses were restricted to high quality studies, studies with either >100 or >1,000 patients, or to studies with definition or adjudication of stroke by a clinical events committee, the precision of the point estimate was reduced, suggesting that the overall result may have been affected by studies with substantial risk of bias. Most notably, the odds ratio (95 % confidence interval [CI]) for stroke in trials of off-pump versus on-pump CABG enrolling >1,000 patients was 1.10 (0.67, 1.72).

These data therefore do not clearly support the hypothesis of a significant reduction in the risk of stroke with routine implementation of off-pump CABG compared with on-pump CABG. With an absolute risk reduction of 0.1 % and a relative risk reduction of 11.0 % with off-pump CABG versus on-pump CABG observed in the CORONARY trial, more than 300,000 patients would be necessary to assess whether off-pump CABG truly

reduces the risk of stroke compared with on-pump CABG with test power of 80 % and alpha (α)=0.05.

Anaortic Off-pump Coronary Artery Bypass Graft Approaches

As discussed above, RCTs and meta-analyses do not consistently support the hypothesis that routine implementation of off-pump CABG might reduce the risk of stroke compared with on-pump CABG. However, the specific technique used to perform off-pump CABG in those RCTs has not been reported in detail.⁷ Off-pump CABG in fact encompasses a variety of surgical techniques that entails different levels of aortic manipulation, including partial or side clamping of the aorta, use of the HEARTSTRING® Proximal Seal System (MAQUET, San Jose, CA, US)³² and total arterial revascularisation without cross-clamping.

Partial clamping entails surgical manipulation, and does not eliminate the clamp-related risk of stroke. In sharp contrast, anaortic approaches avoids any clamping of the aorta during off-pump procedure by performing *in situ* grafting using both mammary arteries and/or T- or Y-grafting. Several studies have suggested that anaortic approaches may minimise the risk of stroke in patients undergoing CABG. In a meta-analysis including 12 observational studies, the anaortic approach was associated with a significant reduction in the risk of stroke compared with both conventional CABG and off-pump CABG with partial clamping.³³ In addition, Halbersma et al. showed very low rates of stroke in a cohort of 400 consecutive patients undergoing off-pump CABG with anaortic approaches.³⁴ When the results were analysed in the perspective of the surgical arm of the Synergy between percutaneous coronary intervention with Taxus and Cardiac Surgery (SYNTAX) trial,³⁵ a clear trend was apparent, suggesting a reduction of the risk of stroke in patients treated with anaortic approaches compared with patients treated with conventional CABG (0.8 % in the study by Halbersma et al. versus 2.2 % in the surgical arm of the SYNTAX trial). Moreover, the 0.8 % risk of stroke associated with anaortic approaches³⁴ closely matched the 0.6 % risk of stroke associated with stenting in the SYNTAX trial.³⁵

Another device that can be used to minimise aortic manipulation is the HEARTSTRING seal. The HEARTSTRING seal is delivered at the site of circular aortotomy to avoid uncontrolled spurting of blood while the graft is sutured.³² After completion of the anastomosis and before tightening of the suture, the device is removed. In a propensity score matched analysis including 4,314 patients, Emmert et al. showed that the occurrence of stroke was significantly lower in patients treated with anaortic approaches using the HEARTSTRING device compared with patients treated with off-pump CABG using partial clamping.³⁶ Moreover, the HEARTSTRING device had similar rates of stroke as total *in situ* arterial revascularisation, which avoids any touch of the aorta and therefore is considered the gold standard technique to minimise the risk of stroke.

Can We Minimise the Risk of Stroke After Coronary Artery Bypass Graft? Techniques and Patient Selection

Accurate risk stratification and careful selection of the strategy of revascularisation are key factors to minimise the risk of stroke. The presence of severe atherosclerotic disease of the ascending aorta may be associated with a stroke rate up to 45 % if no modifications in the operative technique are implemented.³⁷ Depending on the

Table 1: Randomised Clinical Trials Comparing Off-pump Versus On-pump Coronary Artery Bypass Graft

Study	Primary Endpoint	Study Design	Number of Patients	Results
Al-Ruzzeh, 2006	1) NCF at 6 weeks; 2) Angiographic graft patency at 3 months	Single-centre, superiority (NCF); equivalence (angiographic graft patency)	178	Off-pump superior to on-pump CABG
Ascione, 2005	Peri-procedural retinal microvascular damage	Single-centre superiority	20	Off-pump superior to on-pump CABG
Ascione, 2006	Peri-procedural function of the small intestine, liver and pancreas	Single-centre superiority	40	Off-pump superior to on-pump CABG for liver and pancreatic function
BBS, 2010	All-cause mortality, MI, cardiac arrest, cardiogenic shock, stroke, coronary reintervention at 30 days	Single-centre, safety study	341	On-pump as safe as off-pump CABG
Blacher, 2005	Peri-procedural lymphocyte activation	Single-centre, superiority	28	Superiority not shown
Caputo, 2002	Peri-procedural inflammatory marker release	Single-centre, superiority	40	Off-pump superior to on-pump CABG
Carrier, 2003	In-hospital death, MI, neurological injury, renal and respiratory insufficiency	Single-centre, superiority	65	Off-pump superior to on-pump CABG
Cavalca, 2006	Peri-procedural oxidative stress	Single-centre superiority	50	Off-pump superior to on-pump CABG
CORONARY, 2012	Death, stroke, MI, renal failure at 30 days	Multicentre, superiority	4,752	Superiority not shown
Czerny, 2000	Post-operative inflammatory marker and cTn release	Single-centre, superiority	30	Lower cTn release in off-pump CABG
Czerny, 2001	Completeness of revascularisation	Single-centre	80	Equivalence between off-pump and on-pump CABG
Diegeler, 2000	Peri-procedural NCF impairment	Single-centre, superiority	40	Off-pump superior to on-pump CABG
DOORS, 2010	Death, stroke, MI at 30 days	Multicentre, non-inferiority	900	Non-inferiority not shown
Formica, 2009	Peri-procedural inflammatory marker release	Single-centre, superiority	60	Superiority not shown
Gasz, 2004	Peri-procedural inflammatory marker release	Single-centre, superiority	20	Off-pump superior to on-pump CABG
Gasz, 2005	Peri-procedural inflammatory marker release	Single-centre superiority	30	Off-pump superior to on-pump CABG
Gerola, 2004	Peri-procedural all-cause mortality, MI, pulmonary complications, bleeding, wound complications, NCF	Multicentre	160	Equivalence between off-pump and on-pump CABG
Gonenc, 2006	Peri-procedural oxidative stress	Single-centre	42	Off-pump CABG decreases impairment of oxidant/ antioxidant balance
GOPCABE, 2013	Death, stroke, MI, repeat revascularisation, renal replacement therapy	Multicentre, superiority	2,539	Superiority not demonstrated
Gulielmos, 2000	Peri-procedural inflammatory marker and cTn release	Single-centre	20	Off-pump superior to on-pump CABG
Hernandez, 2007	NCF at hospital discharge	Single-centre, superiority	204	Superiority not shown
Jares, 2007	Peri-procedural coagulation parameters measured with TEG	Single-centre, superiority	20	Off-pump superior to on-pump CABG
JOCRI, 2005	Cardiac death, MI, CHF, TVR at 3 years	Multicentre, non-inferiority	167	Off-pump non-inferior to on-pump CABG
Johansson-Synnergren, 2003	Peri-procedural inflammatory marker release and endothelial function	Single-centre	52	Off-pump CABG reduces complement activation
Khan, 2004	Graft patency at 3 months	Single-centre	103	Graft patency lower in the off-pump CABG
Kochamba, 2000	Peri-procedural outcome	Single-centre, safety study	58	Off-pump as safe as on-pump CABG
Kunes, 2007	Peri-procedural inflammatory marker release	Single-centre, superiority	34	On-pump CABG associated with higher release of pentraxin 3
Lee, 2003	In-hospital all-cause death, stroke and length of stay, intra-aortic balloon support post-operatively	Single-centre, superiority	60	Off-pump superior to on-pump CABG
Legare, 2004	Peri-procedural death, MI, stroke, AF, deep sternal wound infection	Single-centre, superiority	300	Superiority not shown
Lingaas, 2006	Graft patency at 12 months	Single-centre	120	Equivalence between off-pump and on-pump CABG

Table 1: Continued

Study	Primary Endpoint	Study Design	Number of Patients	Results
Malik, 2006	Peri-procedural CPK-MB release	Single-centre, superiority	50	Off-pump superior to on-pump CABG
Mandak, 2008	Peri-procedural tissue metabolism	Single-centre, superiority	40	Off-pump superior to on-pump CABG
MASS III, 2010	Death, MI, Stroke, TVR at 5 years	Single-centre	308	Similar incidence of the PE between off-pump versus on-pump CABG
Matata, 2000	Peri-procedural inflammatory marker release and oxidative stress	Single-centre	20	Off-pump CABG significantly reduced the PE
Medved, 2008	In-hospital mortality or morbidity	Single-centre	60	Similar incidence of the PE between off-pump versus on-pump CABG
Michaux, 2006	LVEF and diastolic function (tricuspid and mitral E/A ratio)	Single-centre	50	Similar incidence of the PE between off-pump versus on-pump CABG
Modine, 2010	Peri-procedural renal injury	Single-centre	71	Off-pump CABG attenuates peri-procedural renal injury
Motallebzadeh, 2004	Peri-procedural cerebral injury	Single-centre	35	Off-pump CABG significantly reduced the PE
Motallebzadeh, 2007	Peri-procedural NCF	Single-centre	212	NCF better in the off-pump CABG
Muneretto, 2003	Early and midterm outcomes	Single-centre	176	Similar incidence of the PE between off-pump versus on-pump CABG
Nesher, 2006	Peri-procedural inflammatory marker and CPK-MB release	Single-centre	125	Off-pump CABG reduced the incidence of the PE
Niranjan, 2006	Autologous blood transfusion and post-operative complications	Single-centre	80	Similar incidence of the PE between off-pump versus on-pump CABG
OCTOPUS, 2007	NCF at 3 months	Multicentre, superiority	281	Superiority not shown
Ozkara, 2007	Peri-procedural PAI-1 release	Single-centre	44	Off-pump CABG associated with higher level of PAI-1
Parolari, 2003	Peri-procedural oxygen metabolism	Single-centre	25	No difference in the PE between off-pump and on-pump CABG
Parolari, 2005	Peri-procedural plasma P-selectin and TF levels	Single-centre, superiority	29	Superiority not shown
Penttila, 2001	Peri-procedural changes in myocardial metabolism	Single-centre	22	Off-pump CABG associated with better myocardial energy preservation
PRAGUE-4, 2004	Death, MI, stroke, RF requiring haemodialysis at 30 days	Single-centre	388	No difference in the PE between off-pump and on-pump CABG
PRAGUE-6, 2013	Death, MI, stroke, new RF	Single-centre	206	Off-pump superior to on-pump CABG
Rachwalik, 2006	Peri-procedural respiratory function	Single-centre	42	NA
Rainio, 2007	Peri-procedural retinal micro-embolism	Single-centre	20	Off-pump CABG reduced the incidence of the PE
Rasmussen, 2007	Peri-procedural inflammatory marker release	Single-centre	35	Off-pump CABG reduced the incidence of the PE
Rastan, 2005	Peri-procedural inflammatory marker, CPK-MB and cTn release	Single-centre	40	Off-pump CABG attenuates myocardial injury
ROOBY, 2009	All-cause death, reoperation, new mechanical support, coma, stroke, cardiac arrest, RF requiring dialysis at 30 days. All-cause death, MI, TLR at 1 year	Multicentre, superiority	2,203	Superiority not shown
Sahlman, 2003	Peri-procedural inflammatory and CPK-MB release	Single-centre	50	Off-pump CABG reduced the incidence of the PE
Sajja, 2007	Peri-procedural renal function	Single-centre	116	Off pump CABG associated with better renal function
Selvanayagam, 2004	Peri-procedural LVEF	Single-centre	60	Off-pump CABG associated with better LVEF

Table 1: Continued

Study	Primary Endpoint	Study Design	Number of Patients	Results
SMART, 2003	Completeness of revascularisation and graft patency at 30 days	Single-centre	197	Similar incidence of the PE between off-pump and on-pump CABG
Sousa Uva, 2010	Graft patency at 5 weeks	Single-centre, superiority	150	On-pump superior to off-pump CABG
Tang, 2002	Peri-procedural renal injury	Single-centre	40	Similar incidence of the PE between off-pump and on-pump CABG
Tatoulis, 2006	Systemic vascular resistance at 12 hours	Single-centre	100	PE similar between off-pump and on-pump CABG
Vedin, 2006	NCF at 6 months	Single-centre	80	PE similar between off-pump and on-pump CABG
Velissaris, 2003	Peri-procedural gastric mucosa oxygenation	Single-centre	54	PE similar between off-pump and on-pump CABG
Vural, 1995	Peri-procedural haemodynamic assessment	Single-centre	50	PE similar between off-pump and on-pump CABG
Wan, 2004	Peri-procedural inflammatory marker release	Single-centre	37	Off-pump CABG attenuates marker release
Wandschneider, 2000	Peri-procedural inflammatory marker release	Single-centre	108	Off-pump CABG attenuates marker release
Wehlin, 2004	Peri-procedural inflammatory marker release	Single-centre	37	Off-pump CABG attenuates marker release
Zamvar, 2002	NCF at 10 weeks	Single-centre	60	Off-pump CABG attenuates NC dysfunction

AF = atrial fibrillation; ARF = acute renal failure; CABG = coronary artery bypass graft; CHF = congestive heart failure; CORONARY = CABG Off or On Pump Revascularization Study; CPK = creatine phosphokinase; cTn = cardiac troponin; DOORS = Danish On-Pump versus Off-Pump Randomization Study; GOPCABE = German Off-Pump Coronary Artery Bypass Grafting in Elderly Patients study; JOCRI = Japanese Off-pump Coronary Revascularization Investigation; LVEF = left ventricular ejection fraction; MASS III = Medicine, Angioplasty, or Surgery Study; MI = myocardial infarction; NA = not available; NCF = neurocognitive function; PAI-1 = Plasminogen activator inhibitor-1; PE = primary endpoint; RF = renal failure; ROOBY = Randomized On/Off Bypass study; SMART = Surgical Management of Arterial Revascularization Therapies; TEG = thromboelastography; TF = tissue factor; TLR = target lesion revascularisation; TVR = target vessel revascularization.

individual risk profile of patients, several options can be considered to minimise the risk of stroke. If the risk of stroke appears prohibitive with CABG, and anaortic approaches cannot be used, PCI should be considered as an alternative. In case of severe atherosclerotic disease of the ascending aorta, off-pump CABG with anaortic approaches should be implemented. Total arterial revascularisation with *in situ* grafting using both mammary arteries and/or T- or Y-grafting should be considered the gold standard to minimise the risk of stroke.

When complete revascularisation cannot be achieved with total arterial revascularisation, use of the HEARTSTRING device may help in minimising aortic manipulation. Use of intra-operative epiaortic ultrasound, which can precisely characterise site and extension of atherosclerotic disease, may help the surgical decision-making approach. In the study by Bolotin et al., intra-operative findings of atherosclerotic disease of the ascending aorta with epiaortic ultrasound led to a change in the surgical strategy in 28 % of cases.¹⁰ Moreover, in cases in which on-pump CABG cannot be avoided, epiaortic ultrasound may help in identifying a relatively disease-free portion of the aorta to minimise the risk of atheroembolism when clamping or cannulating the aorta.

Despite some studies suggesting a potential benefit of anaortic approaches for high-risk patients, this technique has not been widely embraced. For several reasons, including the technical requirements for performing graft anastomoses with the beating heart and the concern for long-term patency, most surgeons worldwide still prefer to perform CABG with cardiopulmonary bypass.³⁸ Thus, much of

the evidence derived from the aforementioned studies has been contributed by highly experienced centres with surgeons that have developed high proficiency in performing off-pump CABG. Whether this technique can be safely extended to all cardiac surgical centres, remains to be determined.

Use of epiaortic filters has also been advocated as another possible strategy to minimise the risk of cerebral embolism in patients with severe atherosclerotic disease of the ascending aorta, who are not deemed suitable for anaortic approaches. The filter is inserted through a modified arterial cannula immediately before releasing the cross-clamp, and it remains in the aorta until cardiopulmonary bypass is discontinued. In a study involving 77 patients, implantation of the filters proved to be feasible, safe and uneventful.³⁹ Particulate emboli were retrieved in 44 patients, the predominant origin of which was atheromatous. In a randomised trial including 1,289 patients, particulate emboli were detected in 598 (96.8 %) of 618 successfully deployed filters.⁴⁰ In addition, a significant reduction in post-operative renal complications was apparent in patients in whom filters were implanted compared with the control group.

More controversial appears the management of patients with carotid artery disease that have to undergo CABG. The prevalence of severe carotid disease in this setting is around 6–12 %.⁴¹ Three approaches are commonly used: carotid endarterectomy followed by CABG, combined carotid endarterectomy and CABG, and more recently carotid stenting followed by CABG. In a propensity matched analysis of 350 patients in which these three approaches were compared, Shishehbor et al. showed significantly lower long-term rates of

all-cause death, myocardial infarction and stroke in patients treated with carotid stenting followed by CABG in comparison with both carotid endarterectomy followed by CABG (adjusted hazard ratio [HR] 0.33, 95 % CI 0.15–0.77; $p=0.01$) and combined carotid endarterectomy and CABG (HR 0.35, 95 % CI 0.18–0.70).⁴² However, due to the observational nature of the study, these data should be considered hypothesis generating, and further randomised trials are warranted.

Optimal blood pressure management, prompt recognition and treatment of new onset atrial fibrillation, prevention of rewarming temperature $>37^{\circ}\text{C}$,⁴³ use of alpha-stat pH management⁴⁴ and prevention of hyperglycaemia during surgery⁴⁵ are other recommendations that should be considered depending on the individual risk profile of patients.

Conclusions

Notwithstanding the remarkable improvement in surgical, anaesthetic and medical management, the risk of stroke after CABG has not significantly declined. Risk stratification is of the utmost importance for identifying vulnerable patients. Specifically, pre-existing cerebrovascular disease and atherosclerosis of the ascending aorta are major determinants of the risk of peri-operative stroke, and should be always carefully scrutinised. RCTs and meta-analysis do not clearly support routine implementation of off-pump CABG as a strategy to minimise the risk of stroke. Observational studies have suggested that anaortic approaches might reduce the risk of stroke compared with conventional CABG in patients with severe atherosclerosis of the ascending aorta. Further randomised controlled trials are warranted to confirm this hypothesis. ■

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