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2024 EACTS/EACTAIC/EBCP Guidelines on cardiopulmonary bypass in adult cardiac surgery

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Disclaimer: A clinical guideline aims to apply to all patients with a specific condition. However, there will inevitably be situations where its recommendations are not suitable for a particular patient. While healthcare professionals and others are encouraged to consider these guidelines in their

professional judgment, they do not override the responsibility of healthcare professionals to make decisions tailored to each patient's unique circumstances. Such decisions should be aligned with the latest official recommendations, guidelines from relevant public health authorities, and applicable rules and regulations. It is important that these decisions are made in collaboration with, and agreed upon by, the patient and/or their guardian or carer.

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Central Illustration: Multidisciplinary Approach to Cardiopulmonary Bypass Management.

Keywords: Guidelines • cardiac surgery • cardiopulmonary bypass • cardiac anaesthesia • extracorporeal circulation • minimally invasive extracorporeal circulation • clinical perfusionist • EACTS • EACTAIC • EBCP • recommendations • evidence-based practice

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ABBREVIATIONS

AAGA Accidental awareness during general anaesthesia
ABP Arterial blood pressure
ACP Antegrade cerebral perfusion

Continued

ACT Activated clotting time
AE Adverse effect/event
AFib Atrial fibrillation
AI Artificial intelligence
AKI Acute kidney injury
ALF Arterial line filter
ANP Atrial natriuretic peptide
AOC Area over the curve
aPTT Activated partial thromboplastin time AT Antithrombin
AUC Area under the curve
AVR Aortic valve replacement
bACP Bilateral antegrade cerebral perfusion BIS Bispectral index
BSA Body surface area
CABG Coronary artery bypass grafting
CCB Calcium channel blocker
CECC Conventional extracorporeal circulation CKD Chronic kidney disease
CO Cardiac output
CO_2 Carbon dioxide
CPAP Continuous positive airway pressure CPB Cardiopulmonary bypass
CS Cell salvage
CUF Conventional ultrafiltration
DEHP Di(2-ethylhexyl) phthlate
DHCA Deep hypothermic circulatory arrest DO_2 Oxygen delivery
DTI Direct thrombin inhibitor
EACTAIC European Association of Cardiothoracic Anaesthesiology and Intensive Care
EACTS European Association for Cardio-Thoracic Surgery
EBCP European Board of Cardiovascular Perfusion
ECC Extracorporeal circulation
ECDC European Centre for Disease Prevention and Control
ECLS Extracorporeal life support
ECMO Extracorporeal membrane oxygenation
EEG Electroencephalogram
eGFR Estimated glomerular filtration rate FFP Fresh frozen plasma
GDP Goal-directed perfusion
HA Haemoadsorption
Hb Haemoglobin
HCT Haematocrit
HCU Heater-cooler unit
HIT Heparin-induced thrombocytopenia HPE High-pressure excursion
HTK Histidine-tryptophan-ketoglutarate IABP Intra-aortic balloon pump
iAD Iatrogenic aortic dissection
ICU Intensive care unit
IE Infective endocarditis
IL Interleukin
LCOS Low cardiac output syndrome
LDF Leucodepletion filter
LV Left ventricle
LVEF Left ventricular ejection fraction
MAP Mean arterial pressure
MHCA Moderate hypothermic circulatory arrest MI Myocardial infarction

Continued

MiECC Minimally invasive extracorporeal circulation
MUF Modified ultrafiltration
NAC N-Acetylcysteine
NIRS Near-infrared spectroscopy
NO Nitric oxide
NPP Non-pulsatile perfusion
NTM Non-tuberculous mycobacterium
O_2ER Oxygen extraction ratio
OR Odds ratio
PAC Pulmonary artery catheter
PEEP Positive end-expiratory pressure
pfHb Plasma-free haemoglobin

PMEA Poly-2-methoxyethyl acrylate
PND Permanent neurological dysfunction
PNDmc Mortality-corrected permanent neurological dysfunction
POCD Postoperative cognitive decline
PP Pulsatile perfusions
PPC Phosphorylcholine
PRBC Packed red blood cells
PSI Patient state index
PSM Propensity score matching
PVC Polyvinyl chloride
RAP Retrograde autologous priming
RBV Residual blood volume
RCP Retrograde cerebral perfusion
RCT Randomized controlled trial
RD Risk difference
RIPC Remote ischaemic preconditioning
RR Risk ratio
RRT Renal replacement therapy
$rScO_2$ Regional cerebral oxygen saturation
RV Right ventricle
SIRS Systemic inflammatory response syndrome SLR Systematic literature review
SMB Shed mediastinal blood
SMD Standardized mean difference
STS Society of Thoracic Surgeons
SVRI Systemic vascular resistance index
TCI Target-controlled infusion
TNF Tumour necrosis factor
TOE Transoesophageal echocardiography
TOTM Trioctyl trimellitate
uACP Unilateral antegrade cerebral perfusion
UF Ultrafiltration
UFH Unfractionated heparin
VAVD Vacuum-assisted venous drainage
VCM Vital capacity manoeuvres
VO_2 Oxygen consumption
WMD Weighted mean difference
ZBUF Zero-balanced ultrafiltration

PREAMBLE

Clinical practice guidelines consolidate and evaluate all pertinent evidence on a specific topic available at the time of their formula tion. The goal is to assist physicians in determining the most effec tive management strategies for patients with a particular condi tion. These guidelines assess the impact on patient outcomes and weigh the risk–benefit ratio of various diagnostic or therapeutic

approaches. While not a replacement for textbooks, they provide supplementary information on topics relevant to current clinical practice and become an essential tool to support the decisions made by specialists in daily practice. Nonetheless, it is crucial to understand that these recommendations are intended to guide, not dictate, clinical practice, and should be adapted to each patient's unique needs. Clinical situations vary, presenting a diverse array of variables and circumstances. Thus, the guidelines are meant to inform, not replace, the clinical judgement of healthcare professionals, grounded in their professional knowl edge, experience and comprehension of each patient's specific context. Moreover, these guidelines are not considered legally binding; the legal duties of healthcare professionals are defined by prevailing laws and regulations, and adherence to these guide
lines does not modify such responsibilities.

The European Association for Cardio-Thoracic Surgery (EACTS), the European Association of Cardiothoracic Anaesthesiology and Intensive Care (EACTAIC) and the European Board of Cardiovascular Perfusion (EBCP) constituted a task force of pro
fessionals specializing in cardiopulmonary bypass (CPB) manage ment. To ensure transparency and integrity, all task force mem bers involved in the development and review of these guidelines submitted conflict of interest declarations, which were compiled into a single document available on the EACTS website (https://www.eacts.org/resources/clinical-guidelines). Any alterations to these declarations during the development process were promptly reported to the EACTS, EACTAIC and EBCP.

Funding for this task force was provided exclusively by the EACTS, EACTAIC and EBCP, without involvement from the healthcare industry or other entities.

Following this collaborative endeavour, the governing bodies of EACTS, EACTAIC and EBCP oversaw the formulation, refine ment, and endorsement of these extensively revised guidelines. An external panel of experts thoroughly reviewed the initial draft, and their input guided subsequent amendments. After this detailed revision process, the final document was ratified by all task force experts and the leadership of the EACTS, EACTAIC and EBCP, enabling its publication in the *European Journal of Cardio Thoracic Surgery*, the *British Journal of Anaesthesia* and *Interdisciplinary CardioVascular and Thoracic Surgery*.

Endorsed by the EACTS, EACTAIC and EBCP, these guidelines represent the official standpoint on this subject. They demon strate a dedication to continual enhancement, with routine updates planned to ensure that the guidelines remain current and valuable in the ever-progressing arena of clinical practice.

1. INTRODUCTION

1.1 Background

The current document presents a revision of the 2019 EACTS/ EACTA/EBCP guidelines on cardiopulmonary bypass in adult cardiac surgery, emerging from a collaborative effort among the EBCP, EACTAIC and EACTS to establish guidance for unified clinical prac
tice guidelines (CPB) practice [1, 2]. The previous guidelines pro vided the first comprehensive European guidance based on evi dence, promoting a message of excellence through collaboration

within the cardiac surgical, perfusion and anaesthetic communities. With recent advances in research that unveiled new evidence related to CPB, an update to the 2019 guidelines was necessary. The revised guidelines reaffirm the foundational practices and

incorporate new recommendations that align with the latest

evidence-based medicine and contemporary European clinical practices. They expand the guideline's scope with additional sec tions addressing crucial topics such as temperature management and deep hypothermic circulatory arrest (DHCA). However, the necessity for further research persists, and this iteration of the guidelines emphasizes the ongoing need for scientific inquiry and trials in various CPB domains.

Whereas recent international guidelines cover specific topics like patient blood management and perioperative medication, this document summarizes the evidence and directs readers to these comprehensive guidelines for further details [3, 4]. The task force acknowledges that there have been no significant updates related to CPB, and thus refers to existing materials. Due to length constraints, paediatric CPB has not been included in this edition. These guidelines concentrate on perfusion-related rec ommendations in addressing broad topics such as cardioplegia and minimally invasive surgery.

1.2 What is new

The updated CPB guidelines have undergone a comprehensive review to enhance their clinical applicability and to incorporate the latest evidence since the 2019 edition. Significant additions include new sections that broaden the scope of the guidelines:

- Section 5.8 focuses on tubing, specifically addressing the use of plasticizers in tubing materials.
- Section 6 on monitoring now includes recommendations on neuromonitoring as well as haemodynamic monitoring and management.
- Section 7, Organ protection, compiles evidence on strategies to protect organs during CPB.
- A new section, 9.10, on blood purification, has been introduced.
- Section 10 discusses CPB for specific techniques, focusing on perfusion strategies for aortic and aortic arch operations. • Lastly, Section 12 addresses specific situations during CPB, tackling the management of adverse events.

The goal of these additions is to provide comprehensive cover age of the most current and relevant aspects of CPB, ensuring that the guidelines remain a valuable resource for clinicians in adult cardiac surgery.

2. METHODOLOGY

To ensure that guideline recommendations remain current, the EACTS Council, together with the Board of Directors of the EACTAIC and the Scientific Committee of the EBCP, intends to continuously review and update guidelines based on published standards for the development of clinical practice documents [5]. Recognizing the extensive research and development that has occurred in the field of CPB since the last publication [6] and acknowledging that most guidelines become outdated 5 years after their previous publication [7], a timely, complete joint revision of the CPB guidelines for adult cardiac surgery was decided on.

A task force was established, drawing from a diverse pool of experts within the multidisciplinary field of cardiac surgery. Members were selected for their comprehensive backgrounds and experiences spanning clinical practice and research. The selection process also considered gender diversity and rep resentation from various geographic regions to ensure a broad spectrum of insights and perspectives. The governing bodies of the involved societies agreed upon the guideline's scope, and the task force members established the final table of contents. To critically appraise the new body of evidence, with the assis tance of a medical informatics specialist, the task force con ducted a systematic literature review (SLR) based on the standar dized Population, Intervention, Comparison, Outcome and Time questions format. Literature searches encompassed all studies, including randomized controlled trials (RCTs), registries, non randomized comparative and descriptive studies, case series, cohort studies, systematic reviews and meta-analyses and other expert opinions. An initial SLR, which focused on research involving human subjects, published in English and indexed in MEDLINE, EMBASE and the Cochrane Library, was conducted from May to September 2023 (see search strings for each section in the supplementary material). Additional relevant studies pub lished after September 2023 during the guideline writing and external validation processes were also considered by the task force and included in the document when appropriate. The references selected and published in the document are repre sentative and not all-inclusive. The recommendations listed in this guideline are, whenever possible, evidence-based and focused primarily on RCTs.

In adherence to rigorous policies and methods to ensure unbiased and impartial document development, task force members were mandated to declare any conflicts of interest before commencing the project and to notify the co-chairs of EACTS, EACTAIC and EBCP of any changes until publication of the guideline. The work on recommendations and supporting text was permitted only if members had no relevant conflicts of interest. All sections were written through a close collaboration among the members. The development of each recommenda tion was based on the totality of current scientific and medical knowledge, weighing the risks and benefits of the intervention according to established methods (Tables 1 and 2) [5]. Expert consensus was employed to address critical daily practice issues in areas devoid of robust evidence. A preliminary consensus, achieved through conference calls and in-person meetings and defined by a minimum of 75% agreement among present mem bers, advanced the draft recommendations. An anonymous electronic survey subsequently elicited votes on each recom mendation, accompanied by the corresponding Class of Recommendation and Level of Evidence. An 80% response rate and at least 75% affirmative votes on each recommendation constituted a consensus. Each involved society appointed a peer

Table 1: Levels of evidence

Class of recommendations	De!nition	Suggested wording
Class I	Evidence and/or general agreement that a given treatment or procedure is bene!cial, useful and effective	Is recommended/is indicated
Class II	Con''icting evidence and/or a divergence of opinion about the usefulness/ef!cacy of the given treatment or procedure	
Class IIa	Weight of evidence/opinion is in favour of usefulness/ef!cacy	Should be considered May be considered
Class IIb	Usefulness/ef!cacy is less well established by evidence/opinion	Is not recommended
Class III	Evidence/general agreement that the given treatment/procedure is not useful/effective and may sometimes be harmful	
Data derived from multiple randomized clinical trials or meta analyses		
Data derived from a single randomized clinical trial or from large non-randomized studies		
The consensus of expert opinion and/or small studies, retrospective studies and registries		

Table 2: Classes of recommendations

review committee to scrutinize the document, which was subse quently reviewed and endorsed for publication by the governing bodies of EACTS, EACTAIC and EBCP.

3. TRAINING, EDUCATION AND SERVICE DELIVERY

The operational and service management of CPB is the responsi bility of the clinical perfusionist. To ensure safe and effective clinical practice, perfusionists need adequate training with appropriate knowledge, skills and expertise. Clinical perfusionists are members of the multidisciplinary operative team and work in collaboration with surgeons, anaesthetists and operating room personnel. Perfusion departments must be adequately staffed and resourced to deliver elective and emergency patient care. Establishing standards should govern the effectiveness of care by monitoring of patient outcomes. In addition to regular reporting, assessments of performance and of lessons learned from adverse events should be established.

Description of the evidence. There are notable variations among countries regarding the qualifications, competencies and organi zations for perfusionists. International organizations, such as the EBCP, EACTS and EACTAIC, recommend standardizing the qual ity of education and training in the cardiothoracic field [8, 9]. One recommendation is that graduates of a study programme in perfusion verify this fact with a certificate, as implemented in many European countries [8, 10]. It is widely accepted that clini cal perfusionists should undergo a period of formal applied edu cation and training to gain the necessary knowledge, skills and techniques [8, 10–16].

In Europe, the EBCP has existed since 1991 and is dedicated to the structured training of perfusionists. The profession of perfu sionist is listed as a self-regulated profession by the European Commission, and the EBCP is the designated organization [17]. Accreditation of an educational programme in perfusion is based on satisfying the minimum standards for entry requirements, facilities, syllabus, training and supervision as detailed either by national or international guidelines in Europe according to the regulations of the EBCP [12, 13, 15, 18–20]. The educational pro
gramme should be curriculum-based, covering applied anatomy, physiology, biochemistry, pharmacology and pathology, equip ment, monitoring, clinical management and service delivery.

Clear recommendations on the scope of the syllabus for perfu sion are lacking to date. A recent study determined it should repre sent an average of 60 European Credit Transfer

and Accumulation System (ECTS) learning points in Europe. The professional societies in the present guideline support this number for the perfusion con tent. Professional societies give framework recommendations on content; for Europe, they are offered by the EBCP [21]. Performing a clinical perfusion is a complex technical and medical procedure that requires vigilance and responsible decision-making skills. According to the European Qualifications Framework, a minimum level of education, such as an entry level or final level of at least 6 (bachelor's degree), is therefore essential [10, 22].

The educational programme should be accompanied by clini cal training in an accredited clinical perfusion department [13, 15, 18, 23]. The length of the clinical training varies from 1 to 4 years, depending on the entry requirements for the programme. The training should take place in a European-recognized and

-accredited perfusion training centre. A minimum of 100 super vised perfusion cases [23] must be documented in a logbook. The educational benefit of simulation training in perfusion is increasingly considered indispensable for the acquisition and maintenance of skills, for practising emergency procedures and human factors training, including team and communication training [12, 13, 15, 24]. After completing an educational pro gramme, the trainee's knowledge and skills are assessed by for mal written and practical examinations, leading to certification as a clinical perfusionist [8, 10, 12, 15, 18, 25].

The European Certificate in Cardiovascular Perfusion is valid for 3 years; maintenance of certification requires proof of a certain minimum annual number of clinical cases and regular participation in continuing professional education while main taining professional standards [12–14, 18, 19, 26, 27]. A relevant national or, where appropriate, international perfusion board should accredit training programmes and certification and recer tify clinical perfusionists. Globally, the framework and require ments for individual recertification vary among countries; in Europe, the EBCP is responsible and is designated by the European Economic and Social Committee [17].

Trained and accredited clinical perfusionists should work within an appropriate quality management framework based on documented standard operating procedures; risk assessment; regular checking and recording; leadership, teamwork and com
munication; and peer reviews and audits of practice and out comes [14, 16, 28, 29]. The risk assessment and the respective critical incident report systems should be in place to effectively analyse errors and incidents [28].

Each department, institution or service provider should main tain standard operating procedures or protocols detailing all procedures with proper equipment, the estimated frequency of occurrence, safety measures, required competencies and train ing, record keeping and responsibility for adherence. These standard operating procedures should work as binding agree ments for the healthcare team and describe the areas of respon sibility in which the perfusionists operate the extracorporeal cir culation (ECC) systems [10, 13, 15, 28].

The department for clinical perfusion should be well described within the hospital structure and clearly structured. These requirements include appointing a responsible team leader, holding regular team meetings and practicing closed
loop communication, whereby the sender gives a message, and the recipient repeats it, reducing misunderstanding between team members [10, 13, 28, 29]. Regular briefings, debriefings, team meetings and self-assessments regarding team culture and performance can improve team performance [18], as can human factor training using simulation [28, 30]. Departments should be adequately staffed with personnel and experience [12]. A depart
ment's daily level of certified perfusion staff should be n þ 1, where n is the number of simultaneously running operating rooms. For example, on a day with 3 operating rooms scheduled for CPB, should be 4 perfusionists present in the department [13, 16]. If this is not possible—for example, outside of regular working hours—then the situation should be risk assessed with mitigating actions such as immediate availability of additional emergency equipment and support personnel. Quality assurance and improvement are fundamental to patient outcomes and safety within departments and institutions [12, 14, 16, 28, 31–33].

The healthcare environment in a perfusion department must be safe; errors and untoward incidents should be reported and sys tematically analysed to identify system failures [26, 28].

Departments and national perfusion bodies should ensure that such outcomes are shared locally and nationally to promote shared learning. The accurate reporting of data and outcomes with sub mission to a database or clinical registry enables the success and efficacy of interventions or treatments to be established. Clinical perfusionists should collect and submit such data and use it for quality assurance and improvement [13, 14, 28]. Further details relating to data management systems as an opportunity for quality improvement in perfusion practice are described in section 4.6.

compact miniaturized systems, often used for so-called mini mally invasive extracorporeal circulation (MiECC) procedures, extracorporeal membrane oxygenation (ECMO) and other indications.

Description of the evidence. Few publications focus on the hard ware aspect of heart-lung machines. In most centres, conven tional stationary designs are used mainly in routine cases and complicated operations. Stationary systems may be configured

Recommendation Table 1. **Recommendations for training, education and service delivery**

Recommendations	**Class[a]**	**Level[b]**	**Ref[c]**
It is recommended that perfusionists complete a formal training period in an educational training	**I**		–

programme accredited by the EBCP and/or national authorities.			
It is recommended that perfusionists achieve certification by successfully completing an examination of skills and knowledge. The demonstration of an appropriate level of continued professional development, minimum caseload and professional standards shall maintain the certification.	**I**		–
It is recommended that future perfusionists have at least a level 6 (European Qualifications Framework) bachelor's degree.	**I**		–
Simulation in perfusion should be considered to improve quality of care and patient safety.	**IIa**		**[28, 30]**
It is recommended that perfusion departments be structured around a quality management framework approved by the institution.	**I**		–
It is recommended that each perfusion department have written standard operating procedures for the conduct of CPB.	**I**		–
It is recommended that the perfusion department is adequately staffed, equipped and resourced.	**I**		–
It is recommended that verbal communication among team members in the operating room is standardized and always acknowledged.	**I**		–
Recording and submitting activity and outcomes to a regional database or registry should be considered, and these data should be used for quality assurance and improvement.	**IIa**		**[31–33]**
Reporting and systematically analysing errors or untoward events, including outcomes dissemination for shared learning, is recommended.	**I**		**-**

[a]Class of recommendation.
[b]Level of evidence.
[c]References.
CPB: cardiopulmonary bypass: EBCP: European Board of Cardiovascular Perfusion.

4. HEART-LUNG MACHINE HARDWARE

In recent years, the technological developments of heart-lung machines have led to improvements in hardware and integration of monitoring equipment and software. This new technology allows supervision of the body's metabolic demands and facilitates interventions to maintain adequate organ perfusion, oxygen supply and anticoagulation. The goal is increased safety and easier operation.

4.1 Console with pumps and holders

The console of the heart-lung machine, with its pumps and holders, is the backbone on which disposable CPB sets are mounted. Two basic design philosophies prevail in modern heart-lung machines: the conventional modular and the integrated, modular or a combination of both. There is general agreement on which safety features should be included, as acknowledged in previous guidelines such as those of the Australian and New Zealand College of Perfusionists and the American Society of Extracorporeal Circulation [34, 35]. These safety features include pressure controllers, air detectors, low-level alarms, electrical safety specifications and pump reversal of flow or “runaway” protection. Moreover, the manual operation of these pumps with crank handles is possible. Most systems include an integrated light source and batteries for operating during a power failure. Most importantly, all sensors ensuring the safe conduct of CPB, such as pressure transducers on arterial and cardioplegia lines, bubble detectors on arterial and cardioplegia lines and level sensors on venous reservoirs, should give visual and audible alarm notifications and automatically servo control or shut down the arterial and/or cardioplegia pumps to avoid potentially hazardous incidents, such as overpressurization or massive air embolism.

It is noteworthy to mention the lack of scientific research on console designs. One publication focused on human factors and the design of heart-lung machines and named several key issues with current designs. Namely, workspace design, procedures and communication; component integration; and issues with controls, alarms and displays were discussed [36]. The few other publications that could be found focused mainly on minor aspects of the topic, such as developing universal oxygenator holders [37], improving roller pump control [38] or researching battery performance [39]. More recently, the use of miniaturized extracorporeal heart-lung machines has been

advocated. Several types of devices were categorized, from fundamental devices to devices with more built-in features, such as cardiotomy suction and open venous reservoirs [40]. However, important aspects, such as safety or ergonomics of the design, are rarely explored. Thus, recommendations are based on expert consensus and are mainly in line with the current recommendations from other societies [34, 35].

Several investigations have focused on the design of arterial pumps. Both roller pumps and centrifugal pump heads are in use today. From a safety aspect, there appear to be advantages for centrifugal pump heads, because these pumps have been found to limit the risk of arterial air embolism in a paediatric ex vivo model [41]. They are also believed to be superior in blood handling [42]; however, the evidence is conflicting [43]. If pulsa
tile perfusion is requested, roller pump heads are usually employed. Centrifugal pump heads, in contrast, are typically incorporated in MiECC systems [40].

potential risks. Next to failures of hardware and procedures, perio perative communication issues have also been reported to contrib ute to the higher mortality risk of cardiac patients [47].

Description of the evidence. A Failure Mode and Effects Analysis has identified mechanisms during CPB whereby failing safety equipment or mechanical issues can compromise patient safety. Six different CPB configurations were evaluated [48]. The highest risks across all circuit types were attributed to the embolization of defoamer material, air embolism, spallation, the induction of systemic inflammatory response syndrome (SIRS) and overpres
surization. The 3 most recent surveys on incidents related to CPB listed coagulopathy/heparinization, arterial dissection, aller

gic/anaphylactic reaction and arterial air embolism as the main risks associated with CPB [44–46]. Human factor studies have highlighted several areas for improvement in addition to the mechanical safety of the device, including the organizational cul
ture of safety [49, 50]. Collecting information on adverse events in registries will help prevent such incidents in the future [51]. Perfusionists can use an excellent tool for this purpose: the online Perfusion Improvement Reporting System of the Australian and New Zealand College of Perfusionists [52]. Perfusion safety can thus be enhanced by a multitude of meas
ures, such as the use of dedicated safety equipment (e.g. level detectors, bubble detectors, an arterial line filter [ALF], pressure transducer, one-way vent valve, backup systems) [14, 53]. In a survey published in 2000, a total of 27 safety devices were iden
tified. The authors recommended improvements in coagulation monitoring and incident reporting [44]. The question remains whether new developments, such as MiECC or surgery without CPB, increase or reduce perfusion safety. In a recent

Recommendation Table 2. **Recommendations for a console with pumps and holders**

Recommendations	Class[a]	Level[b]	Ref[c]
It is recommended that pressure monitoring devices be used on the arterial line (pre- and post-oxygenator) and on cardioplegia delivery systems during CPB.	I		-
During CPB procedures, a bubble detector is recommended on all lines going to the patient.	I		-
It is recommended to use a level sensor on the (hardshell) reservoir.	I		-
It is recommended that backups for vital systems or an additional complete heart-lung machine be available at all times.	I		-
A maintenance plan for CPB equipment is recommended.	I		-
The use of centrifugal arterial pumps should be considered for improved haemocompatibility and safety.	IIa		[42]

[a]Class of recommendation.
[b]Level of evidence.
[c]References.
CPB: cardiopulmonary bypass.

4.2 Safety features

The likelihood of death from CPB-related incidents declined over the last few decades to 1 in 4446–4864 patients, whereas severe organ injury or death was 1 in 1453–3220 patients [44, 45] in the 2000s. However, the number of non-fatal incidents remains a con
cern and is reported to be as high as 1 in every 58 patients [46]. Studies on safety and human factors have identified numerous

meta-analysis including 134 RCTs, perioperative outcomes were improved using MiECC or the off-pump technique compared to conventional CPB [54]. However, these findings are challenged by large-scale multicentre RCTs [55] or, more

recently, by 10-year follow-up results [56, 57]. The advent of modular MiECC circuits includes minimally invasive CPB technology combined with traditional circuits and may improve patient safety [58].

Recommendation Table 3. **Recommendations for safety features**

Recommendations	Class[a]	Level[b]	Ref[c]
It is recommended to (electronically) record, report, adjudicate and analyse serious adverse events related to CPB procedures in an efficient and timely manner.	I		-
It is recommended to establish a safety culture within the hospital to minimize adverse events related to CPB.	I		-

[a]Class of recommendation.
[b]Level of evidence.
[c]References.
CPB: cardiopulmonary bypass.

4.3 Oxygen and air, carbon dioxide and volatile anaesthetics supply

Conducting CPB requires constant gas supplies that may include oxygen, air and carbon dioxide (CO_2). These gases should be readily available in the operating room and in a backup supply. Furthermore, the delivery of oxygen, air, CO_2 and volatile anaesthetic agents to the oxygenator is essential for the proper operation of CPB. Monitoring the concentration of the volatile anaesthetic agent administered in the incoming sweep gases and outgoing oxygenator exhaust gases and a safe scavenging system are advisable. The addition of nitric oxide (NO) to the oxygenator is gaining interest in the adult population, but most studies have primarily included children undergoing heart surgery. Some adult studies [59, 60] have indicated a reduced systemic inflammatory response and a lower risk of acute kidney injury (AKI). However, there is no consensus on the optimal and safe dose of NO nor is there concrete advice on safety precautions. Therefore, more research is needed before the clinical application of NO in the oxygenator can be recommended.

volatile anaesthetic agents have frequently been used. Section 9.11 provides a careful analysis of clinical studies in this area. Personnel involved in procedures where CPB is performed are potentially at risk of occupational exposure to volatile anaesthetic agents. Therefore, it is advised to use a scavenging device at the oxygenator's outlet to prevent unwanted exposure [14, 29, 61]. Excessive negative pressures must be avoided when using a scavenging system because it can create a negative pressure gradient across membrane oxygenators, potentially resulting in a rupture of the membrane and oxygenator failure [62]. The standard (ANSI Z79.11) of the American National Standards Institute (ANSI) that addresses scavenging systems for anaesthetic gases states that scavengers should not generate positive pressures exceeding 10 cm of water (7.4 mmHg) or negative pressures exceeding 0.5 cm of water (0.37 mmHg). Therefore, perfusionists must comprehensively understand the effects of volatile anaesthetic agents [62].

Recommendation Table 4. **Recommendations for security and control of gas supply**

Recommendations	Class[a]	Level[b]	Ref[c]
It is recommended that continuous piped supplies of oxygen, air and carbon dioxide be checked before and monitored during CPB with backup cylinder supplies available.	I		-
Monitoring of all incoming and outgoing gases should be considered.	IIa		-
When a supply system for volatile anaesthetic agents is used, a scavenging system at the oxygenator outlet is recommended.	I		-

[a]Class of recommendation.
[b]Level of evidence.
[c]References.
CPB: cardiopulmonary bypass.

Description of the evidence. The gas supply to the oxygenator should be constant and should consist of oxygen and air. Carbon dioxide should be used to flush the CPB circuit before priming to reduce the number of gaseous microemboli in the priming solution. Carbon dioxide can also be used to maintain pH-stat acid-base management when necessary. To ensure safe conditions, monitoring incoming and outgoing gasses should be considered. In the event of a technical fault, a backup supply of gases (gas cylinders) is also advised [14, 28, 29, 61]. During CPB,

4.4 Carbon dioxide flushing of the surgical field

Open heart surgery with CPB carries a risk of systemic gaseous emboli due to microemboli, either after priming a circuit filled with air or air from open cardiac cavities during an operation. Complete de-airing of the CPB circuit and cardiac cavities during open-heart procedures remains challenging. The use of CO_2 to flush the circuit before priming and the insufflation of CO_2 into the cardiac cavities are common practices in many units throughout Europe. CO_2 is more soluble in blood than is nitro gen, which is a major component of atmospheric air. Thus, CO_2 microemboli are easier to dissipate from blood and also thought to be less harmful [63]. The higher density of CO_2 facilitates air

displacement inside the cardiac cavities. However, the benefit of CO_2 flushing is still being debated, and the outcome of a large United Kingdom multicentre trial will hopefully elucidate this issue in more detail [64].

4.4.1 Carbon dioxide flushing of the circuit. The efficacy of CO_2 flushing of the empty perfusion circuit to reduce gaseous microemboli following priming was shown convincingly in several experimental studies, including 1 RCT [65–68]. One study demonstrated that CO_2 flushing of ALF [65] resulted in fewer emboli and a faster embolic clearance time. In order to obtain a CO_2 content of 97% to 98% in the oxygenator, the results from a single-centre study suggested that approxi mately 5 min of CO_2 flushing is necessary. Still, the extended duration did not increase the concentration significantly [68]. CO_2 flushing may be even more critical in new circuit designs with integrated oxygenators and centrifugal blood pumps [67].

4.4.2 Carbon dioxide insufflation of the operative field. Three SLRs and meta-analyses on CO_2 insufflation of the opera tive field have been published to date [69–71], none of which provided any evidence of a beneficial effect on neurocognitive function or S100 protein levels following open heart surgery. However, a significant reduction in gaseous microemboli was noted in several trials [risk difference −0.94, 95% confidence interval (CI) (−1.63 to −0.25)] [71]. An experimental study [72] and observational studies confirmed that CO_2 insufflation reduces gaseous microemboli in the blood [63, 73]. Only 1 single-institution RCT showed superior neurocognitive outcome when CO_2 insufflation was applied [risk ratio (RR) 0.30, 95% CI 0.14–0.63] [74]. However, no correlation could be found between the remaining air in the heart chambers, as validated by transoesophageal echocardiography (TOE) and neurocogni
tive outcome.

The specific technique of CO_2 insufflation and general de airing routines may be essential in reducing gaseous microem boli [75–77]. Ineffective de-airing may lead to underestimating the potential benefits of CO_2 insufflation.

Concern has been voiced over hypercapnic acidosis following CO_2 insufflation [78], which may lead to a decreased heparin effect and, consequently, to an increased risk of thrombus for mation in the circuit [79]. It has been suggested that hypercapnia can be effectively mitigated by using an additional venous reser voir [80].

4.5 Heater-cooler unit

The heater-cooler unit (HCU) is an integrated hardware compo nent of the CPB system. Its use is to maintain the patient's body temperature to the target value assigned for the specific inter vention and for the eventual cooling and rewarming before and after reaching the target core temperature if needed. This goal is obtained by running water at a precise temperature around the fibres of the oxygenator or the coils of the cardioplegia system, usually using the 'countercurrent' physical principle to maximize efficiency and miniaturize the circuit. Previous guidelines recom mended complying with temperature and pressure safety limits

reported in manufacturers' instructions. However, due to the recent *Mycobacterium chimaer*a outbreak, stronger recommen dations were issued, including regular rigorous decontamination and maintenance procedures for HCUs—according to manufac turer's instructions—and placing HCUs outside the operating rooms to prevent contaminated air from reaching the surgical field [81–83]. The scientific evidence regarding HCU-related infective risks during the last 5 years is based mainly on single institutional reports or reviews of the available literature [84–93]. RCTs on this topic are lacking.

Description of the evidence. M. chimaera infection is a systemic disease with a high predicted mortality (40%–65%) and a pro longed latency from infection to clinical manifestations (usually more than 6 years from the index surgery), characterized by multiple granulomatous lesions, responsible for a variable com bination of hepatitis, nephritis, pneumonitis, chorioretinitis, myocarditis, osteomyelitis, encephalitis and myositis, together with prosthetic material endocarditis [81–83]. Systemic symp toms also include malaise, fever and weight loss (often leading to misdiagnoses), and the results of blood culture tests may be inconclusive [81]. Since the declaration of a global outbreak of HCU-related infections, medical knowledge about *M. chimaera,* a non-tuberculous mycobacterium (NTM), has grown substan tially, especially in terms of epidemiological and diagnostic tools to assess the disease [81, 82]. For example, it is now accepted that the eyes should be examined in all suspected cases because of the high diagnostic accuracy [82]. Furthermore, international guidelines on diagnosing, treating and preventing disseminated *M. chimaera* infection following cardiac surgery with CPB were published in 2020, summarizing current medical knowledge [82]. Similarly, a European protocol for the detection, laboratory diag nosis

and environmental testing of *M. chimaera* infections

Recommendation Table 5. **Recommendations for the use of carbon dioxide flush**

Recommendations	Class[a]	Level[b]	Ref[c]
It is recommended that CO_2 flush of the CPB circuit before priming is established as the standard of care to reduce GME.	I		[67, 68]
CO_2 insufflation of the operative field may be considered to reduce emboli.	IIb		[71]
When CO_2 insufflation of the surgical field is used, it is recommended that gas flow be adapted to avoid hypercapnic acidosis.	I		–

[a]Class of recommendation.
[b]Level of evidence.
[c]References.
CO_2: cardon dioxide; CPB: cardiopulmonary bypass; GME: gaseous microemboli.

potentially associated with HCUs was released by the European Centre for Disease Prevention and Control (ECDC) [94]. However, despite the high mortality of this disease, no RCTs have been done to obtain solid scientific evidence on HCU monitoring, decontamination strategies or management inside the operating rooms. When HCU monitoring is considered, an observational study showed that the propidium monoazide polymerase chain reaction (PMA-PCR) has an 85% agreement with standard cultures when using a cycle threshold of < 43. It is superior to standard cultures because it reduces laboratory turn around time (1–2 days vs 8 weeks), thus accelerating the diagno sis of HCU contamination [84].

Initially, most cases were linked to the use of the LivaNova 3T HCU (LivaNova, London, UK). Later, however, contamination was reported in almost all the commercially available HCUs. A recent nationwide Italian study identified 251 HCU devices to be contaminated across the nation with 40 clinical cases of disease over 12 years. Furthermore, a systematic review and meta
analysis highlighted that 180 cases were reported worldwide in 2023, with an overall fatality of 45.5% [95, 96]. It is assumed that the leading cause of contamination is the tap water used in HCUs [81, 82]. Following the outbreak, manufacturers of HCUs have adjusted their instructions for maintenance and recom
mend an increased frequency of disinfection and/or an increase in the concentration of chemicals used for disinfection, with a
demonstrated that verified sterile new HCUs were permanently contaminated by several microbial agents (*M. chimaera* included) with daily use, and none of the pathogens could be permanently eliminated despite the application of all authority/ manufacturer-mandated decontamination procedures [88].

Chand *et al.* showed that aerosols inside the water reservoir of the HCU could escape via its ventilation fan even though the HCU circuits were watertight [89]. These aerosols could reach the patient, especially if the HCUs were oriented with the fan facing towards the surgical field [90]. Also, the cell membrane structure of NTM and its ability to produce biofilms resulted in high resistance to standard and improved disinfection protocols [81–88, 91, 92, 94], as well as in the potential to spread from water circuits by aerosolization [93, 97]; and the concentration of organisms within these aerosolized bubbles could be up to 10 000-fold higher than in the initial water source [97].

Therefore, it is reasonable to consider at this stage that the only effective risk elimination strategy would be the complete separation of the HCU exhaust air from the operating room air either by removing the HCUs from inside the operating rooms or by building airtight HCU-housing devices designed to direct HCUs-exhaust air directly out of the operating room [81, 82, 98].

Recent developments associated with HCUs that do not use water as a heat exchanger may be promising. However, this new technology is not yet thoroughly tested in the clinical environment.

Recommendation Table 6. **Recommendations for a heater-cooler unit**

Recommendations	Class[a]	Level[b]	Ref[c]
It is recommended that protocols for the detection of *Mycobacterium chimaera* infections, potentially associated with HCU, be adopted per institutional policies that follow ECDC standards.	I		[81, 87, 91, 98]
Polymerase chain reaction methods, together with standard cultures, may be	IIb		[84]

considered to increase accuracy thresholds to diagnose HCU contamination by NTM.			
Sampling, cleaning and disinfecting procedures, according to the manufacturer or another validated protocol, must be implemented periodically, at a minimum yearly.	**I**		–
It is recommended that HCUs be placed outside operating rooms whenever possible to prevent the contaminated air from entering the operative field.	**I**		**[83, 98]**
To reduce contamination of the operative field, the use of enclosures designed to direct HCU exhaust air directly out of the operating room and as far away from the patient as possible, maintaining a minimum distance of 2 metres, or the use of a vacuum for clearance of the exhaust, may be considered.	**IIb**		**[92, 93]**

[a]Class of recommendation.
[b]Level of evidence.
[c]References.
ECDC: European Centre for Disease Prevention and Control; HCU: heater-cooler units; NTM: non-tuberculous

mycobacterium. direct impact on medical workers, costs and the environment

overall [81, 82, 85].

A single-centre study demonstrated that applying the manu facturer's instructions for HCU disinfection reduced the total vital counts of all investigated pathogens except for NTM, prov ing the limited efficacy in HCU-water sterilization of these instructions [86]. Another single-centre report assessed the effec tiveness of 3 different recommended protocols for HCU disin fection and found that the best results were achieved when disinfecting with 0.2% chloramine-T together with the use of 0.2-µm water filters [87]. Another observational study

4.6 Patient data management systems and quality improvement

With the development of recently available heart-lung machines, electronic recording of patient data is becoming increasingly common, and it opens the doors to future developments such as quality indicators [33, 99, 100]. Moreover, it can serve as a basis for (inter)national perfusion registers, a source of scientific research [31, 101, 102]. The prerequisite, however, is the correct recording of the relevant data.

Although manufacturers are trying to provide new CPB machines with automatic data recording, this topic has not been addressed in the scientific literature. Thus, recommendations in this area remain unchanged with respect to the previous guidelines [2].

More work needs to be done to integrate and analyse the col lected data into perfusion registries. Machine learning and artifi cial intelligence (AI) may be another next step towards the decision-making support of perfusionists during CPB and in the prediction of mortality [103–106].

Description of the evidence. A survey was conducted to gather sup porting evidence to establish acceptable and appropriate limits for parameters identified in blood flow and pressure monitoring dur ing uncomplicated adult CPB procedures. The findings, which include median, first and third quartile limits for various parame ters, aim not only to support the development of institutional practice protocols but also to aid in creating 'virtual patient' mod els for education, research and product development [107]. In a predictive model based on the Australian and New Zealand College of Perfusion database, several CPB parameters have been identified to have a positive effect on the prediction of 30-day mortality: CPB time, packed red blood cell (PRBC) transfu sions, mean arterial pressure (MAP) <50 mmHg, minimum oxy gen delivery (DO_2) and cardiac index < 1.6 L/min/m^2 [108]. Based on different measured parameters during CPB, some algorithms are proposed to support decision making via AI: management of vacuum-assisted venous drainage (VAVD), man agement of oxygenation at the beginning of CPB, management of MAP, metabolic management through goal-directed perfu sion (GDP) and management of thermal exchanges and haemo globin (Hb) values [109, 110].

A first step towards validating a clinical decision support tool has been developed by modelling a simulated dataset with limited decision options based on input from expert perfusionists [111].

within acceptable temperature and humidity limits as given in the instructions for use standards.

5.1 Cannulas

The distal ascending aorta is the arterial cannulation site of prefer ence in adult cardiac surgery. During cannulation, the systolic arterial blood pressure (ABP) is commonly kept below 100 mmHg to lower the risk of aortic dissection. Cannulation of the ascending aorta can be challenging in older patients or those with extensive aorta calcifications. To reduce the risk of perioperative stroke in such cases, epiaortic ultrasound scanning or computed tomogra phy angiography is helpful in visualizing plaques [112–115].

However, no differences in cerebral embolic load have been demonstrated [114]. A femoral artery approach is favoured in sit uations requiring immediate intervention, such as cardiac arrest, aortic dissection, acute bleeding, or minimally invasive cardiac surgery. Axillary-subclavian artery cannulation is gaining popular ity, especially in cases of aortic dissection, because it maintains antegrade flow in the arch vessels, is less prone to atherosclerotic plaques and has sufficient collateral arteries to the distal arm [116]. In case of axillary cannulation, using of an 8-mm interposi tion graft instead of direct cannulation allows continuous moni toring of the right radial pressure and hence of the cerebral perfu sion pressure when selective ACP is administered via the axillary artery. Other locations, such as the innominate artery, iliac artery and the apex of the left ventricle (LV), are less frequently used. In cardiac reoperations, peripheral cannulation is recommended because it minimizes procedure-related injury and the need for postoperative PRBC transfusions without substantially affecting the 1-year survival rates, postoperative complications or mortality compared to conventional central cannulation techniques [117]. Many different cannula designs are commercially available. The introduction of thin-walled cannulas has made it possible to produce smaller-diameter cannulas without jeopardizing a drop in pressure.

Recommendation Table 7. **Recommendations for patient data management and quality improvement**

Recommendations	Class[a]	Level[b]	Ref[c]
Electronic automated data recording of perfusion parameters is recommended in a perfusion programme for further evaluation and risk stratification.	I		[33, 99, 100]
It is recommended that the perfusionist collects data concerning the conduct of perfusion via a clinical registry or database and uses such data to actively participate in institutional and departmental quality assurance and improvement programmes.	I		[31, 101, 102]
The support of artificial intelligence in data collection and analysis may be considered in relation to the CPB procedure.	IIb		[109, 111]

[a]Class of recommendation.
[b]Level of evidence.
[c]References.
CPB: cardiopulmonary bypass.

5. CARDIOPULMONARY BYPASS—THE DISPOSABLES

The CPB service requires adequate dedicated space—with con venient, easy access for clinical perfusionists to the operating room—to store supplies of disposable equipment and hardware items. Storage areas should be designed or adapted to ensure correct storage conditions. In particular, the storage place should be dark, clean, dry, protected from moisture and maintained

potentially lowering the risk of problems associated with cannulation. Therefore, it is advised that cannulas with pressure dispersion tips be used preferentially to improve peripheral perfusion and reduce mor bidity during heart surgery [118]. In minimally invasive cardiac surgery, the risk of vascular complications during and after cannulation is sig nificantly decreased by using percutaneous intraoperative ultrasound assessment of proper positioning and using a vascular closure device to remove a percutaneous femoral cannula. Several studies demon strate the advantages of femoral cannulations performed with bi-flow cannulae, which improve distal limb perfusion [119, 120].

5.1.2 Venous cannulas. Central venous cannulation can be achieved using a bi-caval, single atrial, or cavo-atrial ('2-stage') approach [121]. To avoid inadvertent kinking, venous cannulas are often wire-reinforced. The appropriate size and venous cannula design are determined by patient size, weight, estimated flow rate, and vessel anatomy. When using femoral access, the venous return can be augmented using a roller pump, a centrifugal pump, or regulated vacuum connected to a hardshell venous res ervoir [122]. VAVD can compensate for the loss in flow caused by the higher resistance of the long smaller-diameter femoral can nula by increasing negative pressure. However, excessive negative pressure can introduce GME [123]. In minimally invasive cardiac surgery, the use of multistage cannulas, swirled multihole cannu las or a self-expandable venous cannula is effective for venous drainage because these cannulas allow optimal venous drainage with low negative drainage pressures [122].

5.1.1 Arterial cannulas. There are 2 types of arterial cannula tips: a central opening tip and a pressure dispersion tip. Both cannulas operate well in vivo, according to a study examining their effective ness. However, cannulas with pressure dispersion tips have the benefit of delivering larger blood flows with lower cannula pressures,

activate the coagulation and may increase haemolysis. Venting heart cavities and/or large blood vessels helps optimize the sur gical view of the heart structures. This blood is generally less activated because its exposure to

damaged tissue is lower than that of pleuropericardial blood. This situation is further strength ened by the observation that a progressive reduction of the blood/air interface reduces haemostatic activation [124].

Description of the evidence. A small RCT consisting of 48 patients showed statistically higher levels of thrombin antithrombin (AT) complexes and D-dimers in patients in whom pleuropericardial blood was returned in the systemic circulation compared to patients in whom the blood was washed by a red blood cell salvage (CS) system [125]. No sig nificant differences in inflammation were noted. A single centre prospective study in a mixed coronary artery bypass grafting (CABG) and valvular surgery population showed a statistically higher postoperative Hb concentration when CS system was used instead of returning pleuropericardial blood to the systemic circulation via a cardiotomy reservoir [126]. Two in vitro studies showed the impact of turbulence, suction tip design and negative pressure on the generation of free plasma Hb and platelet activation [127, 128]. The use of a smart suction device that controls negative pressure helps attenuate free plasma Hb [129]. Another in vitro study showed that com pletely blocked suction tips generate statistically higher amounts of free plasma Hb than suctioning a mixture of blood and air with intermittent blocking of the suction tip [130].

Recommendation Table 8. **Recommendations for choosing cannulas for the cardiopulmonary bypass circuit**

Recommendations	Class[a]	Level[b]	Ref[c]
It is recommended that there is a preoperative agreement between the perfusionist and surgeon on the choice of the size and type of venous and arterial cannulas in order to provide an adequate and safe venous return and an appropriate arterial flow tailored to the needs of the patient and the procedure.	I		-
Epiaortic ultrasonography should be considered to evaluate the ascending aorta for atherosclerotic plaques to decrease the risk of cerebral injuries.	IIa		[112–115]

[a]Class of recommendation.
[b]Level of evidence.
[c]References.

Recommendation Table 9. **Recommendation for the use of venting and suction devices**

Recommendation	Class[a]	Level[b]	Ref[c]
To limit trauma to blood elements, limited use of cardiotomy suction and avoidance of air entrainment in the cardiotomy reservoir and venting lines should be considered.	IIa		[124, 129]

[a]Class of recommendation.
[b]Level of evidence.
[c]References.

5.2 Venting and suction devices

The recuperation of pleuropericardial blood during CPB is important for reducing the need for transfusion of blood prod ucts. However, the required negative pressure, blood–air mixing and contact between blood and non-endothelial surfaces migration rate depends on several factors, such as flow rate, temperature, pH and contact time.

Two types of reservoirs are used during standard CPB: cardiot omy reservoirs and venous reservoirs. Cardiotomy reservoirs collect shed mediastinal blood (SMB) and blood from venting lines. The cardiotomy reservoir contains a defoamer and filters to scavenge solid, gaseous and deformable emboli aspirated from the surgical field.

5.3 Reservoirs

Materials used for manufacturing plastic medical disposables, including reservoirs, are important. Plasticizers necessary for the flexibility of soft shell reservoirs are a concern, because they tend to migrate from the material into the bloodstream. The

Good visibility of volume and 'level' in the venous reservoir is crucial to regulating fluid administration, providing appropriate cardiac output (CO) and ensuring a bloodless and relaxed heart during cardiac surgery procedures.

Venous reservoirs hold the venous blood during CPB and can be open or closed to atmospheric air. An important feature of a hardshell venous reservoir is the integrated pressure relief valve, which prevents pressure build-up. The latter is even more important when VAVD is utilized. This

technique is discussed in section 8.10.

The pros and cons of closed versus open venous reservoirs are disputable. According to the available evidence, each has benefits and drawbacks, but none is clearly superior. Open reservoirs are considered safer and easier to operate, whereas closed reservoirs are considered better regarding biocompatibility and blood preservation [124], but the few clinical studies available have failed to produce hard evidence. A separate cardiotomy reservoir for SMB is advised when using closed venous reservoirs.

Description of the evidence. Closed venous reservoirs contain plasticizers, which make these reservoirs more flexible. A systematic review shows evidence that favours polyvinyl chloride (PVC) products with the additive trioctyl trimellitate (TOTM), because these seem to have the least toxic effect [131].

activation of coagulation and fibrinolysis [137]. Even in a closed system, cardiotomy suction was associated with higher fibrinolysis, as indicated by elevated D-dimers and fibrin degradation products. In cardiotomy suction groups, low activated clotting time (ACT) was related to higher fibrinolysis [138]. However, it was shown that patients with low preoperative haematocrits (HCTs) (<35%) required fewer PRBC transfusions when using closed reservoirs [139]. The observed variation was most likely due to the substantial variation in priming volume (1180 vs 760 ml).

All studies comparing open versus closed reservoirs that have been published to date have serious methodological flaws, such as (i) small sample sizes, (ii) end points that are inconsistent and

poorly defined and cannot be measured objectively, and (iii) a combination of interventions, like the use of cardiotomy suction, which makes it challenging to interpret and apply these findings.

Results from 3 studies on the efficacy of removal of leucocytes and fat particles by cardiotomy filtration from SMB were published [140–142]. The number of circulating leucocytes decreased, according to all investigations. However, whereas some researchers [140, 142] reported a decrease in fat clearance, others [141] could not confirm earlier findings. A different measurement technique is presumably to blame for this disparity. More research with clear clinical end points is required to prove that this technology is beneficial.

One experimental study showed that a significant variability in the opening pressure of the pressure relief valve of commercial hardshell reservoirs may lead to reservoir pressurization when used in conjunction with VAVD [143]. More research is needed to determine the reliability of the integrated pressure relief valve, particularly in maintaining consistent negative pressure.

Recommendation Table 10. **Recommendations for the selection and use of reservoirs**

Recommendations	Class[a]	Level[b]	Ref[c]
The use of a separate cardiotomy reservoir should be considered to decrease the deleterious effect of SMB.	IIa		[135–137]
A closed venous reservoir may be considered to attenuate the inflammatory response and improve biocompatibility when used together with other elements.	IIb		[135–137]

[a]Class of recommendation.
[b]Level of evidence.
[c]References.
SMB: shed mediastinal blood.

There is no difference in biocompatibility between open and closed reservoirs when they are used during valvular surgery, or CABG [132, 133]. The main benefit of the open system was related to usability, according to a narrative study that found no indication that either device was superior [134].

Several studies comparing open and closed reservoirs found a combination of the following measures to be better regarding biocompatibility and blood handling: (i) system coating; (ii) the use of a centrifugal pump; (iii) avoiding cardiotomy suction; and (iv) passive venting. However, it was impossible to pinpoint which aspect was responsible for which benefit [124, 135, 136].

The reinfusion of unprocessed SMB may negate any benefits from either open or closed reservoirs concerning handle bubble removal. Furthermore, the distribution sizes of

5.4 Oxygenators

Membrane oxygenators are the first choice for gas exchange during CPB worldwide [144]. Many investigations have demonstrated that they outperform bubble oxygenators in terms of GME generation, complement activation and neuropsychological results. As a result, no bubble oxygenators are in use any more or even manufactured. However, little effort has been invested in assessing the effect of membrane oxygenator design on outcome metrics.

Description of the evidence. A recent experimental study investigated the GME handling capacity of 5 commercially available oxygenators. They found differences in how different oxygenators bubbles were related to oxygenator design, pressure drop and the presence of prefilters [145]. Under controlled clinical

conditions, 1 RCT involving 9 commercial microporous membrane oxygenators found substantial differences in pressure drop, diffusion capacity, oxygen gradient and heat exchanger performance across the devi ces. There were no variations in platelet loss or free plasma Hb concentration [146]. Furthermore, 2 studies examining the relation ship between shear stress, pressure drop and cell activation found no differences in cell damage between the different hollow fibre membrane oxygenator designs. However, white blood cell activa tion was more pronounced with a flat sheet design.

anaesthesia [153]; alternatively, when added to the oxygenator's sweep gas, they pose the risk of intraoperative awareness [154, 155]. Microporous polypropylene membrane oxygenators do not exhibit increased resistance to volatile anaesthetics. The use of vola
tile anaesthetics does not affect the membrane's chemical structure or the oxygenator's performance over time [156]. This observation was confirmed in an RCT in which no difference in isoflurane con centrations in arterial blood was reported between different poly propylene oxygenators [157]. Finally, 1 prospective investigation found that condensate production reduced total oxygenator func tion. This result was true for both polypropylene and polymethyl penthene oxygenators [158].

Recommendation Table 11. **Recommendations for the selection of an oxygenator**

Recommendations	Class[a]	Level[b]	Ref[c]
Microporous membrane oxygenators are recommended as the standard choice in the CPB procedure.	I		[142, 146]
Polymethylpentene membrane oxygenators are not recommended when volatile anaesthetic agents are used during the CPB procedure.	III		[154–156]

[a]Class of recommendation.
[b]Level of evidence.
[c]References.
CPB: cardiopulmonary bypass.

An RCT comparing 2 membrane oxygenators with an inte grated ALF but different surface coatings found a significant dif ference in postoperative bleeding, transfusions and inflamma tory response as measured by the C-reactive protein
concentration [147]. The data, however, could not be used to determine whether the variations were due to design variables or the various types of coatings applied.

Another RCT [148] used electron microscopy to investigate cellular deposition onto oxygenator fibres under pulsatile or continuous flow conditions. Pulsatile perfusion resulted in less uptake of cellular components and protein on oxygenator fibres. The consequences of pulsatile and continuous flow are thoroughly addressed in section 9.6. The influence of using a haemocompatible coating versus no coating on the incidence of oxygenator failure caused by pathological absorption of fibrinogen, platelets and other blood components was studied in depth. The investigation revealed that coating was protective in reducing oxygenator failure (0.03% vs 4.3%) [149]. Another large retrospective study found no difference in mortality between patients who used radial flow oxygenators and those who used axial flow oxygenators [150]. Interestingly, 1 RCT found that radial flow oxygenators had lower levels of humoral inflammatory response than did axial flow oxygenators [151]. On the other hand, a small prospective audit found more SIRS cases in patients treated with 2 of 3 types of oxygenators, although CRP increase was similar for all groups (p ¼ 0.12) [152].

Results from 2 small RCTs suggested that using polymethylpen tene membrane oxygenators in conjunction with volatile anaes thetic agents during heart surgery is not recommended due to the membrane's low permeability to volatile anaesthetics. As a result, volatile anaesthetic agents delivered through the native lungs con centrate in the plasma, resulting in an unwanted deeper level of

5.5 Pumps

During CPB, a roller or centrifugal pump can replace the cardiac pump function. Centrifugal pumps are non-occlusive and are pre load dependent and afterload-sensitive. For this reason, they should always be combined with a flow probe to ensure adequate flow. High pump afterload requires a high speed of revolutions and may lead to heat generation and protein degeneration. However, at nor mal working conditions, a higher level of haemocompatibility is hypothesized for centrifugal pumps because there is no tubing wear, which makes them ideal for prolonged procedures.

Roller pumps are operator-dependent because occlusion settings need to be set for each procedure. Overocclusion may lead to increased particle spallation of the tubing, tubing rupture and hae molysis. Underocclusion may cause incorrect flow readout. Roller pumps remain the standard for applications when both negative and positive pressures need to be generated, such as for aspirating wound blood, unloading heart chambers, or administrating cardioplegia.

Description of evidence. The impact of various blood pumps on postoperative clinical outcomes was analysed through an SLR and a meta-analysis of the existing literature. Although the meta-analysis contained high-quality RCTs, no differences were observed between roller pumps and centrifugal pumps with respect to the number of patients who received PRBC transfusions or experienced postopera tive blood loss; to the length of stays in the intensive care unit (ICU) and the hospital; and to the number of deaths [43, 134]. These find ings were contradicted by those from a large single-centre RCT showing that centrifugal pumps were

superior to roller pumps when the same extracorporeal circuit was used and when chest tube drain age and massive blood transfusions (>5 units) were compared [159].

pumps. A review based on 33 RCTs found a significantly higher level of free plasma haemoglobin and a significantly lower concentration of haptoglobin when roller pumps were used [160]. Of note was the sig nificant heterogeneity and inconsistency in the included studies. A study investigating in vivo differences in haemolysis between centrifu gal pumps, roller pumps and roller pumps with a dynamic occlusion setting did not observe statistical differences [161]. One single-centre RCT showed significantly lower platelet activation with centrifugal pumps [162]. In contrast, another showed a more than 50% reduction in tissue factor release with centrifugal pumps versus roller pumps but no difference in thrombin-AT III, F1þ 2 or thrombin formation [163]. Another RCT could not demonstrate significant differences in pre-, peri- and postoperative laboratory values in patients having CABG surgery using 3 different centrifugal pumps, a roller pump or a peri
staltic pump [164].

A single-centre RCT studying neuropsychological outcomes before and after elective CABG could not find significant differences between roller and centrifugal pumps. However, more individual test deficits were observed in the roller pump group [165].

oxygenators in removing GME is lacking. A small single-centre RCT investigated the impact of combining an

Data on the relationship between pump type and blood damage are conflicting and seem dependent on operator settings for roller

ALF with a dynamic bubble trap versus an ALF alone during pulmonary endarterec tomy on postoperative cognitive decline (POCD) [166]. The results showed less POCD in patients treated with both devices.

However, this study did not look for confounding factors. There is no difference in efficiency between standalone and inte grated ALF when filter screens of equal pore sizes are used. The latter has the advantage that, depending on its design, it can reduce total circuit priming volume by 100 up to 250 mL. Screen filters may acti vate blood cells, as shown by a small single-centre prospective study using platelet markers and scanning electron microscopy of the filter screen [167]. A major limitation of the study was that the ALF was

not treated with a haemocompatible coating. For centres using MiECC in a configuration without a venous reservoir, a combination of a venous filter or bubble trap with an ALF is advisable.

The integration of an ALF with a leucodepletion filter (LDF) has been of interest for improving organ function. A best-evidence review found no clinical benefit favouring LDF usage [168]. This result

Recommendation Table 12. **Recommendation for selection of a blood pump**

Recommendation	Class[a]	Level[b]	Ref[c]
The use of a centrifugal pump should be considered for expected longer CPB times.	**IIa**		–

[a]Class of recommendation.
[b]Level of evidence.
[c]References.
CPB: cardiopulmonary bypass.

5.6 Arterial line filter

During CPB, there is a risk of the introduction of gaseous, solid and deformable (fat) microemboli in the systemic circulation, which may potentially target major organs. To attenuate this risk, line filters are placed at different locations in the CPB circuit. The most common techniques are screen filtration and depth filtration or a combination of both. The combination of both techniques is used in the cardiotomy reservoir filtering wound blood and in leucocyte filters that remove (activated) leucocytes. Original ALFs were standalone units, whereas nowadays, most are integrated into the membrane oxygenator.

Description of the evidence. In combination with a bubble oxy genator, an ALF significantly reduces GME. The removal efficiency is inversely related to the pore size of the filter screen. A meta analysis of the synergy between (integrated) ALF and membrane

was confirmed by a Cochrane collaboration meta-analysis investigat ing the benefit of using an arterial line LDF versus a standard ALF in valve surgery, which did not show a benefit [169]. A small RCT did not find a difference in outcome but failed to include neuropsycho logical outcomes. This result was confirmed by another RCT investi gating whether an LDF preserved renal function better than an ALF alone during valvular surgery [170]. The results showed a higher inci dence of AKI in the LDF group, and the authors concluded that LDF should not be used for attenuating AKI. In 2 other RCTs assessing the effects of LDF on postoperative morbidity, 1 trial did not find any significant effect using an LDF [171]. In another trial, although an LDF has been shown to reduce the numbers of activated leukocytes, the incidence of clinical outcomes was similar between the LDF and the standard filter groups [172]. Finally, in an RCT comparing LDF with 2 standard filters, there were significantly fewer microemboli measured by transcranial Doppler in those with LDF. However, there was no association with a better neuropsychological outcome [173].

Recommendation Table 13. **Recommendations for the use of arterial line filters**

Recommendations	Class[a]	Level[b]	Ref[c]
ALFs may be considered in order to reduce the number of microemboli.	IIb		-
The routine use of LDFs, when combined with membrane oxygenators, is not recommended.	III		[170, 168, 169]

[a]Class of recommendation.
[b]Level of evidence.
[c]References.
ALFs: arterial line filters; LDF: leucodepletion filters.

5.7 Material and surface treatments

The contact of the blood with the negatively charged surfaces of the heart-lung machine leads to an immediate interaction. Blood reacts with the biomaterials in a process whereby the for eign surfaces immediately bind protein and albumin. Platelets are then accumulated and activated, and in the final stage, thrombi are formed. In addition, the involvement of platelets and complement factors triggers the inflammatory system. In this way, a surface-induced coagulopathy can be triggered. An option to counteract this development is to make the sur faces more biocompatible. The goal of these surface modifica tions is to reproduce the antithrombotic and anti-inflammatory properties of the vascular endothelium. Innovation aimed at antithrombogenic effects (inactivation of thrombin) and at a reduction in platelet adhesion and activation is ongoing. Various surface modifications have been developed for this purpose to target not only thrombin inhibition (antithrombogenic) but also inhibition of platelet adhesion/activation.

The 3 available modifications can be described as follows: (i) biomimetic (bioactive) surfaces with heparin, NO and direct thrombin inhibitors (DTI); (ii) biopassive surfaces such as phos phorylcholine (PPC) albumin and poly-2-methoxyethyl acrylate (PMEA); and (iii) endothelialization of the surfaces aimed at antithrombogenic effects. In the contemporary practice of CPB applications, either biopassive surfaces or a combination of pas sive surfaces and heparin coatings has been applied. Endothelialization and the use of NO and DTI are promising but are not yet widely used in daily routine [174].

Description of the evidence. Three systematic reviews and a meta-analysis investigated the effect of different biocompatible coatings in cardiac surgery on postoperative clinical outcomes [175–178]. One systematic review and meta-analysis assessing 4360 patients in 36 RCTs and clinical outcomes found no differences in postoperative lung dysfunction and mechanical ventilation times when biocompatible bypass circuits were compared with uncoated circuits. However, there was a significantly shorter stay in the ICU when biocompatible bypass circuits were used. The biocompatible coatings were associated with a reduction in PRBC transfusions [odds ratio (OR), 0.88; 95% CI, 0.72–1.08, P ¼ 0.21], atrial fibrilla tion (AFib) (OR 0.66, 95% CI 0.49–0.88) and reduced stay in the ICU by 5 ± 2 h, but not with the number of deaths (OR 0.78, 95% CI 0.39–1.55) [175]. However, heterogeneity of different biocom patible modifications was noted, with 78% of trials using heparin bonded surfaces only [175]. In another systematic review of 14 RCTs, the beneficial effect of heparin or PPC coating was shown on postoperative neurological and pulmonary functions [177].

A single-centre RCT of 78 patients undergoing CABG com pared heparin-albumin, PPC and PMEA-coated circuits with an uncoated control group and demonstrated that heparin coatings resulted in fewer inflammatory responses and less oxidative stress [179].

Others showed the beneficial effects of heparin-bonded cir cuits on blood loss and PRBC transfusion rates, reoperation for bleeding (OR 0.6, 95% CI 0.4–0.8), reduced ICU stay [weighted mean difference −9.3 h, 95% CI −14.7– −3.9 h) and hospital stay (weighted mean difference −0.5 days; 95% CI −0.9 to −0.1 days) [176, 178].

A recent study compared different coatings of PPC, PMEA and heparin bonded in 50 patients each. There were only slight dif ferences in the occurrence of postoperative SIRS, as defined by inflammatory response markers and oxidative stress but without significant clinical relevance, and there were no differences in the amount of bleeding or the need for blood products [179]. The number of comparative studies of biocompatible coatings that focus on major end points, including neurological out comes, kidney function or death, is limited. A relatively large RCT showed a lower incidence of postoperative neurological deviations in the heparin-coated group compared to the non coated group (3.9% vs 9.4%) after CABG surgery [174].

The use of a PPC coating in isolated CABG was associated with lower peak serum creatinine levels (1.19 ± 0.48 mg/dl vs 1.41 ± 0.94 mg/dl; P ¼ 0.048) compared to controls [180].

Several publications describe lowering systemic ACT when using coated systems. An RCT in 241 patients (135 in the heparin albumin–coated group vs 106 in the non-coated group) (ACT: 355.64 ± 34.12 vs 560.38 ± 90.20, P ¼ 0.001) from 2020 showed effects in reduced bleeding (529 ± 268 vs 661 ± 280 ml, P < 0.001) and shorter length of stay, but not in mortality or other occurrences of major adverse events [181]. Another RCT did not show increased thrombin formation when a heparin-coated circuit was used

with an ACT of 300 s [182]. In 2011, *Øvrum et al.* reported a cohort of 5954 patients and a target ACT of 250 with no side effects and no abnormal number of deaths. Although this was not a PRCT study, the large number of patients included shows that the safe implementation of CPB with coating and reduced ACT is undoubtedly possible [183]. Biocompatible coat ings can be considered to reduce the dose of heparin [180, 183].

Even if there are no further results in clinical studies at this time, in animal experiments, nitric oxide-releasing coatings have already shown promising results, but additional clinical research is still needed [184].

In summary, biocompatible surfaces have the potential to reduce the occurrence of postoperative inflammation. In addi tion, with biocompatible coatings, it is possible to reduce the dose of heparin and protamine, and its use may contribute to a reduction in the systemic inflammatory response and the activa tion of the coagulation system during CPB and, therefore, a reduction in postoperative bleeding.

Recommendation Table 14. **Recommendations for material and surface treatments**

Recommendations	Class[a]	Level[b]	Ref[c]
The use of any biocompatible surface treatment to reduce complications should be considered.	IIa		[175–178]
Biocompatible circuit modifications should be considered to protect the lungs from inflammatory responses and limit oxidative stress.	IIa		[175, 179]

[a]Class of recommendation.
[b]Level of evidence.
[c]References.

5.8 Tubing

6. MONITORING

Tubing is a necessary component of the CPB to connect the cir cuit to the patient on the one hand and to interconnect all cir cuit components on the other hand. Different types of tubing are available for CPB in terms of length, thickness, softness and the material from which they are made [185–187].

Description of the evidence. PVC and silicone are currently the most widely used tubing materials. Flexible arterial tubing (sili cone) does not show advantages over standard kit PVC tubing in adult MiECC in terms of preservation of haemodynamic energy from a pulsatile diagonal pump [188].

However, a substantial triboelectric charge is generated in roller pumps using PVC tubing. This charge can potentially dam age electronic components in the extracorporeal pump platform. It is of sufficient magnitude to cause a “painful” discharge event to humans without proper protective or preventive measures [189]. The substitution of PVC tubing for silicone rubber tubing in pump contacting surfaces has reportedly ameliorated this condi tion [190–193]. No detectable accumulated static charge was found in the centrifugal pump model at any flow or humidity level [189]. Tygon tubing is made from a biocompatible di(2- ethylhexyl) phthalate (DEHP) polymer material developed specifi cally for medical device needs (see below). It is more resilient to spallation effects regarding the release of small particles [194].

The lipophilic DEHP is the most used plasticizer; however, DEHP can be released out of the tubing by evaporation, migra tion, rubbing or elution [195]. When using PVC as a biomaterial that contacts lipid-containing substances (e.g. blood), the slow but permanent release of DEHP is expected [196, 197]. There is no evidence of a connection between any pathophysiological inflammatory reaction and the leaching of DEHP and its active metabolites. ‘DEHP-free‘materials leach low levels of detectable DEHP and its metabolites, but they still exist [198]. With thin coatings (also those containing heparin), pronounced differences are noticeable in their function as a barrier against the leaching of DEHP into the blood. Still, they do not provide an absolute blocking of DEHP migration when tested in vitro [199]. The leach ing of DEHP is several times higher (more than 350-fold) than that of its substitute, TOTM. Together with the fact that TOTM is assumed to be far less toxic than DEHP, this proves that a DEHP substitution is feasible and should be considered. The observed lower plasticizer migration rate of tubing material kept in storage for several weeks is of particular interest. Provided that the tech nical properties of the material are not adversely affected, this may lead to the general recommendation of using longer-stored products for PVC medical devices, particularly for critical applica tions such as CPB in high-risk patients [200].

Monitoring during CPB has become an integrated part of ECC hardware and procedures. Effective monitoring of haemody namic parameters and organ function, especially neuromonitor ing, plays a vital role in ensuring patient safety and optimizing outcomes during CPB procedures. monitoring haemodynamic variables and organ function, particularly neuromonitoring.

6.1 Mandatory equipment for safe perfusion

Monitoring of physiological patient variables and CPB performance

is the mainstay of the care of patients by perfusionists. Whereas it is evident and common sense to monitor basic variables such as ABP, pump flow and blood gases, some technologies provide a more in depth insight into patients' DO_2 and tissue oxygenation. Measurement of venous oxygen saturation [201] and continuous blood gas monitoring [202] has gained significant importance. Regional cerebral tissue oxygenation may be assessed by near infrared spectroscopy (NIRS), and the measurement of DO_2 has been suggested as a worldwide standard of

care for evaluating arte rial flow rate. In a recent survey, DO_2 was regularly monitored by 38% of the respondents. Other monitoring tools used were temper ature monitoring (nasopharyngeal) and TOE during the weaning phase [203]. Non-invasive cerebral monitoring, such as regional cer ebral tissue oxygenation and an electroencephalogram (EEG)-based depth of anaesthesia monitoring, is discussed in section 6.2.

Description of the evidence. We previously proposed a list of mon itoring parameters [6] derived from other standards and guideline documents that should be followed by the cardiac surgery team [35, 61]. The list is exhaustive but not limited. Most monitoring devices are undeniably equivalent to good practice and are prob ably used by most perfusionists. For monitoring other variables, there is not always evidence that their use leads to better patient outcomes. If a variable is monitored, the equipment used for measurment should be calibrated, maintained regularly and checked before use. Special consideration should be given to the calibration of arterial pump flow (roller and centrifugal pumps) and pressure transducers (arterial, cardioplegia). Concern was recently raised about the accuracy of radial artery measurements during CPB [204]. This concern has led some to advocate use of the femoral or brachial artery monitoring lines for CPB or to con firm low radial artery pressures with direct measurements from the aortic root. Accurate arterial pump flow measurements are the basis for correct on-pump calculations such as DO_2. It must, therefore, be stated that arterial pump flow should be measured close to the patient to ensure correct arterial outflow readings.

Recommendation Table 15. **Recommendations for tubing and plasticizers**

Recommendations	**Class[a]**	**Level[b]**	**Ref[c]**
It should be considered to use silicone rubber tubing in pump-contacting surfaces or a centrifugal pump to prevent triboelectric charges.	**IIa**		**[190]**
TOTM should be considered over DEHP as a plasticizer for CPB circuits.	**IIa**		**[195, 198–200]**

[a]Class of recommendation.
[b]Level of evidence.
[c]References.
CPB: cardiopulmonary bypass; DEHP: di(2-ethylhexyl)phthalate; TOTM: trioctyl trimellitate.

Arterial roller pump calculated flow or flow measurements upstream of open CPB shunts may not give accurate information on actual arterial flow delivered to the patient and will, therefore, often lead to inaccurate DO_2 calculations. Moreover, measuring venous line flow towards the venous reservoir may give a better understanding of the dynamic circulatory status of the ECC.

systematic review with a meta-analysis [210] including 13/25 RCTs in cardiac surgery could not provide solid evidence for cerebral NIRS monitoring on different clinical outcomes such as death or persistent cognitive or neurological deficit. Likewise, another narra

tive review did not outline improvements in neurocognitive out comes, morbidity or mortality with the use of NIRS in cardiac sur

Recommendation Table 16. **Recommendations for equipment for safe perfusion**

Recommendations	**Class[a]**	**Level[b]**	**Ref[c]**
It is recommended that blood flow going to the patient is monitored by ultrasonic measurement on the arterial line.	**I**		**-**
It is recommended that pressure monitoring devices be used on the arterial line (pre- and postoxygenator) and cardioplegia delivery systems during CPB.	**I**		
Continuous oxygenator arterial outlet temperature monitoring is recommended.	**I**		**-**
It is recommended to monitor SvO_2 and HCT levels continuously during CPB.	**I**		**[201, 202]**
Performance of blood gas analysis at regular intervals or a continuous blood gas measurement is recommended during CPB.	**I**		**-**
It is recommended that patient blood and tissue temperatures be measured simultaneously in multiple locations during CPB to avoid (regional) hyperthermia.	**I**		**-**

[a]Class of recommendation.
[b]Level of evidence.
[c]References.
CPB: cardiopulmonary bypass; HCT: haematocrit; SVO_2: venous oxygen saturation.

6.2 Non-invasive brain monitoring

6.2.1 Regional cerebral saturations. Monitoring the regional cerebral oxygen saturation (rS_cO_2) using disposable sensors with absorptive properties for Hb is a non-invasive technique to assess local cortical tissue perfusion in regions supplied by the anterior and middle cerebral arteries. Low preoperative baseline values (e.g. rS_cO_2 below 50%) and intra- and perioperative decrements (e.g. rScO2 below 15% of baseline) allow early recognition of cerebral malperfusion for various reasons, and monitoring rS_cO_2 is suitable to trigger immediate actions for resolution. NIRS-based algorithms help to improve the cerebral oxygen supply/demand ratio by applying different measures [optimizing head position, perfusion pressure, haematocrit (HCT) and CO_2 partial pressure] [205]. They are part of the (multimodal) neuromonitoring strategy in cardiac surgery, as suggested by professional societies [206, 207]. Still, the available evidence regarding improved clinical outcomes using NIRS is challenging to interpret [208], primarily because of study heterogeneity with a considerable risk of bias and low incidence of clinically relevant cerebral events. An RCT [209] and a recent gery due to significant heterogeneity in the studies investigated [211].

In contrast, other studies and 1 narrative review provided useful evi dence for the association of low preoperative rS_cO_2 values with post operative delirium and intraoperative cerebral desaturation with post operative delirium, cognitive decline or organ dysfunction [212–216].

Furthermore, 1 recent meta-analysis, including 7 RCTs, indi cated a reduced risk of postoperative delirium and/or cognitive dysfunction using NIRS-based algorithms in cardiac surgery [217] and another meta-analysis, including 14 RCTs, showed a lower incidence of POCD [218].

New indications for the use of NIRS have appeared in recent years. These include rS_cO_2 monitoring in patients with non pulsatile blood flow on mechanical circulatory support or ECMO [219]. Determining the individual limits of cerebral autoregulation during CPB is another promising area for NIRS application with rapidly evolving technologies [220, 221]. Results from a single centre RCT revealed that an ABP during CPB to above the lower limit of autoregulation based on AI and NIRS technology, resulted in a reduction of postoperative delirium and improved memory at 1 month postoperatively compared with usual care [222].

Recommendation Table 17. **Recommendation for regional cerebral saturations**

Recommendation	Class[a]	Level[b]	Ref[c]
The use of NIRS-guided algorithms should be considered to detect cerebral hypoperfusion of any origin.	**IIa**		**[208, 209, 213–218]**

[a]Class of recommendation.
[b]Level of evidence.
[c]References.
NIRS: near-infrared spectroscopy.

6.2.2 Depth of anaesthesia monitoring. Intraoperative aware ness is more common in cardiac anaesthesia compared with non cardiac surgery, with a reported incidence of accidental awareness at the United Kingdom's 5th National Audit Project of 0.02% [223]. It negatively influences the neuropsychological status of patients post operatively. Processed EEG monitors are widely used to reduce the incidence of recall during surgery. This is particularly relevant for patients being anaesthetized with total intravenous anaesthesia, because, in contrast to the use of volatile anaesthetics, monitoring of administered intravenous anaesthetic agents is not possible [224].

It has been shown that, during hypothermia, the BIS value is reduced by about 1.2 units per degree Celsius temperature reduction [235–237]. Similarly, during DHCA, there is a strong correlation between the BIS value and temperature [238, 239]. A recent study using SedLine-derived processed electroencephalographic variables during hypothermia and CPB assessed the patient state index (PSI), representing the depth of sedation (with 0 indicating a deeply sedated patient and 100 a fully awake patient). The authors demonstrated a PSI decrease of 0.84 for each degree Celsius during cooling and a PSI increase of 0.7 for each degree Celsius during rewarming [240].

Recommendation Table 18. **Recommendation for depth of anaesthesia monitoring**

Recommendation	Class[a]	Level[b]	Ref[c]
The use of processed EEG monitoring should be considered to reduce the incidence of intraoperative awareness and excess in depth of anaesthesia.	IIa		[231–234]

[a]Class of recommendation.
[b]Level of evidence.
[c]References.
EEG: electroencephalogram.

A recent systematic review with meta-analysis evaluated 12 RCTs on the association between intraoperative EEG monitoring and mortality in adults undergoing cardiac surgery [225]. EEG guided (lighter) anaesthesia procedures could not show a reduc tion in mortality. This outcome is in contrast to those of previous studies, where an association of mortality with deeper anaesthesia was found [226]. As part of multimodal neuromonitoring, an EEG might provide additional information on cerebral perfusion, the occurrence of ischaemia, seizures and cortical burst suppression in cardiac surgery involving hypothermic circulatory arrest [212, 227]. Due to the heterogeneity of current data, conflicting evi dence from several meta-analyses [228–230] exists concerning the ability of EEG-guided anaesthesia to reduce postoperative delir ium or cognitive deficit. However, a recently published multi centre RCT in patients undergoing major surgery clearly demon strated the superiority of light anaesthesia compared with deep anaesthesia with a reduced incidence of postoperative delirium and better cognitive function at 1 year in the light anaesthesia group [231]. According to a meta-analysis and systematic review, bispectral index (BIS)-guided anaesthesia can reduce the risk of intraoperative awareness in surgical patients at high risk of aware
ness compared to clinical signs as a guide for anaesthetic depth [232]. Other studies have failed to demonstrate an advantage of a BIS-guided protocol over end-tidal anaesthetic concentration monitoring, resulting in conflicting evidence regarding BIS usage as part of standard practice [233, 234].

6.2.3 Transcranial Doppler ultrasound. Transcranial Doppler monitoring is used in patients undergoing cardiac surgery under CPB to detect high-intensity transient signals and measure the velocity and direction of the cerebral blood flow by insonation of the middle cere
bral arteries. For the latter purpose, transcranial Doppler monitoring can help identify mechanical causes for cerebral blood flow reduction and hemispheric flow asymmetry and might support strategies for selective antegrade perfusion in aortic surgery [212]. Due to disadvan
tages that may limit the wide application of this technique, including the requirement for special equipment, the need for technical exper tise, the challenges of identifying an acoustic window and insufficient evidence for the association of high-intensity transient signals with intraoperative embolic events and neurological outcomes, transcranial Doppler is not recommended as a standard technique in cardiac sur gery [212]. Further research is needed to better elaborate the role of transcranial Doppler for cerebral autoregulation and neurological out comes in cardiac surgery.

Recommendation Table 19. **Recommendation for transcranial Doppler ultrasonography**

Recommendation	Class[a]	Level[b]	Ref[c]
The use of transcranial Doppler ultrasonography to assess cerebral blood flow may be considered in patients undergoing selective cerebral perfusion.	IIb		[212]

[a]Class of recommendation.
[b]Level of evidence.
[c]References.

6.3 Haemodynamic monitoring

Apart from the electrocardiogram for assessing heart rate, rhythm and myocardial ischaemia, a cannula to measure ABP and a central line to continuously assess central venous pressures, haemodynamic moni toring devices for pre- and post-CPB management include the pul monary artery catheter (PAC), minimally invasive CO monitors (pulse contour analysis) and TOE. They help assess cardiac performance, including regional myocardial function of the LV and the right ventricle (RV), valvular dysfunction, residual defects, and intracardiac air or thrombus.

6.3.1 Pulmonary artery catheter. The PAC generates unique haemodynamic data that can guide therapeutic decision making. However, studies done in the 1990s suggested that its use may trigger higher-intensity treatments without translating into improved out
comes and that it may harm critically ill patients [241]. This

result has led to a reduction in the use of the PAC in cardiac surgery. Earlier observational studies reported up to 35–40% of cases receiving a PAC [242], and recent observational studies report between 9% and 28% [243–245]. None of the newer studies has demonstrated any differ
ence in mortality but a reduced length of stay in patients treated with a PAC [243, 244]. Due to the lack of clinical data, the underlying explanation for a shortened admission cannot be deduced because the data are derived from diagnostic and procedural registries. Of interest, in the most extensive study, hospitals in the upper quartile of PAC usage frequency had a significant reduction in the number of patients with an admission > 7 days, whereas the lowest quartile had a significant increase in the same outcome, indicating that experience and familiarity plays a role in the advantages of the PAC [244]. A retro spective registry study in 1414 patients with cardiogenic shock in the critical care setting demonstrated that the early insertion of the PAC prior to the initiation of mechanical circulatory support was associated with improved survival of patients [246].

Complications specifically associated with the usage of the PAC are extremely rare but may be serious, and they can include pulmonary artery rupture (incidence 0.03–0.2%), PAC knotting (incidence 0.03%) or PAC dislodgement [247].

In the absence of data from randomized trials, the overall recom mendation is to discourage routine use of a PAC, while acknowledg ing both a potential role and a lack of evidence in specific cases.

6.3.2 Minimally invasive haemodynamic monitors using pulse contour analysis. Several devices use an algorithm based on pulse contour analysis in order to calculate CO. Agreement of CO assessments between these minimally invasive pulse contour analysis monitors in comparison to the 'practical' gold standard PAC has been poor. Previous studies on accuracy and precision in non-cardiac and cardiac operations have demonstrated mean percentage errors between 41% and 49%, which is beyond the accepted agreement of a reference standard of 30% or less [248–250]. Minimally invasive CO measurements would be extremely helpful in monitoring haemody namic changes in vulnerable patients during CABG surgery in relation to bleeding, fluid shifts or the effect of anaesthetic agents. However, most previous studies have been performed in patients with normal cardiac function. Conflicting results have been observed in patients with impaired function of the LV with both acceptable and unaccept able bias [251]. Then again, this result may relate to variability in
absolute CO between studies because a recent study demonstrated using the Bland-Altman plot that bias and limits of agreement between thermodilution and pulse contour analysis improved with higher absolute CO, irrespective of the left ventricular ejection frac
tion (LVEF) [252]. No clinical studies report outcomes concerning the application of minimally invasive monitoring. Until further evidence is available, the routine use of pulse contour analysis for CO measure ment cannot be recommended in cardiac surgery patients.

6.3.3 Transoesophageal echocardiography. The use of TOE has increased during the recent decade. In a large observational study comprising > 1 million CABG cases obtained from the Society of

Thoracic Surgeons (STS) database, TOE was used in 40% of cases in 2011 and increased to 62% in 2019 [253]. Comparison of TOE monitored patients with matched no-TOE patients shows improved outcomes in reduced mortality in isolated CABG [253, 254], aortic valve and proximal aortic surgery [255]. In isolated CABG, the lower operative mortality was particularly prominent in higher-risk patients, and TOE was associated with greater odds of unplanned valve proce
dures [253]. Occurrence of oesophageal perforation was similar in TOE and no-TOE procedures (0.01%) [254]. Based on data from the STS database, including > 1200 hospitals, intraoperative TOE use versus no TOE was more strongly associated with hospital and surgeon prac
tice patterns than with any patient-level factor, surgical volume or geographic location [256]. However, improved mortality outcomes could be replicated on the hospital and surgeon level in both aortic valve replacement (AVR) [255] and isolated CABG surgery [254]. TOE has a number of advantages in relation to cannulation and the con
duct of CPB, including detection of anatomical abnormalities that could affect conduct of CPB, confirmation of appropriate placements of cannulas, monitoring of adequate decompression of the left ven tricle, diagnosis and management of iatrogenic arterial dissection and assessment of presence of residual air and adequacy of de-airing before weaning off CPB. In valve surgery, the use of TOE is particularly important for checking the operative result. Despite the lack of data from RCTs, the overall recommendation is to encourage the use of TOE unless there are absolute contraindications. Absolute contraindi
cations for TOE include oesophageal stricture, tracheoesophageal fis tula, oesophageal trauma and oesophageal surgery or oesophagec tomy [257].

However, the use of TOE in cardiac surgery is not without any risks, as demonstrated by a prospective national audit in the United Kingdom showing an associated morbidity of 0.08% (95% CI 0.05–0.13%) and a mortality of 0.03% (95% CI 0.01–0.07%), demanding that the technique should only be performed by experienced and certified clinicians [258].

In the future, a more precise characterization of the cardiac surgery patient who will benefit from TOE is warranted.

Recommendation Table 20. **Recommendations for haemodynamic monitoring**

Recommendations	**Class[a]**	**Level[b]**	**Ref[c]**
A PAC should be considered in selected cases to reduce hospital LOS.	**IIa**		**[243, 244]**
Cardiac output measurement with pulse contour analysis may be considered in selected patients.	**IIb**		**[248, 251]**

TOE is recommended in cardiac surgery procedures unless there is an absolute contraindication.	I		[253–255]

[a]Class of recommendation.
[b]Level of evidence.
[c]References.
LOS: length of stay; PAC: pulmonary artery catheter; TOE: transoesophageal echocardiography.

7. ORGAN PROTECTION

In this section, general measures to protect the organs during CPB are summarized. These measures include remote ischaemic preconditioning, pharmacological measures, such as statins or beta-adrenergic blockers and organ-specific measures concern
ing the brain, heart, kidney and lungs.

7.1 Remote ischaemic preconditioning

Remote ischaemic preconditioning (RIPC) has been advocated as a feasible, harmless and efficient way of protecting organs during car diac surgery. Inducing intermittent ischaemia in one part of the body, typically the upper or lower limbs, induces a response lead ing to increased tolerance of subsequent ischaemic periods in other parts of the body, such as the heart. Many studies have been performed to elucidate possible mechanisms and laboratory and clinical effects on the heart, brain, kidneys, intestine and postopera tive bleeding following heart surgery with CPB. However, the results of the RCTs are not consistent. Confounding factors, such as drugs and anaesthesia protocols, may partly explain the variability.

patients who did not receive propofol (OR 0.53, 95% CI 0.39– 0.71) [263]. Recent publications have shown that perioperative nitrates and sulfonylureas also diminish the effect of RIPC [264, 265]. The effect of RIPC on other organs was also investigated with RCTs. A reduction in AKI was found in patients anaesthe
tized without propofol (OR 0.57, 95% CI 0.41–0.79) [263]. RCTs and meta-analyses assessing RIPC in cardiac surgery were pub lished with discordant results [266, 267]. There is agreement that the study effect is small and that larger RCTs are necessary to confirm the possible benefit of RIPC [267]. Currently, RIPC is not recommended in practice guidelines due to insufficient strength of evidence [268]. The effect of RIPC on the brain was also exten
sively investigated; reduced levels of S100 and NSE were found, but no clinical effects were shown in a recent publication [269]. However, another recent study showed a clinically significant effect on the development of postoperative delirium [270]. Moreover, the effects of RIPC on pulmonary function and bleed
ing were suggested, but the evidence was not convincing [271, 272]. The underlying mechanisms of RIPC have been the subject of many publications [273, 274], but no universally accepted mechanism has been proposed.

Recommendation Table 21. **Recommendation for remote ischaemic preconditioning**

Recommendation	Class[a]	Level[b]	Ref[c]
RIPC should be considered to improve clinical outcomes and reduce myocardial and kidney injury in patients anaesthetized with volatile anaesthetic agents.	IIa		[263, 270]

[a]Class of recommendation.
[b]Level of evidence.
[c]References.
RIPC: remote ischaemic preconditioning.

Description of the evidence. Murry and colleagues first described the positive effects of ischaemic preconditioning prior to pro longed myocardial ischaemia [259]. In cardiac surgery, precondi tioning of the heart, for example, by intermittent clamping of the aorta, carries additional risks and is not a preferred method in modern cardiac surgery. The proof of concept of RIPC in 2007 paved the way for exploring a simple, safe and possibly efficient method to improve the tolerance of the organs to ischaemia during cardiac surgery [260]. Many RCTs have since been pub lished, and the effects of RIPC on myocardial function and other organs have been inconsistent. In 2 large multicentre RCTs, RIPC failed to improve clinical outcomes [261, 262]. However, most patients in both trials received propofol, so the findings might be inconclusive. In a more recent meta-analysis and systematic review, propofol had a marked effect on the results of ischaemic preconditioning [263]. Although RIPC leads to a significant reduction of the area under the curve (AUC) for biomarkers of myocardial injuries in the whole study group [standardized mean difference (SMD) −0.37, 95% CI −0.53 to −0.21], the effects were more marked in patients who did not receive pro pofol [263]. Moreover, a non-significant reduction in acute myo cardial infarction (MI) and postoperative mortality but not AFib was found in

patients not treated with propofol. Also, the com posite end point of AKI, renal replacement therapy (RRT), short term acute MI and mortality was significantly reduced in

7.2 Statins

Most cardiac surgery patients are already on long-term statin treat ment [275]. For those undergoing cardiac procedures, it is often advised to either continue or initiate statin therapy during the perio perative period due to its potential benefits. These benefits include reduced C-reactive protein levels, a decreased incidence of new-onset postoperative AFib and shorter hospital stays [276, 277]. Such clinical practice arises from the known anti-inflammatory properties of statins [278], which could be especially beneficial for patients undergoing car diac surgery with CPB. Although observational studies and a few RCTs underpowered for clinical event comparisons suggest that initiating statin treatment before cardiac surgery might decrease mortality, new onset postoperative AFib and AKI [279, 280], subsequent confirmatory trials did not confirm these clinically meaningful effects. In the STICS (Statin Therapy in Cardiac Surgery) trial, which randomized 1922 patients undergoing elective cardiac surgery, the introduction of rosu vastatin therapy (20mg/day) prior to cardiac surgery did not prevent perioperative myocardial damage or reduce the risk of new onset postoperative AFib [281]. Moreover, the incidence of AKI was notably more prevalent among patients who received rosuvastatin than among those given a placebo [281]. In another extensive single-centre trial involving 615 patients undergoing cardiac surgery, the initiation of a high dose of atorvastatin the day before surgery, which continued perioperatively, resulted in a significantly higher rate of AKI in patients

with chronic kidney disease (CKD) compared to placebo [282]. This trial was subsequently terminated prematurely due to futility. Based on robust RCT data, it is evident that the preoperative introduction of statin therapy for statin-naïve patients undergoing cardiac surgery cur
rently lacks clinical justification.

There remains a lack of definitive evidence on whether chronic users should continue their statin therapy when preparing for car diac surgery. The StaRT-CABG (Statin Recapture Therapy before Coronary Artery Bypass Grafting) trial was recently conducted to assess the impact of a supplementary statin-loading dose on the day of surgery for 2635 patients who had been on statins for a minimum of 30 days prior to undergoing CABG [283]. In this trial, this supplementary statin-loading therapy 2 to 12 h before surgery, in comparison to a placebo, did not show a significant reduction in the rate of MACCE (a composite of all-cause mortality, MI and cer
ebrovascular events) or any of its individual components within 30 days postoperatively. Furthermore, there was no significant effect on the incidence of new-onset postoperative AFib, nor on the durations of ICU and overall hospital stays [283]. In line with earlier research, patients tolerated the additional statin dosage well, with no significant adverse muscle effects, and safety outcomes mirrored these findings [284]. Even without comparative studies, there is a consensus to continue statins during the perioperative period. This practice is thought to enhance adherence to postoperative lipid lowering therapies, which have been consistently linked to notably better long-term survival outcomes following cardiac surgery [285].
findings, the sustained use of beta-adrenergic blockers through the perioperative period remains part of the recommended strat egy for comprehensive medication management.

The decision regarding the initiation of a beta-adrenergic blocker in the immediate preoperative period remains complex. Even though the administration of β-blockers within at least 24 h before isolated CABG surgery has been endorsed by the National Quality Forum since 2007, the overall consensus is still evolving. The primary purpose of pre-CABG β-blocker adminis
tration is to decrease the burden of new-onset postoperative AFib, a condition associated with increased morbidity, pro longed hospital stays, escalated costs and notably reduced sur vival [296]. The evidence of the efficacy of beta-adrenergic blockers in preventing perioperative MI and mortality remains inconclusive [297]. The beneficial effects of beta-adrenergic blockers prior to CABG, in terms of MI and mortality, seem pre dominantly applicable to patients with a recent MI [298, 299]. Moreover, the data remain inconclusive also in patients with a reduced LVEF and those with no recent MI [287]. However, if beta-adrenergic blockers are introduced preoperatively, it is rec ommended that, based on blood pressure and heart rate met rics, short-acting agents be meticulously up-titrated, beginning several days prior to the procedure. The goal of this approach is to diminish the prevalence of supraventricular and ventricular arrhythmias postoperatively [290], although further confirmatory studies are required.

Recommendation Table 22. **Recommendations for statin therapy prior to cardiac surgery with cardiopulmonary bypass**

Recommendations	**Class[a]**	**Level[b]**	**Ref[c]**
It is not recommended to initiate statin therapy shortly before elective cardiac surgery with CPB due to the associated risk of AKI.	**III**		**[280–282]**
It should be considered to continue statin therapy at the current dose during cardiac surgery with CPB.	**IIa**		**[283]**

[a]Class of recommendation.

[b]Level of evidence.
[c]References.
AKI: acute kidney injury; CPB: cardiopulmonary bypass.

7.3 Beta-adrenergic blockers

Many patients scheduled for cardiac surgery are already pre scribed beta-adrenergic blockers due to various cardiovascular conditions [286, 287]. Studies have found that the continuation of beta-adrenergic blockers for both elective and urgent cardiac operations is beneficial in terms of early survival [288, 289], pri marily due to their role in decreasing early postoperative major arrhythmic events [290, 291]. However, long-acting beta-adrener gic blockers might compromise the efficacy of a vasopressor post operatively and may elevate the risk of perioperative bradycardia and hypotension [292, 293]. Hence, switching to short-acting forms could potentially minimize haemodynamic complications for patients taking long-acting preoperative beta-adrenergic blockers. Nonetheless, the favourable risk–benefit profile of con tinuing perioperative beta-adrenergic blocker therapy is particu larly evident in the marked reduction of new-onset postoperative AFib and its associated complications [290, 294, 295]. Given these

7.4 Ultrafiltration

Ultrafiltration is a technique used during CPB for volume man agement and/or reduction of deleterious components. An ultra filter placed into the circuit will remove plasma water and elec trolytes as blood passes through the ultrafilter fibres while withholding proteins and blood elements. The most used techni ques are conventional ultrafiltration (CUF), zero-balanced ultra filtration (ZBUF) and modified ultrafiltration (MUF). The first 2 are used during CPB by diverting blood over an ultrafilter employing a pump or by placing an ultrafilter in a shunt between a high- and low-pressure zone. MUF is used after weaning off bypass but can be combined with CUF during CPB. MUF pumps blood from the aortic cannula through an ultrafilter back into the right atrium. The remaining blood in the CPB cir cuit replaces the removed fluid. Common goals of all these tech niques are blood concentration, filtration of unwanted substan ces and management of electrolyte balance.

Recommendation Table 23. **Recommendations for beta-adrenergic blocker therapy prior to cardiac surgery with cardiopul monary bypass**

Recommendations	Class[a]	Level[b]	Ref[c]
It is recommended that chronic users of beta-adrenergic blockers continue their therapy during the perioperative period of cardiac surgery with CPB to prevent postoperative arrhythmias.	I		[290, 294, 295]
Short-term, low-dose oral beta-adrenergic blocker therapy may be considered in naïve patients to prevent postoperative arrhythmias in cardiac surgery with CPB.	IIb		[297]

[a]Class of recommendation.
[b]Level of evidence.
[c]References.

CPB: cardiopulmonary bypass.

Description of the evidence. A meta-analysis comprising 12 RCTs showed a reduction in the occurrence of low cardiac output syn drome (LCOS) in the ICU, lower ventilation time and less pneu monia in patients receiving CUF [300]. A systematic review and meta-analysis investigating the use of any form of ultrafiltration (MUF, CUF, ZBUF, CUF þ MUF) did not find an association with AKI even in patients with chronic

renal insufficiency [301]. Not included in this systematic review was a recently published single centre observational study of 1641 patients undergoing elective cardiac surgery that reported that removal of a weight-indexed CUF volume of > 32 mL/kg increased the risk of postoperative AKI development. Furthermore, they reported that CUF volume removal of any amount did not mitigate allogeneic blood transfu sion during elective cardiac surgery [302]. A large propensity score matched (PSM) analysis of 40 650 patients could not find lower transfusion requirements in patients with CUF [303]. Except for the tumour necrosis factor (TNF), CUF did not impact pro inflammatory marker removal [304]. A small retrospective analysis investigating the impact of CUF on viscoelastic blood coagulation parameters found an increased clot firmness after CUF, independ ent of the amount of ultrafiltration [305].

A meta-analysis of 5 adult and 2 paediatric RCTs investigating the impact of ZBUF on postoperative recovery found no difference for the LCOS in ICU or ventilation times [306]. This result is in con trast to that of a small RCT, not included in the meta-analysis, that demonstrated fewer blood transfusions and lower morbidity in the ZBUF group [307]. An analysis of a registry that included 73 783 patients collected in 215 hospitals in the United States found lower diuresis and a higher need for the additional use of CUF in the ZBUF group [308]. With the exception of interleukin (IL)-1, one small RCT showed a reduction in IL-6, TNF and C3a when using ZBUF [309]. No association was demonstrated between ZBUF and S100 removal or improved neurocognitive outcome [310].

Recommendation Table 24. **Recommendation for ultrafiltration**

Using ZBUF in combination with bivalirudin anticoagulation may increase bivalirudin elimination by the ultrafilter [311]. A meta-analysis of 13 RCTs with 1236 patients showed a lower PRBC transfusion rate, a higher HCT, less chest tube bleeding and a shorter stay in the ICU for the MUF group [312]. However, whereas the lower number of blood transfusions, improved HCT and less chest bleeding were of significant effect size, the significantly shorter length of stay in the ICU was only by a mean of 0.13 days (3.1 h) and therefore of questionable clinical relevance, particularly because no ICU discharge criteria were included in the relevant studies of this meta-analysis. Two RCTs comprising the same patient population showed better platelet preservation, lower com plement activation and lower blood lactate levels in the MUF group [313, 314]. The impact of MUF on inflammatory markers and haemodynamics is less straightforward. One small RCT showed an increase in inflammatory markers in the MUF group and no differ ence in the patients' haemodynamics [315] whereas another RCT combining veno-venous MUF and CUF showed no difference in inflammatory parameters but better haemodynamics and oxygena tion [316]. A PSM study showed a lower inflammatory response and better oxygenation in a group combining lung perfusion with MUF. The use of MUF lowers the concentration of vancomycin but is not below the inhibitory effect for *Staphylococcus aureus* and S. *epidermidis* [317]. A systematic review and meta-analysis compar ing MUF against CUF did find lower transfusion requirements for MUF but not for CUF. Although the results with CUF were based on limited evidence [318], studies comparing MUF against CUF did not find differences in outcome or in transfusion requirements [319, 320], but the group combining CUF with MUF versus CUF alone had lower TNF and less haemodilution [319]. Less postopera tive bleeding, fewer blood transfusions, improved liver function and shorter hospital stays were documented in patients with liver disease undergoing cardiac valve surgery [321].

Recommendation	Class[a]	Level[b]	Ref[c]
It is recommended to use MUF or CUF combined with MUF in high-risk or anaemic patients to reduce chest tube bleeding and blood transfusions.	I		**[312–314, 316, 319]**

[a]Class of recommendation.
[b]Level of evidence.
[c]References.
CUF: conventional ultrafiltration; MUF: modified ultrafiltration.

7.5 Myocardial management—cardioplegia

Optimal myocardial management and a perfect surgical techni que are among the most crucial steps for a successful result in any cardiac surgical procedure. Several techniques are used in clinical practice today, but only those with experimental and clinical testing results are described. Recommendations for a specific strategy require knowledge of the consequences of sub optimal myocardial protection and methods for assessment of the quality of the used protection techniques.

7.5.1 Type of cardioplegia. The main goal of any cardioplegia technique is to protect myocardial function from ischaemic/ reperfusion damage during aortic cross-clamping to provide a quiet and bloodless operative field. The main principle of cardi
oplegia is the reduction of myocardial oxygen requirements by hypothermia and induction of asystole. These goals can be achieved by inhibiting the fast sodium current or inhibiting cal cium activation of myofilaments. Although this principle is applied to all cardioplegic solutions, they still vary greatly in many other aspects:

- Components
  - Crystalloid versus blood-containing solutions
  - Additional components of the solution (e.g. Kþ-concentra tion, glucose, buffering capacity)
  - Degree of haemodilution

- Delivery
  - Temperature (cold vs tepid vs warm)
  - Multidose versus single dose vs continuous
  - Mode of delivery (ante-, retro- and combined simultane ous ante- and retrograde)

Cardioplegic solutions are generally divided into 2 distinct categories: pure crystalloids or blood/crystalloid mixtures. Hyperkalaemic blood cardioplegia is preferred in most centres worldwide [322], but crystalloid solutions are also commonly used [322]. Pure crystalloid solutions may be of either the intra
cellular [e.g. histidine-tryptophan-ketoglutarate (HTK) solution] (Bretschneider, Custodiol HTK) or extracellular type (e.g. St. Thomas solution), whereas conventional blood cardioplegia is a mix of both a crystalloid solution and blood, typically in a ratio of 4 parts of blood to 1 part of crystalloid solution (4:1) (Buckberg solution). However, many other variations of blood cardioplegia do exist (such as dilution of blood cardioplegia from 1:1 to 5:1, microplegia, del Nido, warm, tepid, cold and various additives) [322]. Although the strategies especially based on HTK, St. Thomas and Buckberg solutions have been evaluated in detail over the last decades, many more (mostly experimental and even clinically more or less untested) modifications of these techniques or even alternative methods are being used.

The most frequently used crystalloid cardioplegic solutions are the single-dose, hyperpolarizing HTK solution, an intracellu lar type and the multidose St Thomas Nr. 2 (Plegisol, Abbott Laboratories, Lake County, IL), an extracellular type of cardiople gia. The almost sodium-free HTK solution commonly leads to hyponatremia in patients [323, 324], but this acute hyponatremia is iso-osmotic and should not be corrected to protect the patient from the serious consequence of hyperosmolarity [324].

The most advanced and individually applicable cardioplegic strategy is the ante- and retrograde use of Buckberg's integrated blood cardioplegia, which has been tested extensively experi mentally and in various clinical studies [325–327]. It can be used safely and efficiently in all adult cardiac surgery cases using cold induction; cold multidose and warm terminal reperfusion; ante and retrograde delivery for routine and complex cases; acute coronary occlusions; second and prolonged cross-clamp peri ods; energy-depleted hearts; and low LVEFs.

In recent years, the del Nido cardioplegic solution (used extensively in congenital cardiac surgery since the early 1990s) is also used for adult cardiac surgery [328]. It can be administered as a single dose for up to 90 min of ischaemia [329], and the requirement of only a single dose seems to reduce CPB, aortic cross-clamp and total operating time. No statistically significant differences were found in most studies comparing del Nido (1:4 blood to crystalloid) with other blood-based solutions. However, several questions are still open for debate, such as safety during prolonged cross-clamp time, patients with reduced RV function and a low LVEF, second cross-clamp period and hae
modilution [330].

Several experimental studies favour the use of blood cardiople gia over crystalloid solutions when comparing the release of car diac enzymes and metabolic response. Nevertheless, the 2 largest RCTs in the field showed no statistical differences in terms of major or minor postoperative clinical outcomes between crystal loid or blood cardioplegia among 1140 randomized patients who underwent CABG [331] and 345 patients after AVR [332]. Furthermore, a systematic review and meta-analysis of 34 RCTs that compared crystalloid with blood cardioplegia in 5044 patients found no difference between the groups regarding the rates of perioperative MI and death; however, a significantly lower incidence of LCOS was observed immediately upon reperfusion with blood cardioplegia [333]. A more recent meta-analysis of 36 RCTs showed similar results in terms of in-hospital deaths (RR 0.96, 95% CI 0.60–1.51) or perioperative MI (RR 0.79, 95% CI 0.55–1.12), but the difference in LCOS disappeared after the inclu sion of more recent studies (RR 0.69, 95% CI 0.48–1.04) [334].

Although the differences in outcomes between crystalloid and blood cardioplegia have been studied extensively, most studies did not report the risk of bleeding complications and transfusion rates. In an RCT including 100 patients, crystalloid cardioplegia was com
pared to blood cardioplegia and was associated with significantly higher intraoperative haemodilution, greater blood loss and more PRBC transfusions [335]. Moreover, in the published 2017 EACTS/ EACTA guidelines on patient blood management [336], the limita
tion of haemodilution has been recognized as a vital part of a blood conservation strategy to reduce bleeding and perioperative transfusion requirements (Class IB recommendation). Thus, due to limited crystalloid fluid content, the use of blood cardioplegia sol
utions should be considered as the preferred strategy in patients with anaemia, low body surface area (BSA) and CKD or patients undergoing complex procedures to reduce haemodilution and the risk of subsequent complications, including AKI, bleeding and the need for transfusions perioperatively.

The most frequently used mode of application for cardiople gia is antegrade, applied directly into the aortic root proximal to the aortic cross-clamp at a pressure of 60–100 mmHg or infused directly into the coronary ostia with pressure monitoring. Retrograde cardioplegia is administered via the direct insertion of a catheter into the coronary sinus, using a flow rate of 200–400 mL/min to a coronary sinus pressure between 30 and 50 mmHg [337]. Higher pressures should be avoided to prevent injury to the coronary venous system [337]. Induction of cardiac arrest is usually slower with retrograde than with antegrade car dioplegia, often 2–4 min instead of 30–60 s. It should be noted that experimental results indicate that the flow to the microvas culature of the RV is inadequate during retrograde cardioplegia and, therefore, the protection of the RV might be incomplete [338]. In more complex cases, where the cross-clamp time is extended or severe coronary disease with poorly developed col laterals or aortic valvular insufficiency is present, combined ante grade plus retrograde cardioplegia can be used to ensure
adequate distribution of the cardioplegia solution [339, 340]. Cardioplegic solutions can be delivered by the antegrade route exclusively if the coronary arteries are not stenosed or occluded. In the latter cases, retrograde delivery allows perfusion of the sub endocardial layer, which is preferred;

however, inconsistent RV and septal protection may occur as a result of inadequate perfu sion if some RV veins draining into the proximal part of the coro nary sinus are missed. Therefore, a combination of antegrade and retrograde delivery is the only way to perfuse all areas of the myocardium when the antegrade path is impaired [325]. Usually, cardioplegia is administered cold and intermittently every 20 to 30 min to maintain cardiac arrest and hypothermia; however, a single-shot cardioplegia may also be applied in low-risk cases with short aortic cross-clamp times. A single-shot approach, often using intracellular crystalloid solutions or the del Nido solu tion, minimizes interruptions during the operation for repeated administration of cardioplegia and facilitates less invasive proce dures. Although the interest in these methods has been continu ously growing, the evidence to support their use in daily practice in high-risk operations is insufficient due to a lack of adequately pow ered RCTs to prove their superiority over conventional approaches [341]. The most recent systematic review and meta-analysis, which compared the del Nido solution with conventional approaches in

[345]. Overall, however, it is difficult to make a clear statement on advantages and disadvantages, which is due to the large number of variables in these studies, such as comparison of different cardio plegia procedures, non-uniform patient populations and different forms of application [346].

The warm induction of blood cardioplegia was developed for patients with acute MI to enhance the recovery of contractile function after hours of ischaemia [347]. It is followed by further cold maintenance and warm terminal reperfusion.

Other blood cardioplegia techniques have used continuous warm antegrade delivery (e.g. Calafiore) or (less commonly used) infusion of continuous warm or tepid cardioplegia through the coronary sinus. In the meta-analysis of 41 RCTs with 5879 patients, in-hospital

deaths, length of stay, incidence of stroke and AFib and the use of an intra-aortic balloon pump (IABP) were compared and did not dif fer between warm versus cold cardioplegia groups [348]. However, warm cardioplegia was associated with a significantly better postop erative cardiac index and lower cardiac enzyme release. In a large prospective study comparing early and late outcomes of patients receiving tepid/warm or cold cardioplegia during isolated CABG, adjusted perioperative mortality rates were not different (OR 1.45, 95% CI 0.95–2.22) but patients in the cold blood cardioplegia group had 1.86 times higher adjusted odds for having an MI compared with the patients in the warm cardioplegia group (OR 1.86, 95% CI 1.36–2.53) [349]. A drawback of warm or tepid cardioplegia is that the poor distribution or interruption of normothermic cardioplegia may induce anaerobic metabolism and warm ischaemic injury. Therefore, normothermic cardioplegia must be delivered continu
ously and homogeneously, which explains its relatively limited popu larity [350]. Small RCTs have indicated some benefits regarding myo cardial metabolic derangements with the use of terminal warm blood-controlled reperfusion (‘hot-shot‘), often administered in a ret rograde fashion at the end of a complex procedure [351].

Recommendation Table 25. **Recommendations for myocardial protection strategies**

Recommendations	Class[a]	Level[b]	Ref[c]
It is recommended that myocardial protective strategies be patient-centred and tailored based on clinical and pathoanatomical conditions and procedural complexity rather than relying on a fixed institutional cardioplegic solution.	I		[325–327]
Blood cardioplegia should be considered in selected patients[d] to reduce haemodilution, bleeding complications and transfusion requirements.	IIa		[335]

[a]Class of recommendation.
[b]Level of evidence.
[c]References.
[d]Patients with anaemia, low body surface area, chronic kidney disease or undergoing complex procedures.

adult patients undergoing cardiac surgery, included 9 observational studies and small RCTs (n ¼ 1501). This meta-analysis showed that the use of the del Nido solution did not result in the reduction of the number of deaths (risk difference 0.0, 95% CI −0.01 to 0.01), a lower release of postoperative myocardial enzymes (SMD, 0.16, 95% CI −0.41 to 0.08) or reduced length of hospital stay (SMD −0.10, 95% CI −0.26 to 0.05) [342]. Due to its single-dose applica tion, del Nido cardioplegia results in reduced ischaemic times. Several studies report reduced reperfusion fibrillation and cardiac enzyme release [343, 344] and lower postoperative kidney injury

7.5.2 Measures in stunned myocardium. LV and RV failures are the most obvious signs of suboptimal myocardial protection. However, one has to remember that other factors (e.g. subopti mal surgical technique, stenosed, occluded graft) may also lead to these serious complications.

Failure of the left ventricle. Because the LV with the interventricu lar septum has approximately 80% of the myocardial muscle mass (Fig. 1A), LV failure occurs instantaneously after suboptimal protection.

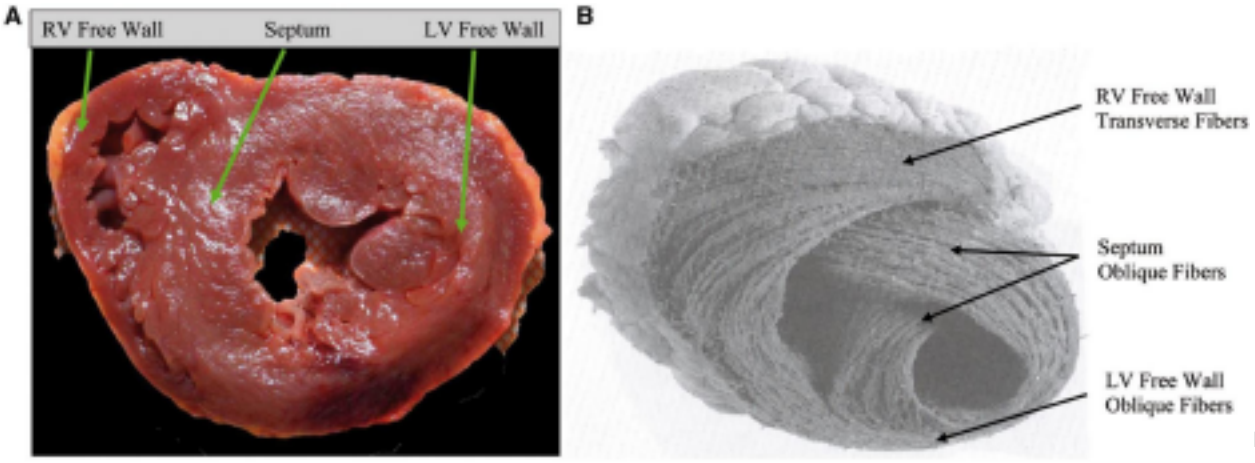


Figure 1: **(A) Cross-section of a heart from a 22-year-old with no cardiac history, who died in an automobile accident**. The relatively thin free wall of the right ventricle contrasts with the more substantial muscle mass of the left ventricle's septal and free walls, which are nearly equal in size and mass. (**B) Fibre orienta tion of the right ventricle and septum**: the free wall consists primarily of transverse fibres, while the septum contains helical or oblique fibres, allowing the septum to twist and shorten while the free wall constricts [354]. (Reprinted from Allen et al. [328], with permission from Oxford University Press). LV: left ventricle; RV: right ventricle.

Failure of the right ventricle. This problem can be related to sub optimal protection of the RV itself or can occur because of sub optimal protection of the LV.

Suboptimal protection of the right ventricle. This problem may be caused by the inadequate delivery of the cardioplegic solution to the RV. It may be found in patients with coronary artery dis ease on a significantly stenosed or occluded right coronary artery or inadequate flow in an open right coronary artery (e.g. aortic insufficiency) when only antegrade delivery is used. Retrograde cardioplegic delivery is independent of these short comings and is therefore preferred in addition to antegrade. However, if a self-inflatable retrograde cardioplegic catheter is used and advanced too far in the coronary sinus, some veins that drain into the coronary sinus might not get perfused adequately with resultant incomplete delivery to the RV and eventually RV failure, especially if retrograde delivery is used exclusively (without combined antegrade).

orientation of the fibres, which is essential for their function, differs from the right to the left ventricle. The free wall of the LV and the septum have oblique fibres (double helix), which lead to twisting and shortening of the LV and a doubling of the ejection fraction (compared to the transverse fibres of the free wall of the RV), which is needed against the high pressures of the left arterial side. The RV-free wall has only transverse fibres, which are compressive and effective only at low pressures. Most of the work of the RV (80%) is done by the septum with its oblique fibres, which results in longitu dinal shortening. This shortening is clinically measured by the tri

cuspid annular plane systolic excursion, a parameter that is well correlated with the RV ejection fraction [327, 352, 353]. However, if the septum is protected suboptimally, RV function is impaired, even up to 1 year in some patients [354].

Overall, a detailed intraoperative assessment of the function ing of the LV and RV allows evaluation of the quality of myocar dial protection and the cause for failure of the LV and RV postoperatively.

Recommendation Table 26. **Recommendation for intraoperative assessment of the functioning of the right and left ventricles**

Recommendation	Class[a]	Level[b]	Ref[c]
It is recommended that intraoperative assessment of LV and RV function by TOE pre- and post CPB be conducted for immediate quality control of the myocardial protection strategy in all patients having cardiac surgery, unless there is a contraindication for TOE.	I		[325, 327, 352, 355]

[a]Class of recommendation.
[b]Level of evidence.
[c]References.
CPB: cardiopulmonary bypass; LV: left ventricle; RV: right ventricle; TOE: transoesophageal echocardiography.

Suboptimal protection of the left ventricle. Another reason for post operative RV failure is the suboptimal protection of the LV, which is explained by the helical structure of the heart (Fig. 1B). The free wall of the RV represents only a tiny portion of the entire muscle mass of the heart, whereas the LV and the septum account for the majority. The ventricular muscle mass consists of fibres; the

7.5.3 Measures in myocardial stunning, hibernation, necrosis and endothelial cell damage. Suboptimal protec tion results in failure of the LV and the RV, which may be due

to (i) reversible systolic and diastolic myocardial dysfunction (myo cardial stunning); (ii) hibernation or (iii) irreversible damage (necrosis) and/or endothelial cell damage.

Stunning can follow quickly after brief periods of myocardial ischaemia. It might last minutes or days and is characterized by nor mal blood flow with depressed function (perfusion/contractility mis match) and responds to inotropic stimulation. Pathophysiologically, it is a manifestation of ischaemia/reperfusion injury (release of oxygen derived free radicals, and influx of calcium into the cells) [356].

In contrast, hibernation is characterized by a perfusion/con tractility match. Both are low and are a chronic, potentially reversible state of segmental dysfunction [357].

Necrosis is the irreversible end stage of all processes involved in ischaemia and reperfusion, with depletion of ATP and may finally reach myocardial contracture ('stone heart').

Damage to the endothelial cells results in swelling and func tional alterations, which are important for subsequent changes in coronary vascular resistance and the endocardial no-reflow phenomenon, as well as impaired microcirculatory flow [358].

parameter for the quality of myocardial protection because (i) it is an endocardial structure and therefore more vulnerable to subopti mal protection; (ii) it represents 50% of the LV muscle mass; and (iii) the septal fibres are oblique (double helix) and are the main portion for RV contraction [355]. Therefore, the tricuspid annular plane systolic excursion (or longitudinal shortening of the RV) is important for RV function [352]. This fact explains why RV function is substantially reduced if the septum is injured during suboptimal myocardial protection [327, 352]. Interestingly, septal dysfunction is rare after off-pump CABG [359]. However, one has also to keep in mind that preoperative septal dysfunction exists and may become worse after suboptimal protection.

It should be considered that specific postoperative parame

pt ters, such as hospital or ICU lengths of stay, arrhythmias and mortality rates, are not exclusively influenced by the e quality of myocardial protection [325, 327].

Recommendation Table 27. **Recommendation for quality assessments of myocardial protection strategies**

Recommendation	Class[a]	Level[b]	Ref[c]
RV and LV functioning, especially septal motion and release of cardiac-specific enzymes, is recommended to be reviewed routinely within the first 24 h postoperatively.	I		**[325, 327, 352, 355]**

[a]Class of recommendation.
[b]Level of evidence.
[c]References.
LV: left ventricle; RV: right ventricle.

7.5.4 Quality of myocardial protection. The success of any cardiac surgical procedure comprises a perfect surgical techni que and the prevention of damage caused by the various perio perative steps, such as surgical access, CPB, myocardial ischae mia, transfusions and others. Myocardial protection to prevent ischaemic damage plays a central role. Like the immediate assessment of the quality of technical excellence via echocar diography or Doppler flow measurements, immediate assess ment of the quality of myocardial protection is often lacking. Nevertheless, septal dysfunction [359] and haemodynamic sup port (inotropes, IABP, temporary assist devices) may occur in patients postoperatively, indicating that myocardial damage is not completely prevented with current cardioplegic techniques and solutions, either because their concept is suboptimal or they were not appropriately applied [327]. Indeed, myocardial protec tion is a 'strategy' rather than a 'magical solution' that anybody can put in anywhere [360].

Many markers have been used and investigated to assess the quality of myocardial protection. Some of them are poor indica tors, such as hospital or ICU length of stay, arrhythmias, ino tropes, mechanical circulatory support devices and in-hospital or 30-day mortality rates. These are not protection-specific and may be influenced by many other causes.

Up to now, the best markers for the quality of myocardial pro tection are cardiac enzyme levels (creatine kinase-MB) [361] or tro ponin [362] and postoperative septal motion, because both depict muscle injury and correlate with early and late mortality [327]. Large postoperative increases in cardiac biomarkers are prognosti cally relevant even in the absence of additional supportive signs of ischaemia [363]. In addition, the interventricular septum is a valid

7.6 Brain protection—Temperature control during cardiopulmonary bypass

Hypothermia is usually defined as a core body temperature below 35°C, and it reduces overall oxygen consumption by the body. It has been used during CPB to provide a degree of pro tection to vital organs. However, the evidence to support this practice has been unclear. It is well-known that hypothermia can protect the brain through different mechanisms (e.g. reduc tion of the metabolic rate; blocking glutamate release; reducing calcium influx; improving recovery of protein synthesis; reducing the formation of reactive oxygen species; increasing the cerebral tolerance to inadequate DO_2 or regulating inflammatory factor expression) [364]. Results from experiments in the laboratory environment suggest that hypothermia may stimulate neuronal death [365], which may have relevant clinical implications for humans. Furthermore, the brain may be exposed to extended periods of hyperthermia (T >37°C) during the rewarming period after hypothermic CPB, and this may exacerbate brain injury [366].

Data from 4 RCTs showed that slow rewarming is associated with a lower incidence of POCD [367–370].

Data from a recent meta-analysis [371], including 58 studies with 9609 patients, showed that postoperative delirium (or delayed neurocognitive recovery) [372] occurred in 48% of the patients undergoing cardiac operations, respectively. This study showed no significant difference in delirium rates between nor
mothermic and hypothermic CPB and other groups of patients categorized by age, type of cardiac operation and MAP. For the

RCTs (7 RCTs, 1274 patients), no significant differences in the rates of delirium when comparing normothermic with hypother mic CPB [0.55 (0.47–0.62) vs 0.58 (0.47–0.69), respectively], were observed. POCD (or postoperative neurocognitive disorders) [372] occurred in 31% of the patients at early follow-up (from discharge to 6 months) and 32% at late follow-up examinations (from 6–12 months) [371]. This meta-analysis showed no differ ence in POCD rates between normothermic and hypothermic CPB in general, for any follow-up interviews at different time points. Furthermore, for RCTs (6 RCTs, 674 patients), there was no difference in postoperative POCD rates when comparing nor mothermic with hypothermic CPB (OR 0.29, 95% CI 0.12–0.55 vs OR 0.37, 95% CI 0.19–0.59). However, subgroup analyses in this meta-analysis revealed that incidences of delirium and POCD were lower after cardiac operations performed with normother mic CPB targeted to an MAP of >70 mmHg [371]. Data from another meta-analysis [373], also from 2022, including 26 RCTs with 5653 patients that looked at brain injury as one of the pri mary outcomes, showed no difference between normothermia and hypothermia (RR 0.87, 95% CI 0.67–1.14) with low certainty due to serious risk of bias. Regarding the outcome POCD, the meta-analysis included 5 RCTs with 607 patients and showed no differences between groups (RR 0.99, 95% CI 0.94–1.04), also with low certainty due to serious risk of bias of the RCTs included. Interestingly, sensitivity analyses restricted to trials at low risk of important bias (5 RCTs) showed higher mortality with hypothermia (OR 1.70, 95% CI 1.05–2.75), with no difference in brain injury (OR 1.01, 95% CI 0.69–1.49) [373]. However, this was a sensitivity analysis, and it should only be interpreted as hypothesis-generating. Both meta-analyses indicate potential benefit for patients in the normothermia groups of patients, with improved cognitive outcomes in 1 and improved mortality in the other. However, whereas the focus of 1 meta-analysis was on cognitive outcomes [371], the other meta-analysis focused on organ dysfunction and mortality [373]. Adequately powered RCTs should be encouraged to address this knowledge gap. remain at risk of premature CKD, even if their renal function ini tially recovers.

7.7.1 Blood pressure. Data from a recent single-centre retro spective study of 6532 patients showed that an MAP <65 mmHg for 10 min or more after CPB was associated with an increased risk of new postoperative RRT (adjusted OR 1.12, 95% CI, 1.06– 1.18) [375]. However, an association between hypotension before and during CPB with RRT was not observed [375]. In this study, the association between intraoperative hypotension and AKI was weaker in comparison to other factors such as renal insufficiency, heart failure, obesity, anaemia, complex or emergency surgery and new-onset postoperative AFib. However, post-CPB hypoten sion is a potentially more accessible modifiable risk factor. Furthermore, data from a more recent single-centre retro spective study of 4984 patients observed that intraoperative systolic BP less than 65 mmHg was associated with a higher risk of a composite primary outcome of stroke, AKI or death during hospitalization. The primary outcome was related to total duration of hypotension (adjusted OR 1.05, 95% CI, 1.02 to 1.08), hypotension outside CPB (adjusted OR 1.06, 95% CI, 1.03–1.10) per 10-min exposure to an MAP of less than 65 mmHg [376].

However, in 2 RCTs, the authors hypothesized that a higher target MAP during CPB would reduce the incidence of AKI after cardiac surgery [377, 378]. Although the range for renal autore gulation is 75 to 160 mmHg in normal conditions [379], the MAP during CPB is typically below the lower limit of this range, and increasing the level of blood pressure during this period would represent a readily achievable renoprotective strategy if demonstrated effective.

The first RCT [377] comprised 300 patients with at least 1 risk factor for AKI. After a standardized fluid loading, the MAP was maintained between 75 and 85 mmHg during CPB with norepi nephrine (high pressure, n ¼ 147) versus 50–60 mmHg in the

Recommendation Table 28. **Recommendations for brain protection**

Recommendations	**Class[a]**	**Level[b]**	**Ref[c]**
Normothermic CPB should be considered to reduce the risk of postoperative neurocognitive dysfunction in situations where adequate oxygen delivery can be maintained.	**IIa**		**[371, 373]**
It is recommended that systemic hyperthermia during CPB be avoided by limiting the oxygenator arterial outlet temperature to a maximum of 37°C.	**I**		**[367–370]**

[a]Class of recommendation.
[b]Level of evidence.
[c]References.
CPB: cardiopulmonary bypass.

7.7 Kidney protection

Cardiac surgery-associated acute kidney injury (CSA–AKI) has an incidence of 5% to 40% and is best defined by Kidney Disease Improving Global Outcomes criteria as an AKI within 1 week of cardiac surgery (reviwed in [374]). It is the result of many perio
perative pathophysiological insults, including the use of CPB.

AKI is associated with longer ICU and hospital stays, higher health care costs and an increased risk of death. Patients with CSA–AKI

control (n ¼ 145). The MAP targets were achieved in both the high MAP (79 ± 6 mmHg) and the control groups (60 ± 6 mmHg; $P < 0.001$). The rate of AKI did not differ by group (17% vs 17%; $P > 0.99$), regardless of the criteria used for AKI. No dif

ference was observed concerning the length of stay in the hospi tal [9.5 days (7.9–11.2) vs 8.2 (7.1–9.4)] and the rate of death at day 28 (2.1% vs 3.4%) and 6 months (3.4% vs 4.8%).

In a second more recent RCT [378], only 90 patients undergoing combined cardiac operations were randomized to the high MAP (MAP > 60 mmHg) versus the standard BP group. The MAP was 47 ± 5 mmHg in the control group and 61±4 mmHg in the high MAP group ($P < 0.001$). Targeting a MAP >60 mmHg compared to a control group with no specific target pressure during CPB did not reduce the incidence of AKI, or of CKD, at 4 months postoperatively. The AKI rate was 38% in the control group and 46% in the high-pressure group (P ¼ 0.44).

A benefit for patients with a higher target MAP during CPB was also not confirmed in a meta-analysis of 2 RCTs comprising 487 patients, looking at AKI as a primary outcome. A high blood pressure target was associated with no difference in AKI (RR 1.30, 95% CI 0.81–2.08) with low-certainty evidence [380].

Furthermore, Vedel *et al.* [381] hypothesized that, compared to a target MAP of 40 to 50 mmHg during CPB, a target MAP of 70 to 80 mmHg during CPB would reduce brain injury after cardiac surgery. Interestingly, they found that the number of patients with postoperative AKI Kidney Disease Improving Global Outcomes grade II (doubling serum creatinine) was higher in the high-target MAP group than in the low-target MAP group.

The Society of Cardiovascular Anesthesiologists (SCA) "Clinical Practice Update for Management of Acute Kidney Injury Associated With Cardiac Surgery" was recently published. They stated that tar geting high blood pressure during CPB did not reduce AKI with a low level of GRADE (Grading of Recommendations Assessment, Development and Evaluation) evidence [382].

In summary, a high blood pressure target may result in little to no difference in patient outcomes, including AKI and deaths and further studies are needed to access the efficacy of a higher blood pressure target among those who undergo cardiac surgery with CPB. It is more important to target DO_2, optimize blood flow from CPB and monitor markers of tissue perfusion (NIRS and $SvcO_2$) rather than use vasopressors to increase ABP (please see also section 9.7 on goal-directed perfusion).

7.7.2 Use of intravenous amino acids. Intravenous amino acids have been shown to increase the perfusion of the kidneys and also to improve the renal functional reserve. A recent multi centre RCT demonstrated in cardiac surgery patients that the perioperative application of intravenous amino acids, including during CPB, reduced AKI compared to placebo from 31.7% to 26.9% (relative risk, 0.85; 95% CI, 0.77–0.94; P ¼ 0.002) [383]. Stage III AKI was decreased from 3.0% to 1.6% (relative risk, 0.56; 95% CI, 0.35–0.87) by the intervention.

7.7.3 Use of N-acetylcysteine. Data from a recent meta analysis [384] from 2022, including 10 RCTs with 1242 patients, showed that N-acetylcysteine (NAC) did not have a significant effect (OR 0.84, 95% CI 0.64–1.10) on AKI. Further subgroup analysis did not show a substantial benefit of NAC in prevent ing AKI. However, there was notable heterogeneity among the included studies that could possibly account for the non significant effect observed. It is worth noting that only 1 RCT administered high dosages of NAC perioperatively, and it is the only included trial to show a significant benefit in reducing the incidence of AKI (OR 0.30, 95% CI 0.11–0.81). Further studies on this dosage and duration of administration should be con ducted to elucidate best the effect of administering NAC. The patient study populations also differed among the included studies, from patients with CKD and different degrees of renal dysfunction to patients who only had risk factors for postoper ative AKI.

Data from another recent meta-analysis [385], also from 2022, including 24 RCTs with 2444 patients, showed no significant dif ference in the rate of AKI between the NAC and the control groups (RR 0.91, 95% CI 0.77–1.08), but the trial sequential anal ysis could not confirm this result. In this meta-analysis, only 29% (717/2444) of the patients had CKD. No difference was observed in the need for RRT, all-cause mortality, MACE, length of stay in the ICU and length of stay in the hospital. However, a subgroup analysis of studies using intravenous NAC (9 RCT, n¼1211) showed that intravenous NAC may reduce the risk of AKI (RR 0.84, 95% CI 0.71–0.99). On the other hand, oral NAC (6 RCT, n¼672) did not affect AKI after cardiac surgery.

A previous meta-analysis [386] from 2018, including 5 RCTs with 678 patients with CKD undergoing cardiac surgery, showed that the use of NAC could reduce the rate of AKI (RR 0.77, 95% CI 0.63–0.94) and that NAC could decrease the adverse cardiac events (RR 0.83, 95% CI 0.70–0.97), but that it may increase the length of stay in the ICU (SMD 2.1, 95% CI 1.61–2.60). There were no statistically significant differences between the 2 groups in the RRT requirement (RR 1.33, 95% CI 0.63–2.81) and the all

cause mortality (RR 0.51, 95% CI 0.25–1.06).

Data from a meta-analysis [387] from 2016, including 14 RCTs that included 1863 patients, showed that using NAC could significantly reduce the incidence of AKI (OR 0.77, 95% CI: 0.62–0.95). The percentage of patients with CKD was not reported.

Recommendation Table 29. **Recommendations for kidney protection**

Recommendations	**Class[a]**	**Level[b]**	**Ref[c]**

Routinely targeting a high MAP using vasoconstrictors is not recommended during CPB to reduce AKI.	**III**		**[377, 378, 380, 381]**
The intravenous infusion of a balanced mixture of amino acids should be considered perioperatively, including during CPB, to reduce the occurrence of AKI.	**IIa**		**[383]**
The perioperative use of intravenous NAC may be considered in patients with CKD to reduce AKI after cardiac surgery.	**IIb**		**[385–387]**

[a]Class of recommendation.
[b]Level of evidence.
[c]References.
AKI: acute kidney injury; CKD: chronic kidney injury; CPB: cardiopulmonary bypass; MAP: mean arterial pressure; NAC: N acetylcysteine.

7.8 Lung Protection

Lung injury and respiratory failure are common complications after cardiac surgery, with an incidence of 9% and a sixfold increase in the mortality rate compared to patients without respiratory failure [388]. CPB activates inflammatory and oxida
tive stress pathways, resulting in pulmonary ischaemia reperfu sion injury. Apart from CPB and patient risk factors, respiratory failure may be exacerbated by positive pressure ventilation, transfusion of blood products and inflammatory responses and pain due to surgical tissue trauma [389]. Intraoperative strat egies to reduce cardiac surgery-associated lung injury include CPB modifications such as MUF (reviewed in section 7.4.); bio compatible circuits or MiECC-associated techniques (reviewed in sections 5.7 and 9.1.); selective pulmonary artery perfusion, continuous positive airway pressure (CPAP) and/or ventilation during CPB and pharmacological interventions with steroids. Here, we focus on selective pulmonary artery perfusion, venti lation strategies such as CPAP, vital capacity manoeuvres (VCM) or ventilation during CPB and steroids as potential inter ventions to reduce lung injury.

7.8.1 Pulmonary artery perfusion. Since 2 single-centre RCTs in 2012 demonstrated that selective pulsatile pulmonary perfu sion with oxygenated blood during CPB reduces lung inflamma tion and improves postoperative oxygenation without any clini cal impact on major end points, only a few studies have been published on the topic [390, 391]. A single-centre RCT of patients with chronic obstructive pulmonary disease compared standard CPB, CPB with pulmonary perfusion with oxygenated blood and CPB with pulmonary perfusion with HTK solution [392]. The trial confirmed CPB-induced inflammatory damage of the lungs in all 3 groups, although a higher oxygenation index was found only
excess of metabolites involved in energy production and detoxi fication of reactive oxygen species [394]. The most recent RCT allocated patients requiring CABG to standard CPB or CPB with pulmonary perfusion with oxygenated blood by maintaining pulmonary flow at 10% of the systemic blood flow during aortic cross-clamping. The value of the trial is limited due to the low number of enrolled patients, but the authors found better oxy genation after pulmonary perfusion, lasting up to 24 h postoper atively [395]. Furthermore, lung biopsies after pulmonary perfu sion demonstrated a better preservation of alveolar basal membrane as seen with electron microscopy, together with a higher expression in bronchiolar epithelial cells of vascular endothelial growth factor (VEGF), inducible-nitric oxide synthase

(i-NOS) and the anti-apoptotic Bcl-2 protein. These findings sug gest that pulmonary perfusion may trigger several anti inflammatory and regenerative pathways in response to the CPB-induced ischaemia-reperfusion injury [395].

The Cochrane Review highlighted the absence of consistent evidence. The potential benefit of pulmonary artery perfusion for all-cause mortality was found to be uncertain (Peto OR 1.78, 95% CI 0.43–7.40, very low-quality evidence), because it also had an effect on serious adverse events (RR 1.12, 95% CI 0.66– 1.89, very low-quality evidence). There was also very low-quality evidence that pulmonary perfusion improves the postoperative PaO_2/FiO_2 ratio (SMD of 27.80, 95% CI 5.67–49.93), leading to the conclusion that the effects of pulmonary artery perfusion are uncertain and that robust evidence for any beneficial effect is currently lacking [396]. In conclusion, overall scientific evidence on the potential benefit of pulmonary perfusion during CPB remains poor, given the single-centre design of the published experiences, the limited sample size, the lack of clearly defined end points and the constant reports of some biochemical improvements but no evident clinical impact.

Recommendation Table 30. **Recommendation for pulmonary artery perfusion**

Recommendation	**Class[a]**	**Level[b]**	**Ref[c]**
Selective pulmonary artery perfusion may be considered to improve respiratory function, especially in patients at high risk of lung complications.	**IIb**		**[390–392, 395]**

[a]Class of recommendation.
[b]Level of evidence.
[c]References.

in those patients undergoing pulmonary perfusion with oxygen ated blood [392]. The same group subsequently reported the results of bronchoalveolar lavage (BAL) specimens sampled from 90 patients with chronic obstructive pulmonary disease random ized to these 3 different strategies. In all 3 groups, profound his tological, cellular and metabolic changes were found in BAL samples. These changes were due to increased inflammatory cells, metabolic acidosis, protease activity, and oxidative stress. However, metabolomics showed that the lung perfused with HTK during CPB showed less severe fatty acid oxidation, reduced oxidative stress and higher induction of anti-inflammatory activ ities, thus suggesting a subtle protective effect of HTK on the lungs [393]. The same authors also investigated peripheral blood samples after applying the same 3 different strategies: again, no difference was observed between patients receiving oxygenated blood and standard CPB, but patients receiving HTK showed an

7.8.2 Lung ventilation techniques during cardiopulmo nary bypass. Whether CPAP, VCM or ventilation during CPB can protect the lungs has been historically assessed only in extremely small clinical RCTs. Two subsequent meta-analyses concluded that, whereas there is improved early postoperative oxygenation with CPAP or VCM during CPB, there was no effect on relevant clinical outcomes [397, 398].

However, several additional recent large RCTs investigated CPAP and low tidal volume ventilation strategies (plus or minus positive end-expiratory pressure) during CPB with clinical out comes as the primary end points. In the single-centre MECANO (Low Tidal Volume Mechanical Ventilation Against No Ventilation During Cardiopulmonary Bypass in Heart Surgery) trial, 1501 patients were randomized either to the low-tidal vol ume mechanical ventilation during CPB (3 mL/kg 5 times/min, with positive end-expiratory pressure of 5 cm H_2O) or to the

no-ventilation group [399]. The incidence of the primary compo site outcome combining death, early respiratory failure, ventila tion support beyond day 2 and tracheal reintubation was similar in both groups, with 15% in the ventilation group versus 18% in

In conclusion, recent large RCTs focussing on clinically rele vant end points during the last 5 years demonstrated no conclu sive evidence that routine CPAP or ventilation during CPB reduces pulmonary complications.

Recommendation Table 31. **Recommendation for lung ventilation techniques during cardiopulmonary bypass**

Recommendation	Class[a]	Level[b]	Ref[c]
The continuation of ventilation or CPAP during aortic cross-clamp is not recommended.	**III**		**[399, 401, 406]**

[a]Class of recommendation.

[b]Level of evidence.
[c]References.
CPAP: continuous positive airway pressure.

the no-ventilation group (OR 0.80; 95% CI, 0.61–1.05). However, a post hoc analysis of this study in a subgroup of 725 patients undergoing isolated CABG surgery demonstrated that patients in the ventilation group had a significantly lower incidence of the composite outcome, including postoperative pulmonary compli
cations and death compared to the non-ventilated group, with 12.5% versus 20.4%, respectively (OR 0.56, 0.37–0.84) [400]. The multicentre RCT Protective Ventilation in Cardiac Surgery (PROVECS) included 488 patients who received either no venti
lation and a low CPAP (<2 cm H_2O) or continued ventilation along with perioperative recruitment manoeuvres and higher positive end-expiratory pressure levels (8 cm H_2O) during CPB. The results showed that postoperative pulmonary complications within 7 days were similar in both groups, with 54.7% in patients assigned to ventilation during CPB and 59.2% in patients assigned to no ventilation [401]. Zhang *et al.* compared a group of non-ventilated patients (n ¼ 138) with 2 ventilated groups during CPB, 1 with an FiO_2 of 30% (n ¼ 138) and the other with an FiO_2 of 80% (n ¼ 137) in a single-centre RCT [402, 403]. Whereas there was no difference between groups in the inci dence of postoperative pulmonary complications, a subanalysis showed that the group of patients with low oxygen ventilation had a significantly lower incidence of moderate and severe pul
monary complications than the non-ventilated group (23% vs 44%, P ¼ 0.001). Another RCT compared 3 different ventilation modes during CPB in 1364 patients: volume-controlled ventila tion, pressure-controlled ventilation and pressure-controlled ventilation–volume guaranteed, based on the hypothesis that the latter protects the lungs. There was no difference between the 3 ventilation groups in postoperative pulmonary complica

tions within 7 days, which was the primary outcome [404]. A retrospective study compared different FiO_2 passive insuffla tion concentrations with fresh gas flow during CPB in 4 groups (n ¼ 900); low FiO_2 (0.21–0.44), intermediate FiO_2 (0.45–0.69) and high FiO_2 (0.7–1.0), and there was no difference in immedi ate postoperative pulmonary function [405]. Fiorentino and col leagues assessed the effect of low-frequency ventilation during CPB on the activation of inflammatory markers in pre- and post CPB lung biopsies from 37 patients compared to collapsed lungs in an RCT. The results showed no difference in the inflammatory responses between the 2 groups. One of the conclusions of this study was that low-frequency ventilation in comparison to col lapsed lungs may even increase the levels of specific inflamma tory cytokines [406].

7.8.3 Steroids. Steroids suppress the inflammatory response to CPB, and their effect on postoperative outcomes was assessed in 2 large multicentre RCTs [407, 408]. In the SIRS (Steroids In caRdiac Surgery) study, 7507 high-risk cardiac surgical patients were randomized to receive either 250 mg of methylprednisolone at anaesthetic induction and 250 mg at the beginning of CPB or placebo [407]. The results demonstrated that methylprednisolone did not have an effect on the composite outcome of death or major morbidity (i.e. myocardial injury, stroke, renal failure or res piratory failure at 30 days) with an incidence of 24% in both groups (RR 1.03, 95% CI 0.95–1.11). The incidence of respiratory failure was similar in the treatment and placebo groups (9% vs 10%); however, the methylprednisolone group had a higher inci dence of myocardial injury (13% vs 11%, P ¼ 0.002). In the DECS (Dexamethasone in Cardiac Surgery) study, 4494 patients were randomly chosen to receive 1 single dose of dexamethasone (1 mg/kg) intraoperatively before initiation of CPB [408]. Similarly to the SIRS study, there was no difference in the primary composite outcome (including death, MI, stroke, renal failure or respiratory failure within 30 days of randomization) between the treatment and placebo groups, with incidences of 7.0% versus 8.5%, respec tively (RR 0.83, 95% CI, 0.67–1.01). Secondary outcomes indicated a potential benefit in the treatment group with reduced inciden ces of prolonged ventilation and a reduction of postoperative pneumonia. A recent meta-analysis of the SIRS and DECS trials, which included 11 989 patients, confirmed that steroid adminis tration did not decrease the risk of death, MI, stroke, renal failure, new AFIB or transfusion [409]. In addition, the results of this meta-analysis revealed that, on the one hand, steroids increased the risk of myocardial injury, but they also lowered the risk of res piratory failure and infection and reduced the length of ICU and hospital stays. Additional meta-analyses assessed the efficacy and safety of steroids in cardiac surgery and confirmed that prophy lactic steroids in cardiac surgery did not reduce mortality [410– 412] and did increase risks of myocardial adverse events [410, 412]. Similar results were described in a recent Cochrane Review, which confirmed evidence that corticosteroids may reduce pul monary but increase cardiac complications [413].

A secondary analysis of the DECS trial in 813 patients identi fied patients with a high preoperative inflammation risk. The pri mary outcome was the interaction of inflammation risk and peak postoperative C-reactive protein reduction associated with dexamethasone treatment [414]. The inflammation risk was based on a newly developed inflammation risk prediction model in patients from the placebo arm of the DECS trial by linear regression with preoperative covariates related to peak postop erative C-reactive protein. C-reactive protein before surgery was the most predictive covariate. The results revealed that the anti inflammatory effect of dexamethasone increased as the inflam mation risk in patients increased (P ¼ 0.002 for interaction), suggesting that a subgroup of patients at high inflammation risk may benefit from treatment with dexamethasone. In summary, prophylactic steroids do not reduce the inci dence of composite clinical outcomes, and they may increase the incidence of myocardial adverse events.

Recommendation Table 32. **Recommendation for steroids**

Recommendation	Class[a]	Level[b]	Ref[c]
The routine use of steroids for lung protection in CPB is not recommended.	III		[407–409, 412]

[a]Class of recommendation.
[b]Level of evidence.
[c]References.
CPB: cardiopulmonary bypass.

7.9 Mesenteric ischaemia

Mesenteric ischaemia following cardiac surgery is a life threatening complication with a high mortality [415]. The

8. PREPARATION FOR CARDIOPULMONARY BYPASS

Prior to the initiation of CPB, vital steps must be completed to ensure patient safety. Emphasis is placed on the system of care that (i) prevents errors, (ii) learns from the errors that do occur and (iii) is built on a culture of safety that involves healthcare professionals, organizations and patients. Adequate preparation for CPB is one of the crucial steps to successful cardiovascular operations.

patho physiology is still debated, but reduced perfusion of the intes tines during CPB seems to have a decisive influence. Apart from patient-specific risk factors, a long time on CPB and inotropes and vasopressors are acknowledged risk factors [415].

Description of the evidence. In the literature, it is suggested that the prevalence of mesenteric ischaemia is below 1%, ranging from 0.06 to 0.72% [415]. A multifactorial process may ulti mately lead to clinical mesenteric ischaemia. Patient-specific risk factors, such as age, pre-existing disease (e.g. kidney dis ease), aortic dissection or re-exploration for bleeding, play a role [415].

Predisposing factors related to CPB are prolonged CPB and aortic cross-clamp times, intraoperative infusion of vasopres sors and inotropes and use of an IABP [415]. On a more funda mental note, CPB promotes nonobstructive mesenteric ischae mia because of reduced flow or vasospasm of the intestine [415]. Even in healthy patients without clinical signs of intestinal ischaemia, increased lactate levels were found in the rectum during routine coronary surgery [416]. Moreover, CPB may induce mesenteric ischaemia by release of cytokines or non pulsatile perfusion (NPP) [417].

A timely identification of mesenteric ischaemia is a diagnostic challenge. Typical signs and symptoms of mesenteric ischaemia are abdominal distension, abdominal pain and reduced bowel sounds and persistent metabolic acidosis and elevated serum lactate levels. However, the sensitivity and specificity of bio markers are limited [415].

Although several innovative imaging modalities are discussed in the literature, a high index of suspicion and early direct explo ration are still the best choices for successful management of this complication [415].

8.1 Checklists

To conclude, it is recommended that a checklist be used during the set-up and initiation of CPB as well as throughout the entire perioperative period (weaning from CPB, post-CPB, emer gency reinstitution of CPB) and during any other procedure or technique performed by perfusionists [30]. The completion of the prebypass checklist should be acknowledged during team time out. The EBCP has provided a checklist on its website that can be adapted to fit the preferences of individual centres. [426]. Also, the American Society of ExtraCorporeal Technology (AmSECT) has published a prebypass checklist [35].

The use of checklists has been well-established in medicine, spe cifically surgery, as well as in other industries. It has been proven that their use can save lives, time and money as well as reduce the rate of complications [418]. It therefore appears logical to assume that pre-CPB checklists will have similar effects, particu larly concerning complications during CPB. Checklists should be used in an appropriate, diligent and professional manner. They should be adapted to the specific working environment, con sider emerging technologies and be revised in a timely manner following the other institutional protocols.

The efficient use of checklists needs to be supported by addi tional safety features, such as multidisciplinary teamwork, pro fessional communication, managerial support and an open safety and adverse incident reporting culture [419].

Description of the evidence. Although pre-CPB checklists have been increasingly used since the early days of CPB [420], evi dence demonstrating a beneficial effect is lacking because the topic has not been investigated in much detail. A few case reports [420–422] and studies of simulation scenarios suggest that adverse incidents can be avoided [423] or detected early [30] by the use of checklists, enabling simulation participants to react faster and more accurately to a potential life-endangering situation during CPB. Such critical incident checklists have been developed for various perioperative incidents in cardiac surgery [424]. One study, based on a survey from the Netherlands, sug gests no correlation between the reported rate of adverse inci dents and the use of a written pre-CPB checklist [46]. Nevertheless, the authors recommend including a pre-CPB checklist in perfusion practice, especially since, in some European Union member states, medical equipment operators are legally required to ensure the proper working order of the medical devices prior to use [425].

Recommendation Table 33. **Recommendations for checklists**

Recommendations	Class[a]	Level[b]	Ref[c]
It is recommended to use an institution-approved CPB checklist during the set-up and prior to initiating CPB.	I		-
It is recommended that completion of the perfusion checklist is acknowledged during the surgical safety checklist "team time out" procedure.	I		-

anaemia has been identified as an independent risk factor for postoperative increased morbidity and mortality [431, 432], including selective cognitive impairment [433]. Transfusion during CPB did not lower the risk associated with preoperative anaemia [432, 434]. Likewise, preoperative reduced renal function [435] and combined reduced renal and liver function [436] increased postoperative morbidity and mortality. Other comorbidities to consider before the opera tion include but are not limited to diabetes, stroke, neurocognitive disorders, allergies, heparin-induced thrombocytopenia (HIT), cold agglutinins and sickle-cell disease.

It is recommended to use a perioperative CPB checklist, including items for perioperative CPB-related incidents.	I		[30]

[a]Class of recommendation.
[b]Level of evidence.
[c]References.
CPB: cardiopulmonary bypass.

Recommendation Table 34. **Recommendation for preoperative assessment**

Recommendation	Class[a]	Level[b]	Ref[c]
A preoperative assessment of the patient with the surgical-anaesthesiological team is recommended in preparation for CPB.	I		-

[a]Class of recommendation.
[b]Level of evidence.
[c]References.
CPB: cardiopulmonary bypass.

8.2 Preoperative assessment

To be fully prepared to put a patient on CPB, perfusionists must have situational awareness about the patient's condition, con comitant diseases and the type of surgical procedure. The proce dure should be planned together with other physicians involved in the pathway of care for the patient. The use of specialized pre-anaesthesia clinics has a beneficial impact on hospital out comes [427, 428], whereas inadequate or incorrect preoperative assessment can harm the patient [429].

Description of the evidence. The institutional preoperative assess ment forms should be fully employed before any initiation of CPB. A written or electronic form should be kept in the patient's medical record. Because the quality of information is improved when using a standardized form [430], we propose such a form [Supplementary Appendix [6]]. It is an essential document where items can be added or left out.

An adequate preoperative patient assessment allows perfusion ists to plan the procedure and anticipate possible complications. A preoperative evaluation should be vital to an institute-wide

9. PROCEDURES DURING CARDIOPULMONARY BYPASS

During CPB, the goals include maintaining and stabilizing parameters that approximate normal physiology for optimal end-organ oxygen ation and function, as well as managing general anaesthesia, pain management, and anticoagulation. In addition, CPB often aims to compensate for deviations from normal physiological conditions.

9.1 Optimizing the circuit

Type of circuit. In the early years of clinical perfusion, the tradi tional set-up for CPB was focused uniformly on safety and maxi mum versatility. With the evolution of off-CPB cardiac surgery, perfusionists, medical engineers and physicians became aware of the need and potential for improving patient outcomes by improving extracorporeal technology itself.

Those interdisciplinary groups intended to optimize the tradi tional or conventional CPB (or conventional extracorporeal cir culation) (CECC) with different aspects of clinical perfusion. It is not entirely clear nor trivial to define CECC. In Europe, CPB, commonly used in the early 2000s, includes the following aspects: arterial roller pump, uncoated open (hardshell) reser voir, CPB system with at least 1500 ml priming solution without dedicated suction blood management. Optimization is using at least 1 or combining several techniques to improve the haemo
dynamic aspects, biocompatibility and reduced haemodilution. The resulting circuits are generally characterized and can be defined as 'optimized CPB'.

An MiECC is defined as a small priming volume, tip-to-tip coating of the circuit, as a closed system, using a centrifugal pump. Because of the absence of a venous reservoir, the poten tial risk of air embolism must be counterbalanced by using venous bubble traps or a venous air-removing device. The arte rial pump must be a centrifugal pump, while all other compo nents, such as the membrane oxygenator, heat exchanger and cardioplegia system, are used in the same way as the CECC.

In addition, intraoperative CS of red blood cells is used instead of cardiotomy suction. In the 2021 update of the Minimal Invasive Extracorporeal Technologies International Society, further possibil ities, such as different vents and modular systems, are mentioned explicitly. Thus, in the current MiECC system, vents and venous res ervoirs are integrated, which makes it possible to use the MiECC procedure for a wider range of cardiac surgery indications [437].

Furthermore, and previously proposed in the 2016 Minimal Invasive Extracorporeal Technologies International Society posi tion paper, a reduced anticoagulation strategy can be consid ered when using these closed and surface-coated circuits. RCTs have shown that a low-ACT strategy with MiECC was associated with a lower need for heparin and protamine and not with thromboembolic events [182, 438]. The use of modular (type IV) MiECC to eliminate further safety concerns regarding air han dling and volume management and enhance technical feasibility for all cardiac surgical procedures is a novel approach, sepa rately endorsed in 2023 [437].

Initially, MiECC systems were developed for CABG. However, all types of cardiac operations have been performed using MiECC systems today. It is important to emphasize that the use of the MiECC concept relates not only to the hardware of a minimized circuit but also to an interdisciplinary team effort to ensure its successful use.

Description of the evidence. The mentioned RCTs comparing MiECC with CECC in the 2019 Guideline were considered as not sufficiently statistically powered to examine the primary end points and were classified as studies at moderate risk of bias [439– 441]. Therefore, systematic reviews and meta-analyses have played a central role in informing the scientific community about the effects of both interventions. The latest systematic review and meta-analysis was published in 2021. This study includes only RCTs (N ¼ 42) directly comparing MiECC and CECC, with n > 40 subjects and more than 2 primary or secondary end points. This meta-analysis could not demonstrate the benefit of MiECC over CECC for the most important end points, such as mortality, stroke, MI and renal failure; however, it did for several individual end points [442]. The incidence of arrhythmia in the CABG subgroup was significantly reduced in the MiECC cohort compared with the CECC cohort. In addition, the composite outcome of death, MI, stroke and renal failure was significantly different, in favour of the MiECC cohort when compared with CECC [442].

In a retrospective study of 763 patients, the new onset of postop erative AFib was monitored for up to 4 weeks postoperatively
comparing MiECC and CECC. The new onset of postoperative AFib was associated both with age and the use of a CECC. The incidence of new-onset postoperative AFib at discharge was more than 3 times higher in patients with CECC (9.4%) than in those with MiECC (3.0%). After PSM, the differences in the incidence of AFib at discharge and the rehabilitation period remained significantly different [443]. A reduction in new-onset postoperative AFib was also shown in other recent studies and in larger studies from before 2019 [439, 444].

The reasons for the findings are not clear. The authors of 1 RCT from 2021, which was published as an abstract only, concluded that the lower inflammatory effects of MieCC may have led to improved microcellular integrity compared to CECC. In that study, aquaporin protein (AQP-4) levels were used as end point markers, and the results showed significantly higher levels in the MiECC group. Furthermore, the microscopic analysis showed increased cellular damage (well-stained CECC) and bright aquaporin protein (AQP-4) with increased secretion to cope with volume overload in MiECC. However, this study with 20 patients was not sufficiently powered to obtain a definitive confirmation of the effect [445].

A recent study published in 2021 gave no indications of improved organ protection based on biomarkers. This RCT with 60 patients showed no improvements in kidney function when minimally invasive systems were used [446].

Two RCTs showed an improved impact on the coagulation system after cardiac surgery with MiECC. The first trial with 60 patients showed that CECC but not MiECC is associated with significant intra operative thrombin generation [447]. This result is in line with the findings of another RCT on 68 patients, which confirmed that patients treated with MiECC did not show thromboembolic events even when the researchers used a reduced anticoagulation strategy [182]. Whether this approach ultimately leads to less bleeding is not yet fully proven, but the results of individual studies, such as a pro
spective cohort study from 2021, suggest that the clotting properties of the blood are improved when reduced anticoagulation strategies are used in conjunction with MiECC [438].

Compared to the group of patients who underwent cardiac surgery using conventional CPB circuits, the MiECC group had a significant reduction in mean postoperative chest tube drainage and rates of PRBC transfusions [448–450]. This finding may partly be based on a reduction in haemodilution. However, chest tube drainage over the first 24 h was similar in both groups as was the rate of reoperation [450]. A larger study (252 MiECC vs 248 CECC) nevertheless demonstrated a significant reduction in reoperation rates due to bleeding with the same amount of bleeding [439].

However, there is an ongoing scientific discussion of results indicating a reduction in blood loss, blood activation, MI, post operative arrhythmias, cerebrovascular events and deaths when MiECC and CECC are compared [449, 450].

In 2019, a large multicentre RCT [COMICS (Conventional versus minimally invasive extra-corporeal circulation in patients undergoing cardiac surgery)] with a composite of post-operative SAEs as the pri mary outcome (occurring up to 30 days after randomization) was initiated [451]. The study was prematurely halted after recruiting 1071 of the planned 3500 patients due to the COVID-19 pandemic. Analysis of the included population showed a reduced relative risk by 25% of a composite of 12 postoperative SAE up to 30 days post
operatively. However, as the trial did not reach its target sample size, the potential benefits of MiECC remain uncertain [452].

From a scientific point of view, the interpretation of the evi dence for optimizing perfusion and MiECC is more robust than in 2019. However, there is still a need for studies with more stat istical power [449, 453]. Consequently, results from meta analyses on hard end points, such as death, have to be con firmed in future large RCTs [449].

It is also worth noting that perfusionists still have controversial views on how to optimize CPB. What is certain, however, is that the introduction and consistent research into the MiECC proce dure, in particular, has led to a rethink about the use of CPB. Many perfusionists have continued to

optimize CPB and thus improve the treatment of our patients.

a deleterious impact on variables related to the haemostatic func tion, but no clinically relevant effect, for example, on bleeding was found [461]. Furthermore, allergic reactions to dextran, as well as to other colloids, should be considered

[462].

The addition of mannitol to the priming solution was once rou tine practice but has been abandoned by most. Recent evidence does not favour adding mannitol to the priming solution [463, 464]. Using normal saline or unbalanced colloid solutions as a pri

Recommendation Table 35. **Recommendations for optimizing the circuit**

Recommendations	Class[a]	Level[b]	Ref[c]
It is recommended to optimize CPB systems, following an MiECC-like approach, to reduce blood loss and haemodilution and increase haemocompatibility.	I		[439, 442, 448, 450]
MiECC should be considered over standard conventional CPB to reduce the incidence of new onset atrial fibrillation after CABG surgery.	IIa		[439, 442–444]

[a]Class of recommendation.
[b]Level of evidence.
[c]References.
CABG: coronary artery bypass grafting; CPB, cardiopulmonary bypass; MiECC: minimally invasive extracorporeal circulation.

9.2 Priming—Composition, volume and autologous priming (antegrade and/or retrograde)

The standard procedure in adult cardiac surgery involves pri ming the CPB circuit with a clear, non-blood fluid before initia tion. This step introduces new obstacles, namely haemodilution and the risk of coagulopathy. The most commonly used priming fluid is a crystalloid electrolyte solution with additives. However, considerable research has been performed to investigate colloid-based priming solution. The interest in minimized perfu sion circuits in recent years led to several studies on the feasibil ity and possible advantages of reducing the amount of priming volume, shortening the circuit or autologous priming. Autologous priming (antegrade and retrograde) is achieved by allowing blood to displace the prime into an external reservoir. This external reservoir is then excluded from the circuit.

Description of the evidence. Despite a wealth of studies, no consen sus has been reached on the optimal composition of the priming solution According to recent surveys, crystalloids are the preferred priming solution in European centres and are exclusively used in Australian centres [454, 455]. The goal of adding colloids to the pri ming solution has been to reduce fluid balance and oedema forma tion. Although this was feasible in some studies [456, 457], a meta analysis showed no difference in colloid osmotic pressure, HCT and transfusion requirements between hydroxyethyl starch and crystal loid solutions [457]. Moreover, a negative effect of hydroxyethyl starch on kidney function has been suggested [456, 458]; thus its use in priming solutions cannot be recommended.

The use of albumin as a colloid did not reduce adverse events in a large RCT [459].

Recently, the use of a dextran 40-based priming solution has been advocated. A recent RCT on the use of hyperoncotic dextran 40 showed better preservation of colloid oncotic pressure com pared to crystalloids [460]. However, in another RCT, dextran had

ming fluid for CPB may lead to hyperchloraemic acidosis [465]. Although there is a lack of RCTs, there is widespread agreement that normal physiological conditions, such as normal pH value and normal electrolyte levels, should be maintained. Acidosis may increase the risk of postoperative complications, e.g. bleeding [466].

PlasmaLyte (Baxter International, Deerfield, IL, USA) is a bal anced crystalloid fluid with an electrolyte constitution similar to that of plasma, with a reduced chloride concentration and no lactate, compared to Ringer's lactate. However, the calcium con centration of the priming solution should be noted, because some solutions may cause hypocalcaemia [467]. Two recent small RCTs comparing Ringer's lactate with PlasmaLyte as a prime solution demonstrated that using PlasmaLyte resulted in less metabolic acidosis [468, 469]. However, larger RCTs with rel evant clinical outcomes are needed to confirm the superiority of PlasmaLyte compared to other balanced crystalloid fluids.

Autologous priming is a method developed for minimized cir cuits where the patient's blood displaces the priming solution in an antegrade or retrograde autologous priming fashion. The number of studies and meta-analyses on this topic has increased significantly [457, 470, 471]. A meta-analysis of RCTs found a sig nificant reduction in PRBC transfusions when autologous pri ming was applied (SMD −0.38 units, 95% CI −0.72 to −0.04) [470]. However, the quality of evidence is moderate, and this intervention requires further investigation.

Several variants of autologous priming are described in the literature. The goal is to reduce priming volume and decrease the haemodilution associated with CPB [471]. The results of 2 recent systematic reviews and meta-analysis support using autologous priming as part of a blood conservation strategy when using CPB [470, 471]. In the publication of Hensley *et al.,* 11 RCTs and 10 observational studies were included.

The authors found a significant reduction in red cell transfusions intraoperatively and during the hospital stay, but no difference in the incidence of kidney injury and stroke [471]. Gupta *et al.* included 12 RCTs and 17 observational studies and reached similar conclusions [470]. One of the challenges of the scientific evaluation of autologous priming is the lack of standardization of the methods used in scientific studies and in clinical practice. Standardization was shown to increase the effects of autologous priming [472].

a more patient-specific approach to determine heparin doses. One option is the Hepcon Haemostasis Management System (HMS, Medtronic, Minneapolis, MN, USA), a point-of-care system that considers body weight, height, gender and information on the CPB circuit (priming volume, amount of UFH added). The method is based on determining a patient's response to UFH (heparin-dose response) by exposing a blood sample to different

Recommendation Table 36. **Recommendations for priming volume in the cardiopulmonary bypass circuit**

Recommendations	Class[a]	Level[b]	Ref[c]
The use of low-molecular-weight starches in priming solutions is not recommended.	III		-
Minimizing priming volumes and using autologous priming (retrograde and antegrade) are recommended as part of a blood conservation strategy to reduce transfusions.	I		[470, 471]
The routine use of mannitol in the priming solution is not recommended.	III		[463, 464]
Maintenance of a normal pH (7.35–7.45) and avoidance of hyperchloraemic acidosis should be considered in order to reduce the risk of postoperative complications.	IIa		[466]
It is recommended that the addition of medications to the pump priming fluid be individualized to the patient and discussed by the clinical team.	I		-

[a]Class of recommendation.
[b]Level of evidence.
[c]References.

9.3 Anticoagulation management

The most commonly used anticoagulant during CPB is unfractio nated heparin (UFH). Heparin binds to AT, thereby potentiating the inactivation of thrombin and factor Xa by antithrombin up to 1000-fold. The ACT assesses the effect of heparin on the coagulation system. This is a point-of-care whole-blood coagu lation test for the intrinsic coagulation system that is influenced by patient and surgical factors, including temperature, haemodi lution, AT levels and platelet counts. Individualized heparin treatment and protamine titration are essential aspects of anti coagulation during CPB. Both of these are discussed in the fol lowing sections. As outlined in section 9.3.3, some situations require alternatives to heparin as an anticoagulant.

9.3.1 Individualized heparin treatment and heparin dosage. During CPB, the interaction between blood and artificial surfaces requires systemic anticoagulation to reduce the risk of clotting and thromboembolism. UFH is the most common anti coagulant used for systemic anticoagulation in CPB; its effect depends on sufficient amounts of AT. The current practice for anticoagulation during CPB procedures indicates that an ACT value of >480 s is considered an appropriate threshold. Therefore, an ACT above 480 s during CPB should be considered in CPB with uncoated equipment and cardiotomy suction. An ACT target before the start of CPB of 480 s with a range of 400 to 500 has been the recent survey result of current practice among Australian hospitals [473]. However, CPB circuits and dif ferent ACT assays can lead to various target values, which are suggested to prevent heparin overdosing during CPB [474–477]. In addition to the classic calculation of the required UFH dose based on body weight, patient-specific heparin management sys tems and approaches are available to achieve the required ACT target value. Methods of individualized heparin management are amounts of UFH. During CPB, the heparinized blood is titrated with protamine in the Hepcon system to determine the current heparin concentration. Finally, after CPB and protamine reversal, the patient's blood is titrated again with low doses of protamine to detect residual heparin. Using a combination of the Hepcon, thromboelastography and the PFA-100 platelet function analyser in CABG did not reveal a difference in postoperative blood loss between patients with individual heparin titration and patients without, as shown in an RCT with 102 patients [478]. One study investigated how Hepcon-based heparin management influenced heparin doses compared to a conservative anticoagulation strat egy in patients having CABG surgery [479]. The study showed no differences in total heparin doses between groups, and there were no differences in PRBC transfusion requirements [479]. Similarly, another study assessing a Hepcon-based anticoagulation strategy revealed no differences in heparin dosing or in postoperative hae mostasis or bleeding compared to ACT-based dosing [480].

In contrast, the use of a Hepcon-based strategy increased

hepa rin dosing in valve surgery compared to an ACT-based strategy [481]. In the Hepcon group, fewer patients showed more than 450 ml blood loss 24 h following surgery. A small study showed that the increase in heparin dosing during a Hepcon-based strategy did not result in less haemostatic activation or postoperative bleeding compared to ACT-based management [482]. In another RCT, Hepcon was compared with calculated heparin doses. This study found higher doses of heparin with Hepcon but no signifi cant benefits in thrombin generation or reduction of bleeding in the postoperative period [483].

A completely different approach was taken in a study based on the assumption that higher doses of heparin can prevent dis seminated intravascular coagulation. The RCT with 269 patients showed that there was no difference in the bleeding rate when comparing groups with higher (450 IU/kg) and lower heparin doses (300 IU/kg) and with HMS-guided dosing [484]. In another

RCT (n ¼ 31), significantly higher anti-factor Xa levels were found in the study group with a higher heparin dose (600 IU vs 300 IU) during CPB (anti-factor Xa: 9.38 U/ml vs 5.04 U/ml, *P* ¼ 0.001). This study was also unable to identify any advantages of higher heparin doses [485].

For anticoagulation with heparin, it must always be consid ered that heparin resistance may be present. If sufficient ACT cannot be achieved despite having exhausted all measures, such as the administration of further doses of heparin, AT concentrate or plasma, alternatives must be considered. These would be alternative surgical procedures such as operating without a heart-lung machine or with MiECC [486].

In summary, individual heparin bolus doses before initiation of and during CPB should be guided by appropriate ACT increases. If patient-specific heparin management systems are available, these can be used to manage more individualized heparin doses. Given the absence of primary end points for peri
operative bleeding and transfusion rates in these studies, larger multicentre studies are necessary to evaluate the benefits of individual heparin management in contemporary practice.

because ACT is also influenced by hypothermia, platelet count and function, factor deficiencies and AT levels. Additional doses of protamine may instead lead to overdosing and worsen the coagulopathy. Protamine-to-heparin dosing ratio strategies vary among institutions and are subject to local conventions. Two recent reviews of the available evidence [489, 492] indicate that the protamine-to-heparin ratio should be kept below 1.0, but the exact ratio and monitoring method remain to be deter
mined. Increasing the protamine-to-heparin ratio leads to increased clot formation time, reduced platelet count and increased platelet-factor 4 levels [489, 490, 493]. To avoid inad vertent clotting of the ECC and preclude going back on CPB urgently, it is important to discontinue the cardiotomy suction

with the start of the administration of protamine [494].

Optimal protamine dosing. The majority of cardiac centres moni tor the effect of protamine with either ACT or activated partial thromboplastin time (aPTT), but both methods have shown weak correlation with heparin and protamine concentrations. The pres ence of heparin can also be assessed by adding heparinase to the

Recommendation Table 37. **Recommendations for heparin administration**

Recommendations	**Class[a]**	**Level[b]**	**Ref[c]**
Individualized heparin and protamine management should be considered to reduce postoperative coagulation abnormalities and bleeding complications in cardiac surgery with CPB.	**IIa**		**[479, 480]**
It is recommended that ACT checks be performed at regular intervals based on institutional protocols and that heparin doses be administrated accordingly, especially in the absence of individual heparin dosing services.	**I**		**-**

[a]Class of recommendation.
[b]Level of evidence.
[c]References.
ACT: activated clotting time; CPB: cardiopulmonary bypass.

9.3.2 Protamine management. A highly basic protein isolated from salmon sperm is the only clinically available agent to reverse the anticoagulation of UH [487]. Protamine sulphate is only administered intravenously for heparin reversal and binds electro
statically to UFH to rapidly reverse its effect, by increasing dissoci ation of the AT/heparin complex. The half-life is relatively short, estimated to be approximately 5 min [488].

Protamine influences coagulation on its own, including reduced platelet activity and aggregation, reduced thrombin generation and enhanced fibrinol ysis [489]. These effects are more pronounced with overdosing of protamine in the process of heparin reversal [490]. Protamine has additional haemodynamic side effects, including an anaphylactic response with pulmonary vasoconstriction, bradycardia and sys temic hypotension [491]. These side effects are partly related to the drug infusion rate, where slower administration results in less severe haemodynamic side effects [489].

Interventions. The protamine dose for reversal of heparin has tra ditionally been calculated either on the initial heparin dose or on the total amount of heparin administered during CPB, includ ing calculation of consumption of heparin during CPB. Additional protamine doses are often given in case of clinical signs of oozing after the operation, although a coagulopathy and prolonged ACTs may not be related to residual heparin, intrinsic clotting time in TEG [489]. An alternative approach is to use the Hepcon, which measures the heparin concentration in the blood sample and estimates the protamine dose needed for reversal. One study showed that the use of the Hepcon device resulted in a highly significant reduction in the total protamine dose compared to ACT-based dosing (mean protamine dose: 14.190 IU vs 24.777 IU; $P < 0.001$) and total blood loss (mean blood loss: 804 ml vs 1416 ml; $P < 0.001$) [495].

Davidsson *et al.* performed a study evaluating a statistical model, where the protamine dose was calculated based on BSA, heparin dose and clearance as well as on the time elapsed between the first bolus of heparin and protamine administration and the preopera tive platelet count [496]. The calculated dose was similar to the dose suggested by Hepcon but has the advantage of eliminating additional costs by not using the Hepcon assay. In another clinical study, the research group evaluated the calculated dose in compar ison with the conventional protamine-to-heparin ratio of 1:1. Despite similar heparin doses in the 2 intervention groups, the amount of protamine was 40% lower in the calculated arm, which was associated with a significantly reduced intrinsic clotting time. ACT levels were comparable in the 2 study arms [497]. These obser vations were confirmed by another research group [498]. Other investigators used stepwise titration of protamine doses in a small RCT (n ¼ 138), resulting in a reduced protamine-to heparin ratio of 1.30 ± 0.10 (control) and 0.81 ± 0.22 (treatment, $P < 0.001$) [499]. However, clinical data do not demonstrate sig nificant reductions in bleeding or in the administration of blood products.

Despite additional clinical studies comparing various ratios of protamine-to-heparin ratios, the current results on bleeding out come are conflicting, which may relate to the multifactorial causes of bleeding after cardiac surgery outside heparin reversal.

In conclusion, protamine is essential to heparin reversal but carries a risk of excessive anticoagulation and bleeding if over dosed. The optimal protamine-to-heparin ratio should be below 1.0. Alternatively, residual heparin should be evaluated either in Hepcon or by thromboelastographic assessment.

does not prevent clotting in stagnant blood, so closed shunts on the heart-lung machine should be recirculated regularly every 15 to 20 min. Separating cardiotomy suction or processing stag nant blood in the venous reservoir may be necessary [505]. Bivalirudin is mainly dependent on renal clearance. Clearance decreases by 20% in patients with an estimated glomerular filtra tion rate (eGFR) of 30 to 59, 60% in patients with an eGFR of 10 to 29 and 80% in patients on dialysis. The bolus dose remains the same in patients with renal impairment, but infusion rates should be reduced [505]. The authors of a recent systematic review concluded that bivalirudin is a safe and effective anticoa gulant for CPB, especially for patients with HIT or heparin resist ance [506].

Recommendation Table 38. **Recommendations for protamine administration**

Recommendations	**Class[a]**	**Level[b]**	**Ref[c]**
A protamine-to-heparin ratio < 1.0 is recommended to avoid overdosing of protamine.	**I**		**[489, 492]**
Individualized heparin–protamine management should be considered to reduce postoperative coagulation abnormalities and bleeding complications after cardiac surgery with CPB.	**IIa**		**[489, 496]**
Cardiotomy suction should be discontinued with the start of the administration of protamine.	**IIa**		**[489]**

[a]Class of recommendation.
[b]Level of evidence.
[c]References.
CPB: cardiopulmonary bypass.

9.3.3 Alternatives to heparin. Heparin and protamine are the mainstays of current practice in anticoagulation and reversal for CPB. However, there are conditions under which anticoagulation should be changed to heparin alternatives, such as DTIs. The most common cause is HIT, which in this context should be per ceived as an immune-mediated inflammatory process resulting in thrombotic sequelae and consumption of platelets, not just the presence of platelet factor-4 antibodies [500]. The timing of the operation in HIT is based on expert opinion, but it should preferentially be deferred until the patient has negative func tional assays, typically after 100 days. In case of an urgent opera tion, DTIs should be used for anticoagulation during CPB, pri marily bivalirudin, but in case of renal impairment, argatroban is preferred [501].

Bivalirudin is given as an intravenous bolus of 1 mg/kg, fol lowed by a continuous infusion of 2.5 mg/kg/h. A bolus of 50 mg of bivalirudin is typically added to the pump prime. The plasma concentration of bivalirudin should be 12 to 15 μg/ml, but drug measurement is unavailable in the clinical setting. Anticoagulation should preferentially be monitored by ecarin clotting time [502]. Still, since this method is also not routinely available, most cardiac centres rely on ACT, with a target of an ACT 2.5 times baseline, typically > 300 s [502]. Of note, the plasma bivalirudin concentration only correlates with ACT and aPTT in the lower ranges (< 5 μg/ml for ACT), and plateaus for aPTT despite an increasing plasma concentration of the drug [503]. When used for anticoagulation during CPB, the main chal lenges are stagnant blood and timing the cessation of an infu sion [504], because no reversal agent is available. Bivalirudin

Argatroban is also a DTI, mainly undergoing hepatic elimina tion and, therefore, the preferred anticoagulant in patients with renal impairment. Argatroban is typically given intravenously as a bolus of 0.1 mg/kg followed by an infusion of 5 to 25 μg/kg/ min, but the rate can be increased up to 40 μg/kg/min. A bolus of 4 mg argatroban can be added to the prime. Similar to the situation with bivalirudin, monitoring should preferentially be done with ecarin clotting time, but ACT targets of > 450 to 500 s have been reported. However, both ACT and aPTT responses depend on the reagent and the method [505]. Previous studies have demonstrated increased bleeding and use of blood prod ucts after CPB [503]. In contrast to bivalirudin, the removal of argatroban by haemofiltration and HA is negligible [505]. Alternatives to bivalirudin, such as plasmapheresis or heparin anticoagulation after the administration of platelet antagonists, are used less frequently [507]. Intraoperative therapeutic plasma exchange before re-exposure to heparin in patients with HIT has been described in 24 patients and was not strongly associated with HIT-related thrombosis or death after cardiac surgery with CPB [508]. Furthermore, the use of cangrelor with heparin in patients with HIT was described in a small case series of 3 patients, where it was found to be convenient, safe and an effec tive alternative intraoperative anticoagulation strategy providing acceptable outcomes [509].

In conclusion, alternatives to heparin include mainly bivalir udin. Indications for their use are primarily in patients with HIT. The major drawbacks of DTIs are the challenges associ ated with proper monitoring and the lack of a reversal agent after CPB.

Recommendation Table 39. **Recommendations for alternative anticoagulation**

Recommendations	**Class[a]**	**Level[b]**	**Ref[c]**
Bivalirudin should be considered as the first-line anticoagulation treatment in patients with acute HIT type 2 who require cardiac surgery.	**IIa**		**[503, 504]**
Anticoagulation with argatroban may be considered in patients with acute HIT type 2 who require cardiac surgery with CPB and have significant renal dysfunction.	**IIb**		**[503, 505]**

[a]Class of recommendation.
[b]Level of evidence.
[c]References.

CPB: cardiopulmonary bypass; HIT: heparin-induced thrombocytopenia.

9.4 Systemic arterial blood pressure during cardiopulmonary bypass

Targeting a sufficient MAP during CPB is vital in order to main tain appropriate perfusion pressures in all end-organs, particu larly the kidneys, the brain and the gastrointestinal tract. Vasoplegic syndrome during CPB may derive from the release of proinflammatory cytokines, anaesthetic drugs, active endocardi tis, systemic inflammatory reaction syndrome and the preopera tive use of angiotensin-converting enzyme inhibitors and cal cium channel blockers (CCBs). Hypertension during CPB may be caused by an inadequate level of anaesthesia/analgesia, a release of catecholamines, vasoconstriction due to

hypothermia and others.

Description of the evidence. A recent RCT compared high-target (70–80 mmHg) to low-target (40–50 mmHg) MAP during CPB in 197 patients who had cardiac surgery and found no differences in terms of cerebral injury [381]. In this study, the pump flow was the same in the 2 groups, and the achievement of the target perfusion pressure was based on the significantly higher amount of norepinephrine used in the high-target group. Of note was a trend towards a higher stroke rate (7.0% vs 1.1%; *P* ¼ 0.06; respectively) and death (4.1% vs 0%; *P* ¼ 0.06; respectively) in the high-target group. A subsequent post hoc analysis found that a higher MAP during CPB was associated with signs of impaired cerebral metabolism [510]. Other RCTs found conflict ing results. No differences in the mortality rate, major neurologi cal or cardiac complications, cognitive complications or deterio ration in functional status were found between patients treated at a target MAP of 80 mmHg and a 'custom'MAP (based on the pre-CPB MAP) [511]. The CCABOT (Cornell Coronary Artery Bypass Outcomes Trial) group [512] randomized patients into a high-MAP (80–100 mmHg) group or a low-MAP (50–60 mmHg) group, finding a significantly higher rate of major cardiac and neurological complications (including MI, cardiogenic shock, cardiopulmonary arrest and stroke with focal deficit) in the low MAP (12.9%) versus the high-MAP (4.8%) group. However, the high-MAP group reached a mean MAP lower than the target (69 ±7 mmHg). In another RCT, less cognitive dysfunction and delir ium were found in patients treated at an MAP of 80 to 90 mmHg versus 60 to 70 mmHg [513]. Miao and associates [514] performed a small RCT comparing patients treated at 70 to 80 mmHg MAP versus 50 to 60 mmHg, finding that patients in the high-pressure group had a lower rate of arterial blood lactates and a shorter mechanical ventilation time and stay in the ICU. In another RCT [378], patients treated with a target MAP > 60 mmHg did not show any reduction in AKI.

A recent systematic review and meta-analysis assessed mor bidity and mortality associated with high versus low blood pres sure targets during CPB that included 8 RCTs and 1116 patients. There were no differences in clinical outcomes, such as delirium, cognitive decline, stroke, AKI or mortality. A small number of tri als (3 RCTs, n ¼ 456) showed that higher blood pressures may have an increased risk of the requirement for a blood transfu sion [515].

In the retrospective series, no differences in MAP during CPB were observed in patients who developed postoperative AKI versus patients with a normal renal outcome [516, 517]; how ever, it was suggested that the optimal MAP during CPB should reflect the preoperative MAP [516]. More recently, the optimal MAP (during CPB and the early postoperative period) was assessed using ultrasound-tagged NIRS based on cerebral blood flow autoregulation [518, 519]. The extent of MAP excursions below the optimal MAP was superior regarding postoperative delirium [519].

Novel approaches to settle optimal blood pressure values have been recently proposed. Targeting the MAP based on cere bral autoregulation decreases the incidence of postoperative delirium in an RCT, including 199 patients [520], and a larger RCT from the same group confirmed these results [222]. Personalization of the MAP during CPB based on cerebral autor egulation explored before CPB using cerebral Doppler is undoubtedly an attractive perspective, although burdened by technical difficulties.

Vasopressors (epinephrine, norepinephrine, vasopressin, terli pressin, phenylephrine, metaraminol, methylene blue, hydroxo cobalamin and combinations) are required to treat vasoplegic syndrome during CPB, which is characterized by low arterial pressure with normal or elevated CO and reduced systemic vas cular resistance and occurs in 5% to 25% of patients undergoing cardiac surgery [222, 521]. In an RCT that enrolled patients treated with angiotensin-converting enzyme inhibitors, methyl ene blue was effective for the prevention/treatment of vasople gic syndrome (compared to saline), resulting in lower blood lac tate levels during and after CPB [522]. In a similar patient population, vasopressin was effective in preventing/treating vas oplegic syndrome compared to saline [523]. The use of hydroxo cobalamin has been reported as a rescue treatment for methyl ene blue-refractory cardioplegic syndrome during CPB [524]. A retrospective single-centre study in 120 patients demonstrated that hydroxycobalamin was associated with a greater reduction in vasopressor requirements than methylene blue in the treatment of vasoplegic syndrome associated with CPB [525]. Angiotensin II was suggested to treat vasoplegic syndrome after CPB [526]. A recent systematic review about the use of angioten sin II for the treatment of post CPB vasoplegia (considering 2 RCTs, 1 retrospective cohort study and case reports) concluded that it is effective in raising blood pressure, without major adverse effects (AEs) [527]. In case of high MAP values during CPB, the depth of anaesthesia should be checked and adequately adjusted before using vasodilators. Different intrave nous vasodilators are available once the level of anaesthesia is guaranteed adequate [sodium nitroprusside, nitroglycerin, milri none, enoximone, phentolamine, urapidil, nicardipine and clevi dipine]. Currently, the existing literature does not contain suffi cient information to provide recommendations on the choice of vasodilators.

performance [530]. The estimated lean body mass can be calcu lated according to the existing equations [531, 532]. The purpose of the pump flow rate is to satisfy the oxygen needs of different organs [i.e. systemic oxygen consumption (VO_2)] through an adequate DO_2. However, the DO_2 is obtained from the product of the pump flow rate multiplied by the oxygen content, which derives from the Hb concentration (g/dL) and the arterial Hb oxygen saturation (SaO_2). Therefore, recent studies suggest determining the adequate pump flow rate based not only on BSA and temperature but also on the DO_2 [533–536]. In addi tion, further potential markers of adequate pump flow are SvO_2, the O_2 extraction ratio (O_2ER), the respiratory quotient (VCO_2/ VO_2), the volume of carbon dioxide produced (VCO_2) and the regional cerebral oxygenation. Increased arterial blood lactate concentrations indicate potential tissue hypoxia, and they are a

Recommendation Table 40. **Recommendations for control of mean arterial blood pressure during cardiopulmonary bypass**

Recommendations	Class[a]	Level[b]	Ref[c]
It is recommended that the MAP be maintained between 50 and 80 mmHg with vasoconstrictors and vasodilators if required, having ensured that the depth of anaesthesia and pump flow rate are sufficient.	I		[381, 511]
The use of vasopressors to increase the MAP to values above 80 mmHg during CPB is not recommended.	III		[381, 510, 517]
Targeting the MAP during CPB within the limits of individualized cerebral autoregulation data, measured under normocapnic conditions before CPB, should be considered whenever the technical and human skills are available.	IIa		[222, 519, 520]
It is recommended that vasoplegic syndrome during CPB be treated with α1-adrenergic agonists and/or vasopressin.	I		[521, 523]
In refractory vasoplegic syndrome, alternative drugs (methylene blue or terlipressin) should be considered, alone or in combination.	IIa		[522, 523]
Hydroxocobalamin or angiotensin II may be considered to treat vasoplegic syndrome during CPB.	IIb		[524–527]

[a]Class of recommendation.
[b]Level of evidence.
[c]References.
CPB: cardiopulmonary bypass; MAP: mean arterial pressure.

9.5 Pump flow management

The target blood flow during CPB is traditionally determined according to BSA and temperature. Under moderate hypothermia-to-normothermic conditions, most perfusionists usually set the pump flow rate between 2.2 and 2.8 L/min/m^2. However, this range of the pump flow rate (based on BSA) can overestimate the metabolic needs of patients who are obese [528]. Therefore, lean body mass has been suggested as a more sensitive estimate of systemic metabolism; however, it may also underestimate metabolic needs in the patients who are obese [529]. As a result, in patients with obesity, the combined use of BSA and lean body mass should be used (avoiding over- and underestimation of metabolic needs), also considering gender, because women tend to have a higher percentage of body fat than men, causing a lower absolute resting metabolic rate [528]. A gender-specific model predicting lean body mass has also been developed and evaluated with good predictive

It is impossible to recommend an optimal pump flow rate when an index is considered alone. However, low values of SvO_2, DO_2 and NIRS and high values of the O_2ER and arterial blood lactate levels during CPB are markers of inadequate perfu
sion associated with adverse outcomes [213, 542, 543]. Furthermore, a large retrospective study showed that a strategy focused on maintenance of an SvO_2 > 75% resulted in a lower rate of stage 1 AKI in patients reaching the goal

delayed marker as the result of a deficient oxygen supply. Finally, renal oxygenation is increased by increasing the pump flow rate, which is a direct component of the DO_2 [537].

Description of the evidence. Retrospective and PSM studies high lighted that patients suffering from postoperative AKI were treated at lower pump flows than patients without AKI [516, 536]. However, older studies (before 1990) found no association between pump flow rate and adverse cerebral, neurocognitive or renal outcomes [538–540].

At present, no RCTs have investigated the association between pump flow rate and outcomes. A retrospective study on conven tional CPB versus MiECC showed that patients treated with mini aturized CPB experienced a significantly lower pump flow rate but had substantially less haemodilution [541]. As a result, the DO_2 was equivalent as was the renal outcome. However, the risk of developing stage 1 AKI was significantly and inversely associ ated with the DO_2 in the pooled groups [541].

[544].

Pump flow rate adjustment based on the Hb content in order to maintain an adequate DO_2 'GDP'is described in section 9.7.

Despite these caveats, more studies have been published that contribute further to the controversy.

Description of the evidence. Two studies were designed to

evalu ate the equivalent energy transduced with PP to patients versus NPP [553, 554]. The first was a trial with 52 patients undergoing AVR and randomized to NPP or PP with the use of a centrifugal blood pump: Despite comparable MAPs during CPB, the surplus energy equivalent pressure [EEP], based on Shepard's formula, was 25% higher than the MAP at the tip of the arterial cannula,

Recommendation Table 41. **Recommendations for pump flow management during cardiopulmonary bypass**

Recommendations	Class[a]	Level[b]	Ref[c]
It is recommended that the estimated pump flow rate be determined before the initiation of CPB based on the BSA and the planned level of hypothermia.	I		-
The adequacy of the pump flow rate during CPB should be considered based on oxygenation and metabolic parameters (SVO_2, O_2ER, r_cSO_2, VCO_2, VCO_2/VO_2 and arterial blood lactate levels).[d] No validated threshold presently exists.	IIa		[213, 542, 543]

It is recommended that a minimal value of DO_2 of 280 ml/min/m^2 be used to reduce the risk of AKI stage 1.	I		[533–536, 545, 546]
Pump flow rates calculated on the basis of lean body mass may be considered as a suggested lower value in patients with obesity.	IIb		[528]

[a]Class of recommendation.
[b]Level of evidence.
[c]References.
[d]VCO_2-derived factors must be measured in the absence of CO_2 flooding of the surgical field.
AKI: acute kidney injury; BSA: body surface area; CPB: cardiopulmonary bypass; DO_2: oxygen delivery; r_cSO_2: regional cerebral tissue oxygen saturation; O_2ER: oxygen extraction ratio; SVO_2: venous oxygen saturation; VCO_2: volume of carbon dioxide produced; VO_2: oxygen consumption.

9.6 Pulsatile versus non-pulsatile flow

The potential benefit of pulsatile perfusion (PP) over conventional NPP has been a matter of never-ending debate during the last 3 decades [547]. Previous RCTs agreed on better renal protection with PP during CPB, with less evident but potential benefits for postoperative pulmonary function [547–550]. However, the previous CPB guidelines also suggested that the literature may be biased, firstly because of the absence of a universal consensus on the definition of pulsatile perfusion and regarding the methods to quantify the induced pulse pressure [2]. Furthermore, an objective measure of the amount of pulsation transduced inside the patient's body is similarly lacking in almost all studies [551]. To further complicate the scenario, one has to bear in mind that most of the CPB components, including pumps, oxygenators and arterial cannulas, are not evaluated for pulsatile flow by manufacturers and are not currently approved for clinical practice with pulsatile flow by the US Food and Drug Administration [551]. Therefore, the consequent use of these procedures in humans, without preclinical solid validation of the intended pulsatile CPB circuit, might hamper patient safety, given the potential for higher peak pressures inside the CPB components, the potential for the generation of microemboli and higher shear stresses elicited inside the CPB machine with their potential consequences on human blood [551, 552].

Another single-centre observational study compared PP to NPP in CABG surgery. It demonstrated that PP was associated with significantly higher pressures inside the CPB circuits compared to NPP, which translated into a not clinically meaningful higher haemolysis with PP induced by roller pumps [555]. In contrast, another single-centre trial, in a limited number of patients having CABG, also investigated haemolysis after randomization to PP or NPP with MiECC. This trial found no differences in haemolysis and no beneficial effect of pulsation on fibrinolysis, renal damage and neuronal damage [556]. Of note is an observational study analysed with a scanning electron microscope of the oxygenator fibres of CPB circuits after PP and NPP. The results demonstrated that axial sections of the oxygenator fibres had a significantly higher mean thickness after NPP than after PP, and superficial views of the fibres demonstrated lower platelet, leucocyte and erythrocyte absorption after PP, thus suggesting better biocompatibility of cannulation site; this translated into a mean surplus haemodynamic energy (SHE) of 5150 ± 2291 ergs/cm^3, well below the value induced by the human heart, though well above the zero value of SHE with NPP [553]. Despite the limited transduced energy, the authors were able to report an increased endothelial nitric oxide synthase activity with PP, responsible for lower systemic vascular resistance index (SVRI) and PVRI values; there were no differences, indeed, in terms of biomarkers of endothelial integrity, haemolysis, transfusion requirements and clinical outcome, except for a transient better preservation of kidney function after PP [553]. The second study randomized patients requiring valve surgery to NPP or PP using roller pumps. The authors demonstrated that EEP and SHE were about 1.5 and 2.0 times higher than NPP [554]. Furthermore, they also applied the fast Fourier transform analysis to assess the energy waveforms in power spectral density and power density ratios and found (i) the power spectral density at low frequencies (0–5 Hz) decreased in both groups compared with the physiological flow; (ii) this drop was more pronounced with NPP; (iv) the higher power density of PP versus NPP was detectable in all frequency ranges but was more evident in the low-frequency range. From a biochemical standpoint, this study also showed a higher serum leakage of biomarkers of renal and cerebral damage after NPP, though the clinical outcomes of these patients were not reported [554].

but only 7.3% higher than the MAP at the radial artery PP [148].

Two studies investigated the cerebral response to NPP [557, 558]. The first RCT investigated the regional cerebral oxygenation by means of NIRS and found no differences from baseline values in perioperative NIRS values for the left and right hemispheres of the brain in patients randomized to PP versus NPP, nor any differences in $rScO_2$ at all time points [557]. Considering the cerebral responses to NPP, a longitudinal single-centre case-control study investigated the impact of NPP CPB on cerebrovascular reactivity at different arterial CO_2 partial pressures ($PaCO_2$ between 30 and 50 mmHg) in comparison with pulsatile flow postoperatively under comparable conditions. This study showed that NPP CPB enhanced cerebrovascular CO_2 reactivity to $PaCO_2$, resulting in more significant vasoconstriction and relative decreases of cerebral blood flow during hypocapnia, with a intermittent blood flow characteristics compared with the PP group. Furthermore, the reperfusion slope, assessed by

means of the oxygen saturation of the thenar muscle tissue after a vascular occlusion test, indicated improved microvascular responsiveness after PP at 24 h after CPB compared with NPP [559].

Finally, only 1 large observational study investigated the impact of PP on clinical outcomes. This single-centre cohort study compared about 2,500 patients undergoing PP or NPP during different periods (i.e. before and after the paradigm shift from NPP to PP CPB) and investigated the impact of the 2 different circulations on AKI, stroke, mortality and length of hospitalization [560]. After correction for confounders and secondary analyses considering the length of CPB and baseline renal function, no differences were found in any primary and secondary clinical outcomes between PP and NPP [560].

Finally, 2 studies reported beneficial effects of IABP-induced PP during CPB in terms of end-organ preservation, endothelial response and inflammation [561, 562]. However, 1 experimental study in pigs highlighted the risk of potential hypoperfusion of the body distal to the IABP catheter, recommending a continuous assessment of the perfusion pressure and CPB flow below the IABP [563]. Indeed, a recent literature review highlighted how different methods can provide pulsatility (roller or centrifugal pumps, IABP). The authors considered 44 articles, mostly RCTs with limited statistical power, and concluded that a marginal improvement in renal and pulmonary outcomes can be obtained by pulsatility generated with an IABP [547]. The same review concluded that it is safe to affirm that PP is non-inferior to NPP, but more research is required on the topic [547]. Despite more recent evidence, the historical dilemma between PP and NPP with inconclusive evidence remains.

Recommendation Table 42. **Recommendations for pulsatile versus non-pulsatile flow**

Recommendations	Class[a]	Level[b]	Ref[c]
Pulsatile perfusion should be considered to improve renal perfusion during CPB and reduce postoperative renal injury, especially in high-risk patients.	IIa		[547, 549, 553–556]
In patients on an IABP in a preoperative setting, it should be considered to maintain pulsation during the intraoperative period, provided that a mean arterial pressure below the IABP can be measured.	IIa		[561–563]

[a]Class of recommendation.
[b]Level of evidence.
[c]References.
CPB: cardiopulmonary bypass; IABP: intra-aortic balloon pump.

potential hazard of NPP on cerebral perfusion; however, the study did not investigate the effects of PP CPB on cerebrovascular CO2 reactivity [558].

Another clinical trial investigated the microcirculatory response to NPP and PP with roller pumps, by means of orthogonal polarization spectral imaging of the sublingual mucosal microcirculation. A shift in microcirculatory blood flow occurred over time with CPB regardless of perfusion mode; however, NPP showed 17% fewer normally perfused vessels compared with the PP group at 90 min of CPB, at the expense of an increase in hyperdynamically flowing vessels. At 1 h and 24 h post CPB, NPP continued to have substantially fewer normally perfused vessels in addition to an increase in slow continuous/

9.7 Goal-directed perfusion

Goal-directed therapy (GDT) relates to perioperative strategies to optimize DO_2 in the tissues, mostly by increasing CO with fluids, inotropes and vasopressors based on algorithms in order to prevent tissue hypoperfusion. Previous RCTs and metanalyses led to robust supportive advice towards GDT in cardiac surgery to reduce postoperative complications and length of stay [2, 564, 565]. GDP uses the same principle as GDT; however, it does so during CPB, with optimization of the pump-flow and DO_2 and the goal of maintaining the DO_2 on CPB above a critical value. Different minimally acceptable DO_2 values during CPB have been published, usually ranging between 250 and

300 ml/min/m^2 without reaching a universal consensus [203, 566, 567]. Despite promising clinical evidence on the role of GDP in perioperative kidney damage, only a few studies investigated the impact of GDP on organs other than the kidneys and on other clinical outcomes such as length of hospital stay or death.

Description of the evidence. In a PSM study, GDP effectively reduced the AKI rate [533]. In 2018, the first RCT confirmed the efficacy of GDP over conventional perfusion in reducing the rate of stage 1 AKI (RR 0.45, 95% CI 0.25–0.83) [568]. Since then, only 1 RCT on GDP has been published by Mukaida and colleagues [545], in which 300 patients were assigned to the DO_2 > 300 mL/min/m^2 strategy, compared to the conventional approach. The GDP titrated to a DO_2 > 300 mL/min/m^2 significantly reduced any stage of AKI (RR 0.48, 95% CI 0.30–0.77). These findings were confirmed for AKI stage 1 but not for AKI stage 2, likely due to the limited incidence of this complication (only 6 events). A recent meta-analysis [546] of the 2 RCTs together with a PSM study [533] showed that GDP reduces the risk of AKI (any stage), with an RR of 0.52 (95% CI 0.38–0.70), but this effect was

significant only for AKI stage 1 and not for more severe AKI. This last observation, however, was limited by a small number of events (4% in the 3 studies). Another systematic review con firmed that GDP effectively reduces stage 1 AKI [382].

An extensive nationwide Australasian analysis of >19 000 patients undergoing CPB with a GDP optimized on DO_2 showed that decreasing DO_2 was significantly associated with the odds of any AKI [569]. Furthermore, a minimum DO_2 was significantly associated with AKI risk and AKI injury or greater AKI classes, representing on average a 7% increase in the likelihood of AKI for every 10 ml/min/m^2 decrease in DO_2. In addition, an optimal DO_2 threshold of 270 ml/min/m^2 was described [569]. Another single-centre registry of >800 patients in North America investi gated STS database-recorded index procedures over 16 months, during which an electronic storage system collecting perfusion data in real time was implemented. The authors showed that continuously measured area-over-the-curve (AOC) calculations below the predefined threshold of a DO_2 <280 ml/min/m^2 trended towards a statistical association with the primary out come of the composite STS morbidity and mortality (i.e. mortal
ity, renal failure, >72 h ventilation, stroke, deep sternal infection, reoperation for bleeding), and the AOC DO_2 <280 ml/min/m^2 was statistically associated with prolonged ventilation >72 h and AKI <72 h [570]. Moreover, the primary end point of composite morbidity and mortality was met for AOC DO_2 <280 ml/min/m^2 in patients undergoing non-isolated CABG surgery and patients with preoperative eGFR <65 ml/min/m^2. Those with preoperative Hb <12.5 g/dl appeared especially vulnerable to STS mortality/morbidity when AOC DO_2 <280 ml/min/m^2 was met [570].

Another single-centre trial, designed to investigate the poten tial role on the renal outcome of the time spent below the threshold of optimal DO_2 values, found that AKI did not corre late with the absolute nadir DO_2 value, but with the AOC below the 300 ml/min/m^2 DO_2 value, i.e. the frequency of episodes and/or the duration of episodes below that threshold and with the cumulative time spent below that threshold (P < 0.001 for both) [571]. Interestingly, these correlations were not described for lower DO_2 values (i.e. 260 and 280 ml/min/m^2). Patients at higher risk were those with DO_2 <300 ml/min/m^2 for more than 15 mins and with CPB times >121 mins with an incidence of AKI of 50% [571].

Another clinical single-centre study focused on the importance of the cumulative time and degree of reduced DO_2, given that AUC–DO_2 is a matter of both the event's frequency and the degree of reduced DO_2 in a given time. The authors assessed whether the cumulative number of events below a DO_2 threshold of 300 ml/min/m^2 was of clinical significance in pre
dicting AKI or the maximal amplitude of a single event below that threshold (i.e. the largest AUC of an individual event com posing the final AUC–DO_2). Interestingly, it was not the total time and degree of reduced DO_2 (i.e. cumulative AUC–DO_2) but the most severe episode in time and degree of a reduced DO_2 (i. e. the maximal amplitude AUC–DO_2) that predicted AKI (OR 4.9, 95% CI 1.2–21.5), and the maximal amplitude AUC was a better predictor of AKI than the cumulative AUC (AUC 0.73, 95% CI 0.61–0.83 vs 0.69, 95% CI 0.57–0.80, AUC difference P ¼ 0.001) [572]. A recent single-centre study of more than 3900 patients showed that DO_2 during CPB was lower in those developing any AKI versus those who did not and lower in those developing AKI stage 2 or 3 versus those in stage 1 or none, identifying a critical DO_2 value of 231 ml/min/m^2 for any AKI and of 103 ml/min/m^2 for stage 2 or 3 [573].

Finally, 2 studies highlighted the importance of individualized GDP [567, 574]. One single-centre trial randomized patients to standard practice or GDP, which was individualized to achieve a less than 20% decline in the $rScO_2$ level from baseline, a less than 20% decline in the MAP from baseline, and avoidance of deep anaesthesia (with BIS levels of 45–60 before and after CPB and 40–45 during CPB). The authors did not find differences in postoperative morbidity and mortality in the overall population. Still, a secondary analysis performed in a subgroup of patients who achieved the prespecified individual targets showed signifi cantly lower morbidity than those who did not reach the targets (RR 3.41, 95% CI 2.19–5.31) [567].

A systematic review assessed whether reduced DO_2 during CPB may be a risk factor for the development of postoperative neurological complications, including cerebrovascular accidents, delirium and postoperative cognitive dysfunction [575]. Results from 10 studies, including 21 875 patients, demonstrated that reduced DO_2 during CPB was associated with postoperative delirium and cerebrovascular accidents.

Another single-centre retrospective study on 1064 patients undergoing CPB managed with GDP (set at DO_2>280 ml/min/m^2) demonstrated DO_2 to be an independent predictor of AKI (OR 0.99, 95% CI 0.00–0.99, P ¼ 0.020) in a way that for each 10 ml/ min/m^2 increase in DO_2, the odds of developing AKI decreased by 4% [574]. However, when DO_2 was plotted across 5 different ranges of preoperative pulse pressures as an indicator of arterial stiffness, the study found a weak correlation with the first 2 stages of pulse pressures (<40 mmHg and 40–60 mmHg, respectively), no correla tion with the category of PP 60 to 80 mmHg and a moderate cor
relation with the 2 highest PP categories, indicating high arterial stiffness (PP 80–100 mmHg: R^2 0.461, P <0.0001; PP >100 mmHg: R^2 0.430, P < 0.001); the variability in the predicted risk of AKI dependent on DO_2 for these 2 PP categories was 46% and 43%, respectively [574]. With regards to neurological complications, a recent review of the literature that included more than 21 000 adult patients, tried to correlate GDP to neurological complications. Eight studies reported reduced intraoperative DO_2 in patients who developed delirium and CVA, but the difference between the mean DO_2 levels for those with and without complications was only stat istically significant in 4 studies. However, the quality of evidence showing that GDP may play a role in minimizing the incidence of neurological events in adult cardiac surgery was low [575].

Recommendation Table 43. **Recommendations for goal-directed perfusion**

Recommendations	Class[a]	Level[b]	Ref[c]
GDP is recommended to reduce the postoperative rate of early stages of acute kidney injury.	I		[545, 546, 568]
It is recommended that GDP be aimed at limiting the nadir of DO_2 and the length of CPB time with low DO_2 values.	I		[570–572]
It may be considered that individualized DO_2 based on preoperative risk factors, peripheral oxygenation and pulse pressure, be identified preoperatively and maintained during CPB.	IIb		[570, 574]
It should be considered to maintain GDP with a lower threshold of DO_2 between 280 and 300 ml/min/m^2 during normothermic CPB in order to improve clinical outcomes.	IIa		[568–571]

[a]Class of recommendation.
[b]Level of evidence.
[c]References.
CPB: cardiopulmonary bypass; DO_2: oxygen delivery; GDPT: goal-directed perfusion therapy.

9.8 Assisted drainage

The use of VAVD was primarily developed in paediatric cardiac surgery but also for minimally invasive cardiac procedures. However, today, VAVD is often used in adult standard CPB as well. A dedicated vacuum controller is connected to the lid of the hardshell venous reservoir to enhance the venous return from the patient. Alternatively, negative pressure may be generated by using a centrifugal pump between the venous cannula and the reservoir [kinetic-assisted venous drainage (KAVD)] [576].

Description of the evidence. One main advantage of assisted venous drainage is the increased venous return compared to gravitational drainage only, allowing a smaller cannula to increase visibility in a narrow operative field, as in minimally invasive heart surgery [577]. In addition, a recent PSM study demonstrated a reduction in AKI and RRT (41% vs 30% and 2.5%

VAVD. In a survey from 2014 in North America on the use of VAVD, the risks identified consisted of pressurized venous reser voirs, the introduction of air through the membrane oxygenator and non-functional VAVD devices [580], emphasizing the need for initial safety checks and monitoring. The increased negative pressure on the venous reservoir by combining VAVD with grav ity drainage may also increase the risk of haemolysis [576]. A trial in adult cardiac patients comparing gravity drainage to different vacuum levels showed that haemolysis increased at −80 mmHg compared to −40 mmHg or gravity drainage [581]. However, another more recent study compared vacuum levels of −40 mmHg and −60 mmHg with gravity drainage in 60 patients. There was no significant increase in haemolysis in either group, suggesting that VAVD up to −60 mmHg can be applied safely and effectively [582]. GME formation is associated with increased negative pressure in VAVD [583]. Although VAVD seems to be safe under the circumstances with controlled negative pressures, clinical air embolism has been reported [576].

Recommendation Table 44. **Recommendations for assisted drainage**

Recommendations	Class[a]	Level[b]	Ref[c]
It is recommended that an approved venous reservoir be used for assisted venous drainage.	I		-
It is recommended that the negative pressures in the venous line be monitored when using assisted venous drainage.	I		-
Excessive negative pressures are not recommended due to the deleterious haemolytic effects.	III		[581]

[a]Class of recommendation.
[b]Level of evidence.
[c]References.

vs 0.5%, respectively), possibly due to less venous congestion with VAVD [578]. Moreover, the reservoir can be positioned closer to the patient, allowing for a marked reduction in priming volume with less haemodilution and the potential for fewer transfusions of PRBCs and other blood products [123, 579]. Therefore, VAVD may be considered to reduce haemodilution, transfusion load, and AKI [123, 578]. On the other hand, several risks and complications have been associated with the use of

9.9 Transfusion strategies during cardiopulmonary bypass

PRBCs and fresh frozen plasma (FFP) transfusions may be required during CPB, whereas, usually, no role exists for platelet or cryoprecipitate transfusions during CPB. PRBCs are typically transfused when the Hb values fall below a critical threshold for adequate DO_2. When considering PRBC transfusions in other

scenarios, this threshold is difficult to identify based on absolute values, and it should be individualized based on the measured DO_2 and on indices of oxygen extraction (SvO_2 and O_2ER). Low values of Hb during CPB have been associated with adverse out
comes in many studies [584–586], and this concept raised the hypothesis of a more liberal transfusion trigger during CPB; how ever, in the presence of a low Hb value, the DO_2 is preserved by increasing the pump flow [535].

Two recent studies identified RBC transfusions during CPB as an independent risk factor for AKI and mortality [108, 587]. Both studies identified DO_2 as an independent risk factor, thus sug gesting a restrictive strategy for PRBC transfusion on CPB.

FFP has been used during CPB as a source of AT for patients with poor heparin responsiveness. However, the use of AT con centrates is an effective way to treat this condition, avoiding the use of FFP.

Description of the evidence. Packed red blood cell transfusions. Few RCTs have compared different Hb or HCT trigger values for PRBC transfusions during CPB. In a small RCT [588], patients with an HCT during CPB between 21% and 25% were randomized for receiving or not receiving RBC transfusions. The results suggest that patients who did not receive transfusions had similar renal outcomes. An RCT of liberal versus restrictive transfusion proto
cols, inclusive of PRBC transfusions for an Hb <7.0 g/dL during CPB in the restrictive group and <9.5 g/dL in the liberal group, resulted in more substantial transfusions for the liberal group but in more adverse events in the restrictive group [589]. However, this study only included transfusion strategies after CPB. A restric
tive transfusion strategy (i.e. a transfusion if the haemoglobin con centration was <7.5 g per decilitre intraoperatively or postopera tively) versus liberal transfusion strategies (transfusion if the

haemoglobin concentration was <9.5 g per decilitre intraopera tively or postoperatively when the patient was in the ICU or was <8.5 g per decilitre when the patient was in the non-ICU ward) were assessed in a large multicentre RCT with 5243 adults. This study demonstrated that a restrictive perioperative transfusion strategy was non-inferior to a liberal strategy regarding postoper ative morbidity and mortality at 1 month and 6 months postoper atively [590, 591]. However, this study included intraoperative and postoperative transfusion strategies. A retrospective study showed that, during CPB, PRBC transfusions are effective if the SvO_2 is <68% and/or the O_2ER is >39% [592].

In an RCT [593], patients were randomly allocated to a mild haemodilution (HCT > 25%) or a moderate haemodilution (HCT

21%–25%) strategy on CPB. These targets were reached using PRBC transfusions and haemofiltration. Patients in the moderate haemodilution group received more PRBC transfusions on CPB but fewer after CPB and showed a worse neurological outcome. However, no data on DO_2 are reported, and the difference in outcome is not attributable to the amount of PRBC transfused.

Existing guidelines suggest transfusing PRBCs if the Hb is <6.0 g/ dL [594] and an acceptable HCT value between 21% and 24% if the DO_2 is maintained above 273 ml/min/m^2 [336]. Leucodepleted PRBC transfusions should be used whenever possible [595].

Fresh frozen plasma transfusions. FFP during CPB has the sole indication of supplementing AT in patients with poor respon siveness to heparin. However, RCTs demonstrated that AT con centrate is more effective than FFP in restoring heparin respon siveness and allows a reduction in FFP transfusions and volume overload, which is also summarized in existing guidelines [336, 594, 596–598]. Prophylactic use of FFP to decrease perioperative bleeding is ineffective and should be abandoned [599, 600].

Recommendation Table 45. **Recommendations for transfusion management during cardiopulmonary bypass**

Recommendations	**Class[a]**	**Level[b]**	**Ref[c]**
Packed red blood cell transfusions			
It is recommended that PRBCs be transfused during CPB if the HCT value is <18% (Hb 6.0 g/dL).	**I**		**-**
For HCT values between 18% and 24%, PRBCs may be considered based on an assessment of the adequacy of tissue oxygenation.[d]	**IIb**		**[592]**

PRBCs are not recommended to be transfused during CPB if the HCT is >24% and DO_2 and extraction are acceptable.	III		[108, 587]
Fresh frozen plasma transfusions			
It is recommended that antithrombin concentrate be used as the primary treatment of antithrombin deficiency to improve heparin sensitivity.	I		[596–598]
If antithrombin concentrate is unavailable, FFP should be considered to treat antithrombin deficiency to improve heparin sensitivity.	IIa		-
FFP should not be used prophylactically during CPB to reduce perioperative blood loss.	III		[599, 600]

[a]Class of recommendation.
[b]Level of evidence.
[c]References.
[d]The DO_2 is maintained at >273 mL/min/m^2 and cerebral oximetry is satisfied.
CPB: cardiopulmonary bypass; DO_2: oxygen delivery; FFP: fresh frozen plasma; Hb: haemoglobin; HCT: haematocrit; PRBC: packed red blood cells.

9.10 Blood purification

Haemoadsorption (HA) is a method of blood purification based on the adsorption principle of mass separation, utilizing a solid substance. A typical HA device consists of a single-use cartridge used during CPB. Blood is circulated continuously through the device and can theoretically facilitate the elimination of both pro- and anti-inflammatory substances. Circulation through the device is limited to a maximum of 24 h before the device must be replaced.

A notable increase in the number of RCTs and observational studies investigating the efficacy and safety of these devices in cardiac surgery has been seen. These investigations are designed to assess potential advantages in the CPB setting, similar to those previously reported in patients with sepsis in the ICU.

Description of the evidence. Current evidence does not permit definitive conclusions regarding the effects of HA on postopera tive outcomes during elective CPB procedures [601]. More trials with patient-relevant outcomes and appropriate sample sizes are required for this patient population. Inconsistent data exist for non-elective and emergency cardiac operations. A non blinded, multicentre RCT of 288 infective endocarditis (IE) pro cedures found no difference in clinically relevant outcomes such as ICU stay, ventilation time, vasopressor use or 30-day mortality [602], highlighting on the one hand, the safety of using HA in this patient population, however, with the absence of clinical benefit. In addition, there was no reduction in postoperative organ dysfunction (as measured by the Sequential Organ Failure Assessment score on day 9 after the operation). In contrast, a small RCT evaluated the safety of HA during an open thoracoab dominal aortic aneurysm operation and found that the number of patients with severe respiratory distress syndrome after CPB was substantially reduced when HA was used. In addition, a recent systematic review encompassing 15 studies (comprising 8 RCTs and 7 observational studies) evaluated the effect of HA fil ters on ICU length of stay and 30-day mortality [603]. For non elective and emergency operations, the meta-analysis revealed a significant decrease in ICU length of stay and 30-day mortality with HA, demonstrating that patients with a high inflammatory burden, such as those with IE, appear to be most susceptible to this effect.

The impact of haemoadsorption on anticoagulation-related drugs is beyond the scope of this guideline and is comprehen sively addressed in the upcoming guideline on patient blood management in cardiac surgery.

9.10.1 Haemoadsorption during routine cardiopulmo nary bypass. Effect of haemoadsorption on cytokine levels. A small RCT (n ¼ 40) reported an initial reduction in inflamma tory markers at the end of CPB. However, variations in IL-8 and TNF were minor and lasted only a short time [604]. These find ings were validated by another RCT [605], which compared the efficacy of HA versus a single dosage of glucocorticoids in lower ing inflammation in 60 patients. The RCT compared glucocorti coids, HA and routine care. They found that methylprednisolone efficiently reduces systemic inflammation following CPB. Compared to HA, there was a larger reduction in pro- and anti inflammatory mediators such as IL-6, IL-8 and TNF with methyl prednisolone. Interestingly, the HA group showed a rise in SIRS markers, specifically CD64 and CD163.

In contrast, 2 small RCTs (n ¼ 37 and n ¼ 30) reported on the efficacy of HA in lowering pro- and anti-inflammatory markers during CPB. Both studies reported no substantial reduc tion in inflammatory markers postoperatively when HA was used during CPB [606, 607], although Bernardi *et al.* [606] observed a significantly increased level of IL-10 in the HA group for the first 24 h after surgery.

Effect of haemoadsorption on circulating endothelial glycocalyx fragments. A recent RCT [608] examined the effect of HA on released soluble endothelial glycocalyx fragments. Heparan sul phate, hyaluronan and syndecan-1 were investigated because these fragments have been identified as possible damage

associated molecular patterns capable of enhancing inflamma tion. The researchers also examined the effect of HA on the atrial natriuretic peptide (ANP) because shedding of the endothelial glycocalix has been linked to elevated ANP levels during CPB. The results indicated that HA significantly lowered heparan sul phate levels after extended (>90 min) CPB but did not affect ANP, syndecan-1 or hyaluronan levels.

Effect of haemoadsorption on circulating microvesicles. During activation, proliferation and apoptosis, circulating microvesicles are secreted or shed from cellular membranes, making them a potential new inflammatory biomarker. Blood cell activation, adhesion and microvesicle release can occur when whole blood is pumped across absorbent polymers. The effect of HA on the function of circulating microvesicles and vesicle concentration was investigated in a subgroup analysis by Bernardi *et al.* [606]. They compared 8 patients with HA to 8 patients without HA undergoing elective heart surgery. In this limited patient cohort, adding an extra foreign surface by HA had no effect on microve sicle function or count. More research is needed to determine the impact of HA on vesicle numbers and function.

Effect of haemoadsorption on plasma-free haemoglobin. A multi centre RCT [609] investigated the ability of dual cartridge HA to reduce plasma-free Hb (pfHb). This reduction may be advanta geous because this measure is an independent predictor of end organ dysfunction and mortality. They found that duration of CPB and the type of operation were linked to higher levels of pfHB. Patients undergoing valve replacement surgery had the largest reduction in pfHB and activated complement levels when dual cartridge HA was used.

Clinical outcome measures. A systematic review and meta-analysis [603] of 15 studies (comprising 8 RCTs and 7 observational studies) examined clinical outcomes in patients who underwent HA treat ment. The outcomes assessed included ICU length of stay, haemo dynamic stability, hospital length of stay and biochemical markers. No significant beneficial effect could be demonstrated when HA was used during regular CPB. These findings align with those of a recent meta-analysis and systematic review [610] that examined the impact of HA usage on mortality in different clinical settings. The authors concluded that there was no evidence of a beneficial effect on mortality when HA was implemented in regular CPB (RR 0.90, 95% CI: 0.64–1.29). Similarly, another systematic review inves tigated the effectiveness of HA during routine CPB. The researchers found inconclusive evidence to support HA during CPB because no clinical advantage could be proven. This result was mostly due to underpowered studies with a significant likelihood of bias [601].

9.10.2 Haemoadsorption during cardiopulmonary bypass for infective endocarditis. Inflammatory markers. An RCT with 20 patients with IE examined the effect of prolonged intra- and postoperative HA (24 h postoperatively) on inflammatory markers [611]. Even though no significant differences in median cytokine levels were found, increased CRP and PCT levels were found in the HA group.

Development of sepsis. A retrospective study compared HA treat ment to conventional care in patients with native mitral valve IE [612]. The clinical effects of intraoperative HA on postoperative sepsis, sepsis-related death and 30-day mortality were studied in 59 patients. The data suggest that intraoperative HA for IE may minimize postoperative sepsis and sepsis-related deaths. A similar finding was seen in a PSM of 202 patients with IE [613]. This study included 135 patients with IE and an active left-side native valve and 67 patients with IE with a prosthetic valve and showed a signif icant reduction in postoperative sepsis and sepsis-related deaths.

Haemodynamic influence. The previously reported retrospective analysis [612] showed improved haemodynamic stability in the HA group, as defined by epinephrine consumption and vascular resist ance. An inverse-likelihood-of-treatment-weighting, retrospective investigation [614] comparing 241 patients with IE (41 HA vs 200 con trols) found no benefit in HA usage. They reported an increase in the need of the HA group for norepinephrine, milrinone, PRBC and plate lets. The RCT by Asch *et al.* [611] validated these findings. The HA group had significantly higher dosages of the vasopressor and signifi cantly higher volume replacement. A more recent RCT [615] com pared 10 patients with HE to 9 control patients and found no differ ence in vasopressor use between the groups. However, significant reductions in the length of ICU stay, time on ventilation and postoper ative transfused blood products were observed in the HA group.

Safety of use. Even though no other trial indicated substantial device-related adverse events, Santer *et al.* [614] compared the use of HA during regular cardiac surgery to regular cardiac sur gery without HA. They found a significantly increased number of reoperations when HA was used.

In summary, the available evidence concerning the efficacy of HA in elective heart surgery is deemed insufficient. Divergent outcomes in randomized controlled studies point to inconsis tencies, which could be attributed to small sample sizes, inad equate treatment durations and a lower inflammatory response during CPB compared to patients with sepsis. Although findings appear to be more promising for patients with IE, there is a pressing need for more extensive, well-designed multicentre studies with well-defined outcomes.

9.11 Anaesthesia and pharmacological management

CPB has a significant effect on the pharmacokinetics and pharmaco dynamics of anaesthetic drugs. This effect is due to haemodilution and the consequently reduced plasma protein concentrations, hypo thermia and drug sequestration during lung isolation [616]. Details regarding volatile and intravenous anaesthetic agents, analgesics, muscle relaxants and inotropes are discussed in this section.

9.11.1 Volatile anaesthetic agents. Haemodilution and hypo thermia counterbalance each other during most phases of CPB, with hypothermia increasing the blood/gas partition coefficient

and haemodilution decreasing it. During rewarming, however, the increase in temperature is faster than the increase in HCT, result ing in a lower blood/gas partition coefficient and thus in increased wash-in and a more rapid increase in depth of anaes thesia [617], which is subsequently reversed towards the end of CPB. These effects of temperature and HCT were assessed with prime volumes of 2 L or more and a drop in temperature to about 30°C. Therefore, they will be less pronounced with the CPB techniques used today, including much lower prime volumes and
milder degrees of systemic hypothermia or normothermia. The administration of volatile anaesthetic agents during CPB is feasible and safe. The administration of these agents has been described in detail elsewhere [618, 619].

Volatile anaesthetic agents cross the commonly used micro porous polypropylene hollow fibre membrane oxygenator, and the oxygenator exhaust volatile concentrations usually correlate with arterial blood concentrations [157, 620, 621], although this was disputed previously [616]. Depth of anaesthesia assessed by BIS monitors correlates with oxygenator exhaust concentrations during near-normothermic CPB but not during hypothermic CPB [157, 621]. Therefore, during CPB, the concentration of vola tile anaesthetics in the oxygenator exhaust line should be moni tored to confirm administration of volatile anaesthetic agents and also to quantify potentially reduced requirements of volatile anaesthetics during hypothermia [622].

Nitrous oxide is highly insoluble in blood and can therefore enlarge air bubbles [623]. Thus, its use immediately before and after CPB may result in potential AEs on neurological outcomes through the expansion of gaseous emboli. Apart from the reduc
tion of the MAP, heart rate, stroke volume (SV) and CO, the car diovascular effects of nitrous oxide before and after CPB include the induction of regional wall motion abnormalities and possibly diastolic dysfunction after CPB [624].

Volatile anaesthetic agents can mimic the activation of myocardial protective pathways, whereas propofol might be an inhibitor [625, 626]. A large international multicentre RCT in 36 centres that

Recommendation Table 46. **Recommendations for the use of haemoadsorption during cardiopulmonary bypass**

Recommendations	Class[a]	Level[b]	Ref[c]
The routine use of HA during CPB is not recommended.	**III**		**[603]**
For patients with infective endocarditis, the use of HA during CPB may be considered.	**IIb**		**[603, 612, 613]**

[a]Class of recommendation.
[b]Level of evidence.
[c]References.
CPB: cardiopulmonary bypass; HA: haemoadsorption.

included 5400 patients undergoing elective CABG surgery showed that the use of a volatile anaesthetic agent did not reduce the rate of all-cause death at 1 year compared to total intravenous anaes thesia (2.8% vs 3.0%; *P* ¼ 0.71) [627]. There were, however, high rates of coadministration of propofol during anaesthesia mainte nance in 59% of patients, and propofol has been shown to inhibit myocardial protective pathways [626, 627]. A post hoc analysis of this trial demonstrated a lower rate of MI with haemodynamic instability and a reduction in the 1-year cardiac mortality of patients receiving volatile anaesthetic agents [628]. A recent sys tematic review and meta-analysis of RCTs in patients undergoing cardiac surgery with CPB assessed 8197 patients from 42 studies and demonstrated that the 1-year mortality was significantly lower in patients receiving volatile anaesthetic agents compared with propofol (5.5 vs 6.8%; OR, 0.76, 95% CI 0.60–0.96). Furthermore, there was a significantly lower rate of MI (OR 0.60, 95% CI 0.39–0.92) and cardiac troponin release (SMD −0.39, 95% CI −0.59 to −0.18) but no difference in short-term mortality or postoperative AKI [629]. Another systematic review and meta analysis of 64 studies did not exclude off-pump cases, and it did not show a beneficial effect of volatile anaesthetic agents regard ing 1-year mortality [630]. The neutral results may be due to the inclusion of off-pump cases, where a myocardial protective mechanism by volatile anaesthetic agents may not be as promi nent when compared to on-pump cases and the associated ischaemia reperfusion injury. A future well-powered large RCT is necessary to further assess whether volatile anaesthetic agents have a potential myocardial protective effect in high-risk patients undergoing CABG surgery with CPB [631].

One recent large meta-analysis of all types of operations com pared propofol and volatile anaesthetic agents in 317 RCTs with 51 107 patients [632], including 50 RCTs (n ¼ 12.113) in cardiac surgical patients. The results demonstrated overall similar postoperative mor bidity and mortality in both groups and advantages in postoperative recovery with propofol anaesthesia. The cardiac surgical subgroup exhibited no differences in mortality and MI, but did have a benefi cial effect of volatile anaesthetic agents regarding myocardial injury. Another recent meta-analysis, including 252 RCTs and 30 757 patients, demonstrated overall decreased survival with propofol in critically ill patients, which was particularly prominent in cardiac sur gical patients (n ¼ 5518) with an RR (95% CI) of 1.46 (1.13–1.89) and *P* ¼ 0.004. If the comparator was a volatile anaesthetic agent, the RR (95% CI) was 1.25 (1.06–1.47) with *P* ¼ 0.009 [633].

In summary, with the results of 2 meta-analyses showing no outcome benefit from volatile anaesthetics and 2

meta-analyses indicating improved mortality with the usage of volatile anaes thetics, there is equipoise regarding mortality outcomes [634].

9.11.2 Intravenous anaesthetics. During CPB, the total concen tration of intravenous anaesthetic drugs is reduced due to haemodi lution. Furthermore, extracorporeal circuits (uncoated, heparin coated, PVC-coated and PPC-coated circuits) can absorb propofol and midazolam, thus reducing blood levels [635–641]. The total of plasma propofol will decrease by 50% to 78% in hypothermic CPB and by 59% to 70% in normothermic CPB [640, 642].

However, propofol is highly protein bound and, therefore, with haemodilution-induced lower blood concentrations of pro teins (such as albumin), the unbound and pharmacodynamically active free fraction increases, to maintain the concentration, off setting the effects of haemodilution [643–645]. Both total and unbound propofol concentrations return to pre-CPB levels within 20 min of CPB [640, 645].

Hypothermia increases the plasma propofol concentration, being 28% higher at 34°C compared with 37°C [646]. Hypothermia, decreased microcirculatory flow and organ perfu sion of CPB affect hepatic metabolism and renal clearance, result ing in prolonged elimination of the half-lives of anaesthetics and slight increases in propofol blood levels. Furthermore, there is increased susceptibility of the central nervous system to propofol with both hypothermic and normothermic bypass, with lower BIS values demonstrated for a similar plasma concentration in on pump surgery compared with off-pump procedures [641, 642, 647, 648]. The hypothermic effects are rapidly reversed during rewarming, and alteration of infusion should be considered [640]. Little evidence is available to guide the selection of a target controlled infusion model. A pilot study has suggested that the Schnider model for TCI underestimates the plasma concentration of propofol during hypothermic CPB [649]. For normothermic CPB, infusion at a rate of ≥5 mg/kg/h results in an on-pump plasma con centration equivalent to the Marsh model effect site concentration of 3 mcg/ml, whereas 4 mg/kg/h results in decrementing the plasma concentration [642]. Sufficient depth of anaesthesia, particularly given the limitations of the aforementioned models, should be ensured with the use of processed electroencephalogram monitoring. The use of dexmedetomidine, in conjunction with propofol or ketamine in RCTs on CPB, has been associated with surrogates of myocardial protection, compared with propofol alone [650, 651]. Its use is probably appropriate for surgery on CPB; however, most studies have examined its use throughout the perioperative period rather than relating it to specific use on CPB, thus limiting the recommendations that can be made. Likewise, remimazolam has been introduced as an intravenous anaesthetic in cardiac sur gery, but data with which to make recommendations are limited.

9.11.3 Intraoperative analgesia. During CPB, similar to pro pofol, haemodilution reduces the concentration of opioids, whereas the reduced concentration of serum proteins increases the active free fraction, thus offsetting this effect [652–654]. Furthermore, like intravenous anaesthetics, decreased microcir culatory flow, particularly during hypothermia, alters hepatic and renal perfusion, causing a small increase in serum levels. Extracorporeal circuits also absorb fentanyl, alfentanil and mor phine and thus reduce blood levels [637, 655, 656].

Fentanyl delivered by intermittent bolus on CPB is associated with a reduction in plasma concentrations of 30% to 60% of pre-CPB val ues, whereas maintenance infusions demonstrate a reduced decre ment in concentration (30%) [657, 658]. Fentanyl is sequestered in the CPB circuit by hydrophobic binding, with the concentration reducing within minutes [655]. Conversely, an increase can occur at the end of the bypass period, because during lung isolation, opioids such as fentanyl and sufentanil have been shown to sequester in the lungs, resulting in increased plasma levels during separation from CPB [652, 653]. Alfentanil shows a similar decrease in concentration on initiation of CPB of approximately 50%, with no difference between bolus and infusion delivery [657, 659].

Remifentanil, delivered by continuous infusion, is an alterna tive method of opioid delivery. When compared with an inter mittent fentanyl bolus, it has been shown to result in fewer epi sodes of hyperglycaemia and other surrogate markers of physiological stress after CPB [660, 661].

Based on the temperature-dependent Hofmann elimination of remifentanil, a remifentanil infusion can be reduced after initiation of CPB by about 30% for each 5°C drop in tempera ture. The dose reduction can start immediately after initiation of CPB if the patient is cooled to 27°C and after 20 min if cooled to 32°C because it takes about 20 to 30 min for the reduced temperature-induced reduction in metabolism by Hofmann elimination to offset the haemodilution-induced reduction in plasma levels [654]. The Minto model for remifen tanil TCI performs acceptably for use during normothermic CPB [662]. Although it has an acceptable precision during hypothermic CPB, there is decreasing precision at lower tem peratures, mandating an adjustment [663]. There is little current evidence on opioid-free techniques for cardiac surgery on CPB [664].

9.11.4 Non-depolarizing muscle relaxants. Historically, pancuronium was used as a neuromuscular blocker in cardiac anaesthesia due to its vagolytic actions, reducing the incidence of bradycardia during induction.

The 5th National Audit Project of the Royal College of Anaesthetists in the United Kingdom, which assessed accidental awareness during general anaesthesia (AAGA), confirmed a high risk of AAGA in cardiac anaesthesia. It also confirmed that AAGA is associated with the use of neuromuscular blocking agents, particularly in cardiac anaesthesia. This finding would support the use of short-acting neuromuscular blockers, in particular to reduce the possibility of awareness with residual blockade dur ing CPB and during weaning from mechanical ventilation [223]. In addition, fast-tracking patients and using enhanced recovery protocols after cardiac surgery would also support the use of short-acting neuromuscular blockade during induction only [665].

Patients undergoing hypothermic CPB are likely to have lowerrecommended [673]. The proto colized use of reversal neuromuscular blocking agent requirements, with altered distribuagents, with routine quantitative neuromuscu lar monitoring tion, decreased metabolism (due to altered metabolic function/perguiding an appropriate reversal strategy, should be fusion of the liver and kidney) and increased duration of actionconsidered, including the use of sugammadex, bearing in (including the effect of reduced acetylcholine mobilization), suggestmind AEs, such as anaphylaxis [674–676]. Non-cardiac ing that intermittent dosing is suitable [666–668]. Requirements aresurgery specific guidance should also be followed in this reduced to a lesser extent during rewarming [666, 669]. Patientsrespect [677, 678].

undergoing hypothermic CPB may be particularly susceptible to Atracurium and rocuronium were used in 90% of cases in residual neuromuscular blockade, given the impact of temperaturethe 6th National Audit Project of the Royal College of on neuromuscular function [670]. Further caution is required whenAnaesthetists in the United Kingdom, which reported the using certain muscles (e.g. adductor pollicis) for neuromuscular monincidence of life threatening allergic reactions during itoring due to the impact of hypothermia [666, 671]. The risk ofanaesthesia and surgery. The incidence of anaphylactic residual neuromuscular blockade following the infusion of cellreactions was 4.2/100 000 admin istrations of atracurium

[679]. The risk of an anaphylactic reac tion, if the risk of atracurium is equal to 1, is 1.42 for rocuronium and 0.78 for mivacurium. In a retrospective analysis of cardiac surgical cases at a single centre, muscle relaxants were involved in 3 out of 19 cases of anaphylaxis with identified causes, with 1 case each involving pancuronium, rocuronium and suxametho nium [680].

salvaged red blood cells after separation from CPB is low [672]. Avoidance of non-depolarizing neuromuscular blocking agents by the use of depolarizing agents is not

Recommendation Table 47. **Recommendations for volatile and intravenous anaesthetics, opioids and neuromuscular block ing agents**

Recommendations	Class[a]	Level[b]	Ref[c]
Oxygenator exhaust concentrations of volatile anaesthetic agents should be considered for monitoring during CPB.	IIa		[157, 621, 622]
It is recommended that approved equipment be used for delivering volatile anaesthetics during CPB.	I		[618, 619]
The administration of nitrous oxide immediately before and after CPB is not recommended.	III		[623, 624]
Volatile anaesthetic agents may be considered for the maintenance of anaesthesia during CPB.	IIb		[627–633]
During the maintenance phase of CPB, it should be considered to administer intravenous anaesthetics and opioids, except remifentanil, at a dose at least as high as prior to CPB.	IIa		[640, 642–646, 652–654]
Intravenous fentanyl administration by intermittent bolus or infusion may be considered.	IIb		[652, 653]
After the initiation of CPB and induction of hypothermia, reducing the dose of remifentanil after 20–30 min by 30% at 32°C, and immediately by 60% with moderate to deep hypothermia below 28°C, may be considered	IIb		[654]
The Minto model for remifentanil may be considered during CPB with normothermia or mild hypothermia, with the expectation that it may underestimate blood levels.	IIb		[662, 663]

Continued

Short-acting non-depolarizing neuromuscular blocking agents should be considered prior to CPB, particularly for fast-track/enhanced recovery protocols.	IIa		[665, 667]
The protocolized use of reversal agents during tracheal extubation should be considered, guided by quantitative neuromonitoring, particularly for fast-track/enhanced recovery protocols.	IIa		[674–676]

[a]Class of recommendation.
[b]Level of evidence.
[c]References.
CPB: cardiopulmonary bypass.

9.11.5 Vasodilators. Vasodilatation and cardiopulmonary bypass. Optimal patient management during CPB is closely related to the modulation of systemic vascular resistance and SVRI. The dilution of catecholamines and linear blood flow are the main causes of acute catecholamine release. SIRS is another important trigger of vasoactive substance release [681].

In general, we observe an increase in levels of angiotensin II, vasopressin, bradykinin, prostaglandin E2, tromboxane A2 and endothelin-1 with a concomitant reduction in the atrial natriu retic factor. This results in an increase in the SVRI [681].

Hypothermia, for example, is a massive stimulus for the release of adrenaline and noradrenaline. The concentration of circulating adrenaline may exceed the pre-CPB concentration by up to 10 times, whereas noradrenaline may increase up to fourfold [681].

The release of catecholamines is responsible for excessive vas oconstriction, which may lead to an irregular blood flow distri bution and trigger metabolic acidosis and reduced organ perfu sion. At the same time, during the cooling period, there is a
reduction in the production of NO [682].

Among the drugs routinely used to manage the systemic vas cular index, CCBs and nitrates play an essential role.

Calcium channel blockers and nitrates. CCBs inhibit calcium flow through the L-type voltage-dependent calcium channels of myocardial and vascular smooth muscle cells [683]. According to their chemical structure, CCBs can be divided among phenyl-alkylamines, benzothiazepines and dihydropyridines. Dihydropyridine CCBs, such as nicardipine, amlodipine and cle
vidipine, remain this group's most commonly used agents for control of ABP. Their primary physiological effect is on smooth vascular muscle, resulting in vasodilation with effects primarily on the arterial side, thereby limiting decreases in preload.

The mechanisms of action of GTN are linked via 2 main pathways:

• A mechanism-based biotransformation pathway that produ ces NO and contributes directly to vasodilation [684]. • A clearance-based biotransformation pathway that produces inorganic nitrite anions (NO_2); this second pathway has no apparent cardiovascular effect and is not converted to NO [684].

During the administration of GTN, the development of toler ance, which is closely related to GTN metabolism, is frequently observed; this effect is categorized as haemodynamic tolerance and vascular tolerance [684].

Only 1 RCT was conducted in 2020. It demonstrated that large doses of GTN administered during CPB improve erythrocyte deformability by activating aquaporin phosphorylation [685].

The use of vasodilators in the perioperative period and

during CPB is certainly part of the clinical management; improving myocardial performances [686]. Also, vasodilators may have a role in certain patients with LCOS and very high sys temic vascular resistances, inducing the relaxation of vascular smooth muscle cells and producing a drop in vascular resistance. It must be clear that the drugs used for the treatment of LCOS may also be used prophylactically to prevent LCOS after cardiac surgery in patients at increased risk (i.e. incomplete revasculari zation or prolonged how ever, it is necessary to resort to their use in only a few cases. Vasoconstrictors are used with much greater frequency. Therefore, no studies recommend the use of vasodilators. The lack of evidence does not allow us to provide clear clinical indi cations about the routine use of vasodilators during CPB.

9.11.6 Positive inotropes/vasopressors. Low cardiac output syndrome. Low cardiac output syndrome is arbitrarily defined as a cardiac index of 2.4 L · min^{-1} · m^{-2} with evidence of end organ dysfunction [686]. The occurrence of LCOS is clinically characterized by a decrease in systemic perfusion secondary to myocardial dysfunction, producing an imbalance between DO_2 and oxygen consumption at a cellular level, finally leading to metabolic acidosis and reduced organ perfusion [687]. Different markers of organ hypoperfusion are used, including, among others, arterial blood lactate levels, venous oxygen saturation and capillary refill time. The leading causes of LCOS after cardiac surgery are myocardial dysfunction, cardiac ischaemia during aortic cross-clamping despite cardioplegia, reperfusion injury, activation of inflammatory and coagulation cascades and unad
dressed pre-existing cardiac disease [686].

Perioperative treatment of pharmacological low cardiac output syndrome. Pharmacological LCOS treatment consists mainly of positive inotropes and/or vasoactive drugs, but the treatment is heterogeneous. The most commonly used drugs, alone or in com
bination, are dobutamine, dopamine, epinephrine, norepinephr ine (catecholamines), milrinone (phosphodiesterase III inhibitor), levosimendan (calcium sensitizer) and vasopressin [686].

Adrenergic vasoactive agents and positive inotropes are used to increase MAP and CO. They stimulate adrenergic receptors and enhance adrenergic post-receptor signalling pathways. The desired final effect is to prevent LCOS or to restore adequate tis
sue and organ perfusion.

Positive inotropes may be seen as the most rational approach in the context of LCOS because they directly increase myocardial contractility; however, they also increase myocardial oxygen consumption, thereby resulting in a risk of further myocardial ischaemic complications, especially in myocardial territories at risk due to imbalance between DO_2 and consumption. Conversely, they may help recruit stunned myocardium. Other vasoactive drugs may also be helpful in patients experiencing LCOS after cardiac surgery. In particular, vasopressors (ie norepi nephrine) increase the afterload by contraction of vascular smooth muscle cells, producing increased blood pressure. Although the increased afterload may cause greater myocardial work, it may improve coronary perfusion and DO_2, subsequently cross-clamp time).

Mild hypocalcaemia is not uncommon after CPB. Intravenous calcium is therefore used to improve myocardial contractility and vascular tone [688]. The administration of $CaCl_2$ in the amount of 5 to 15 mg/kg results in transient increases in ABP, systemic vas
cular resistance, cardiac index, stroke volume and coronary perfu sion pressure and might be helpful in cases of moderate contrac tility reduction or vasoplegia. However,

possible systemic side effects of calcium use, such as the ‘stone heart’ phenomenon, pan creatic cellular injury, temporary impairment of mammary artery graft flow and inhibition of inotropic effects of catecholamines in the postoperative period need to be considered.

Description of the evidence. The use of positive inotropes and vaso pressors in adult patients undergoing cardiac surgery is routine practice; however, the number of RCTs comparing the use of these drugs remains limited, and most evidence is related to the use of levosimendan. The use of positive inotropes and/or vasopressors can be divided into the prophylactic approach (prevention of LCOS and/or vasoplegic shock) or the therapeutic treatment of shock. Some studies have examined the role of inotropic or vasopres sor prophylactic administration in weaning from CPB to preserve and improve organ perfusion. For instance, a small single-centre RCT (n ¼ 49) demonstrated that the pre-emptive use of milri none reduced the need for additional positive inotropes [689]. Also, in off-pump bypass surgery, the pre-emptive use of milri none improved haemodynamic indices [690].

In a European multicentre randomized, open-label trial, milri none and dobutamine were found equally effective in improving general haemodynamic variables in patients experiencing LCOS after cardiac surgery conducted with CPB [691].

Levosimendan has undoubtedly been the most extensively studied drug in recent years for patients experiencing LCOS after cardiac surgery. Several single-centre experiences and non randomized evidence have suggested promising results of levosi mendan in treating LCOS. These results were also summarized in a meta-analysis in 2012, demonstrating that the levosimendan group had lower overall mortality rates (17.4% vs 23.3%) [692].

However, the evidence from 3 large, relatively recent RCTs has shown no beneficial effects on survival, although clearly this out come is influenced by several other factors. These RCTs [namely CHEETAH (Levosimendan to Reduce Mortality in High Risk Cardiac Surgery Patients), LICORN (Effect of Levosimendan on Low Cardiac Output Syndrome in Patients with Low Ejection Fraction undergoing Coronary Artery Bypass Grafting) and LEVO CTS (Levosimendan in Patients with Left Ventricular Dysfunction Undergoing Cardiac Surgery)] analysed the effect of levosimendan in patients with LCOS and/or depressed LVEFs in the periopera tive cardiac surgery period [693–695] and showed that levosimen dan did not affect mortality. In particular, the CHEETAH trial showed no difference in 30-day mortality [693]. The LEVO-CTS study reported the same result, with no difference in 30-day mor tality or other secondary end points [695]. In the CHEETAH study, levosimendan was administered in the postoperative period, whereas in the LEVO-CTS, it was administered preoperatively in patients with an LVEF of 35% or less. The LICORN study random ized 333 patients with LVEFs ≤ 40% and scheduled for isolated or combined CABG to receive levosimendan or placebo after anaes thetic induction. Also, this study found no difference in primary outcome, a composite end point reflecting LCOS within 48 h after drug initiation or the need for RRT at any time postoperatively [694]. Moreover, in 1 study, the centres did not have experience with levosimendan, which may represent a significant limitation because the drug is certainly less easy to manage compared to other positive inotropes.

Subsequently, 2 meta-analyses with slightly different inclusion criteria showed the beneficial effects of levosimendan in patients with severely reduced LVEFs [696, 697]. In patients undergoing

CABG surgery, Levin *et al.* demonstrated in an RCT a significant improvement in 30-day survival with levosimendan, started 24 h before surgery, compared to placebo in patients with preopera tively poor LVEFs (3.8% vs 12.4% mortality) [698]. Similarly, in patients undergoing CABG surgery, a meta-analysis showed lower mortality rates in the levosimendan group (4.9% vs 11.4%) [699]. In a recent pooled analysis of 2 RCTs with 1084 patients (809 under going isolated CABG and 275 undergoing combined surgery), the researchers found no significant difference in mortality at day 90 between the levosimendan and placebo groups [700]. However, a decrease in mortality at day 90 was observed in the isolated CABG subgroup. Another recent meta-analysis assessing preoperative lev osimendan in patients with severe dysfunction of the LV under going isolated CABG surgery included 1225 patients from 6 RCTs [701]. The results revealed that preoperative treatment with levosi mendan was associated with reduced all-cause mortality, low car diac output syndrome, acute kidney injury, postoperative AFIB and the need for circulatory support without compromising safety. In a recent prospective observational study conducted in a study population of patients with poor LVEFs undergoing car diac surgery (n ¼ 60), Khaled *et al.* found that levosimendan improved haemodynamic parameters significantly; however, no effect on mortality was noted in the levosimendan group com pared with conventional inotropic agents [702].

Overall, the pooled results support the idea that the administra tion of levosimendan in cardiac surgery is associated with reduced mortality, particularly after CABG surgery, lower incidence of LCOS and restored adequate organ perfusion as reflected by the lower incidence of AKI and the decreased need for RRT.

Adverse events. Vasopressors and positive inotropes have a curvilin ear dose–response relationship. Most therapeutic effects occur at low doses, whereas side effects and toxicity occur at higher doses. Despite the proven positive haemodynamic effects, positive ino tropes are not free from side effects. The most frequently described side effects are tachycardia, ventricular and supraventricular arrhythmias and an increase in myocardial oxygen consumption [703, 704]. Some differences exist among these drugs. For instance, among vasopressors, AVP vasopressin does not influence pulmo nary vascular resistances as adrenergic vasopressors do [705]. Similarly, among positive inotropes, adrenergic drugs (epinephrine, dobutamine) worsen the diastolic function, whereas milrinone and levosimendan may have more favourable effects in this regard. In summary, in patients with perioperative LCOS, positive ino tropes and/or vasopressor support is likely necessary to maintain tissue perfusion. In addition to preventive measures and other supporting strategies, vasoactive therapy should be instituted promptly to maintain organ perfusion, preserve organ function and reduce tissue damage.

 Recommendation Table 48.

Recommendations for the treatment of perioperative pharmacological low cardiac output syndrome

Recommendations	Class[a]	Level[b]	Ref[c]
Positive inotropes and/or vasopressors are recommended as first-line medical treatment in patients with LCOS during cardiac surgery.	I		[689–691]
Perioperative administration of levosimendan may be considered to improve survival following cardiac surgery in patients with poor LV function and perioperative LCOS.	IIb		[692, 696, 697]
Perioperative administration of levosimendan should be considered to reduce the risk of LCOS in patients with reduced LVEFs undergoing isolated CABG.	IIa		[698–702]

[a]Class of recommendation.

[b]Level of evidence.

[c]References.

CABG: coronary artery bypass grafting; LCOS: low cardiac output syndrome; LV: left ventricle; LVEF: left ventricular ejection fraction.

9.12 Shed mediastinal blood management

Traditionally, SMB—also known as cardiotomy suction blood, pleural and pericardial blood or wound blood—was aspirated back into the heart-lung machine via cardiotomy suckers. Over time, however, it was discovered that shed blood is highly activated and might be asso
ciated with thrombin generation, the activation of coagulation, fibri nolytic and inflammatory pathways that could contribute to higher transfusion requirements [336]. Moreover, reinfusion of SMB is associ ated with neurological injury, cognitive decline and lung injury, which are partly attributed to increased levels of haemolysis and fat in the scavenged blood [706–708]. Collecting shed blood apart from the sys temic blood that flows through the heart-lung machine makes it pos sible to handle this blood separately, e.g. with a cell saver, before returning it to the patient [709]. In this way, the pathological activation caused by SMB may be reduced.

Description of the evidence. It remains crucial that, during the operation, blood loss should be kept to a minimum. Preferably, lost blood should be aspirated away as soon as possible. The longer the blood stays in the chest cavity, outside the blood
stream, the more activated it becomes [707, 710].

During CPB, intraoperative autotransfusion, either with blood directly from the cardiotomy suction or processed using centrifuga tion to concentrate red cells, may be considered part of a blood conservation programme [594]. Clinical studies comparing the retransfusion of unprocessed versus discarded or processed SMB report conflicting results regarding bleeding and transfusion requirements and neurological injury. It has been shown that proc essed or discarded shed blood is associated with decreased expres sion of markers for thrombin generation, platelet activation, inflam mation, neuronal injury and reduced blood loss [706, 711–714].

However, contradictory findings showed more postoperative bleeding and transfusion requirements and no clinical evidence of any neurological benefit when SMB was discarded or processed before a transfusion [710, 715, 716]. Fat particles may partially be removed from shed blood with a dedicated filter membrane in the venous reservoir [141].

In vitro laboratory assays for haemolysis, coagulation, inflamma tion and neurological injury in retransfusing SMB show that this blood may be contaminated. The extent to which this contamination has consequences for the clinical outcome is difficult to estimate. Based on current knowledge, it is justified to avoid the retransfusion of unprocessed SMB as much as possible. If reinfusion is necessary, it is preferable to first process the SMB with a blood cell processor and then filter it [336, 594, 706]. SMB can be collected separately in a suitable cardiotomy reservoir (dual chamber), a blood transfusion bag or a CS reservoir. The best way to deal with SMB depends on the volume of SMB and on the patient's characteristics (e.g. BSA, pre
operative HCT, Hb, platelet count). For example, smaller volumes of shed blood may be discarded, and medium volumes may be proc essed before returning it [711, 712]. With larger quantities, in most cases, the choice must be made to return SMB to the patient because large volumes of cell-salvaged red blood cells may lead to an excessive loss of plasma and may result in impaired coagulation [336, 716]. Furthermore, recent studies have raised concerns that CS is associated with higher infection rates, although this direct effect is almost entirely eliminated by its indirect protective effect through reduced allogeneic blood transfusion [717].

Research results in the area of SMB management are difficult to interpret. On the one hand, the results often come from smaller, single-centre RCTs; on the other hand, the diversity in the quality of the studies is tremendous. Furthermore, it is unfor
tunate that no relevant review article has been published so far.

Recommendation Table 49. **Recommendations for shed mediastinal blood management**

Recommendations	Clas	Leve	Ref[c]

	s[a]	l[b]	
Discarding shed mediastinal blood should be considered.	IIa		[711–713]
Processing and secondary filtration of red blood cells, for example by use of red blood cell salvage, should be considered to decrease the deleterious effects of reinfused shed blood.	IIa		[712, 713]

[a]Class of recommendation.
[b]Level of evidence.
[c]References.

9.13 Emergency (re)institution of cardiopulmonary bypass

Perfusionists regularly work in urgent/emergency situations. They should always be prepared to institute and reinstitute CPB in life-saving settings, whether for an urgent or emergency pro cedure or for reinstitution on CPB after weaning. Perfusionists can be best trained periodically for these emergencies through protocols and/or team simulation sessions.

Description of the evidence. No scientific evidence is available regarding the reinstitution of CPB in emergency situations, but common sense must prevail. For emergency procedures, it is always prudent to have a sterile set-up ready, primed or dry. For reinstitution on CPB after weaning, it is advisable to keep the ECC operable, with sterile tubing on the operating table, until the patient's sternum has been closed. In case of urgent institu
tion or reinstitution of CPB, it is vital to make sure that the patient is adequately anticoagulated such that sufficient heparin has been administered at the earliest point after the decision to reopen is made. National guidelines mention a few recommen
dations for emergency procedures [35]. Every hospital must con sider how recommendations on dry or wet storage of CPB cir cuits can best be implemented regarding sterility and local regulations. After reviewing the available literature and the documents of national societies, the task force is in consensus that a 72-h storage time for primed circuits and a 30-day storage time for dry circuits should be considered as an institutional pol icy. A recent German guideline on ECC for cardiac and circula tory failure also suggests extracorporeal life support (ECLS) for cardiocirculatory failure after cardiac surgery [718].

10.1 Perfusion strategies for arch surgery

Description of the evidence. Open aortic arch replacement requires a period of circulatory arrest. Additional perfusion strat egies can be adopted to provide organ protection. Outcomes are primarily influenced by temperature management and tech niques used for cerebral protection. The introduction of ACP has improved patient outcomes [719–722]. A meta-analysis on aortic arch surgery using ACP, comprising 2632 patients, found that ACP with warmer circulatory arrest temperatures (mean 26.5°C) may reduce the incidence of permanent neurological deficit (OR 1.65, 95% CI 1.06–2.55), postoperative dialysis, ventilator time and ICU length of stay compared to DHCA [719].

ACP can be established in different ways depending on the arterial cannulation site or via balloon occludable perfusion cath eters inserted in the epiaortic vessels after opening the aortic arch [723–726]. Unilateral or bilateral cerebral hemisphere perfusion can be established during aortic arch repair. Unilateral antegrade cerebral perfusion (uACP) can be obtained by cannulating the axillary artery, the innominate artery or one of the common caro tid arteries. An upgrade to bilateral antegrade cerebral perfusion (bACP) can be established with the insertion of an additional bal loon occludable perfusion catheter to the contralateral carotid artery. This is usually combined with an occlusive balloon on the left subclavian artery to avoid the steal phenomenon [727].

Bilateral antegrade cerebral perfusion might be advantageous for patients with an incomplete circle of Willis [728]. A meta analysis of 3548 patients comparing the 2 strategies found that bACP allows for 86 min up to more than 164 min of ACP with a low risk of cerebral damage, compared to 30 to 50 min for uACP [729]. For DHCA above 40 min, bACP may provide superior qual ity of life compared with unilateral perfusion (average 36-Item

Recommendation Table 50. **Recommendations for the emergency institution of cardiopulmonary bypass**

Recommendations	Class[a]	Level[b]	Ref[c]
It is recommended that a set-up CPB circuit be available at all times for emergency procedures.	I		-
After the patient is weaned from CPB, it is recommended that the CPB circuit be kept functional until the patient's chest has been closed.	I		-

It is recommended that ECLS be available at all times.	I		–

[a]Class of recommendation.
[b]Level of evidence.
[c]References.
CPB: cardiopulmonary bypass; ECLS: extracorporeal life support.

10. CARDIOPULMONARY BYPASS FOR SPECIFIC TECHNIQUES

Aortic surgery and specifically aortic arch surgery entail consid erable challenges in the safe conduct of CPB. This is especially true in cases in which DHCA is used. Details of perfusion techni ques for arch surgery, including DHCA and its effect on acid– base homeostasis and associated methods of brain protection, are discussed in the following sections.

There are alternative ways to reach cerebral protection. Retrograde cerebral perfusion (RCP) is achived by reversing the flow in the arterial and venous lines of the CPB circuit to directly perfuse with oxygenated blood the superior vena cava cannula after induc
tion of circulatory arrest [733]. The potential benefit of this technique is the possibility of flushing out embolic debris from the arch arteries. However, the major drawback is the uneven distribution of retro grade flow in the brain, which is mainly due to lower flow, based on pressure limitations, when infusing in the vein. Both Ehrlich and Midulla demonstrated that only 3% to 5% of the oxygenated perfu sate from the superior vena cava reappears as a backflow through
the arch arteries, leading to poor brain perfusion [734, 735]. Several meta-analyses showed no significant differences between ACP and RCP regarding mortality and major neurological postoperative complications (ACP 18.5% vs RCP 11.1%; *P* ¼ 0.28), whereas a trend towards a reduction in the incidence of transient neurological dysfunction existed in ACP (OR 0.85, 95% CI 0.69–1.04) [736, 737].

Furthermore, compared to isolated DHCA, both ACP and RCP were associated with lower postoperative stroke and operative mortality rates: ACP (OR 0.62, 95% CI 0.51–0.75; and OR 0.63, 95% CI 0.51–0.76, respectively) and RCP (OR 0.66, 95% CI 0.54–0.82; and OR 0.57, 95% CI 0.45–0.71, respectively) [738–740]. The challenges of comparing different methods of cerebral protec
tion are confirmed in a recent meta-analysis [741]. Nevertheless, the trend in the most recent aorta guidelines is to recommend selective ACP methods in complex arch procedures [742].

A meta-analysis of more than 7000 patients indicated that DHCA þ ACP has an advantage over DHCA þ RCP in terms of transient neurological dysfunction (95% CI 0.58–0.90, whereas the 2 methods show similar results in terms of permanent neu
rological dysfunction (PND) (pooled RR 0.99, 95% CI 0.75-1.33), early mortality (RR 1.18, 95% CI 0.96–1.46) and stroke (pooled RR 1.39, 95% CI 0.75–2.57) [743].

10.1.1 Perfusion parameters and cannulation strategies. In ACP, the cerebral flow rate should be maintained between 10 and 15 ml/kg/min and adjusted to a Short Form Survey results, 95.1 ± 44.4 vs 87.6 ± 31.3; *P* ¼ 0.070) [730]. However, a recent meta-analysis of retrospective studies including 5100 patients found similar rates of mortality (8.6% vs 9.2% for uACP and bACP, respectively; *P* ¼ 0.78), permanent neurological dysfunction (6.1% vs 6.5%; *P* ¼ 0.80) and transient neurological dysfunction (7.1% vs 8.8%; *P* ¼ 0.46) between bACP and uACP [731]. Assessment of patency and morphology of the circle of Willis with cerebral CTA or RM prior to total aortic arch replacement is advocated by some authorities [732].

right radial arterial pressure of 40 to 80 mmHg. In the case of RCP, the flow must be set to maintain an internal jugular vein pressure of 20 mmHg and range from 100 to 500 ml/min measured by a separate cannula above the valves in that vein [744–748].

Several arterial cannulation sites permit the institution of ACP: the axillary artery, the innominate artery and the left common carotid artery cannulation. Right axillary artery cannulation provides blood flow to the brain and avoids the manipulation of the epiaortic ves
sels, lowering the risk of embolization into right-sided cerebral ves sels as well as facilitating cerebral perfusion. Innominate artery can nulation emerged as an alternative option for arterial cannulation. This artery can be accessed through the sternal incision and appears to be non-inferior to the axillary artery regarding neurological com plications [749]. The carotid artery can be a fast option, especially in case of emergency or in case other cannulation sites are already in use. Furthermore, the common carotid artery is usually larger and less fragile compared to the axillary artery.

In Europe, the right subclavian–axillary approach is the preferred site for arterial cannulation during open arch procedures (54% and 48% for acute and chronic settings, respectively) [750]. This practice is supported in the international registry for aortic dissections where the increasing use of axillary artery was observed (1996–2003: 18.0%; 2004–2010: 33.2%; and 2011–2016: 55.7%; *P* for trend < 0.001) [751]. This trend is supported by a PSM analysis demonstrating decreased
PND (4% axillary plus graft vs 6.7% direct cannulation; *P* ¼ 0.09; *P* ¼ 0.05 among propensity matched pairs) and in-hospital deaths (7% axillary plus graft vs 11% direct cannulation; *P* ¼ 0.06; *P* ¼ 0.020 among PSM) with axillary versus direct aortic cannulation [752]. Similar findings were observed when comparing axillary versus peripheral cannulation in terms of in-hospital deaths (RR 0.59, 95% CI 0.48–0.70) and incidence of permanent neurological deficit (RR 0.71, 95% CI 0.55–0.90) [749].

10.2 Deep hypothermic circulatory arrest

The current practices for aortic arch surgery with regard to neu

roprotection strategies include DHCA and moderate hypother mic circulatory arrest (MHCA) with selective cerebral perfusion. Hypothermia is the safest strategy for organ protection. Several cerebroprotective strategies could be used during aortic arch surgery. These include hypothermia alone or combined with different selec tive cerebral perfusion techniques. Expert consensus in aortic arch surgery distinguishes 4 hypothermic categories (Table 3):

Some evidence suggests that the safe duration of circulatory arrest during isolated deep hypothermia should not exceed 30 to 40 min to prevent neurological injuries [756, 757]. The cerebral metabolic rate decreases by 6–7% per degree Celsius reduction in temperature [758]. Whereas cerebral oxygen consumption decreases by 50% to 60% of baseline value at a core temperature of 25–28°C. Additional cooling does not provide the same decrease in brain oxygen con sumption [759, 760]. Systemic cooling should always be started after CPB has been established, and the temperature gradient between the heat exchanger and the arterial inflow must not exceed 10°C. Temperature measurement from the nasopharyngeal cavity corre lates well with brain temperature [761]. In contrast to hypothermia, even mild hyperthermia can be dangerous in terms of organ protec tion. Increased cerebral temperature can exacerbate ischaemic injury of the brain [762, 763].

Rewarming must start after the surgery on the arch is com pleted and before the CPB is ended. Rewarming too swiftly or an inadvertent hyperthermia can lead to failure of cerebral pro tection. Furthermore, cerebral embolisms are more frequent during warming periods, especially at the moment or just after the removal of the aortic cross-clamp [764–766]. Numerous reports attest to the safety of less deep, moderate hypothermia coupled with selective ACP. Pacini *et al.* reported that moderate hypothermia is a safe tool for cerebral protection in terms of mortality and neurological dysfunction. The 30-day mortality rate was 12.7% in the high-moderate hypothermia group (>25°C) and 13.8% in the low-moderate group (<25°C) without a significant difference (*P* ¼ 0.86). No significant difference in permanent neurological deficits was found between the 2 groups (3.1% moderate hypothermia group vs 1.7% deep hypo thermia group; *P* ¼ 0.72). The same was true for temporary neurological dysfunction (7.9% moderate hypothermia group vs 8.6% deep hypothermia group; *P* ¼ 0.83) [767].

Table 3: Categories of hypothermia [core (rectal/bladder) temperature] [753–755]

Deep hypothermia	14.1–20 °C
Low-moderate hypothermia	20.1–24 °C
High-moderate hypothermia	24.1–28 °C
Mild hypothermia	28.1–34 °C

A retrospective study [768] compared MHCA with DHCA for patients undergoing type A acute aortic dissection with uACP via right axillary artery cannulation. No significant differences were observed in mortality (14.6% for DHCA patients vs 9.2% for MHCA patients, *P* ¼ 0.17), stroke (DHCA 8.5% vs MHCA 8.3%, *P* ¼ 0.87) or temporary neurological dysfunction (DHCA 7.3% vs MHCA 4.9%, *P* ¼ 0.37), suggesting the superiority of moderate hypothermia because colder temperatures are associated with an increased incidence of stroke and visceral dysfunction. In addi tion, DHCA is associated with coagulopathy, systemic inflamma
tory response and end-organ dysfunction [769, 770]. A meta-analysis including 18 comparative studies and 1215 patients looked at temperature selection in ACP [719]. Mean hypo thermic circulatory arrest temperatures were 20.3°C and 26.5°C in the cold and warm groups. The study found significantly increased mortality in the cold group (OR 1.39, 95% CI 1.04–1.86). They found no significant difference in PND, although a trend towards worse outcomes for cold temperatures was seen (OR 1.45, 95% CI 0.98–2.13). A subgroup analysis of 5 studies that included only emergency cases found significantly worse mortality and PND for the cold cohort within unilateral ACP studies [719].

The analysis of the arch international registry revealed that MHCA with ACP for total arch replacement compared with DHCA alone, is a safe and effective neuroprotective strategy. No signifi cant differences in neurological outcomes (DHCA 8.0% vs MHCA 7.8%; *P* ¼ 0.74) or in-hospital mortality (DHCA 13.7% vs MHCA 11.6%; *P* ¼ 0.33) for the 2 temperature groups were found [771].

A recent systematic review including 14 observational studies with 4142 patients showed that when the hypothermic circula tory arrest time was <30 min, the incidence of renal failure in the MHCA group was significantly lower than that in the DHCA group, without any difference between the groups for HCA >30 min (OR 0.76, 95% CI 0.51–1.13) [772]. In a meta-analysis, includ ing 24 studies and 12370 patients, DHCA was associated with a significantly higher postoperative incidence of stroke compared to MHCA (OR 1.46, 95% CI 1.19–1.78) and mild HCA (OR: 1.50, 95% CI [1.14–1.98]). Furthermore, DHCA (≤ 20°C) and MHCA (20.1–25°C) were associated with higher operative mortality compared with mild HCA (≥25.1°C) (OR 1.71, 95% CI 1.23–2.39, and OR 1.50, 95% CI 1.12–2.00, respectively) [773].

In a recent meta-analysis focusing on neuroprotection, includ ing 15 studies with DHCA versus MHCAþACP, significantly reduced mortality (pooled OR 0.64, 95% CI 0.49–0.83) and stroke rate (pooled OR 0.62, 95% CI 0.49–0.79) were found in the MHCAþACP group [774]. A European survey involving 144 cardi othoracic centres showed that DHCA was limited to only 6% of
cases in acute presentation and only 2% in elective status [750]. In North America, deep hypothermia is the predominant strategy and is used in nearly 60% of arch cases. However, higher volume centres appear to have moved towards moderate degrees of hypo thermia, potentially indicating a preference for this strategy [775]. To guarantee optimal DO_2 during arch surgery, Hb values should be maintained above 7.5 g/dl with an HCT exceeding 22%. However, DO_2 is not fundamental during hypothermia due to the reduction in organs metabolism [776, 777].

10.2.1 Neuromonitoring. Neurophysiological intraoperative monitoring is often used during aortic arch surgery to provide a real-time assessment of cerebral status. This approach impacts direct intraoperative decisions on perfusion management and neuroprotective adjustment strategies during these operations [778]. Several modalities have been adopted over the years to track the adequacy of HCA and cerebral perfusion. Cerebral oxi
metry by NIRS, BIS and a continuous output of dual-channel EEG data are the most frequently used modalities. Cerebral oxi metry monitoring using NIRS estimates rScO2, taking advantage of the different absorptive properties of saturated and unsatu rated Hb in the near-infrared spectrum. A reduction of the satu rations measured by NIRS intraoperatively can be linked to post operative neurological injury [779]. Cerebral oximetry, as well as an EEG or BIS, may reveal inadequate contralateral cerebral per fusion in cases of unilateral cerebral perfusion (i.e. patients lack ing an intact circle of Willis) [780].

Transcranial Doppler (TCD) can be used to identify the pres ence of cerebral artery flow during ACP in aortic arch surgery. It can help detect cerebral microemboli and

assess individual lim its of cerebral autoregulation and hence achieve adequate cere bral haemodynamic management during cerebral perfusion [212, 781, 782]. A retrospective study of patients operated on for type A aortic dissection reported similar incidences of mortality between patients monitored with TCD compared with the con trol group (28.6% vs 14%; *P* ¼ 0.21). This outcome was also true for the incidence of new stroke (0% vs 7%; *P* ¼ 0.16). Temporary neurological dysfunction occurred less often in the TCD group (14.8% vs 51.8%; *P* < 0.01) [747].

Recommendation Table 51. **Recommendations for perfusion strategies during aortic arch surgery**

Recommendations	Class[a]	Level[b]	Ref[c]
In patients undergoing aortic surgery with aortic arch involvement, the preference for antegrade arterial inflow cannulation compared to retrograde inflow cannulation should be considered.	IIa		[749, 751, 752]
Nasopharyngeal and core temperature (rectal/bladder) measurements are recommended in patients undergoing aortic arch surgery in HCA.	I		–
Circulatory arrest under moderate hypothermia (20.1–28°C) in combination with antegrade cerebral perfusion for aortic arch reconstruction should be considered.	IIa		[719, 720, 783]
Antegrade systemic perfusion using axillary cannulation should be considered.	IIa		[749, 751, 752]
Antegrade cerebral perfusion should be considered in complex aortic arch procedures.	IIa		[728–730, 741]
Neuromonitoring with bilateral near infrared spectroscopy is recommended in aortic arch surgery/during DHCA.	I		[212, 779, 780, 782]

Continued

Transcranial Doppler ultrasound may be considered in aortic arch surgery for individualized man agement of cerebral perfusion and to detect embolization in aortic arch surgery/during DHCA.	IIb		[212, 781, 782]

[a]Class of recommendation.
[b]Level of evidence.
[c]References.
DHCA: deep hypothermic circulatory arrest; HCA: hypothermic circulatory arrest.

10.3 Acid–base homeostasis (alpha, pH stat) and electrolytes

Metabolic acidosis resulting from tissue hypoxia or electrolyte imbalance may contribute to tissue damage and organ failure in patients undergoing cardiac surgery with CPB. Excessive use of normal saline or unbalanced colloid solutions can potentially lead to electrolyte disturbances and associated metabolic acido
sis due to high plasma chloride levels (>154 mmol/L). The standard approach to acid–base management during CPB with hypothermia in the adult population generally utilizes an alpha stat strategy (uncorrected temperature measurements).

Description of the evidence. The results of a retrospective analysis showed that the presence of moderate perioperative acidosis (pH 7.35) and hyperlactatemia (> 4.0 mMol/L) was associated with a larger 12-h chest drainage volume compared to cases with undis
turbed metabolic state (mean blood loss: 576 vs 406 ml; *P* ¼ 0.001). However, no other outcomes related to these factors were identified [466]. In the subgroup analysis of the TRACS (Transfusion Requirements After Cardiac Surgery) study [784], the presence of arterial blood lactate levels above 3 mMol/L 6 h after surgery was found to be associated with an increased likelihood
of major complications (OR 3.28; 95% CI 1.61–6.69). Three RCTs conducted in the 1990s provided evidence for the use of alpha-stat acid-base management in cardiac surgery in adults with moderate to mild hypothermia. These studies con cluded that alpha-stat acid-base management is associated with better postoperative neurological and neuropsychological out comes compared with the pH-stat method, which uses temperature-corrected blood gas measurements [785–787].

10.3.1 Calcium. Hypocalcaemia may occur during CPB as a result of haemodilution and especially after transfusion of citrated blood products (e.g. fresh frozen plasma). Due to the important physiological role of calcium, especially in cardiac surgery, rele
vant parameters such as bleeding, arrhythmia and

hypotension should be treated immediately if hypocalcaemia occurs.

10.3.2 Potassium and sodium. Elevated potassium levels are frequently observed in patients undergoing CPB resulting from the administration of cardioplegia. If the potassium concentra tion exceeds the threshold of 6.5–7 mmol/L, it is advisable to consider treatment options such as MUF, calcium administration or insulin therapy.

Z-BUF has been proposed as a potential means of alleviating the burden of inflammation. In this procedure, a replacement fluid is infused, followed by the removal of an appropriate volume of fluid by ultrafiltration, which in turn affects electrolyte balance.

10.3.3 Glucose-Insulin-Potassium. A recent meta-analysis examined the role of glucose-insulin-potassium infusion in car diac surgery as an adjunctive therapy to prevent MI and AFib and to improve postoperative outcomes. The analysis included 18 RCTs with 2131 patients undergoing cardiac surgery with CPB [788]. The study showed a reduction in the prevalence of post operative MI, AFib, length of ICU stays and inotropic drug requirements compared to standard care. A large RCT of 930 patients comparing perioperative treatment with glucose insulin-potassium with placebo showed similarly favourable results [789] with a lower rate of serious adverse events during the hospital stay.

10.3.4 Magnesium. The role of intravenous magnesium in the prevention of postoperative arrhythmias after cardiac surgery has been investigated in several small RCTs. Twenty RCTs with 3696 patients were included in a meta-analysis. The results indi cate that magnesium may reduce the incidence of supraventric ular arrhythmias compared with placebo. However, this effect was lost when only higher-quality studies were considered [790]. Magnesium did not affect any other postoperative outcome var iable, such as death, major morbidity or length of stay. A more recent RCT of 389 patients undergoing cardiac surgery demon strated that intraoperative magnesium did not reduce the post operative incidence of AFib [791]. Other RCTs confirmed a posi tive effect on postoperative arrhythmias in a combination therapy of magnesium and amiodarone [792] or magnesium alone in patients with ventricular hypertrophy [793].

Moreover, intravenous magnesium improves postoperative short-term neurological function following cardiac surgery for coronary heart disease [794]. However, these findings were not confirmed in a more recent RCT of similar size [795].

Recommendation Table 52. **Recommendations for acid–base homeostasis and electrolytes**

Recommendations	**Class[a]**	**Level[b]**	**Ref[c]**
Alpha-stat acid-base management should be considered in adult cardiac surgery patients with high-moderate hypothermia due to improved neurological and neurocognitive outcomes.	**IIa**		**[786, 787]**
Magnesium sulphate may be considered perioperatively for prophylaxis of postoperative arrhyth mias and improved cardiac protection/tissue oxygenation.	**IIb**		**[790, 792, 793]**
Magnesium sulphate may be considered perioperatively for improved postoperative neurocogni tive dysfunction.	**IIb**		**[794, 795]**
A perioperative glucose-insulin-potassium regimen may be considered in the prevention of low cardiac output syndrome.	**IIb**		**[788, 789]**

Continued

[a]Class of recommendation.
[b]Level of evidence.
[c]References.

10.4 Pharmacological methods for brain protection during deep hypothermic circulatory arrest

Sodium thiopental, which is an intravenous anaesthetic, may reduce cerebral activity via inhibitory GABA A receptors. It may reduce the cerebral metabolic rate, cerebral oxygen consumption and intracranial pressure. It produces an isoelectric EEG, is fast
acting and is easily titratable. However, it may also prolong seda tion and increase the need for positive inotropes. Regarding the benefit of using sodium thiopental to protect the brain during aortic arch surgery and DHCA, data from retrospective and pro spective cohort studies showed that using sodium thiopental along with DHCA was safe and effective in providing cerebral pro tection. The main limitation of these studies was that there was no comparative control group [796–801]. Common side effects with the administration of sodium thiopental are prolonged seda tion and an increased need for positive inotropes.

Data from an RCT [802] that included 89 patients undergoing valve surgery who were randomized to sodium thiopental or placebo showed the beneficial effects of sodium thiopental in the prevention of neuropsychiatric complications after cardiac surgery. However, a similar study on 300 patients who had CABG procedures [803] could not replicate these findings.

The use of steroids may inhibit lipid peroxidation of neuronal, glial and vascular membranes caused by oxygen free radicals. Its use may protect the brain from swelling and decrease a systemic inflammatory response.
infection, duration of postoperative mechanical ventilation and

lengths of stays in the ICU and the hospital.

In 2015, data from the SIRS trial, a large multicentre RCT [407] comprising 7507 patients undergoing cardiac surgery, showed no difference in primary clinical outcome [30-day mortality and a composite of death and major morbidity (i.e. myocardial injury, stroke, renal failure or respiratory failure) within 30 days] with the use of methylprednisolone compared to placebo.

However, neither the DECS nor the SIRS trial included patients on DHCA undergoing aortic arch surgery.

The use of mannitol may reduce oedema by acting via osmotic diuresis. It also scavenges free radicals. However, the exact mechanism of neuroprotection is unclear. It may mitigate the risk of cerebral oedema, and its use may reduce intracranial pressure and brain water volume.

Data from an observational cohort [804] from the German Registry for Acute Aortic Dissection Type A, comprising 2100 patients, showed a trend towards a reduction in 30-day mortality associated with the use of mannitol; however, this trend was not statistically significant. Furthermore, the use of steroids was associated with a reduction in new postoperative mortality-corrected permanent neurological dysfunction (PNDmc) (10.6% vs 7.1%, adjusted OR 0.50, 95% CI 0.24–0.96). No PNDmc reduction was observed for mannitol or barbiturates. The researchers were unable to demonstrate a significant protective effect of any neuroprotective drug on 30-day mortality or on PNDmc rates during prolonged (≥30 min) cerebral ischaemia.

Recommendation Table 53. **Recommendation for brain protection during deep hypothermic circulatory arrest**

Recommendations	Class[a]	Level[b]	Ref[c]
Sodium thiopental may be considered to protect the brain during aortic arch surgery and DHCA.	IIb		[796–798, 800–802]
Steroids may be considered to protect the brain during aortic arch surgery and DHCA.	IIb		–

[a]Class of recommendation.
[b]Level of evidence.
[c]References.
DHCA: deep hypothermic circulatory arrest.

In 2012, data from the DECS trial [408], a multicentre RCT of 4494 patients undergoing cardiac surgery, showed no difference with the use of dexamethasone 1 mg/kg versus placebo in the primary outcome, which was a composite of death, MI, stroke, AKI and respiratory failure, within 30 days of randomization. Dexamethasone was associated with reductions in postoperative

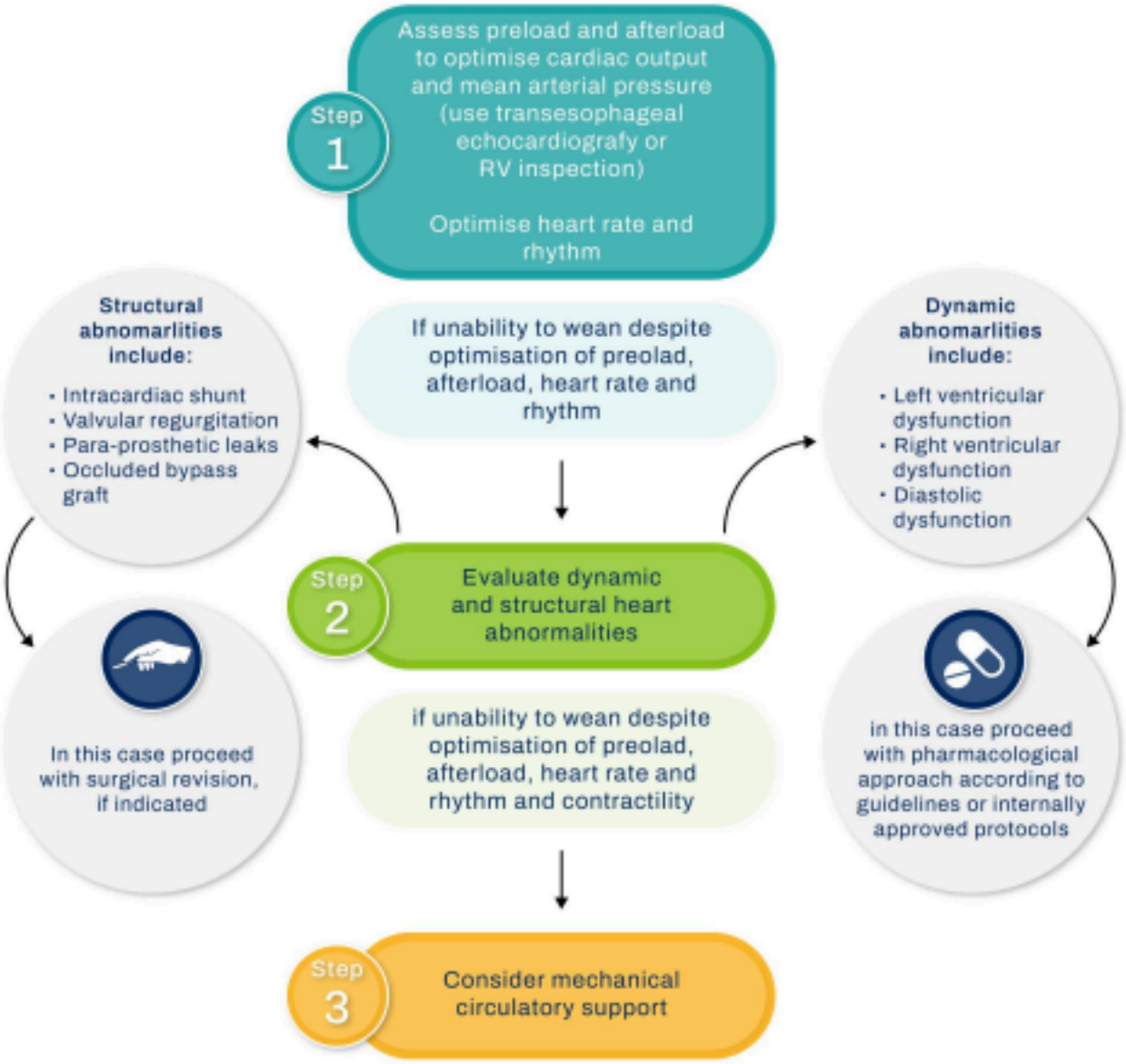
11. SEPARATION FROM CARDIOPULMONARY BYPASS

Weaning from CPB, particularly in compromised haemodynamic situations, may be challenging. The literature on this topic is scarce. Details on available knowledge are outlined in the following sections.

11.1 Weaning checklist

Weaning from CPB is a multidisciplinary effort in which commu nication among all team members is crucial. Especially in chal lenging cases, weaning from CPB might be difficult and requires a standardized approach under TOE guidance [805]. The use of a checklist can structure this process and optimize safety. Weaning scenarios, together with a checklist, can be trained and validated through interactive training sessions and simulations.

Description of the evidence. It is difficult to prove that a cognitive aid, such as a checklist before weaning, might improve patient outcomes. In general, recent research suggests that using a checklist reduces errors of omission and enhances patient safety. No specific study has been performed concerning the use of a weaning checklist by perfusionists. Recently, an electronic device



that warns the personnel in case the ventilator has not been turned on before the patient comes off the bypass was pre sented [806]. Also, research in anaesthesia may be extrapolated. One study compared simulation-based weaning scenarios for anaesthesiologists performed with and without a checklist [423]. The use of a checklist resulted in significantly better performance in completing 5 of the 9 designated tasks. Several authors have proposed checklists, developed using different methods, and have obtained divergent results. It is noteworthy to mention the 4-item checklist [807] and the 7-item checklist [808]. These checklists were suggested in combination with team education and simulation-based learning to help develop crucial skills. Others proposed several structural measures before weaning the

patient from CPB and pointed out that a failed weaning attempt might invoke haemodynamic instability, causing organ injury or dysfunction [809]. A structured approach was used by different

Figure 2: **Proposed algorithm for managing challenging weaning scenarios from cardiopulmonary bypass**. RV: right ventricle.

physicians [421, 810]. The items on the checklist were generated using a Delphi method. The checklists were created by 7 centre specific anaesthesiologists [423] or 90 nationwide anaesthesiolo gists [810]. Simulation-based training was compared to interac tive seminar-based training. The authors concluded that high fidelity simulation-based training improves performance and checklist adherence during CPB weaning [811].

We propose a weaning checklist for cardiac surgery derived from these different checklists (Supplementary Appendix [6]). The checklist may be adjusted to the needs of individual units. A checklist is recommended before the actual weaning process so that teams can restore focus, and no critical steps are omitted.

by a range of factors, including myocardial dysfunction; surgical/per fusion or reperfusion factors; volume and fluid shifts; inflammatory response of variable magnitude; vasodilation; and electrolyte and acid–base imbalances. Additionally, bleeding and coagulation issues pose significant challenges. Heart surgery and CPB can lead to increased bleeding tendencies, and balancing the need to minimize bleeding by ensuring adequate circulation during weaning can be a delicate task.

Cardiac surgery teams closely monitor the patient's vital signs, blood gases and other physiological parameters to address the challenges of weaning from CPB. They may use volume adjust ments and vasoactive medications, along with intraoperative

Recommendation Table 54. **Recommendation for a weaning checklist**

Recommendation	Clas	Leve	Re

	s[a]	l[b]	f[c]
The use of a checklist before the CPB weaning process is recommended to enhance team performance and augment patient safety.	I		-

[a]Class of recommendation.
[b]Level of evidence.
[c]References.
CPB: cardiopulmonary bypass

11.2 Difficult weaning

Separation from CPB after cardiac surgery is a progressive transition from full mechanical circulatory and respiratory support to spontane ous mechanical activity of the lungs and heart. A difficult separation from CPB can be defined in cases where significant, i.e. increasing doses of vasoactive or inotropic support will be necessary, when the first weaning attempt fails or when the patient requires a mechanical device to be separated from CPB [805]. If not adequately treated, a complex separation from CPB often leads to poor outcomes [812]. Denault *et al.*, in a multicentre study, observed that particularly decreased LVEFs; regurgitation of the mitral, aortic or tricuspid valve; urgent or emergency surgery; and extended CPB duration are inde
pendent predictors of complex CPB separation [813]. In addition, Bernard *et al.* identified female sex, diastolic dysfunction and total CPB time as predictive of difficult weaning after surgery [814].

Weaning from the CPB machine requires a multidisciplinary approach. An observational study found a strong correlation between technical errors and teamwork problems caused by lack of information and poor communication in cardiac teams during the weaning phase [815]. The majority of problems with weaning from CPB are related to haemodynamic instability, which can be caused implantation of temporary mechanical circulatory support like an IABP, microaxial flow pumps, ECMO and other ECLS devices, to assist the heart during this critical phase as a bridge to recovery, as has been outlined in the recent 2020 EACTS/ELSO/STS/ American Association for Thoracic Surgery (AATS) expert consen
sus document on post-cardiotomy ECLS in adult patients [816]. Unfortunately, no clear evidence exists to guide the manage ment of difficult weaning from CPB. There is significant variability in using 'multiple positive inotropes' as an indication for postcar diotomy ECLS [816, 817]. However, the decision to institute ECLS is typically based on weighing the risks and benefits of high-dose positive inotropes and LCOS against the potential complications and challenges associated with ECLS [812, 817, 818]. In cases of difficult CPB weaning, we suggest a systematic approach that includes optimizing preload and evaluating dynamic and structural heart abnormalities. TOE plays a crucial role in this process, providing valuable insights for diagnostic and therapeutic decision making (Fig. 2) [805]. Forcing weaning from CPB using high-dose inotropic drugs and vasoconstrictors is not recom mended due to the potential risks involved. Instead, early implanta tion of temporary mechanical circulatory support is recommended in selected cases to improve survival outcomes [812, 816–818].

Recommendation Table 55. **Recommendations for difficult weaning**

Recommendations	Class[a]	Level[b]	Ref[c]
A multidisciplinary approach is recommended in difficult weaning.	I		[815]
Forcing weaning from CPB using high-dose inotropic drugs and vasoconstrictors is not recommended.	III		[817]
Short-term mechanical circulatory support should be considered in difficult weaning scenarios.	IIa		[812, 817, 818]

[a]Class of recommendation.
[b]Level of evidence.
[c]References.
CPB: cardiopulmonary bypass.

11.3 Management of haemostasis

Patient blood management in adult cardiac surgery is thor oughly discussed in the EACTS, EACTAIC and EBCP joint guide lines. Considering the extensive nature of this subject and the constraints of our word limit, we direct readers to these compre hensive guidelines for detailed information [3].

11.4 Temporary mechanical circulatory support

The EACTS, STS and AATS are currently developing dedicated guidelines for the selection and management of patients requir ing temporary mechanical circulatory support

in cardiac surgery. Due to the complexity of this topic and the constraints of our word limit, we refer readers to the 2020 EACTS/ELSO/STS/AATS Expert Consensus Document on Post-Cardiotomy ECLS in adult patients [816] in the expectation of the upcoming joint tempo rary mechanical circulatory support guidelines.

11.5 Residual blood management

A blood conservation strategy includes retransfusion of the remaining residual blood volume (RBV) of the CPB circuit. Both direct retransfusion without processing and postprocessing via red blood CS and ultrafiltration are options for achieving this goal. The most important difference between the 2 techniques is the recovery of red blood cells only (and the discarding of plasma constituents) during red blood CS and the elimination of water-soluble components only during ultrafiltration.

11.5.1 Unprocessed retransfusion. Transferring the RBV into an infusion bag and giving it back to the patient enables direct retransfusion without processing. The impact on the inflammatory response following the retransfusion of unprocessed residual volume was studied in 40 patients [819]. Even though no significant differen
ces in the incidence of postoperative infection were found, ventila tion time and overall stay in the ICU were significantly lower after ultrafiltration [820]. Ringer's acetate solution can be used to chase RBV into the circulation through the arterial cannula. Retransfusion of RBV using Ringer's chase approach was compared to the widely used 'infusion bag'technique in an RCT [821]. This study found that the Ringer's chase approach contributed to preserved platelet func tion, decreased haemolysis and improved haemostasis without sig nificant differences in perioperative blood loss.

11.5.2 Unprocessed retransfusion versus red blood cell salvage. In a pilot study comparing unprocessed RBV with cell salvaged RBV, blood volumes in the chest drains were similar 4 h after surgery. Still, the red blood cell group had lower platelet levels,
a longer clot formation time and less maximum clot firmness [822]. Red blood CS of the CPB circuit residual volume improved postop erative Hb levels but generated high thrombin production, fibrinoly sis activation and poorer fibrinolysis inhibition, which could lead to consumption coagulopathy [823]. Both an RCT and a large retro spective study [824] confirmed that cell saver use of residual blood reduces postoperative blood transfusions, because unnecessary dis carding is prevented. Moreover, the RCT showed a significant decrease in both blood loss and the number of postoperative PRBC transfusions when unprocessed blood transfusions were compared to processed CS blood transfusions. Both groups showed impaired haemostasis and no significant differences in measured coagulation parameters and complement activation [825].

11.5.3 Unprocessed retransfusion versus ultrafiltration. In an RCT involving 200 patients, ultrafiltration of residual pump blood was compared to retransfusion of unprocessed blood. This study demonstrated no effect of ultrafiltration on the transfusion of homologous blood, postoperative haemorrhage or discharge Hb level [826]. In contrast, a prospective RCT showed a lower early morbidity rate and lower blood transfusion needs in the ultrafiltration group [827]. These findings were supported by 2 smaller RCTs comparing ultrafiltration to no ultrafiltration at the end of CPB. Ultrafiltration was linked to an increased inflamma tory response, decreased chest tube drainage, fewer blood trans
fusions and increased post-transfusion Hb levels [315, 820].

11.5.4 Unprocessed retransfusion, red blood cell salvage and ultrafiltration. The clinical outcomes of direct retransfusion, CS and ultrafiltration were compared in a prospective RCT [828]. There were no notable differences in postoperative Hb levels, pla
telet counts, ACTs, aPTT or postoperative chest tube drainage amounts. A smaller trial of 51 patients comparing centrifugation to red blood CS and ultrafiltration found red blood CS to be superior in terms of postoperative Hb gain and free Hb washout [829]. The inclusion of a retransfusion group might have influenced these results, but it was not included due to ethical concerns.

11.5.5 Wash quality of residual blood. An interesting in vitro study examined the difference in wash quality when RBV was processed with CS using either regular saline or a balanced bicarbonate buffered solution [830]. The balanced solution results in superior osmolality and electrolyte profile of the proc
essed volume. More research is necessary to see how the differ ence in wash quality of residual blood might affect outcome. The optimum technique for dealing with the residual volume of the CPB circuit is challenging due to contradicting data. However, whether processed or not, there is agreement that retransfusion of the CPB circuit's residual volume at the end of the operation is part of a blood-saving strategy.

Recommendation Table 56. **Recommendations for residual blood management**

Recommendations	**Class[a]**	**Level[b]**	**Ref[c]**
Retransfusion of the residual volume of the CPB circuit at the end of the procedure is recommended as a part of a blood management programme to minimize allogeneic blood transfusions.	**I**		**-**
Retransfusion of the processed residual volume of the CPB circuit at the end of the procedure should be considered to minimize the risks of allogeneic blood transfusions.	**IIa**		**[823, 827, 829]**

[a]Class of recommendation.
[b]Level of evidence.
[c]References.
CPB: cardiopulmonary bypass.

12. SPECIFIC SITUATIONS DURING CARDIOPULMONARY BYPASS

Cardiopulmonary bypass is a complex procedure associated with a potential risk of AEs. Despite efforts to reduce risks or harm to patients, for example, using safety equipment and safety measures, AEs may still occur [14]. The reported incidence varies from 1 per 138 perfusions in the United States [44] to 1 per 198 in France [45] and 1 per 15 in the Netherlands [46], respectively. The variation in reported incidents suggests that the definition of an AE is not uniform, making reliable reporting difficult. An organization that strives for an error-free team may produce the opposite effect if fear of consequences or blame makes staff less likely to report incidents or errors [831].

According to the surveys mentioned above [44–46], the most frequently reported AEs were inability to achieve an adequate ACT, allergic reactions, dissection of the aorta at the cannulation site, heat-exchange problems and clot formation in the extracor poreal circuit. In addition, AEs have been reported with oxygen ator failure [422, 832–834], obstruction of the cardiotomy filter [835] and electrical failure [836]. The incidence of more serious AEs resulting in injuries or death ranges from 1:2500 [837] to 1:1453 procedures [44] and 1:1236 [46], respectively. The causes of these incidents are multifactorial and include both human factor and equipment-related problems such as disconnections of tubing [838], pump failure and high-pressure excursions (HPE), which were reported as 1.14% in a survey by Myers *et al.* [839] and 1.8% in a study by Hj€arpe *et al.* [834]. In the study by Hj€arpe, 37 patients out of 2024 developed HPE. Large BSA, high HCT level during CPB, previous stroke and emergency surgery were found to be independently associated with HPE. An algorithm against HPE events that includes the administration of heparin, AT, epoprostenol and the institution of haemodilution is proposed to lower the oxygenator inlet pressure and thus avoid oxygenator replacement due to HPE. Not only does HPE cause AEs during CPB, but leaks in the oxy genator or at the interface with the heat exchanger, gas blender or vaporizer can also cause problems. Monitoring gases from the oxygenator gas outlet can help detect an oxygenator failure as early as possible [832].

The hardware set-up differs among institutions and could be improved to optimize patient safety. In a 2009 report, observa tions and interviews revealed inadequate or non-functional positioning of controls, an inability to distinguish one alarm from another and many problems with displays [36].

Iatrogenic aortic dissection (iAD) is an AE with an incidence of 0.06–0.6, depending on cannulation location and most often at the site of the arterial inflow cannula or at the site of the aortic cross-clamp. If iAD is discovered early, mortality is estimated to be 30%, but if iAD remains undetected, mortality will be even higher. Echocardiography is an important tool for the diagnosis of cases of iAD [840].

Air embolism is a rare but feared incident during CPB and can originate from the CPB circuit, the surgical field or vascular access. VAVD carries a particular risk due to the excess pressure in the venous reservoir. To minimize this risk, monitoring the venous reservoir inlet pressure and negative inlet pressure can be benefi cial [841]. A massive air embolism can cause cardiovascular col lapse, and TOE can be used to verify the diagnosis. Treatment of an air embolism depends on the situation and the amount of air entered in the vasculature. Reports of successful management include pharmacological treatment, optimizing tissue oxygena tion, hypothermia and RCP [842]. Hyperbaric oxygen therapy might be considered an option but is often not available [843]. The outcome of a rare event in a stressful situation depends on how quickly the incident is discovered, what equipment is available and how well the team is prepared for an unexpected situation. Critical situation checklists have improved the time to decision and the likelihood of making the right decision [30]. Team training improves AE management during CPB [844]. Also, the ability to use simulations during training has also been shown to promote safe perfusion practice [845, 846].

Other causes of AEs include the human factor with long work ing hours, fatigue [847, 848] and lack of communication and routines. In addition, the perfusionist is exposed to stress during the CPB procedure, peaking at the beginning and at the end of the perfusion period [849].

In an Australian study, 10% of 908 cases of potentially pre ventable deaths were associated with communication issues, including misreporting of the patient's condition or failure to indicate the worsening health condition of the patient [47]. A Dutch study examined verbal communication using video recordings and interviews with the team members involved and identified a number of items essential for safe communication during the CABG procedure, which also led to an understanding of areas for improvement [850]. Thus, communication is an area that needs to be addressed to improve patient safety.

Recommendation Table 57. **Recommendations for dealing with adverse events during cardiopulmonary bypass**

Recommendations	Class[a]	Level[b]	Ref[c]
Checklists, standard operating procedures, simulation training and multidisciplinary evaluations for handling adverse events are recommended.	I		**[30, 844–846]**

It is recommended that reporting systems for adverse events be established, following clinical and national regulations.	I		-

[a]Class of recommendation.
[b]Level of evidence.
[c]References.

13. GAPS IN KNOWLEDGE

Since the publication of the last European CPB guidelines in 2019, several important publications have increased our knowl edge and impacted recommendations for the conduct of CPB.

However, there are still significant gaps in the evidence. First, many sections have insufficient quality of evidence to provide clear recommendations. Moreover, we must acknowl edge the difficulties researchers face in conducting relevant randomized clinical trials in clinical medicine, especially regard ing the conduction of CPB.

Additionally, there has been an improvement in heart-lung machine hardware and a rapid increase in heart-lung machine monitoring equipment and software implementation. Notably, several new developments in this field include the use of artifi
cial intelligence. Therefore, research is needed to evaluate the value of these advances in the conduction of CPB.

Furthermore, although several studies have been published on optimized perfusion circuits and MiECC, including a recently published multicentre randomized trial, the possible advantages or disadvantages of optimizing/minimizing CPB are not suffi ciently clarified.

Many different ideas and strategies have been suggested and investigated regarding myocardial protection. Nevertheless, the evidence is not sufficient to decide whether blood cardioplegia, crystalloid solutions or new concepts such as the del Nido cardi
oplegic solution should be preferred in specific situations and for certain patients.

In addition, aortic arch surgery is another topic in perfusion with clear gaps in the evidence and inherent difficulties for researchers. Consequently, more evidence is required to guide clinicians in choosing optimal strategies for cannulation and per
fusion, including neuromonitoring, monitoring individual cere bral autoregulation thresholds and perfusion temperature.

Finally, difficult weaning is also an important topic in clinical per fusion. However, almost no clear evidence is available in this area.

14. KEY MESSAGES

Cardiopulmonary in cardiac surgery exemplifies a fusion of com prehensive, multidisciplinary knowledge and skills, necessitating collaboration among clinical perfusionists, surgeons, anaesthe tists, intensivists, and patients. This updated guideline, collabora tively developed by EACTS, EACTAIC, and EBCP, integrates new evidence that has emerged since the previous publication to provide updated, evidence-based recommendations when pos sible and incorporates a broader range of topics CPB-related impacting patient outcomes.

Although significant advances have been made, many knowl edge gaps remain unresolved. Bridging these gaps requires a unified effort from all stakeholders involved in cardiac surgery utilizing CPB. This concerted approach will ensure that future revisions of the guidelines become even more comprehensive and practical, leading to universal acceptance and broader clini cal improvements.

These European guidelines are intended to standardize and optimize CPB techniques and perioperative management. The next steps involve disseminating and implementing these rec ommendations into national guidelines and/or clinical practice, along with evaluating their impact through dedicated quality assurance and improvement programs. Such efforts aim to enhance the safety and efficacy of CPB procedures, ultimately improving outcomes in cardiac surgery. Further standardization can only be achieved through multidisciplinary collaboration among cardiac surgeons, anaesthesiologists, and perfusionists. Specialized training programs in accredited schools should sup
port this ongoing improvement.

SUPPLEMENTARY DATA

Supplementary data are available online.

DATA AVAILABILITY STATEMENT

No new data were generated or analysed in support of this research.

CONFLICT OF INTEREST

Adrian Bauer reports a leadership role for LivaNova related to cus tomer meetings for new products. Friedhelm Beyersdorf reports receiving consulting fees from Franz Ko€hler Chemie, Germany, (< 10,000 EUR) and honoraria from AtriCure. Friedhelm Beyersdorf also reports leadership roles in EACTS and DGTHG. Filip De Somer reports receiving a grant and consulting fees from LivaNova, both paid to University Ghent. Filip De Somer also reports a leadership position in EBCP (unpaid). Gudrun Kunst reports receiving honora ria from Edwards for contributions to two discussion workshops in 2024 and 2022, and from BioMerieux for a presentation contribu tion to a webinar. Gudrun Kunst also reports leadership roles for the National Institute of Academic Anaesthesia Royal College of Anaesthesia UK as Grant Officer and Board and Research Council Member, for the Association of Cardiothoracic Anaesthesia and Critical Care UK as Scientific Chair and Board Member, and for the European

Board of Cardiovascular Perfusion as Scientific Chair and Board Member. Frank Merkle reports receiving consulting fees and honoraria from LivaNova and Terumo Europe (both to the institu tion). Benjamin Milne reports receiving consulting fees from Edwards Lifesciences. Milan Milojevic reports receiving a speaker fee from Corcym in relation to ERAS (<1000K) and one from Medtronic in relation to CPB (<1000K). Milan Milojevic also reports a role of Guidelines Program Director at EACTS. Francesco Onorati reports receiving grants from Edwards Lifesciences, and honoraria from Edwards Lifesciences and Abbott. Francesco Onorati reports receiving support from Edwards Lifesciences and Abbott for attending meetings. Francesco Onorati reports participa tion on an advisory board for the IMPACT and INDURE trials. Francesco Onorati reports leadership positions in EBCTS and the Italian Society of Cardiac Surgery. Francesco Onorati also reports receiving equipment from IPP Med. Davide Pacini reports receiving grants from Artivion, Terumo Aortic, Peters, and Corcym. Davide Pacini reports receiving consulting fees and honoraria from Terumo Aortic and Peters. Davide Pacini reports receiving support for attending meetings from Corcym. Davide Pacini reports partici pating on the advisory board for the TRACS trial. Davide Pacini also reports leadership positions for the Italian Society of Cardiac Surgery and the Francis Fontan Foundation. Marco Ranucci reports receiving royalties from LivaNova for a GDP monitor patent. Marco Ranucci reports receiving consulting fees from LivaNova as a per sonal payment, and honoraria from LivaNova and Medtronic as personal payments. Marco Ranucci also reports receiving personal payment from LivaNova for participating on an advisory board.

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