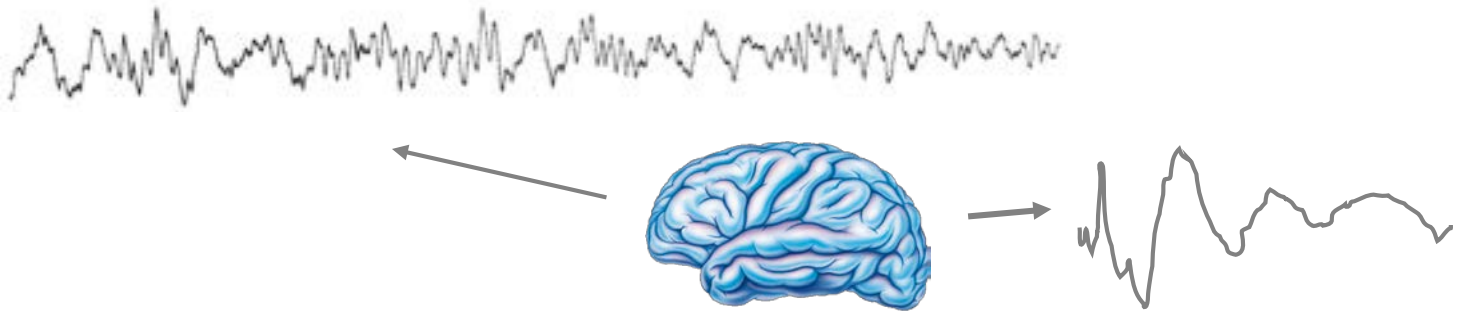
STOCKHOLM • 21-23 SEPTEMBER
SFAI-VECKAN 2015

Monitoring of the Brain during Anaesthesia:

current status of the field



Cor J. Kalkman,
Department of Anesthesiology
Division of Anesthesiology, Intensive Care and Emergency Medicine
University Medical Center, Utrecht, the Netherlands
c.j.kalkman@umcutrecht.nl

STOP
Anesthesia Awareness

1 CASE IS 1 TOO MANY

Intraoperative awareness
(explicit memory formation, conscious recall)

---

a young woman described her terrifying experience during a hernia repair for which she was given inadequate anesthesia. Although paralyzed during the procedure, she recalled in detail operating room events and inappropriate conversations.

"...my awareness during surgery has dramatically changed my whole life. Not a minute goes by that I don't remember the horror of my surgery. In many respects my life has been a nightmare since my surgery."

Tracy J. Awareness in the operating room: a patient's view. In: Sebel PS, ed. Memory and Awareness in Anesthesia: Prentice Hall, 1993, pp. 349-353

Determining if awareness has occurred: the structured Brice interview

1. What is the last thing you remember before going to sleep?
2. What is the first thing you remember waking up?
3. Do you remember anything between going to sleep and waking up?
4. Did you dream during your procedure?
5. What was the worst thing about your operation?

Intraoperative awareness:
incidence in modern anesthesia practice

Sandin RH: *Lancet* 2000; 355: 707-11

- 11785 patients, general anaesthesia

  Interviewed 3 times:

  before they left the post-anaesthesia care unit

  1-3 days after the operation and 7-14 days after the operation.
- 18 cases of awareness

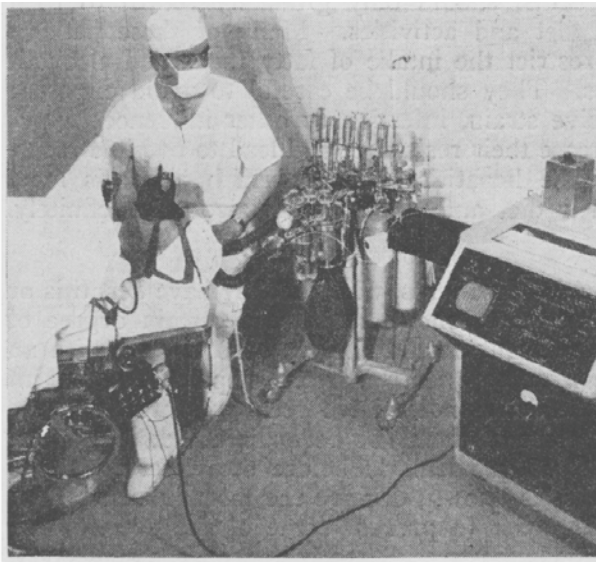
  one case of inadvertent muscle blockade occurred before unconsciousness**.**
- **Incidence of awareness :**

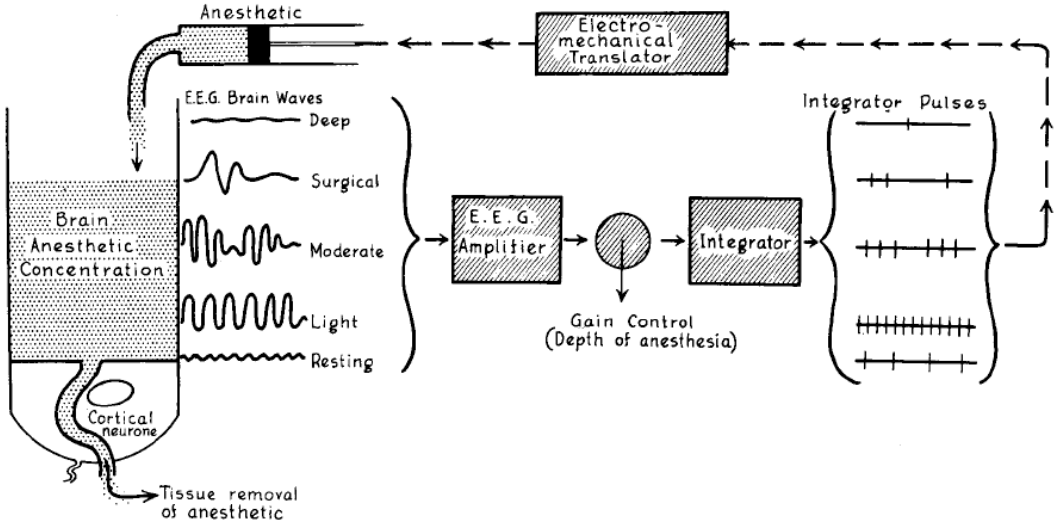
  0.18% in cases in with neuromuscular blocking drugs

  0.10% in the absence of such drugs.
- 17 cases of awareness were identified at the final interview
- no more than 11 would have been detected if an interview had been done only when the patients left the post-anaesthesia care unit.

ELECTROENCEPHALOGRAPHICALLY CONTROLLED ANESTHESIA IN ABDOMINAL SURGERY

CHARLES W. MAYO, M.D.
REGINALD G. BICKFORD, M.B.
and
ALBERT FAULCONER Jr., M.D.
Rochester, Minn.

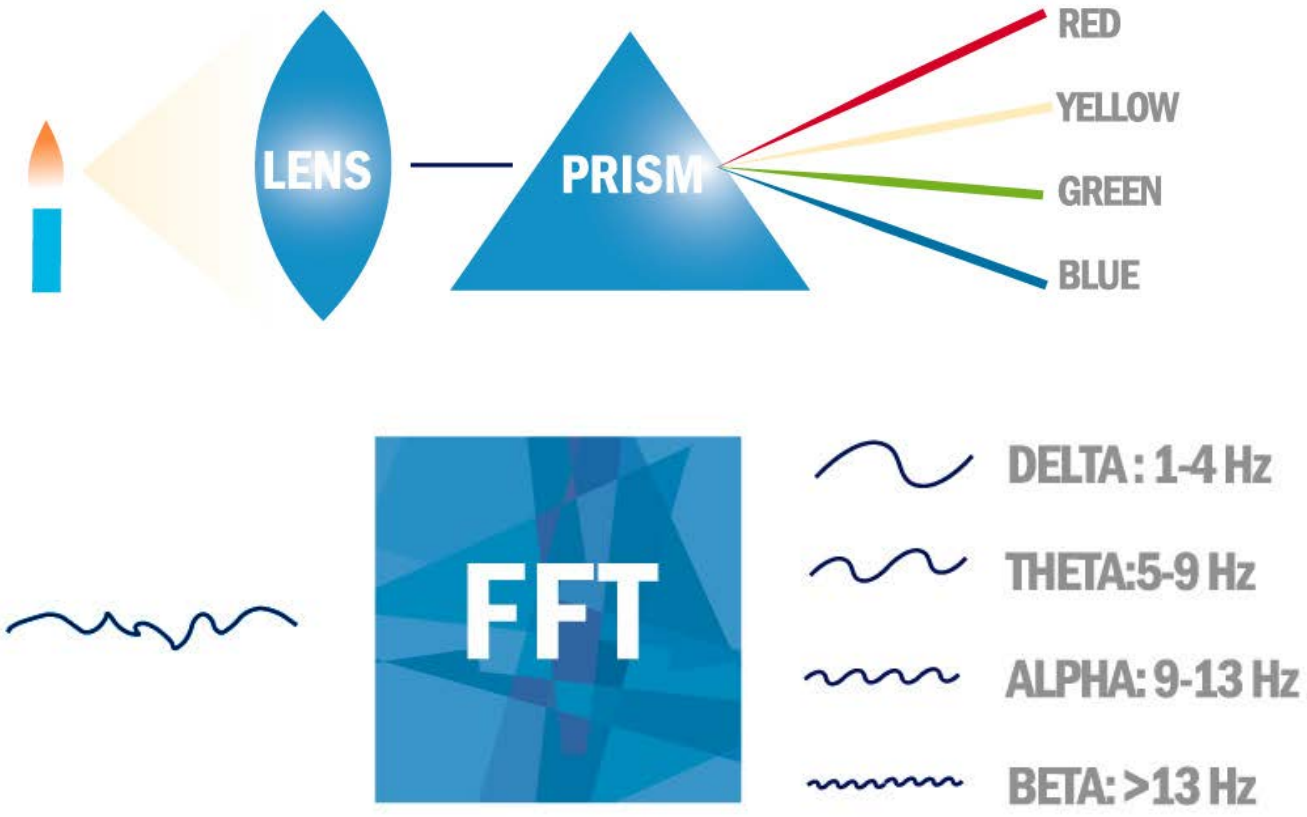




JAMA, 1950, 144;13:1082-83

Aspect A-1000 – the first BIS monitor...

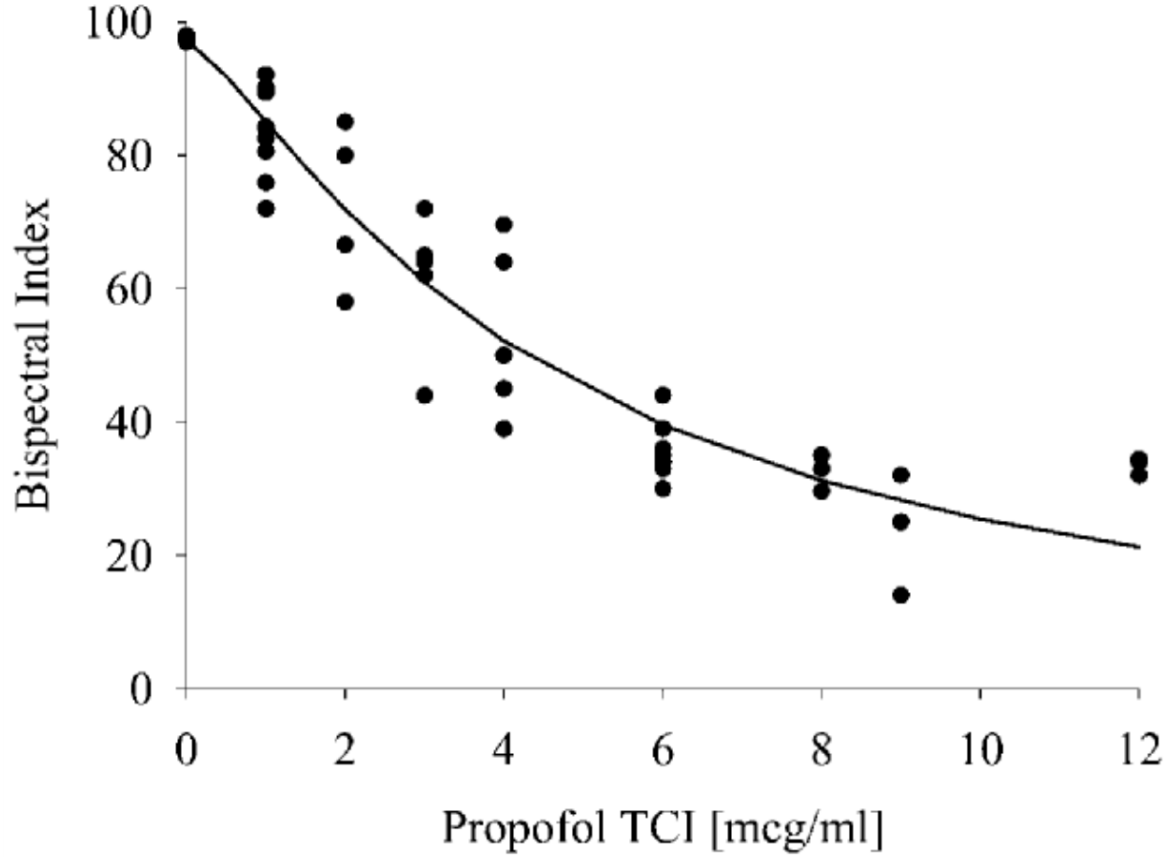
Spectral Analysis
(Fast Fourier Transorm)



Aspect/Covidien BIS monitor...

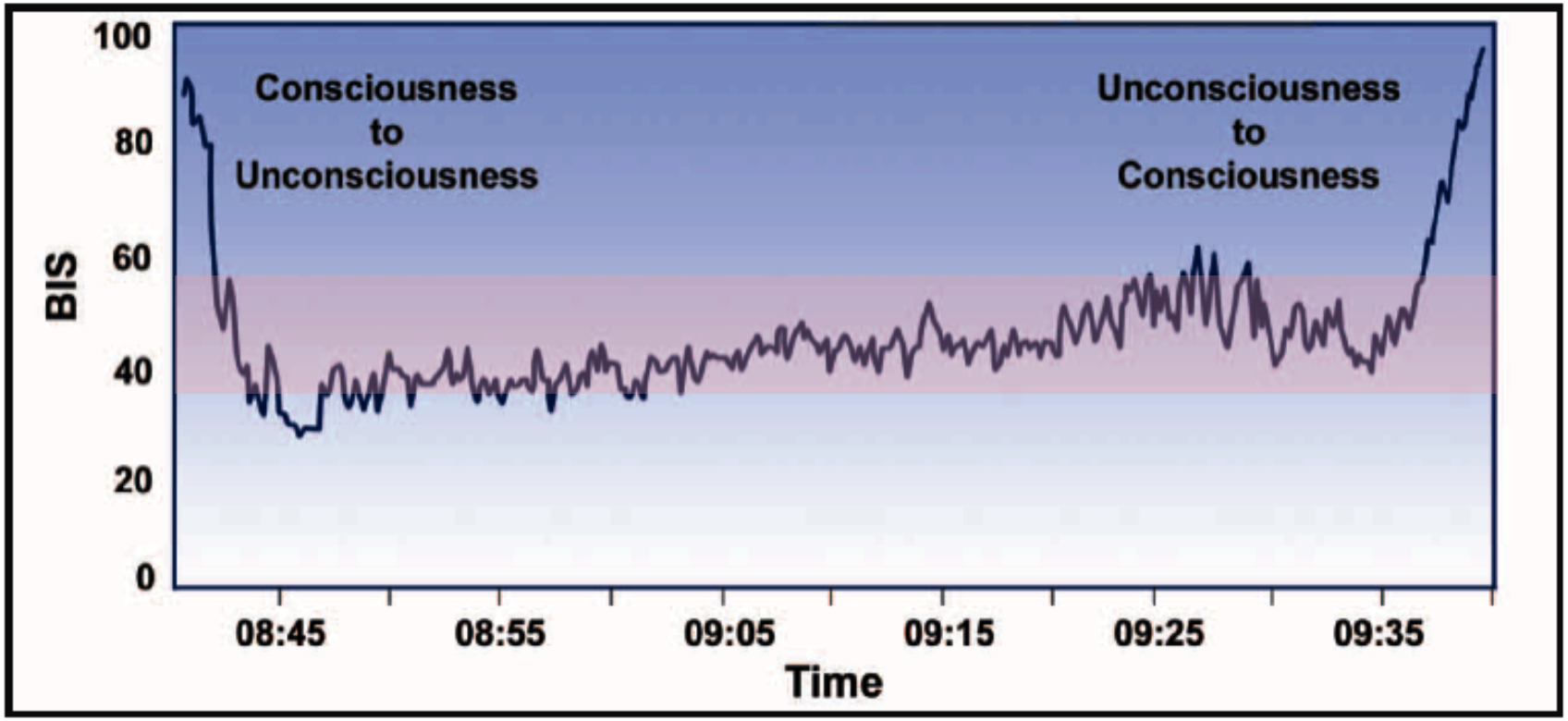
some competitors….

BIS tracks anesthetic concentration of GABA-ergic anaesthetics



Bouillon TW et al, *Anesthesiology*, 2004)

BIS trend (one hour anesthetic)



BIS-monitoring :
evidence-based or confidence-based?

Acta Anaesthesiol Scand 2004; 48: 20–26
Printed in Denmark. All rights reserved

ACTA ANAESTHESIOLOGICA SCANDINAVICA

Reduction in the incidence of awareness using BIS monitoring

A. EKMAN[1], M-L. LINDHOLM[1], C. LENNMARKEN[2] and R. SANDIN[1]
[1]*Department of Anaesthesia and Intensive Care, Regional hospital, Kalmar, and The Karolinska Institute, Stockholm, and* [2]*Department of Anaesthesia and Intensive Care, University Hospital, Linköping, Sweden*

- prospective cohort of 4945 consecutive surgical patients monitored with BIS (target: 40-60)
- interviewed for ER on three occasions.
- compared with a historical group of 7826 similar cases
- Explicit Recall:
  - 2 patients (0.04%) in the BIS-group
  - 14 patients (0.18%) in the control group ($P<0.038$)

Bispectral index monitoring to prevent awareness during anaesthesia: the B-Aware randomised controlled trial

*P S Myles, K Leslie, J McNeil, A Forbes, M T V Chan, for the B-Aware trial group**

Lancet 2004; **363:** 1757–63

- Question: does BIS monitoring prevent awareness in high-risk patients under general anaesthesia?
- High risk :

  cesarean section, high-risk cardiac surgery, trauma surgery, rigid bronchoscopy
- Multicenter RCT: 20 sites around Australia, NZ and SE Asia
- Randomized 2500 patients over 2 years

Australasian ‘B-aware’ trial: **Results**

- Patients were assessed by a blinded observer for awareness:
  - at 2-6 h, 24-36 h, and 30 days after surgery.
- 1227 patients ‘BIS-guided’ and 1238 routine care
- results **awareness:**
  - 2 reports in the BIS"-guided group
  - 11 reports in the routine care group (p=0.022)
- BIS-guided anesthesia reduced the risk of awareness by 82% (approximate 95% CI, 17 - 98 percent).
- BIS monitoring was associated with decreased time to eye opening (P<0.01)

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 13, 2008 VOL. 358 NO. 11

Anesthesia Awareness and the Bispectral Index

Michael S. Avidan, M.B., B.Ch., Lini Zhang, M.D., Beth A. Burnside, B.A., Kevin J. Finkel, M.D., Adam C. Searleman, B.S., Jacqueline A. Selvidge, B.S., Leif Saager, M.D., Michelle S. Turner, B.S., Srikar Rao, B.A., Michael Bottros, M.D., Charles Hantler, M.D., Eric Jacobsohn, M.B., Ch.B., and Alex S. Evers, M.D.

Anesthesia Awareness Monitor No Better Than Older Methods, Study says

Medical News TODAY

Featured Article
Main Category: Pain / Anesthetics
Also Included In: Medical Devices
Article Date: 14 Mar 2008 - 1:00 PDT

Michael Avidan. Mb, B.Ch..

Health

U.S.News & WORLD REPORT

Home > Health
Print | E-mail | Subscribe | Share

New Technology No Better at Spotting 'Anesthesia Awareness'

Study comparing bispectral index monitoring to standard methods found little difference

By Amanda Gardner
Posted 3/12/08

HealthDay

WEDNESDAY, March 12 (HealthDay News) -- A much-touted technology designed to detect when patients are regaining consciousness while under anesthesia during surgery doesn't appear to work any better than standard methods.

Study design

Avidan *et al.*, NEJM, March 13, 2008

- 2000 patients at high risk for awareness
- Randomized to:
  - BIS-guided protocol (BIS 40-60)
  - End-tidal anesthetic gas guided (0.7-1.3 MAC)
- Outcome: awareness (Brice interview 3x)
  - 0 - 24 h
  - 27 - 72 h
  - Day 30 post-surgery

Results

Avidan et al., NEJM, March 13, 2008

- BIS-guided: 967 patients, ETAG guided: 974
- **2 cases of definite anesthesia awareness occurred in each group**
  - (absolute difference, 0%; 95% [CI], −0.56 to 0.57%).
- The BIS value was > 60 in one case of definite anesthesia awareness, and the ETAG concentrations were < 0.7 MAC in 3 cases
- mean time-averaged ETAG concentration:
  - 0.81 ± 0.25 MAC in the BIS group
  - 0.82 ± 0.23 MAC in the ETAG group

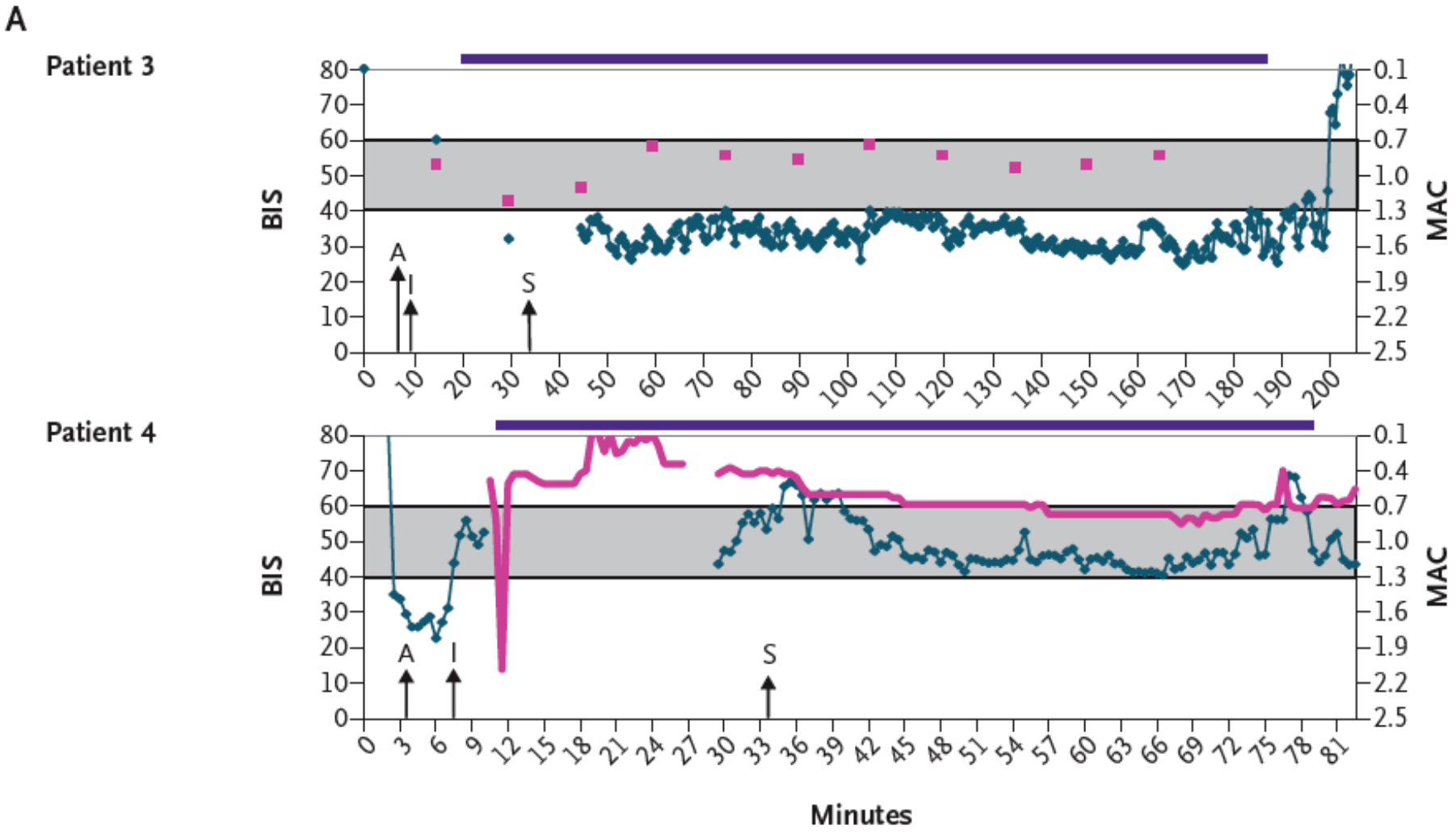
Conclusions

Avidan et al., NEJM, March 13, 2008

- Anesthesia awareness can not predictably be prevented with BIS monitoring
- BIS was not shown to be superior to a protocol based on ETAG concentrations for preventing anesthesia awareness.
- Reliance on BIS technology may provide patients and health care practitioners with **a false sense of security** about the reduction in the risk of anesthesia awareness.

‘definite awareness’, BIS-guided (n=2)

Avidan et al., NEJM, March 13, 2008



Google Finance BETA

Search Finance

e.g. "CSCO" or "Google"

Aspect Medical Systems, Inc. (Public, NASDAQ:ASPM) - Add to Portfolio - Discuss ASPM

6.11
+0.04 (0.66%)
Mar 18 - Close

Open:	6.21	Mkt Cap:	104.13M	P/E:	60.83	Dividend:	N/A
High:	6.24	52Wk High:	17.58	F P/E:	N/A	Yield:	N/A
Low:	5.97	52Wk Low:	4.86	Beta:	2.89	Shares:	17.04M
Vol:	0.00	Avg Vol:	335,000.00	EPS:	0.10	Inst. Own:	95%

After Hours: 6.11 0.00 (0.00%) - Mar 18, 4:45PM ET

Compare | Settings | Historical Prices | Link to chart

Enter ticker here | Add | Nasdaq | Dow Jones | S&P 500 | BABY | MDT | DSCP | more »

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 18, 2011 VOL. 365 NO. 7

Prevention of Intraoperative Awareness in a High-Risk Surgical Population

Michael S. Avidan, M.B., B.Ch., Eric Jacobsohn, M.B., Ch.B., David Glick, M.D., M.B.A., Beth A. Burnside, B.A., Lini Zhang, M.D., Alex Villafranca, M.S., Leah Karl, B.A., Saima Kamal, M.D., Brian Torres, B.S.N., Michael O'Connor, M.D., Alex S. Evers, M.D., Stephen Gradwohl, B.S., Nan Lin, Ph.D., Ben J. Palanca, M.D., Ph.D., and George A. Mashour, M.D., Ph.D., for the BAG-RECALL Research Group.*

BAG-recall Methods

- **Multicenter RCT** (St. Louis, MO, Ann Arbor, MI, Winnipeg, MB):
  - 6041 patients at high risk for awareness
  - BIS-guided (60 - 40) vs. etAG-guided (0.7 -1.3 MAC)
  - assessment of awareness @ 24 -72 h and 30 days

BAG-recall Results

Definite awareness (9 in total):

- **etAG: *2/2861*** (0.07 %)
- **BIS: *7/2852*** (0.24 %), p=0.98

Michigan Awareness Trial

- single center, 3 locations
- ‘unselected’ patients (**not high-risk**)
- blinded assessed for awareness (Brice):
  - at 2-6 h, 24-36 h, and 30 days after surgery.
- 18,836 patients in randomized in total
- ‘definite’ **awareness** (post-hoc analyses):
  - ‘no intervention’ group: **0.15%** (5/3384)
  - anesthetic concentration group: **0.12%** (11/9376)
  - BIS-guided group: **0.05%** (3/6076)

19

- BIS monitoring was not associated with decreased time to eye opening or less PONV

Mashour GA et al., *Anesthesiology* 2012

Michigan Awareness Trial

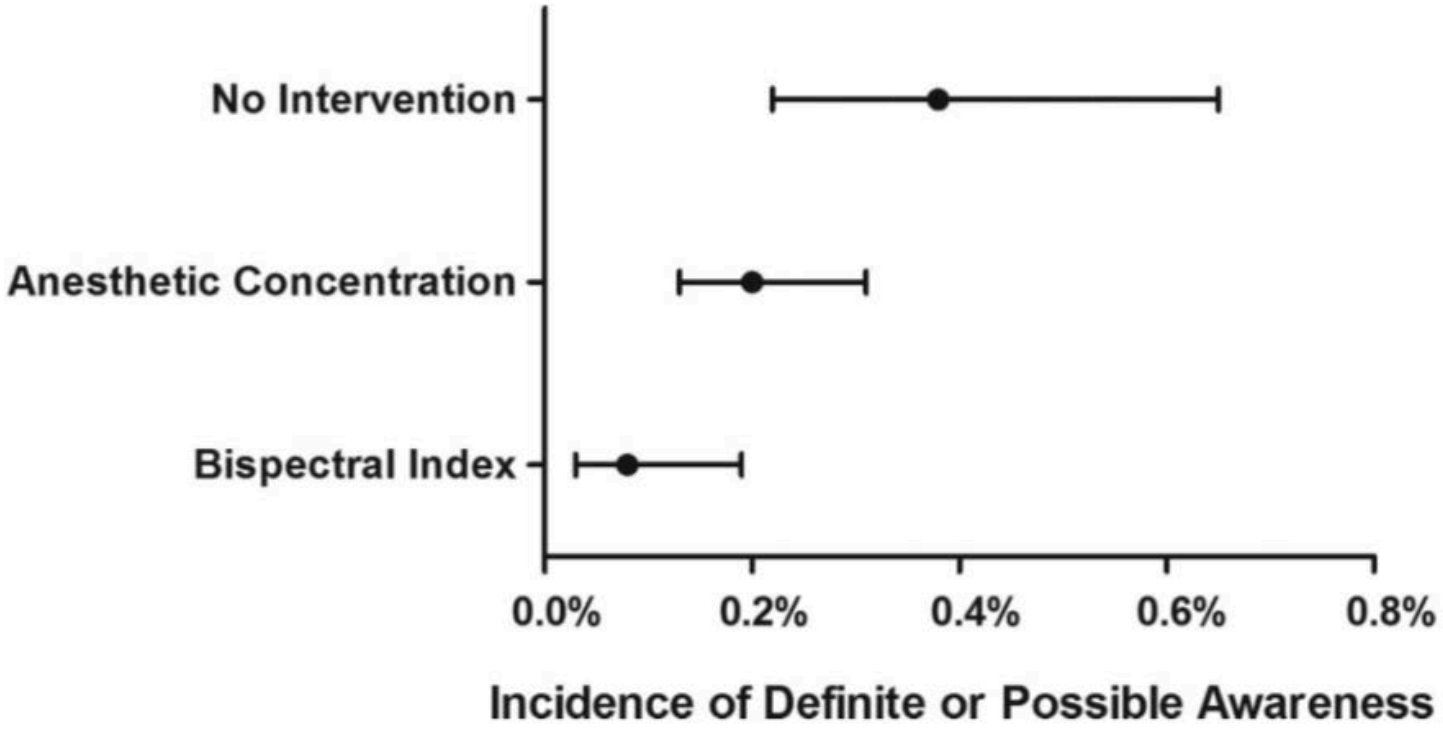


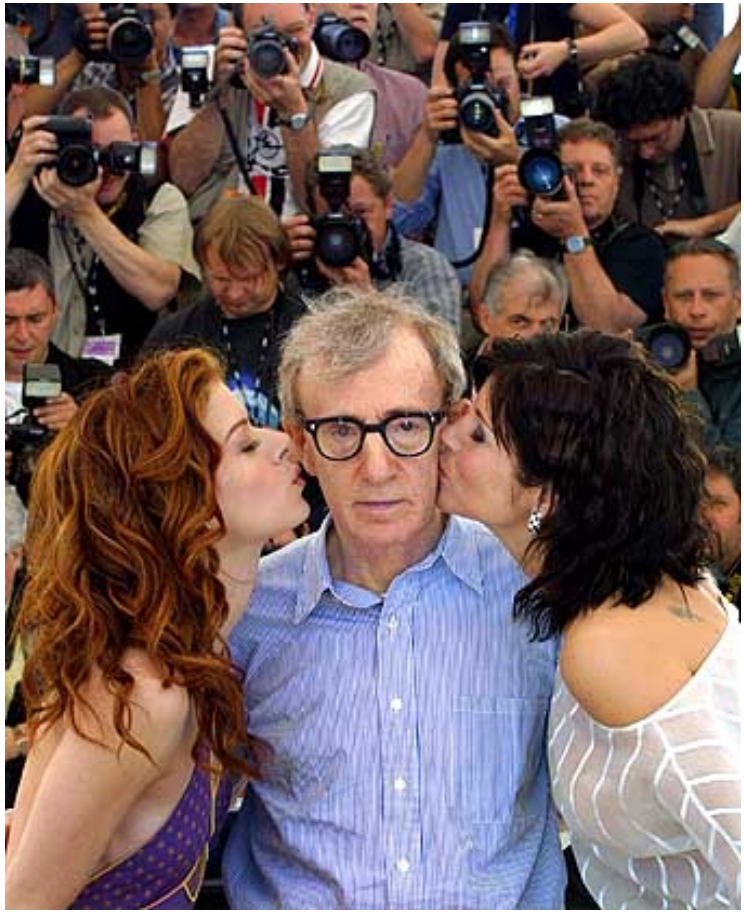
Fig. 3. Secondary outcomes of definite or possible awareness in *post hoc* groups.

Mashour GA et al., *Anesthesiology* 2012

RCTs on the effect of BIS monitoring on the incidence of intraoperative awareness

RCT	author	year	BIS	control	Total n
B-aware (multicenter)	Myles et al.	2004	**2**	**11**	**2465**
B-unaware (monocenter)	Avidan et al.	2008	**2**	**2**	**1941**
BAG-recall (multicenter)	Avidan et al.	2011	**7**	**2**	**5713**
Michigan Awareness Study	Mashour et al.	2012	**11**	**8**	**18836**
Zhang (TIVA Only)	Zhang et al.	2011	**4**	**15**	**5228**
		total	**26**	**38**	**10119**

“My brain? That´s my second favourite organ.”



‘Deep Anaesthesia’ is Bad for the Brain – Deep Anaesthesia Kills

Are we creating a new scare?

May 18, 2014

The Hidden Dangers of Going Under

Anesthesia may have lingering side effects on the brain, even years after an operation

By Carina Storrs | Mar 18, 2014

Two and a half years ago Susan Baker spent three hours under general anesthesia as surgeons fused several vertebrae in her spine. Everything went smoothly, and for the first six hours after her operation, Baker, then an 81-year-old professor at the Johns Hopkins Bloomberg School of Public Health, was recovering well. That night, however, she hallucinated a fire raging through the hospital toward her room. Petrified, she repeatedly buzzed the nurses' station, pleading for help. The next day she was back to her usual self. “It was the most terrifying

(Anesth Analg 2005;100:4–10)

Anesthetic Management and One-Year Mortality After Noncardiac Surgery

Terri G. Monk, MD, MS*, Vikas Saini, MD, FACC†, B. Craig Weldon, MD*, and Jeffrey C. Sigl, PhD‡

*Department of Anesthesiology, Duke University Medical Center, Durham, North Carolina, †The Cardiovascular Specialists LLC, Hyannis, Massachusetts, ‡Aspect Medical Systems, Newton, Massachusetts

independent predictors of 1 yr mortality (5.5%):

- patient **comorbidity** RR = 16.1 (P < 0.001)
- '**cumulative deep hypnotic time**' (BIS < 45):
  RR = 1.24/h (P=0.0121)
- intraoperative systolic **hypotension**:
  RR = 1.036/min (P=0.0125)

"These associations suggest that intraoperative anesthetic management may affect outcomes over longer time periods than previously appreciated…"

Table 3. Cause of Death

Cancer	30 (51.7)
Cardiovascular	10 (17.2)
Renal/liver failure	3 (5.2)
Multiple organ failure	2 (3.4)
Respiratory failure	2 (3.4)
Acquired immunodeficiency syndrome	1 (1.7)
Aspiration	1 (1.7)
Pulmonary emboli	1 (1.7)
Sepsis/infection	1 (1.7)
Unknown	7 (12.1)
Total	58 (100.0)

Values are *n* (%).

Risk of Death Associated with Hours with BIS < 45 with Respect to Cancer Status Before Surgery and Time Since Surgery

	Cancer status	Relative risk per hour BIS <45 (95% CI) Time since surgery: Year 1	Year 2	Total
no cancer	M0	0.78 (0.56–1.07)	0.93 (0.66–1.30)	0.84 (0.64–1.09)
cancer	M1	0.89 (0.60–1.31)	1.33 (0.94–1.89)	1.07 (0.79–1.47)
advanced cancer	M2	1.09 (0.97–1.22)	1.20 (1.05–1.37)	1.12 (1.02–1.24)
	Total	1.04 (0.92–1.16)	1.16 (1.02–1.32)	1.08 (0.99–1.18)

Relative risk per hour with BIS less than 45 (95% Confidence intervals), adjusted for all variables presented in Table 2.

BIS = Bispectral Index; CI = confidence interval.

Lindholm M et al.: Mortality within 2 Years after surgery in relation to low intraoperative Bispectral Index values and preexisting malignant disease. *Anesth Analg* 2009;108:508-12

The Effect of Bispectral Index Monitoring on Long-Term Survival in the B-Aware Trial

Kate Leslie, MBBS, MD, MEpi, FANZCA,*† Paul S. Myles, MBBS, MD, MPH, FANZCA, FCARSCI, FRCA,†§‖
Andrew Forbes, MSc, PhD,¶ Matthew T. V. Chan, MBBS, FANZCA#

- secondary analysis of the B-Aware Trial *(Lancet, 2004)*
- median follow-up time 4.1 years
- 548 patients (22.2%) had died since surgery
  - 220 patients (8.9%) had an MI
  - 115 patients (4.7%) had a stroke
- **hazard ratio for death in patients who recorded BIS values < 40 for 5 min** was **1.41** compared with other BIS-monitored patients (95% CI: 1.02–1.95; *P 0.039)*

***Anesth Analg* 2010;110(3): 816-22**

Association of Perioperative Risk Factors and Cumulative Duration of Low Bispectral Index with Intermediate-term Mortality after Cardiac Surgery in the B-Unaware Trial

Miklos D. Kertai, M.D., Ph.D.,* Nirvik Pal, M.D.,* Ben J. A. Palanca, M.D., Ph.D.,† Nan Lin, Ph.D.,‡ Sylvia A. Searleman, B.S.,§ Lini Zhang, M.D.,§ Beth A. Burnside, B.A.,§ Kevin J. Finkel, M.D.,‖ Michael S. Avidan, M.B., B.Ch., F.C.A.S.A.#; on behalf of the B-Unaware Study Group**

- **We found an association between cumulative duration of low BIS and mortality in cardiac surgery.**
- **this association was independent of both volatile anesthetic concentration and duration of anesthesia**
- **This suggests intermediate-term mortality after cardiac surgery is not causally related to excessive anesthetic dose.**

Anesthesiology 2010; 112:1116–27

Concurrence of Intraoperative Hypotension, Low Minimum Alveolar Concentration, and Low Bispectral Index Is Associated with Postoperative Death

Mark D. Willingham, M.D., M.C.S.I., Elliott Karren, M.D., Amy M. Shanks, M.S., Michael F. O'Connor, M.D., Eric Jacobsohn, M.B., Ch.B., Sachin Kheterpal, M.D., M.B.A., Michael S. Avidan, M.B., B.Ch.

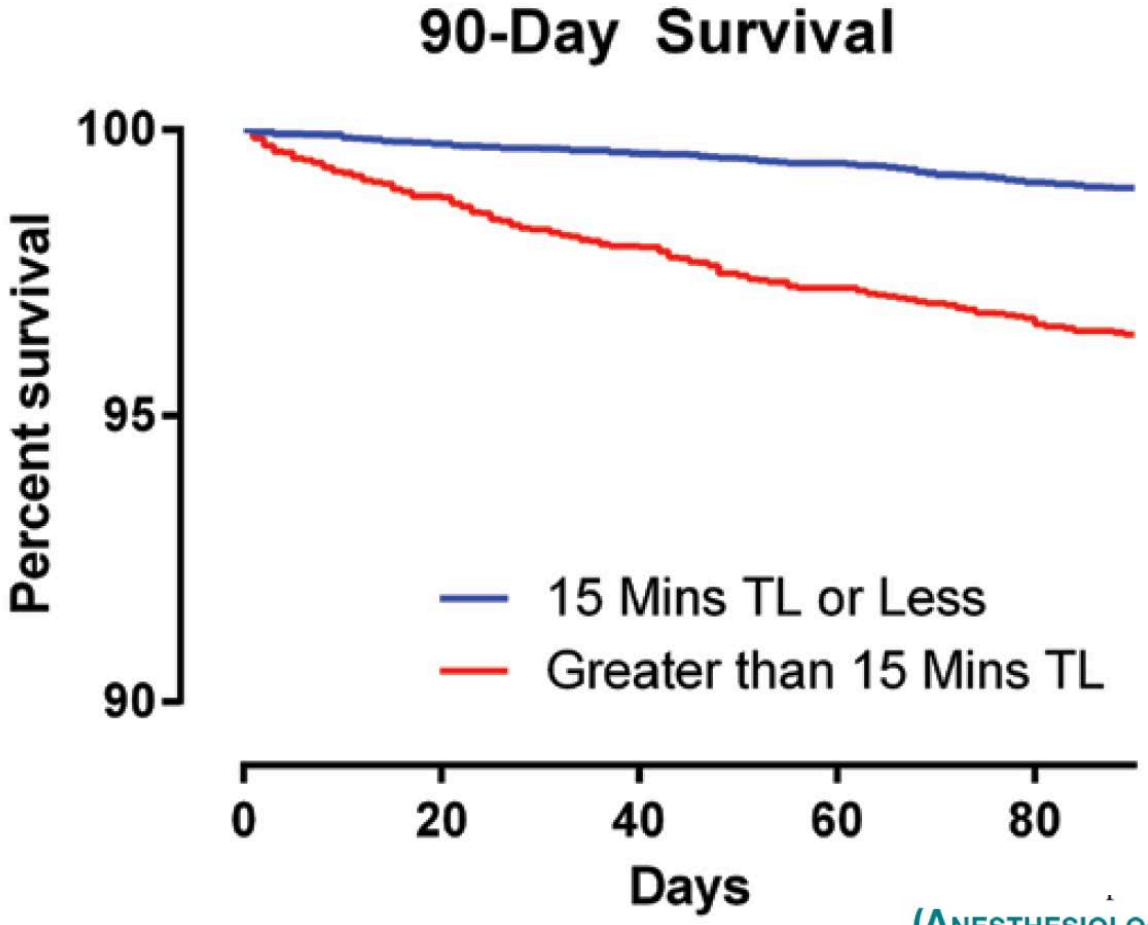
- Retrospective observational study (13,198 patients) from three clinical trials

  (B-Unaware, BAG-RECALL, Michigan Awareness Control Study)
- "**triple low" state:** intraoperative concurrence of: MAP <75 mmHg, MAC <0.8, BIS<45
- after propensity matching, **cumulative duration of triple low** was significantly associated with an **increased risk of mortality at 30 days** (hazard ratio, 1.09; 95% CI, 1.07 to 1.11, per 15 min)

(ANESTHESIOLOGY 2015; 123:00-85)

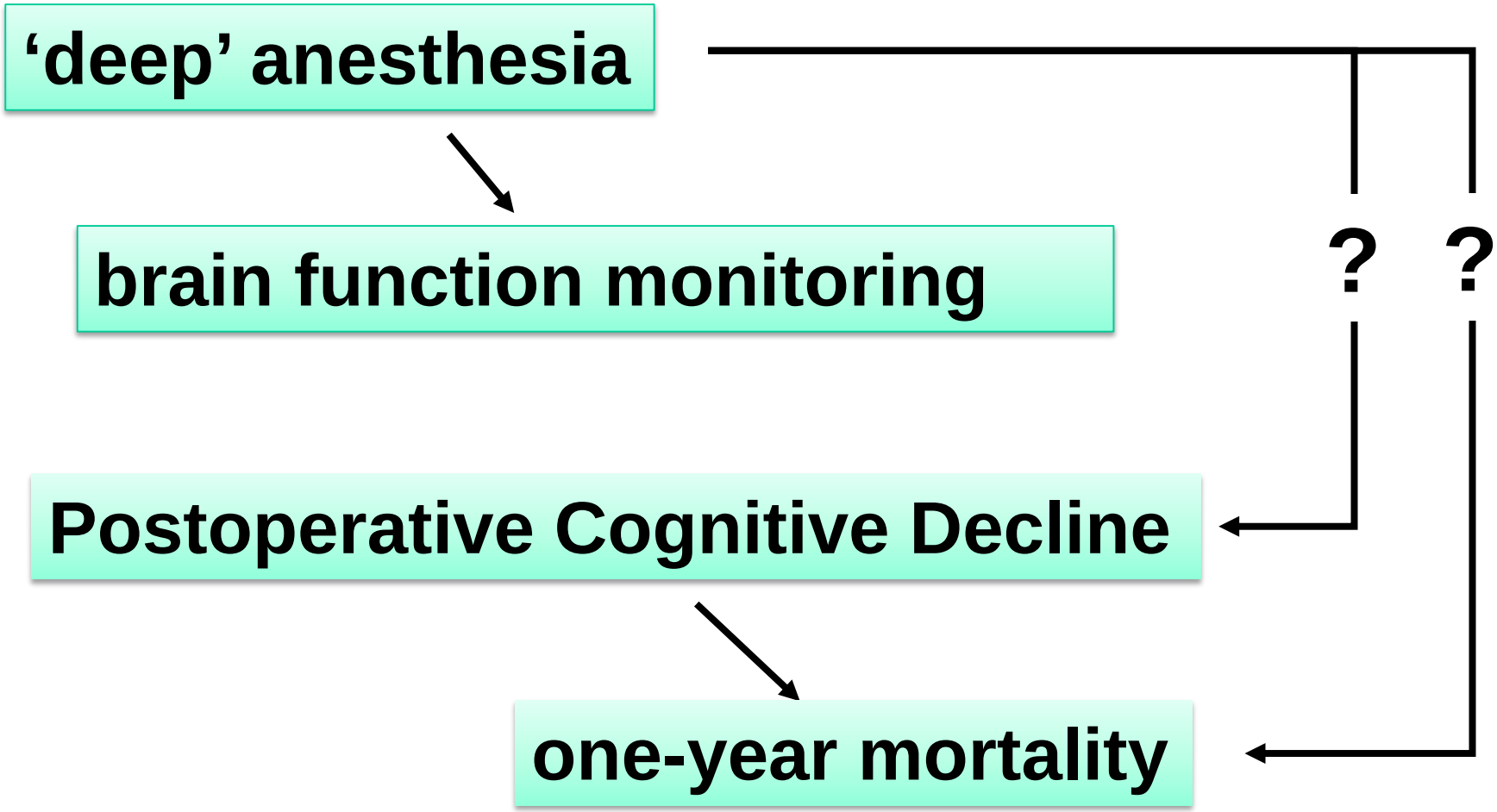
Percent of the study population surviving up to 90 days after surgery.

Patients who experienced greater than 15 cumulative minutes of concurrently low MAP, MAC, and BIS values had decreased postoperative survival to 90 days.

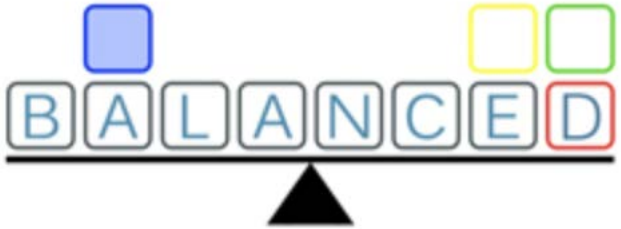


TL = triple low.

(ANESTHESIOLOGY 2015; 123:00-85)



are these associations causal, epiphenomena (markers of severity and poor prognosis) **or coincidental?**



‘Balanced’ trial

- prospective, randomized, double blind, parallel assessment, intention-to-treat, safety and efficacy study
- Patients will be monitored with BIS, randomised **to BIS targets of either 50 or 35**
- Inclusion criteria are: **age ≥60 years**, moderate or high risk (**ASA 3** or 4), surgery lasting ≥2 hours, all general anaesthesia including with major regional block
- primary outcome: **survival at one year after surgery**
  - one year mortality is expected to be 10%.
  - sufficient power to detect 20% reduction → **6500 patients**

Monitoring of the Brain during Anaesthesia: **Take home messages:**

- all processed EEG monitors (BIS, entropy) are able to 'track' brain concentrations of $GABA_a$ agonists (propofol, volatile anesthetics)
- conflicting evidence for reduction incidence of awareness in with BIS monitoring (both unselected and high-risk patients)
- ASA Practice Guideline (2005) still valid:
  - …*EEG monitoring to prevent awareness is not 'standard of care': anesthesiologist decides indication…*
  - intravenous anesthesia with NMB may be the exception
- insufficient evidence for harmful effect of 'deep anesthesia'
  - awaiting trials (BALANCED)