Does perioperative hemodynamic optimization protect renal function in surgical patients? A meta-analytic study

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Objective: **Postoperative acute deterioration in renal function, producing oliguria and/or increase in serum creatinine, is one of the most serious complication in surgical patients. Most cases are due to renal hypoperfusion as a consequence of systemic hypotension, hypovolemia, and cardiac dysfunction. Although some evidence suggests that perioperative monitoring and manipulation of oxygen delivery by volume expansion and inotropic drugs may decrease mortality in surgical patients, no study analyzed this approach on postoperative renal dysfunction. The objective of this investigation is to perform a meta-analysis on the effects of perioperative hemodynamic optimization on postoperative renal dysfunction.**

Data Sources, Study Selection, Data Extraction: **A systematic literature review, using MEDLINE, EMBASE, and The Cochrane Library databases through January 2008 was conducted and 20 studies met the inclusion criteria (4220 participants). Data synthesis was obtained by using odds ratio (OR) with 95% confidence interval (CI) by random-effects model.**

Data Synthesis: **Postoperative acute renal injury was significantly reduced by perioperative hemodynamic optimization when compared with control group (OR 0.64; CI 0.50–0.83; $p = 0.0007$). Perioperative optimization was effective in reducing renal injury defined consistently with risk, injury, failure, and loss and end-stage kidney disease and Acute Kidney Injury Network classifications, and in studies defining renal dysfunction by serum creatinine and/or need of renal replacement therapy only (OR 0.66; CI 0.50–0.88; $p = 0.004$). The occurrence of renal dysfunction was reduced when treatment started both preoperatively and intraoperatively or postoperatively, was performed in high-risk patients, and was obtained by fluids and inotropes. Mortality was significantly reduced in treatment group (OR 0.50; CI 0.31–0.80; $p = 0.004$), but statistical heterogeneity was observed.**

Conclusions: **Surgical patients receiving perioperative hemodynamic optimization are at decreased risk of renal impairment. Because of the impact of postoperative renal complications on adverse outcome, efforts should be aimed to identify patients and surgery that would most benefit from perioperative optimization. (Crit Care Med 2009; 37:2079–2090)**

Key Words: postoperative acute kidney injury; perioperative hemodynamic optimization; high-risk patients; reno-protection; oxygen delivery; cardiac output

Postoperative acute kidney dysfunction is one of the most serious complication in surgical patients and accounts for 18% to 47% of all cases of hospital-acquired acute renal failure (1, 2). Its occurrence is associated with higher rates of gastrointestinal bleeding, respiratory infections, and sepsis (3, 4), augments hospitalization cost (5), and carries an increased mortality both in cardiac (6) and noncardiac surgery (7). Renal impairment may involve prerenal factors (30% to 60%) and progress through acute ischemic or toxic injuries to acute tubular necrosis (20% to 40%) (1). Inflammatory and nephrotoxic factors together with type of surgery, preexisting renal function, and patient comorbidities play a critical role in its occurrence (8). However, most cases of renal impairment share an underlying common hypoperfusive pathogenesis (2). Eighty percent of patients with postoperative renal damage had a previous perioperative episode of hemodynamic instability (9).

There is no reliable evidence suggesting any benefit of specific pharmacologic "kidney-oriented" treatments in preventing postoperative renal injury (10), and the maintenance of renal perfusion remains the most important prophylactic measure to protect renal function (1, 2, 11, 12). Renal perfusion may be preserved by pursuing adequate volemia and cardiac output, mainstay of the so called "hemodynamic optimization" or "goal-directed therapy." This strategy refers to the perioperative monitoring and manipulation of physiologic hemodynamic parameters by means of fluids, red blood cells, and inotropic drugs (13), with the aim to reach normal or supranormal values of cardiac output and oxygen delivery to face the increase in oxygen demand and to prevent organ failure (14). Although some data suggest that hemodynamic optimization may decrease morbidity and mortality in high-risk surgical patients (15, 16), no study has analyzed its effects on postoperative acute renal dysfunction as specific main outcome. This may explain why, in the setting of postoperative acute kidney injury (AKI), the strategy of hemodynamic optimization is defined as a weak recommendation sustained by very low-quality evidence (12).

Because clinical manifestations of acute renal involvement range from short periods of oliguria to need of renal replacement therapy (RRT), one of the major difficulties in studying postoperative renal dysfunction is the lack of an uniform definition (17). The Acute Dialysis Quality Initiative group has proposed the Risk, Injury, Failure, Loss, End-stage kidney disease (RIFLE) criteria to standardize the classification of renal failure (18). On the basis of glomerular filtration rate,

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serum creatinine (SCr) and urine output, RIFLE classification defines three grades of increasing severity—risk, injury, and failure—and two outcome classes—loss and end-stage kidney disease—all associated with an increased risk for hospital mortality (19). Recently, the Acute Kidney Injury Network (AKIN) has suggested a modification of the RIFLE classification by adopting the term AKI to cover the entire spectrum of acute renal failure (20). The AKI classification includes three stages representing an increasing degree of renal impairment, from smaller increases in SCr than those considered in RIFLE to the need of RRT (20).

On the basis of the previous considerations, we performed a meta-analytic study about the effects of perioperative hemodynamic optimization on postoperative acute renal dysfunction. We hypothesized that perioperative hemodynamic optimization would protect renal function, and, therefore, reduce the incidence of postoperative renal injury.

METHODS

Searching, Selection, and Validity Assessment

Studies were searched in MEDLINE, EMBASE, The Cochrane Library databases (January 1980-January 2008) using the following terms as medical subject headings, text, and keywords, both stand-alone or in combination: cardiac output, oxygen consumption, oxygen delivery, resuscitation end points, supranormal oxygen, kidney or renal failure or injury, prerenal azotemia, acute tubular necrosis, oliguric and nonoliguric renal failure, renal blood flow, urinary output, renal protection, diabetic nephropathy, surgery, operative surgical procedures. We identified additional studies in the reference lists of previously published systematic reviews and retrieved articles, and hand-searched for other data sources in the annual proceedings (2003–2007) of the Society of Critical Care Medicine, the European Society of Intensive Care Medicine, the Society of Cardiovascular Anesthesiologists, the Royal College of Anaesthetists, and the American Society of Anesthesiologists. We included abstracts in the attempt to search all available data with the aim of reducing publication bias (21). Publication language was not a search criterion.

Studies were selected according to the following inclusion criteria:

1. Randomized controlled trials (RCTs) on the effects of perioperative hemodynamic goal-directed therapy on mortality or morbidity as main research topic. Goal-directed therapy was defined as perioperative monitoring and manipulation of hemodynamic parameters to reach normal or supranormal values by fluids and/or vasoactive therapy. Studies with no description of perioperative goal-directed therapy, no difference between groups in the optimization protocol, with therapy titrated to the same goal in both groups, or not titrated to predefined end points were excluded.
2. Adult (age 18 years or over) surgical patients as participants of study design. Studies involving mixed population of critically ill, nonsurgical patients, or postoperative patients with already established sepsis or organ failure and undergoing late optimization were excluded (15, 16).
3. Report of definition and incidence of renal injury as postoperative complication. These data were searched in the study or in supplemental appendix, or were obtained by contacting original investigators.

The methodologic quality of RCTs was evaluated according to the Jadad scale (22). The Jadad scale is a validated score based on three items (randomization, blindness, and description of withdrawals and dropouts), and has a maximum score of five points, assigned on the basis of the quality of randomization and blinding method (absent or inappropriate = 0, appropriate but not described = 1, appropriate and described = 2) and of the outcome report of all enrolled subjects (not described = 0, described = 1). The Jadad scoring system was independently evaluated by two investigators (M.G. and M.M.) and, when score differed, the study was further assessed to reach consensus.

Data Abstraction and Study Characteristics

Data were independently collected by two investigators (M.G. and N.B.), with any discrepancy resolved by reinspection of the original article. To avoid transcription errors, the data were input into statistical software and rechecked by different investigators (M.M., T.F.). Data abstraction included patients characteristics (age, sex, baseline morbidity), type of surgery (major or minor, elective or emergent), morbidity/mortality risk definition (high or low), hemodynamic monitoring tools and parameters (systemic arterial pressure, pulmonary artery occlusion pressure, oxygen delivery, cardiac output, mixed venous oxygen saturation, stroke volume, central venous pressure, etc.), anesthesiologic features, hemodynamic goal-directed therapy (timing, end points, and therapeutic intervention), details on acute renal injury (definition, incidence, need of RRT). For each RCT, we searched for description of study design (including means for randomized allocation and blindness), withdrawals and dropouts of enrolled patients.

The primary outcome was worsening of renal function, whichever definition was used, and secondary outcome was mortality.

Quantitative Data Synthesis

Meta-analytic techniques (Analysis software RevMan, version 5.0.0, Cochrane Collaboration, Oxford, UK) were used to combine studies using odds ratios (ORs) and 95% confidence intervals (CIs). A statistical difference between groups was considered to occur if the pooled 95% CI did not include 1 for the OR. An OR of less than 1 favored hemodynamic optimization when compared with control group. Two-sided p values were calculated. A random-effects model was chosen for all analyses, because it involves the assumption that the effects estimated in different studies are not identical but follow some distributions and that studies represent a random sample of the relevant distribution of effects. The combined effects estimate is the mean effect of this distribution. Statistical heterogeneity and inconsistency were assessed by using the Q and I^2 tests, respectively (23, 24). I^2 values around 25%, 50%, and 75% are considered representing low, moderate, and high statistical inconsistency, respectively (23). When the Q test p value was <0.10 and/or the I^2 was $>25\%$, heterogeneity and inconsistency were considered significant.

The main outcome was worsening of renal function, whichever definition was used by the authors of the included studies.

We planned several sensitivity and subgroup analyses for the main outcome on the basis of the following

Quality RCTs. Subgroups were defined on the basis of methodologic quality criteria (Jadad score ≥ 3) (22).

Definition of Renal Dysfunction. The first sensitivity analysis was performed including studies in which postoperative renal injury definition was consistent with the grade risk (R) of RIFLE classification (increase in SCr at least $>50\%$ from preoperative value and/or a reduction in urine output <0.5 mL·kg^{-1}·hr^{-1} for >6 hours) (18). A second sensitivity analysis was performed identifying studies in which postoperative renal injury definition was consistent with stage 1 of AKIN classification (absolute or percentage increase in SCr of ≥ 0.3 mg/dL or $\geq 50\%$, or reduction in urine output <0.5 mL·kg^{-1}·hr^{-1} for >6 hours, or need of RRT) (20). A third subgroup analysis was performed including only studies in which postoperative renal injury was defined on the basis of SCr value (absolute SCr >2 mg/dL (25), increase by $>50\%$ (18, 20) or by >0.5 mg/dL (6) or need of RRT), disregarding urine output.

Timing of Commencement of Hemodynamic Optimization Relative to Surgery. Subgroups were defined as preoperative (if hemo-

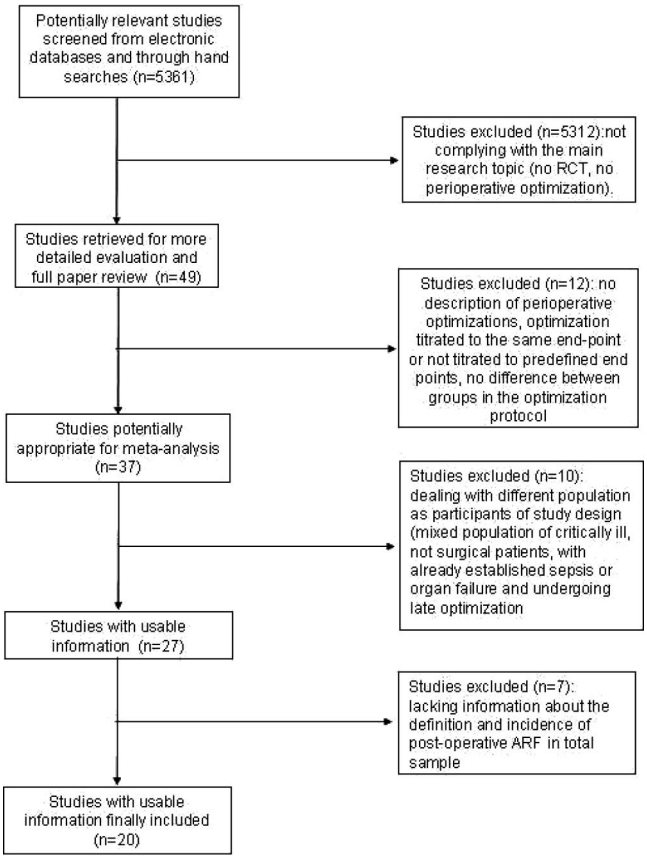

Figure 1. Flow chart summarizing the studies selection procedure for the meta-analysis. *RCT*, randomized controlled trial; *ARF*, acute renal failure.

dynamic monitoring and management was started before surgery), or intraoperative and/or postoperative (if hemodynamic monitoring and management was started during or after the end of surgery).

Treatment. Subgroups were defined as fluids alone or fluids with inotropes, according to the treatment.

Normal and Supranormal Hemodynamic Optimization. The subset analysis included the studies using the original supranormal hemodynamic optimization proposed by Shoemaker et al (26) (cardiac index >4.5 $L \cdot min^{-1} \cdot m^{-2}$, oxygen delivery >600 $mL \cdot min^{-1} \cdot m^{-2}$ or oxygen consumption >170 $mL \cdot min^{-1} \cdot m^{-2}$). The other subgroup included studies aiming at normal values.

Monitoring Tools. The subset analysis included studies using pulmonary artery catheter (PAC) for optimization, and studies using other monitoring devices.

High-Risk Patients. Studies were included in this subgroup analysis if the authors explicitly define patients as at high risk of morbidity/mortality. Definition of high risk was based on need of emergent surgery, and/or elective major surgery in patients with risk criteria defined by perioperative scoring system (27), ASA physical status classification, age >60 years, and preoperative morbidity.

A test for statistical power with α error of 0.05 was calculated for each analysis. A statistical power $\geq 80\%$ was considered adequate.

RESULTS

Trial Flow and Study Characteristics. After initial screening and a subsequent more detailed selection, we identified a pool of 49 RCTs on goal-directed therapy of 5361 studies (Fig. 1). Twelve articles were excluded because they did not comply with the inclusion criteria (no description of perioperative optimization, circulatory optimization titrated to the same end point or not titrated to predefined end points, or no difference between groups in the optimization protocol). Ten studies were excluded because dealing with a mixed population of critically ill, not surgical patients, with already established sepsis or organ failure and undergoing late optimization, and seven articles were excluded because no detail on definition and incidence of postoperative acute renal failure in the total sample was reported or could be retrieved. In eight studies, data on definition and incidence of postoperative acute renal failure were obtained after contacting the authors (26, 28–34).

Finally, 20 articles (26, 28–46) were selected for the analysis. All included articles evaluated the effects of hemodynamic optimization on morbidity (including renal morbidity) as primary or secondary outcome and had a population sample of adult surgical patients, undergoing both elective or emergent procedures (Table 1). The included studies involved a grand total of 4,220 patients. The studies were performed in United States, Europe, Canada, Brazil, and India from 1991 to 2008 (Table 1) and were all published in English.

Data concerning RCTs quality assessment, morbidity/mortality risk definition, population, and type of surgery are presented in Table 1. The methodologic evaluation, according to the Jadad score, showed that 13 studies were considered as high-quality studies. Of 20 studies, nine enrolled "high-risk" patients.

Table 2 shows timing, goals, and modality of perioperative goal-directed therapy. In eight studies, hemodynamic monitoring and management started before surgery. In one study (36), treatment was started either 12 hours or 3 hours before surgery; both groups were pooled together for the purpose of the analysis. In five and seven studies, goal-directed therapy was started during or after the end of surgery, respectively.

In five studies, the treatment group received only plasma expanders (gelofusine, hydroxyethyl starch) and/or blood, whereas in 15 studies optimization was obtained both with fluids (crystalloids and/or colloids and/or blood) and inotropes (dopamine, dobutamine, dopexamine, or epinephrine) with vasodilators (Table 2). In one study (34), either dopexamine or epinephrine were administered in treatment group; both groups were pooled together for the purpose of the analysis.

In 12 studies, hemodynamic monitoring was performed with PAC, with oxygen delivery, cardiac output, mixed venous oxygen saturation, and lactate as goal parameters. In one study (32) the LiDCO plus (Lithium indicator Dilution Cardiac Output) system was used to measure cardiac output. In another study (29), a noninvasive cardiac output measurement (FloTrac), based on the analysis of arterial waveform, was performed. In five studies, an esophageal Doppler was used and stroke volume or the corrected flow time (i.e., the total amount of time the blood is traveling in a forward direction

Table 1. Quality assessment and sample characteristics of the analyzed studies

Author (Year), Country	Blinding	Randomization	Drop-Outs	Jadad Score	Risk Definition	Population	Surgery
Bender et al (35), USA	No	Not adequate	Yes	2		No AMI, CABG, CHF	Elective aortic and vascular
Berlauk et al (36), USA	No	Adequate	Yes	3		Exclusion of high-risk: no AMI, CABG, CHF	Elective peripheral vascular
Bishop et al (37), USA	No	Not adequate	No	1	High risk	Expected blood loss ≥2 L, major fractures requiring transfusion	Emergent trauma
Bonazzi et al (38), Europe	No	Adequate	No	2		EF >50%	Elective vascular
Boyd et al (39), Europe	No	Not adequate	No	1	High risk	Specific high-risk criteria	Emergent or elective Major abdominal or vascular
Chytra et al (28), Europe	No	Not adequate	Yes	2	High risk	Multiple trauma expected blood loss ≥2 L	Emergent trauma
Donati et al (40), Europe	No	Adequate	Yes	3	High risk	ASA II-IV	Elective major abdominal or aortic
Gan et al (41), USA	No	Adequate	Yes	3		ASA I-III, blood loss ≥500 mL	Elective general, urologic, gynecologic
Lobo et al (42), Brazil	No	Adequate	Yes	3	High risk	Age >60 years, previous disease of a vital organ	Elective major abdominal or vascular
Malhotra et al (29), India	No	Adequate	Yes	3	Moderate to high risk	Euroscore ≥3	Elective cardiac (on pump)
McKendry et al (30), Europe	No	Adequate	Yes	3			Elective cardiac (on-pump)
Noblett et al (31), Europe	Yes	Not adequate	Yes	4			Colorectal surgery
Pearse et al (32), Europe	No	Adequate	Yes	3	High risk	Specific high-risk criteria, POSSUM	Elective or emergent major general
Polonen et al (43), Europe	No	Adequate	Yes	3			Elective cardiac (on-pump)
Sandham et al (44), Canada	No	Adequate	Yes	3	High risk	Age >60 years, ASA III–IV	Elective or emergent major abdominal, thoracic, vascular, or orthopedic
Shoemaker et al (26), USA	No	Adequate	Yes	3	High risk	Specific high-risk criteria	Emergent or elective major abdominal
Valentine et al (33), USA	No	Adequate	No	2		Exclusion of high-risk	Elective aortic
Wakeling et al (45), Europe	No	Adequate	Yes	3		POSSUM	Elective major bowel
Wilson et al (34), Europe	Yes	Adequate	Yes	3	High risk	Coexisting medical conditions, POSSUM	Elective major (abdominal, vascular, urologic)
Ziegler et al (46), USA	No	Not adequate	Yes	2		No AMI, CABG, CHF	Elective vascular (aortic and limb salvage)

AMI, acute myocardial infarction; ASA, American Society of Anesthesiologists' physical status classification, CABG, coronary artery bypass grafting; CHF, congestive heart failure; POSSUM, Physiologic and Operative Severity Score for the enUmeration of Mortality and Morbidity (27); Euroscore, European System for cardiac operative risk evaluation; EF, ejection fraction.

within the aorta corrected for heart rate) considered an index of systemic vascular resistance and sensitive to changes in left ventricular preload (47) guided hemodynamic optimization. In one study (40), the estimated oxygen extraction ratio, calculated as the ratio between the difference in arterial and central venous oxygen saturation ($Scvo_2$) to arterial saturation, was the goal parameter.

In 12 studies, worsening of renal function was clearly defined, whereas in eight studies the definition was obtained by the authors (written communications). In 11 and 15 studies, definition of renal dysfunction was consistent with the grade risk (R) of RIFLE and with stage 1 of AKIN classifications, respectively. In 11 studies, postoperative renal injury definition included a SCr value >2 mg/dL (25), a SCr increase by >50% (18, 20) or >0.5 mg/dL (6) or the need of RRT.

Quantitative Data Synthesis. Among the 4,220 patients randomized in the included studies, 290 developed acute renal injury. Of these, 175 belonged to control group (8.3%), and 115 to treatment group (5.4%). Figure 2 shows ORs and 95% CIs for the development of renal injury in each trial as well as the pooled estimate (OR 0.64; 95% CI 0.50–0.83; $p = 0.0007$). No statistical heterogeneity was detected. In three RCTs (35, 38, 46), no patient presented renal injury. A reanalysis of the data, adding a nominal value of 0.5 in all 2×2 cells to enable calculation of OR and retesting of heterogeneity, produced similar result.

Results of all subgroup analyses are provided in Table 3. The RCTs quality sensitivity analysis confirmed the main result.

Both subgroup analyses based on RIFLE and AKIN classification yielded significant differences in renal injury

Table 2. Intervention details of analyzed studies and renal outcome definition

Author	Timing of Optimization	Goals of Optimization	Modality of Optimization	Definition of Acute Kidney Injury
Bender et al (35)	Preop from the morning of surgery for 16 hrs postop	CI $\geq$2.8 L·min^{-1}·m^{-2}, 8 $\leq$ PAOP $\geq$ 14 mmHg, SVR $\leq$1100 dyne·sec/cm^5	Fluids, blood, dopamine, NTP	Increase in baseline creatinine by >1 mg/dL
Berlauk et al (36)	Preop from 12 or 3 hrs before surgery for 18 hrs postop	CI $\geq$2.8 L·min^{-1}·m^{-2}, 8 $\leq$ PAOP $\leq$ 15 mm Hg, SVR $\leq$1100 dyne·sec/cm^5	Fluids, dopamine or dobutamine, NTP, NTG	UO <0.5 mL·kg^{-1}·hr^{-1} for 5 hrs and/or rise in baseline creatinine by >0.5 mg/dL and/or need of RRT
Bishop et al (37)	Postop within 6 hrs after surgery for at least 48 hrs	CI $\geq$4.5 L·min^{-1}·m^{-2}, DO_2 $\geq$670 mL·min^{-1}·m^{-2}, VO_2 $\geq$166 mL·min^{-1}·m^{-2}	Fluids, blood, dobutamine (starting at 5 μg·kg^{-1}·min^{-1})	Creatinine $\geq$2 mg/dL or, with preexisting renal disease, creatinine twice than admission
Bonazzi et al (38)	Preop from the day before surgery to the end of the 2nd postop day	CI >3.0 L·min^{-1}·m^{-2}, DO_2 >600 mL·min^{-1}·m^{-2}, 10 <PAOP <18 mmHg, SVR <1450 dyne·sec/cm^5	Fluids, dobutamine (starting from 2.5 μg·kg^{-1}·min^{-1}), NTG	Worsening of preop function with oliguria requiring high dose furosemide (>250 mg/die) and/or need of RRT
Boyd et al (39)	Preop from ICU admission before surgery for 24 hrs postop	DO_2 >600 mL·min^{-1}·m^{-2}	Fluids, blood, dopexamine (starting at 0.5 μg·kg^{-1}·min^{-1} to a maximum of 8 μg·kg^{-1}·min^{-1})	UO <500 ml/24 hrs despite adequate PAOP
Chytra et al (28)[a]	Postop from ICU admission for 12 hrs postop	SV optimization with FTc between 0.35 and 0.4 sec	Fluids, blood	Need of RRT
Donati et al (40)	Intraop up to 24 hrs postop	O_2ERe ([Sao_2–$Scvo_2$] /SaO_2) <27%	Fluids, blood, dobutamine (starting at 3 up to 15 μg·kg^{-1}·min^{-1})	Creatinine >2 mg/dL or need of RRT
Gan et al (41)	Intraop	SV optimization with FTc between 0.35 and 0.4 sec	Fluids, blood	UO <500 ml/24 hrs or creatinine >30% preop value
Lobo et al (42)	Intraop up to 24 hrs postop	DO_2 >600 mL·min^{-1}·m^{-2}	Fluids, blood, dobutamine (3 μg·kg^{-1}·min^{-1}), dopamine, NTP	Creatinine >3.5 mg/dL or UO <500 mL/24 hrs
Malhotra et al (29)[a]	Postop: from ICU admission for 8 hrs	SVV <10%, CI >2.5 and <4.2 L·min^{-1}·m^{-2}, $ScvO_2$ >70%, DO_2 >450 and <600 m L·min^{-1}·m^{-2}	Fluids, blood, inotropes (not specified), vasodilators	UO <750 ml/24 hrs and/or increase in creatinine by >150 mmol/L (1.7 mg/dL) from preop normal values
McKendry et al (30)[a]	Postop: from ICU admission for 4 hrs	SI >35 mL/m^2	Fluids	Need of RRT
Noblett et al (31)[a]	Intraop	SV optimization with FTc between 0.35 and 0.4 sec	Fluids	Increase in creatinine or need of RRT
Pearse et al (32)[a]	Postop: from ICU admission for 8 hrs	DO_2 >600 mL·min^{-1}·m^{-2}, SV >10%	Fluids, dopexamine (starting at 0.25 mg·kg^{-1}·min^{-1} to a maximum of 1 mg·kg^{-1}·min^{-1})	Need of RRT
Polonen et al (43)	Postop: from ICU admission for 8 hrs	SvO_2 >70%, lactate $\leq$2.0 mmol/L	Fluids, blood, dobutamine (up to 15 μg·kg^{-1}·min^{-1}), vasopressors, vasodilators.	UO <750 ml/24 hrs or increase in creatinine by >1.7 mg/dl from preop normal values
Sandham et al (44)	Preop up to 24 hrs postop	CI >3.5 and <4.5 L·min^{-1}·m^{-2}, 550 <DO_2 < 600 mL·min^{-1}·m^{-2}, MAP >70 mm Hg, PAOP 18 mm Hg	Fluids, blood, inotropes (not specified), vasodilators, vasopressors	Increase in baseline creatinine >50% or need for RRT in patients with preexisting non dialysis ARF

Table 2.—*Continued*

Author	Timing of Optimization	Goals of Optimization	Modality of Optimization	Definition of Acute Kidney Injury
Shoemaker et al (26)[a]	Postop before organ failure	CI >4.5 $L \cdot min^{-1} \cdot m^{-2}$, DO_2 >600 $mL \cdot min^{-1} \cdot m^{-2}$, VO_2 >170 $mL \cdot min^{-1} \cdot m^{-2}$	Fluids, blood, dobutamine, dopamine, NTP	BUN of 50 or more and rising, and urine output of <30 mL/hr after adequate hydration
Valentine et al (33)[a]	Preop from at least 14 hrs before surgery	CI ≥2.8 $mL \cdot min^{-1} \cdot m^{-2}$, 8 ≤ PAOP ≤ 15 mm Hg, SVR ≤1100 dyne·sec/cm^5	Fluids, dopamine (2–9 $\mu g \cdot kg^{-1} \cdot min^{-1}$), NTG, NTP	Oliguria lasting more than 24 hours associated with an increase in serum creatinine >100% over baseline or need of RRT
Wakeling et al (45)	Intraop	SV optimization and rise in CVP <3 mm Hg	Fluids	UO <500 mL/24 hrs or increase in baseline creatinine >30%
Wilson et al (34)[a]	Preop from at least 4 hrs before surgery up to 12–24 hrs postop	DO_2 >600 $mL \cdot min^{-1} \cdot m^{-2}$	Fluids, blood, dopexamine (0.125 $mg \cdot kg^{-1} \cdot min^{-1}$) or adrenaline (0.025 $mg \cdot kg^{-1} \cdot min^{-1}$)	UO <0.5 $mL \cdot kg^{-1} \cdot hr^{-1}$ for >3 hours, or increase in baseline creatinine >50%, or need of RRT
Ziegler et al (46)	Preop from 12 hrs before surgery for 24 hrs postop	SvO_2 ≥65%, Hb ≥10 g/dL, PAOP ≥12 mm Hg	Fluids, blood, dobutamine, NTG, NTP	UO <0.5 $mL \cdot kg^{-1} \cdot hr^{-1}$

Preop, preoperative; Intraop, intraoperative; Postop, postoperative; CI, cardiac index; ICU, intensive care unit; PAOP, pulmonary artery occlusion pressure; SVR, systemic vascular resistance; NTP, nitroprussiate; NTG, nytroglycerine; UO, urinary output; Do_2, oxygen delivery; Vo_2, oxygen consumption; Svo_2, mixed venous oxygen saturation; $Scvo_2$, central venous oxygen saturation; RRT, renal replacement therapy; SV, stroke volume; SI, stroke index; FTc, flow-time-corrected; O_2ERe, estimated oxygen extraction ratio; CVP, central venous pressure; BUN, blood urea nitrogen.

[a]Unpublished data (definition of acute kidney injury provided by the authors).

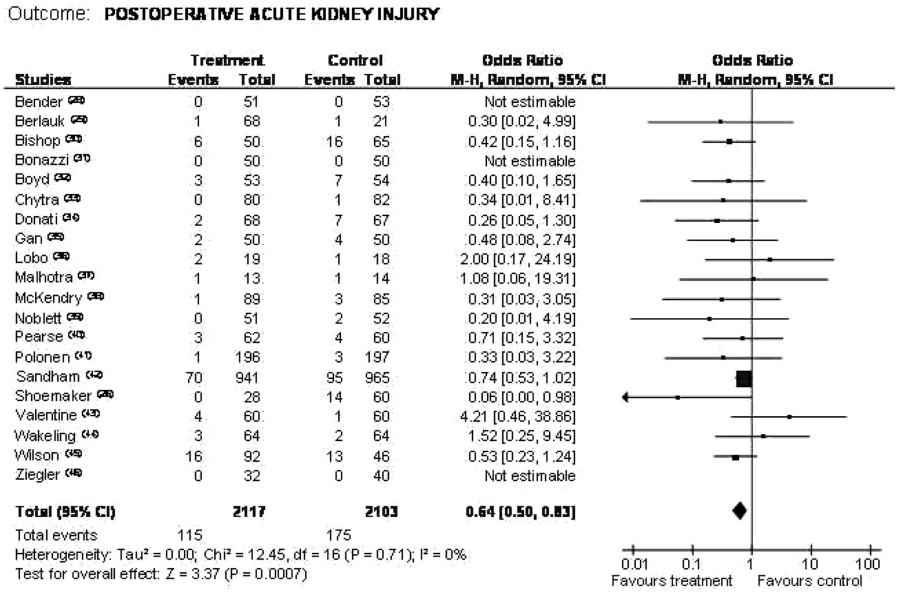

Figure 2. Rates of postoperative acute kidney injury for each of the studies included, whichever definition was used by the authors, with odds ratios (ORs) and 95% confidence intervals (*CI*s). The pooled OR and 95% CI are shown as the total. The size of the box at the point estimate of the OR gives a visual representation of the "weighting" of the study. The diamond represents the point estimate of the pooled OR and the length of the diamond is proportional to the CI.

rate between treatment and control groups (OR 0.68; 95% CI 0.51–0.89; OR 0.66, 95% CI 0.50–0.86, respectively). The pooled OR for developing renal dysfunction in the studies in which postoperative renal injury was defined only by increase in creatinine value or by need of RRT was 0.66 (95% CI 0.50–0.88) (Fig. 3).

A significant difference in renal injury rate favoring treatment was found when hemodynamic optimization started before surgery (OR 0.70; 95% CI 0.53–0.94), as well as when optimization started intraoperatively or postoperatively (OR 0.47; 95% CI 0.27–0.81).

Subgroup analysis showed that fluid administration alone did not reduce renal injury (OR 0.55; 95% CI 0.20–1.47). However, this subanalysis had an inadequate statistical power (31%). A significant decrease in renal injury rate was observed in patients receiving both fluids and inotropes (OR 0.65; 95% CI 0.50–0.85) (Fig. 4).

The subset analysis including studies using supranormal optimization showed an OR of 0.49 (95% CI 0.29–0.83). Targeting goal-directed therapy to maintain normal values yielded similar benefits (OR 0.70; 95% CI 0.52–0.94) (Fig. 5).

The subset analysis including studies using PAC showed a significant reduction in renal injury rate (OR 0.62; 95% CI 0.43–0.90), whereas the OR of studies with monitoring devices other than PAC did not reach statistical significance (OR 0.52; 95% CI 0.25–1.07). However, statistical power of the latter analysis was inadequate (73%).

Postoperative AKI rate was significantly lower in studies enrolling "high-risk" patients (OR 0.64; 95% CI 0.49–0.84); in low-risk patients no difference in renal outcome was observed (OR 0.69; 95% CI 0.3–1.54), although the power of this subgroup analysis was extremely low (19.1%) (Fig. 6).

Mortality was significantly reduced in the perioperative optimized group (OR 0.50; 95% CI 0.31–0.80). High sta-

Table 3. Subgroup analyses of pooled OR of renal injury

	No. Studies (Ref.)	Treatment (n/N)	Control (n/N)	OR (95% CI)	*p* Value	*q* Statistic *p* Value	I^2 (%)	Statistical Power (%)
Quality RCTs (Jadad score ≥3)	13 (26, 29–32, 34, 36, 40–45)	102/1741	150/1699	0.66 (0.50–0.87)	0.003	0.75	0	99.7
Renal injury according to RIFLE	11 (29, 32–34, 35, 37, 39, 40, 42–44)	96/1605	139/1599	0.68 (0.51–0.89)	0.006	0.63	0	98.6
Renal injury according to AKIN	15 (28–30, 32–34, 36–43, 45)	97/1893	145/1839	0.66 (0.50–0.86)	0.002	0.76	0	99.8
Renal injury according to creatinine or need of RRT	11 (28, 30–37, 40, 44)	90/1612	133/1556	0.66 (0.50–0.88)	0.004	0.59	0	99.6
Preoperative optimization	8 (33–36, 38, 39, 44, 46)	94/1347	117/1289	0.70 (0.53–0.94)	0.02	0.41	0	75.6
Intraoperative or postoperative optimization	12 (26, 28–32, 37, 40–43, 45)	21/770	58/814	0.47 (0.27–0.81)	0.006	0.80	0	100
High-risk patients	9 (26, 28, 32, 34, 37, 39, 40, 42, 44)	102/1393	158/1417	0.64 (0.49–0.84)	0.001	0.53	0	99.8
Non high-risk patients	11 (29–31, 33, 35, 36, 38, 41, 43, 45, 46)	13/724	17/686	0.69 (0.31–1.54)	0.37	0.61	0	19.1
Pulmonary artery catether monitoring	12 (26, 33–39, 42–44, 46)	103/1640	151/1629	0.62 (0.43–0.90)	0.01	0.35	10.3	98
Other monitoring devices	8 (28–32, 40, 41, 45)	12/477	24/474	0.52 (0.25–1.07)	0.07	0.87	0	73
Fluids only	5 (28, 30, 31, 41, 45	6/334	12/333	0.55 (0.20–1.47)	0.23	0.74	0	31
Fluids + inotropes	15 (26, 29, 32–40, 42–44, 46)	109/1783	163/1770	0.65 (0.50–0.85)	0.002	0.50	0	100
Fluids + dobutamine	8 (26, 36–38, 40, 42, 43, 46)	12/511	42/518	0.36 (0.18–0.75)	0.006	0.57	0	100
Supranormal target	7 (26, 32, 34, 37–39, 42)	30/354	55/353	0.49 (0.29–0.83)	0.008	0.54	0	98.2
Normal target	13 (28–31, 33, 35, 36, 40, 41, 43–46)	85/1763	120/1750	0.70 (0.52–0.94)	0.02	0.71	0	94.5
Mortality	19 (26, 28–40, 42–46)	138/2123	204/2085	0.50 (0.31–0.80)	0.004	0.004	54.4	99.9

OR, odds ratio; CI, confidence interval; RCT, randomized controlled trial; AKIN, Acute Kidney Injury Network; RRT, renal replacement therapy.

tistical heterogeneity and inconsistency were found (*Q* statistic $p = 0.004$; $I^2 = 54.4\%$).

DISCUSSION

The main result of the present meta-analysis shows that the incidence of postoperative acute renal injury is significantly reduced by perioperative hemodynamic optimization. The kidney normally receives 20% to 25% of total cardiac output resulting in the highest tissue perfusion in the body and its medullary portion of the nephrons is at risk of hypoperfusion, because of low blood flow, and high oxygen demand and extraction (approaching 90%) (48). A decrease in cardiac output not only directly causes renal hypoperfusion, but also activates neurohumoral responses, which promote renal vasoconstriction (1). Maintenance of adequate cardiac output under hemodynamic monitoring may reduce the risk of postoperative renal injury by assuring adequate renal blood flow and reducing renal vasoconstriction.

A major difficulty in studying postoperative renal failure is the lack of a widespread accepted definition (17), and the studies included in the present meta-analysis share this large variability. RIFLE and AKIN classification of renal failure have been recently proposed to overcome this inconsistency. In the perioperative setting, not all the markers of renal dysfunction may have the same clinical impact. Transient postoperative oliguria may not be synonymous of abnormal renal function, because it can be influenced by a number of factors that regulate renal tubular handling of water, and may be the appropriate response to renal hypoperfusion (10). Furthermore, it should not be disregarded that fluid expansion or dopamine use (49) may *per se* directly increase diuresis, without improving renal function. On other side, the need of RRT (50) as well as subtle increases in SCr, usually perceived as fluctuations within the "normal range" (6, 51), are both associated with increased mortality and morbidity. Whichever definition of renal failure we adopt—i.e., definitions provided by the authors or RIFLE and AKIN criteria or variations in creatinine and need of RRT—the results of our study consistently show that renal outcome is significantly improved by goal-targeted hemodynamic manipulation.

Mortality and Perioperative Optimization. In the present meta-analysis, mortality was significantly reduced in the goal-targeted group, but the result was associated with significant heterogeneity and inconsistency. These statistical tests determine whether there are genuine differences underlying the results of the studies (heterogeneity), or whether the variation in findings is compatible with chance alone (homogeneity) (24). Two recent meta-analyses (15, 16) have shown a lower mortality when hemodynamic perioperative optimization was performed in surgical patients. However, in one meta-analysis (15), heterogeneity tests were not performed; whereas in the other (16), the mortality result was affected by significant heterogeneity (*Q* statistic $p = 0.06$) and inconsistency ($I^2 = 35\%$). The presence of significant heterogeneity and inconsistency reduces the strength of evidence (24) and, therefore, no definitive conclusion about the effects of perioperative optimization on mortality can be drawn.

Timing, Means, Target, and Monitoring Tools of Perioperative Optimization and Kidney Injury. All the studies on perioperative hemodynamic optimization had the same starting point, that is fluid loading, and the same end point, that is achieving adequate oxygen delivery. However, they have varied in their approaches to both the timing and the modalities of interventions, the targets, the monitoring tools, and the type of patients enrolled.

The strategy of optimization has been often accomplished before surgery to an-

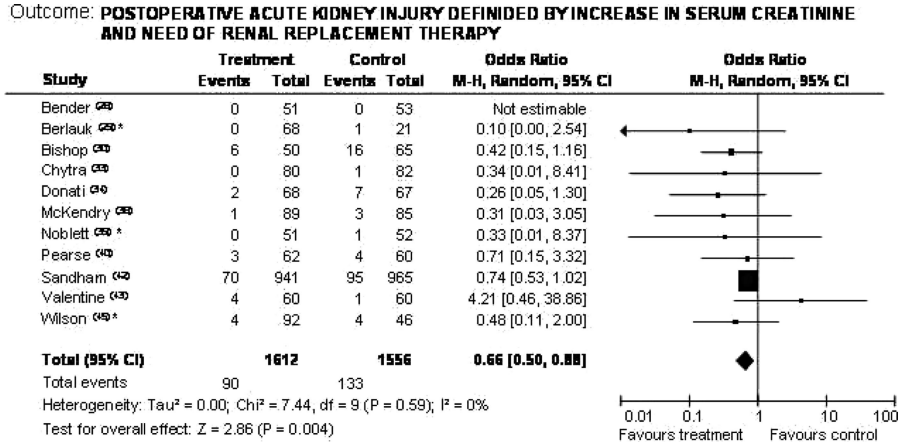

Figure 3. Rates of acute kidney injury including only studies in which postoperative renal injury was defined on the basis of serum creatinine value (absolute serum creatinine >2 mg/dL (25), increase by >50% (18, 20) or by >0.5 mg/dL (6) or need of renal replacement therapy), disregarding urine output, with odds ratios (ORs) and 95% confidence intervals (*CI*s). The pooled OR and 95% CI are shown as the total. The size of the box at the point estimate of the OR gives a visual representation of the "weighting" of the study. The diamond represents the point estimate of the pooled OR and the length of the diamond is proportional to the CI. *Number of events different from total analysis.

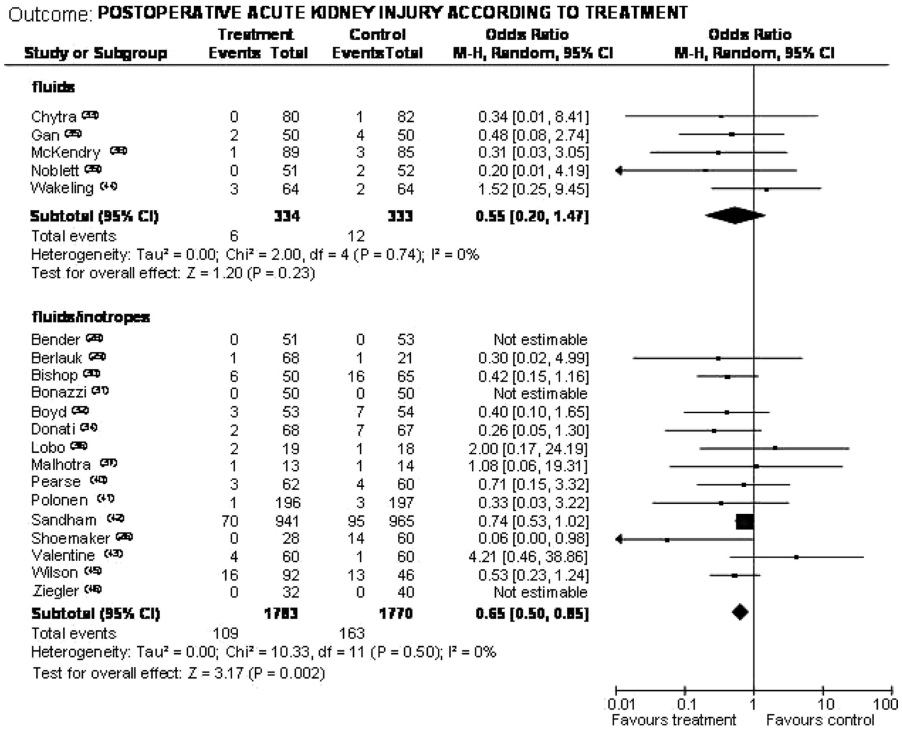

Figure 4. Rates of acute kidney injury in subgroups defined, according to the treatment, as fluids alone or fluids with inotropes, with odds ratios (ORs) and 95% confidence intervals (*CI*s). The pooled OR and 95% CI are shown as the total. The size of the box at the point estimate of the OR gives a visual representation of the "weighting" of the study. The diamonds represent the point estimate of the pooled ORs and the length of the diamonds is proportional to the CI.

ticipate the increase in oxygen demands developing at the time of surgical stress. However, if flow and oxygen debts are paid back soon after, the incidence of postoperative complications may equally decrease (14). Our results show that intraoperative or postoperative optimization is as much effective as preoperative optimization. Therefore, from a "renal standpoint," hemodynamic optimization performed during or soon after surgery is a feasible alternative when preoperative optimization is difficult to pursue.

In some studies (28, 30, 31, 41, 45), the hemodynamic target has been reached by volume loading alone. The evidence supporting the benefit of perioperative fluid hydration on postoperative renal injury is weak deriving from observational studies with historical control groups (52, 53). Our fluid subgroup analysis showed no reduction in kidney injury. The low number of patients, resulting in low statistical power (31%), the lack of homogeneous fluid loading strategies, or the absence in many trials of titration to specific preload targets (e.g., filling pressures) may all explain this result. The result of the subgroup analysis including studies (26, 29, 32–40, 42–44, 46) that have used fluid and inotropic drugs to reach hemodynamic targets suggests that renoprotection may benefit from this association. It is not possible to state if the effects of fluid and inotropes are synergistic or if the beneficial effect of one intervention counteracts the adverse effect of the other. Furthermore, on one side patients with a reduced physiologic reserve may benefit of additional administration of inotropic drugs to increase oxygen delivery and counteract renal hypoperfusion. On the other side, in many trials fluid administration might have been not adequate to increase oxygen delivery, requiring the addition of inotropic drugs. Well-structured RCTs taking into account both preoperative cardiac and renal function, complexity of surgery, and protocolized approach to fluid administration are needed to clarify this issue.

An interesting point of debate in the perioperative optimization issue is how much should oxygen delivery increase. Some studies have set up hemodynamic targets to supranormal values, as proposed by Shoemaker et al (26), whereas others to physiologic values. The subgroup analysis shows that physiologic targets are as much "nephroprotective" as supranormal goals. This result has valuable clinical implications. An aggressive use of fluids and catecholamines carries potential complications such as acute pulmonary edema, arrhythmias, or mismatch between myocardial oxygen supply and requirements with the risk of myocardial ischemia (13). Furthermore, an excessive use of catecholamine may not be devoid of risks on renal function (54, 55).

The original studies on perioperative optimization have used PAC for cardiac output monitoring. Controversy has emerged regarding its use because of the occurrence of complications during cen-

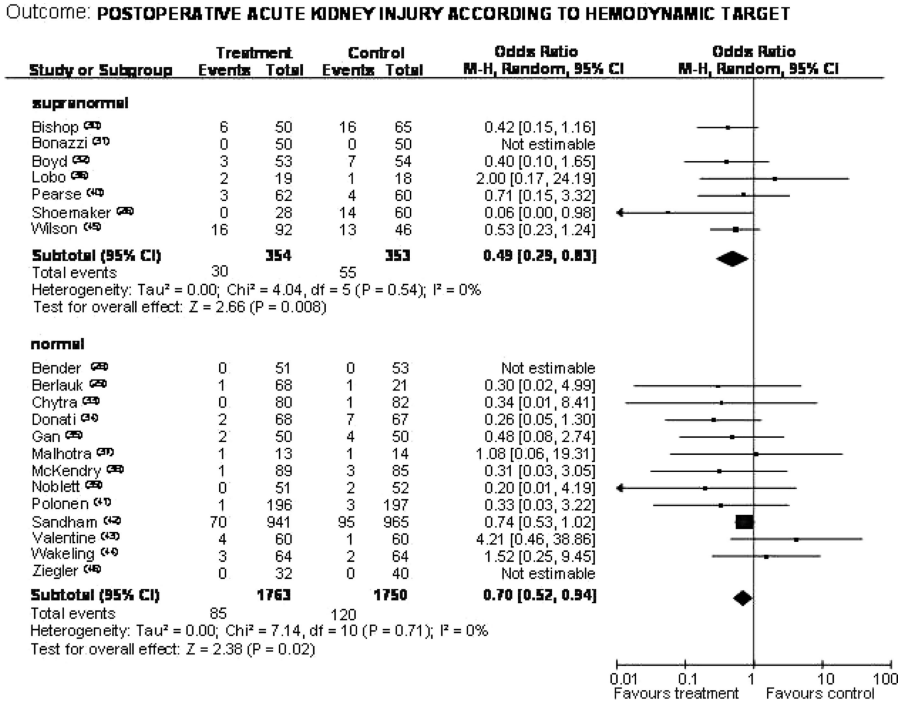

Figure 5. Rates of acute kidney injury in subgroups defined according to the hemodynamic target with odds ratios (ORs) and 95% confidence intervals (*CI*s). The subset analysis included the studies using the original supranormal hemodynamic optimization proposed by Shoemaker et al (26) (cardiac index >4.5 L·min^{-1}·m^{-2}, oxygen delivery >600 mL·min^{-1}·m^{-2} or oxygen consumption >170 mL·min^{-1}·m^{-2}). The other subgroup included studies aiming at normal values. The pooled OR and 95% CI are shown as the total. The size of the box at the point estimate of the OR gives a visual representation of the "weighting" of the study. The diamonds represent the point estimate of the pooled ORs and the length of the diamonds is proportional to the CI.

tral venous access (e.g., arterial puncture, bleeding, air embolism, and pneumothorax), catheterization procedure (dysrhythmias), and catheter residence (venous thrombosis, thrombophlebitis, and pulmonary embolism and infarction) (56). Less invasive monitoring tools have been recently proposed, and, among others, $Scvo_2$ has been suggested as a useful tool for goal-directed therapy (29, 40, 57). Our subgroup analysis on this topic does not clarify this issue. PAC use is associated with a lower incidence of renal dysfunction, while no difference is observed when other monitoring tools are used. However, in the latter analysis the low statistical power does not allow to extrapolate any clinical implication, and warrants further RCTs to clarify if using $Scvo_2$ or other monitoring tools and targets for hemodynamic optimization in surgical patients would provide advantages over PAC.

High-Risk Patients. In the high-risk subgroup analysis, perioperative hemodynamic optimization reduces postoperative renal injury rate. Although high-risk patients represent a small percentage of the surgical population, more than 80% of postoperative deaths occur in this subgroup of patients (58). These patients are likely unable to spontaneously increase cardiac output to meet perioperative oxygen demand increase and are more prone to hypoperfusion-related complications. However, a recent large RCT in high-risk surgical patients (44), included in the present meta-analysis, comparing conventional and goal-directed therapy, has found no significant decrease in acute renal injury rate. This finding may be related to an inadequate statistical power for detecting renal failure reduction, and to the characteristics of total sample resulting in mostly ASA III patients (87%) with relatively good cardiac function (87% were New York Heart Association I or II). Pooling a large number of studies and patients might explain our finding of a decrease in postoperative renal injury in the category of high-risk patients. In the subgroup of low-risk patients, no difference in renal injury rate was observed. Because the event rate in this group of patients was extremely low, approaching the overall rate of postoperative renal failure reported in the literature (1), the low statistical power of this analysis does not allow any clinical meaningful inference. However, the risk to benefit ratio and the cost of perioperative optimization in such low-risk patients should be taken into account.

Validity Limitations and Research Agenda. Main limitations of all meta-analyses include reporting bias, quality assessment, outcome definition, and methodologic heterogeneity of the included studies.

Reporting bias refers to the propensity of trials with positive results to be published as full text and of trials with negative results not to be published or published only in abstract form. To reduce this bias, an attempt was made to include all gray and published reports (21) that met inclusion criteria, and to retrieve unpublished data by contacting the authors of the studies. Some unpublished results were provided by the authors, but no abstract was identified. Available statistical tests are not accurate enough to detect publication bias (59). Visual examination of funnel plot may result in subjective interpretations when the number of studies is small, and the ideal number of studies needed to provide useful information is not yet established (60). Asymmetry in funnel plots is not an accurate predictor of publication bias, because it can derive also from location bias, English language bias, citation bias, duplicate bias, true heterogeneity, poor methodologic design of small studies, inadequate analysis, choice of effect measure, or chance (59, 60). Furthermore, statistical tests that use regression methods or a rank correlation test require at least 30 studies to have sufficient statistical power, and this number may also vary depending on the size of the studies and on the magnitude of the true treatment effect (59).

Biased effect estimates may be produced by suboptimal quality of RCTs, since less rigorous studies are biased toward overestimating an intervention's effectiveness and result in "false positive" conclusions. Quality assessment was evaluated by the Jadad scale (22), that is widely advocated (61, 62) and gives particular weight to the domains most relevant to the control of bias (randomization, blinding, and withdrawals). In the present meta-analysis, most RCTs presented an inappropriate blinding and only one RCT obtained a Jadad score higher than 3.

A strong statistical homogeneity and consistency for the renal outcome was observed and confirmed by the quality

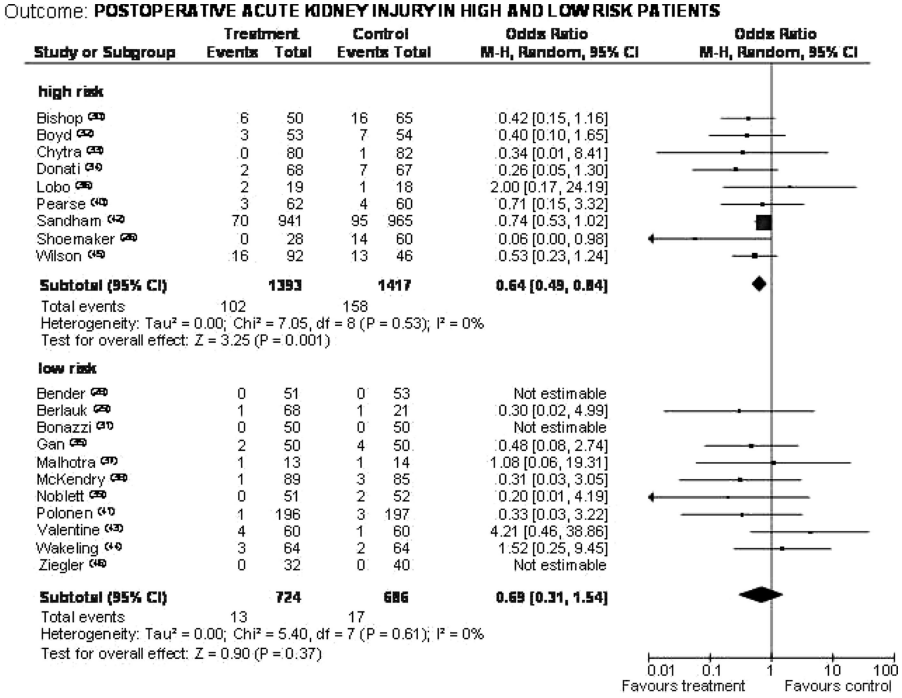

Figure 6. Rates of acute kidney injury in subgroups defined according to the mortality/morbidity risk definition, with odds ratios (ORs) and 95% confidence intervals (*CI*). Risk definition was based on need of emergent surgery, and/or elective major surgery in patients with risk criteria defined by perioperative scoring system (27), ASA physical status classification, age >60 years, and preoperative morbidity. The pooled OR and 95% CI are shown as the total. The size of the box at the point estimate of the OR gives a visual representation of the "weighting" of the study. The diamonds represent the point estimate of the pooled ORs and the length of the diamonds is proportional to the CI.

RCTs analysis. However, clinical heterogeneity among studies cannot be ignored. Although most forms of postoperative renal injury share an underlying common hypoperfusive pathogenesis, specific additional risk factors related to surgery and population exist. Increased intra-abdominal pressure in major abdominal surgery, aortic cross-clamp time during vascular surgery, cold ischemic time in renal transplantation, prolonged cardiopulmonary bypass time with ischemia and reperfusion, inflammation and oxidative stress in cardiac surgery are typical adverse factors associated with postoperative renal injury (1, 2, 11). Furthermore advanced age, diabetes mellitus, preexisting renal and liver impairment, cardiac and peripheral vascular disease, or hypertension impair renal autoregulation (63) and make patients more susceptible to renal damage (7, 10, 17, 64). Postoperative oliguria necessitating diuretics, administration of radio contrast media for diagnostic procedures, perioperative exposure to nephrotoxins such as antibiotics or nonsteroidal anti-inflammatory drugs can further contribute to precipitate renal dysfunction (1, 2, 11). It was not possible to retrieve from the studies included in the meta-analysis individual data regarding the above features, and, therefore, we cannot identify which comorbidities, surgeries, and iatrogenic interventions would most benefit from perioperative optimization.

The impact of AKI on adverse outcome is clinically relevant and every effort should be made to identify patients and surgery at high risk of developing renal failure. Forthcoming trials should deal with renal dysfunction as main outcome, should adopt accurate, precise, and repeatable definitions, and should be performed in well-defined surgical samples with specified risk factors for renal damage. Furthermore, prospective RCTs are needed to clarify if using less invasive monitoring tools, not PAC-derived hemodynamic targets, and protocolized perioperative fluid optimization strategies may play an effective role in protecting renal function after surgery.

CONCLUSIONS

Within the limitations of existing data and of the analytic approaches used in the present meta-analysis, perioperative hemodynamic optimization may prevent postoperative renal dysfunction in selected, nonseptic patients. This nephroprotective strategy would be effective in high-risk patients, if attained by adequate fluid loading associated with inotropic support, and when started in a period that extends from the preoperative one to the first hours postoperatively.

Improving the renal outcome of specific high-risk surgical populations by relatively simple means would be highly desirable from a purely clinical standpoint and also considering appropriate resources allocation. Therefore, efforts should be focused on this often underestimated complication for high-risk surgical patients.

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