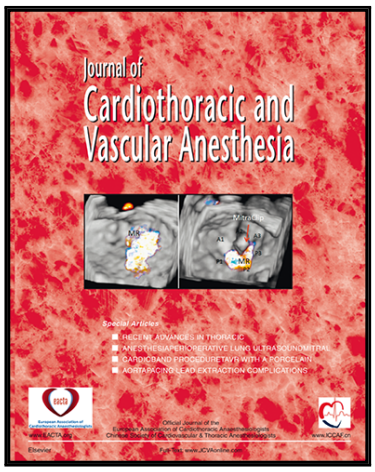
View metadata, citation and similar papers at core.ac.uk

brought to you by CORE

provided by Archivio della Ricerca - Università di Pisa

Accepted Manuscript



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

Chiara Sartini MD , Vladimir Lomivorotov MD , Pieri Marina MD , Juan Carlos Lopez Delgado MD , Baiardo Redaelli Martina MD , Ludhmila Hajjar MD , Antonio Pisano MD , Valery Likhvantsev MD , Evgeny Fominskiy MD , Nikola Bradic MD , Cabrini Luca MD , Maxim Novikov MD , Avancini Daniele PhD , Riha Hynek MD , Rosalba Lembo MSc , Gordana Gazivoda MD , Gianluca Paternoster MD , Chengbin Wang MD , Simona Tamà MD , Gabriele Alvaro MD , Wang Chew Yin MD , Agostino Roasio MD , Ruggeri Laura MD , Chow-Yen Yong MD , Pasero Daniela MD , Luca Severi MD , Pasin Laura MD , Giuseppe Mancino MD , Paolo Mura MD , Mario Musu MD , Spadaro Savino MD , Massimiliano Conte MD , Lobreglio Rosetta MD , Silvetti Simona MD , Votta Carmine Domenico MD , Belletti Alessandro MD , Di Fraja Diana MD , Francesco Corradi MD , Claudia Brusasco MD , Manuela Saporito MD , Alessandro D'Amico MD , Sardo Salvatore MD , Ortalda Alessandro MD , Claudio Riefolo MSc , Monaco Fabrizio MD , Zangrillo Alberto MD , Bellomo Rinaldo MD , Landoni Giovanni MD

PII: S1053-0770(18)31044-9
DOI: https://doi.org/10.1053/j.jvca.2018.11.026
Reference: YJCAN 5001

To appear in: *Journal of Cardiothoracic and Vascular Anesthesia*

Please cite this article as: Chiara Sartini MD , Vladimir Lomivorotov MD , Pieri Marina MD , Juan Carlos Lopez Delgado MD , Baiardo Redaelli Martina MD , Ludhmila Hajjar MD , Antonio Pisano MD , Valery Likhvantsev MD , Evgeny Fominskiy MD , Nikola Bradic MD , Cabrini Luca MD , Maxim Novikov MD , Avancini Daniele PhD , Riha Hynek MD , Rosalba Lembo MSc , Gordana Gazivoda MD , Gianluca Paternoster MD , Chengbin Wang MD , Simona Tamà MD , Gabriele Alvaro MD , Wang Chew Yin MD , Agostino Roasio MD , Ruggeri Laura MD , Chow-Yen Yong MD , Pasero Daniela MD , Luca Severi MD , Pasin Laura MD , Giuseppe Mancino MD , Paolo Mura MD , Mario Musu MD , Spadaro Savino MD , Massimiliano Conte MD , Lobreglio Rosetta MD , Silvetti Simona MD , Votta Carmine Domenico MD , Belletti Alessandro MD , Di Fraja Diana MD , Francesco Corradi MD , Claudia Brusasco MD , Manuela Saporito MD , Alessandro D'Amico MD , Sardo Salvatore MD , Ortalda Alessandro MD , Claudio Riefolo MSc , Monaco Fabrizio MD , Zangrillo Alberto MD , Bellomo Rinaldo MD , Landoni Giovanni MD , A Systematic Review and International Web-Based Survey of randomized controlled trials in the perioperative and critical care

setting: Interventions reducing mortality., *Journal of Cardiothoracic and Vascular Anesthesia* (2018), doi: https://doi.org/10.1053/j.jvca.2018.11.026

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

ACCEPTED MANUSCRIPT

Title

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

Authors

Chiara Sartini, MD[a], Vladimir Lomivorotov, MD[b], Pieri Marina, MD[a], Juan Carlos Lopez Delgado, MD[c], Baiardo Redaelli Martina, MD[a], Ludhmila Hajjar, MD[d], Antonio Pisano, MD[e], Valery Likhvantsev , MD[f], Evgeny Fominskiy, MD[a], Nikola Bradic, MD[g], Cabrini Luca, MD[a], Maxim Novikov, MD[h], Avancini Daniele, PhD[i], Riha Hynek, MD[j], Rosalba Lembo, MSc[a], Gordana Gazivoda, MD[k], Gianluca Paternoster, MD[l], Chengbin Wang, MD[m], Simona Tamà, MD[a], Gabriele Alvaro, MD[n], Wang Chew Yin, MD[o], Agostino Roasio, MD[p], Ruggeri Laura, MD[a], Chow-Yen Yong, MD[q], Pasero Daniela, MD[r], Luca Severi, MD[s], Pasin Laura, MD[t], Giuseppe Mancino, MD[u], Paolo Mura, MD[v], Mario Musu, MD[w], Spadaro Savino, MD[x], Massimiliano Conte, MD[y], Lobreglio Rosetta, MD[z], Silvetti Simona, MD[aa], Votta Carmine Domenico, MD[a], Belletti Alessandro, MD[a], Di Fraja Diana, MD[e], Francesco Corradi, MD[ab], Claudia Brusasco, MD[ab], Manuela Saporito, MD[n], Alessandro D'Amico, MD[n], Sardo Salvatore, MD[w], Ortalda Alessandro, MD[a], Claudio Riefolo, MSc, Monaco Fabrizio, MD[a], Zangrillo Alberto, MD[a], Bellomo Rinaldo, MD[ad], Landoni Giovanni, MD[a].

Declaration of interests: none.

a. Department of Anesthesia and Intensive Care, IRCCS San Raffaele Scientific Institute, Milan, Italy; Vita-Salute San Raffaele University, Milan

b. E. Meshalkin National Medical Research Center, Novosibirsk

c. Hospital Universitari de Bellvitge - Barcelona

d. Instituto do Coracao do Hospital das Clinicas - Sao Paulo

ACCEPTED MANUSCRIPT

e. Division of Cardiac Anesthesia and Intensive Care Unit, AORN dei Colli - Monaldi Hospital, Naples

f. Moscow Regional Research and Clinical Institute, Moscow

g. Department of Cardiovascular Anesthesiology and Cardiac Intensive Medicine, University Hospital Dubrava, Zagreb

h. Saint Petersburg State University, Saint Petersburg

i. San Raffaele Telethon Institute for Gene Therapy (SR-Tiget), IRCCS San Raffaele Scientific Institute

j. Institute for Clinical and Experimental Medicine, Prague

k.Institute of Cardiovascular Diseases "Dedinje", Belgrade

l. Ospedale San Carlo, Potenza

m. Center for Anesthesiology, Beijing Anzhen Hospital, Capital Medical University, Beijing

n. AOU Mater Domini Germaneto, Catanzaro

o. Anaesthesia and Intensive Care, University of Malaya, Kuala Lumpur

p. Department of Anaesthesia and Intensive Care, Ospedale Cardinal Massaia di Asti, Asti

q. Anaesthesia and Intensive Care, Hospital Pulau Pinang, Georgetown

r. Department of Anesthesia and Intensive Care, A.O.U. Città della Salute e della Scienza, Turin

s. Anesthesia and Intensive Care, Azienda Ospedaliera San Camillo Forlanini, Roma

t. S. Antonio Hospital, Padova

u. Hospital Santa Chiara, Pisa

v. Department of Anesthesia and Intensive Care Unit, Policlinico Duilio Casula AOU Cagliari,

w. University of Cagliari, Cagliari

x. University of Ferrara, Ferrara

ACCEPTED MANUSCRIPT

ACCEPTED MANUSCRIPT

y. Mater Dei Hospital, Bari

z. AOU Città della Salute e della Scienza - Molinette, Torino

aa.IRCCS Istituto Giannina Gaslini - Ospedale Pediatrico, Genoa

ab. E.O. Ospedali Galliera, Genova

ac.Azienda Ospedaliera Mater Domini

ad. Monash University

Corresponding author

Giovanni Landoni, MD, Associate Prof

Department of Anesthesia and Intensive Care

IRCCS San Raffaele Scientific Institute

Vita-Salute San Raffaele University

Via Olgettina 60, 20132 Milan, Italy

Email: landoni.giovanni@hsr.it

Phone: 0039-0226436158

Fax: 0039-022643615277

ACCEPTED MANUSCRIPT

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

ACCEPTED MANUSCRIPT

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.

ACCEPTED MANUSCRIPT

ACCEPTED MANUSCRIPT

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

ACCEPTED MANUSCRIPT

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.

ACCEPTED MANUSCRIPT

ACCEPTED MANUSCRIPT

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).

ACCEPTED MANUSCRIPT

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,

ACCEPTED MANUSCRIPT

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

ACCEPTED MANUSCRIPT

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

ACCEPTED MANUSCRIPT

"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

ACCEPTED MANUSCRIPT

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.

Acknowledgments

We thank Maieutics Foundation for sharing the technical expertise for the voting process; dr. Gaetano Lombardi, dr. Federica Morselli, Lara Sussani, Paola Zuppelli, dr. Kim Jun Hyun and dr. Ádám Nagy for their important collaboration in all stages of this paper.

References

1. Mayr VD, Dünser MW, Greil V, et al.: Causes of death and determinants of outcome in critically ill patients. Critical Care 10, 2006

2. Bellomo R, Warrillow SJ, Reade MC. Why we should be wary of single-center trials. Crit Care Med 37:3114-3119, 2009

3. Greco M, Zangrillo A, Mucchetti M, et al.: Democracy-Based Consensus in Medicine. Journal of Cardiothoracic and Vascular Anesthesia 29:506-509, 2015

ACCEPTED MANUSCRIPT

4. Landoni G, Comis M, Conte M, et al.: Mortality in Multicenter Critical Care Trials: An Analysis of Interventions With a Significant Effect*. Critical Care Medicine 43:1559, 2015

5. Pisano A, Landoni G, Lomivorotov V, et al.: Worldwide Opinion on Multicenter Randomized Interventions Showing Mortality Reduction in Critically Ill Patients: A Democracy-Based Medicine Approach. Journal of Cardiothoracic and Vascular Anesthesia 30:1386-1395, 2016

6. Landoni G, Pisano A, Lomivorotov V, et al.: Randomized Evidence for Reduction of Perioperative Mortality: An Updated Consensus Process. Journal of Cardiothoracic and Vascular Anesthesia 31:719-730, 2017

7. Sort P, Navasa M, Arroyo V, et al.: Effect of intravenous albumin on renal impairment and mortality in patients with cirrhosis and spontaneous bacterial peritonitis. The New England journal of medicine 341:403-409, 1999

8. Dorian P, Cass D, Schwartz B, Cooper R, Gelaznikas R, Barr A. Amiodarone as compared with lidocaine for shock-resistant ventricular fibrillation. The New England journal of medicine 346:884-890, 2002

9. Kudenchuk PJ, Brown SP, Daya M, et al.: Amiodarone, Lidocaine, or Placebo in Out-of-Hospital Cardiac Arrest. The New England Journal of Medicine 374:1711-1722, 2016

10. Kudenchuk PJ, Cobb LA, Copass MK, et al.: Amiodarone for resuscitation after out-of-hospital cardiac arrest due to ventricular fibrillation. The New England journal of medicine 341:871-878, 1999

ACCEPTED MANUSCRIPT

ACCEPTED MANUSCRIPT

11. Baudo F, Caimi TM, deCataldo F, et al.: Antithrombin III (ATILL) replacement therapy in patients with sepsis and/or postsurgical complications: a controlled double-blind, randomized, multicenter study. Intensive Care Medicine 24:336-342, 1998

12. Lavrentieva A, Kontakiotis T, Bitzani M, et al.: The efficacy of antithrombin administration in the acute phase of burn injury. Thrombosis and Haemostasis 100:286-290, 2008

13. Warren BL, Eid A, Singer P, et al.: Caring for the critically ill patient. High-dose antithrombin III in severe sepsis: a randomized controlled trial. JAMA 286:1869-1878, 2001

14. Chen ZM, Jiang LX, Chen YP, et al.: Addition of clopidogrel to aspirin in 45,852 patients with acute myocardial infarction: randomised placebo-controlled trial. Lancet 366:1607-1621, 2005

15. de Jonge E, Schultz MJ, Spanjaard L, et al.: Effects of selective decontamination of digestive tract on mortality and acquisition of resistant bacteria in intensive care: a randomised controlled trial. The Lancet 362:1011-1016, 2003

16. de Cal MA, Cerdá E, García-Hierro P, et al.: Survival Benefit in Critically Ill Burned Patients Receiving Selective Decontamination of the Digestive Tract: A Randomized, Placebo-Controlled, Double-Blind Trial. Annals of Surgery 241:424, 2005

17. Krueger WA, Lenhart F-P, Neeser G, et al.: Influence of Combined Intravenous and Topical Antibiotic Prophylaxis on the Incidence of Infections, Organ Dysfunctions, and

ACCEPTED MANUSCRIPT

ACCEPTED MANUSCRIPT

Mortality in Critically Ill Surgical Patients. American Journal of Respiratory and Critical Care Medicine 166:1029-1037, 2002

18. Rocha LA, Martín MJ, Pita S, et al.: Prevention of nosocomial infection in critically ill patients by selective decontamination of the digestive tract. Intensive Care Medicine 18:398-404, 1992

19. Ulrich C, Weerd H-dJE, Bakker NC, Jacz K, Doornbos L, de Ridder VA. Selective decontamination of the digestive tract with norfloxacin in the prevention of ICU-acquired infections: a prospective randomized study. Intensive Care Medicine 15:424-431, 1989

20. Eisenberg MS, Hallstrom AP, Copass MK, Bergner L, Short F, Pierce J. Treatment of ventricular fibrillation. Emergency medical technician defibrillation and paramedic services. JAMA 251:1723-1726, 1984

21. Hallstrom AP, Ornato JP, Weisfeldt M, et al.: Public-access defibrillation and survival after out-of-hospital cardiac arrest. The New England journal of medicine 351:637-646, 2004

22. Jacobs IG, Finn JC, Jelinek GA, Oxer HF, Thompson PL. Effect of adrenaline on survival in out-of-hospital cardiac arrest: A randomised double-blind placebo-controlled trial. Resuscitation 82:1138-1143, 2011

23. Lin S-M, Huang C-D, Lin H-C, Liu C-Y, Wang C-H, Kuo H-P. A MODIFIED GOAL-DIRECTED PROTOCOL IMPROVES CLINICAL OUTCOMES IN INTENSIVE CARE UNIT PATIENTS WITH SEPTIC SHOCK: A RANDOMIZED CONTROLLED TRIAL. Shock 26:551, 2006

ACCEPTED MANUSCRIPT

ACCEPTED MANUSCRIPT

24. Rivers E, Nguyen B, Havstad S, et al.: Early goal-directed therapy in the treatment of severe sepsis and septic shock. The New England journal of medicine 345:1368-1377, 2001

25. Frat J-P, Thille AW, Mercat A, et al.: High-Flow Oxygen through Nasal Cannula in Acute Hypoxemic Respiratory Failure. The New England Journal of Medicine 372:2185-2196, 2015

26. Annane D, Sébille V, Charpentier C, et al.: Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. JAMA 288:862-871, 2002

27. Bilgin YM, van de Watering LMG, Eijsman L, et al.: Double-Blind, Randomized Controlled Trial on the Effect of Leukocyte-Depleted Erythrocyte Transfusions in Cardiac Valve Surgery. Circulation 109:2755-2760, 2004

28. van de Watering LM, Hermans J, Houbiers JG, et al.: Beneficial effects of leukocyte depletion of transfused blood on postoperative complications in patients undergoing cardiac surgery: a randomized clinical trial. Circulation 97:562-568, 1998

29. Fuhrmann JT, Schmeisser A, Schulze MR, et al.: Levosimendan is superior to enoximone in refractory cardiogenic shock complicating acute myocardial infarction*. Critical Care Medicine 36:2257, 2008

30. Levin RL, Degrange MA, Porcile R, et al.: [The calcium sensitizer levosimendan gives superior results to dobutamine in postoperative low cardiac output syndrome]. Revista espanola de cardiologia 61:471-479, 2008

ACCEPTED MANUSCRIPT

31. Cohen TJ, Goldner BG, Maccaro PC, et al.: A comparison of active compression-decompression cardiopulmonary resuscitation with standard cardiopulmonary resuscitation for cardiac arrests occurring in the hospital. The New England journal of medicine 329:1918-1921, 1993

32. Gao C, Chen Y, Peng H, Chen Y, Zhuang Y, Zhou S. Clinical evaluation of the AutoPulse automated chest compression device for out-of-hospital cardiac arrest in the northern district of Shanghai, China. Archives of Medical Science 3:563-570, 2016

33. Tucker KJ, Galli F, Savitt MA, Kahsai D, Bresnahan L, Redberg RF. Active compression-decompression resuscitation: effect on resuscitation success after in-hospital cardiac arrest. Journal of the American College of Cardiology 24:201-209, 1994

34. Wolcke BB, Mauer DK, Schoefmann MF, et al.: Comparison of standard cardiopulmonary resuscitation versus the combination of active compression-decompression cardiopulmonary resuscitation and an inspiratory impedance threshold device for out-of-hospital cardiac arrest. Circulation 108:2201-2205, 2003

35. Ferrer M, Esquinas A, Leon M, Gonzalez G, Alarcon A, Torres A. Noninvasive Ventilation in Severe Hypoxemic Respiratory Failure. American Journal of Respiratory and Critical Care Medicine 168:1438-1444, 2003

36. L'Her E, Duquesne F, Girou E, et al.: Noninvasive continuous positive airway pressure in elderly cardiogenic pulmonary edema patients. Intensive Care Medicine 30:882-888, 2004

ACCEPTED MANUSCRIPT

ACCEPTED MANUSCRIPT

37. Nava S, Grassi M, Fanfulla F, et al.: Non-invasive ventilation in elderly patients with acute hypercapnic respiratory failure: a randomised controlled trial. Age and Ageing 40:444-450, 2011

38. Park M, Sangean MC, de Volpe MS, et al.: Randomized, prospective trial of oxygen, continuous positive airway pressure, and bilevel positive airway pressure by face mask in acute cardiogenic pulmonary edema*. Critical Care Medicine 32:2407, 2004

39. Thompson J, Petrie DA, Ackroyd-Stolarz S, Bardua DJ. Out-of-Hospital Continuous Positive Airway Pressure Ventilation Versus Usual Care in Acute Respiratory Failure: A Randomized Controlled Trial. Annals of Emergency Medicine 52:232-2410, 2008

40. Zhu G-fF, Wang D-jJ, Liu S, Jia M, Jia S-jJ. Efficacy and safety of noninvasive positive pressure ventilation in the treatment of acute respiratory failure after cardiac surgery. Chinese medical journal 126:4463-4469, 2013

41. Brochard L, Mancebo J, Wysocki M, et al.: Noninvasive ventilation for acute exacerbations of chronic obstructive pulmonary disease. The New England journal of medicine 333:817-822, 1995

42. Ferrer M, Valencia M, Nicolas J, Bernadich O, Badia J, Torres A. Early Noninvasive Ventilation Averts Extubation Failure in Patients at Risk. American Journal of Respiratory and Critical Care Medicine 173:164-170, 2006

43. Ferrer M, Sellarés J, Valencia M, et al.: Non-invasive ventilation after extubation in hypercapnic patients with chronic respiratory disorders: randomised controlled trial. Lancet (London, England) 374:1082-1088, 2009

ACCEPTED MANUSCRIPT

ACCEPTED MANUSCRIPT

44. Ferrer M, Esquinas A, Arancibia F, et al.: Noninvasive Ventilation during Persistent Weaning Failure. American Journal of Respiratory and Critical Care Medicine 168:70-76, 2003

45. Nava S, Ambrosino N, Clini E, et al.: Noninvasive mechanical ventilation in the weaning of patients with respiratory failure due to chronic obstructive pulmonary disease. A randomized, controlled trial. Annals of internal medicine 128:721-728, 1998

46. Ornico SR, Lobo SM, Sanches HS, et al.: Noninvasive ventilation immediately after extubation improves weaning outcome after acute respiratory failure: a randomized controlled trial. Critical Care 17, 2013

47. Plant PK, Owen JL, Elliott MW. Early use of non-invasive ventilation for acute exacerbations of chronic obstructive pulmonary disease on general respiratory wards: a multicentre randomised controlled trial. The Lancet 355:1931-1935, 2000

48. de Jong E, van Oers JA, Beishuizen A, et al.: Efficacy and safety of procalcitonin guidance in reducing the duration of antibiotic treatment in critically ill patients: a randomised, controlled, open-label trial. The Lancet Infectious Diseases 16:819-827, 2016

49. Gattinoni L, Tognoni G, Pesenti A, et al.: Effect of prone positioning on the survival of patients with acute respiratory failure. The New England journal of medicine 345:568-573, 2001

50. Guérin C, Reignier J, Richard J-C, et al.: Prone Positioning in Severe Acute Respiratory Distress Syndrome. The New England Journal of Medicine 368:2159-2168, 2013

ACCEPTED MANUSCRIPT

ACCEPTED MANUSCRIPT

51. Mancebo J, Fernández R, Blanch L, et al.: A Multicenter Trial of Prolonged Prone Ventilation in Severe Acute Respiratory Distress Syndrome. American Journal of Respiratory and Critical Care Medicine 173:1233-1239, 2006

52. Amato MB, Barbas CS, Medeiros DM, et al.: Effect of a protective-ventilation strategy on mortality in the acute respiratory distress syndrome. The New England journal of medicine 338:347-354, 1998

53. Brower RG, Matthay MA, Morris A, Schoenfeld D, Thompson BT, Wheeler A. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The New England journal of medicine 342:1301-1308, 2000

54. Villar J, Kacmarek RM, Pérez-Méndez L, Aguirre-Jaime A, Network A. A high positive end-expiratory pressure, low tidal volume ventilatory strategy improves outcome in persistent acute respiratory distress syndrome: A randomized, controlled trial*. Critical Care Medicine 34:1311, 2006

55. Girardis M, Busani S, Damiani E, et al.: Effect of Conservative vs Conventional Oxygen Therapy on Mortality Among Patients in an Intensive Care Unit: The Oxygen-ICU Randomized Clinical Trial. JAMA, 2016

56. Meyhoff CS, Jorgensen LN, Wetterslev J, Christensen KB, Rasmussen LS, Group P. Increased Long-Term Mortality After a High Perioperative Inspiratory Oxygen Fraction During Abdominal Surgery: Follow-Up of a Randomized Clinical Trial. Anesthesia & Analgesia 115:849, 2012

ACCEPTED MANUSCRIPT

57. Brown CHIV, Azman AS, Gottschalk A, Mears SC, Sieber FE. Sedation Depth During Spinal Anesthesia and Survival in Elderly Patients Undergoing Hip Fracture Repair. Anesthesia & Analgesia 118:977, 2014

58. Girard TD, Kress JP, Fuchs BD, et al.: Efficacy and safety of a paired sedation and ventilator weaning protocol for mechanically ventilated patients in intensive care (Awakening and Breathing Controlled trial): a randomised controlled trial. The Lancet 371:126-134, 2008

59. Mansouri P, Javadpour S, Zand F, et al.: Implementation of a protocol for integrated management of pain, agitation, and delirium can improve clinical outcomes in the intensive care unit: A randomized clinical trial. Journal of Critical Care 28:918-922, 2013

60. Feasibility, safety, and efficacy of domiciliary thrombolysis by general practitioners: Grampian region early anistreplase trial. GREAT Group. BMJ 305:548-553, 1992

61. Jerjes-Sanchez C, Ramírez-Rivera A, de García M, et al.: Streptokinase and heparin versus heparin alone in massive pulmonary embolism: A randomized controlled trial. Journal of Thrombosis and Thrombolysis 2:227-229, 1995

62. Rawles JM. Quantification of the benefit of earlier thrombolytic therapy: five-year results of the Grampian Region Early Anistreplase Trial (GREAT). Journal of the American College of Cardiology 30:1181-1186, 1997

63. Sarullo FM, Schicchi R, Schirò M, et al.: [The safety and efficacy of systemic salvage thrombolysis in acute myocardial infarct]. Italian heart journal Supplement : official journal of the Italian Federation of Cardiology 1:81-87, 2000

ACCEPTED MANUSCRIPT

64. Bosel J, Schiller P, Hook Y, et al.: Stroke-related Early Tracheostomy versus Prolonged Orotracheal Intubation in Neurocritical Care Trial (SETPOINT): a randomized pilot trial. Stroke 44:21-28, 2013

65. Rumbak MJ, Newton M, Truncale T, Schwartz SW, Adams JW, Hazard PB. A prospective, randomized, study comparing early percutaneous dilational tracheotomy to prolonged translaryngeal intubation (delayed tracheotomy) in critically ill medical patients*. Critical Care Medicine 32:1689, 2004

66. trial collaborators C, Shakur H, Roberts I, et al.: Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial. Lancet (London, England) 376:23-32, 2010

67. Doig GS, Simpson F, Heighes PT, et al.: Restricted versus continued standard caloric intake during the management of refeeding syndrome in critically ill adults: a randomised, parallel-group, multicentre, single-blind controlled trial. The Lancet Respiratory medicine 3:943-952, 2015

68. Lindner KH, Dirks B, Strohmenger H-U, Prengel AW, Lindner IM, Lurie KG. Randomised comparison of epinephrine and vasopressin in patients with out-of-hospital ventricular fibrillation. The Lancet 349:535-537, 1997

69. Mentzelopoulos SD, Zakynthinos SG, Tzoufi M, et al.: Vasopressin, epinephrine, and corticosteroids for in-hospital cardiac arrest. Archives of internal medicine 169:15-24, 2009

ACCEPTED MANUSCRIPT

70. Mentzelopoulos SD, Malachias S, Chamos C, et al.: Vasopressin, steroids, and epinephrine and neurologically favorable survival after in-hospital cardiac arrest: a randomized clinical trial. JAMA 310:270-279, 2013

71. Hert DS, Vlasselaers D, Barbé R, et al.: A comparison of volatile and non volatile agents for cardioprotection during on-pump coronary surgery. Anaesthesia 64:953-960, 2009

72. Likhvantsev VV, Landoni G, Levikov DI, Grebenchikov OA, Skripkin YV, Cherpakov RA. Sevoflurane Versus Total Intravenous Anesthesia for Isolated Coronary Artery Bypass Surgery With Cardiopulmonary Bypass: A Randomized Trial. Journal of Cardiothoracic and Vascular Anesthesia 30:1221-1227, 2016

ACCEPTED MANUSCRIPT

Figure Legends:

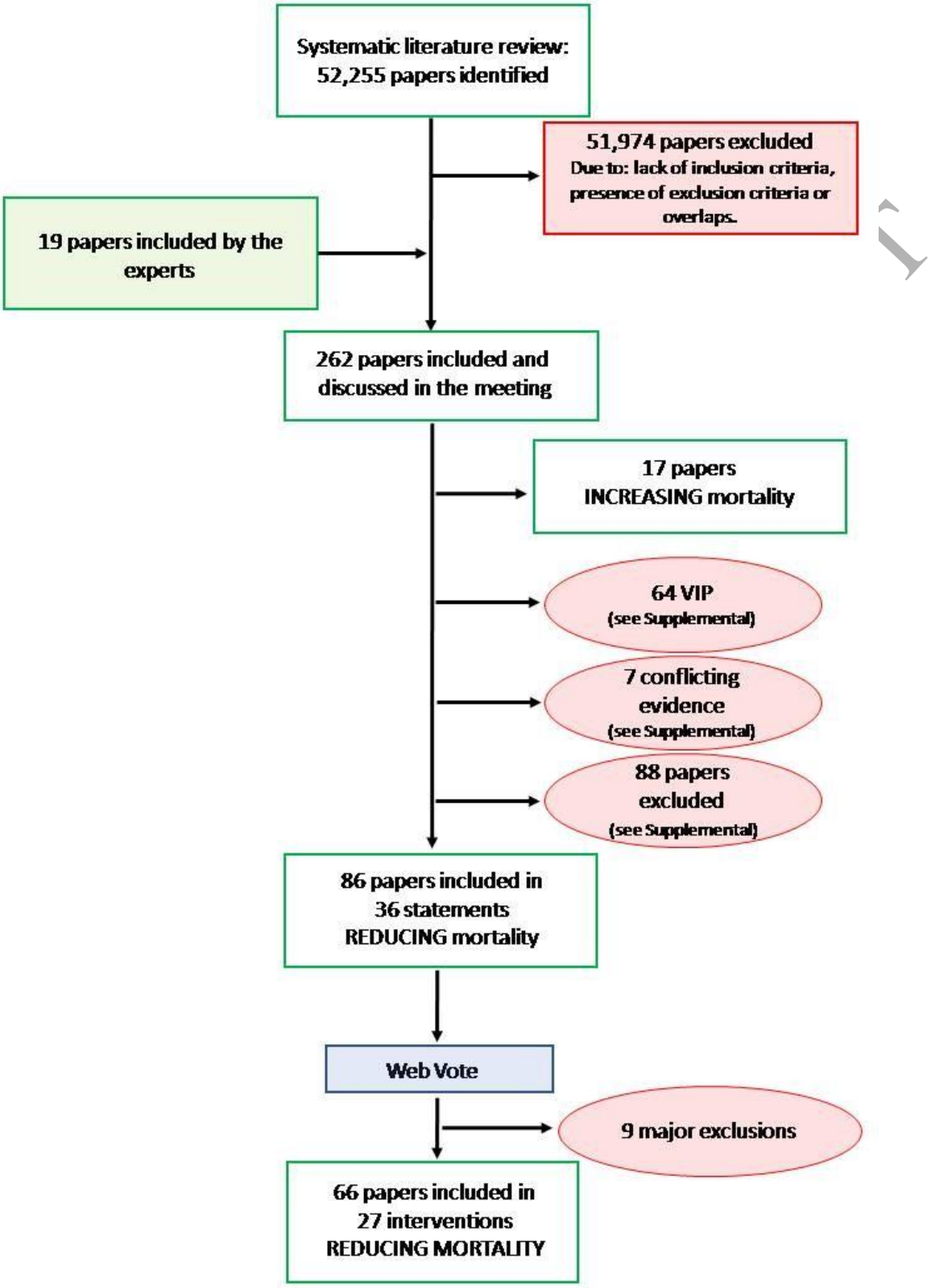


Figure 1: Flow chart of the Consensus process. For details see Supplemental.

ACCEPTED MANUSCRIPT

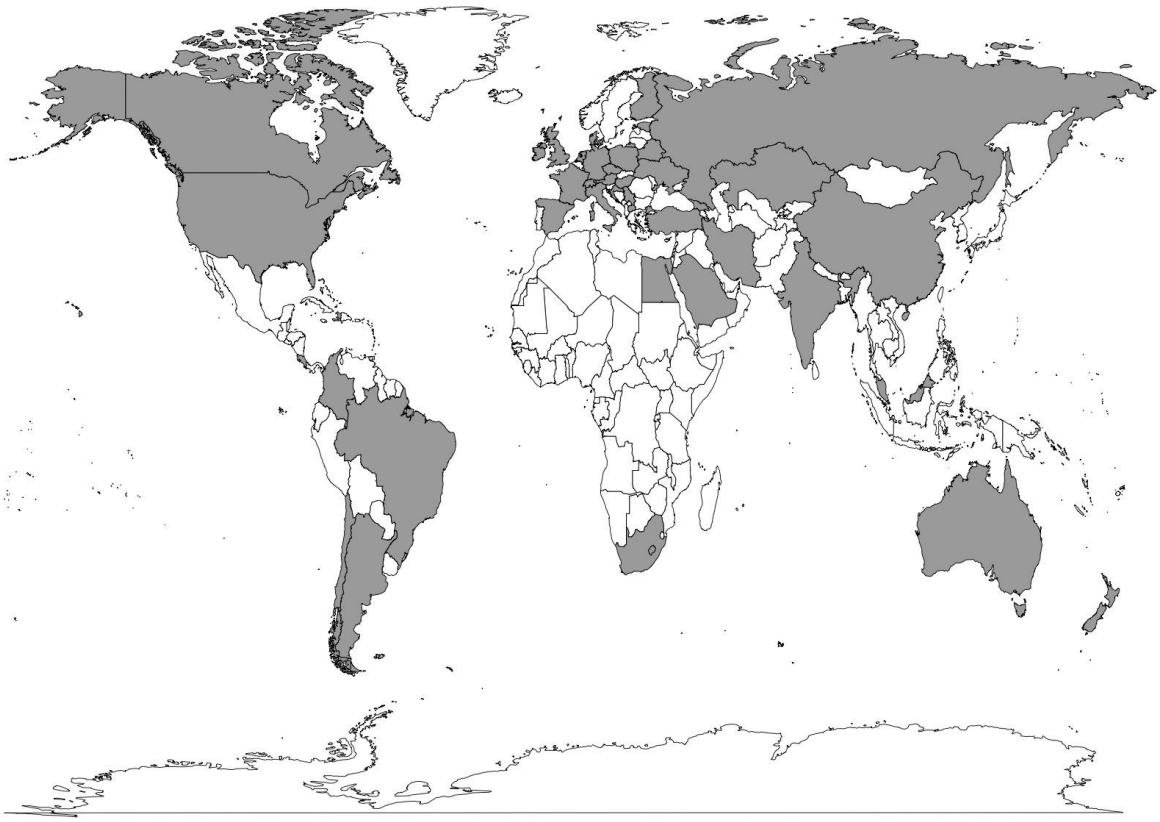


Figure 2: Web Vote countries

ACCEPTED MA

ACCEPTED MANUSCRIPT

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%

ACCEPTED MANUSCRIPT

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%

ACCEPTED MANUSCRIPT

ACCEPTED MANUSCRIPT

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		

ACCEPTED MANUSCRIPT

ACCEPTED MANUSCRIPT

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

ACCEPTED MANUSCRIPT