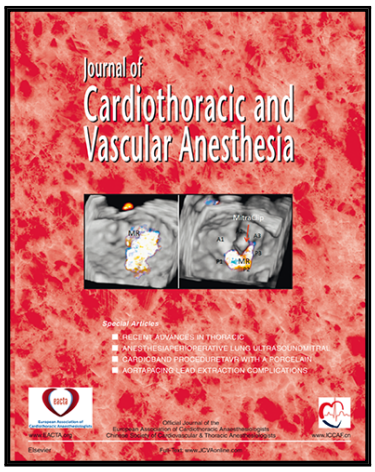

A Systematic Review and International Web-Based Survey of Randomized Controlled Trials in the Perioperative and Critical Care Setting: Interventions Increasing Mortality

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Abstract

Objective: Reducing mortality is a key target in critical care and perioperative medicine. We aimed to identify all nonsurgical interventions (drugs, techniques, strategies) shown by randomized trials, to increase mortality in these clinical settings.

Design:A systematic review of the literature followed by a consensus-based voting process.

Setting:A web-based international consensus conference.

Participants:251 physicians from 46 countries.

Interventions: We performed a systematic literature search and identifiedall randomized controlled trials (RCTs) showing significant increase in unadjusted landmark mortality among surgical or critically ill patients. We reviewed such studies during a meeting by a core group of experts. Studies selected after such review advanced to web-based voting by clinicians in relation to agreement, clinical practice, and willingness to include each intervention into international guidelines.

Measurements and Main Results: We selected 12 RCTs dealing with 12 interventions increasing mortality: diaspirin cross linked hemoglobin (92% of agreement among web voters),overfeeding, nitric oxide synthase inhibitor in septic shock, human growth hormone, thyroxin in acute kidney injury, intravenous salbutamol in acute respiratory distress syndrome, plasma-derived protein C concentrate, aprotinin in high-risk cardiac surgery, cysteine prodrug, hypothermia in meningitis, methylprednisolone in traumatic brain injury, and albumin in traumatic brain injury (72% of agreement).Overall, a high consistency (ranging from 80% to 90%) between agreement and clinical practice was observed.

Conclusions: We identified 12 clinical interventions with randomized trials showing increased mortality, with non-conflicting, and widely agreed-upon clinicians agreement on a global scale.

Introduction

Mortality is generally regarded as the most important outcome measure among critically ill patients. In addition to being a simple, dichotomous, and easy-to-assess endpoint, it represents a natural, immediate, and concrete indicator of therapeutic success in patients admitted to intensive care units (ICUs) or having major surgery. Although mortality rates in ICU patients have considerably decreased in the last years (1), they remain much higher compared with hospital wards, possibly exceeding 40% for the most severe diseases such as septic shock or acute respiratory distress syndrome (ARDS) (2-3).

Perioperative mortality is, in general, low. For example, in-hospital mortality after noncardiac surgery was reported to be around 1% (4). However, it can reach 4-6% after major surgical procedures and in high-risk populations (5,6), and can further increase according to patient-related and surgery-related factors (7). Moreover, given the huge number of major surgical procedures performed annually worldwide (8), even small differences in perioperative mortality may have major public health impact (7,9). Accordingly, studies including mortality as an endpoint should have an important role in guiding therapeutic decisions and, hence, in building guidelines. In particular, since randomized controlled trials (RCTs) represent the highest level of evidence according to the principles of evidence-based medicine (EBM), high-quality RCTs should ideally have a leading role among the different investigations and reports on which guidelines are based. Unfortunately, therapeutic interventions with a solid rationale and, sometimes, with promising "preliminary" evidence may show no advantages, or even detrimental effects in terms of mortality when investigated in large RCTs.

In recent years, our group developed a well-established method, also known as "democracy-based medicine" (7, 9-12), to provide clinicians with a rigorous and widely-agreed selection of published evidence by combining the features (and overcoming some limitations (10, 13)) of classical consensus conferences, international surveys, and systematic reviews. Using this method, our group performed two consensus processes aimed at identifying all nonsurgical interventions (drugs,

techniques, strategies) with a significant effect on mortality in the perioperative period (9, 14-15) and in critically ill patients (11-12), respectively.

As evidence is continuously and rapidly evolving, we have now updated the results of these consensus processes to include all recently published RCTs. Interventions reducing mortality were presented and discussed in a recently published article (16). In the present study, we focus on interventions increasing mortality.

Methods

MEDLINE/PubMed, Scopus, and Embase were searched by six investigators to identify all randomized controlled trials (RCTs) concerning every kind of nonsurgical interventions influencing mortality in critically ill and perioperative patients, without publication time limits. The full MEDLINE/PubMed search strategy is available in the Supplemental Materials. These pieces of information are also reported in our mirror analysis on the intervention reducing mortality (16).

Selected articles had to satisfy all the following criteria: 1) be published in a peer-reviewed journal; 2) be designed as RCT; 3) relate with nonsurgical interventions (drug/technique/strategy); 4) involve the perioperative period or critically ill patients; 5) show a statistically significant increase in mortality.

We considered patients as critically ill when presenting an acute failure of at least one organ and/or need for intensive care and/or emergency treatment, regardless of where they were treated. The perioperative period was defined from patient hospital admission before surgery to patient discharge after the operation.

We considered difference in mortality as statistically significant when present at a specific time point (landmark mortality) with simple statistical tests and without adjustment for baseline characteristics.

We included trials demonstrating a statistically significant increase in mortality in only a subgroup of patients, but this limitation was highlighted in the data collection form.

We excluded papers if one of these criteria was identified at any time of the consensus process: 1) not strictly randomized design (quasi randomized or similar); 2) mortality significance found only after statistical adjustments; 3) a trend toward increase in mortality was identified without reaching the $p<0.05$ level of significance; 4) classification as surgical procedure.

For each intervention we selected two experts, a rapporteur and a discussant, among the attendees. They received the selected papers in advance and were asked to meticulously review the literature, in order to find other RCTs not yet identified. A brief presentation, which included a final statement, was prepared by these experts.

We held a Consensus meeting on the 25th of November 2016 at the Vita Salute University of Milan (Italy). The inclusion or exclusion of each intervention was suggested by the experts and, in case of disagreement among participants, the inclusion of the paper was decided by a vote.

Interventions with a RCT with evidence of mortality increase were selected. These were included in the Consensus process as "full inclusion" and a statement was approved by the participants in person and underwent further steps.

Up to May 2018, through an interactive web questionnaire (http://www.democracybasedmedicine.org), clinicians worldwide had the opportunity to vote in support/against the resulting statements. The related articles were all freely downloadable through a link on the website. All participants were asked to disclose potential conflicts of interest. There was no sponsor or industry support for this consensus conference.

For statements with evidence of mortality increase the following questions were asked:

1) Do you agree with the below sentence? 2) Do you routinely avoid these interventions in your clinical practice? 3) Would you include the avoidance of these interventions into future international guidelines to reduce mortality in critically ill patients?

For each question, the authors included three possible answers: yes/no/"don't know or does not apply". The authors intentionally did not include the possibility to "partially agree" with a statement.

After the web vote, the interventions that reached <67% of agreement were considered as "major exclusions". This lower limit of agreement was chosen because two-thirds of voters represent a "qualified majority" in many political or administrative proceedings. This choice is similar to previous "democracy-based" consensus conferences the authors have conducted in other clinical settings (5,6).

Analysis before the web vote

For all "fully included" studies these variables were recorded and analyzed: 1) the intervention and its comparator; 2) the setting of the trial; 3) the sample size; 4) the presence of blinding; and 5) the duration of follow-up.

Descriptive statistics were used to examine study variables. The difference between two groups was calculated with the Mann-Whitney *U* test, and when more than two groups were involved, Kruskal-Wallis test was used. Relative Risk (RR) for individual studies and relative 95% confidence intervals (CIs) were calculate using RevMan 5.3. software (Review Manager, The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark). Statistical significance was assumed for *p* value less than 0.05.

Analysis after the web vote

We analyzed the answers from the web survey. We prevented double voting by using the e-mail field as the unique identifier. Analyses included only answers without conflict of interests. The results of the web vote are expressed as percentage of positive votes. Null votes were excluded. The percentage of agreement with selected literature, the avoidance in clinical practice and the desire to include the avoidance of the intervention in future guidelines were reported. The responders'

specialty was considered, to assess whether the management differed among anesthesiologists and intensivists. We performed further analysis relating to responders' countries to assess whether clinicians' origin influenced their approach to interventions. For simplification purposes we divided countries into 2 groups: western countries and others. We calculated the gap between agreement and practice use using the ratio between all the answers with concordance and the total number of queries with an answer in both fields ("do you agree" and "do you avoid"). The chi-square test was used to evaluate differences in percentages among countries. Statistical significance was set at $p <= 0.05$ for all analyses. Statistical analysis was performed using STATA 15 software (StataCorp, College Station, TX).

Results

We report, for the first time, a list of all the RCTs ever performed in critically ill and perioperative settings reporting a statistically significant increase in mortality. The complete list of the 262 identified manuscripts with mortality difference and the whole process of selection are reported in Supplemental Materials. The flow chart of the consensus process is summarized in figure 1.

The Journals that more frequently published the 15 ultimately selected manuscripts were the *New England Journal of Medicine* (5 papers), *Lancet* (3 papers) and *Journal of the American Medical Association*(2 papers).

Overall, 251 physicians from 46 countries participated in the web survey. Physicians were divided into three groups: anesthesiologists (n=149), intensive care physicians (n=90) and others (n=12).

The 15 interventions identified during the meeting are listed in Table 1 together with the relative percentage of agreement, avoidance in clinical practice, and willingness to include the avoidance of the specific intervention in future guidelines, while Table 2 shows a summary of the main features of the 15 RCTs (17-31) supporting the topics. The relative risks for the single interventions are presented in Figure 2.

Three interventions (high frequency oscillation ventilation in acute respiratory distress syndrome, high-dose methylprednisolone in severe sepsis and septic shock patients with elevated creatinine levels and metoprolol retard in non-cardiac surgery) did not reach the pre-specified level of agreement and became major exclusions. Accordingly, the final widely-agreed shortlist of the interventions increasing mortality includes 12 topics.

All the interventions (diaspirin cross linked hemoglobin, nitric oxide synthase inhibitor in septic shock, human growth hormone, intravenous salbutamol in acute respiratory distress syndrome, aprotinin in high-risk cardiac surgery, cysteine prodrug, hypothermia in meningitis, methylprednisolone in traumatic brain injury and albumin in traumatic brain injury) were supported by a multicenter RCT, with the exception of overfeeding, protein C zymogen (plasma-derived protein C concentrate, Ceprotin®) in sepsis and thyroxin in acute kidney injury (AKI) all supported by 1 single-center RCT.

The concordance between agreement and avoidance (a positive answer both to “do you agree” and “do you avoid”) is reported in table 3. There was a statistically significant difference between western and other countries for the use of methylprednisolone in sepsis and between anesthesiologists and intensivists for the use of methylprednisolone in traumatic brain injury as reported in Supplemental Materials (sFigure1, sFigure2). No other differences were found according to the specialty of the web responders or their nationality.

For colloids/starches vs crystalloids (2 manuscripts) and for tight glycemic control (5 manuscripts) we identified manuscripts with mortality effects going in opposite directions (mortality increase and mortality decrease) and we decided not to proceed to the web vote (Table 4).

Discussion

Key Findings

All nonsurgical interventions (drugs, techniques, strategies) which have been shown by at least one RCT to significantly affect unadjusted landmark mortality in critically ill adult patients, as well as

in the perioperative period of any adult surgery, were systematically identified. Moreover, we assessed how these interventions were regarded by 251 clinicians (mostly anesthesiologists and/or intensivists) from around the world and the extent to which their opinions translate into reported clinical practice.

Twelve interventions, supported by 12 RCTs were included in the final shortlist of the interventions widely deemed to increase mortality, while other three interventions (each supported by one study) were considered as major exclusions because less than two thirds of web voters agreed.

Of the fifteen interventions that reached the final web vote, only two (aprotinin in high-risk cardiac surgery patients and metoprolol in noncardiac surgery) were investigated in the perioperative period, while the other thirteen were investigated in the critical care setting, mostly sepsis/septic shock (3 papers), acute lung injury/ARDS (4 papers), and trauma (3 papers).This is not surprising, since mortality among critically ill patients is, in general, much higher than in surgical patients. Accordingly, on the one hand, the studies performed in the critical care setting probably include mortality as an endpoint much more often than those performed in the perioperative period, in which mortality is perceived as a less easily tested outcome, given that it is uncommon. On the other hand, as previously discussed (11), RCTs involving critically ill patients succeed more easily in showing statistically significant differences in terms of mortality, particularly when conditions still burdened with high mortality, such as sepsis or ARDS, are investigated.

In general, the concordance between agreement and use was high: for all the interventions, at least 80% of the voters who agreed with the concerns about an increased risk of death declared to avoid that intervention in their clinical practice. However, with the only exception of “overfeeding” in patients with acute lung injury (18), the three interventions with the highest percentage of agreement (>85%), namely diaspirin cross-linked hemoglobin in traumatic hemorrhagic shock (17), overfeeding (18), and human growth hormone (20) were not among those with the best concordance between agreement and avoidance of clinical use.

Relationship to Previous Literature

In contrast with what was observed in the similar consensus processes for perioperative interventions (9) and interventions in critically ill patients (11-12), we did not find a substantial gap between agreement and clinical practice. Moreover, a significant difference between western and other countries in the consistency between agreement and use was only found for 1 out of 12 interventions. These differences among countries may depend, at least in part, on logistic factors (e.g. availability of specific drugs or devices). Indeed, it is easier for clinicians not to use drugs/techniques which are regarded as harmful (regardless of their availability) than to have the organizational and economic resources to use all drugs/techniques considered beneficial. Consistent with this notion, both a gap between literature and clinical practice and the differences among countries have been confirmed for interventions reducing mortality (16).

Compared to the previous studies using "democracy-based" consensus conferences, two important interventions were excluded: insulin for tight glycemic control in surgical and medical ICU patients, and hydroxyethyl starch (HES) in sepsis. Indeed, there is conflicting evidence (studies showing a statistically significant increase in mortality and studies showing a statically significant reduction in mortality) with regard to mortality for both tight glycemic control (32-36) and HES (37-38). In particular, the use of synthetic colloids for fluid resuscitation is still highly debated worldwide (39-40), and HES is now contraindicated in sepsis according to the European Medicines Agency (EMA) and the U.S. Food and Drug Administration (FDA) (39).

Another very interesting comparison with the previous consensus process on perioperative mortality (9) concerns the initiation of □-blockers (particularly metoprolol retard) immediately before non-cardiac surgery: this intervention has moved from 83% agreement and 71% consistency between agreement and avoidance in clinical practice to only 55% of voters now agreeing that this intervention increases mortality. This change occurred despite the fact that the mortality risk of this

intervention was supported by a large multicenter RCT (the POISE trial) (31), confirmed by several meta-analyses (41-43), and supported by the downgrading of recommendations on perioperative □-blockers in the latest update of the European Society of Anaesthesiology/European Society of Cardiology (ESA/ESC) guidelines (4). This suggests, on the one hand, that in the last few years there is probably a greater attention towards cardiac ischemic complications in both the ICU and perioperative settings, and that anesthesiologists and intensivists are developing more familiarity with the use of □-blockers (even in clinical conditions in which these drugs were historically preferably avoided, such as septic shock (44)); on the other hand, it is clear that EBM and guidelines are not the only "sources of inspiration" of clinicians worldwide.

Implications for Clinical Practice and Future Research

Our investigation provides anesthesiologists and intensivists with an updated concise guide to the therapeutic strategies that should be avoided in their daily clinical practice. Although some of the listed interventions include old or niche interventions (e.g. diaspirin cross-linked hemoglobin in traumatic hemorrhagic shock (17)), others have been investigated recently, are currently discussed, still used, and are widely available.

Moreover, the interventions with the lowest agreement and/or reported use, particularly the three identified as "major exclusions" due to a very low agreement, are probably those most deserving high-quality research in the next future.

Finally, one of the most agreed-upon interventions was "overfeeding", with almost 90% of participants believing that an intensive nutritional regimen may increase mortality in ARDS patients and, accordingly, avoiding this strategy in their clinical practice. However, this intervention was supported only by a relatively small single-center RCT again suggesting that EBM does not always represent the only and unquestioned guide for clinicians.

Strengths and Limitations

The main strength of this study is its unique approach to consensus building, which combines EBM and, in particular, the methodology of systematic literature search with the features of international surveys by exploiting the great potential of the Internet. Moreover, the web vote allows investigating how literature evidence is filtered through the views and the experience of clinicians worldwide, and how it translates into clinical practice. Another strength of this approach is the simplicity and immediacy of its message. Consensus conferences and guidelines usually address all aspects related to the treatment of a certain disease or the clinical management of a specific patient population, taking into account all available literature and all possible outcomes, and may accordingly result dispersive. Conversely, this investigation focuses only on mortality, a key outcome in the critically ill and perioperative settings, and on the highest level of the EBM hierarchy (i.e. RCTs).

We acknowledge that the focus on mortality is also a limitation, together with the lack of any clinical consideration about the included interventions. However, as formerly observed, adding more details about the interventions would not have suited our survey methodology (11). Regarding the implications for clinical practice, it is worth mentioning again that two of the identified interventions (e.g. diaspirin cross-linked hemoglobin in traumatic hemorrhagic shock (17) and cysteine prodrug in ARDS (25)) are no longer used or have never entered in clinical practice.

Other limitations in common with previous similar consensus processes have been discussed elsewhere and include the possible selection bias associated with participants to the web vote and the scarcity of RCTs (in particular including mortality among their endpoints) in the perioperative setting (9, 11-12, 45). Moreover, a specific limitation of the present part of the updated consensus process on perioperative and critical care mortality, which deals with interventions increasing mortality, is that none of the included interventions is supported by strong evidence, as in the case of some interventions shown to reduce mortality (e.g. noninvasive ventilation) (7, 11-12, 16). Conversely, all but one interventions increasing mortality are supported by only one RCT, often

with relatively low sample sizes. However, it ethically unjustifiable to perform a large RCT investigating a potentially harmful intervention.

Conclusions

The updated international "democracy-based", web-enabled consensus process identified twelve nonsurgical interventions (drugs, techniques, strategies) increasing mortality in critically ill or surgical patients according to at least one RCT and the results of a web-based survey involving 251 clinicians from 46 countries. Data on self-reported clinical practice about these interventions were also obtained. Our findings may be useful to guide clinical practice and to direct future research.

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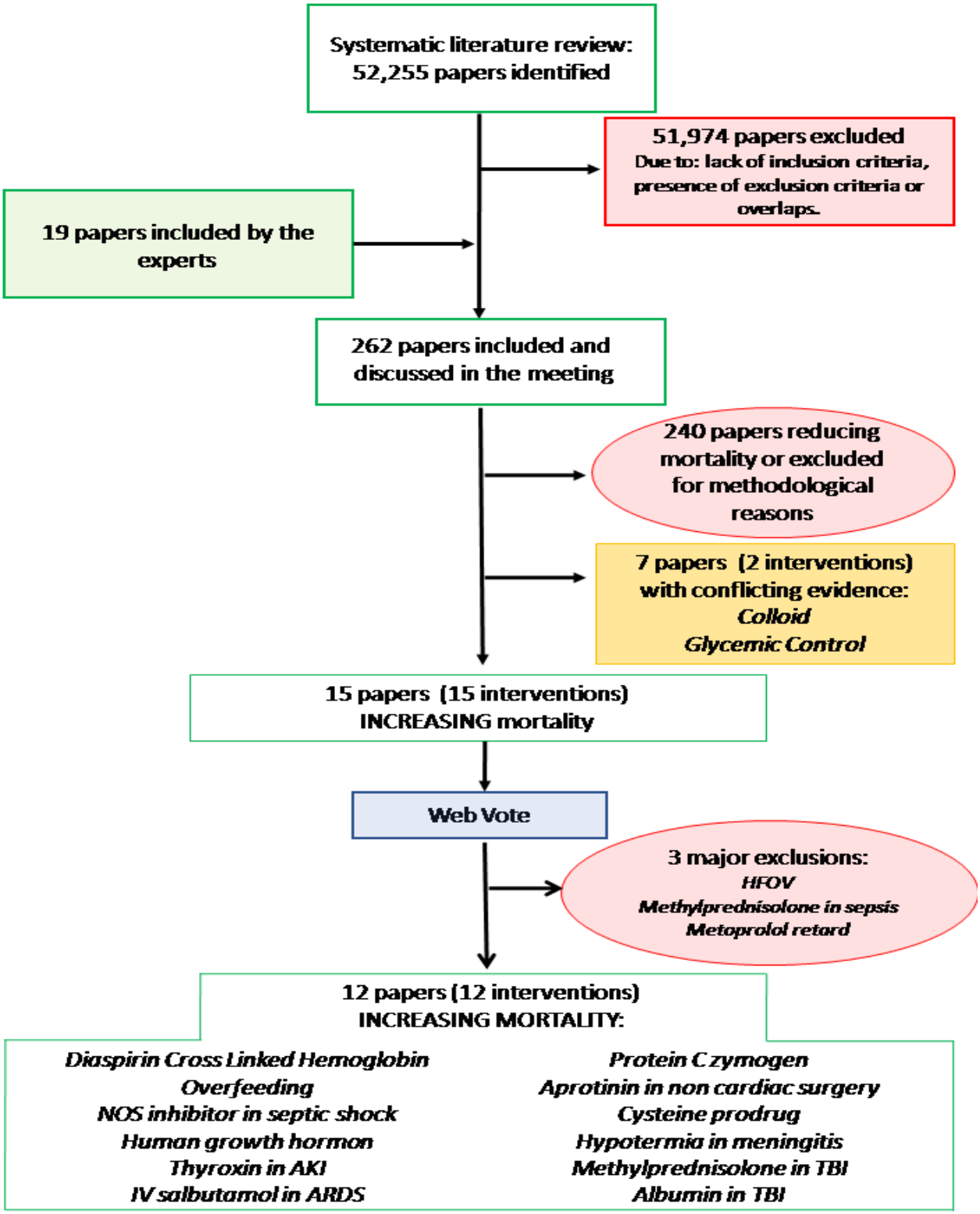

Figure 1. Flow chart of the Consensus Process.

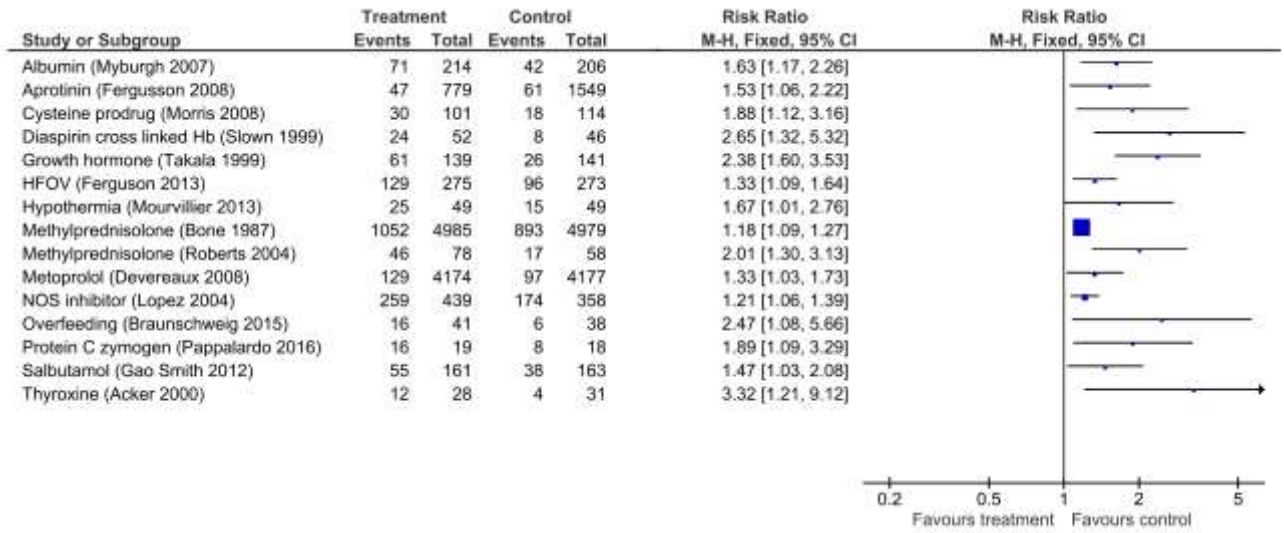

Figure 2. Forest Plot representation of the relative risk for the single interventions.

Table 1. List of the 15 interventions increasing mortality according to at least 1RCT, with the relative percentage of web vote agreement, avoidance and willingness to include the avoidance of the intervention in future guidelines. Grey lines represent the interventions with a web vote agreement < 67%, thus major exclusions interventions.

STATEMENT	AGREEMENT	AVOIDANCE	GUIDELINES
Diaspirin cross linked hemoglobin increases mortality in severe traumatic hemorrhagic shock	92%	77%	78%
Intensive nutrition program (**overfeeding**) increases mortality	88%	81%	82%
Nitric oxide synthase inhibitor 546C88 increases mortality in septic shock	84%	79%	79%
Human growth hormone increases mortality in critically ill patients	83%	84%	79%
Thyroxin for AKI treatment increases mortality in euthyroid intensive care unit patients	81%	79%	74%
Intravenous salbutamol increases mortality in ARDS	81%	76%	76%
Protein C zymogen increases mortality in septic patients	78%	80%	76%
Aprotinin increases 30-days mortality in patients undergoing high-risk cardiac surgery	75%	78%	72%
Cysteine prodrug increases mortality in patients with ARDS	75%	71%	65%
Hypothermia in meningitis increases mortality	72%	75%	75%
Methylprednisolone increases mortality in traumatic brain injury	72%	73%	76%
Albumin increases mortality in traumatic brain injury	72%	70%	71%
High frequency oscillation ventilation increases mortality in ARDS	65%	71%	62%
Methylprednisolone increases mortality **in sepsis** with elevated creatinine levels (>2 mg/dL)	62%	57%	61%
Metoprolol retard increases 30-days mortality in non cardiac surgery	55%	53%	58%

AKI: acute kidney injury; ARDS: acute respiratory distress syndrome

Journal	First author	Year	Intervention	Population	Intervention	Comparator	Sample size	Blinding	Mortality time point	RR [95% CI]
JAMA	Slown EP	1999	Diaspirin cross linked Hb	Severe traumatic hemorragic shock	iv 500 mL diaspirin cross linked Hb	iv 500 mL saline	112	no	28 days	2.65 [1.32 - 5.32]
J Parenter Enteral Nutr	Braunschweig CA	2015	**Overfeeding**	Acute lung injury	Intensive medical nutrition therapy	standard care	78	single	30 days	2.47 [1.08 - 5.66]
Crit Care Med	Lopez A	2004	Nitric oxide synthase inhibitor	Septic shock	Nitric oxide synthase inhibitor	placebo	797	single	28 days	1.21 [1.06 - 1.39]
N Engl J Med	Takala J	1999	**Growth hormone**	Critically ill	Subcutaneous growth hormone	placebo	532	single	in hospital	2.38 [1.60 - 3.53]
Kidney Int	Acker CG	2000	**Thyroxine**	AKI	Thyroxine	placebo	59	single	in hospital	3.32 [1.21 - 9.12]
Lancet	Gao Smith F	2012	**Salbutamol**	ARDS	iv salbutamol	placebo	326	single	28 days	1.47 [1.03 - 2.08]
Intensive Care Med	Pappalardo F	2016	**Protein C zymogen**	Severe sepsis	Protein C zymogen for 72 h	placebo	38	double	30 days	1.89 [1.09 - 3.29]
N Engl J Med	Fergusson DA	2008	**Aprotinin**	Cardiac surgery	Aprotinin	Lysine analogue	2331	single	30 days	1.53 [1.06 - 2.22]

Crit Care Med	Morris PE	2008	**Cysteine prodrug**	ARDS	L-2-oxothiazolidine-4-carboxylic acid	placebo	215	single	30 days	1.88 [1.12 - 3.16]
JAMA	Mourvillier B	2013	**Hypothermia**	Meningitis	Induced hypothermia 34-32° for 48h	standard care	98	single	90 days	1.67 [1.01 - 2.76]
Lancet	Roberts I	2004	**Methylprednisolone**	TBI	iv methylprednisolone for 48 h	placebo	10,008	no	14 days	2.01 [1.30 - 3.13]
N Engl J Med	Myburgh J	2007	**Albumin**	TBI	iv albumin	saline	460	single	24 months	1.63 [1.17 - 2.26]
N Engl J Med	Ferguson ND	2013	**HFOV**	ARDS	HFOV	standard care	548	no	in hospital	1.33 [1.09 - 1.64]
N Engl J Med	Bone RC	1987	**Methylprednisolone**	Sepsis	Methylprednisolone 30 mg/kg, 4 doses	placebo	382	single	14 days	1.18 [1.09 - 1.27]
Lancet	Deveraux PJ	2008	**Metoprolol retard**	Non cardiac surgery	Extended-release metoprolol succinate	placebo	8351	single	30 days	1.33 [1.03 - 1.73]

Table 2. Details of 15 RCTs included in this study: journal of publication, first author, year of publication, intervention, study population, intervention and comparator, trial sample size, presence of blinding, mortality time point and relative risk. Grey lines represent the interventions with a web vote agreement < 67%, thus major exclusions interventions. In bolt the intervention currently available.

AKI: acute kidney injury; ARDS: acute respiratory distress syndrome; Hb: hemoglobin; HFOV: high frequency oscillation ventilation; CI: confidence interval; iv: intravenous; RR: relative risk; TBI: traumatic brain injury

Table 3. Concordance between agreement and avoidance for the 12 interventions increasing mortality and reaching >66% consensus among web voters.

INTERVENTION	CONCORDANCE AGREEMENT/AVOIDANCE %
Methylprednisolone in TBI	90.6%
Overfeeding	89.9%
Salbutamol in ARDS	89.7%
Albumin in TBI	88.0%
Diaspirin cross linked hemoglobin	87.8%
Nitric oxide synthase inhibitor	87.7%
Thyroxine in AKI	87.3%
Hypothermia in meningitis	87.2%
Growth hormone	87.1%
Aprotinin in cardiac surgery	86.8%
Cysteine in ARDS	83.5%
Protein C zymogen in septic shock	80.0%

AKI: acute kidney injury; ARDS: acute respiratory distress syndrome; HFOV: high frequency oscillation ventilation; TBI: traumatic brain injury;

Table 4. Papers with conflicting evidence. Title, journal of publication, first author and year of publication of those papers with conflicting evidence, included in the interventions glycemic control and colloids.

Title	Journal	First Author	Year
Tight glycemic control in diabetic coronary artery bypass graft patients improves perioperative outcomes and decreases recurrent ischemic events.	Circulation	Lazar H. L.	2004
Effects of intensive glycemic control on outcomes of cardiac surgery	Heart Lung	Giakoumidakis K.	2012
Intensive insulin therapy in the critically ill patients	N Engl J Med	Van den Berghe G.	2001
Intensive insulin therapy in the medical ICU	N Engl J Med	Van der Berghe G.	2006
Intensive versus conventional glucose control in critically ill patients.	N Engl J Med	Finfer	2009
Effects of fluid resuscitation with colloids vs crystalloids on mortality in critically ill patients presenting with hypovolemic shock: the CRISTAL randomized trial.	JAMA	Annane D.	2013
Hydroxyethyl starch 130/0.42 versus Ringer's acetate in severe sepsis.	N Engl J Med	Perner A.	2012