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Major themes for 2012 in cardiovascular anesthesia and intensive care

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ABSTRACT
There was major progress through 2012 in cardiovascular anesthesia and intensive care. Although recent meta-analysis has supported prophylactic steroid therapy in adult cardiac surgery, a large Dutch multicenter trial found no outcome advantage with dexamethasone. A second large randomized trial is currently testing the outcome effects of methylprednisolone in this setting. Due to calibration drift, the logistic EuroSCORE has recently been recalibrated. Despite this model revision, EuroSCORE II still overestimates mortality after transcatheter aortic valve implantation. It is likely that a specific perioperative risk model will be developed for this unique patient population. Recent global consensus has prioritized 12 non-surgical interventions that merit further study for reducing mortality after surgery. There is currently a paradigm shift in the conduct of adult aortic arch repair. Recent advances have facilitated aortic arch reconstruction with routine antegrade cerebral perfusion at mild-to-moderate hypothermia. Further integration of hybrid endovascular techniques may allow future aortic arch repair without hypothermia or circulatory arrest. These advances will likely further improve patient outcomes.

Keywords: meta-analysis, steroids, dexamethasone, methylprednisolone, cardiopulmonary bypass, perioperative risk, logistic EuroSCORE, EuroSCORE II, transcatheter aortic valve implantation, consensus conference, volatile anesthetics, levosimendan, insulin, chlorhexidine, intra-aortic balloon counterpulsation, selective decontamination, digestive tract, mortality, noninvasive ventilation, neuraxial anesthesia, clonidine, leukodepletion, oxygen, hemodynamic optimization, aortic arch repair, hypothermia, circulatory arrest, hybrid aortic arch repair.

INTRODUCTION
This article is the fourth in an annual series that provides the opportunity to review major themes for 2012 in cardiovascular anesthesia and intensive care (1-3). The first major theme is the extensive evidence about steroid prophylaxis in cardiac surgery with cardiopulmonary bypass (CPB). This evidence has progressed from single center randomized trials to exhaustive meta-analysis and now has finally reached the era of large multicenter randomized placebo-controlled trials. It is a fine example of the importance of searching for perioperative outcome benefit with non-surgical interventions. This review then highlights the recent focus on improving perioperative risk prediction after cardiac surgery,
particularly in high-risk patients, including those undergoing transcatheter aortic valve implantation. The third selected major theme for 2012 is the ongoing search for non-surgical techniques that can significantly decrease perioperative mortality. In conclusion, this review highlights the paradigm shifts in adult aortic arch repair that have entered clinical practice such as avoidance of deep hypothermia, minimizing circulatory arrest, routine antegrade cerebral perfusion and hybrid techniques. The past year has witnessed significant progress which will likely further improve important clinical outcomes in cardiovascular anesthesia and intensive care.

Can steroids improve survival after cardiac surgery?
Cardiac surgery with CPB stimulates a systemic inflammatory response. This syndrome activates both the humoral and cellular inflammatory pathways with immediate and delayed responses that determine clinical outcomes (4). Since steroids attenuate this robust inflammatory response to CPB, perioperative prophylaxis with these agents has the potential to improve mortality and morbidity after cardiac surgery with CPB (5).

In adult heart surgery with CPB, the outcome effects of preemptive steroid therapy have been systematically evaluated initially by multiple randomized clinical trials and more recently by serial meta-analyses (6-10). This cumulative evidence base strongly suggests that dampening of the CPB-induced inflammatory response with steroids significantly reduces major morbidity endpoints.

This highly positive set of clinical trials provided the clinical impetus for definitive large multicenter randomized trials to evaluate whether steroid prophylaxis affects mortality and major morbidity after adult cardiac surgery with CPB. The first of these trials was recently completed and published (N = 4494: 8 medical centers in the Netherlands) (11). This multicenter double-blind trial randomized adults undergoing cardiac surgery with CPB (2006-2011) to receive a single intraoperative dose of dexamethasone (1 mg/kg) or placebo. The primary trial endpoint was defined as a composite of death, stroke, myocardial infarction, respiratory failure, and renal failure within the first 30 postoperative days. Exposure to dexamethasone did not significantly reduce the risk of the primary endpoint (relative risk 0.83; 95% confidence interval 0.67-1.01; P = 0.07) (11). Despite this non-significant trend of the primary endpoint, dexamethasone prophylaxis did significantly reduce the risk of the following secondary endpoints: duration of postoperative mechanical ventilation (P < 0.001); length of stay in the intensive care unit (P < 0.001); length of hospital stay (P = 0.009); and, delirium (relative risk 0.79; 95% confidence interval 0.66-0.94; P = 0.006). Although dexamethasone exposure was predictably significantly associated with perioperative hyperglycemia, it significantly reduced the risk of postoperative infection (relative risk 0.64; 95% confidence interval 0.54-0.75; P < 0.001). The protection from postoperative infection was primarily due to a significantly reduced risk of postoperative pneumonia (relative risk 0.56; 95% confidence interval 0.46-0.69; P < 0.001) (11). Although this trial was negative for the defined composite primary endpoint, it detected significant benefits in the secondary endpoints that could be further investigated in high risk patients such as those with chronic obstructive pulmonary disease, given its prevalence and perioperative significance in adult cardiac surgery (12, 13).

A second multicenter study of steroids in adult cardiac surgery with CPB, the SIRS (Steroids In CaRdiac Surgery) trial, is currently enrolling patients (full details...
available at www.clinicaltrials.gov, last accessed January 12th 2013). The SIRS trial is a Canadian-based multicenter trial (N = 7,500) that is randomizing adult cardiac surgical patients to methylprednisolone (250 mg on anesthetic induction and 250 mg again on CPB) or placebo. The primary trial endpoint is mortality at 30 days after randomization. Although the SIRS trial was initiated in 2007, study enrollment is progressing rapidly. By October 31st 2012, about 5,000 patients had been enrolled at 65 sites in 134 countries (personal communication from Dr R. Whitlock, principal investigator of the SIRS trial). It is likely that subject recruitment will be completed early. The results of this trial may be published by 2014, and will likely significantly influence the future of steroid prophylaxis in adult cardiac surgery with CPB. If the SIRS trial demonstrates that exposure to methylprednisolone decreases mortality, it will significantly strengthen the rationale for routine steroid prophylaxis in adult cardiac surgery with CPB. If the SIRS trial demonstrates no effect on mortality, it may identify, through prudent subgroup analysis, high-risk populations that may benefit from steroid therapy, as was the case for the Dutch dexamethasone trial. In this scenario, it is likely that future steroid trials will focus on the high-risk adult cardiac surgical groups that had demonstrated outcome benefit in these 2 landmark trials.

In complex adult cardiothoracic surgery such as aortic arch procedures with deep hypothermic circulatory Chinese adults arrest, steroid prophylaxis for neuroprotection is very common, despite a paucity of high-quality evidence (14-16). A recent evaluation of adult deep hypothermic circulatory arrest in confirmed the contemporary popularity of this practice (17). The advent of large registries, such as the International Registry of Acute Aortic Dissection, the Italian Emilia Romagna Cardiac Surgery Registry and the German Registry of Acute Aortic Dissection Type A, provides the opportunity to evaluate steroid prophylaxis in complex thoracic aortic surgery (18-20). It is likely that future trials from these large adult cardiac registries will explore the effects of steroid prophylaxis on outcomes after adult aortic arch repair. Furthermore, large randomized trials of adult elective aortic arch repair are also required to determine the outcome benefits of steroid therapy in elective deep hypothermic circulatory arrest.

In pediatric cardiac surgery with CPB, steroids are widely utilized despite a limited evidence base (21-23). Recent multicenter observational trials have paved the way for larger more definitive randomized trials, targeted to high-risk pediatric CPB, including the neonatal period (24, 25). In conclusion, steroids may improve meaningful clinical outcomes after adult cardiac surgery with CPB. The results of the SIRS trial will likely determine whether this intervention will become routine in this clinical setting. It is also likely that definitive multicenter randomized trials will test whether steroids improve important outcomes after pediatric cardiac surgery with CPB.

**Can perioperative outcome after cardiac surgery be better predicted?**

The EuroSCORE (European System for Cardiac Operative Risk Evaluation) has been a major perioperative risk calculator for cardiac surgery since its initial development in 1999 (26-28). When the initial additive model was subsequently shown to overestimate mortality in high-risk patients, the logistic EuroSCORE model was developed to address this lack of calibration (29). Despite this model compensation, recent evaluations have demonstrated a significant drift in calibration of both EuroSCORE models (30, 31). This error in calibration is measured by the observed-to-expected (O/E) mortality ratio: the Eu-
roSCORE models consistently overestimate mortality, as reflected by an O/E mortality ratio below 1. A recent calibration trial demonstrated that the logistic EuroSCORE had a significant calibration drift over 10 years: the O/E ratio declined from 0.76 to 0.37 due to the decreasing mortality after adult cardiac surgery over time (32).

The EuroSCORE II model was recently developed as an effort to better calibrate the European risk prediction model for adult cardiac surgery (available as an online calculator at www.euroscore.org, last accessed January 12th 2013) (33). A single-center English trial (N=5,576) validated EuroSCORE II by demonstrating its superiority for predicting mortality as compared to the logistic EuroSCORE (34). A multicenter European trial (N=12,325) demonstrated that EuroSCORE II has fair calibration till 30% predicted mortality above which it tended to overpredict mortality, consistent with data from a recent Italian single-center study (N=1,090: 2010-2011) (35, 36). A multicenter trial from Great Britain and Ireland (N=23,740; 2010-2011) found that overall EuroSCORE II had good calibration with an O/E ratio of 0.91 (37). A consistent message from all these validation studies is that EuroSCORE II still requires ongoing periodic calibration, especially for high-risk patients (34-37). It is also important to note that, although EuroSCORE II was not primarily developed to predict mortality after transcatheter aortic valve implantation or major morbidity after adult cardiac surgery, these applications are widespread (38).

Transcatheter aortic valve implantation (TAVI) is already 10 years old and has become a global therapy in selected high-risk patients with aortic stenosis (39). Despite this rapid integration into the clinical mainstream of adult cardiac surgery, the prediction of outcome risk after TAVI still depends on established generic adult cardiac surgical risk models such as the logistic Euroscore, EuroSCORE II and the Society of Thoracic Surgeons (STS) PROM score (Predicted Risk of Operative Mortality) (40). Recent trials have demonstrated that the STS PROM score is significantly superior to the logistic EuroSCORE for predicting mortality after TAVI, although neither model was specifically calibrated for this procedure (41, 42). A recent French single-center study (N=453: 2006-2011) demonstrated that EuroSCORE II was superior to the logistic EuroSCORE and the STS PROM score for predicting 30-day mortality after TAVI, especially in the transfemoral TAVI cohort (43). Although the EuroSCORE models overestimate mortality after TAVI, they continue to influence clinical decision-making in this patient population due to a lack of a validated TAVI risk score (44). This is a major research opportunity for the European TAVI registries, since logistic regression analysis of their datasets could lead to the development and validation of a EuroSCORE TAVI model (45-48). It is likely that in the near future such a risk scoring system for TAVI will be developed, based on the methodology followed for the development of the current EuroSCORE models (26-28).

Which non-surgical interventions decrease perioperative mortality?

Despite recent advances, a paucity of high-quality evidence remains to guide clinical decision-making in cardiovascular anesthesia and intensive care (49, 50). Systematic reviews of non-surgical perioperative interventions have significantly helped to define which ancillary interventions have a significant potential to decrease mortality and major cardiac complications (51). The priority to save lives in the perioperative setting is further underlined by the fact that minor reductions would save thousands of lives, given that over 220 million
Major themes for 2012 in cardiovascular anesthesia and intensive care

Is there a paradigm shift in adult aortic arch repair?

Adult aortic arch repair has traditionally included a period of deep hypothermic circulatory arrest that has allowed neuroprotection and direct visualization for aortic arch reconstruction (61, 62). This traditional paradigm was gradually modified to include cerebral perfusion adjuncts such as retrograde cerebral perfusion and antegrade cerebral perfusion (ACP) which can be unilateral or bilateral (63-65). There has been a gradual trend over time towards favoring ACP with the debate focused on whether ACP should routinely be unilateral or bilateral (66, 67).

The common practice of ACP in adult aortic arch repair has recently challenged the traditional role of deep hypothermia for neuroprotection, given the fact that cerebral perfusion has hardly been interrupted (68, 69). Recent trials from experienced centers have begun to demonstrate the clinical efficacy of adult aortic arch repair with routine ACP and moderate hypothermia (70-72). A major caveat from these recent studies is that the degree of systemic hypothermia selected must be matched carefully to the expected duration of circulatory arrest and aortic arch pathology (70-73). While further trials are required from centers around the world to corroborate these trends, it is likely that the practice of profound hypothermia for adult aortic arch repair will gradually evolve towards mild-to-moderate degrees of hypothermia with routine ACP. In this paradigm, monitoring of bilateral cerebral perfusion with near-infrared spectroscopy is clinically indicated, especially in the setting of unilateral ACP (74, 75). Despite the popularity of unilateral ACP, bilateral ACP is still recommended when aortic arch reconstruction times will be prolonged over 40 minutes because evidence suggests a better cerebral protection in this setting (76).
A future paradigm shift in adult aortic arch repair may be the avoidance of circulatory arrest altogether (77, 78). This approach is possible in open aortic arch repair by utilizing a branched aortic arch graft with a ‘branch-first continuous perfusion’ technique that allows minimal interference with vital organ perfusion (77, 78). An extension of this technique is the concept of hybrid total aortic arch repair with avoidance of deep hypothermia and circulatory arrest (79, 80). In this hybrid technique, the aortic arch vessels are anastomosed to a branched arterial graft in a sequential fashion with minimal interruption of perfusion. An endovascular stent is then deployed across the aortic arch to effect the arch repair, whether for aneurysm or dissection (79, 80). It is likely that the hybrid concept will be integrated into adult aortic arch repair in a progressive fashion. It is important, however, that the outcome effects of this novel approach are measured against the current excellent outcomes after open arch repair (81). Although open adult aortic arch repair will likely shift away from profound hypothermic circulatory arrest as a routine, the clinical niche of hybrid aortic arch repair remains to be determined in future clinical studies (82).

CONCLUSION

The past year has seen significant strides forward in cardiovascular anesthesia and intensive care. Recent high-quality evidence suggests that steroids should still not be a routine in adult cardiac surgery with cardiopulmonary bypass. EuroSCORE II was launched in 2012 to refine perioperative risk calculation after cardiac surgery. Worldwide consensus has highlighted potentially life-saving perioperative therapies for urgent translational research. Adult aortic arch repair has been revolutionized with advances in perfusion and hybrid technology. As a result of these strides forward, patient outcomes will likely continue to improve.

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Major themes for 2012 in cardiovascular anesthesia and intensive care

15

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