

## Reducing Mortality in Acute Kidney Injury Patients: Systematic Review and International Web-Based Survey

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**Objective:** To identify all interventions that increase or reduce mortality in patients with acute kidney injury (AKI) and to establish the agreement between stated beliefs and actual practice in this setting.

**Design and Setting:** Systematic literature review and international web-based survey.

**Participants:** More than 300 physicians from 62 countries.

**Interventions:** Several databases, including MEDLINE/PubMed, were searched with no time limits (updated February 14, 2012) to identify all the drugs/techniques/strategies that fulfilled all the following criteria: (a) published in a peer-reviewed journal, (b) dealing with critically ill adult patients with or at risk for acute kidney injury, and (c) reporting a statistically significant reduction or increase in mortality.

**Measurements and Main Results:** Of the 18 identified interventions, 15 reduced mortality and 3 increased mortality. Perioperative hemodynamic optimization, albumin in cirrhotic patients, terlipressin for hepatorenal syndrome type 1, human immunoglobulin, peri-angiography hemofiltration, fenoldopam, plasma exchange in multiple-myeloma-associated AKI, increased intensity of renal replacement therapy (RRT), CVVH in severely burned patients, vasopressin in septic shock, furosemide by continuous infusion, citrate in continuous RRT, N-acetylcysteine, continuous and early RRT might reduce mortality in critically ill patients with or at risk for AKI; positive fluid balance, hydroxyethyl starch and loop diuretics might increase mortality in critically ill patients with or at risk for AKI. Web-based opinion differed from consensus opinion for 30% of interventions and self-reported practice for 3 interventions.

**Conclusion:** The authors identified all interventions with at least 1 study suggesting a significant effect on mortality in patients with or at risk of AKI and found that there is discordance between participant stated beliefs and actual practice regarding these topics.

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**KEY WORDS:** acute kidney failure, mortality, critical care, anesthesia, consensus, renal failure, acute renal injury, survival, web vote, consensus conference

**A**CUTE KIDNEY INJURY (AKI) is a major healthcare problem with impact on morbidity, mortality, and health resource utilization.<sup>1-3</sup> Despite considerable progress in intensive care medicine, up to 67% of critically ill patients may develop some degree of AKI, as defined by the RIFLE (risk, injury, failure, loss, end-stage renal disease) classification, and approximately 5% to 6% of ICU patients require renal replacement therapy.<sup>1</sup> Even small increases in creatinine levels or biomarkers<sup>4</sup> correlate with increased mortality, and when patients require renal replacement therapy, the risk of death rises dramatically.<sup>2,5</sup> It is conceivable that the speed and appropriateness of therapy might affect survival of critically ill patients. However, to date, there is no specific treatment that increases survival in patients with or at high risk of AKI.

The authors systematically identified interventions reported to increase or reduce mortality in critically ill patients with or at risk for AKI. Their aim was to establish the agreement between stated beliefs and actual practice in this setting and guide further research into such interventions. In order to achieve this goal, an innovative strategy was applied.<sup>6,7</sup> After first identifying of the key topics based on systematic database search and contact with experts, a web-based voting system was developed. After that, each topic was debated in a formal meeting and consensus achieved. The consensus statements were placed on the web for a second round of voting by the web-based physician community. The authors asked whether the voting physicians agreed with the statements or not, and if, independently on the statements, they would use a given treatment in their clinical setting. This method provided a new way to integrate consensus with self-reported practice.

## MATERIALS AND METHODS

Pertinent papers were searched independently in PubMed, BioMedCentral, EMBASE, and Cochrane Library (updated February 14, 2012). A sensitive PubMed search with no time limits was used to systematically identify all published papers concerning interventions influencing survival in critically ill patients with or at risk for AKI. The full search strategy is available in the supplemental appendix and yielded 691 results.

Further topics were identified by a core group of experts who worked from May 2008 to February 2012 and backward snowballing, ie, cross-checking of references, was implemented to discover further interventions. Recent reviews on AKI also were studied to identify further papers, and experts in the field were contacted.

Papers were evaluated by the consensus meeting and included only if they fulfilled all the following criteria: (a) published in a peer-reviewed journal, (b) dealt with critically ill adult patients with or at risk for AKI, and (c) reported a statistically significant reduction or increase in mortality. During the first phase, while screening the literature, the authors preferred a comprehensive approach so that no pertinent papers would be excluded.

From January 1, 2012 to February 14, 2012, a web site allowed participants to vote in support of or against the selected interventions and to submit further topics.

A meeting was held on February 14, 2012 at the Vita-Salute University of Milan, Italy among most of the authors of the present manuscript (anesthesiologists, intensive care specialists, and nephrologists). All the suggested topics were discussed, and for each topic, it was decided if: (a) the most recent evidence had been collected, (b) the impact on mortality was supported by either randomized controlled trials or meta-analyses of randomized controlled trials, case-matched

studies, or other studies, and (c) the evidence had been derived entirely or partially from patients with or at risk of AKI.

Topics then were presented by a selected reporter. After discussion, a position statement was approved describing the intervention, the reasons for the inclusion, the challenges in evaluating it, and the grading according to the GRADE classification (Table 1).<sup>8</sup> In this classification, each statement is defined by a number (1 or 2) and by a letter (A, B, or C). The number represents the strength of the recommendation based on comparison of known risks with expected benefits. A strong recommendation is represented by a value of 1 while a value of 2 indicates a weak recommendation or suggestion. The following letter describes the methodologic quality of the supporting evidence. A, B, and C correspond to high, moderate, and low/very low quality, respectively.<sup>8,9</sup> After discussion, a position statement was approved describing the intervention, the reasons for the inclusion, and the challenges in evaluating it.

Major exclusions were represented by therapies that could determine a specific mortality reduction or increase but without providing sufficient information to be able to derive data or conclusions on mortality in AKI patients.

Final statements were presented online (February 15, 2012 to April 1, 2012). Via an interactive web questionnaire, both in-person and web participants were asked again to agree or disagree with the topics and statements from the meeting (Do you agree with the statements? Yes; No; Don't know) and if they personally would consider the therapy or strategy in their daily practice (Do you recommend this therapy to increase survival? Definitely; Probably; Not sure; Probably not; Definitely not) (Fig 1).

The authors included the option "don't know" in the questionnaire to allow respondents to state that they had no opinion or had never thought about a particular issue. Since methodologic research suggests that there is no difference in response rate depending on the inclusion or exclusion of the "don't know" option (if less than 40%), the authors reported only the "yes" and "no" frequencies.<sup>10</sup>

Throughout the process, all participants (either those voting via web or those participating in person) were asked to disclose all potential conflicts of interest. The interactive web questionnaire asked voters to declare any potential conflict of interest for each intervention without specifying the details of the nature of this conflict. All in-person participants had to complete the same questionnaire. There was no sponsor or industry support for this consensus conference.

The consensus process through the web involved the international cohort of participants who voted on the topics before and after the Milan meeting. Double votes were prevented using the email field as the unique identifier.

## Statistical Analysis

Statistical analysis was done using Stata 11. The authors compared the answers given by meeting participants and web voters. They used chi square or Fisher's exact test where appropriate. They defined a  $p$  value  $< 0.05$  as statistically significant. The authors used Cohen's kappa to investigate the agreement between the 2 questions, ie, if evidence-based opinion agrees with self-reported clinical practice. They considered agreement to be satisfactory when  $k > 0.4$  and identified disagreement when  $k \leq 0.4$ .

## RESULTS

Overall, 311 participants from 62 countries (Supplemental Material 2) participated in the consensus process. The consensus process identified 18 topics<sup>11-35</sup> with at least 1 paper published in a peer-reviewed journal suggesting a statistically significant effect on mortality.

Perioperative hemodynamic optimization,<sup>11</sup> albumin in cirrhotic patients,<sup>12,13</sup> terlipressin for hepatorenal syndrome type

Table 1. Grading Recommendations

Grading Recommendations			
Grade of Recommendation/ Description	Benefit v Risk and Burdens	Methodologic Quality of Supporting Evidence	Implications
1A/strong recommendation, high-quality evidence	Benefits clearly outweigh risk and burdens or vice versa	RCTs without important limitations or overwhelming evidence from observational studies	Strong recommendation, can apply to most patients in most circumstances without reservation
1B/strong recommendation, moderate-quality evidence	Benefits clearly outweigh risk and burdens or vice versa	RCTs with important limitations (inconsistent results, methodologic flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies	Strong recommendation, can apply to most patients in most circumstances without reservation
1C/strong recommendation, low-quality or very-low-quality evidence	Benefits clearly outweigh risk and burdens or vice versa	Observational studies or case series	Strong recommendation but may change when higher-quality evidence becomes available
2A/weak recommendation, high-quality evidence	Benefits closely balanced with risks and burden	RCTs without important limitations or overwhelming evidence from observational studies	Weak recommendation, best action may differ depending on circumstances or patients' or societal values
2B/weak recommendation, moderate-quality evidence	Benefits closely balanced with risks and burden	RCTs with important limitations (inconsistent results, methodologic flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies	Weak recommendation, best action may differ depending on circumstances or patients' or societal values
2C/weak recommendation, low-quality or very-low-quality evidence	Uncertainty in the estimates of benefits, risks, and burden; benefits, risk, and burden may be closely balanced	Observational studies or case series	Very weak recommendations; other alternatives may be equally reasonable

Abbreviation: RCT, randomized, controlled trial.

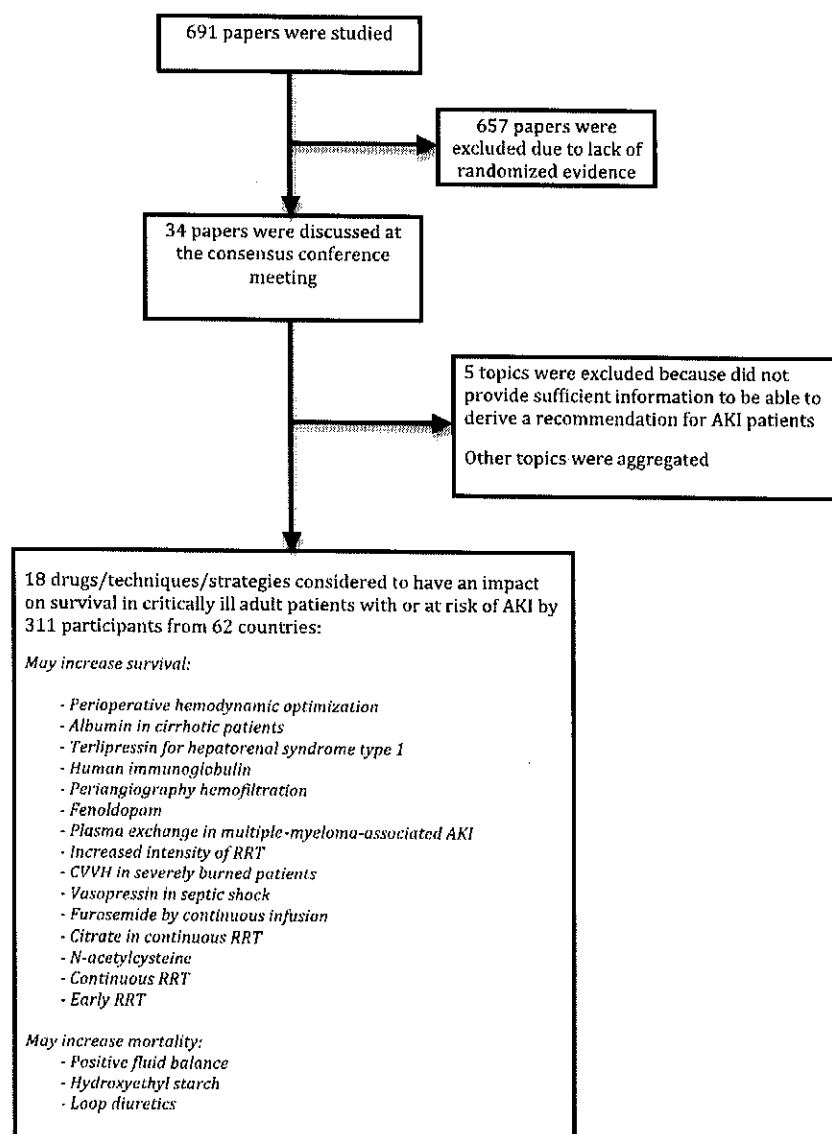


Fig 1. Flow chart on the selection of the topics with an effect on mortality in critically ill adult patients with or at risk for AKI.

1,<sup>14</sup> human immunoglobulin,<sup>15</sup> periangiography hemofiltration,<sup>16</sup> fenoldopam,<sup>17</sup> plasma exchange in multiple-myeloma-associated AKI,<sup>18</sup> increased intensity of renal replacement therapy (RRT),<sup>19-21</sup> CVVH in severely burned patients,<sup>22</sup> vasopressin in septic shock,<sup>23,24</sup> furosemide by continuous infusion,<sup>25</sup> citrate in continuous RRT,<sup>26</sup> N-acetylcysteine,<sup>27,28</sup> and continuous<sup>29</sup> and early RRT<sup>30,31</sup> might reduce mortality in critically ill patients with or at risk for AKI; positive fluid balance,<sup>32,33</sup> hydroxyethyl starch,<sup>13,34</sup> and loop diuretics<sup>35</sup> might increase mortality in critically ill patients with or at risk for AKI.

All the 18 topics, with the discussed papers, the consensus statement and web agreement (ranging between 69% and 97%) are reported in Tables 2 and 3.

Major exclusion criteria (associated with changes in mortality in critically ill patients but not having all the inclusion

criteria for this consensus process) were represented by insulin therapy,<sup>36</sup> use of nesiritide,<sup>37,38</sup> the transfusion of aged red blood cells,<sup>39</sup> the use of postoperative aspirin,<sup>40</sup> and the use of a preoperative intra-aortic balloon pump.<sup>41</sup>

#### Opinion and Self-reported Practice

Web vote expressed an overall good level of agreement with recommendations (range 86%-97%) and suggestions (range 69%-96%). Six suggestions, however, (not routinely using plasma exchange in multiple-myeloma AKI, vasopressin in septic shock, continuous infusion of furosemide, N-acetylcysteine, continuous RRT anticoagulation with citrate, and avoiding loop diuretics) showed a statistically significant difference between meeting participants and web voters (Fig 2).

Table 2. Topics (Drugs, Techniques, or Strategies) with Published Evidence of Reduction in Mortality in Critically Ill Patients with or at Risk for AKI

Therapies That Might Increase Survival				
Drug/Technique/Strategy	Author (year)	Recommendation/Suggestion (GRADE)	Final Statement	Web Vote Agreement (%)
Perioperative hemodynamic optimization	Brienza (2009)	The consensus conference recommended the use of perioperative hemodynamic optimization with the intent to increase survival in postoperative AKI. (1C)	Optimization of hemodynamic parameters is a cornerstone of intensive care medicine and anesthesia. Accordingly, there is a wide consensus that hemodynamic optimization is important in improving survival. However, interventions to optimize hemodynamics are heterogeneous in nature, targets, timing, design, and technology. This heterogeneity creates uncertainty about the precise nature of what treatments and/or technologies should be applied to achieve it. A meta-analysis found that in surgical patients, including some with AKI, perioperative hemodynamic optimization increased survival. This effect was most strongly observed in patients with the highest illness severity. In light of the above considerations, a strong recommendation appears justified for this intervention.	97%
Albumin in patients with cirrhosis and spontaneous bacterial peritonitis	Sort (1999); Wiedermann (2010)	The consensus conference recommended the use of albumin with the intent to increase survival in cirrhotic patients with spontaneous bacterial peritonitis-associated AKI. (1B)	Human 20% albumin commonly is used to expand intravascular volume in patients with sepsis especially in the setting of hypoalbuminemia. It appears a physiologically logical volume expander in septic patients with advanced liver disease. A multicenter RCT found that 20% albumin fluid resuscitation increased survival and reduced the rate of AKI in cirrhotic patients with spontaneous bacterial peritonitis. In addition, a subgroup analysis of a meta-analysis of fluid resuscitation in patients with liver dysfunction reported a survival benefit with 20% albumin and a subgroup analysis of septic patients from a large multicenter RCT showed a trend confirming these findings. <sup>51</sup> A strong recommendation can be made for the use of albumin in patients with cirrhosis and spontaneous bacterial peritonitis.	93%
Terlipressin for HRS type 1	Solanki (2003)	The consensus conference recommended the use of terlipressin with the intent to increase survival in HRS 1-associated AKI. (1C)	Terlipressin is a longer acting vasopressin analog. It has been tested as a treatment for HRS type 1, a type of AKI associated with advanced liver disease. A small randomized trial found that terlipressin increased short-term survival in HRS type-1 patients. A meta-analysis found a trend to increased survival in HRS patients. <sup>52</sup> The beneficial effect of terlipressin on renal function in patients with HRS type 1 is established; HRS is a major predictor of mortality in patients with cirrhosis, and the practice of administering terlipressin in HRS type 1 is now widespread. These observations make it biologically plausible that terlipressin might improve survival and justify a strong recommendation that it should be considered to improve survival in HRS type-1 patients.	92%
Human immunoglobulin	Keane (1991)	The consensus conference suggested not routinely using human immunoglobulin with the intent to increase survival in AKI. (2C)	Human immunoglobulin has theoretical value as a treatment of patients with AKI, especially in the setting of sepsis. This putative effect provided the biologic rationale for a small single-center RCT. The study found increased survival with immunoglobulin therapy in a group of patients with mostly septic AKI. However, the study was single center and reported an effect of implausible magnitude. In addition, subsequent studies have failed to confirm a survival benefit. <sup>53</sup>	96%

Periangiography hemofiltration for contrast-induced AKI	Marenzi (2003)	The consensus conference suggested routinely using periangiography hemofiltration with the intent to increase survival in contrast-induced AKI. (2B)	Furthermore, human immunoglobulin therapy can be immunosuppressive and has been reported to induce AKI. Any recommendation to consider human immunoglobulin for the treatment of AKI with the intent to increase survival can only be weak in nature. Treatment of high-risk patients about to receive radiopaque contrast with a dialytic technique may optimize patient preparation and decrease renal exposure to contrast during an angiographic procedure, providing a rationale for this intervention. A single-center RCT found that periangiography CVVH decreased mortality in high-risk patients. However, the 2 study groups were treated differently in other respects (eg, admission to ICU for the active intervention group v no-ICU support for the control group). Subsequent studies <sup>56-58</sup> and meta-analyses <sup>57</sup> have failed to support the initial study. Therefore, any recommendation to use periangiography hemofiltration for contrast-induced AKI to increase survival can, therefore, only be weak in nature.	94%
Fenoldopam	Landoni (2007)	The consensus conference suggested not routinely using fenoldopam with the intent to increase survival in AKI. (2B)	Fenoldopam is a dopamine-receptor agonist with the potential to reduce afterload and increase renal blood flow in patients with AKI or at high risk of AKI. A meta-analysis of randomized studies, many involving AKI patients, found a survival improvement with its administration. However, many of the studies were small and the patients were heterogeneous and the studies considering contrast media AKI were excluded. One large study is underway in the cardiac surgery setting (Clinical trial number NCT00621790). Any recommendation to use fenoldopam to increase survival can, therefore, only be weak in nature.	93%
Plasma exchange in multiple-myeloma-associated AKI	Zucchelli (1988)	The consensus conference suggested not routinely using plasma exchange with the intent to increase survival in myeloma-associated AKI. (2C)	Multiple myeloma is associated with a high risk of AKI. One type of AKI seen with multiple myeloma is due to light chain nephrotoxicity. Light chains can be removed by plasma exchange. This effect provided a biological rationale for a small single-center RCT. This study found a benefit on 1-year mortality. This study, however, combined plasma exchange with hemodialysis and compared it with peritoneal dialysis, making it difficult to assess the efficacy of plasma exchange per se. <sup>59</sup> In addition, the treatment of multiple myeloma has changed dramatically since the publication of the study and other larger studies of plasma exchange in this setting were inconclusive. <sup>59,60</sup> Finally, light chain removal technology also has evolved and allows removal of light chains without the need for plasma exchange. Any recommendation to consider plasma exchange for the treatment of myeloma-associated AKI with the intent to increase survival can only be weak in nature.	89%
Increased intensity of RRT by daily hemodialysis or CVVHD or high-flow CVVH	Schiffi (2002), Ronco (2000), Saudan (2006)	The consensus conference suggested not using increased dialysis intensity with the intent to increase survival in severe AKI. (2C)	The concept that dialysis intensity might affect survival in patients with severe AKI has been a subject of interest almost since the development of RRT. For each one of the above interventions, there is one single-center RCT showing a beneficial effect on survival. However, 2 large, phase III, level 1 studies recently have contradicted these findings. <sup>61,62</sup> As a consequence, a recommendation to increase the intensity of RRT cannot be made.	87%

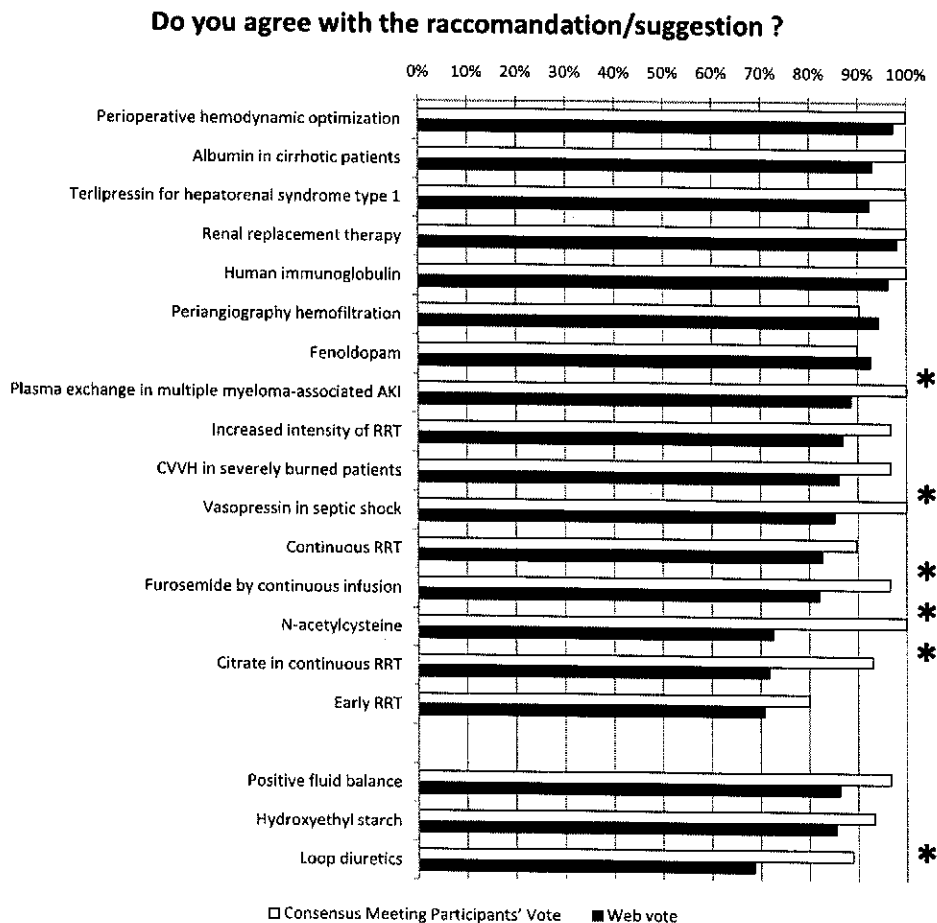
Table 2 (continued)

Therapies That Might Increase Survival				
Drug/Technique/Strategy	Author (year)	Recommendation/Suggestion (GRADE)	Final Statement	Web Vote Agreement (%)
CVVH in severely burned patients	Chung (2009)	The consensus conference suggested not routinely using CVVH in severely burned patients with the intent to increase survival. (2C)	Patients with severe burns are at risk of major fluid shifts, fluid overload and sepsis. The use of CVVH may help minimize the consequences of such derangement and help increase survival. A small, single-center, historic controls-based study found that such patients with AKI treated with CVVH had decreased mortality. No other controlled studies have replicated these findings and only a weak recommendation can be made to support its use to increase survival in these patients.	86%
Vasopressin in septic shock	Kiser (2005); Gordon (2010)	The consensus conference suggested not routinely using vasopressin with the intent to increase survival in sepsis-induced AKI. (2C)	Vasopressin is a vasoconstrictive hormone used in the treatment of septic shock. It has the potential to improve glomerular filtration rate because of its intrarenal hemodynamic effects. A post hoc analysis of a large RCT evaluated the efficacy of vasopressin with norepinephrine versus norepinephrine alone in septic shock patients in stage R of the RIFLE classification of AKI. This study found a decrease in mortality on log-rank testing, which, however, could not be confirmed on multivariate analysis. Any recommendation to use vasopressin to increase survival in these patients can, therefore, only be weak in nature.	85%
CVVHDF compared with conventional intermittent dialytic therapy in critically ill patients with AKI	Bellomo (1993)	The consensus conference suggested not routinely using CVVHDF instead of intermittent HD with the intent to increase survival in severe AKI. (2C)	CVVHDF has theoretic physiologic advantages over intermittent hemodialysis, which provides a rationale for believing that it may offer a survival advantage when compared with IHD. A single-center retrospective study found that patients treated with CVVHDF had increased survival compared with historic controls treated with IHD. However, subsequent studies (observational and randomized) have failed to confirm these findings. <sup>63-65</sup> Accordingly, any recommendation to use CVVHDF or other forms of CRRT to decrease mortality in patients with AKI can only be weak.	82.59
Furosemide by continuous infusion	Kunt (2009)	The consensus conference suggested not routinely using furosemide by continuous infusion with the intent to increase survival in AKI. (2C)	If a loop diuretic (eg, furosemide) is administered to patients with AKI, administration by continuous infusion may be more effective in achieving volume control without major swings in intravascular volume. A small single-center RCT with serious methodologic flaws demonstrated reduction in 30-day mortality in patients receiving continuous infusion of furosemide after cardiac surgery when compared with patients treated with boluses of furosemide. However, previous RCTs <sup>66-69</sup> and a meta-analysis <sup>70</sup> summarizing them did not show similar findings. Only a weak recommendation can be made to use continuous infusion of furosemide instead of furosemide boluses in patients with AKI.	82%
				73%

NAC in contrast-induced nephropathy and/or in cardiac surgery	Marenzi (2006); Wijeyesundera (2007)	The consensus conference suggested not routinely using NAC with the intent to increase survival in contrast-induced AKI. (2C)	NAC is an antioxidant agent and a sulfhydryl group donor. Because oxidative injury is considered to be important in the pathogenesis of AKI after contrast or cardiac surgery, NAC has been studied as protective treatment. In the setting of contrast-induced nephropathy, a single-center study found a survival benefit. However, a subsequent large multicenter RCT <sup>71</sup> and multiple meta-analyses <sup>72,73</sup> found no effect on patient survival. In the setting of cardiac surgery, only a small single-center RCT found a survival benefit with NAC treatment. This finding also has not been confirmed by subsequent trials <sup>74</sup> and meta-analyses. <sup>75,76</sup> These findings only justify a weak recommendation for considering NAC as a treatment to improve survival in patients exposed to radiocontrast or cardiac surgery.	
Citrate in continuous RRT	Oudemans-vanStraaten (2009)	The consensus conference suggests not routinely using citrate in CRRT with the intent to increase survival in severe AKI. (2C)	CRRT with citrate-based anticoagulation increasingly is being used. Citrate has the advantage of achieving circuit anticoagulation without exposing the patient to systemic anticoagulation. A single-center RCT compared citrate CRRT with CRRT using nadroparin (an LMWH) for anticoagulation. This study found no effect on filter life and a marked increase in bleeding complications when using LMWH. It also found an increased survival in patients treated with citrate. This result, however, can be explained partly with the risks associated with treating CRRT patients with LMWH. Other studies by comparing citrate CRRT with other non-LMWH forms of anticoagulation failed to show a survival advantage. <sup>77,78</sup> Therefore, any recommendation to use continuous RRT with citrate to increase survival can only be weak in nature.	72%
Early renal replacement therapy	Seebra (2008); Demirkilic (2004)	The consensus conference suggests not routinely using early RRT with the intent to increase survival in severe AKI. (2C)	Early intervention with RRT in patients with severe AKI may decrease the consequences of AKI-associated fluid overload, uremia, and electrolyte disturbances. However, there is no agreed definition of the meaning of "early" and different studies have used different ways to define it. Nonetheless, a meta-analysis that included observational studies and small RCT's found that early RRT may be associated with a reduction in mortality. One small, single-center observational study with important methodologic shortcomings was included in this meta-analysis and found that in cardiac surgery, early CVVHDF was associated with decreased mortality. Only a weak recommendation can be made for the use of early CVVHDF.	71%

Abbreviations: AKI, acute kidney injury; CRRT, continuous renal replacement therapy; CVVH, continuous veno-venous hemofiltration; CVVHDF, continuous veno-venous hemofiltration with dialysis; HD, hemodialysis; HRS, hepatorenal syndrome; ICU, intensive care Unit; IHD, intermittent hemodialysis; LMWH, low-molecular-weight heparin; NAC, N-acetylcysteine; RCT, randomized, controlled trial; RIFLE, risk, injury, failure, loss, end-stage renal disease; RRT, renal replacement therapy.





**Fig 2. Agreement with the recommendation/suggestion.** Percentage of the participants to the consensus meeting (white) and the web voters (black) who agreed with the suggestion/recommendation expressed by the consensus conference. The star (\*) indicates a statistically significant difference ( $p < 0.05$ ).

The answers concerning self-reported clinical practice are displayed in Figure 3 and show a statistically significant difference in self-described clinical behavior between those who belonged to the panel and the physicians from all over the world for terlipressin and fenoldopam (less used by web voters) and for avoidance of positive fluid balance (less commonly pursued by web voters). (See Table 3.)

Among both consensus-meeting participants and web voters, there was moderate-to-substantial agreement between opinion and self-reported practice only for 3 interventions (terlipressin, albumin, and perioperative optimization). Among web voters, there was moderate-to-substantial agreement between opinion and self-reported practice also in avoidance of a positive fluid balance. There was only a weak correlation between the opinion about the avoidance of starch-based fluids and self-reported use of starch-containing fluids.

Supplemental Material 3 shows the details of these data together with the agreement between questions assessed by Cohen's kappa.

Declarations of any conflicts of interests assessed for each intervention ranged from 0.3% to 2.2% per intervention, and the exclusion of these participants did not affect the overall results.

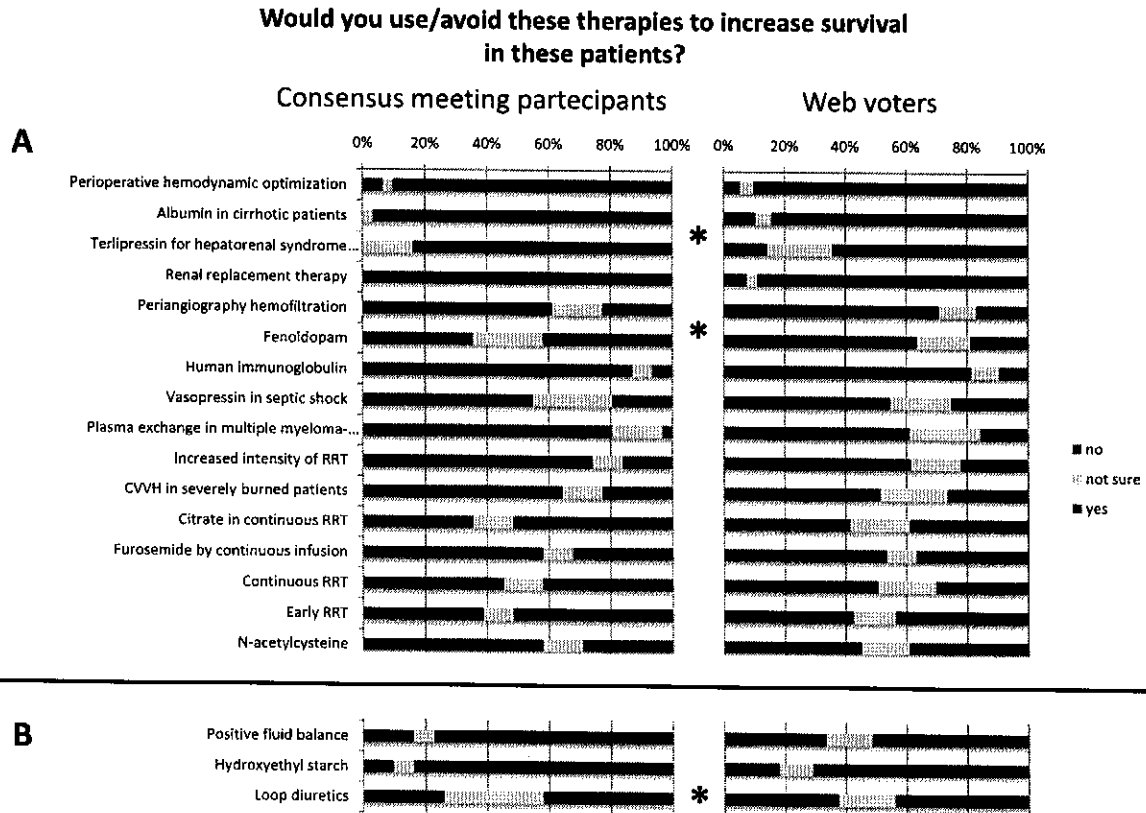
## DISCUSSION

### Key Findings

The authors identified all 18 interventions with at least 1 paper published in a peer-reviewed journal reporting a statistically significant effect on mortality in patients with or at risk of AKI. They issued consensus recommendations and suggestions following a consensus conference according to the GRADE methodology. They obtained information on opinion and self-reported practice from participants in the consensus meeting and from clinicians who voted via a web-enabled approach. The authors found that while opinions generally were similar between meeting participants and web-voters, there were significant differences of opinion in relation to 30% of interventions and 15% of self-reported practice. More strikingly, there was little concordance between registered opinion and self-reported practice for most of the interventions assessed.

### Previous Literature and Methodology

The development of AKI in critically ill patients is unquestionably associated with an increased risk of morbidity



**Fig 3. Self-reported use or avoidance of selected therapies.** For each topic, both participants and web voters were asked if they would have used (A) or avoided (B) the selected treatments to increase survival in patients with AKI. They were given 5 possible answers: definitely, probably yes, don't know, probably not, definitely not. For the sake of clarity, they were summarized into 3 categories: yes, not sure, and no. The star (\*) indicates those topics where the difference between meeting participants' and web vote was significant. (Color version of figure is available online.)

and mortality.<sup>42</sup> Furthermore, the population of patients at risk for its development is increasing.<sup>43</sup> As a consequence, early identification of the patients at risk and an effective treatment are the main targets in the management of this population.<sup>44</sup> Many strategies or drugs have been proposed as treatments of AKI. Moreover, other drugs are known or supposed to cause AKI. Nevertheless, so far no systematic review reported the impact on mortality of these strategies or drugs. For the first time, the authors identified and discussed 18 strategies or interventions, medical and nonmedical, in which at least 1 paper reported an effect on mortality in patients with or at risk for AKI.

On the basis of the encouraging results of 2 previous international web-based consensus conferences,<sup>6,7</sup> the authors used a similar innovative methodology to identify the topics that might reduce/increase mortality in patients affected by or at risk for AKI; they adopted a new combined approach that associated critical review of the evidence from literature, consensus, and worldwide web voting. Moreover, they introduced the GRADE methodology to evaluate selected papers. This is a helpful tool to avoid subjective judgments, since it is based on a systematic, explicit, and reliable approach to interpret evidence.<sup>45</sup> The aim of this approach was twofold. On one hand, the authors aimed to review the literature with a critical evaluation by a panel. On the other hand, they aimed to

give to the web-based worldwide community of physicians the opportunity to evaluate the relevance and reliability of the recommendations and suggestions proposed by the panel during the consensus meeting, independently from the level of evidence. Furthermore, physicians participating in the web-based vote offered an insight into the relationship among evidence, consensus, and daily self-reported practice. This process agrees with the view that the quality and validity of consensus statements must be assessed by the readers, as is the case for other literature.<sup>46</sup>

This strategy led to interesting results. First of all, the authors identified 18 relevant interventions. Second, none of the 18 interventions, either reducing<sup>11-31</sup> or increasing<sup>13,32-35</sup> mortality, was supported by high-quality evidence. Therefore, only a few recommendations could be made. The consensus recommended the use of albumin in patients with cirrhosis and spontaneous bacterial peritonitis and the avoidance of HES-containing fluids on the basis of strong evidence.<sup>12,13,34</sup> Moreover, it recommended using terlipressin in patients with hepatorenal syndrome type 1 and perioperative hemodynamic optimization based on lower-quality evidence.<sup>11,14</sup> Of relevance, since the generation of the consensus recommendation that starch-based fluids should be avoided, 2 multicenter, double-blind, randomized controlled trials have provided level-1 evidence to support this position.<sup>47-49</sup> Interestingly,

Table 3. Topics (Drugs, Techniques, or Strategies) with Published Evidence of Increase in Mortality in Critically Ill Patients with or at Risk for AKI

Therapies That Might Increase Mortality				
Drug/Technique/ Strategy	Author (year)	Recommendation/Suggestion (GRADE)	Final statement	Web Vote Agreement (%)
Positive fluid balance	Payen (2008); Bouchard (2009)	The consensus conference suggested avoiding positive fluid balance with the intent to increase survival in AKI. (2C)	A positive fluid balance in AKI patients appears common and may contribute to vital organ congestion and dysfunction and thereby might increase mortality. Conversely, avoidance of a positive fluid balance may be protective. Two observational studies performed in adult patients found that a positive fluid balance was independently associated with an increased risk of death in critically ill patients with AKI or in patients with severe sepsis (many with AKI). Given the weakness of the available evidence, only a <i>weak</i> recommendation can be made to avoid a positive fluid balance and/or fluid overload in patients with AKI.	86%
HES	Brunkhorst (2008); Wiadernmann (2010)	The consensus conference recommended avoiding HES solutions for fluid resuscitation with the intent to increase survival in severe AKI. (1B)	HES is a colloidal intravascular volume expander used worldwide for fluid resuscitation in many clinical conditions. A large multicenter non-blinded RCT using high-molecular-weight HES found that, when compared to resuscitation with a lactated crystalloid solution, HES administration increased mortality in critically ill patients, many of whom had AKI. Several other trials <sup>79,82</sup> and recent meta-analyses have raised concerns about the safety of HES solutions in terms of adverse renal events and mortality. A 7,000-patient double-blind randomized controlled trial comparing saline with HES resuscitation in the ICU (NCT 00935168) recently has completed recruitment and is following patients for 90-day all-cause mortality. Until the results of this study have been reported, a strong recommendation can be made to avoid the use of HES solutions for fluid resuscitation.	86%
Loop diuretics	Mehta (2002)	The consensus conference suggested avoiding loop diuretics with the intent to increase survival in AKI. (2C)	Loop diuretics frequently are administered to patients with AKI to prevent or attenuate fluid overload or to increase urine output and transform oliguric AKI into nonoliguric AKI. An observational study found increased mortality in patients with AKI treated with diuretics after correction for other confounding factors. A subsequent observational study <sup>81</sup> and 2 subsequent meta-analyses, <sup>82,83</sup> however, only found a nonsignificant trend towards increased mortality, and no randomized controlled trials have confirmed this harmful effect. Thus, a <i>weak</i> recommendation can be made to avoid diuretics in patients with AKI.	69%

Abbreviations: AKI, acute kidney injury; HES, hydroxyethyl starch; ICU, intensive care unit; RCT, randomized, controlled trial.

however, at the time of the web-based vote, almost 20% of respondents disagreed with this recommendation.

Moreover, a small randomized, controlled trial compared terlipressin to norepinephrine in hepatorenal syndrome type 1 and suggested that norepinephrine is less expensive and as safe and effective as terlipressin in reducing renal dysfunction and mortality in this setting.<sup>50</sup> This result might have downgraded (from recommendation to suggestion) the terlipressin statement.

Of the remaining 14 topics, 12 received a suggestion not to be used routinely in order to increase survival in AKI patients.<sup>15-31</sup> The methodologic quality of the papers was not high enough, clinical plausibility was low, or in some cases, subsequent studies challenged or even contradicted these findings. Therefore, the consensus panel could not suggest the routine use of these therapies for the specific purpose to reduce mortality.

Finally, the avoidance of loop diuretics and of positive fluid balance was suggested based on low-quality evidence.<sup>32,33,35</sup>

A few considerations about the web vote are relevant. First, as expected, agreement was higher among in-person participants than among web voters, although this difference was not statistically significant in most cases. All the topics in which a significant difference was noted were suggestions with the only exception of the answers to the second question about terlipressin. This may be due to the low quality of the available evidence or to the lack of approval for terlipressin use in many countries.

Second, self-reported clinical practice agreed with web-expressed opinion only for a few interventions, all of them being positive recommendations (ie, albumin, terlipressin, and hemodynamic optimization). Instead, all suggestions showed weak agreement between practice and opinion, raising the point that opinion based on the available literature is not the only determinant of clinical practice. Identifying these specific areas of uncertainty and practice variation allows clinicians to focus on important topics for future interventional trials.

### Strengths and Limitations of the Study

In the authors' study, for the first time, they identified all the 18 topics with at least 1 paper suggesting a statistically significant effect on survival in patients with or at risk for AKI. No systematic review on survival in AKI patients and no consensus process with these characteristics yet have been reported. For the first time, the authors' approach enabled clinicians from multiple countries to show concordance and/or discordance with consensus opinion in what might be aptly named a democratic process. Finally, by allowing participants to register opinion and self-reported practice, they were able to demonstrate the significant gap between such opinion and actual self-reported practice. A future web-enabled, point-prevalence assessment of actual practice and self-reported determinants of clinical choices theoretically is possible. These steps are crucial in the evolution of the understanding of the translation of research into practice.

The major limitation of this manuscript is represented by the low quality of literature concerning the vast majority of the interventions discussed. Such limited evidence weakens

the strength of the authors' statements. Yet, it is not different from other areas of intensive care practice. They tried to overcome this limitation through a new approach that combined the critical review of the evidence to consensus with worldwide web voting. They also sought to uncover implicit subjectivity by introducing GRADE methodology. The authors are aware that web-registered opinion is not necessarily an expression of opinion at the bedside with individual patients and that such opinion is not a static clinical stance. However, at present, no electronic means exist to reliably record dynamic opinion. They are similarly aware that self-reported practice and actual practice are not concordant. However, electronic means of capturing actual practice are available, and the authors hope to improve their process of web-enabled assessment of translation into practice by recording actual care in a point-prevalence manner in future evolutions of their web-based approach.

The authors also noted that there is considerable heterogeneity among the 18 treatments that they identified. For instance, "perioperative hemodynamic optimization" is a general intervention with broad application; whereas the use of "terlipressin for treating type-1 hepatorenal syndrome" is highly specific and targeted. Furthermore, some interventions for which there is evidence (although not necessarily a positive recommendation by the authors) seem apparently contradictory (for instance, "hemodynamic optimization" and "avoiding a positive fluid balance"), and this could be explained, at least in part, from the specific clinical situations studied in the individual papers.

### CONCLUSION

In conclusion, the authors identified all the 18 interventions that have at least a paper published in a peer-reviewed journal with a statistically significant effect on survival in patients with or at risk for AKI. There are current supportive evidence, consensus opinion, web-based agreement and self-reported practice that terlipressin is considered appropriate for and given to patients with hepatorenal syndrome type 1, albumin to cirrhotic patients with spontaneous bacterial peritonitis and perioperative hemodynamic optimization pursued with the aim of decreasing mortality in patients with or at high risk of AKI. However, despite broad agreement that starch-based fluids should not be given, there is only mild agreement between the view that starch-containing fluid should be avoided and self-reported avoidance of such fluids. In the field of AKI, the relationship among evidence, consensus, clinician opinion, and self-reported practice is complex and highly variable.

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#### APPENDIX A. SUPPLEMENTARY DATA

Supplementary data associated with this article can be found in the online version at [10.1053/j.jvca.2013.06.028](https://doi.org/10.1053/j.jvca.2013.06.028).

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