In-Depth Topic Review

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Prevention and Treatment of Acute Kidney Injury in Patients Undergoing Cardiac Surgery: A Systematic Review

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Key Words
Acute kidney injury, prevention · Cardiac surgery · Healthcare costs

Abstract
Background: Acute kidney injury (AKI) is common in patients undergoing cardiac surgery and is associated with a high rate of death, long-term sequelae and healthcare costs. We conducted a systematic review of randomized controlled trials for strategies to prevent or treat AKI in cardiac surgery. ***Methods:*** We screened Medline, Scopus, Cochrane Renal Library, and Google Scholar for randomized controlled trails in cardiac surgery for prevention or treatment of AKI in adults. ***Results:*** We identified 70 studies that contained a total of 5,554 participants published until November 2008. Most studies were small in sample size, were single-center, focused on preventive strategies, and displayed wide variation in AKI definitions. Only 26% were assessed to be of high quality according to the Jadad criteria. The types of strategies with possible protective efficacy were dopaminergic agents, vasodilators, anti-inflammatory agents, and pump/perfusion strategies. When analyzed separately, dopamine and N-acetylcysteine did not reduce the risk for AKI. ***Conclusions:*** This summary of all the literature on prevention and treatment strategies for AKI in cardiac surgery highlights the need for better information. The results advocate large, good-quality, multicenter studies to determine whether promising interventions reliably reduce rates of acute renal replacement therapy and mortality in the cardiac surgery setting.
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Introduction

Acute kidney injury (AKI) is a frequent and important complication in hospitalized patients, occurring in up to 5% of all patients [1]. The incidence of AKI is especially high in patients undergoing cardiac surgery, reaching 50% by some definitions [2]. The mortality rate in this population is 1–5% in patients who develop AKI and up to 24% in patients who require acute renal replacement therapy for AKI [3]. In addition, the mortality rate in cardiac surgery patients with renal injury increases progressively with the degree of renal impairment [4], and AKI is an independent predictor of mortality after cardiac surgery [5]. AKI doubles the total postoperative cost of

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cardiac surgery patients and nearly doubles intensive care unit costs [2]. Thus, for many reasons any reduction in risk of AKI would be beneficial, but methods to prevent AKI in cardiac surgery patients have not been established.

There are several reasons to conduct clinical trials and study AKI after cardiac surgery. The timing of injury is known; the injury is homogenous in nature relative to other populations in which AKI is frequently studied; and about 800,000 patients undergo cardiac surgery worldwide each year, allowing for large sample sizes and providing a unique opportunity for controlled interventions [6]. The predominant causes of AKI are hypoperfusion and inflammation due to cardiopulmonary bypass (CPB). CPB has also been shown to cause AKI due to nonpulsatile flow causing vasoconstriction and ischemic renal injury [7]. However, even patients undergoing surgery off CPB ('off-pump') are at risk for AKI, suggesting alternative mechanisms for injury.

Given the large population of cardiac surgery patients and the substantial impact of AKI in this population, efforts to treat AKI through various interventions have been attempted. However, no single agent has been shown to prevent AKI in cardiac surgery. Previous systematic reviews have examined AKI in cardiac surgery, but these have focused on individual interventions only [8, 9]. Other reviews have examined AKI in the broader perioperative period of cardiothoracic and abdominal surgery, which use disparate surgical techniques and may introduce more heterogeneity into the study sample [10]. We conducted this review to evaluate the conduct and outcomes of clinical trials of AKI prevention and treatment in cardiac surgery, to highlight the strengths and limitations of the current evidence, and to guide an agenda for future research.

Methods

We conducted, analyzed, and reported this systematic review in accordance with consensus guidelines [11].

Data Sources

We screened Medline (1950 to November 2008), Scopus (1966–2008), Cochrane Renal Library, and Google Scholar for the relevant studies. Reference lists and bibliographical data from all retrieved articles and reviews were also searched. The terms 'kidney diseases', 'cardiovascular surgical procedures', 'cardiopulmonary bypass', and 'renoprotection' were used. The search strategy in Scopus used the terms 'renal protection', 'renoprotec', 'acute kidney failure', 'kidney failure', 'kidney diseases', 'kidney disease', 'cardiovascular surgery', 'cardiovascular procedures', and 'cardiopulmonary bypass'. An expert librarian was consulted for assistance in conducting a comprehensive search to identify randomized control trials investigating preventive and therapeutic measures for AKI in cardiac surgery. Two reviewers (M.P. and S.N.) independently screened the citations and those considered potentially relevant were retrieved for full-text review.

Study Eligibility and Selection

Articles published as full manuscripts in English were included. The studies were limited to humans and to all adults from age 19 to 80 years and above, with no upper age limit specified. Randomized controlled trials (RCTs) involving patients undergoing cardiac surgery (coronary artery bypass grafting, CABG; valve surgery, or combined CABG/valve surgery; elective, emergent, or not specified) were included. Studies that assessed kidney injury by methods of serum creatinine or creatinine clearance/glomerular filtration rate were eligible. Eligible interventions included methods of prevention or treatment of AKI administered anytime before, during, or after surgery. These included medical therapies as well as procedure-based therapies such as CPB modification and early renal replacement therapy. Healthcare service interventions such as level of care preceding or following surgery were not eligible.

Comparison was with no therapy, placebo, or with standard care for the institution, such as maximal hydration. Review outcomes were incidence of AKI (defined by individual study authors using one of several definitions for AKI) or change in serum creatinine, creatinine clearance, or GFR, incidence of acute renal replacement therapy and mortality. Renal outcomes were abstracted regardless of whether they were a primary or secondary trial outcome.

Patients with all degrees of renal function prior to surgery were included. Studies describing outcomes for patients who were on renal replacement therapy prior to surgery or who had received a kidney transplant were excluded from analysis.

Data Extraction

We used a comprehensive data collection form to record study characteristics: type of surgery (CABG, valve surgery, combined CABG/valve, elective, urgent), demographics of the participants (age, sex), and baseline mean serum creatinine or GFR. We characterized the timing of the intervention as preoperative (commencing outside operating room), intraoperative (commencing after anesthesia induction, initiated within 30 min before or after CPB), or postoperative (commencing after surgery, outside the operating room). Interventions were described by principal agent, route, and dose administered and were grouped according to their principal mechanism of action as follows: interventions that increase renal blood flow (vasodilators); interventions that induce natriuresis or diuresis; anti-inflammatory interventions, and interventions that work through other mechanisms of actions. Outcomes for creatinine, creatinine clearance/GFR, and incidence of acute renal replacement therapy and mortality were recorded for each study. Data extraction was performed independently by two reviewers (M.P. and S.N.) and disagreements were resolved by consensus.

Quality Assessment

All RCTs were evaluated for study quality using the Jadad score [12]. This score awards one point each for randomization,

appropriateness of randomization, blinding, appropriateness of blinding, and description of withdrawal and dropouts, with a maximum score of 5. As studies involving pump strategies do not uniformly describe blinding techniques, we confirmed the quality characteristics of these studies using randomization, allocation concealment, blinded outcome assessment, and intention-to-treat analysis [8]. Patients excluded and lost to follow-up were recorded. Using these criteria, we classified the studies as good, moderate, and low quality (table 1).

Data Analysis

All trials were two- or three-arm interventions and administered parallel in design. Three-arm trials involved two separate interventions analyzed against a single control group. Outcomes were reviewed separately for prevention and treatment cohorts. Overall results for each intervention class were mathematically pooled using techniques that accounted for within- and between-study heterogeneity [13, 14]. For studies that reported a continuous outcome (e.g. change in creatinine, creatinine clearance, or eGFR), we compared the standard difference in means in treatment and control groups. For trials that only reported continuous outcomes, we converted the standard difference in means to log odds ratios via the following formula: log odds ratio = $\pi \times$ standard difference/square root [3]. The variance calculation was based on the following: log odds SE = square root (π ^ 2 $\times$ standard difference SE ^ 2/3). The log odds variance was equal to the log odds SE ^ 2. This allowed pooling of studies that only reported continuous outcomes with those that reported categorical outcomes. We formally assessed heterogeneity of treatment effects between studies with the Cochrane Q and the I^2 statistics. Publication bias was not assessed due to high statistical heterogeneity [15, 16]. All analyses were performed using Comprehensive Meta Analysis Software Version 2.0 (Englewood, N.J., USA).

Results

Retrieval of Studies and Study Characteristics

Our search of Medline yielded a total of 169 citations for individual review. Scopus retrieved 194 citations for review. Additional searches of the Cochrane Renal Library (Issue 4, 2008), PubMed, and Google Scholar produced 29 additional citations for review. We also studied reference lists and bibliographical data from all retrieved articles and reviews for any additional relevant material (fig. 1). A total of 70 studies (5,554 patients) met eligibility criteria [17–86] (table 1).

Twenty-one different countries were represented, with the highest number of studies coming from the UK (n = 9), Turkey (n = 9), Germany (n = 9), USA (n = 7), and Italy (n = 7). Sixty-four studies involved CABG, and 27 involved valvular surgeries. Study size ranged widely from 14 to 388 patients. Nine studies comprised groups of 20 patients or fewer; 17 studies had more than 100 patients, and only 6 studies had more than 200 patients. The majority (93%), including the larger studies, were single-center studies and only 5 trials included more than one center (table 1, footnote). Five studies described an industry sponsor. Sixty-six studies examined prevention strategies and 4 examined treatment strategies. Patients with preoperative chronic kidney disease (CKD) were excluded from 10 studies. Definitions of AKI were not uniform. Criteria for initiation of acute renal replacement therapy were not standardized across studies.

Thirty studies were designed to analyze the effects of interventions that primarily increase renal blood flow (vasodilators). These interventions included dopamine, dopexamine, fenoldopam, angiotensin-converting enzyme inhibitors (captopril, enalaprilat), diltiazem, prostacyclin, nifedipine, PGE-1, sodium nitroprusside and theophylline. All of the studies amongst the vasodilator cohort were designed to evaluate effects on prevention of AKI and none of the studies in this cohort evaluated effects on treatment of an established AKI.

Twelve studies were designed to analyze the effects of interventions that primarily induce natriuresis or diuresis or both. These interventions included atrial natriuretic peptide, brain natriuretic peptide, urodilatin, and diuretic agents (loop diuretics and mannitol). Ten studies amongst this natriuretic cohort were designed to evaluated effects on prevention of AKI and 3 studies were designed to evaluate effects on treatment of an established AKI.

Fourteen studies were designed to analyze the effects of interventions that primarily counteract inflammation (anti-inflammatory agents). These interventions included N-acetylcysteine, aspirin, glutathione, corticosteroids, and leukodepletion. All of the studies amongst this anti-inflammatory cohort were designed to evaluate effects on prevention of AKI.

Interventions that have been studied previously but could not be assigned to one of the above 3 cohorts included clonidine, albumin infusion, isotonic saline infusion, insulin therapy, early continuous veno-venous hemofiltration and interventions such as the off-pump technique and pulsatile technique. Amongst these only 1 study addressing the role of continuous veno-venous hemofiltration was designed to treat an established AKI and all other interventions were studied in a prevention setting.

Quality

There were 18 studies of good quality, 15 studies of moderate quality, and 37 studies of low quality. Forty-seven studies (67%) had 5% or fewer patients excluded or

Table 1. Characteristics of included randomized controlled trials

Source	Intervention	Trial type	Inclusion of CKD patients	Number of patients	Mean age years	Male %	Jadad score[1]
Anti-inflammatory							
Adabag et al. [18], 2008	NAC	Prevention	Yes	102	71	100	5
Amano et al. [19], 1994	Glutathione	Prevention	No	19	57.5	NR	3
Barr and Kolodner [22], 2008	NAC, fenoldopam	Prevention	Yes	79	74.2	65.8	4
Bolcal et al. [25], 2006	Leukodepletion	Prevention	Yes	50	56.9	72	3
Burns et al. [28], 2005	NAC	Prevention	Yes	295	69.1	78.7	5
Fischer et al. [41], 2005	NAC	Prevention	NR	40	66	77.5	5
Gerrah et al. [44], 2004	Aspirin	Prevention	Yes	94	68.5	78	1
Haase et al. [45], 2007	NAC	Prevention	Yes	60	68.6	73.3	5
Loef et al. [54], 2004	Dexamethasone	Prevention	No	20	63.7	85	3
McBride et al. [58], 2004	Methylprednisolone	Prevention	Yes	36	61.45	97.2	2
Ristikankare et al. [67], 2006	NAC	Prevention	Yes	77	70.5	80.5	5
Sisillo et al. [73], 2008	NAC	Prevention	Yes	254	72.5	49	5
Tang et al. [78], 2002	Leukodepletion	Prevention	Yes	44	63.5	85	3
Wijeysundera et al. [81], 2007	NAC	Prevention	Yes	177	73.5	59.5	5
Natriuretics/diuretics							
Chen et al. [33], 2007	Nesiritide	Prevention	Yes	36	77.5	61.5	4
Hayashida et al. [47], 2000	ANP	Prevention	NR	18	60.3	80	2
Mahesh et al. [55], 2008	Furosemide	Prevention	Yes	42	71.3	73.8	4
Mentzer et al. [59], 2007	Nesiritide	Prevention	Yes	272	63.9	78.5	5
Meyer et al. [60], 1997	Urodilatin	Treatment	Yes	14	59.4	NR	3
Nuutinen and Hollmen [64], 1976	Furosemide	Prevention	NR	45	35.1	53.3	1
Sezai et al. [70], 2000	ANP	Prevention	NR	40	63.5	87.5	3
Sezai et al. [71], 2007	ANP	Prevention	No	124	67.25	70.2	3
Sirivella et al. [72], 2000	Mannitol, furosemide, DA	Treatment	Yes	100	71	62.5	3
Smith et al. [74], 2008	Mannitol	Prevention	Yes	47	74.7	72.3	5
Sward et al. [77], 2004	ANP	Treatment	Yes	59	69.7	71	5
Yallop et al. [84], 2008	Mannitol	Prevention	No	40	63.2	75	5
Vasodilators							
Abe et al. [17], 1993	PGE1	Prevention	NR	20	55	NR	3
Amano et al. [20], 1995	Diltiazem	Prevention	NR	23	54.4	NR	2
Berendes et al. [23], 1997	Dopexamine	Prevention	NR	44	61.5	59.1	3
Bergman et al. [24], 2002	Diltiazem	Prevention	Yes	24	72.5	92	5
Bove et al. [27], 2005	DA, fenoldopam	Prevention	Yes	80	68.5	72.5	4
Caimmi et al. [29], 2003	Fenoldopam	Prevention	Yes	160	69	66.3	2
Carcoana et al. [30], 2003	DA, mannitol	Prevention	Yes	100	64	72	5
Cogliati et al. [34], 2007	Fenoldopam	Prevention	Yes	193	70	0.6	5
Colson et al. [35], 1990	ACE inhibitor	Prevention	Yes	18	58	100	3
Costa et al. [36], 1990	DA, nitroprusside	Prevention	Yes	36	58.6	NR	3
Dehne et al. [37], 2001	Dopexamine	Prevention	NR	36	63.4	100	2
Dural et al. [39], 2000	DA, mannitol	Prevention	No	36	53.7	63.9	3
Gatot et al. [43],2004	DA	Prevention	Yes	82	65	NR	5
Halpenny et al. [46], 2001	Fenoldopam	Prevention	No	31	64	24.3	3
Kaya et al. [48], 2007	Sodium nitroprusside	Prevention	Yes	240	61.1	63.7	5
Kramer et al. [50], 2002	Theophylline	Prevention	No	56	60.4	75	4
Lassnigg et al. [52], 2000	DA, furosemide	Prevention	Yes	123	63.3	68.3	4
Lema et al. [53], 1998	DA, phenylephrine	Prevention	Yes	17	65	85	2
Monaco et al. [61], 2005	DA	Prevention	Yes	67	65.8	70.7	2
Morgera et al. [62], 2002	Prostacyclin	Prevention	NR	34	61.5	91.2	3
Myles et al. [63], 1993	DA	Prevention	Yes	52	61.6	63	4
Piper et al. [66], 2003	DA, diltiazem	Prevention	Yes	60	67.7	66.7	5
Ryckwaert et al. [68], 2001	ACE inhibitor	Prevention	Yes	14	63.2	92.9	4

Table 1 (continued)

Source	Intervention	Trial type	Inclusion of CKD patients	Number of patients	Mean age years	Male %	Jadad score[1]
Sumeray et al. [76], 2001	DA	Prevention	Yes	36	63.4	91.7	5
Tang et al. [80], 1999	DA	Prevention	No	40	58.7	60	2
Witczak et al. [82], 2008	Nifedipine	Prevention	Yes	20	66.8	80	5
Woo et al. [83], 2002	DA	Prevention	Yes	42	65.5	58.5	3
Yavuz et al. [85], 2002	DA	Prevention	No	22	56.1	91	2
Yavuz et al. [86], 2002	DA, diltiazem	Prevention	No	60	59.3	86.7	2
Operative							
Ascione et al. [21], 1999	Off-pump	Prevention	Yes	50	61.6	90	2
Carrier et al. [31], 2003	Off-pump	Prevention	Yes	65	70	76.9	3
Celik et al. [32], 2005	Off-pump	Prevention	Yes	60	67.1	51.7	3
Kocakulak et al. [49], 2005	Off-pump pulsatile	Prevention	NR	40	53.7	77.5	2
Masoumi et al. [57], 2008	Off-pump	Prevention	NR	124	58.9	83	3
Onorati et al. [65], 2007	Off-pump pulsatile	Prevention	Yes	100	68	93	3
Sajja et al. [69], 2007	Off-pump	Prevention	Yes	116	60.3	88.8	3
Straka et al. [75], 2004	Off-pump	Prevention	Yes	388	62.5	81.5	3
Tang et al. [79], 2002	Off-pump	Prevention	Yes	40	66	80	3
Other							
Boldt et al. [26], 2008	Albumin	Prevention	Yes	50	82.5	50	2
Demirkilic et al. [38], 2004	Early CVVHDF	Treatment	Yes	61	60.5	NR	2
Durmaz et al. [40], 2003	RRT	Prevention	Yes	44	56.2	79.4	2
Gandhi et al. [42], 2007	Insulin	Prevention	NR	371	63	69	5
Kulka et al. [51], 1996	Clonidine	Prevention	NR	50	57.5	78	3
Marathias et al. [56], 2006	Hydration with 0.5% normal saline	Prevention	Yes		64.1	95	2

Multicenter trials: Burns et al. [28], Kaya et al. [48], Mentzer et al. [59], Meyer et al. [60], and Sward et al. [77]. Industry sponsor: Barr and Kolodner [22], Chen et al. [33], Gandhi et al. [42], Halpenny et al. [46], and Kramer et al. [50].

NAC = N-Acetylcysteine; ANP = atrial natriuretic peptide; DA = dopamine; ACE = angiotensin-converting enzyme; NR = not reported; RRT = renal replacement therapy; CVVHDF = continuous veno-venous hemodiafiltration.

[1] Jadad score awards one point for randomization, appropriateness of randomization, blinding, appropriateness of blinding, and description of withdrawal and dropouts, with a maximum score of 5.

lost to follow-up, with 34 (49%) of these studies having 0% excluded. Fifteen studies (21%) had >5% excluded or lost to follow-up, with a range of 6–29%. Seven studies did not report patients excluded or lost to follow-up. All studies assessed kidney function uniformly between the intervention and control groups. The frequency of assessing kidney function was variable between studies, ranging from a frequency of every 8 h (as in a good-quality study [77]) to measurements on days 1, 5, and 15 [69], with 9 studies not reporting the method of assessment.

AKI

The incidence of AKI as a dichotomous outcome was reported in 22 studies (2,674 patients). AKI was not uniformly defined in these studies. Continuous endpoints were reported in 43 studies (2,148 patients). Amongst the prevention cohort trials, there were 9 interventions that commenced preoperatively, 53 administered intraoperatively, and 5 postoperatively (table 2).

The following agents from the vasodilator group were associated with a reduction in AKI: fenoldopam and angiotensin-converting enzyme inhibitors; whereas the other vasodilator agents were noted to have no effect on the incidence of AKI. Anti-inflammatory agents including N-acetylcysteine were not associated with any reduction in AKI. The following agents from the natriuretic and/or diuretic cohort were associated with a reduction in AKI: atrial natriuretic peptide, B-natriuretic peptide, urodilatin; whereas the remaining agents from this group were noted to have no effect on the incidence of AKI.

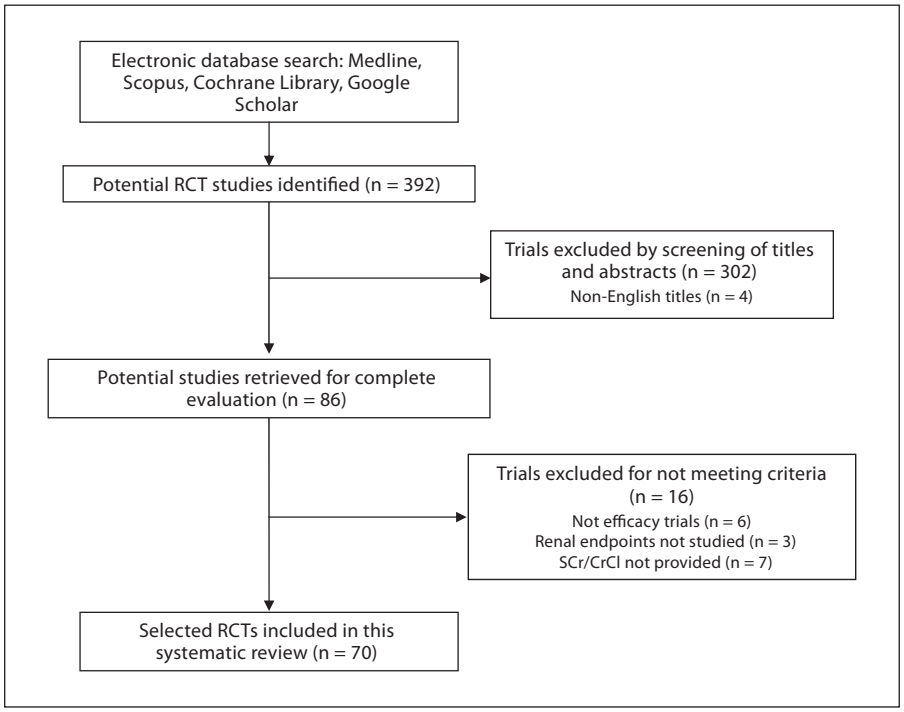

Fig. 1. Flowchart of study selection.

Amongst the other interventions that were reviewed, the off-pump surgical technique and pulsatile flow techniques were associated with a reduction in the incidence of AKI, whereas interventions such as clonidine, albumin infusion, isotonic saline infusion, and insulin therapy were not associated with a reduction in AKI.

Acute Renal Replacement Therapy

The incidence of acute renal replacement therapy was provided in 21 studies comprising 2,172 patients [18, 25, 27, 28, 32–34, 40, 45, 52, 55, 56, 60, 61, 67, 69, 71, 75, 77, 81, 82]. Predefined criteria for acute renal replacement therapy initiation were provided in 7 of these studies and were not uniform across studies [25, 27, 40, 55, 56, 77, 81]. In 1 case, initiation was determined by blinded nephrologists without specific parameters described [81]. In another study, prophylactic hemodialysis was the intervention and thus acute renal replacement therapy parameters were needed for both groups [40]. Other studies did not describe criteria for initiation of acute renal replacement therapy.

None of the individual trials showed a clear benefit in terms of reducing the incidence of acute renal replacement therapy in the cardiac surgery setting and none of the trials were adequately powered to study this outcome.

Mortality

Data on mortality were reported in 18 studies comprising 2,227 patients. As mortality is a competing endpoint for AKI, we considered any study that described both of these outcomes as a composite endpoint; however, no such studies were found.

None of the cohorts (vasodilator agents, anti-inflammatory agents, natriuretic/diuretic agents and agents with other mechanisms of action) demonstrated a reduction in mortality and none of the trials were adequately powered to study this outcome.

Comment

This systematic review demonstrates that a large number of RCTs to prevent or treat AKI after cardiac surgery have been performed over the past 30 years. The majority of trials were small, single-center, methodologically and statistically heterogeneous, rated to be of low methodological quality, and most were not powered to detect differences in hard endpoints such as mortality and acute renal replacement therapy. In addition, the definitions of AKI were quite variable and many trials instead examined continuous changes in kidney function. However, analysis of these existing trials shows that there may be

Table 2. Study details by intervention

Source	Intervention	Control	Timing of intervention	Baseline renal function[1]	Outcomes
Anti-inflammatory					
Adabag et al. [18], 2008	NAC p.o., 600 mg b.i.d. ×14 doses	Placebo	Pre	1.9 ± 0.7/40 ± 10	AKI, D
Amano et al. [19], 1994	Glutathione i.v., 200 mg/kg	Placebo	I	1.1 ± 0.2/NR	Mean SCr
Barr and Kolodner [22] 2008	Fenoldopam i.v., 0.1 μg/kg/min	Placebo + NAC or Fenoldopam + NAC	I	NR/34 ± 2	Mean CrCl
Bolcal et al. [25], 2006	Leukodepletion	CPB alone	I	1.8 ± 0.6/NR	Mean SCr, R
Burns et al. [28], 2005	NAC i.v., 600 mg × 4 doses	5% dextrose	I	1.2 ± 0.4/NR	AKI, R, D
Fischer et al. [41], 2005	NAC i.v., 100 mg/kg, 20 mg/kg/h infusion	Placebo	I	1.0 ± 0.4/NR	Mean SCr
Gerrah et al. [44], 2004	Aspirin p.o., 100 mg daily until surgery	Placebo	Pre	2.8 ± 1.6/31 ± 14	Mean S r
Haase et al. [45], 2007	NAC i.v., 300 mg/kg over 24 h	5% dextrose	I	1.0 ± 0.3/78 ± 24	AKI, R
Loef et al. [54], 2004	Dexamethasone i.v., 1 mg/kg plus 0.5 mg/kg	Placebo	I	1.0 ± 0.2/104 ± 10	Mean CrCl
McBride et al. [58], 2004	Methylprednisolone i.v., 30 mg/kg	Placebo	I	1.1 ± 0.2	Mean SCr
Ristikankare et al. [67] 2006	NAC i.v., 150 mg/kg, 50 mg/kg, 100 mg/kg+	Placebo	I	1.5 ± 0.4/NR	AKI, R, D
Sisillo et al. [73], 2008	NAC i.v., 1,200 mg every 12 h ×4 boluses	Placebo	I	1.3 ± 0.4/46 ± 8	AKI, D
Tang et al. [78], 2002	Leukodepletion	CPB alone	I	1.1 ± 0.2/NR	Mean SCr
Wijeysundera et al. [81] 2007	NAC i.v., 100 mg/kg bolus, 20 mg/kg/h infusion	5% dextrose	I	1.4 ± 0.4/44 ± 11	AKI, R
Diuretics					
Mahesh et al. [55], 2008	Furosemide i.v., 4 mg/h	Normal saline	I	1.1 ± 0.3/65 ± 34	AKI, R, D
Nuutinen and Hollmen [64], 1976	Furosemide i.v., varying doses w/UOP <40 ml/h	Placebo	I	NR/89 ± 17	Mean CrCl
Sirivella et al. [72], 2000	Furosemide, ethacrynic acid, bumetanide	Osmitrol, furosemide, DA	Post	1.8 NR/NR	R
Smith et al. [74], 2008	Mannitol i.v., 0.5 g/kg	Hartmann's solution	I	1.8 ± 0.3/33 ± 10	Mean SCr
Yallop et al. [84], 2008	Mannitol i.v., 5 ml/kg, 10% solution	Hartmann's solution	I	1.1 ± 0.2/NR	Mean SCr
Vasodilators					
Abe et al. [17], 1993	PGE-1 i.v., 0.02 μg/kg-min	Normal saline	I	NR/89 ± 8	Mean CrCl
Amano et al. [20], 1995	Diltiazem i.v., 0.1 mg/kg bolus, 2 mcg/kg/min inf.	Placebo	I	NR/90 ± 10	Mean CrCl
Berendes et al. [23], 1997	Dopexamine i.v., 0.5, 1.0, 2.0 μg/kg/min	Placebo	Pre	NR/NR	Mean CrCl
Bergman et al. [24], 2002	Diltiazem i.v., 0.25 mg/kg bolus, 1.7 μg/kg/min infusion	Placebo	I	1.8 ± 0.1/NR	Mean SCr
Bove et al. [27], 2005	Fenoldopam i.v., 0.05 μg/kg/min	DA i.v., 2.5 μg/kg/min	I	1.6 ± 0.7/50 ± 21	AKI, R, D
Caimmi et al. [29], 2003	Fenoldopam i.v., 0.1–0.3 μg/kg/min	DA or dobutamine i.v., renal doses+	I	1.8 ± 0.3/51 ± 22	Mean SCr
Carcoana et al. [30], 2003	DA ± mannitol i.v., 2 μg/kg/min or 1 g/kg	Placebo	I	1.1 ± 0.2/96 ± 27	Mean SCr
Chen et al. [33], 2007	Nesiritide i.v., 0.005 μg/kg/min	Placebo	I	1.7 ± 0.6/40 ± 11	AKI, R, D
Cogliati et al. [34], 2007	Fenoldopam i.v., 0.1 μg/kg/min	Placebo	I	1.8 ± 0.4/39 ± 10	AKI, R
Colson et al. [35], 1990	Captopril p.o., 100 mg b.i.d. ×2 days	Placebo	Pre	1.2 ± 0.2/107 ± 12	Mean CrCl
Costa et al. [36], 1990	DA i.v., 2.5 μg/kg/min	Placebo; DA; nitroprusside	I	NR/37 ± 10	Mean CrCl
Dehne et al. [37], 2001	Dopexamine i.v., 1 μg/kg/min	Placebo	I	NR/61 ± 13	Mean CrCl
Dural et al. [39], 2000	DA i.v., 0.3 μg/kg/min	No treatment; 20% mannitol i.v., 1 mg/kg/h	I	1.1 ± 0.4/NR	Mean SCr
Gatot et al. [43], 2004	DA i.v., 3–5 μg/kg/min	Normal saline	Post	1.1 ± 0.2/NR	Mean SCr
Halpenny et al. [46], 2001	Fenoldopam i.v., 0.1 μg/kg/min	Placebo	Post	1.1 ± 0.2/107 ± 36	Mean CrCl
Hayashida et al. [47], 2000	ANP i.v., 0.05 μg/kg/min	Control	I	NR/48 ± 7	Mean CrCl
Kaya et al. [48], 2007	SNP i.v., 0.1 mg/kg/h	Normal saline	I	1 ± 0.2/77 ± 21	AKI
Kramer et al. [50], 2002	Theophylline i.v., 0.25 mg/kg/h	Normal saline	I	0.8 NR/NR	AKI
Lassnigg et al. [52], 2000	DA i.v., 2 μg/kg/min+	Normal saline; furosemide 0.5 μg/kg/min	I	1.0 ± 0.2/96 ± 37	AKI, R, D
Lema et al. [53], 1998	DA i.v., 2 μg/kg/min	Phenylephrine	I	1.5 ± 0.4/74 ± 37	Mean SCr
Mentzer et al. [59], 2007	Nesiritide i.v., 0.01 μg/kg/min	Placebo	I	1.1 ± 0.4/80 ± 29	Mean SCr, D
Meyer et al. [60], 1997	Urodilatin i.v., 20 ng/kg/min ×7 days	Placebo	Post	2.7 ± 0.6	Mean SCr, R, D
Monaco et al. [61], 2005	DA i.v., 3 μg/kg/min	Placebo	Pre	1.9 ± 0.2	Mean SCr, R, D
Morgera et al. [62], 2002	Prostacyclin i.v., 2 ng/kg/min	Placebo	I	NR/96 ± 22	AKI
Myles et al. [63], 1993	DA i.v., 200 μg/min	5% dextrose	I	1.0 ± 0.2/NR	Mean SCr

Table 2 (continued)

Source	Intervention	Control	Timing of intervention	Baseline renal function[1]	Outcomes
Piper et al. [66], 2003	DA i.v., 2.5 μg/kg/min	Normal saline; diltiazem i.v., 2 μg/kg/min	Post	NR/74 ± 34	Mean CrCl
Ryckwaert et al. [68], 2001	Enalaprilat i.v., 1 mg every 6 h over 2 days	Placebo	I	1.2 ± 0.2/70 ± 14	Mean CrCl
Sezai et al. [70], 2000	Human ANP i.v., 0.03–0.05 μg/kg/min	Placebo	I	NR/91 ± 20	AKI
Sezai et al. [71], 2007	Human ANP i.v., 0.02 g/dl/min	NR	I	NR/NR	R, D
Sumeray et al. [76], 2001	DA i.v., 2.5 μg/kg/min	5% dextrose	I	NR/77 ± 3	Mean CrCl
Sward et al. [77], 2004	Recombinant hANP i.v., 50 ng/kg/min	NR	treatment	1.2 ± 0/NR	R, D
Tang et al. [80], 1999	DA i.v., 2.5–4.0 μg/kg/min	Placebo	I	1.3 ± 0.1/NR	Mean SCr
Witczak et al. [82], 2008	Nifedipine i.v., 0.25–0.60 μg/kg/min	Placebo	I	2.7 ± 1.0/35 ± 10	Mean CrCl, R
Woo et al. [83], 2002	DA i.v., 3 μg/kg/min × 48 h	NR	I	1.1 ± 0.2/NR	Mean SCr
Yavuz et al. [85], 2002	DA i.v., 2 μg/kg/min	Placebo	Pre	NR/71 ± 35	Mean CrCl
Yavuz et al. [86], 2002	DA i.v., 200 μg/kg/min	Placebo/diltiazem; diltiazem and DA	I	NR/77 ± 49	Mean CrCl
Operative					
Ascione et al. [21], 1999	Off-pump	On-pump	I	NR/91 ± 26	Mean CrCl
Carrier et al. [31], 2003	Off-pump	On-pump	I	NR/NR	AKI, D
Celik et al. [32], 2005	Off-pump	On-pump	I	1.4 ± 0.3/NR	Mean SCr, R
Kocakulak et al. [49], 2005	Pulsatile flow	Continuous flow	I	1.5 ± 1.1/NR	Mean SCr
Masoumi et al. [57], 2008	Off-pump	On-pump	I	NR/NR	AKI, D
Onorati et al. [65], 2007	Pulsatile flow	Standard IABP	I	1.2 ± 0.4/80 ± 25	AKI
Sajja et al. [69], 2007	Off-pump	On-pump	I	1.5 ± 0.5/52 ± 9	AKI, R
Straka et al. [75], 2004	Off-pump	On-pump	I	NR/NR	R, D
Tang et al. [79], 2002	Off-pump	Pulsatile CPB	I	1.1 ± 0.2/NR	Mean SCr
Other					
Boldt et al. [26], 2008	Albumin 5% i.v., 500 ml	HES 6% i.v., 500 ml	I	1.3 ± 0.4/47 ± 20	Mean SCr
Demirkilic et al. [38], 2004	Early CVVHDF	Standard CVVHDF	Post	>3 NR/NR	D
Durmaz et al. [40], 2003	Postoperative prophylactic hemodialysis	Standard indications for renal replacement therapy	Post	3.4 ± 0.8/NR	AKI, D
Gandhi et al. [42], 2007	Insulin i.v., continuously	Insulin i.v., intermittently	I	NR/NR	AKI
Kulka et al. [51], 1996	Clonidine i.v., 4 μg/kg	Placebo	Pre	NR/94 ± 19	Mean CrCl
Marathias et al. [56], 2006	0.5% normal saline i.v., 1 ml/kg/h over 12 h	Fluid restriction	Pre	3.3 ± 0.5/26 ± 2	AKI, R

NAC = N-Acetylcysteine; ANP = atrial natriuretic peptide; DA = dopamine; NR = not reported; RRT = renal replacement therapy; CVVHDF = continuous veno-venous hemodiafiltration; AKI = acute kidney injury; D = death; R = acute renal replacement therapy; Pre = preoperative; Post = postoperative; I = intraoperative; CrCl = creatinine clearance; SCr = serum creatinine; CPB = cardiopulmonary bypass.

[1] Serum creatinine ± SD/creatinine clearance ± SD. Serum creatinine in mg/dl (converted from μmol/l) rounded to the nearest 10th, creatinine clearance in ml/min rounded to nearest 1. For further details of interventions, refer to original references.

benefits associated with some interventions for the prevention of AKI. This review calls for good-quality, large-population trials of individual or combination of agents.

In general, strategies to prevent AKI were effective if administered preoperatively and intraoperatively. Strategies for treatment of AKI were far less numerous and thus it is difficult to draw conclusions about their efficacy relative to prophylaxis strategies. Our exploratory analyses revealed that most types of prophylactic strategies were protective for AKI. In particular, fenoldopam, ANP/nesiritide and off-pump CABG demonstrated excellent efficacy for the prevention of AKI. There was no evidence for benefit from preoperative administration of dopamine or N-acetylcysteine.

The primary endpoints in the majority of trials contained in this review were continuous changes in creatinine or creatinine clearance/GFR rather than the most clinically important endpoints of acute renal replacement therapy and mortality. Furthermore, in the 22 studies that utilized categorical outcomes for AKI, the definition of AKI was highly variable. Acute renal replacement therapy and/or mortality were considered primary outcomes in only 5 studies; most studies did not have adequate statistical power for non-primary outcomes.

There are many challenges to consider when designing and executing future trials for the prevention or treatment of AKI in cardiac surgery. The first challenge relates to patient selection. If one chooses to study an intervention that has potential adverse side effects, only those at the highest risk of AKI should be enrolled. These may include patients undergoing redo cardiac surgeries or those with CKD. Second, since AKI may be multifactorial after CPB, multiple agents acting through different pathways may need to be administered simultaneously or in succession in order to effectively reduce AKI. Third, the selection of the correct endpoint for these trials is vital. Early phase 1 and 2 trials should measure surrogate endpoints such a AKI defined by serum creatinine using RIFLE or AKIN criteria or changes in novel biomarkers of AKI. Larger phase 3 and 4 studies should examine the ability of the interventions to reduce hard endpoints, such as dialysis, death, length of stay, and long-term events such as cardiovascular events, CKD, and long-term death.

Our study has several strengths. We performed a comprehensive search to compile relevant studies, screening over 500 citations. Article identification, eligibility assessment, and data abstraction were performed independently and in duplicate, to minimize potential biases inherent in these tasks. Through these methods, we included a large number of studies for systematic review and meta-analysis, encompassing a wider scope than previous reviews evaluating a similar question.

Our review also has some limitations. Only studies written in English were included, resulting in the exclusion of four studies (one in Chinese, one in Japanese, and two in Italian). Trials were in general small, underpowered, and of poor methodological quality. Risk factors for AKI, such as CKD, were not consistently reported in a standardized fashion. Trials included in this review had variable definitions of AKI and none of the included trials reported the recently proposed AKIN criteria to define AKI. Future trials should follow these criteria to consistently define AKI and should also have predefined trial criteria for the initiation of renal replacement therapy [89].

Conclusions

AKI in cardiac surgery patients is common and is associated with significant morbidity and mortality. A method of preventing this common complication is urgently needed. Most studies were underpowered to demonstrate a beneficial effect on acute renal replacement therapy and mortality. The beneficial effect on AKI alone is enough impetus for a more thorough investigation into prophylaxis and treatment strategies. Large, good-quality, multicenter trials needed to demonstrate benefits of prevention of AKI and reduction in rates of acute renal replacement therapy and mortality in the cardiac surgery setting.

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