Major themes for 2009 in cardiothoracic and vascular anesthesia

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ABSTRACT

The hybrid operating room is the venue for transcatheter therapy with the convergence of three specialties: cardiac surgery, cardiovascular anesthesiology, and interventional cardiology. Transcatheter aortic valve replacement is proof that cardiac specialists have embraced the endovascular revolution. Since pharmacologic and ischemic myocardial conditioning are safe and effective, they are currently the focus of multiple trials. Angiotensin blockade, anemia and endoscopic saphenous vein harvesting worsen outcome after coronary artery bypass grafting (CABG). Although off-pump CABG is equivalent to on-pump CABG, it may improve outcomes in high-risk groups. Although percutaneous coronary intervention (PCI) significantly decreases mortality after myocardial infarction, the evidence is less convincing for intra-aortic balloon counterpulsation. Even though prasugrel was recently approved for platlet blockade in PCI, it may be superceded by ticagrelor. Although PCI and CABG appear equivalent for multivessel coronary disease, CABG lowers revascularization rates and also has superior outcomes in diabetics and the elderly. Hetastarch and N-acetylcysteine both increase bleeding and transfusion in cardiac surgery. Factor VII can treat life-threatening bleeding, but its safety requires further evaluation. Since eltrombopag and romiplostim stimulate platelet production, they may have a future role in hemostasis after cardiac surgery. Even though fenoldopam, atrial natriuretic peptide and sodium bicarbonate are nephroprotective, further trials must confirm these findings. Intensive insulin therapy offers no further outcome advantage and significantly increases hypoglycemic risk. The past year has witnessed the advent of a new clinical venue, new devices, and new drugs. The coming year will most likely advance these achievements.

Keywords: *hybrid operating room, transcatheter aortic valve replacement, transcatheter mitral valve repair, ischemic preconditioning, pharmacologic conditioning, levosimendan, volatile anesthetics, angiotensin-converting enzyme inhibitors, anemia, hetastarch, coronary artery bypass grafting, endovascular saphenous vein graft harvesting, percutaneous coronary intervention, intra-aortic balloon counterpulsation, sodium bicarbonate, atrial natriuretic peptide, fenoldopam, intensive insulin therapy, prasugrel, ticagrelor.*

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INTRODUCTION

This article is the first of its kind for this journal, and we thank the editorial board for the invitation to review the highlights of 2009 in cardiothoracic and vascular anesthesia. The dominant themes for 2009 will initially be outlined in the introduction of this article and then subsequently

explored in depth in the in the body of the article. Transcatheter valve therapy in the emerging environment of the hybrid operating room (OR) will likely disseminate even more globally, as further approvals from regulating agencies are obtained in new countries and for new devices. The venue for these breakthrough technologies will likely increasingly be the hybrid OR, best understood as merging the advantages of the cardiac catheterization laboratory and the operating room. This new perioperative venue will continue to facilitate novel interventions as specialists embrace the unfolding endovascular revolution in cardiovascular medicine.

Perioperative myocardial conditioning of the myocardium has gained increasing attention as trials consistently demonstrate enhancement of clinical outcomes after cardiac surgery with exposure to volatile anesthetics, levosimendan and ischemia, both local and remote. It is likely that these perioperative techniques will gradually be integrated into the conduct of cardiothoracic and vascular procedures, as the outcome advantages are demonstrated in adequately powered trials with meaningful clinical end-points. In contrast, perioperative exposure to angiotensin blockade and anemia independently predict adverse outcome after coronary artery bypass grafting (CABG). The outcome advantages of off-pump CABG appear to be confined to high-risk patients. Endoscopic saphenous vein harvesting may increase the risks of coronary graft thrombosis to worsen clinical outcomes after CABG. In contrast, the aggressive management of ST-elevation myocardial infarction (STEMI) with percutaneous coronary intervention (PCI) consistently improves outcomes across multiple trials. The indications for intra-aortic balloon counterpulsation in STEMI have recently been questioned as the outcome advantages are not substantial in recent trials. Although prasugrel appears likely to replace clopidogrel, the future of oral thienopyridine platelet blockade may be moving to direct and reversible blockade with ticagrelor, pending the results of large trials currently in progress.

With these advances in platelet blockade, the role of PCI may continue to expand in the management of multivessel coronary artery disease (CAD). Although PCI appears equivalent to CABG for multivessel CAD in select groups, it still has a significantly higher risk of revascularization and adverse outcomes in diabetics and patients >65 years old. It is likely that the interventional management of CAD will be integrated in the hybrid OR in the future search for the best combined approach to CAD.

Since bleeding and transfusion after cardiac surgery independently predict adverse outcome, the impaired hemostasis associated with hetastarch and N-acetylcysteine is concerning. The perioperative safety of factor VII in severe bleeding requires further study. The advent of the thrombopoeitin agonists such as eltrombopag and romiplostim offers the opportunity to boost preoperative platelet levels which may have a clinical niche in the cardiac surgical patient.

Similarly to bleeding and transfusion, renal dysfunction independently predicts adverse outcome after cardiac surgery. Pilot data suggest that fenoldopam, atrial natriuretic peptide and sodium bicarbonate may be nephroprotective after cardiac surgery. Although further trials are indicated to explore their efficacy and safety, the search for nephroprotective agents in our specialty is a priority, given the outcome importance of maintaining renal function perioperatively.

In a similar fashion, ongoing trials have explored the safety and efficacy of perioperative glucose management. Although goal

glucose level ≤180 mg/dL enhance clinical outcome after adult cardiac surgery, these outcome advantages are not universal. Tighter glucose control for levels in the range of 80-110 mg/dL not only does not offer any clinical advantage but substantially increases the risk of hypoglycemia.

TRANSCATHETER VALVE INTERVENTIONS

Aortic valve

Transcatheter aortic valve implantation (TC AVI) is a major innovation in our specialty and consequently has received considerable attention (1-4). This technology will generalize further in the USA if the landmark PARTNER trial (Placement of AoRTic TraNscathetER Valve Trial: full details available at www.clinicaltrials. gov, last accessed March 2nd 2010) demonstrates significant outcome improvement.
It is essential that the anesthesia team thoroughly understands the entire TC AVI procedure as their focused and integrated participation is essential for the success of this challenging procedure, including transesophageal echocardiography (TEE) (5-8). The major phases in the conduct of TC AVI each have their complications (9-11). Vascular access may be complicated by arterial rupture, apical tearing, and aortic dissection. Malsizing of the aortic prosthesis may be complicated by valve embolization, aortic annulus rupture and aortic dissection. Errors in rapid transvenous ventricular pacing may allow ventricular ejection to interfere with balloon valvuloplasty and subsequent valve deployment. Errors in aortic prosthesis positioning may be complicated by valve prolapse, valve embolization, coronary occlusion as well as rupture of the aortic root and left ventricular outflow tract. The successful management of complications depends on rapid and ef-

fective multidisciplinary teamwork in the hybrid OR setting (9-13).
The hybrid OR will likely also significantly impact the interventional management of CAD (14). A recent trial (N = 366) demonstrated that completion angiography after CABG in a hybrid OR allowed diagnosis of graft inadequacies in 12 % of cases. These lesions were all corrected there and then in the hybrid OR with either PCI or surgical revision. The hybrid OR has brought advanced fluoroscopy to the intraoperative management of CAD with significant effect. This is analogous to the effect of TEE on the conduct of cardiac surgery, where the ability to image the structures of interest and receive immediate feedback has fundamentally altered our specialty forever (15, 16).

Mitral valve

Transcatheter mitral valve therapy has recently progressed far beyond balloon valvuloplasty for mitral stensosis and these many of the novel therapies are currently in clinical trials (17-19). Transcatheter Alfieri mitral valve repair is now possible with an array of technologies that enable leaflet edge-to-edge union. Percutaneous mitral annuloplasty is also possible through stenting of the coronary sinus that is closely related to the mitral annulus. It is likely that these 2 therapeutic approaches may be combined in the future to significantly enhance the durability of the repair, as evidenced by the surgical approach (20). Furthermore, the hybrid operating room will likely become their natural venue as cardiothoracic surgeons master these innovative approaches that have established their safety and efficacy in clinical trials (21). Indeed, it is logical that dual transcatheter aortic and mitral valve interventions will be possible in the near future once the individual technologies have entered clinical practice.

PERIOPERATIVE CONDITIONING FOR MYOCARDIAL PROTECTION

Volatile anesthesia

Volatile anesthetics have been demonstrated to condition the myocardium protectively to better tolerate ischemia-reperfusion (22, 23). The outcome importance of this important characteristic of our volatile anesthetics was investigated in a massive multicenter Italian CABG cohort study (N = 34 310: 64 centers) (24). Exposure to volatile anesthesia significantly lowered perioperative mortality (P = 0.035), especially if there was prolonged duration (P = 0.022) or if the volatile agent was isoflurane (P = 0.039). These positive findings add more weight to the argument that the contemporary cardiac anesthetic should include a volatile component for optimal outcome (25).

Levosimendan

Levosimendan is a calcium-sensitizing inodilator that may exert beneficial outcome effects when administered as soon as possible after anesthetic induction, including reduced troponin release (P = 0.0003) and hospital stay (P = 0.05) (26, 27). A recent meta-analysis (cumulative N = 440: 10 trials) confirmed that levosimendan exposure significantly reduced mortality after cardiac surgery (odds ratio 0.35; 95 % confidence interval 0.18-0.71; P = 0.003) (28). These encouraging observations have spawned multiple clinical randomized trials across both in adult and pediatric heart surgery to more fully explore perioperative benefits due to levosimendan (full details available at www.clinicaltrials.gov, last accessed March 17th 2010).

Ischemic conditioning

Although ischemic preconditioning confers significant ischemic tolerance to the myocardium, its perioperative application has mostly been evaluated in small trials. Recent meta-analysis (cumulative N = 933: 22 trials) confirmed its outcome benefits after cardiac surgery: protection against ventricular arrhythmias (odds ratio 0.11; 95 % confidence intervals 0.04-0.29; P = 0.001) and inotrope sparing (odds ratio 0.34; 95 % confidence interval 0.17-0.68; P = 0.002) (29).

Given the cumulative benefits of this intervention, its perioperative safety and efficacy should be further evaluated in adequately powered clinical trials (29, 30).

Remote ischemic conditioning

Remote ischemic preconditioning is defined as ischemic myocardial protection following brief ischemia of a remote tissue and has mainly been studied in small clinical trials (31). Recent trials have confirmed that this technique significantly reduced the release of cardiac injury biomarkers after PCI as well as both noncardiac and cardiac surgery (32-36).

These promising data have generated the mandate for a family of perioperative trials (N = 40: full details available at www. clinicaltrials.gov, last accessed March 15th 2010). If the promise from the pilot trials is consistently demonstrated across this latest trial set, then this technique will gradually enter the mainstream of clinical practice.

SURGICAL MANAGEMENT OF CORONARY ARTERY DISEASE

The dangers of perioperative angiotensin blockade

Angiotensin-converting enzyme inhibitor (ACEI) therapy has already been highlighted as an independent predictor for significant perioperative hypotension (37-39). A large observational study (N = 10 023 CABG patients: 1996-2008) demonstrated that preoperative ACEI exposure signifi-

cantly increased mortality (P = 0.04), renal dysfunction (P = 0.0002), atrial fibrillation (P < 0.0001), and inotropic support (P < 0.0001) (40) Furthermore, recent data indicate that the perioperative vasoplegia associated with ACEI is dose-dependent (41). Based on these recent observations, it is reasonable to discontinue ACEI before CABG, as is currently recommended in noncardiac surgery (42). The vasoplegia associated with ACEI exposure has been managed successfully with vasopressin given either prophylactically or therapeutically (43, 44).

The dangers of preoperative anemia

A massive observational trial (N = 10 025: 1998-2007 demonstrated that preoperative anemia independently predicts mortality after elective CABG (45). Furthermore, it also independently predicts postoperative renal dysfunction (46).

These observations should trigger a greater focus with a new set of trials in cardiac surgery to test the safety and efficacy of preoperative hemoglobin augmentation with interventions such as erythropoietin.

The controversy about endoscopic saphenous vein graft harvesting

Endoscopic saphenous vein harvesting has entered mainstream clinical practice due to its cosmetic and wound advantages. Since there may be more manipulation with this technique, there is conceptually the danger of venous endothelial trauma and possible loss of long-term patency (47). In a large observational CABG study (N = 1753 in endoscopic harvest group; N = 1247 in open harvest group) endoscopic venous harvesting significantly increased the risks of death, myocardial infarction or repeat revascularization (hazard ratio 1.22; 95 % confidence interval 1.101-1.47; P = 0.04) (48). In contrast, a larger single center study (N = 5825: 1998-2007) demonstrat-

ed that this technique was safe and effective as it did not independently predict adverse outcomes (49).

Consequently, adequately powered randomized trials are required to resolve this controversy. These trials may have limited subject enrollment as patients may be reluctant to be randomized to endoscopic saphenous vein harvesting, given its well-known outcome disadvantages.

The controversy about the pump in CABG

Since the maturation of off-pump CABG, its comparison with on-pump CABG has been an ongoing question (50). A massive cohort comparison (N = 63.047: n = 48.658 on-pump CABG; n = 14.389 off-pump CABG) demonstrated no significant differences in perioperative mortality and stroke with the off-pump cohort experiencing clinically marginal increases in hospital length of stay and cost (51).

A second cohort comparison (N = 14.766 from 1997-2007: n = 7.083 off-pump CABG; n = 7.683 on-pump CABG) demonstrated that the off-pump technique preferentially reduced mortality in high risk patients (P = 0.005) (52). These 'real-world' analyses suggest that the CABGtechniques appear equivalent, except in high-risk subsets where the off-pump technique may offer outcome advantages.

The controversy in CABG was further explored in a recently published randomized trial (N = 2203) (53). This trial demonstrated that after one year, the off-pump cohort had significantly worse outcomes and graft patencies.

This trial has multiple limitations in its design, including multiple confounders such as surgical inexperience, operative risk, and aprotinin exposure (54-56). In summary, this randomized trial reflects the off-pump learning curve and its findings should be confined to that domain.

PERCUTANEOUS CORONARY INTERVENTION

PCI for myocardial infarction

Although primary PCI is effective in STEMI, its efficacy in 'real-world' settings is still debated. (57). To address this concern, a recent meta-analysis included randomized trials (N = 8140: 23 trials) and observational studies (N = 185.900: 32 studies) (58). Compared to fibrinolysis, primary PCI reduced mortality in randomized trials (odds ratio 0.66; 95 % confidence interval 0.51-0.82) and in observational studies (odds ratio 0.77; 95 % confidence interval 0.62-0.95). In the set of observational studies, primary PCI had no significant long-term clinical outcome benefits. This meta-analysis suggests that the substantial benefits of PCI in STEMI are relevant in clinical practice beyond the domain of strictly controlled randomized trials.

Furthermore, PCI should be routinely undertaken within 6 hours after fibrinolyis. A recent randomized trial (N = 1.059) demonstrated that this approach significantly decreased the incidence of an adverse outcome endpoint (relative risk 0.64; 95 % confidence interval 0.47-0.87; P = 0.004), defined as a composite of death, reinfarction, recurrent ischemia, congestive heart failure, or cardiogenic shock within 30 days (59).

Intra-aortic balloon pump therapy in myocardial infarction

Although intra-aortic balloon counter-pulsation (IABP) has been recommended for STEMI with cardiogenic shock, the evidence supporting this recommendation was examined in a recent meta-analysis (60). In the analysis of 7 randomized trials (N = 1.009), IABP did not improve outcome, and significantly increased stroke and bleeding. In the analysis of 9 observational studies (N = 10.529), IABP only decreased mortality in STEMI managed with primary fibrinolysis (95 % confidence interval 16 %-20 %; P < 0.0001). The evidence supporting IABP in STEMI is weak at best.

The new platelet blockers prasugrel and ticagrelor

Prasugrel is a novel thienopyridine that blocks platelets more reliably than clopdogrel. Both these agents block the adenosine diphosphate P_2Y_{12} receptor and both requires biotransformation in the liver to form the active drug metabolites (61). In acute coronary syndromes, prasugrel was superior to clopidogrel for ischemic reduction (hazard ratio 0.81i; 95 % confidence interval 0.73-0.90; P < 0.001), but at the expense of bleeding risk (hazard ratio 1.32; 95 % confidence interval 1.03-1.68; P = 0.03) (62).

A multicenter global randomized trial (N = 3534) also demonstrated the superiority of prasugrel over clopidogrel in STEMI, based on the composite endpoint of cardiovascular death, MI or stroke (hazard ratio 0.68; 95 % confidence interval 0.54-0.87; P = 0.0017) (63). An important perioperative observation from this trial was that prasugrel significantly increased bleeding after CABG (P = 0.0033).

The thienopyridines, clopidogrel and prasugrel, bind irreversibly to the platelet ADP P_2Y_{12} receptor after hepatic biotransformation and are therefore indirect irreversible platelet inhibitors (64). The novel thienopyridine, ticagrelor, binds directly to the platelet ADP $P2Y_{12}$ receptor and requires no hepatic activation (64). In acute coronary syndromes (N = 18.624), ticagrelor was superior to clopidogrel, based on the composite endpoint of cardiovascular death, MI or stroke (hazard ration 0.84; 95 % confidence interval 0.77-0.92; P < 0.001) (65). Ticagrelor did not significantly increase bleeding after CABG in this

large trial. Given these positive outcome effects, this drug will likely disseminate throughout clinical practice.

PCI or CABG for multivessel coronary artery disease

A large single center observational trial (N = 3.720: 2004-2005) demonstrated that at 3 years PCI significantly increased death (hazard ratio 1.62; 95 % confidence interval 1.07-2.47) and MI (hazard ratio 1.65; 95 % confidence interval 1.15-2.44) (66).

In a larger pooled analysis (N = 7.812: 10 trials), CABG was superior to PCI for mortality reduction only in 2 subgroups, namely diabetics (hazard ratio 0.70; 95 % confidence interval 0.56-0.87; P = 0.014) and the elderly (hazard ratio 0.82; 95 % confidence interval 0.70-0.97; P = 0.002) (67). Further trials are required to explore the survival benefits of CABG in multivessel CAD.

Perioperative bleeding and transfusion

Excessive bleeding after cardiac surgery significantly increases the risks of prolonged mechanical ventilation, prolonged stay in the intensive care unit stay (P < 0.001), and death (P < 0.001) (68). Volume resuscitation with the artificial colloid hetastarch in off-pump CABG (N = 156: I liter of hetastarch versus I liter of albumin) significantly increased mediastinal bleeding (P < 0.001), transfusion risk (P = 0.012), and transfusion dose (packed red blood cells P = 0.017; fresh frozen plasma P = 0.009; and, platelets (P = 0.013) (69). Although N-acetylcysteine can be nephroptotective perioperatively, it can significantly increase mediastinal bleeding (P = 0.008), red blood cell transfusion P = 0.02) and the risk of receiving ≥5 units of red blood cells (P = 0.005) (70).

A recent meta-analysis (cumulative N = 298: 5 trials) explored the safety and efficacy of factor VII therapy for hemostasis in cardiac surgery (71). This trial demonstrated no significant reduction in surgical re-exploration (P = 0.42), mortality (P = 0.90), and a trend towards increased stroke (P = 0.09). In a randomized adult cardiac surgical trial (N = 172), exposure to factor VII significantly reduced surgical re-exploration (P = 0.03) and allogeneic transfusion (P = 0.01) with no significant increase in serious adverse events (72). Further trials are required to more adequately explore the safety and efficacy of this hemostatic intervention in cardiac surgery with massive bleeding.

Can the kidney be protected after cardiac surgery?

The search for nephroprotective strategies in cardiac surgery is ongoing. In a small randomized trial (N = 92), fenoldopam significantly reduced the risk of renal replacement therapy (P = 0.037) (73). A larger randomized trial (N = 504) demonstrated that perioperative atrial natriuretic peptide is nephroprotective (P < 0.0001) and significantly reduces postoperative complications (P = 0.0208) (74). In a pilot randomized trial (N = 100), perioperative sodium bicarbonate infusion significantly reduced renal injury after on-pump cardiac surgery (odds ratio 0.43; 95 % confidence interval 0.19-0.98; P = 0.043) (75). These promising nephroprotective agents are currently being further evaluated in more than 50 randomized trials (full details available at www.clinicaltrials.gov, last accessed March 19th 2010).

In contrast, a large trial (N = 563) implicated pentastarch exposure as a significant predictor of renal dysfunction after cardiac surgery (odds ratio per mL/kg 1.08; 95 % confidence interval 1.04-1.12; P = 0.001). This trial also demonstrated that this nephrotoxicity is dose-dependent with a threshold value of 14 ml per kilogram body weight (76). Given the current focus on the importance of renal function in adult

cardiac surgery, it is likely that the ongoing clinical development of perioperative nephroprotective interventions will remain a priority.

Does tight glucose control matter?

Tight perioperative management of glucose remains controversial in cardiac surgery (77). In a recent large randomized trail in critically ill adults (N = 6.014), intensive insulin therapy significantly increased mortality (odds ratio 1.14; 95 % confidence interval 1.02-1.28; P = 0.02) and severe hypoglycemia (P < 0.001) (78).

Recent meta-analysis of intensive insulin therapy in the intensive care unit (N = 13 567: 26 trials) has demonstrated that this intervention decreased mortality in the surgical intensive care unit (relative risk 0.63; 95 % confidence interval 0.44-0.91) but not in medical (relative risk 1.0; 9 % % confidence interval 0.78-1.28) or mixed intensive care units (relative risk 0.99; 95 % confidence interval 0.86-1.12) (79). The Society of Thoracic Surgeons recommends insulin infusion to maintain perioperative glucose levels below 180 mg/Dl (80).

CONCLUSIONS

The hybrid operating room is likely to become the ideal venue for transcatheter cardiovascular therapy. Transcatheter aortic valve implantation will gradually encourage further innovations as the revolution in transcatheter management of cardiovascular diseases matures. Myocardial conditioning with volatile anesthetics and levosimendan significantly protect the heart against ischemia to improve perioperative outcomes. Remote ischemic conditioning appears is not only safe and effective but also is the subject of multiple ongoing perioperative trials. Perioperative angiotensin blockade and anemia significantly worsen outcome after CABG. Off-pump CABG with experienced perioperative teams may improve outcomes in high-risk patients. Endoscopic saphenous vein harvesting may compromise graft patency. The management of STEMI should almost always include PCI, but the evidence for IABP in this important disease is far less conclusive.

The novel platelet blockers prasugrel and ticagrelor are likely to transform current practice of antiplatelet therapy in cardiovascular diseases. Although PCI is a reasonable option in multivessel CAD, CABG offers a survival advantage in diabetics and the elderly. Hetastarch and N-acetylcysteine may worsen bleeding and transfusion in cardiac surgery. Although factor VII can arrest massive bleeding, further trials are required to explore its safety. Recent randomized trials have shown that fenoldopam, atrial natriuretic peptide and sodium bicarbonate are significantly nephroprotective in cardiac surgery. Although perioperative glucose management (goal glucose level ≤180 mg/dL) improves outcome in adult cardiac surgery, this benefit is not universal across all hospital settings. More intensive insulin therapy is not indicated since it does not improve outcome and carries a significant hypoglycemic risk. The year 2009 has witnessed major advances cardiothoracic and vascular anesthesia with new devices, new clinical venues, and new drugs.

No conflict of interest acknowledged by the authors.

REFERENCES

1. Cook DJ, Rehfeldt KH. Catheter-based aortic valve replacement. J Cardiothorac Vasc Anesth 2009; 23: 277-279.
2. Fassl J, Walther T, Groesdonk HV, et al. Anesthesia management for transapical transcatheter aortic valve implantation: a case series. J Cardiothorac Vasc Anesth 2009; 23: 286-291.

3. Augoustides JG, Wolfe Y, Walsh EK, et al. Recent advances in aortic valve disease: highlights from a bicuspid valve to transcatheter aortic valve replacement. J Cardiothorac Vasc Anesth 2009; 23: 569-576.

4. Covello RD, Maj G, Landoni G, et al. Anesthetic management of percutaneous aortic valve implantation: focus on challenges encountered and proposed solutions. J Cardiothorac Vasc Anesth 2009; 23: 280-285.

5. Klein AA, Webb ST, Tsui S, et al. Transcatheter aortic valve insertion: anaesthetic implications of emerging new technology. Br J Anaesth 2009; 103: 792-799.

6. Covello RD, Ruggeri L, Landoni G, et al. Transcatheter implantation of an aortic valve: anesthesiological management. Minerva Anesthesiol 2010; 76: 100-108.

7. Dumont E, Lemieux J, Doyle D, Rodés-Cabau J. Feasibility of transapical aortic valve implantation fully guided by transesophageal echocardiography. J Thorac Cardiovasc Surg 2009; 138: 1022-1024.

8. Fassl J, Augoustides JG. Transcatheter aortic valve implantation-part 1: development and status of the procedure. J Cardiothorac Vasc Anesth 2009. Epub ahead of print. PMID: 19942452.

9. Wong DR, Cheung A, Webb JG, et al. Technical considerations to avoid pitfalls during transapical aortic valve implantation. J Thorac Cardiovasc Surg 2010. Epub ahead of print. PMID: 20122700.

10. Ducrocq G, Francis F, Serfaty JM, et al. Vascular complications of transfemoral aortic valve implantation with the Edwards SAPIEN prosthesis: incidence and impact on outcome. Eurointervention 2010; 5: 666-672.

11. Masson JB, Kovac J, Schuler G, et al. Transcatheter aortic valve implantation: review of the nature, management and avoidance of procedural complications. JACC Cardiovascular Interv 2009; 2: 811-820.

12. Wendt D, Eggebrecht H, Kahlert P, et al. Experience and learning curve with transapical aortic valve implantation. Herz 2009; 34: 388-397.

13. Guinot PG, Depoix JP, Etchegoyen L, et al. Anesthesia and perioperative management of patients undergoing transcatheter aortic valve implantation: analysis of 90 consecutive patients with focus on perioperative complications. J Cardiothorac Vasc Anesth 2010. Epub ahead of print. PMID: 20188592.

14. Zhao DX, Leacche M, Balaguer JM, et al. Routine intraoperative completion angiography after coronary artery bypass grafting and 1-stop hybrid revascularization results from a fully integrated hybrid catheterization laboratory/operating room. J Am Coll Cardiol 2009; 53: 232-241.

15. Minhaj M, Patel K, Muzic D, et al. The effect of routine intraoperative transesophageal echocardiography on surgical management. J Cardiothorac Vasc Anesth 2007; 21: 800-804.

16. Eltzschig HK, Roseberger P, Loffler M, et al. Impact of intraoperative transesophageal echocardiography on surgical decisions in 12,566 patients undergoing cardiac surgery. Ann Thorac Surg 2008; 85: 845-852.

17. Augoustides JG, Atluri P Progress in mitral valve disease: understanding the revolution. J Cardiothorac Vasc Anesth 2009; 23: 916-923.

18. Rahimtoola SH. The year in valvular heart disease. J Am Coll Cardiol 2009; 53: 1894-1908.

19. Piazza N, Asgar A, Ibrahim R, et al. Transcatheter mitral and pulmonary valve therapy. J Am Coll Cardiol 2009; 53: 1837-1851.

20. Fischer GW, Anyanwu AC, Adams DH. Intraoperative classification of mitral valve dysfunction: the role of the anesthesiologist in mitral valve reconstruction. J Cardiothorac Vasc Anesth 2009; 23: 531-543.

21. Treasure T. Are randomized trials needed in the era of rapidly evolving technologies? Eur J Cardiothorac Surg 2009; 35: 474-478.

22. Pagel PS. Cardioprotection by volatile anesthetics: established scientific principle or lingering clinical uncertainty? J Cardiothorac Vasc Anesth 2009; 23: 589-593.

23. Landoni G, Bignami E, Oliviero F, et al. Halogenated anaesthetics and cardiac protection in cardiac and non-cardiac anaesthesia. Ann Card Anaesth 2009; 12: 4-9.

24. Bignami E, Biondi-Zoccai G, Landoni G, et al. Volatile anesthetics reduce mortality in cardiac surgery. J Cardiothorac Vasc Anesth 2009; 23: 594-599.

25. Landoni G, Virzo I, Bignami E, et al. Any rationale for propofol use in cardiac surgery. J Cardiothorac Vasc Anesth 2010. Epub ahead of print. PMID: 20096601.

26. De Hert SG, Lorsomradee S, van den Eede H, et al. A randomized trial evaluating different modalities of levosimendan administration in cardiac surgery patients with myocardial dysfunction. J Cardiothorac Vasc Anesth 2008; 22: 699-705.

27. Zangrillo A, Biondi-Zoccai G, Mizzi A, et al. Levosimendan reduces cardiac troponin release after cardiac surgery: a meta-analysis of randomized controlled studies. J Cardiothorac Vasc Anesth 2009; 23: 474-476.

28. Landoni G, Mizzi A, Biondi-Zoccai G, et al. Reducing mortality in cardiac surgery with levosimendan: a meta-analysis of randomized controlled trials. J Cardiothorac Vasc Anesth 2010; 24: 51-57.

29. Walsh SR, Tang TY, Kullar P, et al. Ischaemic preconditioning during cardiac surgery: systematic review and meta-analysis of perioperative outcomes

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in randomized clinical trials. Eur J Cardiothorac Surg 2008; 34: 985-994.

30. Lee HT. Mechanisms of ischemic preconditioning and clinical implications for multiorgan ischemic reperfusion injury. J Cardiothorac Vasc Anesth 1999; 13: 78-91.

31. Walsh SR, Tang TY, Sadat U, et al. Remote ischemic preconditioning in major vascular surgery. J Vasc Surg 2009; 49: 240-243.

32. Takagi H, Manabe H, Kawai N, et al. Review and meta-analysis of randomized controlled clinical trials of remote ischemic preconditioning in cardiovascular surgery. Am J Cardiol 2008; 102: 1487-1488.

33. Hoole SP, Heck PM, Sharples L, et al. Cardiac remote ischemic preconditioning in coronary stenting (CRISP Stent) study: a prospective randomized control trial. Circulation 2009; 119: 820-827.

34. Kloner RA. Clinical application of remote ischemic preconditioning. Circulation 2009; 119: 776-778.

35. Venugopal V, Hausenloy DJ, Ludman A, et al. Remote ischaemic preconditioning reduces myocardial injury in patients undergoing cardiac surgery with cold-blood cardioplegia: a randomized controlled trial. Heart 2009; 95: 1567-1571.

36. Walsh SR, Boyle JR, Tang TY, et al. Remote ischemic preconditioning for renal and cardiac protection during endovascular aneurysm repair: a randomized controlled trial. J Endovasc Ther 2009; 16: 680-689.

37. Kheterpal S, Khodaparast O, Shanks A, et al. Chronic angiotensin-converting enzyme inhibitor or angiotensin receptor blocker therapy combined with diuretic therapy is associated with increased episodes of hypotension in noncardiac surgery. J Cardiothorac Vasc Anesth 2008; 22: 180-186.

38. Augoustides JG. Angiotensin blockade and general anesthesia: so little known, so far to go. J Cardiothorac Vasc Anesth 2008; 22: 177-179.

39. Levin MA, Lin HM, Castillo JG, et al. Early on-cardiopulmonary hypotension and other factors associated with vasoplegic syndrome. Circulation 2009; 120: 1664-1671.

40. Miceli A, Capoun R, Fino C, et al. Effects of angiotensin-converting enzyme inhibitor therapy on clinical outcome in patients undergoing coronary artery bypass grafting. J Am Coll Cardiol 2009; 54: 1778-1784.

41. Shahzamani M, Yousefi Z, Frootaghe AN, et al. The effect of angiotensin-converting enzyme inhibitor on hemodynamic instability in patients undergoing cardiopulmonary bypass: results of a dose-comparison study. J Cardiovasc Pharmacol Ther 2009; 14: 185-191.

42. Augoustides JG. Should all antihypertensive agents be continued before surgery? In: Fleisher LA (ed): Evidence-Based Practice of Anesthesiology Saun-

ders Elsevier, Philadelphia Chapter 9: 49-54, 2009.

43. Holt NF, Haspel KL. Vasopressin: a review of therapeutic applications. J Cardiothorac Vasc Anesth 2009. Epub ahead of print. PMID: 19945299.

44. Hasija S, Makhija N, Choudhury M, et al. Prophylactic vasopressin in patients receiving the angiotensin-converting enzyme inhibitor ramipril undergoing coronary artery bypass graft surgery. J Cardiothorac Vasc Anesth 2009. Epub ahead of print. PMID: 19875309.

45. van Straten AH, Hamad MA, van Zundert AJ, et al. Preoperative hemoglobin level as a predictor of survival after coronary artery bypass grafting: a comparison with the matched general population. Circulation 2009; 120: 118-125.

46. van Straten AH, Hamad MA, van Zundert AA, et al. Risk factors for deterioration of renal function after coronary artery bypass grafting. Eur J Cardiothorac Surg 2010; 37: 106-111.

47. Markar SR, Kutty R, Edmonds L, et al. A meta-analysis of minimally invasive versus traditional open vein harvest technique for coronary artery bypass graft surgery. Interact Cardiovasc Thorac Surg 2010; 10: 266-270.

48. Lopes RD, Hafley GE, Allen KB, et al. Endoscopic versus open vein-graft harvesting in coronary-artery bypass surgery. New Engl J Med 2009;361: 235-244.

49. Ouzounian M, Hassan A, Buth KJ, et al. Impact of endoscopic versus open saphenous vein harvest techniques on outcomes after coronary artery bypass grafting. Ann Thorac Surg 2010; 89: 403-408.

50. Scott BH, Seifert FC, Grimson R, et al. Resource utilization and off-pump coronary artery surgery; factors influencing postoperative length of stay - an experience of 1,746 consecutive patients undergoing fast-track cardiac anesthesia. J Cardiothorac Vasc Anesth 2005; 19: 26-31.

51. Chu D, Bakaeen FG, Dao TK, et al. On-pump versus off-pump coronary artery bypass grafting in a cohort of 63,000 patients. Ann Thorac Surg 2009; 87: 1820-1826.

52. Puskas JD, Thourani VH, Kilgo P, et al. Off-pump coronary artery bypass disproportionately benefits high-risk patients. Ann Thorac Surg 2009; 88: 1142-1147.

53. Shroyer AL, Grover FL, Hattler B, et al. On-pump versus off-pump coronary-artery bypass surgery. N Engl J Med 2009; 361: 1827-1837.

54. Puskas JD, Mack M, Smith CR. On-pump versus off-pump CABG. N Engl J Med 2010; 362: 851.

55. Augoustides JG. On-pump versus off-pump CABG. N Engl J Med 2010; 362: 852.

56. Taggart DP. On-pump versus off-pump CABG. N Engl J Med 2010; 362: 852.

57. Verheught FW. Reperfusion therapy for ST-segment

elevation myocardial infarction: trials, registries, and guidelines. Circulation 2009; 119: 3047-3049.

58. Huynh T, Perron S, O'Loughlin J, et al. Comparison of primary percutaneous coronary intervention and fibrinolytic therapy in ST-segment-elevation myocardial infarction: bayesian hierarchial meta-analyses of randomized controlled trials and observational studies. Circulation 2009; 119: 3101-3109.

59. Cantor WJ, Fitchett D, Borgundvaag B, et al. Routine early angioplasty after fibrinolysis for acute myocardial infarction. N Engl J Med 2009; 360: 2705-2718.

60. Sjauw KD, Engstrom AE, Vis MM, et al. A systematic review and meta-analysis of intra-aortic balloon pump therapy in ST-elevation myocardial infarction: should we change the guidelines? Eur Heart J 2009; 30: 459-468.

61. Bhatt DL. Prasugrel in clinical practice. New Engl J Med 2009; 361: 940-942.

62. Wiviott SD, Braunwald E, McCabe CH, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. New Engl J Med 2007; 357: 2001-2015.

63. Montalescot G, Wiviott SD, Braunwald E, et al. Prasugrel compared with clopidogrel in patients undergoing percutaneous coronary intervention for ST-elevation myocardial infarction (TRITON - TIMI 38): a double-blind, randomized controlled trial. Lancet 2009; 373: 723-731.

64. Wallentin L. P2Y(12) inhibitors: differences in properties and mechanisms of action and potential consequences for clinical use. Eur Heart J 2009; 30: 1964-1977.

65. Wallentin L, Becker RC, Budaj A, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. New Engl J Med 2009; 361: 1045-1057.

66. Li Y, Zheng Z, Xu B, et al. Comparison of drug-eluting stents and coronary artery bypass surgery for the treatment of multivessel coronary disease: three year follow-up results from a single institution. Circulation 2009; 119: 2040-2050.

67. Hlatky MA, Boothroyd DB, Bravata DM, et al. Coronary artery bypass surgery compared with percutaneous coronary intervention for multivessel disease: a collaborative analysis of individual patient data from 10 randomised trials. Lancet 2009; 373: 1190-1197.

68. Christensen MC, Krapf S, Kempel A, et al. Costs of excessive postoperative hemorrhage in cardiac surgery. J Thorac Cardiovasc Surg 2009; 138: 687-693.

69. Hecht-Dolnik M, Barkan H, Taharka A, et al. Hetastarch increases the risk of bleeding complications in patients after off-pump coronary artery bypass surgery: a randomized clinical trial. J Thorac Cardiovasc Surg 2009; 138: 703-711.

70. Wijeysundera DN, Karkouti K, Rao V, et al. N-acetylcysteine is associated with increased blood loss and blood product utilization during cardiac surgery. Crit Care Med 2009; 37: 1929-1934.

71. Zangrillo A, Mizzi A, Biondi-Zoccai G, et al. Recombinant activated factor VII in cardiac surgery: a meta-analysis. J Cardiothorac Vasc Anesth 2009; 23: 34-40.

72. Gill R, Herbertson M, Vuylsteke A, et al. Safety and efficacy of recombinant activated factor VII: a randomized placebo-controlled trial in the setting of bleeding after cardiac surgery. Circulation 2009; 120: 21-27.

73. Roasio A, Lobreglio R, Santin A, et al. Fenoldopam reduces the incidence of renal replacement therapy after cardiac surgery. J Cardiothorac Vasc Anesth 2009; 2: 23-26.

74. Sezai A, Hata M, Niino T, et al. Influence of continuous infusion of low-dose human atrial natriuretic peptide on renal function during cardiac surgery: a randomized controlled study. J Am Coll Cardiol 2009; 54: 1058-1064.

75. Haase M, Haase-Fielitz A, Bellomo R, et al. Sodium bicarbonate to prevent increases in serum creatinine after cardiac surgery: a pilot double-blind, randomized controlled trial. Crit Care Med 2009; 37: 39-47.

76. Rioux JP, Lessard M, De Bortoli B, et al. Pentastarch 10 % (250 kDa/0.45) is an independent risk factor of acute kidney injury following cardiac surgery. Crit Care Med 2009; 37: 1293-1298.

77. Floyd TF, Horak J. Con: Tight perioperative glycemic control. J Cardiothorac Vasc Anesth 2009; 23: 906-908.

78. Finfer S, Chittock DR, Su SY, Blair D, et al; The NICE - SUGAR Study Investigators. Intensive versus conventional glucose control in critically ill patients. New Engl J Med 2009; 360: 1283-1297.

79. Griesdale DEG, de Souza RJ, van Dam RM. Intensive insulin therapy and mortality among critically ill patients: a meta-analysis including NICE - SUGAR study data. CMAJ 2009; 180: 821-827.

80. Lazar HL, McDonnell M, Chipkin SR, et al. The Society of Thoracic Surgeons practice guideline series: blood glucose management during adult cardiac surgery. Ann Thorac Surg 2009; 87: 663-669.