

BMJ Open Carbon dioxide surgical field flooding and aortic NO-touch off-pump coronary artery bypass grafting to reduce Neurological injuries after surgical coronary revascularisation (CANON): protocol for a randomised, controlled, investigator and patient blinded single-centre superiority trial with three parallel arms

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ABSTRACT

Introduction Neurological injuries remain a major concern following coronary artery bypass grafting (CABG) that offsets survival benefit of CABG over percutaneous coronary interventions. Among numerous efforts to combat this issue is the development of off-pump CABG (OPCABG) that obviates the need for extracorporeal circulation and is associated with improved neurological outcomes. The objective of this study is to examine whether the neuroprotective effect of OPCABG can be further pronounced by the use of two state-of-the-art operating techniques.

Methods and analysis In this randomised, controlled, investigator and patient blinded single-centre superiority trial with three parallel arms, a total of 360 patients will be recruited. They will be allocated in a 1:1:1 ratio to two treatment arms and one control arm. Treatment arms undergoing either aortic no-touch OPCABG or OPCABG with partial clamp applying carbon dioxide surgical field flooding will be compared against control arm undergoing OPCABG with partial clamp. The primary endpoint will be the appearance of new lesions on control brain MRI 3 days after surgery. Secondary endpoints will include the prevalence of new focal neurological deficits in the first 7 days after surgery, the occurrence of postoperative cognitive dysfunction at either 1 week or 3 months after surgery and the incidence of delirium in the first 7 days after surgery. Data will be analysed on intention-to-treat principles and a per protocol basis.

Ethics and dissemination Ethical approval has been granted for this study. Results will be disseminated through peer-reviewed media.

Trial registration number NCT03074604; Pre-results.

Strengths and limitations of this study

- CANON study is the first study to evaluate the neuroprotective effectiveness of aortic no-touch off-pump coronary artery bypass grafting technique and the practice of carbon dioxide surgical field flooding using a prospective randomised controlled design.
- Meticulous methodology of neurological injuries assessment employed in the CANON study will allow for a thorough evaluation of the studied surgical techniques influence on the central nervous system.
- Data provided by the CANON study may impact clinical practice regarding the choice of the most favourable technique for surgical coronary revascularisation.
- CANON study is conducted within a single clinical setting which may influence the speed of participant recruitment.
- In the CANON study, loss to 3-month follow-up is possible.

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INTRODUCTION

Background and rationale

Neurological complications of cardiac surgery are well recognised, common and clinically important. They have been classified into types 1 and 2 by the American College of Cardiology and the American

Heart Association.¹ Type 1 neurological injuries are overt and include stroke and transient ischaemic attack (TIA), whereas more subtle complications like delirium and postoperative cognitive dysfunction (POCD) are classified as type 2 neurological injuries. The frequency of stroke associated with coronary artery bypass grafting (CABG) depends on patient variables and the type of surgery performed, ranging from 1.6% to 3%.² Meanwhile, the incidence of delirium and POCD during the first week after cardiac surgery was reported in up to 50% and 80% of patients, respectively.^{3,4} Although type 2 neurological injuries are not as devastating as stroke, they are associated with negative hospital outcomes including a tenfold increased risk of death and a fivefold increased risk of nosocomial complications.⁵

The principal aetiology of intraoperative brain damage is embolic, followed by hypoperfusion and inflammation.² In order to reduce the negative impact of such mechanisms, various strategies have been proposed. Noteworthy among them are preventative operative techniques, especially the off-pump CABG (OPCABG). This method has been introduced to avoid potentially harmful effects of cardiopulmonary bypass (CPB) and involves performing surgery on a beating heart. In spite of its theoretical advantages, the neuroprotective effects of this approach remain a subject of intense debate.⁶ However, an up-to-date meta-analysis revealed no difference between OPCABG and CPB-CABG with respect to all-cause mortality and myocardial infarction while OPCABG was associated with a significant reduction in the odds of cerebral stroke.⁷ Additionally, it is important to note that most studies reporting no difference in neurological complications between on-pump and off-pump procedures do not take into account that OPCABG is not a homogenous technique. One of its modifications (ie, aortic no-touch OPCABG, also known as 'no-touch' OPCABG) avoids any kind of aortic manipulation by using both in situ internal mammary arteries as the only source of blood supply to the coronary grafts. This may be effective in reducing particulate microembolism because numerous studies showed embolic showers in transcranial Doppler ultrasonography during clamping and unclamping of ascending aorta⁸ while avoiding this manoeuvre by using devices for proximal venous graft anastomoses showed reduction in neurological injury compared with CPB-CABG.⁹ Recent meta-analyses found that 'no-touch' OPCABG was associated with lower risk of cerebrovascular accident as compared with OPCABG with partial clamp ('traditional' OPCABG).^{10,11} Additionally, the neuroprotective value of the 'no-touch' OPCABG has been preliminarily tested in our previous pilot study. This investigation showed a significantly lower incidence of POCD in patients who underwent 'no-touch' OPCABG compared with 'traditional' OPCABG.¹²

While 'no-touch' OPCABG technique primarily reduces the number of solid microemboli, formation of gaseous microemboli remains a threat to the patients' central nervous system. However, the harmful impact of these

factors may be limited by the practice of using carbon dioxide (CO₂) flooding to displace air in the surgical field. Carbon dioxide is 25 times more soluble in blood than air, does not form bubbles and is rapidly discharged from the system through breathing. It has been used in cardiac operations since 1950s, but remains relatively underused in CABG. Although the reports on the neuroprotective qualities of CO₂ surgical field flooding are sparse and do not focus distinctly on CABG, they consistently show its efficiency in reducing postoperative neurological injury following open heart surgery.¹³

Objectives

The objective of this study is to investigate the value of employing the 'no-touch' OPCABG technique and the practice of CO₂ surgical field flooding for the prevention of type 1 and 2 neurological injuries following surgical coronary revascularisation. In particular, we aim to assess the incidence of new lesions on control brain MRI, new focal neurological deficits, delirium and POCD following different techniques of surgery. We hypothesise a reduction in postoperative brain dysfunctions in patients treated with both of the examined methods.

Trial design

The CARbon dioxide surgical field flooding and aortic NO-touch OPCABG to reduce Neurological injuries after surgical coronary revascularisation (CANON) trial is designed as a randomised, controlled, investigator and patient blinded single-centre superiority trial with three parallel arms and a primary endpoint being the appearance of new lesions on control brain MRI 3 days after surgery.

METHODS

Study setting

The study will take place in the Department of Cardiac Surgery, Dr Antoni Jurasz Memorial University Hospital, Bydgoszcz, Poland. This is a tertiary care centre that performs more than 400 CABG annually. The off-pump method is used as standard in all of these surgeries and both its 'traditional' and 'no-touch' variants are used regardless of the extent of required revascularisation.

Eligibility criteria

Participants will be recruited among patients above 60 years of age and expecting elective and/or urgent CABG for multivessel coronary disease. They will be assessed with Mini-Mental State Examination (MMSE) and the Hospital Anxiety and Depression Scale (HADS) by a trained physician at the time of admission. Patients scoring below age-adjusted and education-adjusted cut-off scores in MMSE and/or above 8 on the subscales of HADS will be excluded from this research. Other exclusion criteria for this study will be as follows: neurological deficit of any aetiology, previous psychiatric illness, use of tranquilisers or antipsychotics, alcohol or drug abuse, history of cardiac surgery, preoperative left ventricular ejection fraction less than 30%, extracranial carotid artery stenosis

of more than 70%, body mass index of more than 35 kg/m², any contraindication for MRI (eg, MRI-incompatible implantable device and claustrophobia) and emergent and salvage setting. Additionally, patients with isolated left anterior descending coronary artery disease will be excluded from this study as, in this condition, standard of care requires performing 'no-touch' OPCABG and prevents randomisation.¹⁴

Interventions

Patients will be randomised into two treatment arms and one control arm. Treatment arms will undergo either 'no-touch' OPCABG or 'traditional' OPCABG applying CO₂ surgical field flooding. Control arm will undergo 'traditional' OPCABG. To reduce the bias of surgeon's experience and preference, all interventions will be carried out by two persons. The operators will be qualified specialist who performed at least 500 procedures of each type before joining this research.

All patients will undergo OPCABG through a median sternotomy. To obtain heart exposure, deep pericardial traction sutures (Lima stitch) will be applied. Target vessels will be stabilised using Octopus Medtronic coronary stabiliser and occluded with bulldog clamp. All the left anterior descending coronary artery lesions will be bypassed with left internal mammary artery graft (LIMA graft). Other coronary bypasses, for patients in study arm 2 (treatment group operated on with 'traditional' OPCABG applying CO₂ surgical field flooding) and in study arm 3 (control group operated on with 'traditional' OPCABG), will be performed with the use of vein grafts anastomosed proximally onto the aorta. For patients in study arm 1 (treatment group operated on with 'no-touch' OPCABG), only skeletonised internal mammary artery grafts will be used (ie, LIMA graft, right internal mammary artery graft (RIMA graft) or a Y-graft that uses RIMA anastomosed onto LIMA) to allow for complete arterial myocardial revascularisation. However, in the rare event that the aforementioned approach is insufficient to reach all target vessels, a reversed (great) saphenous vein graft or a radial artery graft may be used to extend the LIMA or RIMA. In study arm 2, the chest cavity will be insufflated with CO₂ at a flow above 5L/min during the entire surgical procedure. To accurately assess the anastomotic quality of all grafts in every study arm, intraoperative transit time flow measurement will be used.

All interventions in this study will be performed under the same anaesthetic protocol. All patients will be treated before and after surgery according to the current European Society of Cardiology Guidelines.

Modifications

The final decision on the type of surgery to be performed will be based on patients' safety and will be made by the surgeon after intraoperative assessment.

Outcomes

The primary endpoint of this study will be the appearance of new lesions on control brain MRI 3 days after

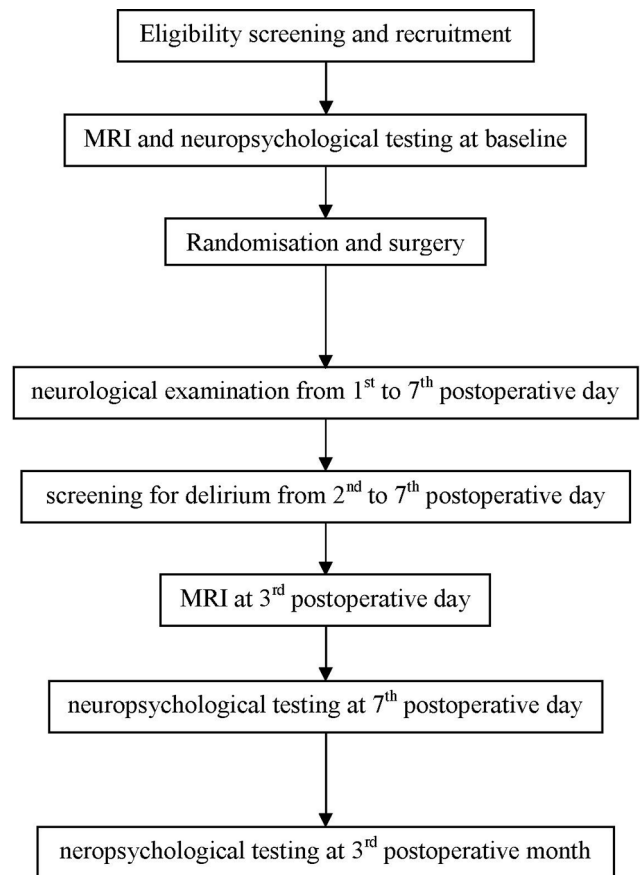


Figure 1 Single patient diagnostics process.

surgery. Secondary endpoints will include the prevalence of new focal neurological deficits in the first 7 days after surgery, the occurrence of POCD at either 1 week or 3 months after surgery and the incidence of delirium in the first 7 days after surgery.

Participant timeline

The participant timeline is outlined in [figure 1](#).

Sample size

Sample size was calculated for the primary endpoint, that is, the appearance of new lesions on control brain MRI. Prior data indicate that the incidence of this complication after cardiac surgical procedures is 30%.¹⁵ Consequently, the expected failure rate is 0.3 in study arm 3 (control group operated on with 'traditional' OPCABG). Based on our pilot research, a 50% reduction in neurological injury in study arm 1 (treatment group operated on with 'no-touch' OPCABG) is predicted.¹² Accordingly, the presumed true failure rate for experimental subjects in this group is 0.15. A sample size of 120 patients in study arm 1 and 120 patients in study arm 3 are needed to reject the null hypothesis that the failure rates for experimental and control subjects are equal with probability (power) 0.8. The type 1 error probability associated with this test of this null hypothesis is 0.05. An uncorrected χ^2 statistic will be used to evaluate this null hypothesis.

Currently, there is not enough evidence to allow for prediction of neurological injury rate in study arm 2

(treatment group operated on with 'traditional' OPCABG applying CO₂ surgical field flooding). Consequently, the number of patients who will be operated using this technique is arbitrarily set at 120 in line with study arm 1 and study arm 3.

Recruitment

At the time of admission to the hospital, patients who meet the criteria of eligibility for this study will be invited to enter the trial in a one-on-one interview with the principal investigator.

Allocation

Patients will be assigned in a 1:1:1 ratio to the three arms of the study according to a computer-generated list of random numbers. The allocation sequence will be concealed from the researchers enrolling and assessing participants in consecutively numbered, opaque and sealed envelopes. The sequence generation and the envelopes will be prepared by an investigator with no clinical involvement in the trial. They will be stored in a closed locker in the operating block. The randomisation will take place after the completion of all baseline assessments, immediately before surgery. A member of the surgical team will open the next consecutively numbered envelope and perform the designated intervention.

Blinding

Investigators and patients will be blinded to study arm allocation. Unfortunately, some participants may deduce that they were assigned to the study arm 1 (treatment group operated on with 'no-touch' OPCABG) due to the absence of vein harvest wounds on their lower limbs. On the contrary, presence of vein harvest wounds is not indicative of any surgical procedure, as even patients treated with 'no-touch' OPCABG may receive vein grafts. Considering that this potential for unblinding may also affect the investigators, patients will be instructed not to disclose any information about the surgery and to cover their legs during the follow-up assessments. Any cases of unblinding and their reasons will be recorded and reported along with the trial's results.

Data collection methods

MRI assessment

Brain MRI will be performed at baseline and 3 days post-operatively. A 1.5-T scanner will be used (Optima MR450w, GE Healthcare, Waukesha, USA) with a 12-channel coils. Both examinations will consist of morphological imaging and functional imaging. The morphological imaging will be the same for both scans. A high-resolution, three-dimensional (3D) inversion recovery fast spoiled gradient echo T1-weighted images will be used for the brain volumetric assessment and anatomical reference. Chronic white matter lesions will be assessed with a high-resolution 3D fluid-attenuated inversion recovery (FLAIR) sequence.¹⁶ Both chronic and new microbleeds will be detected using a susceptibility-weighted imaging (SWI) sequence.¹⁷

The functional imaging will include an analysis of the diffusion and perfusion within the brain tissue. A multi-b-value single shot echo-planar imaging scan ($b=0, 20, 50, 100, 200, 400, 600, 800, 1000$ and 1500s/mm^2) will be used to perform both a conventional diffusion-weighted image (DWI) analysis and an imaging based on the intra-voxel incoherent motion (IVIM) theory.¹⁸ Conventional DWIs, including apparent diffusion coefficient maps, will be used to count acute ischaemic lesions. Biexponential fits will be applied to calculate pseudo-diffusion coefficient (D^*), perfusion fraction (f) and pure molecular diffusion coefficient (D) on the basis of the IVIM model.¹⁹ Whole brain perfusion will be assessed with the use of a non-contrast enhanced 3D pseudo-continuous arterial spin labelling (ASL) technique.²⁰ Additionally, the baseline examination will include an analysis of microstructural white matter integrity with diffusion tensor imaging (DTI) scan at 25 directions.²¹

The MRI scans will be evaluated independently by two experienced neuroradiologists blinded to patients' group allocations, with disagreements resolved by consensus. Brain lesions detected on postoperative DWI and SWI that are not present on pretreatment images will be classified as new. The location, number and volume of these lesions will be evaluated. FLAIR images, SWI and conventional DWIs will be analysed using a dedicated custom clinical software READY View (GE Healthcare, Waukesha, USA). For postprocessing and calculations of IVIM parameters IVIM AW V.4.6 (GE Healthcare, Waukesha, USA) and Olea Sphere V.3.0 (Olea Medical, La Ciotat, France) will be applied. Voxel-based brain volumetry as well as ASL and DTI analysis will be performed using FMRIB Software Library V.5.0 (Analysis Group, FMRIB, Oxford, UK).

Neurological assessment

Clinical neurological status will be examined by a neurologist preoperatively and once every day until 7 day after surgery. The occurrence of postoperative TIA will be defined as a transient episode of focal neurological dysfunction caused by brain, spinal cord or retinal ischaemia, without acute infarction, while stroke will be diagnosed on the basis of the presence of acute infarction in postoperative MRI or the persistence of symptoms for at least 24 hours.²² National Institutes of Health Stroke Scale will be used to categorise severity of stroke (none, minor, moderate, moderate/severe, severe) and modified Rankin Scale will be used to measure disability.

Neuropsychological assessment

A single experienced neuropsychologist blinded to patients' group allocations will perform neurocognitive assessment. Examination will be conducted preoperatively, as well as 7 days and 3 months after surgery in the same quiet and seclude environment with a battery of well-established tests chosen according to the Statement of Consensus on Assessment of Neurobehavioral Outcomes after Cardiac Surgery.²³ It will include the Stroop test (consisting colours' names with meaning incongruent with ink they are printed in) comprising two subtasks,

part A (time required to read the words aloud ignoring the ink colour) assessing speed of processing and part B (time required to name the colours of the ink in which the words are printed) assessing attention, automaticity and parallel distributed processing; the Trail Making Test part A (time required to connect numbered circles in ascending order) assessing psychomotor speed and the Trail Making Test part B (time required to connect circles containing numbers and letters in ascending and alternating order) assessing selective attention and shifting ability; the Digit Span Test forward (number of correctly recalled digit strings in original order of presentation) assessing auditory attention and short-term retention and the Digit Span Test backward (number of correctly recalled digit strings in reverse order of presentation) assessing verbal working memory; and Rey Auditory Verbal Learning Test (number of correctly recalled words on five trials) assessing learning and immediate and delayed memory functions. The same form of each test will be used preoperatively and postoperatively. Currently, there is no one definition of POCD. In this research, it will be described as a decline from preoperative performance of more than 20% on two or more tests according to the definition provided by Martens *et al*²⁴ and used in our pilot study.¹²

Delirium assessment

Two psychologists trained in delirium assessment and blinded to the type of surgery performed will screen all participants after surgery. The initial examination will take place no sooner than 24 hours postoperatively. The purpose of this timing is to avoid confounding results with postanaesthetic emergence delirium which is usually of short duration and minimal clinical consequence.²⁵ Following examinations will be performed twice daily at 0800 and 2000 hours until 7 day after surgery. The diagnosis of delirium will be based on Confusion Assessment Method for the Intensive Care Unit (CAM-ICU).²⁶ It is valid, reliable and recommended by the current 2013 Pain, Agitation and Delirium Clinical Practice Guidelines for adult ICU patients.²⁷ The polish version of CAM-ICU employed in this study is available at www.proicu.pl.

Immediately before each screening for delirium, assessment of sedation or agitation will be performed using Richmond Agitation-Sedation Scale (RASS).²⁸ Based on its results, three motoric subtypes of delirium will be determined. According to the classification provided by Peterson *et al*,²⁹ hypoactive delirium will be diagnosed when RASS is consistently negative or neutral (RASS -3 to 0), hyperactive delirium will be diagnosed when RASS is consistently positive (RASS +1 to +4) and mixed delirium will be diagnosed when, during the episode, RASS is alternately negative or neutral (RASS -3 to 0) and positive (RASS +1 to +4). Patients who are unresponsive (RASS -5 to -4) will be defined as comatose and excluded from further assessment.

Statistical analysis

The statistical analysis will follow the intention-to-treat approach, with each patient being analysed as a member of the study arm assigned by randomisation, regardless of treatment subsequently received. The treatment arms undergoing either 'no-touch' OPCABG or 'traditional' OPCABG applying CO₂ surgical field flooding will be compared against the control arm undergoing 'traditional' OPCABG for all analyses. To calculate primary and secondary outcomes, χ^2 test will be applied. Up-to-date version of STATISTICA (StatSoft, Tulsa, OK, USA) will be used to conduct all statistical analyses.

Data monitoring

A data monitoring committee will not be established for this study due to known minimal risks of all applied interventions.

The progress of the study will be evaluated every 6 months. The principal investigator will consolidate data acquired by individual researchers and thus be the only person with access to the entire dataset. He will review source documents and identify any problems with data gathering (eg, insufficient recruitment or retention of participants, inadequate or insufficient research staff, missing data). The principal investigator has the right to terminate or modify the trial according to certain circumstances (eg, danger to participants' safety or insufficient recruitment).

Harms

There are no safety concerns related to this study. Currently, all interventions evaluated in this research are considered equivalent and are routinely used in contemporary medicine. There are no known harmful side effects of using MRI scanners on patients without contraindications to this diagnostic method, and there were many studies that used MRI in this clinical setting before.¹⁵ A neurological, neuropsychological and delirium assessment designed for this study is entirely non-invasive. Nevertheless, if any adverse effects occur, they will be reported to the principal investigator during research staff's briefings held in the morning of every working day.

Ethics and dissemination

This study obtained the approval of the Bioethics Committee at Collegium Medicum in Bydgoszcz (KB 60/2017) and will be completed according to the standards established in the Declaration of Helsinki. Modifications to the protocol will require a formal amendment and permission from the aforementioned Bioethics Committee.

The principal investigator will introduce the trial to potential participants. Patients will be provided with both verbal and written information about the study. They will then be able to have an informed discussion about its details. Written consent will be required to partake in this research.

All study-related information will be stored in locked file cabinets while electronic databases will be password protected. Coded identification numbers will be

used to conceal personal information on all laboratory specimens and data collection forms. Participants' study information will not be released outside of the study, except as necessary for monitoring by the Bioethics Committee at Collegium Medicum in Bydgoszcz.

Results will be disseminated in peer-reviewed media using the CONSORT statement recommendations.

DISCUSSION

At this point, there is very little research on the neuroprotective effectiveness of individual OPCABG techniques. Given this lack of data, studies that compare the frequency of neurological injuries following CPB and off-pump procedures usually use 'traditional' OPCABG as their reference. However, in this clinical situation, 'traditional' OPCABG may in fact be the least favourable of all off-pump methods. Therefore, the debate between supporters and critics of performing surgery on a beating heart may be greatly influenced by the results of this investigation. If the studied techniques prove to have better neuroprotective value than 'traditional' OPCABG, they should be considered the standard of off-pump surgery to which the CPB-CABG needs to be compared. Consequently, the advantages of avoiding CPB may become more apparent.

Essentially, data provided by this study may impact clinical practice regarding the choice of the most favourable technique for surgical coronary revascularisation. If the research demonstrates outstanding neuroprotective effectiveness of any studied treatment, it should be considered state of the art for reducing neurological injuries following CABG. Taking into account that such complications threaten a substantial number of people undergoing CABG every year, results of this investigation may reduce their extensive economic and societal impact.

Finally, the meticulous design of neurological injuries assessment employed in this study needs to be emphasised. Combined with a thorough analysis of clinical data, it may give insights into the underlying mechanisms of postoperative neurological complications that are beyond the initial assumptions of this research. For example, apart from testing its hypothesis, our preliminary investigation has yielded some interesting results regarding the predictive value of a recently developed angiographic grading tool for short-term cognitive outcomes of OPCABG.³⁰ Therefore, by providing a vast wealth of neuropsychiatric and radiological data, this project may have a profound impact on the research field in pioneering and facilitating its further development.

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Correction notice This article has been corrected since it first published. The author surnames and first names were the wrong way round in the original version

and have now been corrected.

Contributors SK conceived the study and is a guarantor. SK, PW, SZ, KM, TR, PD, SM, TM, AL and BA designed the trial. SK drafted the protocol aided by SZ and KM. All authors decided to submit this final version of the protocol.

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Competing interests None declared.

Ethics approval Bioethics Committee at Collegium Medicum in Bydgoszcz.

Provenance and peer review Not commissioned; externally peer reviewed.

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REFERENCES

- Eagle KA, Guyton RA, Davidoff R, *et al.* ACC/AHA guidelines for coronary artery bypass graft surgery: executive summary and recommendations. *Circulation* 1999;100:1464–80.
- Oi K, Arai H. Stroke associated with coronary artery bypass grafting. *Gen Thorac Cardiovasc Surg* 2015;63:487–95.
- Rudolph JL, Jones RN, Levkoff SE, *et al.* Derivation and validation of a preoperative prediction rule for delirium after cardiac surgery. *Circulation* 2009;119:229–36.
- Rasmussen LS. Postoperative cognitive dysfunction: incidence and prevention. *Best Pract Res Clin Anaesthesiol* 2006;20:315–30.
- Inouye SK. Delirium in older persons. *N Engl J Med* 2006;354:1157–65.
- Yanagawa B, Nedadur R, Puskas JD. The future of off-pump coronary artery bypass grafting: a North American perspective. *J Thorac Dis* 2016;8:S832–S838.
- Kowalewski M, Pawliszak W, Malvindi PG, *et al.* Off-pump coronary artery bypass grafting improves short-term outcomes in high-risk patients compared with on-pump coronary artery bypass grafting: meta-analysis. *J Thorac Cardiovasc Surg* 2016;151:60–77.
- Falk V. Stay off-pump and do not touch the aorta!. *Eur Heart J* 2010;31:278–80.
- Bassano C, Bovio E, Uva F, *et al.* Partially anaortic clampless off-pump coronary artery bypass prevents neurologic injury compared to on-pump coronary surgery: a propensity score-matched study on 286 patients. *Heart Vessels* 2016;31:1412–7.
- Pawliszak W, Kowalewski M, Raffa GM, *et al.* Cerebrovascular events after no-touch off-pump coronary artery bypass grafting, conventional side-clamp off-pump coronary artery bypass, and proximal anastomotic devices: a meta-analysis. *J Am Heart Assoc* 2016;5:e002802.
- Kowalewski M, Suwalski P, Pawliszak W, *et al.* Risk of stroke with "no-touch" – as compared to conventional off-pump coronary artery bypass grafting. An updated meta-analysis of observational studies. *Int J Cardiol* 2016;222:769–71.
- Szwed K, Pawliszak W, Anisimowicz L, *et al.* Short-term outcome of attention and executive functions from aorta no-touch and traditional off-pump coronary artery bypass surgery. *World J Biol Psychiatry* 2014;15:397–403.
- Ganguly G, Dixit V, Patrikar S, *et al.* Carbon dioxide insufflation and neurocognitive outcome of open heart surgery. *Asian Cardiovasc Thorac Ann* 2015;23:774–80.
- Windecker S, Kolh P, Alfonso F, *et al.* 2014 ESC/EACTS guidelines on myocardial revascularization: the task force on myocardial revascularization of the European Society of Cardiology (ESC) and

- the European Association for Cardio-Thoracic Surgery (EACTS) developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). *Eur Heart J* 2014;35:2541–619.
15. Sun X, Lindsay J, Monsein LH, *et al.* Silent brain injury after cardiac surgery: a review: cognitive dysfunction and magnetic resonance imaging diffusion-weighted imaging findings. *J Am Coll Cardiol* 2012;60:791–7.
 16. Maekawa K, Baba T, Otomo S, *et al.* Low pre-existing gray matter volume in the medial temporal lobe and white matter lesions are associated with postoperative cognitive dysfunction after cardiac surgery. *PLoS One* 2014;9:e87375.
 17. Michałowska I, Furmanek MI, Smaga E, *et al.* Evaluation of brain lesions in patients after coronary artery bypass grafting using MRI with the emphasis on susceptibility-weighted imaging. *Kardiochir Torakochirurgia Pol* 2015;12:1–7.
 18. Le Bihan D, Breton E, Lallemand D, *et al.* Separation of diffusion and perfusion in intravoxel incoherent motion MR imaging. *Radiology* 1988;168:497–505.
 19. Wong SM, Zhang CE, van Bussel FC, *et al.* Simultaneous investigation of microvasculature and parenchyma in cerebral small vessel disease using intravoxel incoherent motion imaging. *Neuroimage Clin* 2017;14:216–21.
 20. de Havenon A, Haynor DR, Tirschwell DL, *et al.* Association of collateral blood vessels detected by arterial spin labeling magnetic resonance imaging with neurological outcome after ischemic stroke. *JAMA Neurol* 2017;74:453.
 21. van Norden AG, de Laat KF, van Dijk EJ, *et al.* Diffusion tensor imaging and cognition in cerebral small vessel disease: the RUN DMC study. *Biochim Biophys Acta* 2012;1822:401–7.
 22. Hicks KA, Tchong JE, Bozkurt B, *et al.* ACC/AHA Key Data elements and definitions for cardiovascular endpoint events in clinical trials: a report of the American College of Cardiology/American Heart Association Task Force on clinical data standards (writing committee to develop cardiovascular endpoints data standards). *J Nucl Cardiol* 2014;22:1041–144.
 23. Murkin JM, Newman SP, Stump DA, *et al.* Statement of consensus on assessment of neurobehavioral outcomes after cardiac surgery. *Ann Thorac Surg* 1995;59:1289–95.
 24. Martens S, Neumann K, Sodemann C, *et al.* Carbon dioxide field flooding reduces neurologic impairment after open heart surgery. *Ann Thorac Surg* 2008;85:543–7.
 25. Munk L, Andersen G, Møller AM. Post-anaesthetic emergence delirium in adults: incidence, predictors and consequences. *Acta Anaesthesiol Scand* 2016;60:1059–66.
 26. Ely EW, Inouye SK, Bernard GR, *et al.* Delirium in mechanically ventilated patients: validity and reliability of the confusion assessment method for the intensive care unit (CAM-ICU). *JAMA* 2001;286:2703–10.
 27. Barr J, Fraser GL, Puntillo K, *et al.* Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. *Crit Care Med* 2013;41:263–306.
 28. Sessler CN, Gosnell MS, Grap MJ, *et al.* The richmond agitation-sedation scale: validity and reliability in adult intensive care unit patients. *Am J Respir Crit Care Med* 2002;166:1338–44.
 29. Peterson JF, Pun BT, Dittus RS, *et al.* Delirium and its motoric subtypes: a study of 614 critically ill patients. *J Am Geriatr Soc* 2006;54:479–84.
 30. Pawliszak W, Szwed K, Szwed M, *et al.* Predictive value of the SYNTAX score for short-term cognitive outcomes after off-pump coronary artery bypass surgery. *Int J Cardiol* 2016;209:9–11.