SPECIAL ARTICLE

Randomized Evidence for Reduction of Perioperative Mortality: An Updated Consensus Process

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Objective: **Of the 230 million patients undergoing major surgical procedures every year, more than 1 million will die within 30 days. Thus, any nonsurgical interventions that help reduce perioperative mortality might save thousands of lives. The authors have updated a previous consensus process to identify all the nonsurgical interventions, supported by randomized evidence, that may help reduce perioperative mortality.**

Design and Setting: **A web-based international consensus conference.**

Participants: **The study comprised 500 clinicians from 61 countries.**

Interventions: **A systematic literature search was performed to identify published literature about nonsurgical interventions, supported by randomized evidence, showing a statistically significant impact on mortality. A consensus conference of experts discussed eligible papers. The interventions identified by the conference then were submitted to colleagues worldwide through a web-based survey.**

Measurements and Main Results: **The authors identified 11 interventions contributing to increased survival (perioperative hemodynamic optimization, neuraxial anesthesia, noninvasive ventilation, tranexamic acid, selective**

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decontamination of the gastrointestinal tract, insulin for tight glycemic control, preoperative intra-aortic balloon pump, leuko-depleted red blood cells transfusion, levosimendan, volatile agents, and remote ischemic preconditioning) and 2 interventions showing increased mortality (beta-blocker therapy and aprotinin). Interventions then were voted on by participating clinicians. Percentages of agreement among clinicians in different countries differed significantly for 6 interventions, and a variable gap between evidence and clinical practice was noted.

Conclusions: **The authors identified 13 nonsurgical interventions that may decrease or increase perioperative mortality, with variable agreement by clinicians. Such interventions may be optimal candidates for investigation in high-quality trials and discussion in international guidelines to reduce perioperative mortality.**

ALL SURGICAL PROCEDURES are associated with a certain risk of both intraoperative and postoperative adverse events that in some cases can be fatal. However, perioperative mortality generally is perceived as relatively low, especially at individual center level and for elective noncardiac surgery in patients without particular risk profiles. Overall all-cause mortality after noncardiac surgery has been reported to be 1% to 4%.[1] Moreover, due to the relatively low mortality rate and the complexity of the clinical setting, it is not easy to investigate the impact of therapeutic interventions, which could have significant, though small, effects on perioperative mortality. Accordingly, this matter has never received great attention in the medical literature.[2] However, of the more than 230 million patients who undergo major surgical procedures worldwide every year, more than 1 million die within 30 days.[3] Thus, even small reductions in perioperative mortality may save many lives.

To achieve a comprehensive view of this issue and to better understand which drugs, techniques, or strategies should be used (or avoided) by clinicians in an effort to reduce mortality, large collaborative research projects are required and a systematic and effective identification of the interventions that potentially may affect mortality is vital.

Since 2010, the authors have developed an innovative approach to consensus that allowed them to accomplish a comprehensive and widely agreed upon overview of interventions that might affect mortality in different clinical settings, including the perioperative period of any surgical procedure, cardiac surgery, critically ill patients, and acute kidney injury.[4–8] Because evidence seems to be evolving constantly and rapidly, the authors conducted an update of a previous consensus process on ancillary (nonsurgical) interventions (drugs/techniques/strategies) that have been shown by at least 1 randomized controlled trial (RCT) or meta-analysis of RCTs to affect perioperative mortality in any adult surgical setting. In addition to a systematic literature search, consensus meeting, and web-based survey about the agreement on the included interventions, the authors investigated the reported use of such interventions in clinical practice and the possible gap between literature evidence and clinical practice. Furthermore, comparison with the previous consensus process gave the opportunity to appreciate how rapidly evidence has evolved.

METHODS

A systematic MEDLINE/PubMed, Scopus, and Embase search with no time limits that was updated March 6, 2015, was performed by 4 experienced investigators (GL, AP, AB, LR) to identify all of the published literature with randomized evidence of mortality reduction or increase in the perioperative period (see Appendix 1 for the full search strategy). The authors found additional articles through a cross-check of references and suggestions by experts in the field of perioperative medicine. A website allowed participants worldwide to vote in support of or against the nominated interventions and to submit comments or to report additional articles for inclusion until the day of the consensus meeting.

Only the studies that satisfied all the following criteria were considered: (1) publication in a peer-reviewed journal, (2) assessment of a nonsurgical intervention (drug/technique/strategy) in adult patients undergoing any type of surgery, (3) achievement of a statistically significant reduction or increase in mortality, and (4) conducted as randomized trial or meta-analysis of RCTs.

The in-person meeting was held March 6, 2015, at the Vita-Salute University, Milan, Italy, and involved anesthesiologists, intensive care specialists, cardiologists, surgeons, and epidemiologists. During this face-to-face consensus conference, for each intervention, participants were asked to decide whether (1) the most recent evidence had been collected, (2) the effect on mortality was supported by RCTs or meta-analyses of RCTs, (3) the supporting evidence was derived from a primary or a subgroup analysis, (4) the evidence was derived entirely or partially from a surgical population, (5) the intervention was applicable to all patients or to subgroups only, and (6) mortality was the study endpoint or was included in a composite endpoint.

Each intervention was presented by a rapporteur and commented on by 1 or 2 discussants; the consensus process involved the international cohort of participants who voted on the interventions before and after the Milan meeting. A position statement was approved describing the reasons for the inclusion. The studies or interventions that did not meet the aforementioned criteria became major exclusions, and reasons for exclusion were detailed (Tables S1 and S2).

The final interventions and their statements were presented online at the website www.democracybasedmedicine.org (Table 1). Participants worldwide had the opportunity, through the web survey, to support or challenge the interventions and statements from the meeting for the 5 months between March and August 2015. The following 3 questions were asked: (1) Do you agree with this sentence? (Yes/No/Do not know); (2) Do you routinely use this intervention in your clinical practice? (Yes/No/Does not apply); (3) Would you include this intervention into future international guidelines to reduce perioperative mortality? (Yes/No/Do not know)

For the interventions increasing mortality, the second and third questions were asked in an opposite fashion: Do you routinely avoid this intervention in your clinical practice? Would you suggest that future international guidelines should contraindicate

Table 1. Topics (Drugs and/or Nonsurgical Techniques or Strategies) With Randomized Published Evidence of a Reduction/Increase in Perioperative Mortality

Topics	Sentences	Agreement
Increasing survival		
Perioperative hemodynamic optimization	According to 5 meta-analyses of RCTs, perioperative hemodynamic optimization can reduce mortality in high-risk surgical patients. Uncertainty remains about which invasive devices and/or therapeutic interventions are to be preferred. This topic merits further investigation. Do you agree with the above sentence?	95%
Insulin glycemic control	According to 2 RCTs and 1 meta-analysis of RCTs, continuous insulin infusion can reduce perioperative mortality. The ideal glycemic target is still to be determined and might change in different settings. The authors strongly recommend caution when using tight glycemic control because of the risk of hypoglycemic episodes. This topic merits further investigation. Do you agree with the above sentence?	88%
Noninvasive ventilation	According to 3 small RCTs, noninvasive ventilation reduces mortality in acute respiratory failure after solid organ transplantation, lung resection, and cardiac surgery. This topic merits further investigation. Do you agree with the above sentence?	88%
Levosimendan	According to 1 small RCT and 4 meta-analyses of RCTs, levosimendan may reduce 30-day mortality in patients with low ejection fraction undergoing cardiac surgery. This topic merits further investigation. Do you agree with the above sentence?	88%
Leuko-depleted red blood cells transfusion	According to 2 RCTs, patients undergoing cardiac surgery might benefit from leukocyte depletion of transfused blood by filtration. This topic merits further investigation. Do you agree with the above sentence?	86%
Preoperative IABP	According to 1 small RCT and 4 meta-analyses of RCTs, preoperative IABP can have a beneficial effect on mortality in specific high-risk patient groups undergoing CABG. This topic merits further investigation. Do you agree with the above sentence?	85%
Volatile agents	According to 2 meta-analyses of RCTs, volatile anesthetics might reduce 30-day mortality in patients undergoing coronary artery bypass graft surgery. This topic merits further investigation. Do you agree with the above sentence?	85%
Tranexamic acid	According to 1 meta-analysis of RCTs, low-dose tranexamic acid may reduce mortality. This topic merits further investigation. Do you agree with the above sentence?	84%
Neuraxial anesthesia	According to 4 meta-analyses of RCTs, neuraxial anesthesia may reduce short-term mortality compared with general anesthesia in noncardiac surgery. This topic merits further investigation. Do you agree with the above sentence?	81%
Remote ischemic preconditioning	According to 1 RCT, remote ischemic preconditioning provides perioperative myocardial protection and might improve late survival in patients undergoing elective coronary artery bypass grafting surgery. This topic merits further investigation. Do you agree with the above sentence?	80%
Selective decontamination of digestive tract	According to 1 meta-analysis of RCTs, selective decontamination of the digestive tract in critically ill surgical patients might reduce mortality. This topic merits further investigation. Do you agree with the above sentence?	67%
Increasing mortality		
Beta-blockers	According to 1 large RCT and 3 meta-analyses, beta-blockers started immediately before noncardiac surgery can increase perioperative mortality in patients with, or at risk for, atherosclerotic disease. Nonetheless, the consensus conference recommends to maintain chronic beta-blocker therapy in the perioperative period. Do you agree with the above sentence?	83%
Aprotinin	According to 1 RCT, aprotinin increases 30-day mortality in adult patients undergoing cardiac surgery. Do you agree with the above sentence?	73%

Abbreviations: CABG, coronary artery bypass grafting; IABP, intra-aortic balloon pump; RCT, randomized controlled trial.

this intervention to reduce perioperative mortality? The authors did not include the possibility to "partially agree" with a statement; therefore, every answer refered to the full sentence. The option to answer "do not know" was included in the questionnaire to allow responders to state that they had no opinion or had never thought about that particular issue. Because methodologic research suggests, as previously mentioned,[6,8] that there is no difference in response rate depending on the inclusion or exclusion of the "do not know" option (if less than 40%),[9] only the "yes" and "no" frequencies were reported in the results if not otherwise indicated.

After the second and last web vote, the interventions that reached less than 67% of agreement were considered as major exclusions (see Tables S1 and S2). The interventions with an impact on mortality that were approved after the web vote, with

Table 2. Randomized Clinical Trials and Meta-Analyses of Randomized Clinical Trials Documenting a Mortality Reduction or an Increase in Mortality in the Postoperative Period

Topics Improving Survival	First Author	Journal	Year	RCT or META of RCTs	Number of Randomly Assigned Patients	Country
Increasing Survival						
Perioperative hemodynamic optimization	Cecconi et al.[10]	*Crit Care*	2013	Meta-analysis	315	United Kingdom
	Gurgel et al.[11]	*Anesth Analg*	2011	Meta-analysis	5,056	Brazil
	Hamilton et al.[12]	*Anesth Analg*	2011	Meta-analysis	4,805	United Kingdom
	Brienza et al.[13]	*Crit Care Med*	2009	Meta-analysis	4,220	Italy
	Poeze et al.[14]	*Crit Care Med*	2005	Meta-analysis	5,733	Netherlands
Insulin for glycemic control	Giakoumidakis et al.[15]	*Heart Lung*	2012	RCT	212	Greece
	Haga et al.[16]	*J Cardiothorac Surg*	2011	Meta-analysis	1,492	United Kingdom
	Van den Berghe et al.[17]	*N Engl J Med*	2001	RCT	1,548	Belgium
Noninvasive ventilation	Zhu et al.[18]	*Chin Med J*	2013	RCT	95	China
	Auriant et al.[19]	*Am J Respir Crit Care Med*	2001	RCT	48	France
	Antonelli et al.[20]	*JAMA*	2000	RCT	40	Italy
Levosimendan	Harrison et al.[21]	*J Cardiothorac Vasc Anesth*	2013	Meta-analysis	1,155	United States
	Landoni et al.[22]	*Crit Care Med*	2012	Meta-analysis	5,480	Italy
	Maharaj and Metaxa.[23]	*Crit Care*	2011	Meta-analysis	729	United Kingdom
	Landoni et al.[24]	*J Cardiothorac Vasc Anesth*	2010	Meta-analysis	440	Italy
	Levin et al.[25]	*Rev Esp Cardiol*	2008	RCT	137	Argentina
Leuko-depleted red blood cell transfusion	Bilgin et al.[26]	*Circulation*	2004	RCT	474	Netherlands
	Van de Watering et al.[27]	*Circulation*	1998	RCT	914	Netherlands
Preoperative IABP in high-risk CABG	Zangrillo et al.[28]	*Crit Care*	2015	Meta-analysis	625	Italy
	Sá et al.[29]	*Coron Artery Dis*	2012	Meta-analysis	345	Brazil
	Theologou et al.[30]	*Cochrane Database Syst Rev*	2011	Meta-analysis	255	United Kingdom
	Qiu et al.[31]	*J Cardiothorac Surg*	2009	RCT	221	China
	Dyub et al.[32]	*J Card Surg*	2008	Meta-analysis	2,363	Canada
Volatile agents	Landoni et al.[33]	*Br J Anaesth*	2013	Meta-analysis	3,642	Italy
	Landoni et al.[34]	*J Cardiothorac Vasc Anesth*	2007	Meta-analysis	1,922	Italy
Tranexamic acid	Ker et al.[35]	*BMJ*	2012	Meta-analysis	10,488	United Kingdom
Neuraxial anesthesia	Guay et al.[36,37]	*Anesth Analg, Cochrane Database Syst Rev*	2014	Meta-analysis	3,006	Canada
	Pöpping et al.[38]	*Ann Surg*	2014	Meta-analysis	2,201	Germany
	Rodgers et al.[39]	*BMJ*	2000	Meta-analysis	9,559	New Zealand
	Urwin et al.[40]	*Br J Anaesth*	2000	Meta-analysis	1,578	United Kingdom
Remote ischemic preconditioning	Thielmann et al.[41]	*Lancet*	2013	RCT	329	Germany
Selective decontamination of the digestive tract	Nathens and Marshall.[42]	*Arch Surg*	1999	Meta-analysis	Not available	Canada
Increasing mortality						
Beta-blockers	Wijeysundera et al.[43,44]	*Circulation, J Am Coll Cardiol*	2014	Meta-analysis	12,391	Canada, United States
	Blessberger et al.[45]	*Cochrane Database Syst Rev*	2014	Meta-analysis	19,211	Austria
	Devereaux et al.[46]	*Lancet*	2008	RCT	8,351	Canada
	Bouri et al.[47]	*Heart*	2014	Meta-analysis	10,529	United Kingdom
Aprotinin	Fergusson et al.[48]	*N Engl J Med*	2008	RCT	2,331	Canada

Abbreviations: CABG, coronary artery bypass grafting; IABP, intra-aortic balloon pump; META, meta-analysis; RCT, randomized clinical trial.

the references to the articles of RCTs or meta-analyses of RCTs supporting the evidence, are reported in Table 2 if overwhelming evidence was not published thereafter.

Throughout the process, all participants (either those voting via web or those participating in person) were asked to disclose all potential conflicts of interest. Analyses were repeated to include only answers without conflict of interests. There was no sponsor or industry support for this consensus conference.

Subanalyses were performed by country, to assess the relationship between the clinicians' opinion and the source of the evidence, and by the responders' specialty, to assess whether the approach to perioperative management differed among specialists in anesthesia and other healthcare professionals.

The gap between agreement and practice was measured by calculating the ratio of all the answers with consistency between agreement and use or avoidance in clinical practice over the total number of responses. Double votes were prevented by using the e-mail field as the unique identifier.

The ClinicalTrials.gov register for each intervention on the final list was surveyed to assess the current level of interest for testing each identified intervention.

Statistical Analysis

From the data provided in the articles, the relative risk reduction or increase, absolute risk reduction or increase, and number needed to treat or harm were calculated. The results of the web vote are expressed as percentage of positive votes. The percentage of agreement of the following data are reported: (1) selected literature; (2) use/avoidance in clinical practice; and (3) inclusion in future guidelines. Statistical analysis was performed using Stata 13 software (StataCorp, College Station, TX).

The chi-square or Fisher exact test was used to evaluate differences in percentages among countries and specialists. Statistical significance was set at $p < 0.05$.

RESULTS

Thirteen interventions were selected by 500 clinicians from 61 countries. The 13 interventions selected using the web survey were supported by 39 articles[10–48] (12 RCTs and 27 meta-analyses of RCTs). The following 11 interventions[10–42] were reported to increase survival: perioperative hemodynamic optimization in high-risk surgical patients, neuraxial anesthesia compared with general anesthesia, noninvasive ventilation in acute respiratory failure, tranexamic acid, and selective decontamination of the gastrointestinal tract in critically ill patients—all in noncardiac surgery; insulin for tight glycemic control, preoperative intra-aortic balloon pump (IABP) in high-risk patients undergoing coronary artery bypass graft surgery, leuko-depleted red blood cells transfusion, levosimendan in patients with low ejection fraction, volatile agents, and remote ischemic preconditioning (RIPC) in patients undergoing coronary artery bypass graft surgery—all in cardiac surgery.

The 2 interventions found to increase mortality were the use of beta-blocker therapy in the immediate preoperative period of noncardiac surgery and the administration of aprotinin in cardiac surgery patients.[43–48] The following countries included in the study had the highest number of voters: Australia, Italy, and the United Kingdom. Most participants were specialized in anesthesiology and intensive care (Table 3).

The articles were published between 1998 and 2015, with an increase in the number of articles in recent years and an increase in the studies' sample size (Fig 1). When focusing on RCTs, and therefore excluding meta-analyses of RCTs, a limited trend toward the number of patients included and in the number of centers included over the 16 years (1998-2013) were observed (Tables S3 and S4; Fig S1).

The journals that published the 39 articles with differences in mortality are reported in Table 4. The most frequent origins of the publishing authors were Canada, Italy, and the United Kingdom with 7 manuscripts each; authors from Canada, The Netherlands, and China published the highest number of RCTs (Table S5).

The percentages of agreement of the web voters with the previously identified interventions and their supporting statements ranged between 95% for perioperative hemodynamic optimization to 67% for selective decontamination of the digestive tract (see Table 1). The percentage of agreement among specialists of different countries was not statistically different for 8 of the 13 interventions, with the highest concordance seen for volatile agents (Table 5). There was no concordance in the other 5 of the 13 interventions (see Table 5). The consistency between agreement and practice varied from 79% for volatile agents to 35% for RIPC (Table 6).

The routine use of each drug/technique/strategy always was lower than the agreement for the same type of intervention. The less-used interventions were selective decontamination of the digestive tract (15%) and remote ischemic preconditioning (22%), and the most used were volatile agents (80%) and preoperative hemodynamic optimization (74%). Aprotinin was the most avoided intervention (78%) and the only intervention in which clinical practice exceeded the agreement (Table 5). Statistically significant differences among represented countries in the use or avoidance of the interventions were observed for 8 of the 13 interventions (Table 5). When asked whether the interventions should be included in future guidelines, there was a general agreement above 67% for 10 interventions. Interestingly, opinions among the represented countries about the necessity of including interventions into future guidelines always were statistically significantly different for strategies

Table 3. Number of Voters from Each Country and Number of Anesthesiologist and/or Intensive Care Physicians Among Voters

	Number of voters	Percentage
Country		
Australia	56	11%
Italy	50	10%
United Kingdom	37	7%
Other Western countries	170	34%
Other countries	187	37%
Total	500	100%
Profession		
Anesthesiologist and/or intensive care physician	411	82%
Others	89	18%
Total	500	100%

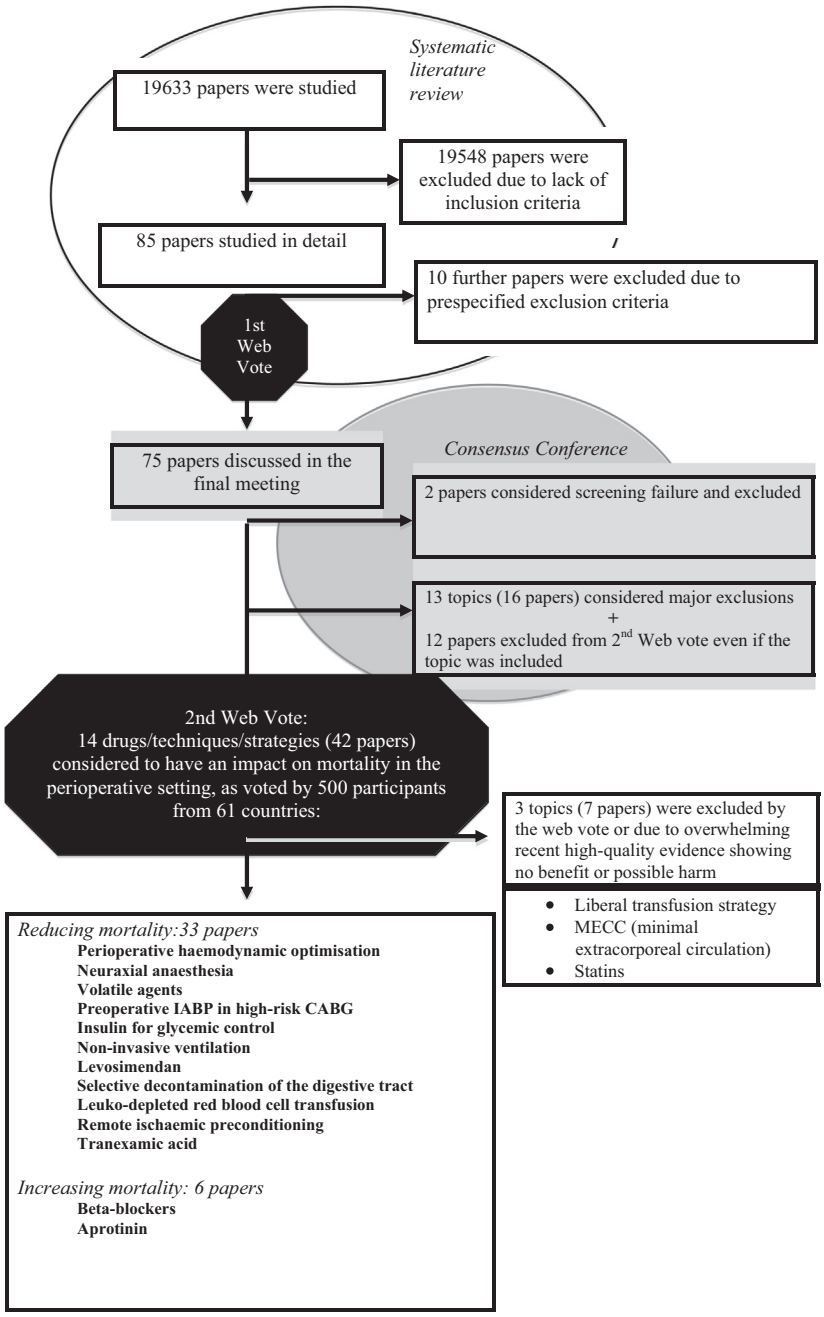

Fig 1. Flow chart on the web-based conference and selection of the interventions with an effect on mortality in the perioperative setting.

increasing survival, whereas no difference was observed for interventions increasing mortality.

When comparing the opinions of anesthesiologists and intensive care specialists with other healthcare professionals about interventions reducing perioperative mortality, no statistically significant differences were observed. Conversely, for the interventions that might increase perioperative mortality (beta-blocker therapy and the use of aprotinin), intensive care specialists reported statistically significantly higher percentages of avoidance compared with other specialists (Table S6).

Declarations of a potential conflict of interest for each of the interventions ranged from 0% to 1.2%, and the exclusion of these participants did not affect the results.

Several major study exclusions were identified and are reported in Tables S1 and S2, with the reason for exclusion. Notably, 2 interventions that reached the final stage of the web vote were excluded because they did not reach the minimum general agreement, set at 67%. In fact, the percentage of agreement was 55% for liberal transfusion strategy and only 42% for minimal extracorporeal circulation. One intervention

Table 4. Number of Articles Published by Each Journal

Journal	Number of Articles
Anesth Analg	3
Circulation	3
Cochrane Database Syst Rev	3
Crit Care	3
Crit Care Med	3
J Cardiothorac Surg	3
J Cardiothorac Vasc Anesth	3
Br J Anaesth	2
BMJ	2
Lancet	2
N Engl J Med	2
Am J Respir Crit Care Med	1
Ann Surg	1
Arch Surg	1
Chin Med J	1
Coron Artery Dis	1
Heart	1
Heart Lung	1
J Am Coll Cardiol	1
JAMA	1
Rev Esp Cardiol	1

(preoperative statin therapy in statin-naïve patients)[49–51] was excluded after completion of the web vote because large, high-quality RCTs showing no benefit and possible harm were published thereafter.[52,53]

The list of the 132 ongoing trials identified on the ClinicalTrials.gov register for the 13 interventions is provided in Table S7, with different interests shown among the international community, ranging from 36 ongoing trials on perioperative tranexamic acid to no studies on aprotinin and leukodepleted red blood cells transfusion.

DISCUSSION

Key Findings

The authors identified all nonsurgical interventions (drugs, techniques, or strategies) that have been shown by at least 1 RCT or meta-analysis of RCTs to affect mortality significantly in the perioperative period of any adult surgery. Moreover, the authors analyzed how these interventions are regarded by a large cohort of colleagues worldwide and to what extent they translate into reported clinical practice. Through a well-proven "democratic" consensus process that has been described widely,[4–8,54] the systematic review of literature was limited to the highest levels of evidence-based medicine (EBM) hierarchy and filtered through the views and experience of 500 clinicians from 61 countries. This is a unique feature of this consensus process, which allows physicians to directly provide their opinion on perioperative interventions associated with an increase or reduction in survival. In this way, the authors were able to determine the level of interest and perceived importance of these interventions. As such, it may become a pragmatic (patients') "survival guide" to be used by anesthesiologists, intensivists, and other specialists in their daily practice. Interestingly, the authors found differences among different countries and, only in a few cases, among different specialists.

Finally, this study provided the opportunity to analyze the existing gap between medical literature and clinical practice in the complex field of perioperative medicine. Furthermore, as an update of the consensus process conducted in 2011,[5] it allowed for an assessment of how rapidly EBM evolved, suggesting the need for continuous and quick updating (not only of literature, but also of industry beliefs) and for the conduct of high-quality RCTs focused on major outcomes such as mortality.

Relationship to Previous Literature

The present findings were of particular interest when compared with those of the first international web-based consensus process on perioperative mortality, which was held in 2011 and results of which were published in 2012.[5] Although the number of interventions identified was almost the same, 3 of the 13 interventions that were included previously were excluded in the present update (chlorhexidine oral rinse, α_2-adrenergic agonists, and perioperative supplemental oxygen), whereas 2 new interventions were included (tranexamic acid and RIPC). Chlorhexidine oral rinse and α_2-adrenergic agonists were excluded due to the publication of subsequent studies not confirming a survival benefit[55] or even reporting, in contrast to previous investigations, an increase in mortality.[56] The presence of conflicting results of the 2 identified studies[57,58] in addition to low agreement and the lack of a convincing underlying mechanism[59,60] were the main reasons for the exclusion of perioperative supplemental oxygen.

Regarding the 2 new interventions included, additional corroborating evidence has become available for tranexamic acid, which previously was excluded due to the lack of clear evidence of a survival benefit in the perioperative period, and the only trial suggesting a reduction in mortality with RIPC[41] had not yet been published at the time of the first consensus process.

The authors also found an increased number of studies in support of a favorable effect on mortality for 6 of the 9 interventions that have been confirmed to improve survival: neuraxial anesthesia, volatile agents, insulin for glycemic control, noninvasive ventilation, levosimendan, and preoperative IABP. In particular, the number of supporting studies has risen dramatically (from 1 to 5) for the last 2 interventions.

Regarding interventions reducing survival, the number of supporting studies has increased greatly (from 1 to 4) for beta-blockers.

Another interesting comparison was with the similar consensus process conducted to identify interventions that can affect mortality in critically ill patients.[7] The same therapeutic intervention can be beneficial in a clinical setting and harmful in another. In fact, both intensive insulin therapy and hemodynamic optimization (with supranormal oxygen delivery as a target) have been found possibly to be life-saving in the perioperative period and to potentially increase mortality in critically ill patients. Furthermore, intensive insulin therapy might be beneficial only among cardiac surgery patients but not among those undergoing noncardiac interventions, as suggested by the Normoglycaemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation (NICE-SUGAR) trial.[61]

Table 5. Percentages of Agreement and Use of the Interventions Identified as Increasing Survival or Mortality Overall and Divided by Countries

Intervention	Question	Total	Australia	Italy	United Kingdom	Other Western Country	Other	p Value
Increasing survival								
Perioperative hemodynamic optimization	Agree	95%	85%	98%	94%	94%	98%	0.001
	Use	70%	38%	88%	70%	70%	74%	<0.001
	Guidelines	89%	67%	94%	85%	88%	95%	<0.001
Insulin for glycemic control	Agree	88%	78%	88%	83%	91%	91%	0.068
	Use	66%	49%	70%	66%	64%	71%	0.061
	Guidelines	76%	57%	74%	65%	74%	86%	0.001
Noninvasive ventilation	Agree	88%	95%	98%	95%	85%	85%	0.047
	Use	56%	42%	80%	48%	57%	54%	0.007
	Guidelines	77%	70%	95%	83%	69%	80%	0.008
Levosimendan	Agree	88%	81%	98%	88%	86%	88%	0.176
	Use	41%	13%	82%	16%	42%	40%	<0.001
	Guidelines	67%	39%	86%	67%	62%	73%	0.001
Leuko-depleted red blood cell transfusion	Agree	86%	76%	84%	95%	87%	89%	0.220
	Use	52%	66%	39%	29%	63%	45%	0.001
	Guidelines	77%	68%	65%	70%	75%	85%	0.037
Preoperative IABP in high-risk CABG	Agree	85%	73%	98%	88%	78%	90%	0.001
	Use	46%	22%	71%	57%	37%	51%	<0.001
	Guidelines	69%	45%	88%	70%	54%	82%	0.000
Volatile agents	Agree	85%	88%	87%	83%	84%	84%	0.965
	Use	76%	75%	67%	65%	76%	80%	0.357
	Guidelines	75%	58%	84%	71%	70%	82%	0.019
Tranexamic acid	Agree	84%	82%	86%	84%	86%	80%	0.746
	Use	65%	39%	65%	65%	74%	66%	<0.001
	Guidelines	65%	39%	65%	65%	74%	66%	0.011
Neuraxial anesthesia	Agree	81%	75%	89%	69%	79%	84%	0.123
	Use	65%	46%	60%	60%	70%	70%	0.021
	Guidelines	74%	57%	72%	64%	74%	82%	0.012
Remote ischemic preconditioning	Agree	80%	90%	75%	81%	76%	83%	0.333
	Use	12%	0%	13%	0%	6%	22%	<0.001
	Guidelines	47%	22%	52%	56%	37%	61%	0.001
Decontamination of the digestive tract	Agree	67%	61%	82%	72%	68%	62%	0.136
	Use	14%	4%	22%	10%	16%	15%	0.142
	Guidelines	45%	31%	54%	65%	40%	46%	0.045
Increasing mortality								
Beta-blockers	Agree	83%	88%	76%	83%	89%	78%	0.055
	Avoid	57%	57%	59%	56%	65%	49%	0.087
	Guidelines	70%	61%	80%	66%	70%	71%	0.386
Aprotinin	Agree	73%	87%	94%	44%	70%	69%	<0.001
	Avoid	77%	71%	65%	52%	84%	78%	0.010
	Guidelines	67%	74%	65%	59%	64%	69%	0.733

NOTE. Agree: Do you agree with the above sentence? Use/Avoid: Do you routinely use/avoid this intervention in your clinical practice? Guidelines: Would you include this intervention into future international guidelines to reduce perioperative mortality?/Would you suggest that future international guidelines should contraindicate this intervention to reduce perioperative mortality?

Abbreviations: CABG, coronary artery bypass grafting; IABP, intra-aortic balloon pump.

Implications for Clinical Practice

Although mortality after elective surgery is relatively low,[1,62] even a small improvement in survival may translate into thousands of lives saved each year, given the enormous number of surgical procedures performed worldwide. Physicians treating surgical 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 mortality in their patients. Guidelines can provide helpful information about interventions that may influence mortality but also include recommendations on many other aspects and therefore are often dispersive, usually focused on a certain type of patient or surgery, and have some limitations, including not always strictly adhering to EBM.[54] Through this consensus methodology, for the first time to authors' knowledge, all interventions for which there was sufficient, nonconflicting, and widely agreed-upon evidence of an impact on perioperative mortality in any adult surgical setting are listed together.

Despite the fact that the percentage of agreement was above 80% for most of the interventions improving survival, the consistency between agreement and use in clinical practice often was much lower; the same was true for the less-expensive, widely available, and easy-to-perform interventions. These findings may boost research on interventions with a high level of agreement and therefore should be considered priority

Table 6. Percentage of Consistency Between Agreement and Practice for Each Intervention Increasing Survival (1-11) and Increasing Mortality (12-13)

Intervention	Percentage Concordance
1. Volatile agents	79%
2. Tranexamic acid	75%
3. Perioperative hemodynamic optimization	73%
4. Insulin for glycemic control	73%
5. Neuraxial anesthesia	71%
6. Noninvasive ventilation	67%
7. Preoperative IABP in high-risk CABG	63%
8. Leuko-depleted red blood cell transfusion	62%
9. Levosimendan	56%
10. Selective decontamination of the digestive tract	48%
11. Remote ischemic preconditioning	35%
12. Aprotinin	75%
13. Beta-blockers	71%

Abbreviations: CABG, coronary artery bypass grafting; IABP, intra-aortic balloon pump.

to determine without doubt whether they are beneficial and therefore increase their widespread use.

Overall, however, the percentage of agreement and the consistency with both clinical use and the potential inclusion into international guidelines suggested that EBM remains the ideal benchmark of clinical practice, although greater efforts should be made to remove or mitigate those factors (eg, ingrained beliefs, "academic" traditions, discordant hints from guidelines and opinion leaders, or simply the time needed by physicians to digest recently published evidence) that prevent clinical practice from readily adapting to the evolving evidence. In this regard, the intervention of liberal transfusion strategy, the most interesting major exclusion (Tables S1 and S2), is emblematic. Although it was one of the topics with the highest level of evidence (3 recent RCTs found a reduced mortality in the perioperative setting with liberal transfusion strategies), it has been excluded due to low agreement among web voters. Along with the novelty of the message, this probably was due to the existence of guidelines recommending exactly the opposite. Notably, a recent meta-analysis[63] confirmed that EBM was in favor of a liberal transfusion strategy in surgical patients, and the results of the Transfusion Requirements in Cardiac Surgery (TRICS) III trial[64] hopefully will provide clearer insights about this topic.

New Evidence

The body of biomedical literature is growing, and new evidence on critical interventions is produced continuously. As a consequence, additional evidence in support of a given intervention has become available since the last web vote. In particular, recent meta-analyses reported a survival benefit associated with the use of volatile agents in cardiac (but not in noncardiac) surgery[65]; perioperative hemodynamic optimization[66] and preoperative IABP[67] also were associated with benefits.

In contrast, although RIPC was included among interventions that may reduce mortality, 2 multicenter RCTs published by the *New England Journal of Medicine* in the time interval between the consensus and the writing of this manuscript demonstrated that RIPC had no effect on clinically relevant outcomes,[68,69] even if there still was the possibility that the use of propofol in this setting may impair the beneficial effects of RIPC. This "pendulum effect," however, is part of the nature of EBM.[70]

Importantly, recent trials on preoperative statin therapy in statin-naïve patients offered another example of rapidly changing evidence. Even though statin therapy was associated with reductions in mortality in some older RCTs and a meta-analysis of RCTs,[49–51] 2 large RCTs published after the consensus vote demonstrated not only that statins did not reduce mortality but may instead increase the risk of developing acute kidney injury in cardiac surgery patients.[52,53] The authors of this study therefore decided to exclude this intervention from those associated with mortality reduction.

In addition to recently published evidence, ongoing studies hopefully will provide definitive answers on several interventions. Three large, multicenter RCTs on levosimendan use in cardiac surgery currently are ongoing,[71,72] and a large trial on tranexamic acid use in coronary artery surgery (ATACAS trial) recently has been completed.[73] In addition, the authors identified 132 studies registered as "currently recruiting" on ClinicalTrials.gov on these 13 topics.

Strengths and Limitations

The main strength of this study was that it combined EBM with a unique methodology, which allowed the authors to investigate the real views and the therapeutic approaches of clinicians worldwide. The analysis of consistency between agreement and use/avoidance showed that reported clinical practice often adapts slowly to evidence and emphasized the need to rethink the paths that lead from literature to clinical practice. The reason for this discrepancy between agreement and use/avoidances patterns was not investigated and was a limitation of this study. Nevertheless, this finding provided an interesting area for future investigation.

Conversely, the comparison with the previous consensus process, of which this study represented an update, clearly showed how fast evidence evolves. Furthermore, evidence now is stronger for most of the previously included interventions, and this may promote their implementation into clinical practice.

Another strength of this study was the comparison of web voters' responses among different countries, which demonstrated that healthcare probably is less "global" than it is perceived to be. In particular, the opinions about the need to include the interventions in future guidelines always were significantly different among different countries. This may reflect, for example, a different attitude toward medico-legal issues or different local cultures. Unfortunately, the reason for such differences among countries was not investigated.

The rapid change of evidence also was a limitation of this study, as reflected by the new evidence on some of the interventions (eg, RIPC, statins) that has become available since the final web vote. Lack of definitive evidence on different interventions has been acknowledged during the consensus conference and led to position statements that could be classified as conditional sentences ("may reduce") and

highlighted the need for further investigations. The authors decided to keep their survey as simple as possible by providing only 3 possible answers to the statements (agree, not agree, do not know). Although this might be a limitation, it nevertheless allowed the authors to determine which topics physicians all over the world considered to be supported by the strongest evidence as more important and therefore should be implemented most easily, should a definitive trial be performed. When developing the survey, the authors did not separate the possibility to agree with the effect of the intervention on mortality from the possibility to agree with the need for further investigation, and the authors acknowledge that this was a limitation of this study. Nevertheless, it is difficult to believe that someone who agrees that a certain intervention may save lives would not be willing to test the same intervention to obtain definitive evidence.

Other limitations were shared with the previous consensus process and included the scarcity of randomized research in the perioperative setting, the possibility that many other interventions showing favorable effects on important outcomes other than mortality may be of similar value on survival, and the lack of any detail (definitions, doses, timing, odds ratios, confidence intervals, to name but a few) about the included interventions, which are only listed and very briefly contextualized. However, a textbook recently was dedicated to the detailed discussion of all the interventions included in the previous consensus process,[74] and a second edition detailing the updated interventions is underway.

CONCLUSIONS

This updated international web-based consensus conference process identified 13 interventions supported by randomized evidence suggesting their role in reducing or increasing perioperative mortality in adults undergoing any surgical intervention. Moreover, the analysis of web voting confirmed that there is a gap between evidence and clinical practice and that both the perception of medical literature and the clinical conduct of physicians are significantly different among countries for many of the included interventions. Future research and funding should better define the role of these interventions and major exclusions and should investigate the possible means to reduce both the gap existing between evidence and clinical practice and the differences among various countries. It is desirable that at least the most robust among the identified interventions be discussed soon in international guidelines on perioperative mortality reduction.

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APPENDIX A. SUPPLEMENTARY MATERIAL

Supplementary data are available in the online version of this article at http://dx.doi.org/10.1053/j.jvca.2016.07.017

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