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Continuing Medical Education and Professional Development (CEPD) for practising clinicians is the cornerstone of our ability to provide high-quality, safe patient care and the major advances that continue to be made in anaesthesia and critical care must play a key part in this. Furthermore, formal performance assessment and revalidation, if not already in place, are just around the corner for all of us. Whatever the statutory requirements, we owe it to our patients and the quality and safety of the care we provide for them to ensure that we keep up to date in all areas of our practice, giving due consideration to new drugs and techniques that might improve patient outcomes still further. We may feel that with the ever-increasing workload and demands of complex patient care, we have no time to update our knowledge and skills, preferring to employ techniques with which we are familiar, supported by the sound clinical knowledge and judgement that we have acquired over many years. However, the development of anaesthetic techniques, equipment and pharmacology does not stand still and equally the sophistication of diagnostic tools for our patients means that we are able to obtain much better and more timely information than in the past. In some ways, the more we know, the more difficult it is to make a balanced judgement on the optimal care of a patient. Yet, how much more informative it is to know the actual jugular venous $P_0$, or intracranial pressure than simply to make a judgement based on clinical interpretation?

The demands made of anaesthetists both in theatre, in pain management and in critical care mean that being able to find sufficient time to attend CEPD meetings, particularly outside one’s own local environment, let alone overseas, is increasingly difficult. This means that for many of us there is limited opportunity to concentrate and learn in an undisturbed way and, importantly, to hear the views of experts in their chosen field. Inevitably, we rely to a great extent on information supplied in academic journals and textbooks together, increasingly, with the use of the Internet.

Without an enormous amount of time and a range of available journals, it is often difficult to obtain a balanced view about new areas of anaesthesia and critical care. What we really need is an expert to assess the current topic in question and to produce an objective commentary and judgement on the various papers that have been written during recent months. This is exactly the principle on which The Year in Anaesthesia and Critical Care is based. It provides an alternative concept of book-based CEPD, which concentrates on extracting information from a number of recent papers and assessing it in a meaningful and readable way. New books
appear on a regular basis but most are either orientated towards examinations and assessment processes during training, or are specialist textbooks in a particular field of either anaesthesia, pain management or critical care. Few are aimed at CEPD for established career-grade clinical anaesthetists, but this, with its now established format and concept, is such a book.

No book of this kind should attempt to be comprehensive, and the editors have selected four key sections of recent development: perioperative care, clinical pharmacology, monitoring and equipment, and critical care. Each section begins with an excellent and objective editorial section, which includes an overview and summary of the subject area, individual comment and references. Key subjects within these four sections are then reviewed in more detail by experts in the field, who concentrate on a number of key publications that have occurred during the year, looking at the main findings and recommendations of each and then co-ordinating these to provide more detailed response and comment. The reader is thus able to have expert opinion and comment at two levels – both for the individual detailed subject area and more generally in the field, which is the subject of the particular section of the book. Laid out as it is, in sections and sub-sections, each with comprehensive headings, it is both easy to read and concentrate upon and importantly, one only needs to read a small section at a time to gain relevant information. Interruptions do not disturb one’s flow of thought and learning unduly.

There is no doubt that the opportunity to concentrate on specific topic areas rather than the need to be comprehensive in terms of subject content makes for a much more readable and interesting book. Even at the level of studying for examinations, key comment and review by experts do much to help one’s understanding of a subject and the research and scientific basis behind new developments and techniques. While this selective approach is exemplified in all parts of the book, the section on perioperative care serves to illustrate the theme and its value. The section concentrates on four very relevant, topical, but unconnected areas: perioperative blood component therapy and haemostasis, perioperative respiratory care, ambulatory anaesthesia and perioperative cardioprotection. For clinical anaesthetists wishing to read material to increase their knowledge, this combination has all the right ingredients. It develops themes about which they may already know a considerable amount but wish to be updated, leads them through new ideas and techniques and, finally, provides a detailed look at a more specialist area of work that would be of interest even if they were not acutely involved with it. It provides the opportunity to read about the advantages and disadvantages of new developments at length and to reason through recent research and publications that inform the choice of technique. Each author introduces new concepts that all clinicians should consider and allows us to obtain a balanced view, particularly in subject areas where our experience is limited and inevitably biased.

Although review articles are also an excellent way of keeping up to date and enhancing one’s knowledge, inevitably they concentrate on specific topics and contain much of the authors’ own opinions rather than looking at the variety of views from others and allowing the reader to exercise their own judgement. This
book allows an objective discussion and comment to be made about all the articles written around a certain subject by others and then allows the reader to make a balanced judgement based upon the recommendations made. For continuous education to have an impact on one’s opinion and clinical practice, one must be allowed to judge for oneself and not simply feel spoon-fed by others’ opinions. The innovative format of this book and the ease with which one can read and concentrate on it makes it an ideal opportunity to enhance one’s education in anaesthesia, critical care and pain management and the breadth of subjects covered will, I am sure, have widespread appeal.
Part I

Perioperative care
Unsettled issues in the field of perioperative care

HANS-JOACHIM PRIEBE

Introduction
Numerous advances have been made in the field of perioperative care during the past couple of years. Part I of this edition of the *Year in Anaesthesia and Critical Care* focuses on four areas of perioperative care: perioperative blood component therapy and haemostasis (Chapter 1), perioperative respiratory care (Chapter 2), perioperative cardioprotection (Chapter 3) and ambulatory and outpatient anaesthesia (Chapter 4). The following introduction to the section on perioperative care will concentrate on some aspects of perioperative cardioprotection and respiratory care that have recently received special attention – be it because they carry the potential for considerable impact on perioperative care or because the issues are far from being settled and provide ground for ongoing debate and controversy. Although this outline can only briefly address very few aspects of perioperative care, and, by necessity, will have to ignore the vast majority of topics relevant to perioperative care, it will reflect the broad scope of perioperative care.

Perioperative cardioprotection
In patients with coronary artery disease, the incidence of perioperative myocardial ischaemia and infarction remains high and is associated with adverse outcomes [1]. Consequently, the quest for cardioprotective strategies continues. Various approaches have been taken.

Myocardial conditioning
Rapid restoration of coronary blood flow following coronary artery occlusion is of the utmost importance in limiting myocardial injury. However, as reperfusion *per se* elicits myocardial injury, additional strategies are sought to attenuate reperfusion injury following myocardial ischaemia.
Ischaemic preconditioning

One such widely publicized strategy is ischaemic preconditioning, the phenomenon of cardioprotection by controlled brief periods of myocardial ischaemia prior to a subsequent prolonged period of myocardial ischaemia |2,3|. Although numerous experimental studies have demonstrated a cardioprotective effect of ischaemic preconditioning protocols, and despite evidence that human myocardium can be preconditioned |4–6|, the concept has not been adopted in routine clinical practice for various theoretical as well as practical limitations |7,8|.

Most studies were performed in animals with normal hearts and in patients with normal myocardial performance. Experimental and clinical evidence for a cardioprotective effect of ischaemic preconditioning in diseased hearts is limited. Intentionally eliciting ischaemia in an already damaged myocardium is valid reason for concern. Furthermore, except for cardiac surgery and coronary interventions, it is impossible to predict the beginning of a sustained period of myocardial ischaemia. This is a major limitation because the effectiveness of ischaemic preconditioning is crucially dependent on the exact timing of the brief episodes of myocardial ischaemia prior to the subsequent prolonged period of myocardial ischaemia. Even if applied in cardiac surgery, intermittent clamping and unclamping of either the aorta or coronary arteries may provoke distal embolization of atherosclerotic plaque material. Lacking these drawbacks, current cardioplegic techniques are likely to provide equivalent, if not superior, cardioprotection. The rather brief period (20–30 s) of severe myocardial ischaemia during coronary artery balloon angioplasty and stent placement and the use of distal perfusion catheters make ischaemic preconditioning during percutaneous coronary intervention unnecessary. Thus, the benefit of ischaemic preconditioning in diseased hearts in routine clinical practice remains to be determined.

Pharmacological preconditioning

Another strategy for cardioprotection is pharmacological preconditioning. A number of pharmacological substances are possible triggers or effectors of ischaemic preconditioning |7|. Amongst the substances that simulate ischaemic preconditioning without actually inducing myocardial ischaemia, and which have been investigated in humans, are adenosine, adenosine agonists, the K<sub>ATP</sub> channel opener nicorandil, delta opioids and nitrates |7|. Under most experimental and certain clinical conditions |9,10|, the cardioprotective effect of pharmacological preconditioning (66–85% reduction in infarct size) is similar to that initially reported for ischaemic preconditioning (75% reduction in infarct size) |6|. However, not all clinical studies confirm effective cardioprotection by pharmacological preconditioning per se |7,8|.

Anaesthetic preconditioning

Anaesthetic-induced cardioprotection is a special form of pharmacological preconditioning |11–16|. It describes the phenomenon whereby exposure of the myocardium to an anaesthetic drug (in most cases to volatile anaesthetics) prior to
the onset of myocardial ischaemia attenuates the extent of myocardial infarction, myocardial stunning and ventricular dysrhythmias following coronary reperfusion. Anaesthetic and ischaemic preconditioning are similarly effective in protecting the myocardium against prolonged ischaemia [11].

Our understanding of the mechanisms involved in anaesthetic preconditioning is primarily based on experimental investigations. For anaesthetic preconditioning to be effective, the beginning of a sustained period of myocardial ischaemia must be predictable. Consequently, all clinical studies that have thus far documented a cardioprotective effect of anaesthetic preconditioning were performed in patients undergoing cardiac surgery [17–24]. The clinical relevance of anaesthetic preconditioning in non-cardiac surgery remains to be determined. Even in cardiac surgery, the benefit of anaesthetic preconditioning is not uniformly accepted [25].

**Remote preconditioning**

Remote preconditioning is one of two novel cardioprotective strategies that have recently been described (the other being postconditioning; see below). It refers to the phenomenon of myocardial protection (or protection of any organ) derived from prior brief periods of ischaemia and reperfusion of non-cardiac organs [8,26]. Remote preconditioning can be elicited by intermittent brief periods of cross-clamping of various arteries (renal, mesenteric and iliac arteries; infrarenal aorta) [27,28] or upper limb ischaemia (by intermittent inflation of a blood pressure cuff or use of a tourniquet) [29]. It may be as cardioprotective as ischaemic preconditioning [28].

Remote preconditioning by intermittent occlusion of intra-abdominal vessels has the obvious clinical drawback of requiring laparotomy and carrying the risk of organ damage in patients with pre-existing organ dysfunction and vascular disease. Large clinical studies are required to determine ultimate feasibility and clinical benefit of this strategy.

**Postconditioning**

The phenomenon of cardioprotection by postconditioning was first described in 2003 in an open chest canine model of coronary artery occlusion and reperfusion [30]. Rather than allowing uninterrupted coronary artery reperfusion following occlusion, reperfusion is interrupted by brief sequences of coronary occlusions and reperfusion [31]. The initial experimental studies showed that, following a 1-h coronary artery occlusion, an algorithm consisting of three sequences of 30-s reperfusion of coronary blood flow followed by 30 s of reocclusion of the coronary artery before subsequent uninterrupted reperfusion for 3 h reduced myocardial infarct size to a similar extent as observed during ischaemic preconditioning [31,32].

Pre- and postconditioning share several of the ligand triggers and intracellular pathways [33]. What remains to be determined are the exact mechanisms by which postconditioning protects the heart and the relationship between, and the overlap
of mechanisms involved in pre- and postconditioning [34]. The phenomenon of postconditioning has been observed in dogs, rabbits, mice and rats [31], and recently in pigs [35]. There is now preliminary evidence for a cardioprotective effect of postconditioning in humans as well [36–38].

**Anaesthetic postconditioning**

In the case of anaesthetic postconditioning, the volatile anaesthetic is introduced immediately upon reperfusion. Its cardioprotective effect has been documented [19,39–41]. Anaesthetic postconditioning has considerable potential advantages in the clinical setting: it is practically feasible; it could be provided to patients arriving in the hospital, the operating room or the cardiac catheterization laboratory with ongoing myocardial ischaemia; and it could be provided during coronary reperfusion following percutaneous coronary interventions or coronary artery bypass graft surgery, or possibly even organ transplantation. It remains to be determined whether the cardioprotective effects of anaesthetic pre- and postconditioning are additive [42] or not [41], and whether one form is superior to the other [43]. The ultimate myocardial protective strategy may be a combination of all, that is of pre-, post-, remote and pharmacological conditioning [8].

**Intensive medical therapy**

More than 1 million coronary artery stents were inserted in the United States in 2004 [44], and approximately 85% of stent placements are presently performed electively in patients with stable coronary artery disease [45]. Whereas percutaneous coronary intervention (PCI) reduces mortality and the incidence of myocardial infarction in patients with acute coronary syndromes [46], this is not necessarily the case in patients with stable coronary artery disease [47,48]. Considering the increasing rate of coronary stent placements in patients with stable coronary artery disease, the increasing evidence for a highly beneficial effect of optimized medical therapy on outcome in patients with stable coronary artery disease, and considering the markedly elevated perioperative risks associated with surgery in patients with coronary stents [49,50], a critical evaluation of the benefits of PCI in addition to optimal medical therapy was needed.

The Clinical Outcomes Utilization Revascularization and Aggressive Drug Evaluation (COURAGE) randomized trial compared the effect of combined PCI and optimal medical therapy with optimal medical therapy alone on the risk of death and non-fatal myocardial infarction [51]. Included were patients with stable coronary artery disease, those with an initial Canadian Cardiovascular Society (CCS) class IV angina who subsequently stabilized under medical therapy, and those with a coronary artery stenosis of at least 70% in at least one proximal epicardial artery and objective electrocardiographic evidence of myocardial ischaemia, or at least one coronary artery stenosis of at least 80% accompanied by classic angina. Excluded were patients with persistent CCS class IV angina, a highly positive stress
test, refractory heart failure or cardiogenic shock, an ejection fraction of less than 30%, revascularization within the previous 6 months, and a coronary anatomy unsuitable for PCI.

All patients randomized to either group received daily anti-platelet therapy with aspirin and clopidogrel, anti-ischaemic therapy with long-acting metoprolol, amlodipine and isosorbide mononitrate alone or in combination, and secondary prevention with angiotensin-converting enzyme inhibitors. In addition, all patients were aggressively treated pharmacologically to reduce serum concentrations of low-density lipoprotein (LDL) cholesterol and to increase serum concentrations of high-density lipoprotein (HDL) cholesterol by modification of lifestyle and/or medication.

The main finding of this trial was the following: PCI in addition to intensive medical therapy did not reduce myocardial infarction and mortality during a follow-up period of 2.5–7.0 years. The 4.6-year cumulative rates of myocardial infarction and death were 19% in the combined PCI and medical therapy group and 18.5% in the medical therapy alone group, with a mortality rate of approximately 8% in both groups (no significant differences). At 5 years, 74% and 72% of patients in the combined PCI and medical therapy group and in the medical therapy alone group, respectively, were free of angina.

Several limitations of this study need to be considered before drawing final conclusions. Of the 35,539 patients who were initially screened, only 3071 (8.6%) met all inclusion criteria, and 2287 (6.4%) consented to participate in the study (combined PCI and medical therapy group: \( n = 1149 \); medical therapy alone group alone: \( n = 1138 \)). The low number of patients enrolled in the study compared with that initially screened is of concern. Patients with severe ventricular dysfunction, a highly positive stress test or clinical instability were excluded.

Drug-eluting stents were used in only 31 (2.7%) of the 1149 patients in the PCI group, because they were not available until the late phase of patient recruitment. Although there are presently no good data to indicate that drug-eluting stents reduce the incidence of myocardial infarction and death in patients with stable coronary artery disease compared with bare metal stents [52–58], on-label use of drug-eluting stents seems to reduce the rate of repeat revascularization [55,57]. It is thus conceivable that more frequent use of drug-eluting stents might have resulted in a lower rate of repeat revascularization and angina and, in turn, a better outcome in the combined PCI and medical therapy group.

In addition, approximately one-third of patients in the medical group required coronary revascularization for control of angina and acute coronary syndromes during the median follow-up of 4.6 years. With PCI being effective in ameliorating angina and in treating acute coronary syndromes, it cannot be entirely excluded that the relatively high crossover rate from the combined PCI and medical therapy group to the medical therapy alone group might have biased the results in favour of medical therapy alone, which might have contributed to the similar degree of symptom control and cardiovascular event rate at 5 years. However, during the same
time period additional revascularization was also necessary in 21.1% of patients in the PCI group.

This is the first trial that routinely used stents in combination with what is presently considered optimal medical therapy. Despite the limitations, this study strongly suggests that even in the presence of objective evidence of baseline myocardial ischaemia and extensive coronary artery disease, PCI added to intensive medical therapy does not necessarily reduce the incidence of major cardiovascular events compared with intensive medical therapy alone during the several subsequent years. The findings may partly be explained by differences in atherosclerotic plaque morphology associated with stable coronary artery disease compared with acute coronary syndromes [1,59]. Myocardial ischaemia and anginal symptoms are usually associated with stable plaques. These plaques tend to have thick fibrous caps, small lipid cores and considerable amounts of smooth muscle cells and collagen, but few macrophages [60,61]. They ultimately undergo inward (constrictive) remodelling with narrowing of the coronary lumen that is readily detected by coronary angiography. As the potential for acute rupture is relatively low, stable plaques are less likely to cause acute coronary syndromes.

By contrast, vulnerable plaques tend to have thinner fibrous caps, larger lipid cores, fewer smooth muscle cells, more macrophages and less collagen. They undergo outward (expansive) remodelling with less narrowing of the coronary lumen. As a result, vulnerable plaques do not usually cause significant coronary stenosis and clinical symptoms before rupture and subsequent precipitation of an acute coronary syndrome. In other words, coronary lesions that cause acute coronary syndromes are not necessarily severely stenotic (and not necessarily readily detectable by coronary angiography), and severely stenotic lesions (readily detectable by coronary angiography) that cause anginal symptoms are not necessarily unstable. As stable plaques are less likely to trigger an acute coronary event, it should not come as a total surprise that focal management of even severe coronary artery stenoses by coronary artery revascularization (be it by PCI or surgically) does not reduce the incidence of major cardiovascular events. Following PCI, vulnerable plaques will continue to exist unchanged. Presumably by improving endothelial function and plaque stability, lipid-lowering therapy more successfully reduces the incidence of cardiac events than the severity of the stenosis [62].

Consistent with the results of previous studies [63,64], the observed clinical event rates associated with optimal medical therapy were lower than projected in the trial design [51]. This finding is in agreement with a meta-analysis showing that PCI is ineffective in reducing major cardiovascular events compared with medical management [65]. This may reflect reduced plaque vulnerability due to aggressive medication and intervention for cardiac risk factors. Existing clinical practice guidelines acknowledge the effectiveness of intensive medical therapy and, accordingly, state that even in patients with symptomatic, extensive, multivessel coronary artery disease, PCI can be safely deferred in patients with stable coronary artery disease, if optimal medical therapy is provided [66,67]. Short-
term pretreatment with atorvastatin in patients with acute coronary syndromes undergoing early invasive strategy conferred an 88% risk reduction of 30-day major adverse cardiac events [68]. Preoperative use of lipid-lowering therapy in patients undergoing coronary artery bypass graft surgery was associated with improved survival to hospital discharge compared with patients not receiving lipid-lowering therapy [69].

The Coronary Artery Revascularization Prophylaxis (CARP) trial failed to demonstrate a long-term benefit of prophylactic preoperative coronary revascularization (by PCI or coronary artery bypass graft surgery) [70]. Consistent with the results of the COURAGE trial [51], lack of benefit by preoperative coronary revascularization may partly be explained by the long-term aggressive medical therapy in revascularized as well as non-revascularized patients. All of this adds further evidence for a benefit of aggressive perioperative medical therapy in patients with stable coronary artery disease, and for the lack of added benefit from preoperative coronary revascularization. Aggressive perioperative medical therapy may well be one of the most important, if not the most important, cardioprotective intervention.

**Anti-platelet drug therapy**

Dual anti-platelet therapy with aspirin and a thienopyridine reduces ischaemic cardiac events and deaths after coronary stenting and is, therefore, recommended in the European Society of Cardiology [71] and the American College of Cardiology/American Heart Association practice guidelines for the treatment of patients undergoing percutaneous coronary intervention and for the medical treatment of patients with non-ST-segment-elevation acute coronary syndromes [72–74]. However, dual anti-platelet therapy is often prematurely discontinued by patients and healthcare providers, resulting in greatly increased risk of stent thrombosis, myocardial infarction and death [75,76]. Interruption of aspirin accounted for up to 15% of recurrent acute coronary syndromes in patients with established stable coronary artery disease [77].

The recent science advisory from the American Heart Association, the American College of Cardiology, the Society for Cardiovascular Angiography and Interventions, the American College of Surgeons and the American Dental Association emphasizes the importance of 12 months of dual anti-platelet therapy after placement of a drug-eluting stent [78]. Amongst the various recommendations made by the science advisory, the following are the most relevant for the perioperative care of patients with coronary artery stents:

- Before implantation of a stent, the physician should discuss the need for dual antiplatelet therapy. In patients not expected to comply with 12 months of thienopyridine therapy, whether for economic or other reasons, strong consideration should be given to avoiding a DES [drug-eluting stent].
In patients who are undergoing preparation for percutaneous coronary intervention and are likely to require invasive or surgical procedures within the next 12 months, consideration should be given to implantation of a bare-metal stent or performance of balloon angioplasty with provisional stent implantation instead of the routine use of a DES.

Healthcare providers who perform invasive or surgical procedures and are concerned about periprocedural and postprocedural bleeding must be made aware of the potentially catastrophic risks of premature discontinuation of thienopyridine therapy. Such professionals who perform these procedures should contact the patient’s cardiologist if issues regarding the patient’s antiplatelet therapy are unclear, to discuss optimal patient management strategy.

Elective procedures for which there is significant risk of perioperative or postoperative bleeding should be deferred until patients have completed an appropriate course of thienopyridine therapy (12 months after DES implantation if they are not at high risk of bleeding and a minimum of 1 month for bare-metal stent implantation).

For patients treated with DES who are to undergo subsequent procedures that mandate discontinuation of thienopyridine therapy, aspirin should be continued if at all possible and the thienopyridine restarted as soon as possible after the procedure because of concerns about late-stent thrombosis.

The corresponding recommendations by the European Society of Cardiology are similar, but do not specifically address the management of anti-platelet medication in the perioperative period [71]:

- **following bare metal stent implantation in stable coronary artery disease**: administration of ticlopidine or clopidogrel in addition to aspirin for 3–4 weeks (I A);
- **following placement of drug-eluting stents**: clopidogrel administration for 6–12 months (I C);
- **following coronary brachytherapy**: clopidogrel administration for 12 months (I C);
- **following non-ST-segment-elevation acute coronary syndrome**: clopidogrel administration for 9–12 months (I B).

*(Recommendation class I = evidence and/or general agreement that a given diagnostic procedure/treatment is beneficial, useful and effective. Levels of evidence: A, data derived from multiple randomized clinical trials or meta-analyses; B, data derived...)*
from a single randomized clinical trial or large non-randomized studies; C, data derived from retrospective studies or registries.)

As yet, there is no evidence for a benefit of ‘bridging’ stent patients with glycoprotein IIb/IIIa or anti-thrombin drugs. It remains to be seen whether poor responsiveness (‘resistance’) to aspirin \[79\] and clopidogrel \[80\] correlates with adverse clinical events.

Safe and effective perioperative management of dual anti-platelet therapy is an integral part of perioperative cardioprotection. The management will have to balance the risk of bleeding associated with continuation of anti-platelet therapy against the ischaemic risks associated with discontinuation of anti-platelet drugs \[49,50,75,81,82\].

**Perioperative respiratory care**

Clinicians continue to struggle with several perioperative respiratory management issues, mostly because evidence-based data supporting one approach over the other are missing. Whenever ‘hard’ data are missing, clinical ‘experience’ tends to lead the way – with often unpredictable outcomes.

**Prediction of postoperative complications**

Postoperative pulmonary complications – the most important ones being atelectasis, pneumonia, respiratory insufficiency and exacerbation of pre-existing pulmonary disease – are as frequent and clinically relevant as postoperative cardiac complications \[83\]. However, the issue of perioperative pulmonary morbidity and mortality receives considerably less attention than its cardiac ‘counterpart’.

The impact of clinical factors on postoperative pulmonary complications and the benefit of preoperative respiratory testing remain a matter of continued debate. Scientifically valid conclusions on the basis of existing data are limited by preponderance of observational rather than hypothesis-driven studies, inadequate sample sizes, non-uniform definitions and non-blinded assessment of postoperative pulmonary complications, and questionable statistical analyses.

The American College of Physicians recently addressed this issue and developed a guideline to ‘guide clinicians on clinical and laboratory predictors of perioperative pulmonary risk before non-cardiothoracic surgery’ and to ‘evaluate the efficacy of strategies to reduce the risk for postoperative complications’ \[83\]. The guideline specifically applies to adult patients undergoing non-cardiothoracic surgery. It is based on two systematic reviews of the literature \[84,85\]. Based on an extensive review of the literature, the American College of Physicians made six recommendations \[83\]:
'All patients undergoing non-cardiothoracic surgery should be evaluated for the presence of the following significant risk factors for postoperative pulmonary complications in order to receive pre- and postoperative interventions to reduce pulmonary risk: chronic obstructive pulmonary disease, age older than 60 years, American Society of Anesthesiologists (ASA) class of II or greater, functionally dependent and congestive heart failure.' Obesity and mild or moderate asthma were not identified as significant risk factors for postoperative pulmonary complications.

Patients undergoing the following procedures are at higher risk for postoperative pulmonary complications and should be evaluated for other concomitant risk factors and receive pre- and postoperative interventions to reduce pulmonary complications: prolonged surgery (> 3 hours), abdominal surgery, thoracic surgery, neurosurgery, head and neck surgery, vascular surgery, aortic aneurysm repair, emergency surgery, and general anesthesia.

A low serum albumin level (< 35 g/L) is a powerful marker of increased risk for postoperative pulmonary complications and should be measured in all patients who are clinically suspected of having hypoalbuminaemia; measurement should be considered in patients with 1 or more risk factors for perioperative pulmonary complications.

All patients who after preoperative evaluation are found to be at higher risk for postoperative pulmonary complications should receive the following postoperative procedures in order to reduce postoperative pulmonary complications: (1) deep breathing exercises or incentive spirometry and (2) selective use of a nasogastric tube (as needed for postoperative nausea or vomiting, inability to tolerate oral intake, or symptomatic abdominal distension).

Preoperative spirometry and chest radiography should not be used routinely for predicting risk for postoperative pulmonary complications.

The following procedures should not be used solely for reducing postoperative pulmonary complication risk: (1) right-heart catheterization and (2) total parenteral nutrition or total enteral nutrition (for patients who are malnourished or have low serum albumin levels).

The major procedure-related factors (surgical site, duration of surgery, anaesthetic technique and emergency surgery) were associated with higher likelihoods of postoperative complications than the major patient-related factors (advanced age, ASA physical class ≥ 2, functional dependence, chronic obstructive pulmonary disease and congestive heart failure).

The data regarding the value of spirometry in predicting increased risk for postoperative pulmonary complications in non-cardiothoracic surgeries were found to be inconsistent. While spirometry is frequently used to diagnose restrictive or
obstructive pulmonary disease, such diagnoses do not seem to result in reliable individual preoperative risk stratification. In addition, there is no convincing evidence that information derived from spirometry is clinically more relevant than that derived from patient history and physical examination. Evidence did not support a benefit of preoperative spirometry in preoperative pulmonary risk stratification and, thus, does not support the routine preoperative use of spirometry even in the presence of major patient- or procedure-related risk factors.

Preoperative chest radiography in patients older than a particular age is frequently part of institutional practice guidelines. However, chest radiography rarely provides information not already expected from medical history and physical examination. Not surprisingly then, even pathologic preoperative chest radiographs rarely influenced perioperative management. Only limited evidence supports the use of chest radiography in patients with cardiopulmonary disease, older than 50 years of age, scheduled for upper abdominal, thoracic or abdominal aortic aneurysm surgery. Based on the systematic reviews, the American College of Physicians concluded that ‘preoperative pulmonary function testing or chest radiography may be appropriate in patients with a previous diagnosis of chronic obstructive pulmonary disease or asthma’.

Large randomized controlled studies will be necessary to evaluate the impact of these guidelines on outcome.

Prediction of difficult mask ventilation

Despite technical advances in airway equipment, airway problems remain a major concern. Whereas a large body of literature addresses the prediction of difficult intubation, only very few studies have looked at predictive factors of difficult mask ventilation. This is the more surprising as successful mask ventilation may become a life-saving rescue intervention in cases of failed intubation. In turn, inability to mask ventilate carries the potential for considerable morbidity and mortality.

Of 22,660 prospectively studied attempts at mask ventilation in adults during a 24-month period at a university hospital, 37 (0.16%) were of grade 4 (impossible to ventilate) and 313 (1.4%) of grade 3 (difficult to ventilate). The combination of grade 3 or 4 mask ventilation and difficult intubation occurred in 84 (0.37%) attempts. Independent predictors of grade 3 mask ventilation (difficult to ventilate) were body mass index (BMI) of $\geq 30$ kg/m$^2$, a beard, Mallampati classification III or IV, age $\geq 57$ years, severely limited mandibular protrusion and a history of snoring. Independent predictors of grade 4 mask ventilation (impossible to ventilate) were a history of snoring and a thyromental distance of less than 6 cm. Independent predictors of the combination of grade 3 or 4 mask ventilation and difficult intubation were limited or severely limited mandibular protrusion, thick/obese neck anatomy, history of sleep apnoea, history of snoring and a BMI of $\geq 30$ kg/m$^2$.

Of considerable clinical relevance is the answer to the question: what happened in those 37 patients in whom mask ventilation was impossible? Intubation was uncomplicated in 26 (70%) and difficult in 10 (27%) cases, and impossible (requiring
emergent cricothyrotomy) in only one case (approximately 3%). It is comforting to know that, although impossible mask ventilation may be associated with difficult intubation, endotracheal intubation will still be possible in the vast majority of cases. However, the rather low incidence of complete inability to ventilate by mask (0.16%), and the finding that only one of 37 patients that could not be ventilated by mask required surgical airway access, may reflect an effective *a priori* decision for awake fibreoptic intubation in patients with anticipated difficult ventilation and intubation.

As difficult mask ventilation can occur as unexpectedly as difficult intubation, the (comforting) finding of ultimately successful intubation in almost all patients despite the inability to ventilate by mask, re-emphasizes the utmost importance of effective pre-oxygenation (reflected by an expired oxygen concentration of preferably \( \geq 90\% \) during a tight mask fit). Effective pre-oxygenation will 'bridge' the time between recognizing the inability to ventilate by mask and ultimately gaining access to the airway.

As a beard was found to be a risk factor for difficult mask ventilation, the authors feel obliged to inform their patients of this risk. Of the various risk factors for difficult mask ventilation identified, a beard was the only one that can be modified. This poses the question as to whether patients should be advised to preoperatively shave their beard.

The finding of limited or severely limited mandibular protrusion as being an independent predictor of difficult or impossible mask ventilation, re-emphasizes – in accordance with the American Society of Anesthesiologists Task Force on Management of the Difficult Airway [92] – the relevance of an evaluation of mandibular protrusion as part of a standard preoperative physical examination.

The investigation triggers a couple of general remarks on studies trying to identify predictors of adverse outcome. Undoubtedly, this study identified certain features that were *associated* with difficult airway management. For example, independent predictors of the combination of difficult or impossible mask ventilation and difficult intubation in 84 cases were limited mandibular protrusion, thick/obese neck anatomy, history of sleep apnoea, history of snoring and a BMI of \( \geq 30\) kg/m². However, these predictors were also present in 9.8% (\( n = 1348 \)), 11% (\( n = 1455 \)), 4.8% (\( n = 682 \)), 27% (\( n = 3560 \)) and 64% (\( n = 9039 \)), respectively, of approximately 14 000 cases of unproblematic mask ventilation and intubation. Put differently, almost all patients who had predictors of difficult or impossible ventilation by mask and difficult intubation were, in fact, easy to manage.

This finding underlines an important principle: as long as the adverse outcome we are trying to predict is relatively rare (in this case, impaired mask ventilation and difficult intubation in just 84 (0.37%) of 22 660 attempts), then even in the presence of independent risk factors, outcome will not be adversely affected in almost all of these patients. Such very low positive predictive values will considerably limit the clinical usefulness of any predictor or predictive tests [93].
The publication by Kheterpal et al. [91] raises an intriguing question regarding the timing of administration of the muscle relaxant in routine clinical practice. It is a commonly taught practice (often a dictum) to withhold muscle relaxants until effective mask ventilation has been established (with the curious exemption of rapid sequence induction). In the case of failed mask ventilation, the patient should be awoken (following a failed attempt at intubation or without such an attempt) and fibreoptic endotracheal intubation performed. The findings by Kheterpal et al. seem to contradict such conventional wisdom. First, a considerable number of patients are likely to have received muscle relaxants before effective mask ventilation had been established. This is suggested by 4775 (21.1%) cases of mask ventilation grade 2, defined as 'ventilated by mask with oral airway/adjuvant with or without muscle relaxant'. Second, of the 37 patients with impossible mask ventilation, only one patient had not received a muscle relaxant before the first attempt at intubation [94]. This patient was intubated without difficulty. Four patients had received a non-depolarizing muscle relaxant before failure of mask ventilation was observed. One of these required emergency cricothyrotomy. The remaining 32 patients received succinylcholine after inability to mask ventilation had been noted and before the first attempt at intubation.

One is tempted to interpret the findings as showing that the 97% intubation success rate following inability to ventilate by mask was due to the early administration of the muscle relaxant, either before or immediately after recognition of inability to ventilate by mask. It is highly questionable that endotracheal intubation could have been that successfully performed in the absence of muscle relaxation, or that these patients could have safely been awoken. These findings would support the view (including my own) that the earliest possible administration of the muscle relaxant may well be the most effective tactic [95,96].

**Ventilatory strategy**

Controversy continues as to the optimal perioperative ventilatory strategies in patients with normal lungs [97,98] (see also Chapter 2). The main objective of an optimal ventilatory strategy is to keep the regional end-inspiratory stretch – an indicator of ventilatory stress – as low as possible, thereby reducing the potential for alveolar injury and inflammation [97,98]. Present guidelines strongly support the use of tidal volumes ($V_T$) of 6 ml/kg predicted body weight in patients with acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) [99].

Comparable guidelines for patients without acute lung injury (ALI) or ARDS are lacking. The results of smaller randomized controlled trials of perioperative ventilatory strategies during major surgery have been inconsistent [97]. There is, however, preliminary evidence for a lung-protective effect of a ventilation strategy with a $V_T$ of less than 10 ml/kg predicted body weight and positive end-expiratory pressure (PEEP) compared with a more conventional strategy with a $V_T$ higher than 10 ml/kg and no PEEP [97–104]. When trying to put these findings into proper clinical
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perspective, it is important to realize that existing evidence for a lung-protective effect of lower tidal volumes in patients with normal lungs is mostly based on retrospective studies, and on surrogate markers of outcome (such as inflammatory mediators), rather than on clinical outcome variables [97].

When patients with predisposing factors for the development of acute or ventilator-induced lung injury (e.g. pulmonary oedema or inflammation, restrictive lung disease, lung resection or cancer surgery) subsequently receive ‘hits’ such as sepsis, aspiration or transfusion, they may develop the clinical picture of ALI/ARDS [97]. According to this multiple ‘hit’ theory, large tidal volumes may constitute the primary hit (thereby inducing or exacerbating pulmonary inflammation) or a subsequent hit. By this reasoning, all surgical patients are at risk of developing ventilation-induced lung injury and would thus ‘deserve’ lung-protective ventilation.

Taking the various factors into consideration, it appears sensible to recommend avoiding high tidal volumes (i.e. > 10 ml/kg predicted body weight) and plateau airway pressures (i.e. > 15–20 cmH\(_2\)O), even in surgical patients without any evidence of lung disease [97]. PEEP of at least 5 cmH\(_2\)O should be applied to avoid atelectasis and maintain oxygenation. There is, however, no sound scientific basis on which to base a recommendation for a reduction in tidal volumes to less than 10 ml/kg predicted body weight when plateau pressure is not higher than 16 cmH\(_2\)O [97] (see also Chapter 2). However, even in the absence of a high airway plateau pressure, cyclic recruitment and derecruitment of small airways or lung units may contribute to lung injury [105].

By the same reasoning, in patients with increased risk for the development of acute or ventilator-induced lung injury (due to either underlying risk factors or exposition to subsequent ‘hits’), it seems equally sensible to recommend a lower \(V_T\) of 6 ml/kg predicted body weight [101]. Higher PEEP may be required to counteract the adverse effect of lower tidal volumes and plateau pressures on the formation of atelectasis.

It is, of course, to be expected that at comparable tidal volumes, long-term mechanical ventilation with or without extrapulmonary ‘hits’ will be more injurious than short-term ventilation without such ‘hits’. Rather than applying a fixed ventilatory strategy to all patients during anaesthesia, the strategy should take into account the underlying medical condition of the patient and the type of surgery, and be individualized accordingly [97,98] (see also Chapter 2).

**Extubation strategy**

Whereas detailed guidelines exist for the airway management during induction of anaesthesia [92], no such guidelines exist for the period during and immediately following tracheal extubation. This is surprising because tracheal extubation is merely the logical consequence of tracheal intubation, and the need for continued control of the airway persists after extubation. Furthermore, the incidence of
complications associated with extubation may be higher than the incidence during intubation [106]. Eighteen of the 156 perioperative claims for difficult airway management between 1985 and 1999 included in the ASA Closed Claims database were associated with extubation in the operating room [87].

In most cases of problems occurring after extubation, supportive care will re-establish adequate oxygenation and ventilation, but sometimes reintubation becomes unavoidable. As reintubation will usually be more difficult than the initial intubation (due to the frequently emergent nature, the accompanying hypoxaemia and cardiovascular instability, the lack of patient cooperation, insufficient time for adequate preparation, and limited access to the airway), and as airway emergency and repeated intubation attempts have been associated with adverse outcome (including death and brain damage) [87,107], an effective extubation strategy should have a low reintubation rate. In addition, it should allow oxygenation and ventilation and facilitate reintubation in case of failure to tolerate extubation.

The ASA Task Force on Difficult Airway Management recommends a preformulated strategy for extubation of the difficult airway [92]. The extubation strategy of the difficult airway should be adjusted to the type of surgery, the medical condition of the patient, and the experience and preference of the anaesthetist. It should include (a) consideration of the merits of extubation in the awake versus the unconscious state; (b) consideration of clinical factors that may impair respiration after extubation; (c) a preformulated airway management plan in case the patient is unable to tolerate extubation; and (d) consideration of the use of a device that can facilitate reintubation.

The airway exchange catheter (AEC) is such a device. It is introduced through the endotracheal tube before extubation and is left in situ after removal of the endotracheal tube until the need for reintubation is considered minimal. By maintaining access to the airway, it facilitates reintubation in case of failure to tolerate extubation. Endotracheal reintubation via an indwelling AEC was successful in 92–100% of cases [108–110]. Compared with patients without an indwelling AEC in place at the time of reintubation, the first-pass success rate for reintubation was significantly higher (87% vs. 17%), episodes of severe hypoxaemia (6% vs. 19%) and multiple intubation attempts were fewer (10% vs. 77%), oesophageal intubation was less frequent (0% vs. 18%), and there was less need for additional rescue airway devices and techniques and surgical airways (6% vs. 90%) [110]. Nevertheless, although complications during AEC-facilitated reintubation may be relatively infrequent, they do occur and may be severe. In addition, of a total of 329 patients with known or suspected difficult airway who had been extubated over an AEC during a 9-year period, 87 (26.4%) required reintubation [110].

All in all, the concept of an AEC-facilitated ‘staged’ extubation strategy is an attractive one, on a theoretical basis as well as on the basis of demonstrated benefit in selected patients. In experienced hands, it has a satisfactory success rate without requiring overly sophisticated equipment and skills. Especially when using a paediatric-size AEC, patient tolerance seems to be excellent, vocalization
is preserved, and the risks of airway trauma and pulmonary aspiration are small \[108-110\]. Since tolerance of extubation cannot reliably be predicted, it is reassuring to know that an AEC facilitates reintubation in the vast majority of patients with difficult airway. Even if the initial attempt at reintubation fails in the presence of severe respiratory insufficiency, a jet-stylet-type AEC allows capnography, oxygen insufflation and jet ventilation, thereby ‘bridging’ the time required to obtain additional airway equipment and qualified help. By maintaining access to the airway, an indwelling AEC may justify an earlier trial of extubation without taking unnecessary risk, thereby avoiding ‘prophylactic’ continuation of endotracheal intubation or tracheotomy. However, only well-designed, controlled prospective trials will be able to ultimately determine the most effective extubation strategy \[111\].

**Conclusion**

It is hoped that improvement in perioperative cardioprotection by myocardial conditioning, intensive medical therapy, and safe and effective management of dual anti-platelet therapy; and improvement in perioperative respiratory care by reliable preoperative respiratory risk stratification, reliable prediction of difficult mask ventilation, and correct choices of ventilatory and extubation strategies will result in improved patient outcome. Although intuitively to be expected, a causal relationship between the discussed approaches and interventions and improved ultimate outcome remains to be established by large, well-designed clinical trials.

This introduction has touched on just a very few aspects of perioperative care. The following chapters of Part I of *The Year in Anaesthesia and Critical Care* reflect the multitude and diversity of factors that govern the large field of perioperative care, all of which are affecting patient outcome.

**Addendum**

After completion of this editorial, the American College of Cardiology (ACC)/American Heart Association (AHA) published their revised guidelines on perioperative cardiac evaluation and care for non-cardiac surgery \[112,113\]. The guidelines were developed in collaboration with the Society of Cardiovascular Anesthesiologists, and the Writing Committee was chaired by Professor Lee A. Fleisher, a prominent anaesthetist. Amongst other topics, the revised guidelines contain fully updated, highly relevant evidence-based recommendations for preoperative clinical assessment and cardiac testing, preoperative coronary revascularization, perioperative cardiac medication, and for the management of patients presenting with coronary artery stents. All recommendations are classified, and the level of evidence on which the classifications are based is reported. These
revised guidelines constitute a large source of detailed information regarding all aspects of perioperative cardiac care and a critical analysis of data available on this clinically important subject. Detailed knowledge of these guidelines can be expected to improve the overall quality of perioperative patient management.

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Introduction

Blood transfusion requirements are increasingly used as a quality measure for many types of surgery. Greater patient awareness of the potential risks of transfusions, ranging from transfusion reactions to the transmission of variant Creutzfeldt–Jakob disease (CJD), has led to increased efforts to perform surgery without transfusion or decrease the number of blood donor exposures. These trends are also needed for logistic reasons. The number of blood donors is decreasing, partly as a result of legislation limiting eligibility such as previous recipients of allogeneic blood, and partly because of changing public priorities. The introduction of testing for variant CJD could cause a large decrease in donations, because of public fears concerning the consequences of testing (for example, on insurance policies). The number of patients undergoing procedures with a high risk of blood loss may increase as the population grows older. Many blood services are experiencing reduced blood stocks despite increasing efficiency by moving stocks more actively and using strategies such as electronic issue direct from the blood bank. These measures are decreasing blood wastage rates but could be insufficient to maintain the supply chain.

Many techniques are available to anaesthetists that may modify blood loss and transfusion requirements. There are now a large number of investigations in the literature showing those interventions that work well in different patient groups, but many questions still remain. Few studies have compared drugs with similar effects (for example, different anti-fibrinolytics) or evaluated interactions between different strategies (for example, perioperative cell salvage and anti-fibrinolytics). There have been few cost-effectiveness studies to help clinicians make a business case for the development of new services or funding of new drugs (for example, a cell salvage service or preoperative medication with erythropoietin). Finally, as these drugs become more widely used in trials, concerns regarding their overall safety profile are emerging. This chapter reviews recent publications covering each of these issues.
Perioperative anti-fibrinolytic treatment

Anti-fibrinolytics in cardiac surgery
Cardiac surgery is a major consumer of blood stocks; some estimates suggest that 20–30% of all blood is used in this setting. Greater blood use is associated with greater infection rates, longer hospital and intensive care stays, increased rates of re-exploration, and higher mortality [1]. Although many observational studies have examined this association, it is always difficult to determine whether blood transfusions cause these adverse effects or whether this is a form of confounding by indication. In other words, does blood cause the problem or is it simply associated with other, more important, causes of morbidity? Still, it is beneficial to both patients and blood stocks to utilize interventions that are effective in reducing blood transfusions in cardiac surgery. This specialty is particularly focused on exposure to blood, because many patients were previously infected with HIV and hepatitis C, and because transfusion rates are one of the outcomes scrutinized in the public domain.

Anti-fibrinolytic drugs decrease blood loss in cardiac surgery. This has been shown in multiple trials and confirmed in a Cochrane systematic review, last updated in 2003 [2]. Specifically, the review concluded that no further trials were needed for aprotinin, but that large trials were needed to evaluate cost-effectiveness and to compare effectiveness with other drugs, namely tranexamic acid and aminocaproic acid (both lysine analogues). Aprotinin is considerably more expensive than the other drugs. It may also have more diverse clinical effects than the lysine analogues as it is a serine protease enzyme inhibitor acting at potentially multiple sites.

The use of anti-fibrinolytic drugs for high-risk cases is recommended in most cardiac surgery clinical guidelines, including a recent comprehensive guideline published by the Society of Cardiovascular Anesthesiologists [3]. As a result, assessments of the effectiveness and safety of these drugs is problematic in ‘real life’. There are, broadly speaking, two approaches: first, to use large observational cohorts to examine the association between the drugs and relevant clinical outcomes, using appropriate statistical methods to adjust for confounding factors; and, second, to perform meta-analyses of the available trial data to produce pooled estimates of the incidence of important clinical outcomes. Several high-profile studies have been published on this subject over the past 2 years. These are presented below, followed by a commentary.

The risk associated with aprotinin in cardiac surgery

Background. It is well established from randomized controlled trials (RCTs) that aprotinin limits blood loss in cardiac surgery with cardiopulmonary bypass. There is also RCT evidence that tranexamic acid and aminocaproic acid reduce blood
These therapies are recommended in clinical guidelines and embedded in routine practice worldwide. Relatively few data exist concerning the incidence of adverse effects with these drugs. In this prospective observational cohort study of 4374 patients undergoing coronary revascularization, the authors evaluated the relative safety of aprotinin (1295 patients), aminocaproic acid (883) and tranexamic acid (822) versus no drug (1374 patients). The authors hypothesized that the use of anti-fibrinolytic drugs was unsafe and increased renal, cardiovascular and neurological complications. Complex statistical methods were used to adjust for relevant covariates, including 97 potential risk factors.

**Interpretation.** In propensity-adjusted, multivariable logistic regression, use of aprotinin was associated with doubling of risk for dialysis-dependent renal failure for patients undergoing complex surgery (odds ratio [OR] 2.59; 95% confidence interval [CI] 1.36–4.95) and primary surgery (OR 2.34; 95% CI 1.27–4.31). Aprotinin was associated with a 55% greater risk of myocardial infarction or heart failure and a 181% increased risk of stroke or encephalopathy. No increased risk was observed for tranexamic or aminocaproic acid. All three drugs decreased blood loss to a similar extent (mean reduction in blood loss ranging from 676 to 827 ml; \( P < 0.001 \) for all three drugs).

The authors concluded that in view of the association between aprotinin and serious organ damage, the continued use of aprotinin is not prudent, and that tranexamic and aminocaproic acid are equally efficacious but safer alternatives.

**Mortality associated with aprotinin during 5 years following coronary artery bypass graft surgery**


**Background.** Concerns regarding the short-term adverse effects of aprotinin have been raised by cohort studies. However, there are no data concerning whether possible short-term risks are associated with increased longer term mortality. This study reported long-term mortality at 6 weeks, 6 months and annually for 5 years after coronary artery bypass graft (CABG) surgery among 3876 patients followed up in the previous cohort study discussed above (*N Engl J Med* 2006; 354: 353–65). Fewer patients were included because 7 of the 69 study centres did not undertake long-term follow-up. Deaths after 5 years were compared using various complex multivariable statistical methods that adjusted for possible confounders.

**Interpretation.** Aprotinin treatment was associated with significantly higher 5-year mortality (20.8%) compared with control (12.7%), aminocaproic acid (15.8%) and tranexamic acid (14.7%). After statistical adjustment for the many potential confounders, the higher 5-year mortality remained for aprotinin compared with the control group, whichever statistical model was used (covariate adjusted hazard ratio for death 1.48, 95% CI 1.19–1.85; adjusted odds ratio for death with propensity adjustment 1.48, 95% CI 1.13–1.93; \( P = 0.005 \)). This effect was observed for the entire cohort and for the subgroup who survived their index hospital admission. Neither aminocaproic nor tranexamic acid was associated with increased mortality. The authors concluded that their earlier findings appear to translate into an excess mortality with aprotinin use (Fig. 1.1).
Fig. 1.1 Long-term mortality by patient characteristics and risk indices. CABG, coronary artery bypass graft surgery; PCTA, percutaneous transluminal coronary angioplasty surgery. Complex surgery was defined as surgery under any of the following conditions: a history of coronary artery bypass grafting, valve surgery, non-coronary angioplasty or stenting, or other cardiac or vascular non-cardiac surgery, combined current heart surgery; or current surgery in emergency status or urgent status with evidence of congestive heart failure preoperatively. Adapted scores for risk indices are based on various in-hospital indices and scores (Cleveland Clinic score, Society of Thoracic Surgeons score, additive European system for cardiac operative risk evaluation (EuroSCORE), logistic EuroSCORE, and Department of Veterans Affairs score). P values were calculated using two-tailed χ² comparisons among the three groups. Source: Mangano et al. (2007).
A propensity score case–control comparison of aprotinin and tranexamic acid in high-transfusion-risk cardiac surgery


**Background.** There are relatively few data directly comparing aprotinin (widely considered the most effective blood-sparing drug in cardiac surgery) with tranexamic acid (a cheaper alternative). The authors hypothesized that aprotinin would be superior to tranexamic acid. They used prospectively collected data on 10 870 patients undergoing cardiac surgery with cardiopulmonary bypass (CPB) in a single centre over 5 years. Of these, 586 patients received aprotinin and the remaining patients received tranexamic acid. The authors then used propensity scoring to try to match patients who received aprotinin with those who received tranexamic acid. They used 20 variables to try to match important differences between patients other than the anti-fibrinolytic drug received. The outcomes were stroke, acute renal failure requiring dialysis, acute deterioration in renal function, acute myocardial infarction, infection and in-hospital death.

**Interpretation.** The propensity-matching model generated 449 aprotinin patients matched to 449 tranexamic acid patients. Seventy-five to eighty per cent of patients were transfused (with 30–35% of patients receiving ≥5 red cell units), confirming that a high-risk group for transfusion was studied. There were no statistically or clinically significant differences in the use of red blood cells, fresh-frozen plasma (FFP) or platelets between the propensity-matched groups, although differences trended towards higher platelet and FFP use with aprotinin. There was no difference in myocardial infarction, stroke, infection or in-hospital mortality. Aprotinin use was associated with higher risk of deterioration in renal function (24% vs. 17%; \( P = 0.01 \)) and a trend to higher acute renal failure requiring dialysis (5.6% vs. 3.1%; \( P = 0.08 \)). This association was strongest for patients with pre-existing renal dysfunction. The authors acknowledged the many potential limitations in the study design. They nevertheless concluded that their data raise concerns that aprotinin could adversely affect renal function, particularly in patients with pre-existing renal dysfunction.

Meta-analysis comparing the effectiveness and adverse outcomes of antifibrinolytic agents in cardiac surgery

Brown Jr, Birkmeyer NJO, O’Connor GT. Circulation 2007; 115: 2801–13

**Background.** There are ongoing questions regarding the safety and effectiveness of anti-fibrinolytic drugs in cardiac surgery. This group performed a systematic review and meta-analysis of available data. They compared outcomes for each drug versus control, and where possible compared drugs with each other.

**Interpretation.** Randomized controlled trial data from 138 trials were evaluated for outcomes including total blood loss, transfusion of red cells, re-exploration, mortality,
stroke, myocardial infarction, dialysis-dependent renal failure and renal dysfunction (defined as 0.5 mg/dl increase in serum creatinine concentration from baseline). All drugs had similar effectiveness for decreasing blood loss (226 to 348 ml per case) and for decreasing the proportion of transfused patients. Only high-dose aprotinin reduced re-exploration rates (relative risk [RR] 0.49; 95% CI 0.33–0.73). There were no detected risks or benefits of any drug for mortality, stroke, myocardial infarction or dialysis-dependent renal failure (Fig. 1.2). However, high-dose aprotinin increased the risk of renal dysfunction (RR 1.47; 95% CI 1.12–1.94) (Fig. 1.3). In head-to-head comparison, aprotinin reduced blood loss more by an average of <300 ml per case, but there was no difference in the number of patients transfused. Other outcomes were similar between the drugs.

**Comment**

These studies confirm that all anti-fibrinolytic drugs are effective in decreasing blood loss in cardiac surgery. The question is which is most effective and, perhaps more importantly, do side-effects occur that outweigh this benefit? Ideally, the

![Relative risk (random effects)](image)

**Fig. 1.2** Adverse outcomes by anti-fibrinolytic agent compared with placebo. The relative risks (RR) of adverse outcomes (mortality, stroke and myocardial infarction) by anti-fibrinolytic drug vs. placebo are plotted. The RR (square) and 95% CIs (horizontal bars) summarize the effect using a random-effects model. Effects left of 1.0 favour the anti-fibrinolytic drug over placebo; effects to the right favour placebo over anti-fibrinolytic drug. When the horizontal bars cross 1.0, the effect is not significantly different from the comparison group; this is the case for all agents and for all adverse events (mortality, stroke, myocardial infarction) plotted here. Source: Brown et al. (2007).
safety profile would be determined in a large RCT powered to detect mortality, renal failure or the other outcomes described above. The problem is that these events are rare, so the trial would need to be very large and, therefore, unlikely to be funded or completed.

The two publications by Mangano and colleagues are striking and potentially worrying because, based on a very large number of patients, they appear to document a clear association between aprotinin use and harm, both when short- and long-term outcomes were evaluated. Although the study was not randomized, the data were collected prospectively, were apparently of high quality, and included many potentially important variables. There is some biological plausibility in the increased incidence of thrombotic complications, because aprotinin is an anti-fibrinolytic therapy given to a group of patients in whom the general therapeutic strategy is to use a variety of anti-coagulant and anti-platelet drugs to decrease coronary artery occlusion. In addition, aprotinin is known to have multiple incompletely understood biological actions and may be concentrated in renal tubules, which could explain the renal dysfunction.

The study by Karkouti and colleagues adds fuel to this fire by further suggesting a possible association with renal dysfunction, although the findings were less concerning for other outcomes. The key issue is whether the statistical handling of these observational data creates a fair comparison between the drug and the control groups. The methods used are well recognized, detailed and complex. Regression methods and the use of propensity matching essentially try to create

![Fig. 1.3 Renal failure and dysfunction by anti-fibrinolytic drug compared with placebo. The relative risks (RR) of renal complications (dialysis-dependent renal failure and renal dysfunction defined as an increase in serum creatinine concentration of ≥0.5 mg/dl) by anti-fibrinolytic drug vs. placebo are plotted. The RR (square) and 95% CIs (horizontal bars) summarize the effect using a random effects model. The only statistically significant effect shown here is the increased risk of renal dysfunction with the use of high-dose aprotinin vs. placebo. Source: Brown et al. (2007).]
a ‘quasi-randomized’ trial. The problem is that the groups can never be truly equal because clinicians chose to use a certain drug (or no drug) based on their experience and interpretation of available evidence. The comparisons could be considered unequivocal only if the included variables completely adjusted for clinician decisions, which can never be certain. Since surgeons and anaesthetists probably believed that blood sparing was most effective with aprotinin, they will probably have chosen it for the most difficult patients. This is bias by indication.

The meta-analysis by Brown uses data from RCTs, in which bias by indication was not present. These studies were mostly powered to detect decreased blood loss or transfusions, which is where the weakness of this approach to examine adverse effects arises. The completeness and consistency of reporting adverse outcomes vary, so it is difficult to be sure all were included. However, this potential reporting bias should have been distributed equally across different trial groups, so that, even if not all events were captured, this hopefully occurred equally. In addition, trials may not represent the ‘real world’ because patients excluded from protocols may be those more likely to suffer adverse effects in routine practice. The meta-analysis found no excess of thrombotic events or renal failure. Aprotinin in high dose seemed to decrease re-explorations but also increase renal dysfunction (but not renal failure).

What do these trials tell us about the use of anti-fibrinolytic drugs in CABG surgery? At present, we cannot be sure whether aprotinin has clinically important adverse effects compared with either placebo or the other drugs. A pragmatic view would be as follows. First, an anaesthetist/surgeon team should examine their own transfusion outcomes. For cases with low probability for transfusion (such as elective primary CABG), the safest practice is probably to avoid anti-fibrinalytics. Second, teams should identify and examine patients at high risk for transfusion and/or re-exploration (such as complex procedures or redo surgery). The use of anti-fibrinolytics should be evaluated in the context of the whole package of blood-sparing therapies. Specifically, cell salvage is of proven value in these cases, and the use of restrictive transfusion triggers postoperatively is safe. The choice between the three anti-fibrinolytic drugs is currently difficult, but a recent ‘sting in the tail’ following publication of these studies may make clinicians shy away from aprotinin until further data are available. A US Food and Drug Administration safety committee was reassured by safety data provided by Bayer (the manufacturer of Trasylol®) after publication of the above studies, but the company subsequently disclosed a large data set which may demonstrate ‘increased risk for death, kidney failure, congestive heart failure and stroke.’ At the time of writing, these data are still being analysed. A clearer answer is likely after analysis of these data and the completion and publication of the BART study, which will be the largest head-to-head comparison of all three drugs in preventing major bleeding complications in cardiac surgery.

Note added in press. Bayer have withdrawn aprotinin following early stopping of the BART study by the data monitoring committee, because of higher mortality in the patients treated with aprotinin.
Anti-fibrinolytics in paediatics

Tranexamic acid reduces intraoperative blood loss in paediatric patients undergoing scoliosis surgery


Background. Excessive bleeding often occurs during paediatric scoliosis surgery. The authors hypothesized that administration of tranexamic acid would reduce bleeding and transfusion requirements during scoliosis surgery. They randomly assigned patients to receive either 100 mg/kg of tranexamic acid before incision, followed by an infusion of 10 mg/kg/h during surgery, or a saline (placebo) control group. The primary outcome measures were blood loss and transfusion requirements.

Interpretation. Forty-four patients were randomized. In the tranexamic acid group, blood loss was reduced by 41% compared with placebo (mean 1230 vs. 2085 ml; \( P < 0.01 \)). The amount of blood transfused was less in the tranexamic acid group, but did not reach statistical significance (mean 615 ml vs. 940 ml; \( P = 0.08 \)). The clinical effect was most marked in the patients with secondary scoliosis rather than idiopathic scoliosis. In a regression analysis, tranexamic acid was an independent predictor of blood loss, together with American Society of Anesthesiologists (ASA) physical class and preoperative platelet count. No adverse events were noted in any patient. The authors concluded that tranexamic acid is effective in reducing perioperative blood loss in paediatric scoliosis surgery.

Comment

Reducing or avoiding transfusions in children is highly desirable. Any long-term risks from transfusion (including variant CJD) have greater potential to affect those who will live for many years after exposure to blood. This was a well-performed single-centre study. The authors provide a power analysis based on their own data for blood loss during scoliosis surgery and studied the intended number of patients. They proved their hypothesis that bleeding would be reduced. The reduction in red cell transfusion volume was clinically but not statistically significant and could have been an effect of the small sample size. In addition, blood tends to be administered in fixed volumes and may behave less like a continuous variable, which could have contributed to the less impressive effects. It was interesting that the effect was greatest in the secondary scoliosis group, and the authors comment that this could be related to the high fibrinolytic activity described in Duchenne muscular dystrophy [6]. Although no adverse effects were described, this is not surprising in a small randomized trial. Clinicians using tranexamic acid in children should remain vigilant for complications, particularly thrombotic events. In addition, the interaction between tranexamic acid and other blood conservation strategies, particularly perioperative cell salvage, is not yet known.
Section summary

Anti-fibrinolytic drugs are effective in reducing blood loss in surgery. The papers reviewed show this for cardiac and paediatric scoliosis surgery. A recently published meta-analysis of 43 trials in orthopaedic surgical procedures also confirmed this effect [7]. In 23 trials, the odds ratios for allogeneic transfusion were 0.43 (95% CI 0.28–0.64) for aprotinin and 0.17 (95% CI 0.11–0.24%) for tranexamic acid. The recent publications concerning aprotinin show that we may not fully understand the clinical effects of these drugs. The meta-analysis in orthopaedic surgery was careful to point out that there were inadequate data concerning safety in this setting. These papers come at a time when allogeneic transfusions are safer than ever, but more expensive and in ever shorter supply. Few of these studies have evaluated the interaction of these drugs with other blood-sparing strategies, such as cell salvage. One recently published small RCT compared aprotinin, tranexamic acid and control in 180 patients undergoing first time CABG surgery, all of whom received cell salvage [8]. In this study, both drugs further decreased transfusion exposure compared with controls but aprotinin was superior to tranexamic acid.

Until more data are available, clinicians need to consider each patient individually, asking themselves questions such as: What is the risk of major bleeding in this case? How important is avoiding transfusion to this patient? Could I use other methods of blood conservation? Finally, is this patient at high risk of relevant complications such as renal failure or thrombosis?

Organizational changes to optimize blood use and reduce blood transfusions

There are many studies of individual strategies to reduce blood transfusions. However, few studies have evaluated the impact of organizational change. This section describes two recent publications, one in which several strategies were combined as a complex intervention; the other a simple evaluation of the potential effect of tailoring transfusions to individual patients.

A cluster randomized, controlled trial of a blood conservation algorithm in patients undergoing total hip arthroplasty


**Background.** Many patients undergoing orthopaedic surgery require blood transfusion. Various individual strategies decrease transfusion requirements, including preoperative erythropoietin (EPO) therapy, preoperative donation and deposit of autologous blood, and restrictive transfusion triggers. Few studies
have evaluated the impact of a combined strategy or protocol on transfusion requirements. In this study, a blood conservation algorithm (Fig. 1.4) was devised. It included oral iron and preoperative erythropoietin therapy for patients with a haemoglobin concentration (Hb) < 130 g/l, preoperative autologous donation of 1–2 red cell units for patients with Hb > 130 g/l, and a restrictive transfusion trigger of 70 g/l postoperatively in asymptomatic patients. Using a cluster randomized design, the effectiveness of the algorithm was tested by comparing outcome in 14 hospitals with the algorithm and 15 hospitals without such algorithm. Data from 60 patients undergoing primary hip joint arthroplasty were included for each hospital.

**Interpretation.** Before introduction of the algorithm (see Fig. 1.4), the mean allogeneic transfusion rate was 25.6% (range 14.9–47.4%) in the control and 25.2% (range 13.8–50.6%) in the intervention hospitals. After introduction of the algorithm, the allogeneic transfusion rates (mean 26.1% [range 3.3–43.3%]) in the control vs. mean 16.5% [range 3.0–32.8%] in the intervention hospitals; \( P = 0.02 \) and the overall (allogeneic and autologous) transfusion rates (mean 39.7% in the control vs. mean 27.4% in the intervention hospitals; \( P = 0.04 \)) were lower in the intervention hospitals. At the same time, the rate of autologous pre-donations (control hospitals 25.8% vs. intervention hospitals 27.1%) and the proportion of patients receiving autologous transfusions (control hospitals 15.9% [range 0–46.8%] vs. intervention hospitals 12.5%)

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**Fig. 1.4** Blood conservation algorithm for elective total hip joint arthroplasty. Source: Wong et al. (2007). ABD, autologous blood donation.
I · PERIOPERATIVE CARE

[range 3.3–29.1%]) were similar between hospitals. The major difference between the
groups was the use of preoperative EPO (0.6% [range 0–5.1%] in control hospitals vs.
20.1% [range 3.7–36.7%] in intervention hospitals; \( P < 0.001 \)). Perioperative cell salvage
was not part of the blood conservation strategy but was used more frequently in the
control hospitals (19.6% vs. 1.3%). When allogeneic transfusions were used, the mean
number of transfused units was similar in both groups (control group 2.1 per patient
vs. intervention group 2.0 per patients). Hospital length of stay and incidence of major
complications (highest incidence 3.3% in any centre) were similar. The authors concluded
that a comprehensive approach to blood conservation can reduce allogeneic transfusion
in patients undergoing primary hip joint arthroplasty.

Comment

This study is important because it evaluated the effect of an algorithm incorporating
several individual components combined for a complex intervention (see Fig. 1.4).
The cluster randomized design meant that the intervention was evaluated in the
real world, and the authors comment that adherence to different components of
the algorithm varied between centres in the intervention group, which is obvious
from the data presented. Introduction of the algorithm clearly benefited patients:
in the intervention hospitals: the absolute risk of allogeneic transfusion was 9.6%
lower than in the control hospitals. This equates to avoiding blood transfusion in
about 1 out of 10 patients. The authors comment that this rate could be even higher
if clinicians followed it more universally. It is difficult to decide which part of the
algorithm was most important, but the data suggest that it was the use of preoperative
EPO in 20% of cases. The pattern of autologous predonation and transfusion was
similar. The mean lowest postoperative Hb value was slightly higher in the algorithm
group (94.1 g/l vs. 90.9 g/l; \( P = 0.04 \)), suggesting that postoperative anaemia was also
less severe. Unfortunately, the authors did not include any data concerning the
transfusion triggers actually used, so it is difficult to assess how closely this aspect
of the algorithm was followed. Pre-transfusion Hb value was > 100 g/l in 5.2% of
transfusions in the intervention group and in 15.5% of transfusions in the control
hospitals. This suggests significant non-compliance with restrictive transfusion
triggers.

Surprisingly, there are no data on overall allogeneic blood use in the intervention
and control hospitals. The authors state that: ‘if allogeneic blood was given, the
mean number of units was 2.1 in the control hospitals and 2.0 in the intervention
hospitals.’ Given that autologous use was similar, this does not suggest a major
saving of allogeneic blood. From the data presented, I estimate that about 20 units
of allogeneic units were saved per 100 cases managed with the algorithm. This,
combined with greater transfusion avoidance, could be clinically important.

However, a key question is whether the strategy is cost-effective. Two of the
key interventions were expensive: first, autologous donation, which was similar in
intervention and control hospitals; second, preoperative EPO for anaemic patients,
which was the major difference between groups (greater use in the intervention
hospitals). Many centres have now abandoned autologous pre-donation because of
high expense and evidence suggesting that it may increase overall exposure to blood
transfusions. A Cochrane systematic review, updated in 2004, found that RCTs were of low quality and reported high overall transfusion rates [9]. Although the risk of allogeneic transfusion was decreased by 64% (RR 0.36; 95% CI 0.25–0.51), the risk of receiving any blood transfusion (allogeneic and/or autologous) was actually increased by preoperative autologous blood donation (ABD) (RR 1.33; 95% CI 1.10–1.61).

Preoperative EPO therapy is expensive, both in terms of drug costs and the need to deliver treatment to patients preoperatively. In this trial, EPO was provided free by manufacturers and a cost-effectiveness analysis was not included. Previous trials and systematic reviews have shown that EPO can decrease transfusion exposure and allogeneic blood use. However, it is unlikely to be cost-effective. Even as the costs of allogeneic blood increase, there will need to be a dramatic cost reduction in EPO before it is cost-effective when assessed against allogeneic blood savings. This is particularly true if baseline blood use is lowered with modern surgical and anaesthetic techniques, cell salvage for selected cases and more restrictive transfusion triggers. What is needed is more evidence for other benefits of EPO, such as improved recovery rates and quality of life; these are lacking in published studies. More work is also needed to examine which patients benefit most and what dosing schedule is most cost-effective. A recently published trial of patients presenting for orthopaedic surgery with a haematocrit of 30–39% found that two EPO doses were effective in achieving the preoperative target haematocrit of 40% in 63% of cases [10]. This is half of the widely recommended schedule of four doses of EPO.

Another unknown is the safety profile of perioperative EPO. As in the case of anti-fibrinolytics, rare adverse outcomes make this assessment difficult. In 2006, two large trials of long-term EPO therapy in patients with non-dialysis-dependent renal failure were published [11,12]. They failed to show any benefit but reported increased harm due to thrombotic events when anaemia was corrected to normal values. Given the current safety of allogeneic blood in terms of infections, it is difficult to be sure that EPO is safer than a blood transfusion.

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**A retrospective study evaluating single-unit red blood cell transfusions in reducing allogeneic blood exposure**


**Background.** Most transfusion guidelines recommend single-unit transfusions followed by reassessment, but most clinicians still prescribe a minimum of two units of red cells when a transfusion decision is made. This single-centre study used retrospective analysis of adult patient data to assess the potential impact of single-unit transfusions. The authors used the observed change in haemoglobin (Hb) concentration per unit to assess likely savings if different transfusion triggers and targets (ranging from 7 to 9 g/dl) had actually been used.

**Interpretation.** The authors evaluated 302 transfusion events; 78.5% were two-unit transfusions and the rest single-unit transfusions. Mean pre-transfusion Hb value was
The authors estimated that, if the target Hb value was ≥9, ≥8, or ≥7 g/dl, a single-unit transfusion would have been sufficient in 42%, 80% and 98% of patients, respectively. They estimated that this could save 0.21, 0.57 or 0.82 red cell units per patient, respectively.

Comment
This was a simple study that made many assumptions based on purely retrospective data, but it gives a clear message. The traditional view that a single unit of red cells suggests no transfusion requirement and that two units is the minimum useful dose has no scientific basis. Recent studies indicating potential adverse effects from allogeneic blood exposure and equivalent outcomes when restrictive transfusion triggers are used suggest that the target Hb value for an individual patient should be documented and transfusions administered to achieve this target. Although many clinicians probably use a relatively low Hb value as transfusion trigger, they frequently still prescribe multiple red cell units. This may ‘overshoot’ the intended Hb value (if one was identified) and potentially increase the risk of complications, such as fluid overload. A cheap and simple change in practice of using single red cell units could have a significant impact on allogeneic blood use, reduce transfusion exposure and still maintain Hb concentration at the upper end of the ‘safe’ 7–10 g/dl range quoted in most guidelines.

Anaemia, transfusion triggers and outcomes

Preoperative hematocrit levels and postoperative outcomes in older patients undergoing non-cardiac surgery


Background. Anaemia is prevalent in elderly patients presenting for surgery. This group also has a high risk of cardiovascular complications, particularly after non-cardiac surgery. Although most elderly patients undergo preoperative Hb measurement, the influence of preoperative anaemia and polycythaemia on postoperative mortality and cardiovascular complications is poorly understood. This study investigated the association between preoperative haematocrit and outcome in patients aged > 65 years, using a large observational database (the Veterans Administration National Surgical Quality Improvement Program database).

Interpretation. Data from 310,311 patients aged > 65 years who underwent non-cardiac surgery between 1997 and 2004 were included. The relation between preoperative haematocrit (measured within 3 months for 99%, and within 1 month for
79% of cases) and 30-day postoperative mortality was examined, adjusting for multiple patient- and surgery-related variables that also predicted mortality. Adjusted mortality increased by a mean of 1.6% (95% CI 1.1–2.2%) for every percentage point deviation from the normal haematocrit range of 39.0–53.9% (Table 1.1). A similar increased risk was observed for a composite outcome of 30-day mortality or cardiac event. In subgroup analysis, the association was limited to males and non-emergency surgery. Among surgical subspecialties, the mortality increase per percentage point deviation from the normal range was greatest for orthopaedic surgery (3.1% per 1% haematocrit deviation) (Table 1.2).

Comment
This study is subject to the limitations of any observational cohort study. There was a clear association for anaemia and polycythaemia with mortality and cardiovascular complications. However, it is not clear whether preoperative anaemia and polycythaemia cause harm, or if the association is explained by other confounding factors. Despite adjusting for 45 other wide-ranging independent associations (such as ASA physical class, complexity of procedure, type of surgery, various chronic disease states and a number of biochemical variables), it is impossible to know whether an abnormal haematocrit value per se causes adverse outcomes. This study did not include any data about perioperative transfusions or postoperative haematocrit values. It therefore does not tell us how to manage patients with anaemia or polycythaemia. At best, the study generates the hypothesis that preoperative anaemia is important, and emphasizes the need for more research. For non-cardiac surgery the prevalence of preoperative anaemia was 43%, so better evidence about perioperative anaemia management is relevant to many patients worldwide. The findings differ from a similar study in patients refusing blood transfusions, in which excess mortality was most prevalent in patients with cardiovascular disease [13]. As Wu and colleagues state, their data indicate the need for trials of different management strategies for patients with abnormal preoperative haematocrit values to determine whether modification of this risk factor alters outcomes.
### Table 1.1 Thirty-day mortality risk per percentage point deviation from normal haematocrit range among different subgroups

<table>
<thead>
<tr>
<th>Haematocrit (%)</th>
<th>No. of cases</th>
<th>Thirty-day crude mortality rates (%)</th>
<th>Thirty-day crude cardiac event rates (%)</th>
<th>Adjusted odds ratio for 30-day death (95% confidence interval)</th>
<th>Adjusted odds ratio for 30-day death or cardiac events (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;18.0</td>
<td>129</td>
<td>35.4</td>
<td>14.6</td>
<td>2.42 (1.55–3.79)</td>
<td>2.41 (1.55–3.73)</td>
</tr>
<tr>
<td>18.0–20.9</td>
<td>304</td>
<td>26.8</td>
<td>8.6</td>
<td>1.68 (1.22–2.30)</td>
<td>1.52 (1.12–2.07)</td>
</tr>
<tr>
<td>21.0–23.9</td>
<td>1292</td>
<td>16.6</td>
<td>4.9</td>
<td>1.09 (0.89–1.33)</td>
<td>1.11 (0.93–1.34)</td>
</tr>
<tr>
<td>24.0–26.9</td>
<td>5172</td>
<td>14.9</td>
<td>4.4</td>
<td>1.33 (1.16–1.52)</td>
<td>1.27 (1.13–1.44)</td>
</tr>
<tr>
<td>27.0–29.9</td>
<td>14339</td>
<td>11.2</td>
<td>3.7</td>
<td>1.25 (1.12–1.40)</td>
<td>1.25 (1.13–1.38)</td>
</tr>
<tr>
<td>30.0–32.9</td>
<td>24678</td>
<td>8.4</td>
<td>3.1</td>
<td>1.21 (1.08–1.35)</td>
<td>1.19 (1.08–1.31)</td>
</tr>
<tr>
<td>33.0–35.9</td>
<td>35742</td>
<td>5.8</td>
<td>2.5</td>
<td>1.22 (1.10–1.36)</td>
<td>1.20 (1.09–1.32)</td>
</tr>
<tr>
<td>36.0–38.9</td>
<td>51314</td>
<td>3.5</td>
<td>1.8</td>
<td>1.15 (1.04–1.28)</td>
<td>1.12 (1.03–1.23)</td>
</tr>
<tr>
<td>39.0–41.9</td>
<td>66487</td>
<td>2.2</td>
<td>1.3</td>
<td>1.04 (0.93–1.15)</td>
<td>1.10 (1.01–1.20)</td>
</tr>
<tr>
<td>42.0–44.9</td>
<td>61928</td>
<td>1.7</td>
<td>1.0</td>
<td>1.02 (0.91–1.13)</td>
<td>1.06 (0.97–1.17)</td>
</tr>
<tr>
<td>45.0–47.9</td>
<td>34354</td>
<td>1.5</td>
<td>0.9</td>
<td>1 [Reference]</td>
<td>1 [Reference]</td>
</tr>
<tr>
<td>48.0–50.9</td>
<td>11358</td>
<td>1.8</td>
<td>1.0</td>
<td>1.12 (0.94–1.32)</td>
<td>1.12 (0.97–1.30)</td>
</tr>
<tr>
<td>51.0–53.9</td>
<td>2577</td>
<td>3.1</td>
<td>1.4</td>
<td>1.48 (1.15–1.91)</td>
<td>1.42 (1.13–1.78)</td>
</tr>
<tr>
<td>≥54</td>
<td>637</td>
<td>5.6</td>
<td>2.9</td>
<td>1.56 (1.06–2.31)</td>
<td>1.55 (1.09–2.22)</td>
</tr>
</tbody>
</table>

The analysis was adjusted for American Society of Anesthesiologists class, serum albumin, emergency operation, disseminated cancer, functional status, work relative value unit, serum urea nitrogen, do-not-resuscitate order, surgical subspecialty, age, myocardial infarction in previous 6 months, white blood cell count, weight loss, ascites, dyspnoea, serum aspartate transaminase, impaired sensorium, platelet count, concurrent pneumonia, chronic obstructive pulmonary disease, congestive heart failure in previous 30 days, serum creatinine, serum sodium, serum bilirubin, dialysis, coma, steroid use, alkaline phosphatase, previous stroke with neurological deficit, bleeding disorder, surgical wound class, smoker, angina admission in prior 30 days, ventilator dependence, use of preoperative blood transfusion and acute renal failure.

Source: Wu et al. (2007).
Silent myocardial ischaemia and haemoglobin concentration: a randomized, controlled trial of transfusion strategy in lower limb arthroplasty


**Background.** Orthopaedic surgery patients frequently require blood transfusions. Although restrictive transfusion trigger values have become widely adopted, the optimum trigger value for patients with ischaemic heart disease is uncertain. This study used Holter monitoring to compare the effect of a restrictive and a liberal red cell transfusion strategy on the incidence of silent myocardial ischaemia (SMI) in patients without signs or symptoms of ischaemic heart disease (IHD) who underwent lower limb arthroplasty.

**Interpretation.** In a multicentre controlled trial, 260 patients undergoing elective hip or knee replacement surgery were randomized to a restrictive (Hb value 8 g/dl) or liberal (Hb value 10 g/dl) transfusion trigger. Patients were monitored for SMI from 12 h preoperatively to 72 h postoperatively. The primary outcome was the ischaemic load, namely the mean time of SMI per hour over the monitored period. In the restrictive vs. liberal group, mean postoperative Hb value was 9.9 g/dl vs. 11.1 g/dl, transfusion rate 34% vs. 43%, and the incidence of SMI 19% vs. 24% (P = 0.41). There was no overall difference in the ischaemic load between the restrictive (median 0 min/h; range 0 to
4.2 min/h) and liberal group (median 0 min/h; range 0–19.5 min/h). Among patients who experienced SMI, the mean ischaemic load was smaller in the restrictive group than in the liberal group (0.5 min/h vs. 1.5 min/h; ratio 0.32; \( P = 0.011 \)).

**Comment**

There is uncertainty regarding how to manage anaemic patients with IHD in the perioperative period. There are no adequately powered RCTs to guide decisions. Expert opinion, supported by the physiological rationale that reduced oxygen content is potentially harmful in the high oxygen extraction coronary circulation, is that higher transfusion triggers should be used for patients with coronary disease. Most guidelines suggest a Hb trigger of 8–9 g/dl, aiming for a concentration of 9–10 g/dl [14]. This advice is supported by cohort studies that found associations between Hb concentrations <9–10 g/dl and adverse outcomes in the critical care and perioperative settings [13,15]. In the Transfusion Requirements in Critical Care (TRICC) trial subgroup analysis, the survival curves of patients with IHD were superior in the liberal group (transfusion trigger <10 g/dl) than in the restrictive group (transfusion trigger <7 g/dl), although the difference was not statistically significant and the study was not powered for this analysis [16]. Grover and colleagues therefore set out to answer an important question in a group of patients who frequently suffer perioperative anaemia and have high transfusion rates. Unfortunately, this study does not provide definitive answers for several reasons: first, the study was powered for a higher mean rate of SMI (30%) than was observed; second, their intention was to recruit 660 patients to achieve adequate power, but recruitment was slower than anticipated and funding ran out before completion; third, the transfusion protocols did not achieve a clinically important separation of the groups, and the restrictive group had a relatively high mean Hb concentration. Therefore, although the study was designed to show equivalence between transfusion triggers for Hb values of 8 g/dl and 10 g/dl and the incidence of perioperative SMI, it does not prove this relationship. The authors also excluded patients with signs of more severe or unstable IHD, which is the group of greatest interest. However, the study does show that about 20% of patients undergoing major orthopaedic surgery experience SMI, and it probably excludes a large adverse effect from a moderately restrictive transfusion practice.

**Section summary**

The increasing trend to early postoperative discharge and limited follow-up after major surgery raises concerns that cardiovascular morbidity or other important consequences of anaemia may be missed. A recently published study showed that a cohort of orthopaedic patients took 1–2 months to recover from a mean Hb concentration of 10.4 g/dl at postoperative day 1 [17]. If surgeons and anaesthetists become more restrictive with transfusions (based on present recommendations), patients will be exposed to a significant period of postoperative anaemia. Similar observations have been made in critically ill patients managed with restrictive transfusion triggers in the intensive care unit (ICU). In a multicentre cohort
study, 25% of intensive care survivors managed with a mean transfusion trigger of 7.8 g/dl had a Hb concentration <9 g/dl at ICU discharge [18]. Of these, 25% had documented IHD with a similar prevalence of anaemia. A third of the patients still had a Hb concentration <10 g/dl when discharged home [19]. Considering the previously reported association between postoperative anaemia and adverse outcomes (Wu et al. 2007), the findings of Grover and colleagues and those of the TRICC trial (the only large RCT comparing two transfusion triggers) should be interpreted with caution. More studies are needed to determine whether restrictive transfusion triggers are safe for all patients, or whether increased morbidity occurs as a consequence of postoperative anaemia. The FOCUS trial is an ongoing trial that may answer some of these questions. It will recruit 2600 patients undergoing hip fracture surgery, comparing a liberal with a symptomatic transfusion trigger. The outcomes are based on function and cardiovascular status. The trial protocol was recently published, and the results are eagerly awaited [20].

Paediatrics

Transfusion strategies for patients in paediatric intensive care units


**Background.** The optimal haemoglobin (Hb) threshold for red cell transfusions in critically ill children is unknown. The authors hypothesized that a restrictive transfusion strategy using leuco-depleted red cells would be as safe as a liberal transfusion strategy. The authors randomized 637 stable critically ill children aged between 3 days and 14 years who had Hb concentrations <9.5 g/dl within 7 days of intensive care admission. A total of 320 patients were randomized to a Hb transfusion threshold of 7 g/dl and 317 to a threshold of 9.5 g/dl. The primary outcome was the proportion of patients who died during the 28 days after randomization, had concurrent dysfunction of two or more organ systems (termed MODS) or progression of MODS, as evidenced by worsening of one or more organ dysfunctions.

**Interpretation.** Mean Hb values in the restrictive and liberal groups were 8.7 g/dl and 10.8 g/dl, respectively (mean difference 2.1 g/dl; P<0.001). In the restrictive group, 54% of patients did not receive transfusions compared with 2% in the liberal group (P<0.001). Patients in the restrictive group received 44% fewer transfusions, and the mean blood use was 0.9 vs. 1.7 transfusions per patient (P<0.001). New or progressive MODS developed in 38 patients in the restrictive group, compared with 39 in the liberal group (absolute risk reduction with the restrictive strategy 0.4%; 95% CI –4.6% to 5.4%). There were 14 deaths in each group and no difference in the measured adverse events, which included organ dysfunction, nosocomial infections, days of mechanical ventilation and ICU stay (Table 1.3). The authors concluded that in stable critically ill children a Hb transfusion trigger of 7 g/dl decreases transfusions without increasing adverse outcomes.
<table>
<thead>
<tr>
<th>Variable</th>
<th>Restrictive strategy group</th>
<th>Liberal strategy group</th>
<th>Absolute risk reduction, odds ratio or difference in means (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary outcome</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>New or progressive MODS – no./total no. (%)†</td>
<td>38/320 (12)</td>
<td>39/317 (12)</td>
<td>0.4 (–4.6 to 5.5)</td>
<td>NI‡</td>
</tr>
<tr>
<td><strong>Age (days)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤28</td>
<td>1/11 (9)</td>
<td>0</td>
<td>–9.1 (–26.1 to 7.9)</td>
<td>1.00</td>
</tr>
<tr>
<td>29–364</td>
<td>14/143 (10)</td>
<td>20/142 (14)</td>
<td>4.3 (–3.2 to 11.8)</td>
<td>0.28</td>
</tr>
<tr>
<td>&gt; 364</td>
<td>23/166 (14)</td>
<td>19/167 (11)</td>
<td>–2.5 (–9.6 to 4.7)</td>
<td>0.51</td>
</tr>
<tr>
<td><strong>Country§</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Belgium</td>
<td>3/66 (5)</td>
<td>4/66 (6)</td>
<td>0.74 (0.16–3.43)</td>
<td>0.70</td>
</tr>
<tr>
<td>Canada</td>
<td>32/205 (16)</td>
<td>28/203 (14)</td>
<td>1.16 (0.67–2.00)</td>
<td>0.60</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>2/26 (8)</td>
<td>5/23 (22)</td>
<td>0.30 (0.05–1.73)</td>
<td>0.17</td>
</tr>
<tr>
<td>United States</td>
<td>1/23 (4)</td>
<td>2/25 (8)</td>
<td>0.52 (0.04–6.18)</td>
<td>0.61</td>
</tr>
<tr>
<td><strong>Severity of illness (PRISM score)†¶</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 (lowest quartile)</td>
<td>3/64 (5)</td>
<td>4/66 (6)</td>
<td>1.5 (–6.3 to 9.4)</td>
<td>1.00</td>
</tr>
<tr>
<td>1–4 (second quartile)</td>
<td>13/128 (10)</td>
<td>11/111 (10)</td>
<td>–0.3 (–7.9 to 7.4)</td>
<td>0.94</td>
</tr>
<tr>
<td>5–7 (third quartile)</td>
<td>6/54 (11)</td>
<td>6/67 (9)</td>
<td>–2.2 (–13.0 to 8.7)</td>
<td>0.69</td>
</tr>
<tr>
<td>≥8 (highest quartile)</td>
<td>16/74 (22)</td>
<td>18/75 (24)</td>
<td>2.4 (–11.1 to 15.9)</td>
<td>0.73</td>
</tr>
<tr>
<td><strong>Suspended protocol – no./total no. (%)</strong></td>
<td>18/39 (46)</td>
<td>13/20 (65)</td>
<td>18.9 (–7.3 to 45.0)</td>
<td>0.17</td>
</tr>
<tr>
<td><strong>Secondary outcomes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Measures of severity of organ dysfunction</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of dysfunctional organs</td>
<td>1.6 ± 1.4</td>
<td>1.5 ± 1.2</td>
<td>–0.1 (–0.26 to 0.13)</td>
<td>0.87</td>
</tr>
<tr>
<td><strong>PELOD score</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>After randomization</td>
<td>9.8 ± 11.9</td>
<td>8.4 ± 10.9</td>
<td>–1.4 (–3.1 to 0.4)</td>
<td>0.16</td>
</tr>
<tr>
<td>On day 1</td>
<td>6.3 ± 6.8</td>
<td>5.2 ± 6.2</td>
<td>–1.1 (–2.1 to –0.1)</td>
<td>0.09</td>
</tr>
<tr>
<td>Highest daily score after day 1</td>
<td>10.2 ± 13.3</td>
<td>8.9 ± 11.9</td>
<td>–1.2 (–3.2 to 0.8)</td>
<td>0.34</td>
</tr>
</tbody>
</table>
### Change in score

<table>
<thead>
<tr>
<th>Variable</th>
<th>Restricted strategy</th>
<th>Liberal strategy</th>
<th>Difference (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in score</td>
<td>3.8 ± 10.9</td>
<td>3.8 ± 9.9</td>
<td>-0.1 (-1.7 to 1.5)</td>
<td>0.97</td>
</tr>
<tr>
<td>Average daily score</td>
<td>5.0 ± 6.1</td>
<td>4.2 ± 5.1</td>
<td>-0.8 (-1.7 to 0.1)</td>
<td>0.13</td>
</tr>
</tbody>
</table>

### Average daily score

<table>
<thead>
<tr>
<th>Variable</th>
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<th>Liberal strategy</th>
<th>Difference (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in score</td>
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<td>3.8 ± 9.9</td>
<td>-0.1 (-1.7 to 1.5)</td>
<td>0.97</td>
</tr>
<tr>
<td>Average daily score</td>
<td>5.0 ± 6.1</td>
<td>4.2 ± 5.1</td>
<td>-0.8 (-1.7 to 0.1)</td>
<td>0.13</td>
</tr>
</tbody>
</table>

### Clinical outcomes – no./total no. (%)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Restricted strategy</th>
<th>Liberal strategy</th>
<th>Difference (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death In ICU</td>
<td>11/320 (3)</td>
<td>8/317 (3)</td>
<td>-0.9 (-3.6 to 1.7)</td>
<td></td>
</tr>
<tr>
<td>From any cause during 28-day study</td>
<td>14/320 (4)</td>
<td>14/317 (4)</td>
<td>0 (-3.2 to 3.2)</td>
<td></td>
</tr>
<tr>
<td>Nosocomial infections</td>
<td>65/320 (20)</td>
<td>79/317 (25)</td>
<td>4.6 (-1.9 to 11.1)</td>
<td></td>
</tr>
<tr>
<td>At least one adverse event</td>
<td>97/320 (30)</td>
<td>90/317 (28)</td>
<td>-1.92 (-9.0 to 5.2)</td>
<td></td>
</tr>
<tr>
<td>Reactions to red cell transfusion</td>
<td>3/320 (1)</td>
<td>6/317 (2)</td>
<td>1.0 (-0.9 to 2.8)</td>
<td></td>
</tr>
<tr>
<td>Duration of care (days)</td>
<td>6.2 ± 5.9</td>
<td>6.0 ± 5.4</td>
<td>-0.14 (-1.1 to 0.8)</td>
<td>0.76</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>9.5 ± 7.9</td>
<td>9.9 ± 7.4</td>
<td>0.46 (-0.7 to 1.7)</td>
<td>0.39</td>
</tr>
</tbody>
</table>

### Source

Lacroix et al. (2007).
**Comment**

This is a landmark study. The authors used a restrictive strategy similar to the TRICC study in critically ill adults, namely a transfusion trigger of 7 g/dl aiming to maintain a Hb concentration of 8–9.5 g/dl. They showed this was as safe as more liberal blood use. The main benefit was a dramatic reduction in blood exposure and blood use in critically ill children. The number needed to treat to avoid transfusions with the restrictive practice compared with liberal blood use was only two, which is a huge clinical effect. The authors had to choose a composite endpoint because mortality is low in paediatric ICUs, so a sufficiently powered trial for this endpoint was not feasible. The study was designed to show equivalence, and the authors predefined this as the upper limit of the 95% confidence interval for the primary outcome being <10% higher in the restrictive groups compared with the liberal group. This value in the trial was +4.6% so the data suggested that, at worst, about 1 in 20 children might suffer worsening organ failures with the restrictive practice, but most likely this outcome was similar for the groups. The possibility remains that a restrictive transfusion strategy has adverse effects that were not detected in the study, but there is little to suggest this, especially as ICU length of stays were similar. As was the case after publication of the TRICC trial in adults, the next challenge will be to translate the findings of this study into clinical practice. Doing so will avoid unnecessary transfusions for many thousands of sick children.

**Conclusion**

There are proven interventions that clearly avoid transfusions in the perioperative period. Perhaps the most effective and cheapest of these remains a clear documentation of a transfusion trigger and a target haemoglobin range, achieved using tailored (single unit) transfusions whenever possible. We still lack a clear understanding of the risks of anaemia in older patients and those with cardiovascular disease. Until further trials are published, clinicians need to use their experience and physiological monitoring to judge what haemoglobin value is safe in the perioperative period. As the risk–benefit profile of anti-fibrinolytics is, if anything, less certain now than previously, it is best to use an individualized approach. Local audit of practice will identify those surgeries, surgeons or anaesthetists for whom blood losses and transfusion requirements are greater than departmental or national averages. In some cases, particularly high-risk surgeries such as complex or revision cardiac surgery and revision hip arthroplasty, the risk–benefit will probably favour the use of an anti-fibrinolytic and/or perioperative cell salvage whenever possible. This approach is also appropriate for patients who decline or wish to avoid blood transfusions. For more expensive therapies, such as preoperative EPO and/or autologous donation, cost-effectiveness is likely to become increasingly important given the financial constraints in many healthcare systems. At present, the safety and continued availability of allogeneic blood probably make these therapies unjustified.
in most health services. However, in the likely case that allogeneic blood becomes scarcer and more expensive, and/or the cost of EPOs decreases, the balance could shift. In anticipation of this situation we need to further improve our understanding of the safety of the various blood-sparing drugs and strategies. Several ongoing trials and studies will hopefully provide some clarification of these issues in the near future.

References


