



Deep anaesthesia and poor outcomes: the jury is still out

The ideal anaesthetic depth is where the risk of operative recall or awareness is as low as possible, regardless of what is happening surgically, and where blood pressure and heart rate are kept optimal for the individual patient. Emergence from an appropriate level of anaesthesia should be prompt and uncomplicated, and without side-effects. To date, the norm has been for deeper anaesthesia, facilitated by modern short-acting drugs.

Historically, the depth of anaesthesia was assessed using clinical observation of the patient and their haemodynamic responses. Advances in technology have resulted in the development of a number of methods for monitoring the depth of anaesthesia, including the bispectral index (BIS):¹ a numerical scale based on electrical activity in the brain, where complex electroencephalogram signals are converted to a single number using algorithms. The precise details of this signal processing remain commercial secrets.^{1,2} Despite technology to filter electromyographic signals, BIS can be affected by the use of muscle relaxants. In volunteer anaesthetists, onset of paralysis resulted in decreased BIS in the complete absence of any anaesthesia.³ Likewise, some neuromuscular paralysis reversal agents increase BIS.⁴ BIS has been reported to be no better than end-tidal anaesthetic concentration monitoring,^{5,6} but despite these reports, it is widely used. BIS decreases as anaesthesia deepens and a value of 40–60 is typical during maintenance of anaesthesia.

The relationship with mortality and depth of anaesthesia, as monitored by BIS, is confusing. Meta-analysis of observational studies confirms excess late mortality when BIS is low,^{7,8} and no definitive randomised controlled trials have been done. The combination of low blood pressure with low BIS, but low minimum alveolar concentration of volatile anaesthetics (deeper anaesthesia despite low anaesthetic concentration) has also been linked to excess early deaths.⁹

An adequately powered randomised controlled trial to define the effect of anaesthetic depth on outcome is needed. In *The Lancet*, Timothy Short and colleagues¹⁰ report the results of a randomised controlled trial of light and deep anaesthesia, defined as target BIS values of 50 and 35, respectively. We congratulate the authors for completing this important study, which aimed to determine whether deeper anaesthesia, as defined

by low BIS, is associated with increased mortality 1 year after surgery in older patients (ie, ≥ 60 years) who were at relatively high risk of complications. Short and colleagues concluded that survival was not different between the BIS 35 and BIS 50 groups.

The study has some limitations, which the authors have recognised. The most important limitation is that the target BIS levels were not achieved in the main intention-to-treat group. In the patients in whom the BIS target was achieved (the per-protocol group), survival between the two BIS groups was not different; however, the numbers of patients to whom this applied was much lower than the sample size calculation. The trial was underpowered because the mortality rate (on which the trial had been powered) was lower than expected. The trial design was pragmatic and aimed to be generalisable; however, the patient population was restricted to patients older than 60 years, with an American Society of Anesthesiologists grade 3 or 4, and receiving volatile anaesthesia.

The results of this study do not concur with previous observational studies in which deeper anaesthesia was associated with poorer long-term survival.^{7,8} Short and colleagues conclude that lighter anaesthesia was not associated with lower 1-year mortality than deeper anaesthesia; however, because the lack of a difference between the two groups of patients does not mean that there was no difference, deeper

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anaesthesia could yet be linked to poorer outcome. Deeper anaesthesia should therefore not be assumed to be safe in this specific group of patients. There are a few possible reasons for this conclusion: deeper anaesthesia is associated with lower blood pressures, which might compromise organ blood flow. Although blood pressure was controlled in the study by Short and colleagues, the use of vasoconstrictors might also reduce vital organ blood flow. Reduction in flow to organs such as the heart and kidney might result in organ failure, which would then potentially result in excess mortality. Therefore the uncertainty remains, and the jury is still out.

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Anaesthetic depth and complications after major surgery: an international, randomised controlled trial

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Summary

Background An association between increasing anaesthetic depth and decreased postoperative survival has been shown in observational studies; however, evidence from randomised controlled trials is lacking. Our aim was to compare all-cause 1-year mortality in older patients having major surgery and randomly assigned to light or deep general anaesthesia.

Methods In an international trial, we recruited patients from 73 centres in seven countries who were aged 60 years and older, with significant comorbidity, having surgery with expected duration of more than 2 h, and an anticipated hospital stay of at least 2 days. We randomly assigned patients who had increased risk of complications after major surgery to receive light general anaesthesia (bispectral index [BIS] target 50) or deep general anaesthesia (BIS target 35). Anaesthetists also nominated an appropriate range for mean arterial pressure for each patient during surgery. Patients were randomly assigned in permuted blocks by region immediately before surgery, with the patient and assessors masked to group allocation. The primary outcome was 1-year all-cause mortality. The trial is registered with the Australian New Zealand Clinical Trials Registry, ACTRN12612000632897, and is closed to accrual.

Findings Patients were enrolled between Dec 19, 2012, and Dec 12, 2017. Of the 18 026 patients screened as eligible, 6644 were enrolled, randomly assigned to treatment or control, and formed the intention-to-treat population (3316 in the BIS 50 group and 3328 in the BIS 35 group). The median BIS was 47·2 (IQR 43·7 to 50·5) in the BIS 50 group and 38·8 (36·3 to 42·4) in the BIS 35 group. Mean arterial pressure was 3·5 mm Hg (4%) higher (median 84·5 [IQR 78·0 to 91·3] and 81·0 [75·4 to 87·6], respectively) and volatile anaesthetic use was 0·26 minimum alveolar concentration (30%) lower (0·62 [0·52 to 0·73] and 0·88 [0·74 to 1·04], respectively) in the BIS 50 than the BIS 35 group. 1-year mortality was 6·5% (212 patients) in the BIS 50 group and 7·2% (238 patients) in the BIS 35 group (hazard ratio 0·88, 95% CI 0·73 to 1·07, absolute risk reduction 0·8%, 95% CI -0·5 to 2·0). Grade 3 adverse events occurred in 954 (29%) patients in the BIS 50 group and 909 (27%) patients in the BIS 35 group; and grade 4 adverse events in 265 (8%) and 259 (8%) patients, respectively. The most commonly reported adverse events were infections, vascular disorders, cardiac disorders, and neoplasms.

Interpretation Among patients at increased risk of complications after major surgery, light general anaesthesia was not associated with lower 1-year mortality than deep general anaesthesia. Our trial defines a broad range of anaesthetic depth over which anaesthesia may be safely delivered when titrating volatile anaesthetic concentrations using a processed electroencephalographic monitor.

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Introduction

Current practice for general anaesthesia involves the use of drug doses and combinations that ensure unconsciousness and suppression of potentially harmful haemodynamic responses during surgery in all patients. Patients who are sensitive to anaesthetics therefore receive more drug than necessary. With the development of processed electroencephalographic monitors such as the bispectral index (BIS), it is now possible to individualise the depth of anaesthesia.¹

Using BIS as a measure of anaesthetic depth, observational studies have explored an association between increasing anaesthetic depth and mortality.²⁻⁹

A meta-analysis¹⁰ of these studies revealed a 21% increase in mortality associated with deep anaesthesia. However, most of these studies did not report blood pressure, and those studies that did showed a stronger relationship between deep anaesthesia and complications when blood pressure was also low.^{7,8} Several small randomised studies did not find this association between anaesthetic depth and mortality.¹¹⁻¹⁵

Because it is unclear whether actively intervening to prevent deep anaesthesia can reduce mortality and other complications after surgery, we did the Balanced Anaesthesia Study to compare light and deep general anaesthesia in patients at risk of complications after

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*A complete list of sites and investigators in the Balanced Anaesthesia Study is provided in the appendix

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See Online for appendix

Research in context

Evidence before this study

An association between increasing anaesthetic depth and decreased postoperative survival has been shown in observational studies; however, evidence from randomised controlled trials is required to establish causality. We searched PubMed on Aug 20, 2019, using the terms “bispectral index”, “mortality”, and “randomised controlled trial” for published randomised controlled trials comparing light general anaesthesia with deep general anaesthesia in adult patients having major surgery. Reference lists of extracted articles were manually searched for other relevant articles. Of 35 articles, we found three relevant trials, with two more found by manual searching. Two small trials (n=114 and n=200) recruited highly selected populations of patients aged 65 years and older with fractured neck of femur, one trial (n=381) was stopped after an interim analysis because of futility, mortality was a secondary outcome in one large trial of patients aged 40 years and older (n=921), and one trial (n=200) was a feasibility trial. We did not identify an adequately sized trial addressing the relationship between anaesthetic depth and mortality.

Added value of this study

In this large, international, randomised controlled trial that enrolled patients aged 60 years and older with significant comorbidity and at increased risk of complications after major surgery, we found **no evidence that light general anaesthesia (bispectral index 50) was superior to deep general anaesthesia (bispectral index 35) in reducing 1-year mortality.** There was **one confirmed case of awareness (in the bispectral index 50 group)** and **no difference in cardiovascular or septic outcomes.**

Implications of all the available evidence

This study provides the first adequately powered randomised comparison of light and deep anaesthesia with respect to postoperative survival. The study defines a **broad range of anaesthetic depth over which anaesthesia might be safely delivered when titrating volatile anaesthetic concentrations using a processed electroencephalographic monitor.** **The low incidence of awareness supports the safety of targeting a bispectral index of 50 using relatively low doses of volatile anaesthetics in older patients.**

major surgery. Our primary hypothesis was that light general anaesthesia would lead to a decrease in all-cause mortality 1 year postoperatively, compared with deep general anaesthesia.

Methods

Study design and patients

The Balanced Anaesthesia Study was an international, randomised, patient-blinded, and assessor-blinded trial comparing two levels of anaesthetic depth in older patients with significant comorbidity. The rationale, design, and pilot testing of the trial were reported previously.^{14,16}

We studied patients aged 60 years and older, with an American Society of Anesthesiologists (ASA) physical status of 3 or 4, who were having surgery with expected duration of **more than 2 h**, and an anticipated hospital stay of at least 2 days. Patients received **volatile anaesthetic-based general anaesthesia with or without major regional anaesthesia.** Exclusion criteria included inability to place electrodes and monitor the BIS because of the site of surgery; planned wake-up test; **use of nitrous oxide, propofol infusion for maintenance of anaesthesia, or ketamine at an infusion rate of more than 25 mg/h⁻¹;** or expected to be uncontactable at 1 year. All patients provided written informed consent.

Randomisation and masking

On the day of surgery, patients completed the 12-item WHO Disability Assessment Schedule (WHODAS 2.0) and the Charlson comorbidity index.^{17,18} Patients were then randomly assigned in a 1:1 ratio using a web-based randomisation service to either the BIS target 50 group

or the BIS target 35 group in permuted blocks of eight patients according to region.

Anaesthetists had knowledge of the group assignment of patients. Patients and research staff who were responsible for postoperative patient assessments were not aware of group assignment. Adherence to BIS targeting was monitored throughout the trial by a data analyst who had no other involvement in the trial. Sites with unsatisfactory BIS targeting were actively managed, using feedback of BIS tracking, educational material, and, if necessary, site withdrawal from the trial. Electronic records were used whenever possible, to avoid biased recording.

Procedures

To reduce the risk of a blood pressure difference between groups becoming a confounding factor, attending anaesthetists chose a mean arterial pressure (MAP) target range appropriate for their patient and confirmed whether they would use major regional anaesthesia as part of the anaesthetic technique, before learning of the group allocation. The randomised BIS targets were 50 and 35 (referred to as the BIS 50 and BIS 35 groups, respectively). These targets were chosen on the basis of previous published research,^{6,11,19,20} audit data from a large hospital database, where these targets were close to the first and third quartiles of mean BIS in a similar group of patients, and the manufacturer's recommendations for appropriate targets for general anaesthesia. After induction of anaesthesia, anaesthetists were required to maintain anaesthesia within five BIS units of the target, while maintaining MAP within their chosen target range, but not to pursue the BIS target to the extent of using doses of drugs that could compromise patient

safety. All drugs administered during anaesthesia were recorded.

Maintenance of anaesthesia was defined as the time epoch from 10 min after induction of anaesthesia until discontinuation of volatile anaesthetic administration at the end of surgery. Mean values for BIS, MAP, and volatile anaesthetic administration were calculated for each patient. Data were then expressed as medians of these means. Volatile anaesthetic concentrations were converted to minimum alveolar concentration (MAC) equivalents and expressed as a fraction, with no age adjustment.

Patients were followed up in the postanaesthesia care unit, on the first three postoperative days, at hospital discharge, and at 30 days and 1 year after surgery. The Brice questionnaire for awareness was administered once on day 1, 2, or 3, and again on day 30.²¹ The 15-item quality of recovery score was administered on days 1, 2, 3, and 30 postoperatively.²² At day 30 and 1 year, the WHODAS 2.0 was repeated to determine new-onset disability. Patients with continuing pain also completed the modified brief pain inventory at 30 days and 1 year²³ and the neuropathic pain questionnaire at 1 year.²⁴

Outcomes

The primary outcome was 1-year all-cause mortality. Secondary outcomes were the incidences of myocardial infarction, cardiac arrest, pulmonary embolism, stroke, a composite of these four cardiovascular outcomes, sepsis, surgical site infection, a composite of these two septic outcomes, total intensive care unit stay, awareness during anaesthesia, WHODAS 2.0 score at 30 days and 1 year, disability-free survival (defined as alive and less than a 4-point decline in WHODAS 2.0 score at 1 year²⁵), persistent pain, and cancer recurrence.

All secondary outcomes were adjudicated by an endpoint adjudication committee, comprising an internal medicine physician (chair), an intensive care physician, and two anaesthetists. Members of the endpoint adjudication committee did not participate in the trial and adjudicated all secondary outcomes while masked to group allocation, using source documentation. The trial included full adverse event reporting using the coding and procedures of the Medical Dictionary of Regulatory Activities (MedDRA) system.²⁶ Random site monitoring was done by the project office.

Statistical analysis

The primary and secondary outcomes were initially analysed using an intention-to-treat population that included all patients who were randomly assigned and had induction of general anaesthesia for surgery. These patients were followed up for the duration of the trial unless they withdrew consent, in which case data were censored at the time of withdrawal.

The expected probability of 1-year survival was 90%.^{14,16} With a type I error of 0.05, we calculated that enrolment of 6500 patients was required to detect a reduction in

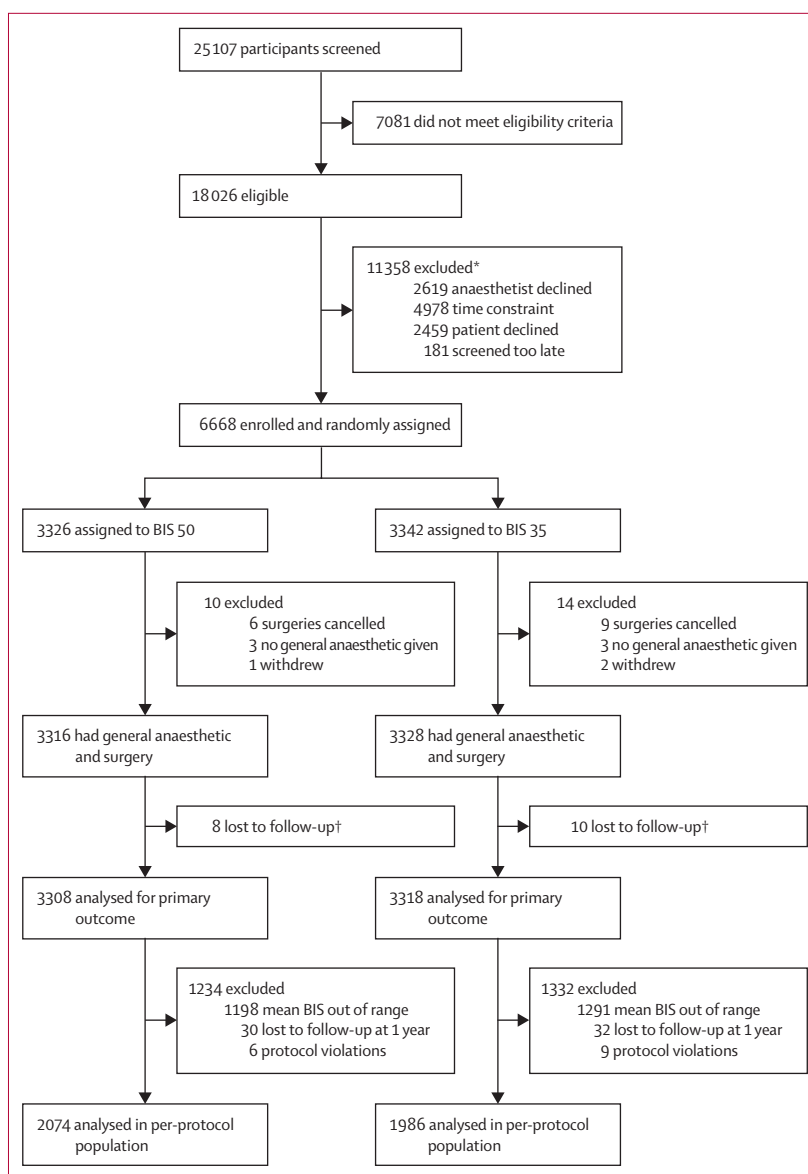


Figure 1: Trial profile

BIS=bispectral index. *Some patients had multiple reasons for exclusion. †Does not include those with recorded censor data.

mortality in the BIS 50 group of 20% with a power of 0.8. The sample size was inflated by 2% to account for withdrawals and loss to follow-up and the probability reduced to 0.049 to allow for one interim analysis.

Baseline characteristics were summarised by group using means and SDs, medians and IQRs, or counts and percentages as appropriate. Participant disposition, including reasons for withdrawal from the study at each stage, were recorded.

The primary outcome was compared between groups using a log-rank test stratified by region. Results are summarised as hazard ratios (HRs) with 95% CI generated from a Cox regression model, which included

	BIS 50 (n=3316)	BIS 35 (n=3328)
Age, years	72 (7)	72 (7)
Sex		
Male	2111 (64%)	2110 (63%)
Female	1205 (36%)	1218 (37%)
Bodyweight, kg	79 (67–93)	79 (67–93)
Body-mass index, kg/m ²	28 (24–32)	28 (24–32)
ASA physical status*		
3	3158 (95%)	3144 (95%)
4	158 (5%)	183 (5%)
Operation for cancer	1531 (46%)	1576 (47%)
Preoperative WHODAS 2.0 score	18 (14–25)	18 (14–25)
Preoperative Charlson comorbidity index	6 (4–9)	6 (4–9)
Preoperative haemoglobin, g/L ⁻¹	131 (119–144)	131 (117–143)
Preoperative creatinine, mmol/L ⁻¹	85 (71–104)	84 (71–103)
Albumin, g/L ⁻¹	39 (36–42)	39 (36–42)
Country		
Australia	1279 (39%)	1291 (39%)
China	540 (16%)	530 (16%)
New Zealand	669 (20%)	678 (20%)
UK and Europe	280 (8%)	285 (9%)
USA	548 (17%)	544 (16%)
Type of surgery		
Cardiac	53 (2%)	60 (2%)
Head and neck	77 (2%)	86 (3%)
Intra-abdominal	1528 (46%)	1525 (46%)
Orthopaedic	361 (11%)	344 (10%)
Spinal	267 (8%)	249 (7%)
Thoracic	234 (7%)	234 (7%)
Vascular	634 (19%)	649 (20%)
Other	162 (5%)	181 (5%)
Planned postoperative care in ICU	479 (14%)	499 (15%)
Coexisting medical conditions		
Cancer	1641 (50%)	1647 (50%)
Cardiovascular disease	1278 (39%)	1248 (38%)
Stroke or neurological disease	567 (17%)	529 (16%)
Respiratory disease	773 (23%)	749 (23%)
Diabetes	1028 (31%)	1008 (30%)
Peptic ulcer disease	385 (10%)	393 (12%)
Rheumatoid arthritis or connective tissue disease	318 (10%)	313 (9%)
Renal disease	249 (8%)	276 (8%)
Liver disease	215 (7%)	218 (7%)

Data are mean (SD), n (%), or median (IQR). BIS=bispectral index. ASA=American Society of Anesthesiologists. WHODAS 2.0=12-Item WHO Disability Assessment Schedule, which estimates the amount of disability; scores of 24 or more indicate at least moderate disability. ICU=intensive care unit. *Includes the protocol violation of one ASA physical status 2 patient.

Table 1: Characteristics of the patients at baseline

randomised treatment and region as factors. Patients who were lost to follow-up were censored to the last time that they were known to be alive after hospital discharge. A two-tailed p value of 0.049 was taken to

indicate statistical significance. Sensitivity analyses were done whereby all those lost to follow-up at 1 year were assumed to be dead.

Secondary outcomes were compared between groups using the Mantel-Haenszel χ^2 test with stratification according to region and were summarised as common odds ratios (OR) and 95% CIs. The Holm-Bonferroni adjustment for multiplicity was applied to the secondary outcomes.

A per-protocol analysis was also done after removing all patients with mean BIS values more than five points from the BIS target, patients who were lost to 1-year follow-up and patients who had major protocol violations. These included patients who did not meet trial inclusion criteria and patients who inadvertently received prohibited drugs for maintenance of anaesthesia.

Study oversight was provided by an independent data monitoring committee appointed by the New Zealand Health Research Council, which included a review of the results from the planned interim analysis after 2000 patients had been randomly assigned and completed the study.

The trial is registered with the Australian New Zealand Clinical Trials Registry, ACTRN12612000632897, and is closed to accrual.

Role of the funding source

The funders of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the Article. TGS had full access to all the data in the study. TGS and KL had final responsibility for the decision to submit for publication. There was no commercial involvement in this trial.

Results

Patients were enrolled between Dec 19, 2012, and Dec 12, 2017, at 73 centres in seven countries (ie, Australia, China, Ireland, New Zealand, the Netherlands, the UK, and the USA). Of the 18026 patients screened as eligible, 6644 were enrolled, randomly assigned to treatment or control, and formed the intention-to-treat population (3316 in the BIS 50 group and 3328 in the BIS 35 group; figure 1). The median number of patients enrolled per site was 48 (IQR 20–145); a complete list of sites and their recruitment to the trial is provided in the appendix (pp 3–6).

The mean age of patients was 72 years (SD 7); 4221 (63%) were male and 2423 (37%) were female, 3107 (46%) had surgery for cancer and 3053 (46%) had abdominal surgery. There were no differences between groups in any of the measured baseline variables (table 1). The ethnicity of patients is reported in the appendix (p 9). Of the intention-to-treat population, 80 patients (1%) were lost to follow-up at 1-year, with censored data available for 62 of these patients.

BIS and MAP targeting, and volatile anaesthetic use are summarised in table 2 and displayed in figure 2. Electronic recording of the BIS was available for

	BIS 50 (n=3316)	BIS 35 (n=3328)
Duration of surgery, min	200 (145–272)	195 (144–274)
Major regional local anaesthesia	576 (17%)	573 (17%)
BIS	47.2 (43.7–50.5)	38.8 (36.3–42.4)
Mean arterial pressure, mm Hg	84.5 (78.0–91.3)	81.0 (75.4–87.6)
MAC of volatile anaesthetic	0.62 (0.52–0.73)	0.88 (0.74–1.04)
Volatile anaesthetic		
Isoflurane	126 (4%)	157 (5%)
Sevoflurane	2252 (68%)	2158 (65%)
Desflurane	1187 (36%)	1328 (40%)
Inotrope or vasopressor use	2538 (77%)	2853 (86%)
Postanaesthesia care unit		
Number who attended	3314 (91%)	3030 (90%)
Number given analgesia	1954 (65%)	1919 (63%)
Number given antiemetic	626 (21%)	609 (20%)
Duration of stay, min	90 (60–144)	92 (60–150)

Data are n (%) or median (IQR). 9% of patients received more than one volatile anaesthetic. BIS=bispectral index. MAC=minimum alveolar concentration.

Table 2: Intraoperative characteristics

6445 (97%) cases, blood pressure for 5980 (90%) cases, and volatile anaesthetic concentrations for 5995 (90%) cases. There were no differences in duration of anaesthesia nor use of major regional anaesthesia between groups. Anaesthetists reported difficulty with BIS tracking for 3307 (50%) cases and that targeting BIS 50 was more difficult than targeting BIS 35. The median BIS was 47.2 (IQR 43.7–50.5) in the BIS 50 group and 38.8 (36.3–42.2) in the BIS 35 group, with 4272 (66%) patients being within five units of the target and a BIS separation of 8.4 between the two groups. MAP was 3.5 mm Hg (4%) higher and volatile anaesthetic use was 0.26 MAC (30%) lower in the BIS 50 group than the BIS 35 group. 2602 (39%) patients received a mean MAC of less than 0.7 during maintenance of anaesthesia.

1-year mortality was 6.5% (212 patients) in the BIS 50 group and 7.2% (238 patients) in the BIS 35 group (table 3). The HR was 0.88 (95% CI 0.73 to 1.07), with no heterogeneity in mortality between regions (HR 0.89, 0.74 to 1.07; appendix p 14). The absolute risk reduction was 0.8% (–0.5 to 2.0). The Kaplan-Meier survival curves for the two groups are provided in figure 3.

Testing of the effects of the distribution of the various demographic variables on the result found no significant confounding between groups that could account for the result (appendix p 14). In the sensitivity analysis of 1-year mortality, the HR was 0.89 (95% CI 0.74–1.06), indicating that missing data were not a source of bias in the study result.

The influence of anaesthetic depth on the secondary outcomes is summarised in table 3. There was one case of awareness in the BIS 50 group. Anaesthetic depth had no effect on quality of recovery from anaesthesia, hospital

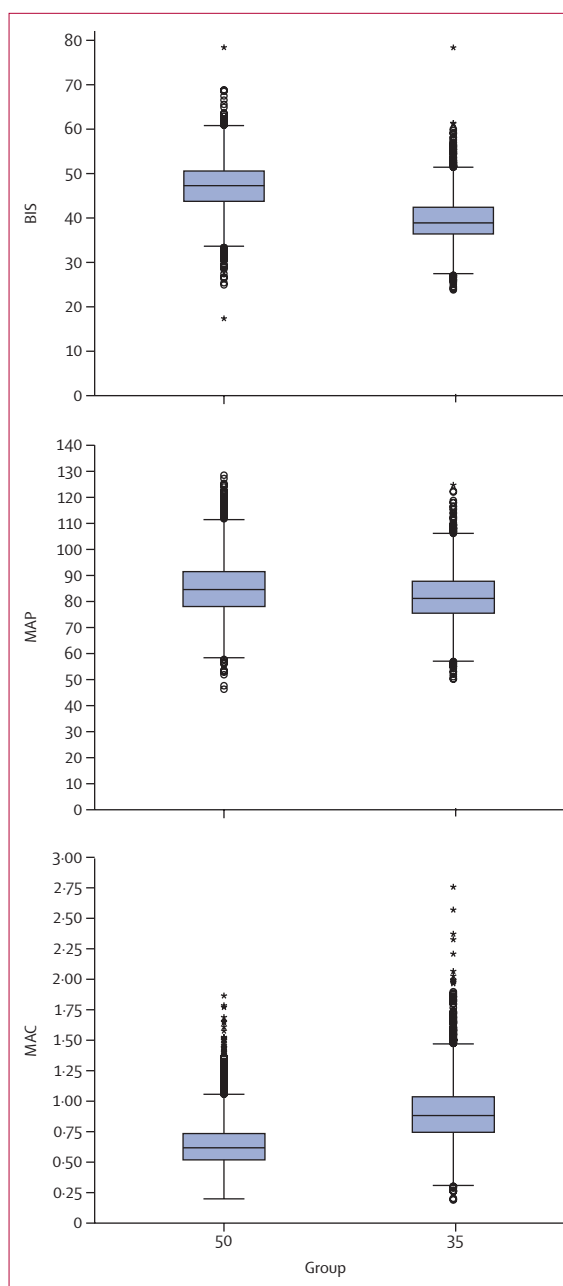


Figure 2: BIS, MAP, and MAC of volatile anaesthetic in patients receiving BIS target 50 and BIS target 35 anaesthesia

Data are expressed as median of means with IQR. The whiskers are 1.5 times the IQR, the open circles >1.5 times the IQR, and the asterisks >3 times the IQR. BIS=bispectral index. MAP=mean arterial pressure. MAC=minimum alveolar concentration.

length of stay, or any of the cardiovascular or septic outcomes. At 1 year, disability-free survival was similar in both groups. There was a significant difference between the groups in the severity, but not incidence, of neuropathic pain at 1 year.

The per-protocol population comprised 4060 (61%) patients (figure 1). 2489 patients were excluded for mean

	BIS 50 (n=3316)	BIS 35 (n=3328)	Ratio (95% CI)* or p value
Primary outcome			
All-cause mortality	212 (6%)	238 (7%)	0.88 (0.73–1.07)
Secondary outcomes			
Myocardial infarction	77 (2%)	77 (2%)	1.00 (0.73–1.38)
Cardiac arrest	23 (1%)	12 (<1%)	1.9 (0.96–3.9)
Pulmonary embolism	33 (1%)	43 (1%)	0.77 (0.49–1.22)
Stroke	43 (1%)	33 (1%)	1.31 (0.83–2.1)
Sepsis	204 (6%)	219 (7%)	0.93 (0.76–1.13)
Surgical site infection	240 (7%)	212 (6%)	1.15 (0.95–1.39)
Unplanned ICU admission	170 (5%)	190 (6%)	0.89 (0.72–1.10)
Awareness during anaesthesia	1	0	..
WHODAS 2.0 score			
30 days post surgery	18 (14–25)	18 (13–25)	0.78
1 year post surgery	16 (13–23)	16 (13–23)	0.19
Disability-free survival at 1 year	2035 (68%)	2021 (68%)	1.05 (0.94–1.17)
Persistent pain			
Day 30	729 (22%)	745 (22%)	0.98 (0.87–1.10)
Day 30 score	230 (90–440)	205 (80–405)	0.14
1 year	250 (8%)	224 (7%)	1.13 (0.93–1.36)
1 year score	213 (60–460)	224 (76–524)	0.32
Neuropathic pain			
1 year	237 (7%)	211 (6%)	1.13 (0.93–1.38)
1 year score	140 (60–300)	180 (70–355)	0.038
Recurrence of cancer at 1 year	216 (14%)	211 (13%)	1.02 (0.85–1.25)
Exploratory outcomes			
Composite of mortality, myocardial infarction, cardiac arrest, pulmonary embolism, and stroke	333 (10%)	360 (11%)	0.92 (0.79–1.08)
Composite of sepsis and surgical site infection	372 (11%)	359 (11%)	1.05 (0.90–1.22)
Other outcomes			
Quality of recovery score			
Day 1	101 (86–114)	101 (86–116)	0.66
Day 2	109 (93–124)	108 (92–123)	0.53
Day 3	104 (89–118)	104 (88–118)	0.64
Day 30	132 (118–142)	132 (118–142)	0.89
Duration of postoperative hospital stay, days	6 (4–10)	6 (3–9)	0.54

Data are n (%), n, or median (IQR), unless otherwise stated. Quality of recovery score was the 15-item score; its range is 0 to 150, with 150 being excellent in all domains. BIS=bispectral index. ICU=intensive care unit. WHODAS 2.0=WHO Disability Assessment Schedule, which estimates the amount of disability; scores of 24 or more indicate at least moderate disability. *Hazard ratio for BIS 50 compared with BIS 35 for primary outcome; odds ratio for BIS 50 compared with BIS 35 for other outcomes.

Table 3: Primary, secondary, exploratory, and other outcomes

BIS being more than five units from the target, 62 for being lost to follow-up at 1 year, and 15 for major protocol violations, which included receiving nitrous oxide or propofol infusion for maintenance of anaesthesia, having an ASA score of 2, or being younger than age 60 years. Baseline characteristics for the per-protocol group are provided in the appendix (p 10). Data on BIS and MAP targeting, and volatile anaesthetic use are also provided in the appendix (p 11). There was no significant difference in the primary outcome within

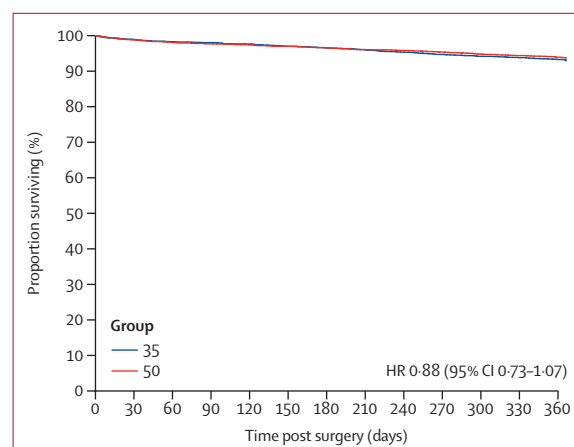


Figure 3: Kaplan-Meier curve showing survival to 1 year after surgery in patients receiving BIS target 50 and BIS target 35 anaesthesia
HR=hazard ratio. BIS=bispectral index.

1 year of surgery, OR 0.86 (95% CI 0.67–1.09; appendix p 15). There were also no significant differences between groups in any of the secondary outcomes (appendix p 12).

Adverse events are summarised in the appendix (p 13). Grade 3 events (severe or medically significant) occurred in 954 (29%) patients in the BIS 50 group and 909 (27%) patients in the BIS 35 group; and grade 4 adverse events (life-threatening) in 265 (8%) and 259 (8%) patients, respectively. The most commonly reported adverse events were infections, vascular disorders, cardiac disorders, and neoplasms.

Discussion

In this international, randomised controlled trial, we evaluated the influence of two levels of anaesthetic depth on postoperative survival and serious complications in older patients (≥ 60 years) with significant comorbidity presenting for major surgery. **At 1 year, there was no evidence of a difference in mortality or the incidence of complications between the two groups.** The quality and time course of recovery from anaesthesia and surgery were **similarly unaffected.**

The strengths of this study include its **large size** and the number of participating sites in **seven countries.** We achieved a clinically significant difference in volatile anaesthetic concentration between the two groups, with **MAC values 30% lower** in the BIS 50 group than the BIS 35 group, while maintaining patient safety. Patient sensitivity to anaesthetic drugs was managed by individualised titration to target BIS values. The potential confounder of blood pressure was mitigated by requiring anaesthetists to choose appropriate MAP targets for their patients before knowing their treatment allocation. There was a **small (4%) difference in median MAP** between groups, but we do not consider this large enough to affect the validity of our result. **Observational studies of the relationship between blood pressure and**

outcome only report adverse effects at MAP less than 70 mm Hg, well below the mean values recorded in both groups in our study.^{7,27} There was a significant difference between groups in the severity, but not the incidence, of neuropathic pain at 1 year. The difference was 2.5% of the neuropathic pain scale and this is unlikely to be clinically meaningful.

We assessed patients for awareness on two occasions, using the widely cited Brice questionnaire. Only one patient had confirmed awareness during surgery. The incidence of awareness was previously reported to be 0.08–0.24% in BIS-monitored patients having major surgery.^{19,20,28} Our finding is important when considering that 39% of patients received less than 0.7 MAC of volatile anaesthetic throughout surgery. This low incidence of awareness supports the safety of targeting a BIS of 50 using relatively low doses of volatile anaesthetics in older patients.

A limitation of our study is that we did not achieve our target BIS values in the two groups, which might have decreased our ability to confirm a difference if one existed. However, the per-protocol analysis also found no difference in 1-year mortality or other outcomes, which supports the robustness of our findings. A further limitation is that 1-year mortality was 2% lower than anticipated, possibly because of fewer patients with an ASA physical status of 4 being recruited than expected. The incidence of the cardiovascular and septic secondary outcomes was also lower than expected from recent studies of older patients.^{29,30} Our study was limited to general anaesthesia maintained with volatile anaesthetics and provides no information about maintenance of anaesthesia with intravenous propofol.

Our findings contrast with those of previous large observational studies of anaesthetic depth and complications.^{2–9} These studies were limited by lack of randomisation and the potential for confounding by low blood pressure, which was not reported in most of these studies and is more likely with higher volatile anaesthetic administration.^{2–6,8,9} Our findings are more robust and generalisable than the previous small randomised trials, which did not achieve enough BIS separation¹² or were done in specific surgical groups.^{13,15}

In conclusion, in a large, multicentre, comparative efficacy trial, we found no evidence that mortality and serious complications of anaesthesia and surgery were influenced by targeting a BIS of either 50 or 35. This finding defines a broad range of anaesthetic depth over which anaesthesia may be safely delivered when titrating volatile anaesthetic concentrations using a processed electroencephalographic monitor.

Contributors

TGS, DC, and KL conceived of the trial. TGS was the chief investigator. TGS, DC, DSM, and KL were responsible for the day-to-day running of the trial. CF did the statistical analysis. TGS and KL wrote the first draft of the Article, and all authors revised this draft. All authors read and approved the final version.

Declaration of interests

TGS is a consultant to Becton Dickinson (Australia) and has received research funding from Boehringer Ingelheim. All other authors declare no competing interests.

Data sharing

Individual, deidentified participant data used in these analyses will be shared 2 years after publication by request from any qualified investigator after approval of a protocol, statistical analysis plan, and receipt of a signed data access agreement via the Research Office of Auckland District Health Board, New Zealand; and after obtaining the approval of the New Zealand Health and Disability Ethics Committees for the project and data release.

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Deep anaesthesia

Reading the Balanced Anaesthesia Study,¹ which found no difference in the 1-year all-cause mortality between light (median bispectral index [BIS] 47.2 [IQR 43.7–50.5]) and deep (median BIS 38.8 [36.3–42.2]) anaesthesia after major surgery in older patients at risk of postoperative complications, was a pleasure. The study aimed to recruit all patients older than 60 years with an American Society

of Anesthesiologists (ASA) score of 3 or 4. However, the generalisability of Timothy G Short and colleagues' conclusion is limited by only 5% of patients having an ASA status of 4. Lindholm and colleagues² found comorbidity, as measured by ASA physical status, to be one of the most powerful predictors of mortality in patients with a low BIS. Patients with an ASA score of 4 had a hazard ratio (HR) of 11.5 (95% CI 4.37–30.4) for 2-year mortality. Furthermore, because 6269 (94.4%) of 6644 patients in the Balanced Anaesthesia Study were either white or Chinese, further investigation within other minority groups is required.

Kertai and colleagues³ found contrasting results when investigating the effect of low BIS on cardiac and non-cardiac surgeries. Cumulative duration of low BIS was shown to be independently associated with intermediate mortality (HR 1.29, 95% CI 1.12–1.49) for cardiac surgery, whereas there was no association with non-cardiac surgery (1.03, 0.93–1.14).⁴ However, a study looking at hip fracture repairs found that light anaesthesia in patients with comorbidities was significantly associated with reduced mortality (HR 0.43, 95% CI 0.19–0.97).⁵ Given the variation in previous studies, and because 1933 (47.6%) of the 4060 surgeries in this study¹ were intra-abdominal and only 63 (1.6%) were cardiac, appropriate subgroup analyses of the various operation types would have been useful to show any correlations.

I declare no competing interests.

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I read with great interest the article by Timothy G Short and colleagues¹ about their Balanced Anaesthesia Study that investigated mortality in older patients (aged ≥60 years) undergoing major surgery who were randomly assigned to light general anaesthesia (bispectral index [BIS] target 50) or deep general anaesthesia (BIS target 35). This trial showed no difference in 1-year all-cause mortality between patients assigned to light general anaesthesia or deep general anaesthesia. However, in addition to the limitations mentioned in Short and colleagues' discussion, I note certain other serious issues that need to be addressed.

A so-called triple low state, which is often defined as a mean blood pressure of less than 75 mm Hg, a BIS of less than 45, and a minimum alveolar concentration (MAC) of less than 0.8, is a stronger predictor of 30-day postoperative mortality than BIS as an independent measure.^{2,3} In certain studies on this topic, a low MAC is also defined as being less than 0.7.⁴ Why this triple low state indicates a patient's sensitivity to anaesthesia is hypothesised to be because of the fact that these measures connote fragility or underlying disease, which predispose to a higher rate of complications. However, a causal association between a triple low state and mortality was not supported by a large retrospective case series⁴ or a prospective analysis.⁵ Another interesting aspect is that individually considering a mean blood pressure of less than 75 mm Hg, a BIS of less than 45, or a MAC of less than 0.8 is

unremarkable in terms of correlations with postoperative mortality.

The role of a low BIS in postoperative mortality being important is undisputed. However, an analysis of the patients who had intraoperative triple low states in the study population could have increased the lucidity of discussion on this topic.

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In their study, Timothy G Short and colleagues¹ showed no difference in 1-year all-cause mortality in patients who were randomly assigned to a bispectral index (BIS) target of 35 versus a BIS target of 50. We feel that this study is important, but we have questions about the goal BIS values chosen for the two groups.

Medtronic, who developed the BIS brain monitoring system, recommends a target BIS range of 40–60 for surgical anaesthesia. Rather than aiming for the extremes of this range (ie, 40 vs 60), the authors randomly assigned patients in one group to a BIS value lower than this range (ie, 35). The other group was randomly assigned to a BIS target value of 50, which is described as light general anaesthesia. Rather than being light,

a BIS value of 50 is exactly in the middle of Medtronic’s recommended target range. Instead, we wish that this group had been randomly assigned to a higher BIS target, such as 60 or even more, which would have better approximated the goal of light general anaesthesia. The authors were comfortable with a target less than the recommended range in the BIS 35 group, so why did they not use a target of 60 or more in the comparison group?

We worry that anaesthetists will use this study as an excuse to over-anaesthetise patients. The study shows that aiming for a higher BIS value is safe and could save money through the use of less volatile anaesthetic and fewer vasopressors, but this result would have been even more impactful had a higher upper BIS value been chosen.

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In a landmark trial, Timothy G Short and colleagues¹ randomly assigned 6644 older patients (aged ≥60 years) undergoing major surgery to either general anaesthesia with a bispectral index (BIS) target of 35 or general anaesthesia with a BIS target of 50, while maintaining an appropriate mean arterial blood pressure. Short and colleagues¹ assumed 1-year all-cause mortality to be 10% with deeper anaesthesia and powered their trial to detect an absolute risk reduction (ARR) of 2% (from 10% to 8%).² However, the absence of a difference between the two groups does not mean that there is no difference; “uncertainty remains and the jury is still out”.³ We suggest how a better estimate of the effect of anaesthetic depth on mortality could be made by use of the data already available via

an alternative per-protocol analysis (appendix).

This trial was pragmatic. As such, the intention-to-treat analysis shows what would happen if anaesthetists were to aim for a BIS of 35 rather than 50. Difficulty complying with the trial protocol reduced the separation in anaesthetic depth between groups to less than the BIS separation target of 15 (appendix). On the basis of an ARR of 0.8% (95% CI –0.5 to 2.0), the authors conclude that 1-year all-cause mortality did not differ between the two groups. However, claiming non-inferiority is only appropriate if every value within the CI corresponds to a difference of non-clinical importance.⁴

For evidence of the underlying effect of deeper anaesthesia, the per-protocol estimate is of most interest. The authors did a per-protocol analysis by removing all patients with BIS values of more than 5 points from the BIS target, patients who were lost to 1-year follow-up, and patients who had major protocol violations. This removal increased the BIS separation, but reduced power. The authors’ per-protocol analysis shifted the hazard ratio for mortality, which suggests that, as the separation between groups increases, there is a stronger effect on mortality, but the loss of power makes it difficult to know for sure (appendix).

The ideal per-protocol analysis would show what difference in mortality would be expected if both groups had the same mean deviation from target. Answering this question is possible with the available data and requires refitting the Cox regression model for the primary outcome, and, in addition to the randomised intervention, adding an extra covariate representing each patient’s deviation from their BIS target (ie, 50 or 35, depending on the group). As all patients can be used for this analysis, there will be no loss of power and, if a lower BIS is associated with increased mortality, adding this covariate will actually increase the power of the study.⁵

See Online for appendix



For Medtronic’s BIS recommendations see <https://www.medtronic.com/content/dam/covidien/library/us/en/product/brain-monitoring/bis-tiva-anaesthesia-brochure.pdf>

The estimated effect of the intervention calculated from this new model, if consistent with the potential for harmful effects from deep general anaesthesia for important secondary outcomes (appendix), might yet convince the jury.

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The minimum alveolar concentration (MAC) of volatile anaesthetic agents is the concentration required to prevent movement with noxious stimulation in 50% of people.¹ Lower concentrations than the MAC typically prevent memory formation. The MAC is conventionally reported with reference to healthy people aged 40 years and was reported like so in the Balanced Anaesthesia Study.² However, the MAC decreases by approximately 6–7% per decade of life.³ In the Balanced Anaesthesia Study,² the mean patient age was 72 years (SD 7). We calculated the estimated median age-adjusted MAC to be 0.78 (IQR 0.65–0.91) in the high bispectral index (BIS) group

(BIS target 50) and 1.10 (0.93–1.30) in the low BIS group (BIS target 35).

A human volunteer study⁴ showed that BIS can be reduced to less than 50 with the administration of neuromuscular blocking agents in the absence of sedative hypnotics. Most patients in the Balanced Anaesthesia Study probably received neuromuscular blocking agents. However, although most patients did not remember their procedures, it remains possible that some were conscious, paralysed, and distressed during surgery, especially when BIS readings were 50 or higher.

Two facts are highly informative: (1) no currently available monitor reliably detects consciousness when neuromuscular blocking drugs are administered; and (2) based on findings from the ENGAGES trial⁵ and Balanced Anaesthesia Study,² post-operative outcomes are apparently not worse in older patients (those ≥60 years) receiving higher anaesthetic concentrations. Therefore, the following recommendations seem prudent for older surgical patients requiring general anaesthesia: minimise the administration of neuromuscular blocking agents, and, when patients must be pharmacologically paralysed, err on the side of more, rather than less, anaesthesia.

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Authors' reply

We thank everyone for their interest in our study.¹ We would like to reiterate that the Balanced Anaesthesia Study was an intention-to-treat randomised controlled trial designed to show a 2% absolute difference in mortality between groups. We aimed to confirm the finding from several observational studies that there is a roughly 20% increase in mortality in sick, older patients (aged ≥60 years) receiving deep anaesthesia.²

Blood pressure targets were set to reduce the risk of confounding. Our trial was quite different to the observational studies that reported an association between anaesthetic depth and mortality in that our study tested whether an intervention to control depth within tight, predetermined parameters is effective (ie, that, in terms of postoperative mortality, the anaesthetic depth is intrinsically causal). The difficulty that many anaesthetists had titrating anaesthesia to a specific target does not alter the result of our study. This difficulty is simply clinical reality, and the study was not underpowered to test our hypothesis.

Our per-protocol analysis supported our conclusion that increasing anaesthetic depth did not increase mortality. Perhaps including a larger number of patients, a sicker group of patients (ie, those with an American Society of Anesthesiologists physical status of 4), or more accurate bispectral index (BIS) targeting could produce a different result, but it is probable that this difference would shrink towards clinical irrelevance.

In response to Luzius A Steiner and colleagues, we did not conclude that there was no difference between the two groups, only that we did not observe a difference. Our trial was not designed to test non-inferiority.

Urvi Karamchandani and Varun Suresh imply that we should give equal importance to observational data as we give to data from our randomised controlled trial, but these methods of study are very different and should not be directly compared. Nevertheless, we have planned a secondary analysis of our data to investigate further relationships between anaesthetic depth, anaesthetic agent sensitivity, and blood pressure (ie, the triple low state), and the effect of these factors on mortality. A subgroup analysis by operation would only include small numbers of patients and would not provide useful information. We are not aware of any effects that racial differences have on anaesthetic depth and outcome that would support investigating such a hypothesis.

Stephen M McHugh and colleagues report on **Medtronic's recommendations for BIS targeting, but these recommendations were based on the use of the monitor to ensure adequate hypnosis during anaesthesia.** The BIS targets in our study were based on large-scale observational data of values actually recorded while patients were under routine anaesthesia. The targets chosen were close to the first and third quartiles for mean BIS recorded in an audit of a large tertiary hospital's anaesthetic database.²

We appreciate Philip E Vlisides and colleagues' suggestions; however, we did not age-adjust our volatile anaesthetic doses because such an adjustment is made by use of pooled population data derived from a small number of individuals, has wide CIs, and could confound any statistical treatment. **We do not believe that the observation of low BIS values in awake, unstimulated, unintubated volunteers given rocuronium is relevant to this study.**³ We only had one report of awareness during anaesthesia, despite enrolling 6644 patients having major surgery.

We stand by our conclusion that, in the context of strict blood pressure control and in older patients at risk of

postoperative complications, both BIS targets were similar in terms of their influence on anaesthetic mortality.

We declare no competing interests.

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Lifting bans on pregnant girls in school

The debate about whether to permit girls to attend school after becoming pregnant has been in the headlines in Sierra Leone, Tanzania, and elsewhere.¹ Advocates for permitting girls to remain in school affirm that education is a human right.² Critics propose that permitting girls to return might encourage more adolescent pregnancy, even as countries seek to reduce adolescent childbearing.³ Evidence on the consequences of girls returning to school after they become

pregnant is limited, and identifying the effect on subsequent outcomes can be challenging.⁴ Allowing pregnant girls in school mitigates one adverse consequence of pregnancy (ie, having to drop out), and the benefits of being in school might disincentivise second pregnancies. Peers who interact with pregnant classmates might also update their beliefs about pregnancy, either favourably or unfavourably.

We examined Demographic and Health Surveys data from nine countries in Africa that overturned bans on girls returning to school after pregnancy between 1993 and 2015 (appendix p 3). Across these nine countries, the average pregnancy rate among girls aged 14–20 years was 14.4% in the year of the policy change that allowed pregnant girls in school (the year of the policy change varied across countries). 2 years before the policy change, the pregnancy rate was at 13.7%, showing that the rate subsequently rose by 0.7%.

2 years after the policy change, the average pregnancy rate across countries was 13.3%: an absolute reduction. We calculated the expected pregnancy rate—based on the trend in the 2 years before the policy change—and observed how different the actual pregnancy rate was relative to the expected rate. If the pregnancy rate had continued to change at the same rate in the 2 years after the policy change as it had in the 2 years before the policy change, the average rate across the nine countries would have been 15.1%. However, the observed rate 2 years after the lifting of the ban is just 13.3%. Although the change in pregnancy rate varies across countries, the rate after the policy change falls in six of nine countries relative to expectations (appendix p 1); two of those declines are statistically significant. The proportion of girls who report both having been pregnant and currently attending school rises across countries in the 2 years after the policy change.

This evidence suggests that allowing girls who have been pregnant to attend school is unlikely to boost

For the Demographic and Health Surveys Program datasets see <https://dhsprogram.com/data/availabledatasets.cfm>

See Online for appendix



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