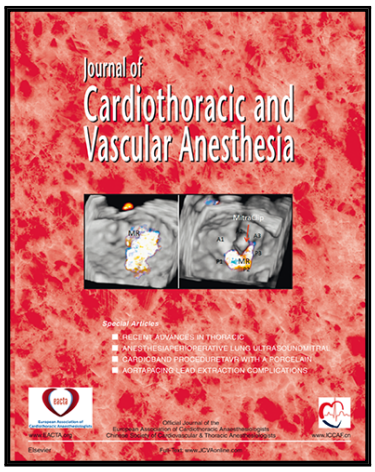


# A Systematic Review and International Web-Based Survey of randomized controlled trials in the perioperative and critical care setting: Interventions reducing mortality.

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Title

# A Systematic Review and International Web-Based Survey of randomized controlled trials in the perioperative and critical care setting: Interventions reducing mortality.

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**Abstract**

**Background**

We aimed to identify interventions documented by randomized controlled trials (RCTs) that reduce mortality in adult critically ill and perioperative patients, followed by a survey of clinicians' opinion and routine practice to understand the clinicians' response to such evidence.

**Methods**

We performed a comprehensive literature review to identify all topics reported to reduce mortality in perioperative and critical care settings according to at least 2 RCTs or to a multicenter RCT or to a single center RCT plus guidelines. We generated position statements that were voted online by physicians worldwide for agreement, use, and willingness to include in international guidelines.

**Results**

From 262 RCTs manuscripts reporting mortality differences in the perioperative and critically ill settings, we selected 27 drugs/techniques/strategies (66 RCTs, most frequently published by NEJM -13 papers-, Lancet -7- and JAMA -5-) with an agreement ≥67% from over 250 physicians (46 countries). Non-invasive ventilation was the intervention supported by the largest number of RCTs (n=13). The concordance between agreement and use (a positive answer both to "do you agree" and "do you use") showed differences between western and other countries and between anesthesiologists and ICU physicians.

**Conclusions**

We identified 27 clinical interventions with randomized evidence of survival benefit and strong clinician support in support of their potential life-saving properties in perioperative and critically ill patients with non-invasive ventilation having the highest level of support. However, clinician views appear affected by specialty and geographical location.

## Introduction

The perioperative care and intensive care unit (ICU) are settings with a high mortality risk[1], and this has led to the performance of several studies with the aim to improve outcomes. High quality scientific clinical research, however, is more difficult to perform in this specific hospital setting, due to practical issues (for example randomization in emergent situations) and ethical issues (for example, lack of patient's informed consent to be included in the study). Multicenter randomized controlled trials (mRCTs) are, therefore, limited in number, with only a few published mRCTs large enough to provide significant information on survival. International guidelines and recommendations exist, but do not cover all the variables encountered by clinicians in clinical practice. Thus, many studies are single-center RCTs (sRCTs), which are easier to perform, but contain many sources of bias[2] affecting the quality of subsequent guidelines. In recent years, democracy-based medicine (DBM)[3] has gained popularity, as this tool allows every physician to agree or not with published evidence based medicine (EBM) findings and to state their routine practice on the identified issue.

Our group has previously performed a review of all the mRCTs showing mortality reduction in critically ill patients[4]. This analysis gathered all multicenter randomized evidence about critically ill patients and focused on mortality. However, the information contained in sRCT was not considered. Interestingly, this analysis found that several treatments of respiratory and/or cardiac dysfunction, including non-invasive ventilation and mild hypothermia for cardiac arrest, might reduce mortality of critically ill patients. Therefore, the identification of factors associated with reduced mortality in critically ill patients may also be important for cardio-thoraco-vascular anesthesiologists and intensive care specialists, as all such patients present impaired cardiovascular and/or respiratory reserve.

In an effort to perform a more comprehensive evaluation of all the elements influencing mortality in critically ill patients, we now performed an updated DBM consensus conference on mortality

reduction in critically ill patients taking into account all existing published randomized evidence.

**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.**

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 reduction 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.

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

Trials demonstrating a statistically significant reduction/increase in mortality in only a subgroup of patients were included, but this limitation was highlighted in the data collection form.

Papers were excluded in case 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 reduction/increase in mortality was identified without reaching the $p<0.05$ level of significance; 4) classification as surgical procedure.

For each topic two experts, a rapporteur and a discussant, were selected 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 the experts. They divided each topic into subtopics if necessary.

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

Topics with a mRCT or with at least two sRCTs or with only one sRCT but supported by guidelines 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 all potential conflicts of interest. There was no sponsor or industry support for this consensus conference.

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

1) Do you agree with the below sentence? 2) Do you routinely use this intervention in your clinical practice? 3) Would you include this intervention into future international guidelines to reduce perioperative/critically ill patient mortality?

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. Value are expressed as frequency and percentage. 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. Statistical significance was assumed for *p* value less than 0.05.

**Analysis after the web vote**

The answers from the web survey were analyzed. Double votes were prevented 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 use/avoidance in clinical practice and the desire to include the intervention in future guidelines were reported. The responders' specialty was considered, to assess whether the management differed among anesthesiologists and intensivists. Further analysis relating to responders' countries were performed to assess whether clinicians'

origin influenced their approach to interventions. For simplification purposes, all countries were divided in 2 groups: western countries and others. The gap between agreement and practice use was also calculated 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 use/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 identified all RCTs ever performed in critically ill patients and the perioperative setting reporting a statistically significant reduction in mortality. The complete list of the 262 identified manuscripts is reported in Supplemental Materials (Table s2) with their subsequent selection shown in the flow chart (Figure 1) and detailed in the Supplemental Materials (Table s1, s4, s5, s6).

The final list of 27 interventions and 66 manuscripts[7-72] which reached consensus after the web vote is presented in table 1 and in supplemental materials (table s3) together with the relative percentage of agreement, use and willingness to include in future guidelines. Non-invasive ventilation was the intervention supported by the largest number of RCTs (n=13) followed by decontamination of the digestive tract (n=5). Nine further topics did not reach the pre-specified 67% agreement among the web voters and are reported in table 2 as major exclusions.

The Journals that more frequently published the 66 selected manuscripts were NEJM (13 papers), Lancet (7) and JAMA (5). Overall, 251 physicians from 46 countries (Figure 2) participated in the web survey. Physicians were divided into three groups: anesthesiologists (n=149), intensive care physicians (n=90) and others (n=12).

The concordance between agreement and use (a positive answer both to “do you agree” and “do you use”) is reported in table 3. There was a statistically significant difference between western and other countries for non-invasive ventilation (NIV) in chronic obstructive pulmonary disease (COPD), tranexamic acid and high flow nasal cannula (HFNC) (Figure s1). Also between anesthesiologists and ICU physicians the difference was significant for early tracheostomy, NIV in respiratory failure, early thrombolysis, and volatile anesthetics in cardiac surgery (Figure s2).

## Discussion

*Key Findings*

We identified all nonsurgical interventions (drugs, techniques, or strategies) with randomized evidence (at least 1 mRCT or 2 sRCTs or 1sRCT supported by guidelines) of a mortality reduction in the setting of adult perioperative or critical care medicine. A web vote among more than 250 physicians from over 40 countries selected the 66 manuscripts (27 interventions) with an agreement of $\geq$67% and showed a variable degree of agreement for clinical use and intention to include in future guidelines of such interventions.

NIV was the most extensively studied and documented intervention to reduce mortality in critically ill patients, with 13 manuscripts grouped into 3 different settings (COPD exacerbation, acute respiratory failure and weaning after extubation). The highest degree of agreement (99%) was observed for early defibrillation in out of hospital cardiac arrest, but ventilation topics were also extremely popular: 99% of agreement for NIV in COPD; 90% for NIV in respiratory failure; 97% for protective ventilation and 96% for prone positioning in severe acute respiratory distress syndrome (ARDS).

The percentage of clinical use was always less than agreement. This implies that costs and logistics have a role in the widespread application of numerous potentially life-saving interventions or that,

as previously suggested[6], there is a gap between medical literature and clinical practice, possibly due to the complexity and heterogeneity of the involved settings.

We also identified differences between western and other countries, suggesting that some interventions are not widespread or not available everywhere. For example, NIV and HFNC had overall high percentage of agreement, but lower concordance between agreement and use in non-western countries. This can be explained only in part by lack of personnel and resources, since tranexamic acid, a cheap drug nowadays included in many guidelines (obstetric hemorrhage, massive trauma bleeding), is significantly less used in non-western countries.

*Relationship to Previous Literature*

Our results could be compared with previous consensus processes conducted by the same authors to identify the interventions that can affect mortality in the perioperative period and in critically ill patients[4-6].

Most of the interventions already discussed in previous consensus processes are growing both in terms of agreement and concordance between agreement and use, suggesting that such evidence is consolidating over time. Exceptions are represented by volatile anesthetics, selective decontamination of the digestive tract and leukocyte depleted blood transfusions, which are losing support.

Several interventions were not reported in previous consensus processes mainly because only supported by non-multicentre studies, supported by recent RTCs, because of upgrading of the current process. They include thrombolysis after acute myocardial infarction/pulmonary embolism (AMI/PE), clopidogrel after AMI, epinephrine in cardiac arrest, amiodarone in cardiac arrest, restrictive inspiratory fraction, underfeeding post-refeeding syndrome, early tracheostomy, goal

directed therapy, HFNC, procalcitonin-guided antibiotics discontinuation, mechanical chest compression devices, vasopressin in cardiac arrest, antithrombin III, and hydrocortisone in sepsis.

Four interventions (hypothermia, intra-aortic balloon pump, remote ischemic preconditioning and locoregional anesthesia) were included in previous consensus conferences but not in the present final short list of 27 included topics because new RCTs had evidence against their use or showed futility.

Notably we had two interventions with "conflicting evidence" (at least one RCT showing mortality decrease and one RCT showing mortality decrease). Insulin (4 RCTs) and colloids (2 RCTs) were very debated during the meeting without reaching consensus.

*Implications for Clinical Practice*

Anesthesiologists and ICU physicians treating surgical and critically ill patients make everyday decisions on which anesthetic techniques to apply, drugs to administer (or avoid), and other nonsurgical strategies to use, often without knowing whether those decisions actually affect survival in their patients. Guidelines can provide useful information, but often do not focus on survival and describe the effect of drugs, techniques and interventions on intermediate outcomes. Through this consensus methodology, all interventions for which there was sufficient, non-conflicting, and widely agreed-upon evidence of an impact on perioperative and critically ill adult patients mortality were identified. Moreover, these results reflect real-world scenarios on a global scale.

Our findings emphasize once again, that the evidence of EBM is often not conclusive, not well defined and sometimes even antithetical. From this perspective, EBM appears to have, in itself, some intrinsic limitations. Therefore, in the "real word", EBM cannot be the only resource for clinicians in their daily decision-making. The democracy-based consensus process, grouping together the opinions of hundreds of clinicians from all over the world, can integrate the other

"tools" (e.g., guidelines, expert opinions, systematic reviews, surveys) and contribute to giving a critical assessment of the available literature by combining the best research evidence with clinical expertise. This "fusion" maybe a useful strategy to assess the interaction between evidence and practice.

*Strengths and Limitations*

We acknowledge that our study presents several limitations. First of all, most of the trials performed in the critical care or high-risk perioperative setting are relative small studies since investigators might have difficulties to enroll a large number of patients in these clinical contexts. To attenuate the risk of including randomized studies at high risk of type I error (such as small single center studies) the authors decided to include in the final statements only interventions demonstrated by at least 2 RCTs or a mRCT or by a single RCT supported by guidelines. We acknowledge that some interventions (e.g. echocardiography, extracorporeal membrane oxygenation) have dramatically changed the way we daily manage our patients but have never been validated in RCTs with mortality outcomes, so we could not include them in this consensus process.

The main strength of this study, however, was the combination of EBM with the DBM, which allowed the authors to really understand the current opinion and therapeutic approaches of clinicians worldwide.

*Conclusions*

We performed a systematic review of all the randomized literature with mortality differences in the perioperative and critically ill settings (262 manuscripts) and we then selected those interventions supported by at least 2 RCTs or a mRCT or by a single RCT plus guidelines. We then surveyed

more than 250 clinicians from 46 countries and further selected 66 manuscripts dealing with 27 interventions with a high percentage of agreement on use and of willingness to include in future guideline. We found that despite overall agreement there were differences in perception and self-reported use between anesthesiologist's and clinicians form western vs. non-western countries. Our findings highlight the complex interaction between evidence, training, culture, resources and geography and suggest the need to investigate the impact of affordable interventions in different settings.

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**Figure Legends:**

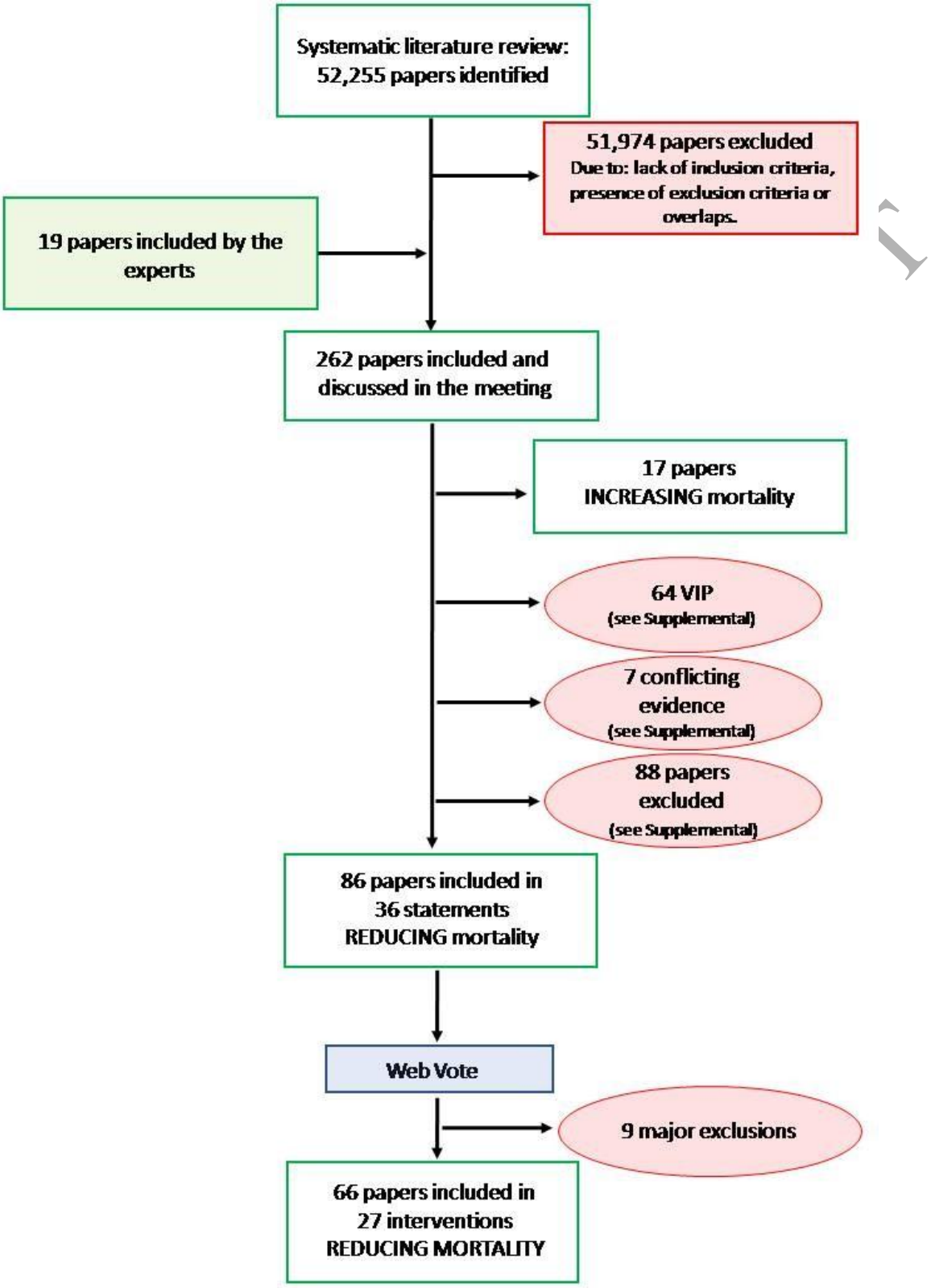


Figure 1: Flow chart of the Consensus process. For details see Supplemental.

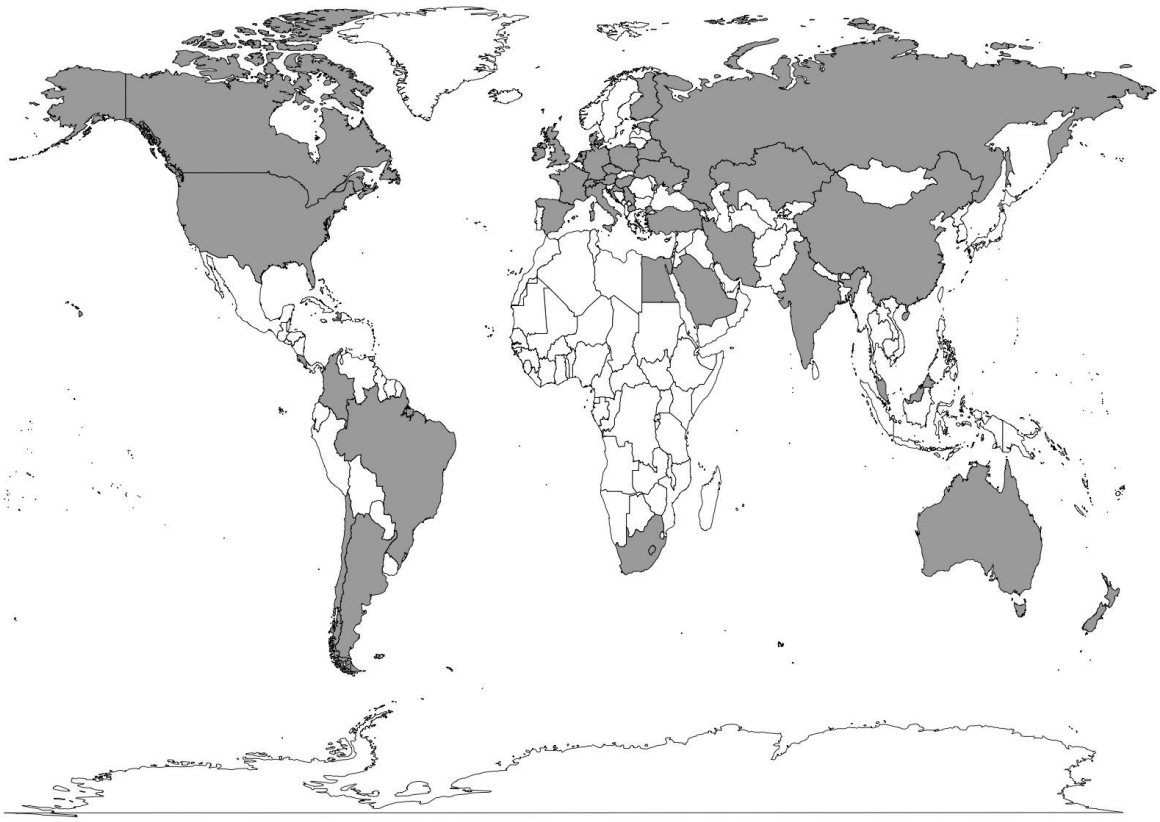

Figure 2: Web Vote countries

Table 1: List of the 27 topics which reached an agreement of >67% in the final web vote together with in order of percentage of agreement ("do you agree with the statement?" and with percentage of reported use ("do you routinely use these interventions in your clinical practice?") and with willingness to have these topics included in future guidelines ("would you include these interventions into future international guidelines to reduce perioperative mortality?").

| STATEMENT | AGREEMENT | USE | GUIDELINES |
|---|---|---|---|
| **Early defibrillation** by trained rescuers reduces hospital mortality in out of hospital cardiac arrest | 99% | 94% | 100% |
| **Non-invasive ventilation** reduces mortality in patients with **chronic obstructive pulmonary disease** | 99% | 96% | 98% |
| **Protective ventilation** with low tidal volumes (6 ml/kg) reduces mortality | 97% | 97% | 97% |
| **Early thrombolytic therapy** in acute myocardial infarction and pulmonary embolism reduces mortality | 96% | 85% | 94% |
| **Prone positioning** reduces mortality in early severe acute respiratory distress syndrome patients (P/F< 150) especially if it is used early and in relatively long sessions (17-18 hours) | 96% | 79% | 94% |
| **Tranexamic acid** in traumatic bleeding patients reduces 28-day mortality | 95% | 86% | 92% |
| **Clopidogrel** reduces mortality after acute myocardial infarction | 93% | 87% | 90% |
| **Avoidance of deep sedation** reduces mortality | 93% | 90% | 94% |
| **Non-invasive ventilation** reduces mortality in **acute respiratory failure** in patients with pulmonary edema and/or hypoxemic-hypercapnic respiratory failure | 90% | 89% | 92% |
| **Albumin** reduces mortality in patients with cirrhosis and spontaneous bacterial peritonitis | 88% | 82% | 88% |
| **Non-invasive ventilation** reduces mortality during the **weaning** after extubation | 86% | 81% | 88% |
| **Epinephrine** reduces mortality in cardiac arrest | 84% | 94% | 92% |
| **Amiodarone** reduces mortality to hospital admission in out-of-hospital cardiopulmonary resuscitation | 83% | 71% | 81% |
| **Restrictive inspiratory oxygen fraction** reduces mortality in intensive care unit patients and in the perioperative setting | 83% | 70% | 70% |
| **Underfeeding** reduces mortality **in** patients with **refeeding** syndrome | 82% | 68% | 82% |
| **Volatile** anaesthetics reduce mortality in cardiac surgery | 81% | 78% | 78% |

| | | | |
|---|---|---|---|
| **Early tracheostomy** in severe stroke and early percutaneous tracheotomy in medical patients requiring prolonged ventilation (>14 days) reduce mortality | 80% | 75% | 79% |
| **Leukocyte-depleted blood transfusions** reduce mortality in cardiac surgery | 79% | 59% | 79% |
| **Goal directed therapy** reduces hospital mortality in patients with septic shock | 77% | 76% | 79% |
| **High flow nasal cannulae** reduces mortality in patients with acute respiratory failure | 77% | 61% | 75% |
| **Procalcitonin**-guided antibiotic discontinuation reduces mortality of critically ill patients | 76% | 61% | 75% |
| **Mechanical chest compression** devices reduce short term mortality in cardiac arrest | 75% | 50% | 75% |
| **Selective decontamination** of the digestive tract reduces mortality of critically ill patients | 74% | 32% | 66% |
| **Vasopressin** with or without steroids reduces mortality cardiac arrest patients | 70% | 34% | 65% |
| **Levosimendan** reduces mortality in patients with cardiogenic shock and low cardiac output syndrome | 70% | 57% | 66% |
| **Antithrombin III** reduces mortality in septic and burn injured patients | 67% | 33% | 62% |
| **Hydrocortisone** reduces mortality in septic shock | 67% | 66% | 70% |

**Table 2: Major Exclusions after the Web Vote. These topics did not reach 67% of agreement. Here are listed as Pubmed identification number (PM ID), journal of publication, first author, year of publication, relative statement approved during the meeting and percentage of agreement after the web vote.**

| PM ID | JOURNAL | FIRST | YEAR | STATEMENT | AGREEMENT |
|---|---|---|---|---|---|
| 15333422 | Anesth. Analg | Crimi et al. | 2004 | **Vitamin C** reduces mortality in ICU patients | 59% |
| 27162802 | J Res Pharm Pract. | Zabet et al. | 2016 | | |
| 15557131 | Am. J. Respir. Crit. Care Med. | Confalonieri et al. | 2004 | **Hydrocortisone** reduces mortality in community acquired pneumonia | 54% |
| 11574732 | Blood Purif. | Nemoto et al. | 2001 | **Polymyxin B fibers** reduce mortality | 52% |
| 12495686 | J. Hosp. Infect | Nakamura et al. | 2003 | | |
| 19531784 | JAMA | Cruz et al. | 2009 | | |
| 24108526 | JAMA | Morelli et al. | 2013 | **Esmolol** reduces mortality in patients with septic shock | 51% |
| 26955704 | Zhonghua Yi Shi Za Zhi | Xinqiang et al. | 2015 | | |
| 26387030 | Clin Drug Investig | Wang et al. | 2015 | | |
| 19934423 | JAMA | Olasveengen et al. | 2009 | **Atropine** reduces mortality to hospital admission in out of hospital cardiac arrest | 49% |
| 17804841 | N. Engl. J. Med. | Corwin et al. | 2007 | **Erythropoietin** reduces mortality in critically ill (including trauma) patients, especially those with APACHE score <20 | 47% |
| 12472324 | JAMA | Corwin et al. | 2002 | | |
| 25586270 | Acta Orthop | Gregersen et al. | 2015 | A **liberal red blood cell transfusion** strategy reduces mortality in cardiac and non cardiac surgery | 36% |
| 25401417 | Anesthesiology | de Almeida et al. | 2015 | | |
| 25760354 | N. Engl. J. Med. | Sloan et al. | 2015 | | |
| 17095947 | Crit. Care Med. | Angstwurm et al. | 2007 | **Selenium** reduces mortality in patients with sepsis | 33% |
| 3307570 | Am. Rev. Respir. Dis. | Eisenberg et al. | 1987 | The use of **pulmonary artery catheter** reduces mortality in critically ill patients | 27% |
| 1929610 | Ann. Surg. | Berlauk et al. | 1991 | | |
| 3191758 | Chest | Shoemakeret al. | 1988 | | |
| 20926981 | Shock | Yu et al. | 2011 | | |

**Table 3: Concordance between agreement and use for all topics reaching > 67% of agreement after the Web Vote.**

| TOPIC | CONCORDANCE agreement/self-reported actual use % |
|---|---|
| Protective ventilation | 98 |
| NIV in COPD | 97 |
| NIV in pulmonary edema and hypoxemic/hypercapnic RF | 93 |
| Early defibrillation | 93 |
| Avoidance of deep sedation | 93 |
| Goal directed therapy in septic shock | 93 |
| Clopidogrel AMI | 91 |
| Tranexamic acid in traumatic bleeding | 90 |
| NIV after extubation | 89 |
| Early tracheostomy | 88 |
| Underfeeding post refeeding syndrome | 88 |
| Albumin in cirrhosis | 88 |
| Early thrombolysis in AMI/PE | 87 |
| Restrictive $FiO_2$ | 87 |
| Epinephrine in cardiac arrest | 87 |
| Volatile anesthetics in cardiac surgery | 84 |
| Prone positioning in severe ARDS | 83 |
| Amiodarone CPR | 82 |
| Hydrocortisone in septic shock | 81 |
| Levosimendan cardiogenic shock | 80 |
| Procalcitonin guided antibiotics | 80 |
| Leucocyte deplete blood in cardiac surgery | 79 |
| Mechanical chest compression | 76 |
| High flow nasal cannulae in ARF | 75 |
| Antithrombin III in septic and burned | 74 |
| Vasopressin in cardiac arrest | 70 |
| Selective decontamination | 62 |

AMI: acute myocardial injury; ARDS: acute respiratory distress syndrome; ARF: acute respiratory failure; CPR: cardiopulmonary resuscitation; COPD: chronic obstructive pulmonary disease; $FiO_2$: inspiratory oxygen fraction; NIV: non-invasive ventilation; PE: pulmonary embolism