

Andrew Rhodes
Maurizio Cecconi
Mark Hamilton
Jan Poloniecki
Justin Woods
Owen Boyd
David Bennett
R. Michael Grounds

Goal-directed therapy in high-risk surgical patients: a 15-year follow-up study

Received: 29 October 2009
Accepted: 7 March 2010

© Copyright jointly held by Springer and ESICM 2010

Electronic supplementary material

The online version of this article (doi:10.1007/s00134-010-1869-6) contains supplementary material, which is available to authorized users.

A. Rhodes (✉) · M. Cecconi · M. Hamilton · J. Woods · D. Bennett · R. M. Grounds
Department of Intensive Care Medicine,
St George's Healthcare NHS Trust,
London SW17 0QT, UK
e-mail: andyr@sgul.ac.uk
Tel.: +44-208-7255699

J. Poloniecki
Department of Medical Statistics,
St George's University of London,
London SW17 0QT, UK

O. Boyd
Department of Intensive Care Medicine,
Brighton and Sussex University Hospitals
NHS Trust, London SW17 0QT, UK

Abstract *Purpose:* Goal-directed therapy in the perioperative setting has been shown to be associated with short-term improvements in outcome. This study assesses the longer-term survival of patients from a previous randomized controlled trial of goal-directed therapy in high-risk surgical patients. *Methods:* All patients from a previous randomized controlled study were followed up for 15 years following randomization to ascertain their length of survival following surgery. Factors that may be associated with increased survival were evaluated to determine what influenced long-term outcomes.

Results: Data from 106 of the original 107 patients (99%) were available for analysis. At 15 years, 11 (20.7%) of the goal-directed therapy patients versus 4 (7.5%) of the control

group were alive ($p = 0.09$). Median survival for the goal-directed group was increased by 1,107 days (1,781 vs. 674 days, $p = 0.005$). Long-term survival was associated with three independent factors: age [hazard ratio (HR) 1.04 (1.02–1.07), $p < 0.0001$], randomization to the goal-directed group of the study [HR 0.61 (0.4–0.92), $p = 0.02$], and avoidance of a significant postoperative cardiac complication [HR 3.78 (2.16–6.6), $p = 0.007$]. *Conclusions:* Long-term survival after major surgery is related to a number of factors, including patient age and avoidance of perioperative complications. Short-term goal-directed therapy in the perioperative period may improve long-term outcomes, in part due to its ability to reduce the number of perioperative complications.

Keywords Long term outcome · Surgery · Hemodynamics

Introduction

Intensive care is an expensive and scarce resource, and it is widely assumed that the care provided supports patients whilst they are critically unwell in order to gain time for recovery. There are few conditions that intensive care is able to cure, and it therefore remains unclear whether the interventions are able to influence and modify the

underlying biology of the disease that brought the patient into hospital.

Many high-risk surgical cases are admitted to an intensive care environment in the perioperative period, on both a planned and unplanned basis. Although some of these admissions are as a direct result of the complexity of the surgical procedure, it is more commonly due to the patients having multiple comorbidities that limit their

physiological reserve and render them at higher than normal risk of postsurgical morbidity and mortality [1, 2]. Treatment of these patients focuses on improving cardiovascular and respiratory status whilst at the same time providing adequate analgesia. As part of this approach, goal-directed hemodynamic therapy is increasingly used to provide a rational series of goals for treatment.

There are many studies that have demonstrated that goal-directed care in the perioperative period can reduce subsequent mortality and morbidity associated with these procedures [3–12]. There are few data, however, that follow up these patients outside of a 28-day setting or give any insight into whether these protocols simply aid the recovery process, prevent complications, or can actually modify the underlying biology and have a long-term impact on survival.

The hypothesis of this study is that goal-directed therapy in the perioperative period will reduce the complication rate and mortality seen in the short term, but is unlikely to have a disease-modifying impact, thus rendering ultimate survival down to the underlying disease process. In order to assess this hypothesis we decided to carry out a long-term (15 years) follow-up analysis of an interventional randomized controlled trial in perioperative patients on the Intensive Care Unit. We expected to see that, although the short-term mortality was improved with the protocol, over time this effect would decrease as the underlying condition with which the patient presented had a more significant impact on life expectancy.

Methods

This study was approved by the Wandsworth Research Ethics Committee on the proviso that no patients or their families would be contacted. This study is a long-term follow-up of patients who were entered into a randomized controlled trial at St George's Hospital from November 1990 to May 1992 into the effects of a deliberate perioperative increase in oxygen delivery for patients undergoing high-risk surgery (see the Electronic Supplementary Material, ESM) [4]. In that study 107 patients were randomized preoperatively to receive either goal-directed augmentation of their cardiorespiratory systems to try and achieve global tissue oxygen delivery of 600 ml/(min m² body surface area) or to receive best possible perioperative care in an intensive care unit within the knowledge and care of best practice at that time.

For the present study, survival status and where applicable date of death of all patients from the original study were determined from individual patient National Health Service (NHS) hospital records and a subsequent query of the NHS registry database using the patient's specific NHS numbers as the identifying code. These dates were then corroborated by cross-checking dates of

death with the UK National Registry for births, deaths, and marriages. The survival status of those identified as being alive at the time of the follow-up was then further cross-referenced with existing general practice records to confirm whether or not the patient was still alive.

Statistical analysis

All data are presented as mean (standard deviation) when normally distributed, and median (interquartile range) when not. Normality was assessed with the D'Agostino–Pearson test. Differences between discrete variables were assessed with Fisher's exact test. Survival analysis was performed by constructing Kaplan–Meier curves, with data censored at 15 years (5,479 days) following the date of enrolment of the last patient into the original study. The log-rank (Mantel–Cox) test was used to assess differences between survival curves.

In order to identify factors independently associated with survival, a Cox regression model was constructed. The following variables were tested to see if they were significantly associated with survival: age, sex, body mass index, postoperative Acute Physiology and Chronic Health Evaluation (APACHE) II score, study arm, duration of hospital stay, development of perioperative complication, immediate postoperative mixed venous oxygen saturation, oxygen delivery, and lactate. In addition, any of these variables that had a probability of being associated with survival of <0.05 were then added into a Cox multiple regression model. To ascertain whether or not the previously demonstrated effects of short-term survival benefit impacted on longer-term longevity, the survival analysis was repeated using 28 days post randomization as the baseline point. These data are presented as a hazard ratio (HR) together with its 95% confidence interval (CI).

Results

One hundred seven patients were enrolled into the original study, and all were included in the intention-to-treat analysis for 28-day mortality. The study was stopped early by the local research and ethics committee after 107 patients had been enrolled due to there being a significant reduction in mortality in the protocol group (22.2 vs. 5.7%, $p = 0.015$) at 28 days. The patients in the protocol group had received therapy with the intention of increasing global oxygen delivery to a value of over 600 ml/(min m²) during the perioperative period. The levels of global oxygen delivery were significantly higher in the perioperative period for the protocol patients ($p < 0.001$). Further specific details of the protocol can be found in the original publication [4]. At the time of randomization, the

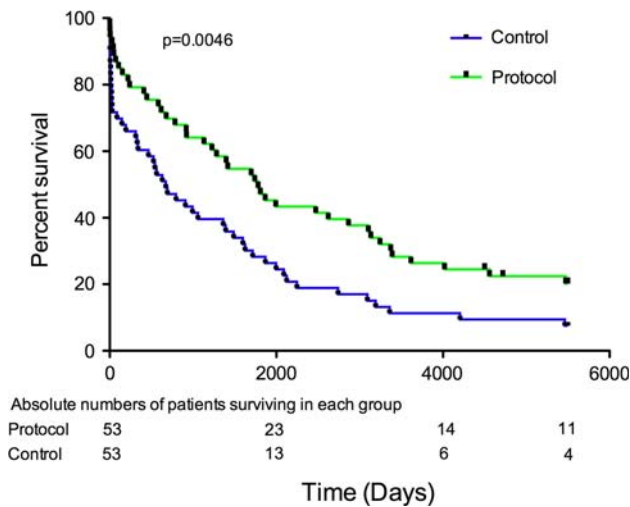


Fig. 1 Kaplan–Meier survival analysis of patients grouped according to study arm (protocol or control)

two groups were well balanced in terms of baseline demographics, operation type and numbers, and specific high-risk criteria. There were similar proportions of protocol and control patients who underwent vascular surgery (57 vs. 52%, $p = 0.70$) and major abdominal surgery (32 vs. 37%, $p = 0.69$). Of particular note, both groups also contained a similar number of patients undergoing high-risk emergency procedures (40 vs. 31%, $p = 0.42$). More details of the original study can be found in the Electronic Supplementary Material.

Survival analysis from randomization

In this long-term follow-up study, outcome data were available on 106 out of the original 107 patients (99%), with 1 patient from the control group being lost to follow-up. For further analysis there were therefore 53 patients in each study arm. At 15 years post randomization there were 11 (20.7%) patients alive in the protocol group and 4 (7.5%) in the control group ($p = 0.09$). The survival curves for the 15 years following randomization showed a significantly improved survival for protocol patients ($p = 0.005$) (Fig. 1). The median survival for the protocol group patients was increased by 1,107 days [1,781 vs.

674 days, HR 1.8 (95% CI 1.2–2.8), $p = 0.005$], or just over 3 years (Table 1).

Data were also analyzed for all patients (protocol plus control) together. The development of a postoperative complication had a profound impact on long term survival. When split into those with and without complications, there was a significant survival advantage for those who did not develop a perioperative complication [1,993 vs. 542 days, HR 2.0 (95% CI 1.3–3.0), $p < 0.0001$]. For those with renal complications there were no survivors beyond 2,000 days, and for those with cardiovascular complications beyond 3,000 days (Fig. 2). Patients in the control group had significantly longer survival if they avoided complications in the perioperative period [median survival of 1,868 vs. 116 days, HR 5.0 (2.6–9.9), $p < 0.0001$], whereas this was not the case for the protocol patients [2,233 vs. 1,697 days, HR 1.0 (0.6–1.9), $p = 0.42$] (Fig. 3).

The following factors were significantly associated with survival on univariate analysis: age, body surface area, baseline postoperative APACHE II score, study arm, development of a postoperative complication, type of surgery performed, and postoperative baseline oxygen delivery index (ESM Fig. 1). On multiple regression analysis using a Cox regression plot, the following variables remained independently associated with survival: age [HR 1.04 (1.02–1.07), $p < 0.0001$], study arm [HR 0.61 (0.4–0.9), $p = 0.02$], and development of a significant cardiac postoperative complication [HR 3.8 (2.2–6.6), $p < 0.0001$] (ESM Fig. 2).

Survival analysis from 28 days post randomization

Fifteen patients died during the first 28 days following randomization. At 28 days, data were available for 50 patients in the protocol group and for 41 in the control group. At 15 years, 11 (22%) patients in the protocol group and 4 (10%) in the control group were still alive ($p = 0.11$). The protocol group had a consistently, although nonsignificantly, increased survival (Fig. 4). The median survival of the protocol group as compared with controls was increased from 1,409 to 1,836 days [HR 1.43 (95% CI 0.9–2.3), $p = 0.18$].

The development of a significant complication within 28 days of randomization had a major impact on longer-term survival. Patients with a complication survived a

Table 1 Outcome data described as median survival in days together with the HR and its 95% confidence interval

	Protocol	Control	HR	95% CI	p
Survival from randomization	1,781	674	1.811	1.2–2.8	0.005
Survival from 28 days post randomization	1,836	1,409	1.433	0.9–2.3	0.18
	No complication	Complication	HR	95% CI	p
Survival from randomization	1,993	542	1.96	1.3–3.0	<0.0001

Fig. 2 Survival analysis from randomization according to whether or not the patients developed a significant complication in the 28 days following surgery: **a** any complication, **b** cardiac complication, **c** respiratory complication and, **d** renal complication

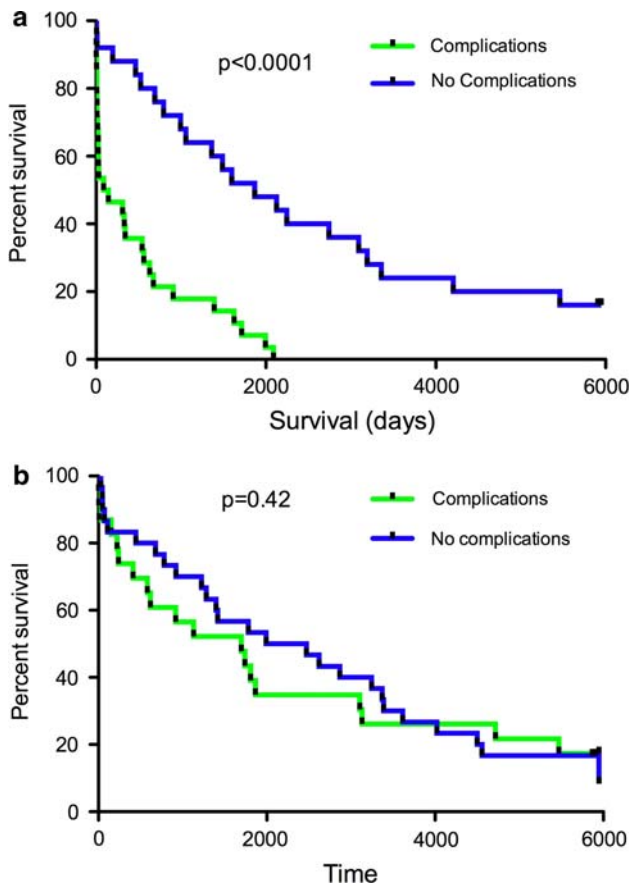
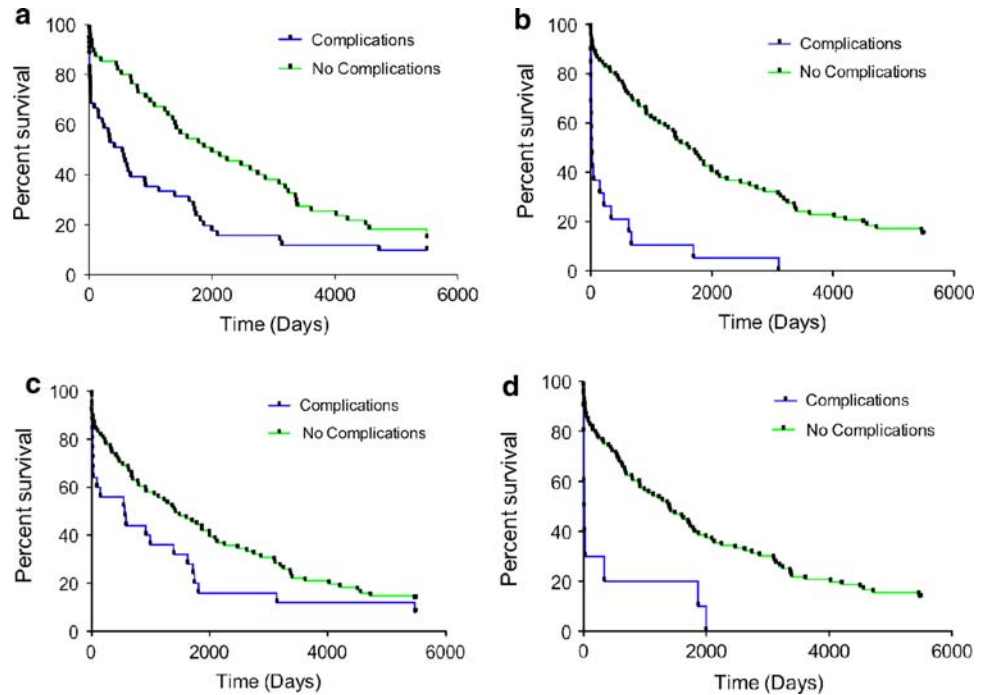


Fig. 3 Survival curve analysis depending on the development or not of a complication within 28 days of randomization according to whether in the **a** control group or **b** the protocol group

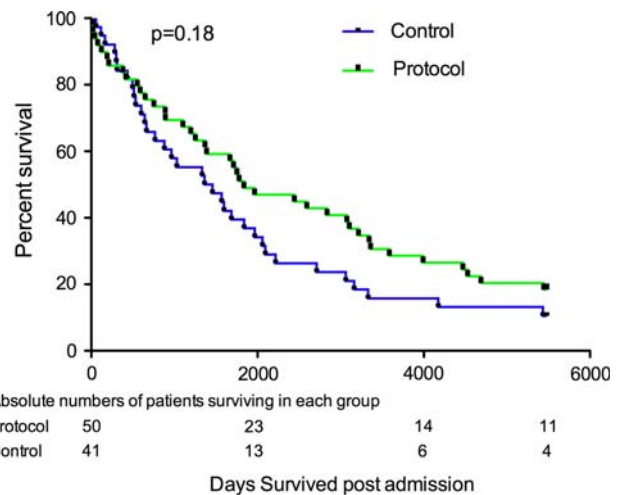


Fig. 4 Survival analysis of patients grouped according to study arm (protocol or control) starting at the time-point of day 28 post randomization

median of 1,363 as compared with 2,839 days for those who avoided a complication ($p = 0.002$). The development of a cardiac complication was associated with the worst outcome, with median survival shortening from 3,361 to 1,712 days ($p < 0.001$).

Cox regression analysis demonstrated the following factors to be independently associated with reduced survival: increasing age at randomization [HR 1.04 (1.02–1.07), $p = 0.002$] and development of a significant cardiac complication in the postoperative period [HR 2.50 (1.2–5.2), $p = 0.013$] (ESM Figs. 3 and 4).

Discussion

This long-term follow-up study of a randomized controlled clinical trial into deliberate perioperative elevation of oxygen delivery demonstrates an improvement in long-term survival for those patients who underwent goal-directed therapy. This could have implications when assessing the economic benefits of short-term interventions such as this, as the upfront resource costs can be countered by the impact on longevity. This may have implications for the assessment of future trials and of critical care use for surgical patients.

The results suggest that there is a long-term survival benefit for patients who underwent goal-directed resuscitation of their cardiovascular system, with this group having more than twice as many survivors 15 years after the initial surgery. This difference was apparent at all times during that period. Our results suggest that this survival benefit was mainly due to the ability of the initial therapy to reduce the number of postoperative complications in the goal-directed therapy group. In particular, those patients who did not develop a postoperative cardiac complication seemed to derive the greatest benefit.

The survival curves following randomization were significantly different, suggesting that the effect of the intervention may be longer-reaching than was previously thought. In order to test this, we repeated the analysis, resetting the baseline at 28 days. This has obvious implications, as the two groups are not now equivalent and other confounding factors may interact with our model. The survival curves after this point were not significantly different. The important point to consider is that, if the intervention used in the trial was simply delaying deaths, the analysis post 28 days would be expected to show increased mortality for the protocol group subsequent to this time point—or in other words patients who did not die early would die later. It is of course not possible to identify which patients have their death simply delayed; however, this is not what we found. In this study the survival curves, although not significantly different, demonstrated the opposite effect, with the goal-directed therapy group continuing to show a benefit, suggesting that, if anything, the short-term benefit was maintained for the entire 15-year follow-up period.

Our analysis found three factors to be associated with increased long-term survival benefit: age, randomization to protocol, and avoidance of a significant postoperative complication. These three factors are independent of one another, although they may not be mutually exclusive. For instance, the patients randomized to the protocol group developed fewer complications, and thus will have done even better. The avoidance of a complication has a significant impact on longevity, even if the patients were randomized to an accepted standard of care. Importantly, in the group of patients who did develop at least one

complication, randomization to the goal-directed group was still associated with a positive effect on survival post 28 days. This is a very important finding. Indeed, while it is not possible to predict with 100% accuracy which patients will develop a complication, goal-directed therapy appears to have an effect on long-term survival even if it cannot completely avoid the development of a complication.

Our results are in keeping with many larger datasets that have followed up postoperative patients beyond the traditional 30-day follow-up period, albeit not following a goal-directed hemodynamic protocol [13, 14]. The definition of mortality from major surgery is absolutely clear, but the definition and collection of data that relate to perioperative complications are far less so, making comparisons across surgical technique and institutions difficult [15]. Current estimates of postoperative complication rates in the developed world suggest that rates between 3% and 17% may be reflective of current practice [16, 17]. In 2004 the cost of treating surgical complications alone was an additional US \$25 billion to the US healthcare system [17]. Of note in the last few years is the recognition of the long-term health consequences/associations that result from perioperative complications, with alarming reductions in life expectancy. In 2005, Khuri et al. [14] reported a series of over 105,000 patients from the Veterans Affairs as part of the National Surgical Quality Improvement Program (NSQIP), showing a reduction in median life expectancy of 69% for any 1 of 22 perioperative complications experienced. The occurrence of a 30-day postoperative complication was more important than any pre- or intra-operative factors, even after excluding deaths at 30 days, in predicating long-term survival after major surgery. Although the largest study to date, similar effects are being reported for various operations and complications, suggesting a consistently negative impact on long-term survival of perioperative complications [18, 19]. The nature of the complication and the type of procedure has generally been reflected in the degree to which life expectancy has been affected. However, a recent report of over 10,500 patients suggests that, even if perioperative organ dysfunction completely resolves, there is still a negative effect on/association with long-term survival [20]. It is not illogical to assume that trying to reduce perioperative complications would lead to significant improvements in surgical outcome and possibly life expectancy.

Our study has a number of significant limitations that need to be borne in mind when interpreting the results. Firstly, the original study was stopped early because of excess mortality in the control group and only contained 107 patients, which limits the statistical power of our results. Secondly the original study was not powered beyond 30-day mortality and was not designed for

long-term follow-up. Thirdly the cause of death was not established for each patient (due to the potential inaccuracy of death certification), only their survival status.

In conclusion, we have shown that short-term intervention such as perioperative goal-directed augmentation of global oxygen delivery may have longer-lasting effects on survival than was previously considered. We believe that it is possible that these effects are at least in part due to their ability to reduce major complications in the perioperative period. These techniques deserve greater study,

in particular to confirm this suggestion of a longer-term impact on quality of life and longevity. Our study also shows that critical care treatment can have much longer beneficial health implications than those related to the immediate physiological changes. This has important implications for other treatment trials in critical care, and must be borne in mind when critical care follow-up studies, which tend to focus on various negative physiological and psychological outcomes, are placed in a wider health context.

References

1. Boyd O, Jackson N (2005) How is risk defined in high-risk surgical patient management? *Crit Care* 9:390–396
2. Pearse R, Harrison D, James P, Watson D, Hinds C, Rhodes A, Grounds RM, Bennett E (2006) Identification and characterisation of the high-risk surgical population in the United Kingdom. *Crit Care (London, England)* 10:R81
3. Shoemaker WC, Appel PL, Kram HB, Waxman K, Lee TS (1988) Prospective trial of supranormal values of survivors as therapeutic goals in high-risk surgical patients. *Chest* 94:1176–1186
4. Boyd O, Grounds RM, Bennett ED (1993) A randomized clinical trial of the effect of deliberate perioperative increase of oxygen delivery on mortality in high-risk surgical patients. *JAMA* 270:2699–2707
5. Sinclair S, James S, Singer M (1997) Intraoperative intravascular volume optimisation and length of hospital stay after repair of proximal femoral fracture: randomised controlled trial. *BMJ* 315:909–912
6. Wilson J, Woods I, Fawcett J, Whall R, Dibb W, Morris C, McManus E (1999) Reducing the risk of major elective surgery: randomised controlled trial of preoperative optimisation of oxygen delivery. *BMJ* 318:1099–1103
7. Polonen P, Ruokonen E, Hippelainen M, Poyhonen M, Takala J (2000) A prospective, randomized study of goal-oriented hemodynamic therapy in cardiac surgical patients. *Anesth Analg* 90:1052–1059
8. Venn R, Steele A, Richardson P, Poloniecki J, Grounds M, Newman P (2002) Randomized controlled trial to investigate influence of the fluid challenge on duration of hospital stay and perioperative morbidity in patients with hip fractures. *Br J Anaesth* 88:65–71
9. Gan TJ, Soppitt A, Maroof M, el-Moalem H, Robertson KM, Moretti E, Dwane P, Glass PS (2002) Goal-directed intraoperative fluid administration reduces length of hospital stay after major surgery. *Anesthesiology* 97:820–826
10. Kern JW, Shoemaker WC (2002) Meta-analysis of hemodynamic optimization in high-risk patients. *Crit Care Med* 30:1686–1692
11. Pearse R, Dawson D, Fawcett J, Rhodes A, Grounds RM, Bennett E (2005) Early goal-directed therapy after major surgery reduces complications and duration of hospital stay. A randomised, controlled trial [ISRCTN38797445]. *Crit Care (London, England)* 9:R687–R693
12. Poeze M, Greve J, Ramsay G (2005) Meta-analysis of hemodynamic optimization: relationship to methodological quality. *Crit Care (London, England)* 9:R771–R779
13. Silber JH, Rosenbaum PR, Trudeau ME, Chen W, Zhang X, Kelz RR, Mosher RE, Even-Shoshan O (2005) Changes in prognosis after the first postoperative complication. *Med Care* 43:122–131
14. Khuri SF, Henderson WG, DePalma RG, Mosca C, Healey NA, Kumbhani DJ (2005) Determinants of long-term survival after major surgery and the adverse effect of postoperative complications. *Ann Surg* 242:326–341 discussion 341–323
15. Hutter MM, Rowell KS, Devaney LA, Sokal SM, Warshaw AL, Abbott WM, Hodin RA (2006) Identification of surgical complications and deaths: an assessment of the traditional surgical morbidity and mortality conference compared with the American College of Surgeons-National Surgical Quality Improvement Program. *J Am Coll Surg* 203:618–624
16. Weiser TG, Regenbogen SE, Thompson KD, Haynes AB, Lipsitz SR, Berry WR, Gawande AA (2008) An estimation of the global volume of surgery: a modelling strategy based on available data. *Lancet* 372:139–144
17. Mangano DT (2004) Perioperative medicine: NHLBI working group deliberations and recommendations. *J Cardiothorac Vasc Anesth* 18:1–6
18. Gawande AA, Thomas EJ, Zinner MJ, Brennan TA (1999) The incidence and nature of surgical adverse events in Colorado and Utah in 1992. *Surgery* 126:66–75
19. Kable A, Gibberd R, Spigelman A (2008) Predictors of adverse events in surgical admissions in Australia. *Int J Qual Health Care* 20:406–411
20. Bihorac A, Yavas S, Subbiah S, Hobson CE, Schold JD, Gabrielli A, Layon AJ, Segal MS (2009) Long-term risk of mortality and acute kidney injury during hospitalization after major surgery. *Ann Surg* 249:851–858