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Original Article

Nonsurgical Strategies to Reduce Mortality in Patients Undergoing Cardiac Surgery: An Updated Consensus Process

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Objective: A careful choice of perioperative care strategies is pivotal to improve survival in cardiac surgery. However, there is no general agreement or particular attention to which nonsurgical interventions can reduce mortality in this setting. The authors sought to address this issue with a consensus-based approach.
Design: A systematic review of the literature followed by a consensus-based voting process.
Setting: A web-based international consensus conference.
Participants: More than 400 physicians from 52 countries participated in this web-based consensus conference.
Interventions: The authors identified all studies published in peer-reviewed journals that reported on interventions with a statistically significant effect on mortality in the setting of cardiac surgery through a systematic Medline/PubMed search and contacts with experts. These studies were discussed during a consensus meeting and those considered eligible for inclusion in this study were voted on by clinicians worldwide.
Measurements and Main Results: Eleven interventions finally were selected: 10 were shown to reduce mortality (aspirin, glycemic control, high-volume surgeons, prophylactic intra-aortic balloon pump, levosimendan, leuko-depleted red blood cells transfusion, noninvasive ventilation, tranexamic acid, vacuum-assisted closure, and volatile agents), whereas 1 (aprotinin) increased mortality. A significant difference in the percentages of agreement among different countries and a variable gap between agreement and clinical practice were found for most of the interventions.
Conclusions: This updated consensus process identified 11 nonsurgical interventions with possible survival implications for patients undergoing cardiac surgery. This list of interventions may help cardiac anesthesiologists and intensivists worldwide in their daily clinical practice and can contribute to direct future research in the field.

Key Words: cardiac surgery; perioperative; consensus; mortality; mortality reduction; review

OVER SEVERAL DECADES, improvements in surgical and anesthetic techniques have led to a reduction in mortality among patients undergoing cardiac surgery.[1,2] Isolated cardiac interventions now generally are perceived as relatively low-risk procedures. However, perioperative mortality is about 2%, 3%, and 4.3% for coronary artery bypass graft, aortic valve replacement, and mitral valve replacement, respectively.[3–5] Furthermore, the number of elderly patients with comorbidities and poor preoperative functional status scheduled for multiple cardiac procedures is increasing, thus increasing mortality risk.[6–9]

Using a novel approach to consensus building, all non-surgical interventions (drugs, techniques, and strategies) with literature evidence of a significant effect on mortality were identified systematically, briefly assessed, and described by the first international consensus conference on mortality reduction in cardiac anesthesia and intensive care.[10] After the initial work, this innovative consensus process, which later was called "democracy-based medicine,"[11] has been refined and applied to different clinical settings, such as the perioperative period for any surgery,[12,13] acute kidney injury,[14] and critical care.[15,16] Here, the results of the updated democracy-based, web-enabled consensus conference on mortality reduction in patients undergoing cardiac surgery are presented.

Methods

Cardiac anesthesiologists, cardiac surgeons, intensivists, and cardiologists participated in this updated consensus conference in cardiac surgery mortality. They participated in person, through e-mail, or through the congress website (Fig 1).

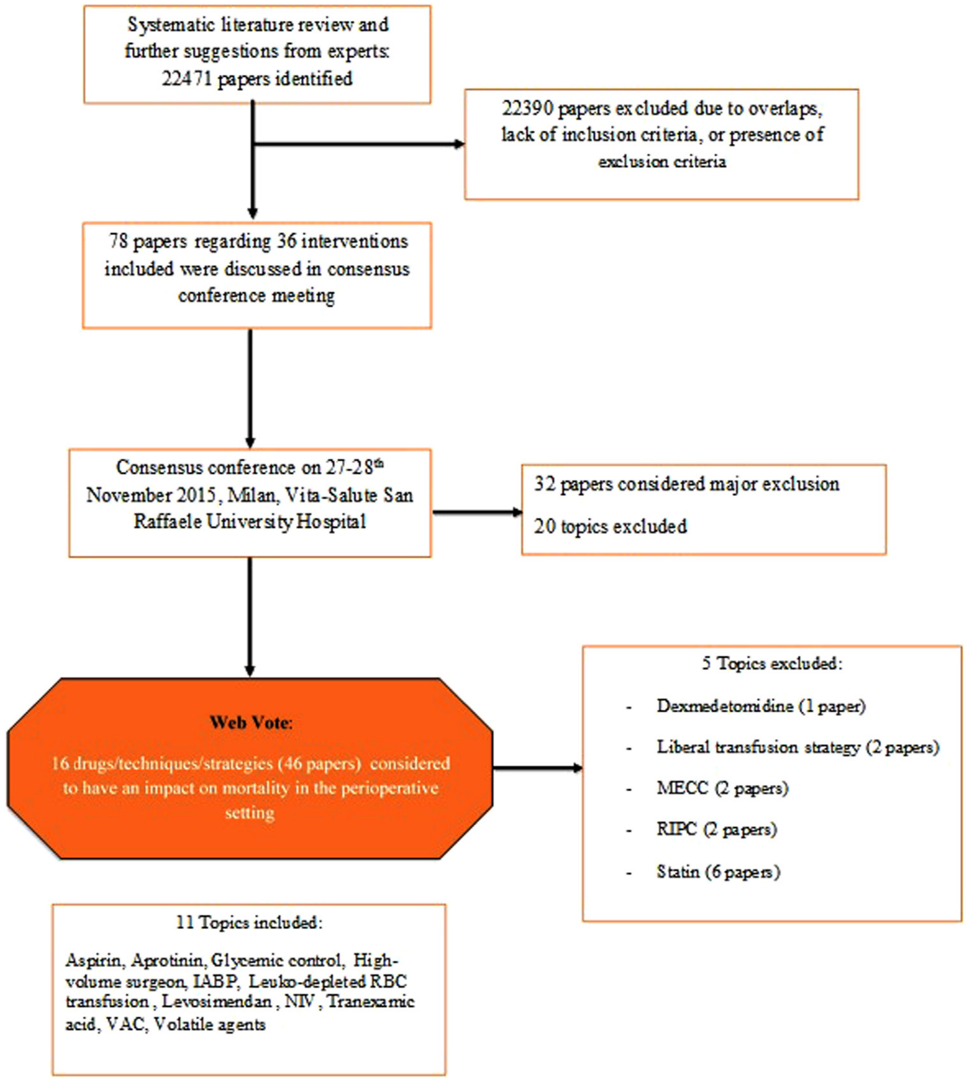

Fig 1. Flowchart of the consensus process. The first step was a systematic literature review followed by a consensus conference meeting and a web vote, with a threshold of required agreement ≥67%. At the end of the process, 11 topics were selected. IABP, intra-aortic balloon pump; MECC, minimal extracorporeal circuit; NIV, noninvasive ventilation; RBC, red blood cell; RIPC, remote ischemic preconditioning; VAC, vacuum-assisted closure.

Medline/PubMed, Scopus, and Embase were searched by 4 investigators (GL, SS, EF, MBR, CS) with no publication time limits, and the results were updated on November 27, 2015, to identify all randomized controlled trials (RCTs) and non-RCTs of any nonsurgical intervention reported to increase or decrease mortality in cardiac surgery patients (see Supplemental material 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. Only the studies that fulfilled all of the following criteria were accepted as valid for inclusion into this consensus conference: (1) published in a peer-reviewed journal, (2) included patients undergoing cardiac surgery who also underwent ancillary (ie, nonsurgical) treatments (drug/technique/strategy), and (3) nonsurgical interventions with a statistically significant reduction/increase in mortality. 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. Length of follow-up varied among the studies.

The consensus meeting was held November 27, 2015, at the Vita-Salute University of Milan, Italy, during which time all interventions were discussed by a core group of expert physicians (all of them among the authors of this article). The aims of the consensus conference were to establish whether: (1) the most recent evidence had been collected; (2) the reduction or increase in mortality was supported by either RCTs or meta-analyses of RCTs, case-matched studies, meta-analyses of case-matched studies, or other studies; (3) the evidence had been derived from a subgroup or a primary analysis; (4) the evidence had been derived entirely or partially from a cardiac surgical population and, when among a cardiac surgical population, whether it was applicable to every cardiac intervention or to certain subgroups only; (5) the drug/technique/strategy was used in the operating room or in an intensive care unit; and

(6) mortality was the endpoint or mortality was included in a composite endpoint.

Two experts, a rapporteur, and a co-rapporteur, previously selected among the attendees, presented each intervention, describing the reasons for it being considered as included or excluded. After the brief presentation, a discussion among the participants was started and, in case of disagreement, the decision whether to include an intervention was voted on by those present. Afterwards, for each intervention included, a final statement was created, discussed, and corrected during the meeting.

Several studies were excluded on methodologic grounds because of lack of reproducibility or generalizability, low methodologic quality, major baseline imbalances between intervention and control groups, major design flaws, contradiction by subsequent larger trials, modified intention-to-treat analysis, effect found only after adjustments, and lack of biologic plausibility. The studies or interventions that did not meet the aforementioned criteria became major exclusions.

Through an interactive web questionnaire (http://www.democracybasedmedicine.org), participants had the opportunity to vote in support of or against the suggested interventions (Table 1) up to October 2016. Clinicians were asked whether they agreed or disagreed with the validity of each intervention and whether they used or avoided each intervention in clinical practice. The articles supporting each intervention were all freely downloadable through a link situated near the statements describing them. The following 3 questions were asked: (1) Do you agree with this sentence? (2) Do you routinely use this intervention in your clinical practice? (3) Would you include this intervention in future international guidelines to reduce perioperative mortality? For the interventions that increased mortality, the following questions were asked in an opposite fashion: (1) Do you routinely avoid this intervention in your clinical practice? (2) Would you suggest that future international guidelines contraindicate this intervention to reduce perioperative mortality? For each question, the authors included the option "don't know" and "does not apply" in the

Table 1
Drugs, Techniques, and Strategies That Might Affect Mortality in Cardiac Surgery

Grading	Interventions Reducing Mortality	Statement
2B	Aspirin	We suggest that early postoperative aspirin and low dose preoperative aspirin might reduce mortality in patients undergoing CABG. This evidence comes from 2 non-RCTs.
2B	Glycemic control	We suggest that postoperative strict glycemic control might reduce mortality in patients undergoing cardiac surgery. However, we recommend caution when using this strategy because hypoglycemic episodes might result in increased mortality. This evidence comes from 3 RCTs and 1 meta-analysis of RCTs.
1C	High-volume surgeon	High-volume surgeon is associated with reduced mortality in patients undergoing cardiac surgery, especially valve procedures. This evidence comes from 3 non-RCTs.
2B	Prophylactic IABP	We suggest that the prophylactic use of IABP in high-risk patients undergoing CABG might reduce mortality. This evidence comes from 1 RCT, 4 meta-analyses of RCTs, and 1 meta-analysis of both RTCs and non-RCTs.
1B	Levosimendan	We recommend the use of levosimendan in low ejection fraction patients undergoing CABG to reduce mortality. This evidence comes from 1 RCT, 3 meta-analyses of RCTs, 1 meta-analysis of RCTs with subanalysis performed in cardiac surgery, and 2 meta-analyses of RCTs involving mostly cardiac surgery studies.
2B	Leuko-depleted RBC transfusion	We suggest that transfusion of leuko-depleted RBC might reduce mortality in cardiac surgery patients requiring a high number of RBC units. This evidence comes from 2 RCTs.
2B	NIV	We suggest that postoperative NIV might reduce mortality after cardiac surgery, especially in patients with acute respiratory failure. This evidence comes from 1 RCT and 1 meta-analysis of RCTs.
2C	Tranexamic acid	We suggest that tranexamic acid might reduce mortality in patients undergoing cardiac surgery. This evidence comes from a network meta-analysis including RTCs and non-RTCs.
1C	VAC	We recommend VAC therapy to reduce mortality in patients with deep sternal wound infection after cardiac surgery. This evidence comes from 1 meta-analysis including non-RCTs.
2B	Volatile agents	We suggest that volatile anesthetics (desflurane, isoflurane, and sevoflurane) might reduce mortality in patients undergoing CABG procedures. This evidence comes from 2 meta-analysis of RCTs and a metaregression.
Grading	**Interventions Reducing Survival**	**Statement**
1B	Aprotinin	We recommend against the use of aprotinin in low and intermediate risk patients undergoing cardiac surgery. This evidence comes from one RCT and one meta-analyses including RTCs and non RTCs.

NOTE. All these Interventions were in at least one published manuscript documenting statistically significant differences in mortality.
Abbreviations: IABP, intra-aortic balloon pump; NIV, noninvasive ventilation; RBC, red blood cell; RCT, randomized controlled trial; mRCT, multicenter randomized controlled trial; VAC, vacuum-assisted closure.
Definition of grading
1: Benefits clearly outweigh risks and burdens (or vice versa).
2: Benefits closely outweigh risks and burdens (or vice versa).
A: RCTs without important limitations or overwhelming evidence from observational studies.
B: RCTs with important limitations (inconsistent results, methodologic flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies.
C: Observational studies or case series.

questionnaire to allow respondents to state that they had no opinion on a particular issue or do not have the possibility to use a particular drug.

Because methodologic research suggested that there was no difference in response rate depending on the inclusion or exclusion of the "don't know" option (if < 40%),[17] only the "yes" and "no" frequencies were reported in the results, if not otherwise indicated.

After the web vote, the interventions that reached < 67% of agreement were considered as major exclusions along with those excluded during the meeting. Similar to previous "democracy-based" consensus conferences the authors have conducted in other clinical settings,[13,16] this lower limit of agreement was chosen because two-thirds of voters represented a "qualified majority" in many political or administrative proceedings. Details about major exclusions are reported in Tables S1 and S2. Gaps between literature evidence and clinical practice were assessed by calculating the difference between the answer to the following 2 questions: (1) Do you agree with this sentence? (2) Do you routinely use this intervention in your clinical practice?

Table 2
Studies Documenting a Mortality Reduction or an Increase in Mortality in the Perioperative Period

Intervention Improving Survival	Type of Study	Journal	Year	Author	Follow-Up	Agreement*
Reduce mortality						
Aspirin	Non-RCT	N Eng J Med	2002	Mangano[18]	In hospital	90%
	Non-RCT	Ann Surg	2012	Cao et al[19]	30 days	
High-volume surgeon	Non-RCT	N Eng J Med	2003	Birkmeyer et al[20]	In hospital	90%
	Non-RCT	J Cardiothorac Vasc Anesth	2014	Papachristofi et al[21]	In hospital	
	Non-RCT	Heart Lung Circ	2015	Ch'ng et al[22]	30 days	
Glycemic control	Meta-analysis of RCTs	J Cardiothorac Surg	2011	Haga et al[23]	N/A	85%
	RCT	Heart Lung	2013	Giakoumidakis et al[24]	In hospital	
	RCT	N Eng J Med	2001	Van den Berghe et al[25]	In hospital	
	RCT	Eur Heart J	2006	Ingels et al[26]	In hospital	
Prophylactic IABP	Meta-analysis of RCTs	Cochrane Database Syst Rev	2011	Theologou et al[27]	N/A	67%
	Meta-analysis of RCTs and non RCT	J Card Surg	2008	Dyub et al[28]	N/A	
	Meta-analysis of RCTs	Crit Care	2015	Zangrillo et al[29]	N/A	
	RCT	J Cardiothorac Surg	2009	Qiu et al[30]	In hospital	
	Meta-analysis of RCTs	Cochrane Database Syst Rev	2007	Field et al[31]	N/A	
	Meta-analysis of RCTs	Coron Artery Dis	2012	Sá et al[32]	N/A	
Leuko- depleted RBC transfusion	RCT	Circulation	1998	van de Watering et al[33]	60 days	87%
	RCT	Circulation	2004	Bilgin et al[34]	In hospital	
Levosimendan	Network Meta-analysis of RCTs	Br J Anaesth	2015	Greco et al[35]	N/A	74%
	RCT	Rev Esp Cardiol (Engl Ed)	2008	Levin et al[36]	In hospital	
	Meta-analysis of RCTs	J Cardiothorac Vasc Anesth	2013	Harrison et al[37]	N/A	
	Meta-analysis of RCTs	Crit Care Med	2012	Landoni et al[38]	N/A	
	Meta-analysis of RCTs	Crit Care	2011	Maharaj and Metaxa[39]	N/A	
	Meta-analysis of RCTs	J Cardiothorac Vasc Anesth	2010	Landoni et al[40]	N/A	
	Meta-analysis of RCTs	Am J Kidney Dis	2016	Zhou et al[41]	N/A	
NIV	Meta-analysis of RCTs	Crit Care Resusc	2013	Olper et al[42]	N/A	84%
	RCT	Chin Med J (Engl)	2013	Zhu et al[43]	In hospital	
Tranexamic acid	Systematic review and network meta-analysis	BMJ	2012	Hutton et al[44]	N/A	83%
VAC	Meta-analysis of non-RCTs	PloS One	2013	Falagas et al[45]	N/A	90%
Volatile agents	Meta-analysis of RCTs	J Cardiothorac Vasc Anesth	2007	Landoni et al[46]	N/A	84%
	Meta-analysis of RCTs	J Cardiothorac Vasc Anesth	2013	Bignami et al[47]	N/A	
	Meta-analysis of RCTs	Br J Anaesth	2013	Landoni et al[48]	N/A	
Increase mortality						
Aprotinin	RCT	N Eng J Med	2008	Ferguson et al[49]	30 days	81%
	Meta-analysis of RCTs and non-RCT	PloS One	2013	Meybom et al[50]	N/A	

Abbreviations: IABP, intra-aortic balloon pump; N/A, not applicable; NIV, noninvasive ventilation; RBC, red blood cell; mRCT, multicenter randomized controlled trial; VAC, vacuum-assisted closure.

*Agreement of web voters: percentage of voters who agreed with the lifesaving or life-threatening properties of the topics

The interventions with an effect on mortality that were approved after the web vote, with the references to the articles supporting the evidence, are reported in Table 2 if overwhelming evidence was not published thereafter.

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 Stata13 software (Stata Corp, 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

The consensus process flowchart is shown in Figure 1. The web survey identified the following 10 interventions that decreased unadjusted landmark mortality: aspirin,[18,19] high-volume surgeon,[20–22] glycemic control,[23–26] prophylactic intra-aortic balloon pump (IABP),[27–32] leuko-depleted red blood cell transfusion (RBC),[33,34] levosimendan,[35–41] noninvasive ventilation (NIV),[42,43] tranexamic acid,[44] vacuum-assisted closure (VAC),[45] volatile agents,[46,48] and aprotinin[49,50] was identified as the only intervention that increased mortality. The associated sentences written by the experts during the consensus conference meeting held in Milan on the 11 interventions that reduced or increased mortality in cardiac surgery patients, according to the articles, are presented in Table 1.

Table 3
Number of Articles Published by Each Journal

Journal	Number of articles
J Cardiothorac Vasc Anesth	5
N Eng J Med	4
J Cardiothorac Surg	2
Br J Anaesth	2
Cochrane Database Syst Rev	2
Circulation	2
PLoS One	2
Crit Care	2
Ann Surg	1
Eur Heart J	1
Coron Artery Dis	1
Heart Lung Circ	1
Rev Esp Cardiol (Engl Ed)	1
Crit Care Med	1
Am J Kidney Dis	1
Chin Med J (Engl)	1
Crit Care Resusc	1
J Card Surg	1
Heart Lung	1
BMJ	1

Table 4
Number of Voters From Each Country and Number of Anesthesiologists or ICU Physicians Among Voters

	Number of Voters	%
Country		
Australia-New Zealand	85	19
Europe	166	36
Other western countries	27	6
Others	180	39
Profession		
Anesthesiologist or ICU specialist	370	81
Others	88	19

Abbreviation: ICU, intensive care unit.

The 11 interventions selected using the web survey were supported by 33[18–50] articles published between 1998 and 2015, with length of follow-up ranging from in the hospital up to 60 days after surgery (see Table 2). Additional details (journal, year, type of article) and percentages of agreement of the web voters for the 33 articles reporting on differences in mortality are reported in Table 2. The journals that published the 33 articles with differences in mortality are reported in Table 3. Overall, 458 clinicians from 52 countries participated in the web survey and more than 80% were anesthesiology or intensive care specialists (Table 4).

The percentages of agreement were as high as 90%. The concordance between routine use of each drug/technique/strategy and agreement for the same type of intervention (ie, the percentage of colleagues who agree with the effectiveness of the intervention and also routinely use it in their clinical practice) is reported in Table 5. The lowest concordance was for VAC (40%) and the highest was for glycemic control (83%).

The percentage of agreement among different countries (Table 6) was statistically different for 8 of the 11 interventions, with the lowest concordance seen for the intervention called "high-volume surgeon." The concordance between routine use of each drug/technique/strategy and agreement for the same type of intervention for country is reported in Table S3.

Table 5
Percentage of Concordance Between Agreement and Practice for Each Intervention

Topic	%
Levosimendan	55
High-volume surgeon	50
VAC	40
Volatile agents	67
IABP	62
Glycemic control	83
NIV	66
Leuko depleted	53
Aspirin	72
Tranexamic acid	72
Aprotinin	65

Abbreviations: IABP, intra-aortic balloon pump; NIV, noninvasive ventilation; VAC, vacuum-assisted closure.

Table 6
Percentages of Agreement and Use of the Interventions Identified Divided by Countries

		A-NZ	EU	Others	Western	p Value
Levosimendan	Agree, n (%)	27 (41)	111 (78)	125 (86)	17 (77)	< 0.001
	Use, n (%)	10 (13)	78 (51)	70 (45)	10 (45)	< 0.001
	Guidelines, n (%)	19 (32)	95 (74)	113 (81)	12 (63)	< 0.001
High-volume surgeon	Agree, n (%)	70 (92)	134 (89)	134 (89)	24 (92)	0.81
	Use, n (%)	22 (43)	86 (65)	75 (56)	14 (64)	0.050
	Guidelines, n (%)	48 (81)	108 (81)	103 (82)	18 (75)	0.86
VAC	Agree, n (%)	48 (89)	140 (97)	130 (85)	19 (90)	0.009
	Use, n (%)	50 (78)	126 (85)	97 (63)	18 (90)	< 0.001
	Guidelines, n (%)	43 (83)	125 (91)	114 (82)	16 (89)	0.19
Volatile agents	Agree, n (%)	38 (73)	117 (83)	135 (89)	18 (82)	0.06
	Use, n (%)	45 (76)	126 (82)	137 (83)	23 (100)	0.087
	Guidelines, n (%)	34 (68)	100 (78)	130 (89)	17 (81)	0.006
Prophylactic IABP	Agree, n (%)	28 (44)	103 (71)	120 (74)	15 (65)	< 0.001
	Use, n (%)	22 (30)	76 (49)	78 (48)	8 (32)	0.018
	Guidelines, n (%)	21 (40)	88 (64)	102 (73)	10 (53)	< 0.001
Glycemic control	Agree, n (%)	50 (63)	145 (88)	157 (91)	23 (85)	< 0.001
	Use, n (%)	43 (56)	130 (81)	131 (78)	19 (76)	< 0.001
	Guidelines, n (%)	39 (53)	127 (85)	142 (86)	20 (80)	< 0.001
NIV	Agree, n (%)	45 (66)	127 (89)	144 (88)	15 (71)	< 0.001
	Use, n (%)	38 (54)	144 (74)	120 (74)	13 (57)	0.004
	Guidelines, n (%)	36 (56)	115 (87)	125 (86)	13 (65)	< 0.001
Leuko-depleted RBC transfusion	Agree, n (%)	53 (78)	124 (93)	123 (86)	19 (83)	0.019
	Use, n (%)	51 (67)	89 (60)	69 (46)	17 (71)	0.006
	Guidelines, n (%)	50 (75)	109 (85)	105 (79)	16 (76)	0.30
Aspirin	Agree, n (%)	61 (86)	132 (88)	149 (93)	21 (91)	0.30
	Use, n (%)	60 (82)	123 (80)	121 (78)	23 (96)	0.20
	Guidelines, n (%)	59 (84)	119 (84)	131 (92)	21 (91)	0.22
Tranexamic acid	Agree, n (%)	58 (76)	127 (88)	126 (84)	14 (64)	0.016
	Use, n (%)	57 (71)	138 (88)	119 (73)	19 (76)	0.003
	Guidelines, n (%)	53 (76)	120 (83)	109 (81)	17 (74)	0.50
Aprotinin	Agree, n (%)	61 (82)	104 (75)	105 (75)	20 (83)	0.48
	Use, n (%)	71 (95)	116 (80)	104 (75)	20 (87)	0.004
	Guidelines, n (%)	58 (88)	91 (71)	95 (77)	19 (86)	0.044

NOTE. Data are presented as number (%).
Abbreviations: A-NZ, Australia-New Zealand; EU, Europe; NIV, noninvasive ventilation; RBC, red blood cell; VAC, vacuum-assisted closure.

When comparing the opinions of anesthesiologists and intensive care specialists with other physicians, no statistically significant differences were observed (Table 7). The concordance between routine use of each drug/technique/strategy and agreement for the same type of intervention for job is reported in Table S4. Major study exclusions were identified and are reported in Table S1, with the reason for exclusion (see Table S2).

Notably, 4 interventions that reached the final stage of the web vote were excluded because they did not reach the minimum general agreement of 67%. One more intervention (preoperative statin therapy in statin-naïve patients) was excluded after completion of the web vote because large, high-quality RCTs showing no benefit and possible harm were published thereafter.[51,52]

Discussion

Key Findings

All nonsurgical interventions, including drugs, techniques, and strategies, which have been shown in at least 1 study published in a peer-reviewed journal to significantly affect mortality in patients undergoing cardiac surgery, were identified. In particular, the authors found that aspirin, glycemic control, high-volume surgery, prophylactic IABP, levosimendan, leuko-depleted RBC transfusion, NIV, tranexamic acid, VAC, and volatile agents might reduce mortality, whereas aprotinin likely increases mortality.

The authors also found the existence of a gap between the medical literature and clinical practice, confirming their previous findings in other perioperative and intensive care settings.[13,16] Furthermore, as an update of the consensus process conducted in 2010,[10] the present study demonstrated the evolution of evidence-based medicine (EBM) in the field of cardiac anesthesia and intensive care, pointing to the continuous need for high-quality studies focused on major outcomes, such as mortality, in order to promptly update beliefs and modify clinical practice accordingly. In fact, this analysis of concordance between agreement and use/avoidance confirms that clinical practice often adapts slowly to evidence: emblematically, only 40% of voters declared using VAC despite this being 1 of the 3 interventions with the highest

Table 7
Percentages of Agreement With and Use of the Interventions According to Specialty

		Other	Anesthesiologist or Intensive Care Specialist	p Value
Levosimendan	Agree, n (%)	32 (73)	229 (74)	0.87
	Use, n (%)	21 (45)	133 (40)	0.56
	Guidelines, n (%)	27 (64)	198 (69)	0.50
High-volume surgeon	Agree, n (%)	50 (96)	289 (89)	0.099
	Use, n (%)	40 (83)	145 (55)	< 0.001
	Guidelines, n (%)	37 (79)	225 (82)	0.58
VAC	Agree, n (%)	49 (92)	266 (90)	0.65
	Use, n (%)	44 (88)	231 (74)	0.032
	Guidelines, n (%)	42 (88)	237 (86)	0.72
Volatile agents	Agree, n (%)	36 (92)	255 (84)	0.17
	Use, n (%)	32 (73)	277 (84)	0.058
	Guidelines, n (%)	31 (84)	234 (82)	0.77
Prophylactic IABP	Agree, n (%)	41 (79)	206 (65)	0.055
	Use, n (%)	35 (70)	136 (40)	< 0.001
	Guidelines, n (%)	35 (73)	172 (61)	0.13
Glycemic control	Agree, n (%)	47 (85)	304 (85)	0.88
	Use, n (%)	42 (81)	261 (74)	0.32
	Guidelines, n (%)	44 (83)	264 (79)	0.48
NIV	Agree, n (%)	37 (86)	272 (84)	0.69
	Use, n (%)	34 (72)	232 (69)	0.69
	Guidelines, n (%)	33 (80)	240 (80)	0.94
Leuko-depleted RBC transfusion	Agree, n (%)	37 (84)	262 (87)	0.55
	Use, n (%)	25 (57)	187 (57)	0.98
	Guidelines, n (%)	28 (70)	234 (82)	0.078
Aspirin	Agree, n (%)	50 (93)	287 (89)	0.44
	Use, n (%)	46 (87)	260 (80)	0.24
	Guidelines, n (%)	46 (88)	265 (87)	0.75
Tranexamic acid	Agree, n (%)	38 (81)	266 (83)	0.77
	Use, n (%)	37 (76)	277 (80)	0.51
	Guidelines, n (%)	32 (74)	250 (82)	0.24
Aprotinin	Agree, n (%)	33 (73)	243 (78)	0.45
	Use, n (%)	31 (72)	265 (84)	0.064
	Guidelines, n (%)	24 (63)	224 (79)	0.024

Abbreviations: IABP, intra-aortic balloon pump; NIV, noninvasive ventilation; RBC, red blood cell; VAC, vacuum-assisted closure.

percentage of agreement. Similarly, although the evidence about the perioperative use of aspirin existed for several years and, accordingly, 90% of respondents agreed with its usefulness, only 72% of respondents implemented this strategy in their clinical practice. This study's findings also suggest that, quite surprisingly, research itself also moves rather slowly in a field that is characterized by high complexity and morbidity and by an increasing level of risk compared with the authors' previous consensus conference in the cardiac surgical setting, published 6 years ago[10]; the total number of possible "recommendations" to reduce mortality is practically the same, and the overall amount and quality of evidence have not changed substantially for most of the interventions.

Relationship to Previous Literature

The first international consensus conference on mortality reduction in cardiac anesthesia and intensive care was held in 2010, and results were published in 2011.[10] Since then, although the total number was similar (11 *v* 10), 3 of the 10 interventions that previously were included have been excluded in the present update (statins, beta-blockers, and old RBC transfusion), whereas 4 new interventions have been included (leuko-depleted RBC transfusion, tranexamic acid, NIV, and VAC). Most remarkably, the literature evidence of a significant effect on mortality has strengthened for all 7 interventions included in both consensus conferences. For example, the survival benefit of aspirin, high-volume surgeon, volatile agents, IABP, and levosimendan was supported by only 1 study for each intervention at the time of the first consensus conference, whereas now the number of investigations reporting a significant reduction in mortality was 2 for aspirin, 3 for high-volume surgeon and volatile agents, 6 for IABP, and 7 for levosimendan. Moreover, the number of interventions supported by randomized evidence (RCTs or meta-analyses including RCTs) has increased proportionally, leading to an overall increase in the level of evidence.

It also is interesting to note that, compared with the similar consensus conferences on perioperative treatments[12,13] and critical care medicine,[15,16] the number of RCTs showing significant differences in mortality was much lower. In the perioperative setting, the authors identified 13 interventions supported by 39 articles among RCTs and meta-analyses of RCTs,[13] and in critical care, even if the search was limited to multicenter RCTs (mRCTs), the authors were able to include 15 interventions supported by 24 multicenter RCTs.[15,16] Conversely, although in cardiac surgery the authors extended their analysis to any kind of investigation, they found only 33 articles, only 9 of which were RCTs.

Remarkably, the comparison among the different consensus conferences also showed how the same therapeutic intervention can be beneficial in a clinical setting and harmful in another. For example, strict glycemic control has been found to be beneficial in cardiac surgery and harmful in critically ill patients. Moreover, although beta-blockers were included in the first consensus conference as improving survival, this intervention has been excluded in the present update, mainly because randomized evidence suggested that only arrhythmias (but not mortality) are reduced by beta-blocker administration in cardiac surgery. Consistently, the initiation of beta-blockers immediately before noncardiac surgery has been included among the interventions that might increase mortality in the perioperative period of any surgery.[12,13]

Implications for Clinical Practice and Future Research

Although expert opinion remains pivotal in directing clinical practice, especially in fields in which high-quality literature evidence is lacking, an "alternative" approach, such as the democracy-based consensus process, may usefully integrate the other "tools" (eg, guidelines, expert opinions, systematic reviews, surveys) that help clinicians in their decision-making. In fact, the opinions of hundreds of experts from all over the world can contribute to give the right weight to the poor literature available, providing a concise but comprehensive guide to the strategies that may really (or, at least, conceivably) and practicably have an impact on survival in cardiac surgery patients.

The authors' findings confirmed the existence of a wide gap between literature evidence and clinical practice and important differences in both beliefs and clinical practice among different countries, as already found in other settings.[13,16] In fact, even though the percentage of agreement was $> 80\%$ for 9 of 11 interventions affecting survival, the consistency between agreement and use in clinical practice most often was $< 70\%$. In most cases, the differences among countries concerned not only the use in clinical practice, but also the agreement itself with the usefulness of the interventions in terms of patient survival; these interventions probably are those that need further research.

Strengths and Limitations

The strengths of the reported approach to consensus building have been discussed before.[12–16] In the present study, in particular, the authors focused on cardiac anesthesia and cardiac intensive care to summarize EBM regarding mortality. Through a well-proven "democratic" consensus process that previously has been described widely previously,[11–16,53] the systematic review of literature was filtered through the views and the experience of 458 clinicians from all around the world, allowing for a pragmatic guide with strict adherence to EBM intended to improve patient survival and to direct future research.

A limitation of the present study was the rather overall low level of evidence of the included interventions which, together with the continuous evolution of evidence, did not allow for, in most cases, definitive conclusions. For example, even though tranexamic acid was included among the interventions that might improve survival in patients undergoing cardiac surgery, a recent large multicenter RCT, published after the conclusion of the consensus conference, failed to show a survival benefit in 4,631 patients randomly assigned to receive tranexamic acid or placebo during coronary artery bypass graft procedures, although it did show a favorable effect on blood losses and the need for blood products transfusion.[54] Moreover, although a moderate bulk of evidence has accumulated in the last 5 years about the role of levosimendan in mortality among cardiac surgery patients, 2 large RCTs (CHEETAH[55,56] and LEVO-CTS[57,58]) recently published in the *New England Journal of Medicine* failed to show any survival benefit with levosimendan administration in cardiac surgery patients.

As in the previous consensus conferences, the authors did not investigate the reasons for the differences among countries or the gap between agreement and clinical practice. However, this was not the scope of the present study and would have affected the simplicity and agility of the web-based voting process, which, in the authors' opinion, also was a strength. Other limitations demonstrating commonality with the previous consensus conferences conducted by the authors included, as discussed earlier,[13] the lack of details about the included interventions, which were only listed and very briefly contextualized.

Conclusions

This updated, international, web-based consensus conference process identified 11 interventions supported by widely agreed-on evidence suggesting an effect on mortality among patients undergoing cardiac surgery. The analysis of web voting confirmed that there was a gap between evidence and clinical practice and that both the perception of literature evidence and the clinical attitude of cardiac anesthesiologists and intensivists were significantly different among different countries for many of the included interventions. Future research should investigate the possible means to reduce both the gap existing between evidence and clinical practice and the differences among different countries. Hopefully, at least the interventions supported by the strongest evidence should be included in international guidelines on the perioperative care of patients undergoing cardiac surgery.

Appendix A. Supporting Material

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1053/j.jvca.2017.06.017.

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