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Top 5 Papers in Anaesthesia and ICM in the past 12-months

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The Five Studies

- SPICE III – NEJM June 2019
- PROBESE Trial – JAMA 2019
- ROSE trial– NEJM
- ENGAGES - JAMA 2019
- GA vs TIVA – NEJM 2019

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The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Early Sedation with Dexmedetomidine in Critically Ill Patients

Y. Shehabi, B.D. Howe, R. Bellomo, Y.M. Arabi, M. Bailey, F.E. Bass, S. Bin Kadiman, C.J. McArthur, L. Murray, M.C. Reade, I.M. Seppelt, J. Takala, M.P. Wise, and S.A. Webb, for the ANZICS Clinical Trials Group and the SPICE III Investigators*

N ENGL J MED 380;26 NEJM.ORG JUNE 27, 2019

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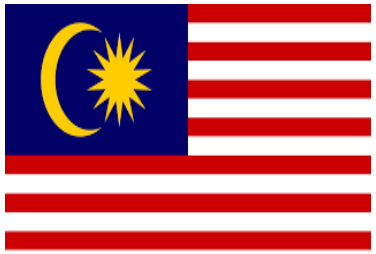
Background/Rationale

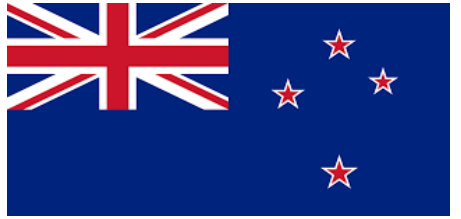
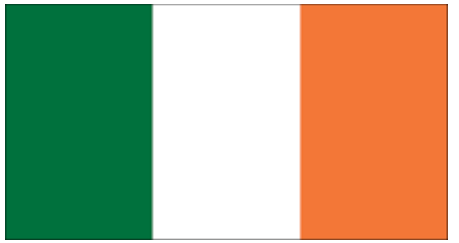
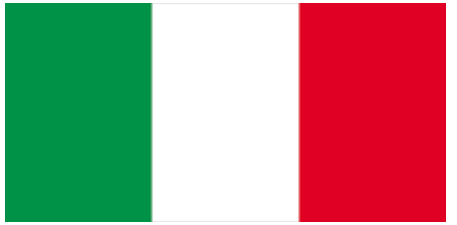
- Dexmedetomidine is potent alpha-agonist
- Initial studies suggested:
  - Reduced times to extubation
  - Increase in coma and delirium free-days
  - Prevention of delirium
  - Possible reduced mortality
- Many studies used the comparator as benzodiazepines

Methods

- Open labelled
- Randomised Controlled trial
- International – 78 ICUs in 8 countries





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Population

- Inclusions:
  - Age 18+
  - Mechanically ventilated
  - Sedated
  - Ventilation expected for >24hrs
- Exclusions:
  - Less than 18years
  - Ventilated >12hours
  - Acute primary brain injury

Interventions

	Standard Group	Dexmedetomidine Group
Sedation Goal	Pain relief as determined by the treating clinician Light sedation: RASS -2 - +1 targeted CAM-ICU: once RASS -2	
Drug delivery	Propofol or midazolam	1µg/kg/hr Max 1.5µg/kg/hr Propofol allowed
Duration		Max 28-days
Contraindicated drugs	Dexmedetomidine (relative) Remifentanil Clonidine	Benzo use discouraged Remifentanil Clonidine

Outcomes

- All cause mortality at 90-days
- Secondary
  - 180-day mortality
  - Transfer to a nursing home
  - cognitive function@180-days Short IQCODE
  - EQ-5D-3L@180 days.
  - Coma, delirium and ventilator free-days @day 28
- Stats
  - 90% power to detect a 4.5% absolute reduction in mortality
  - Baseline mortality 24%
  - 4000pts

Results

- 4000pts
- November 2013 and Feb 2018
- 2.4% (96) lost to follow up or withdrew consent
- 1948 Dexmedetomidine vs. 1956 usual care

No between group differences for baseline characteristics

Main Outcomes

Table 2. Clinical Outcomes.*

Outcome	Dexmedetomidine (N = 1948)	Usual Care (N = 1956)	Odds Ratio (95% CI)	Adjusted Risk Difference (95% CI)†
Death from any cause at 90 days: primary outcome — no. (%)	566 (29.1)	569 (29.1)	1.00 (0.87 to 1.15)	0.0 (–2.9 to 2.8)
Secondary outcomes				
Death at 180 days — no./total no. (%)	609/1935 (31.5)	610/1946 (31.3)	1.01 (0.88 to 1.16)	0.1 (–2.8 to 3.1)
Institutional dependency at 180 days — no./total no. (%)	89/1323 (6.7)	94/1337 (7.0)	0.96 (0.73 to 1.27)	–0.3 (–2.1 to 1.5)
Mean score on Short IQCODE at 180 days (95% CI)‡	3.14 (3.11 to 3.17)	3.08 (3.05 to 3.11)		0.06 (0.02 to 0.11)
Mean score on the EQ-5D-3L questionnaire (95% CI)§	69.8 (68.5 to 71.1)	70.2 (69.0 to 71.5)		–0.4 (–2.2 to 1.3)
Median no. of days free from coma or delirium (IQR)¶	24.0 (11.0 to 26.0)	23.0 (10.0 to 26.0)		1.0 (0.5 to 1.5)
Median no. of ventilator-free days (IQR)¶	23.0 (0.0 to 26.0)	22.0 (0.0 to 25.0)		1.0 (0.4 to 1.6)

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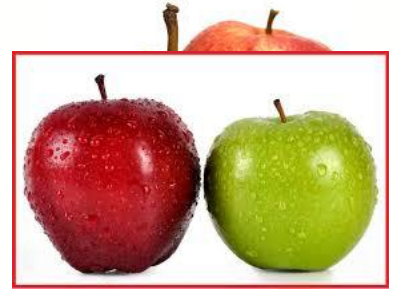
SEDATION PRACTICES

- RASS targets achieved in only ~55% of patients
- Usual sedation
  - Mainly Propofol based (60%)
  - 12% Midazolam
  - 20% Propofol and Midazolam
- Treatment group
  - 65% required additional Propofol sedation

Conclusions

- No difference in 90-day mortality
- Dexmedetomidine was insufficient alone or as the primary agent
- Associated with more reported adverse events
- Subgroup analysis
  - Suggested that dexmedetomidine may cause increased deaths in older patients (above 63)

Why didn't it work?



- Initial trials
  - Were not comparative to usual care
- Patients were often more deeply sedated than required
- Both groups required additional sedatives
- Experience with the treatment was poor

Should this change what we do

- Yes
  - No evidence of benefit with Dexmedetomidine
    - Delirium/coma free days
    - Ventilator-free days
  - Not cost effective
    - Dexmedetomidine is ~10x more expensive than usual sedatives

Lessons Learnt

- Sedation practices are difficult to change
- Most clinicians chose deep sedation
- Deep sedation is associated with poor outcomes
  - **Expected mortality 24% vs Observed of 29%**
  - **Expected treatment group mortality was 19.5%**

JAMA June 18, 2019 Volume 321, Number 23

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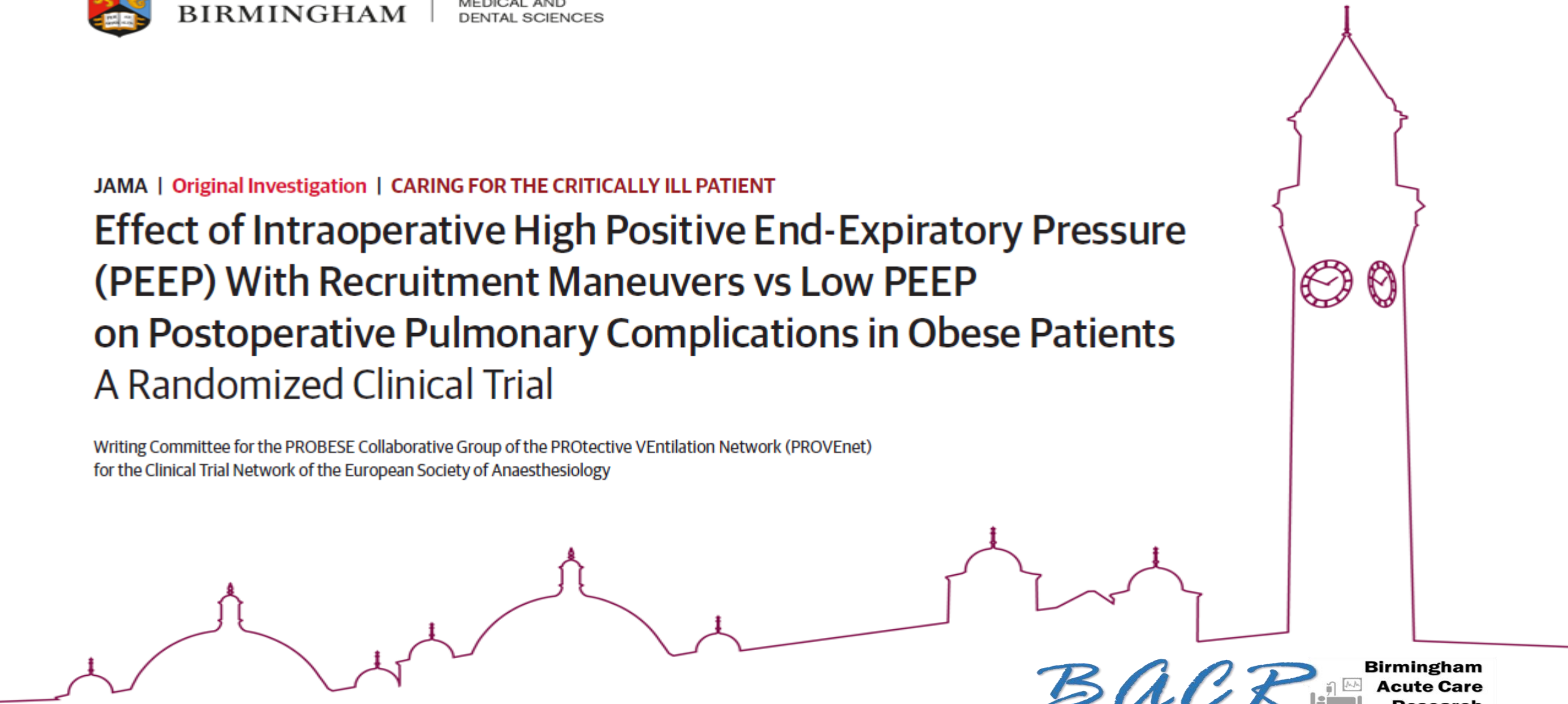
JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Effect of Intraoperative High Positive End-Expiratory Pressure (PEEP) With Recruitment Maneuvers vs Low PEEP on Postoperative Pulmonary Complications in Obese Patients

A Randomized Clinical Trial

Writing Committee for the PROBESE Collaborative Group of the PROtective VEntilation Network (PROVEnet) for the Clinical Trial Network of the European Society of Anaesthesiology



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Rationale

- Obese patients have greater risk of PPCs (18% vs 9%)
- PPCs associated with poorer short and long term outcomes
- Uncertainty regarding best ventilatory strategy:
  - LPV with low PEEP beneficial
  - High PEEP thought to cause haemodynamic instability

Population

- Inclusions:
  - Adults
  - BMI ≥35
  - Surgery ≥2hours under GA
  - ARISCAT Score ≥26
- Exclusions:
  - Neuro & Cardiac surgery
  - Chemo or Radiotherapy
  - Previous lung surgery
  - Severe COPD or cardiac dx
  - One-lung ventilation

Interventions

	Standard Group	High PEEP group
Ventilation	7mls/kg Predicted Body Weight	
PEEP	4cmH_20	12cmH_20
Recruitment	None	Post intubation Every hour At the end of surgery
Manoeuver	N/A	Stepwise increase in TV and PEEP till a Pplat of 40-50cmH_20
Oxygen	≥0.4 with SpO_2≥92%	

Primary Outcome – PPCs within 5-days

Respiratory Infection	Patient has received antibiotics for a suspected respiratory infection and met one or more of the following criteria: new or changed sputum, new or changed lung opacities, fever, white blood cell count > 12 109 l
Respiratory Failure	Postoperative PaO2 < 8 kPa (60 mmHg) on room air (mild –responds to 2L O2, moderate >2L or severe: need for NIV or IPPV)
ARDS	Berlin Definition
Pleural effusion	Chest radiograph demonstrating blunting of the costophrenic angle, loss of sharp silhouette of the ipsilateral hemidiaphragm in upright position, evidence of displacement of adjacent anatomical structures or (in supine position) a hazy opacity in one hemithorax with preserved vascular shadows
Pulmonary infiltrates	Chest radiograph demonstrating new infiltrates within the lungs
Atelectasis	Lung opacification with a shift of the mediastinum, hilum or hemidiaphragm toward the affected area, and compensatory over-inflation in the adjacent non-atelectatic lung
Pneumothorax	Air in the pleural space with no vascular bed surrounding the visceral pleura
Bronchospasm	Newly detected expiratory wheezing treated with bronchodilators
Aspiration Pneumonitis	Acute lung injury after the inhalation of regurgitated gastric contents

Secondary Outcomes

- Each of the PPC composites
- Extra-pulmonary complications
- Hospital free-days at 90-days
- Hypoxia
- Hypotension
- Bradycardia
- In-hospital mortality

The POWER & The STATS

- 2013 patients in total
  - 80% power and alpha error of 0.05
  - Detect an relative risk reduction in PPCs of 0.75
  - Baseline PPC incidence assessed at 20%
  - 1% drop out rate

Results

- International trial between 2014-18 in 23 Countries in 77 sites
- 1976pts were analysed
- Mean BMI 44 vs. 43 (high vs low PEEP)
- TV 7mls/kg/PBW in each group
- PEEP 12 vs 4
- 98% received per protocol recruitment manoeuvers
- High PEEP group had higher Ppeak but lower Driving Pressures

Outcomes

- Primary outcome
  - 21.3 % vs. 23.6% RR of 0.93 (0.82-1.04) p=0.23
- Higher rates of Pleural effusion in High PEEP group
- Secondary endpoints
  - No differences
  - Increased rates of hypoxia in Low PEEP
  - Increased rates of hypotension and bradycardia in High PEEP

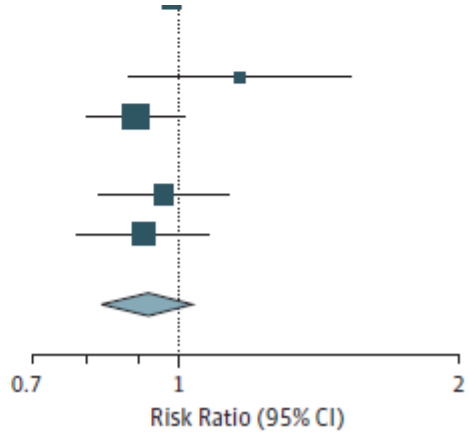
Conclusions

In Obese patients an intra-operative high PEEP strategy with recruitment maneuvers does not reduce PPCs compared with a low PEEP strategy

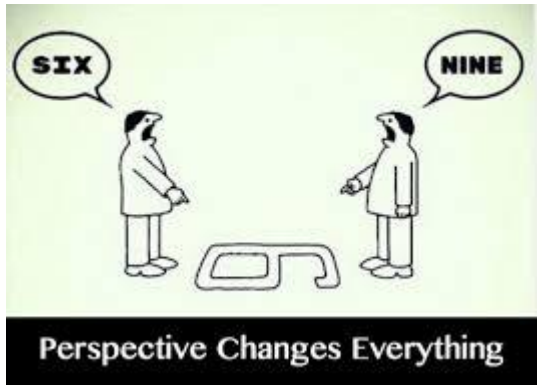
Considerations

Figure 2. Risk Ratio for Postoperative Pulmonary Complications (PPCs) in Prespecified Subgroups

Subgroups of Patients	High PEEP No. With PPC	High PEEP Total No.	Low PEEP No. With PPC	Low PEEP Total No.	Risk Ratio (95% CI)	*P* Value for Interaction
Type of surgery						
Nonlaparoscopic	79	240	74	253	1.09 (0.90-1.32)	
Laparo						
Body ma						
<40						
≥40						
Peripher						
<96						
≥96						
Type of incision						
Peripheral	32	126	25	126	1.16 (0.89-1.53)	.11
Upper abdominal	179	863	208	861	0.90 (0.80-1.02)	
Waist-to-hip ratio, cm						
<1.0	97	467	100	457	0.97 (0.83-1.13)	.65
≥1.0	98	447	112	449	0.92 (0.78-1.08)	
All patients	211	989	233	987	0.93 (0.83-1.04)	
Intraoperative adverse events						
Hypoxemia[I]			49 (5.0)		134 (13.6)	−8.6 (−11.1 to −6.1)	0.51 (0.40 to 0.65)	<.001
Hypotension[J]			313 (31.6)		170 (17.2)	14.4 (10.7 to 18.2)	1.43 (1.31 to 1.56)	<.001
Bradycardia[K]			98 (9.9)		59 (6.0)	3.9 (1.5 to 6.3)	1.27 (1.11 to 1.45)	.001
Mortality during hospital stay			12 (1.2)		5 (0.5)	0.7 (−0.1 to 1.5)	1.41 (0.95 to 1.81)	.09



Should this change what we do



- Depends on you!
  - If you use High PEEP – consider stopping
  - If you use Low PEEP – Safe
  - If you use no PEEP –Use some PEEP

- Recommend tailoring ventilation to the individual and surgery

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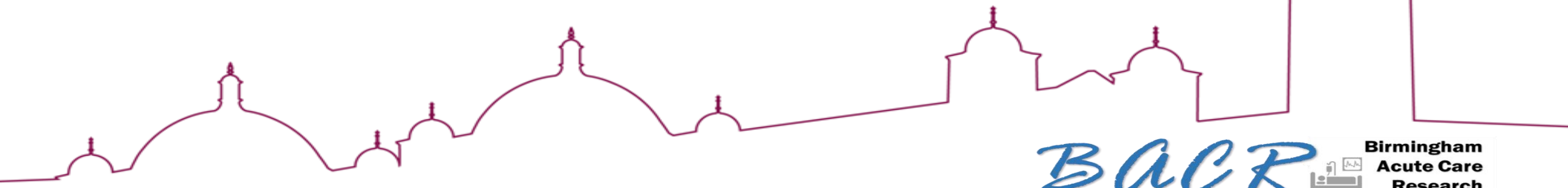
The NEW ENGLAND JOURNAL of MEDICINE

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 23, 2019 VOL. 380 NO. 21

Early Neuromuscular Blockade in the Acute Respiratory Distress Syndrome

The National Heart, Lung, and Blood Institute PETAL Clinical Trials Network*



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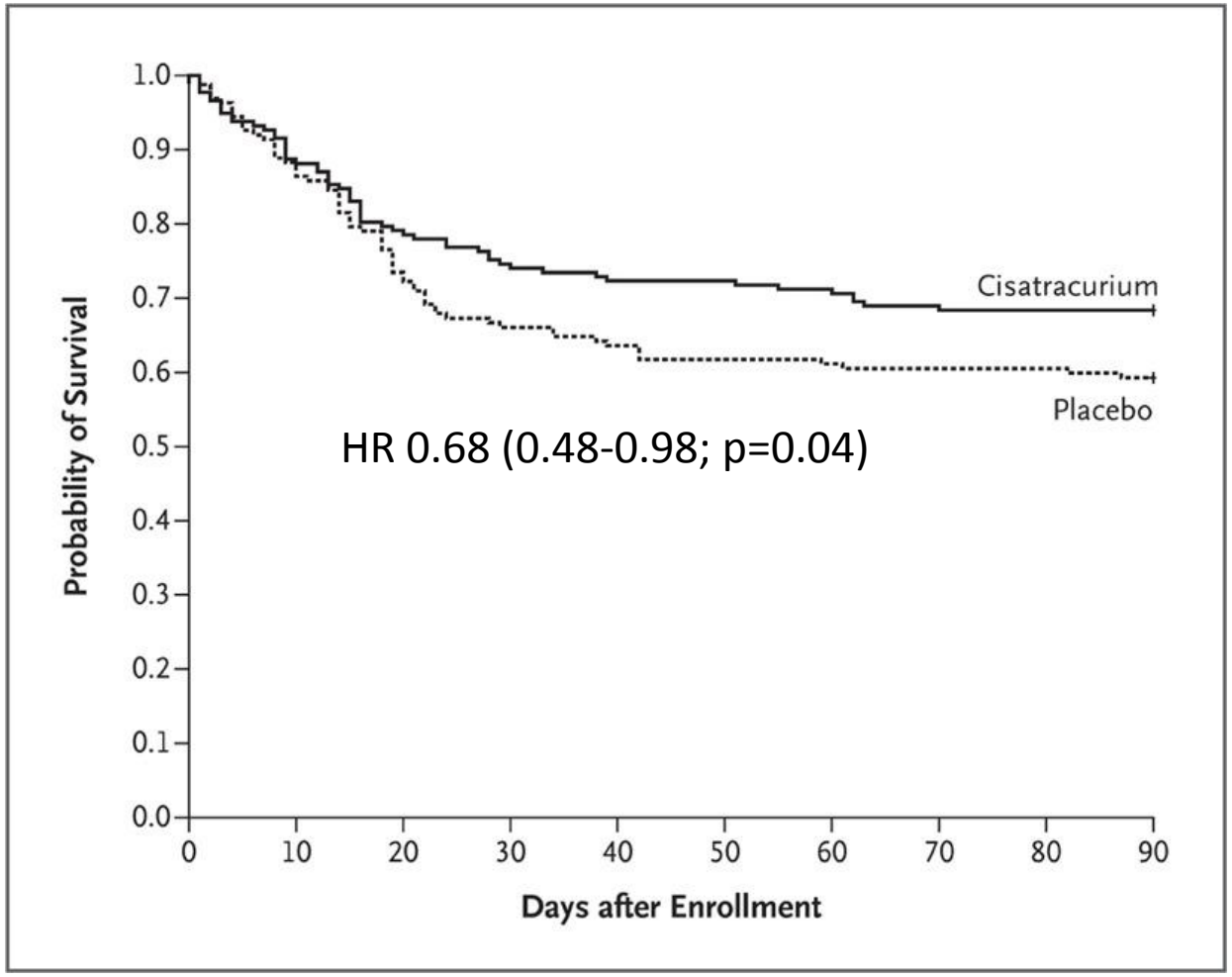
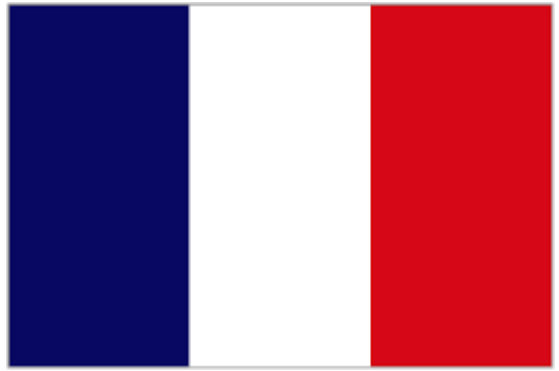
The History



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 16, 2010 VOL. 363 NO. 12

Neuromuscular Blockers in Early Acute Respiratory Distress Syndrome



Why repeat?

- Study was a decade old – change in practice
- Not been widely adopted
- Concerns regarding deep sedation vs light sedation
- Concerns regarding NMB and outcomes

NMB with deep sedation vs. usual care with light sedation

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Population

- Inclusions:
  - Mechanically ventilated <48hours
  - P:F ratio <150mmHg (PEEP 8)
  - ARDS
- Exclusions:
  - Neuro & Cardiac surgery
  - Chemo or Radiotherapy
  - Previous lung surgery
  - Severe COPD or cardiac dx
  - One-lung ventilation

Interventions

	Standard Group	High PEEP group
Ventilation	Low tidal volume (6mls/kg) with high PEEP	
Sedation	Light with RASS -1 - 0	Deep with RASS -4
NMB	None	15mg Cisatracurium bolus 37.5mg/hr for 48hrs
Proning	At discretion of the physician and to wait 12hours.	
Fluids	Conservative approach recommended	

Outcomes

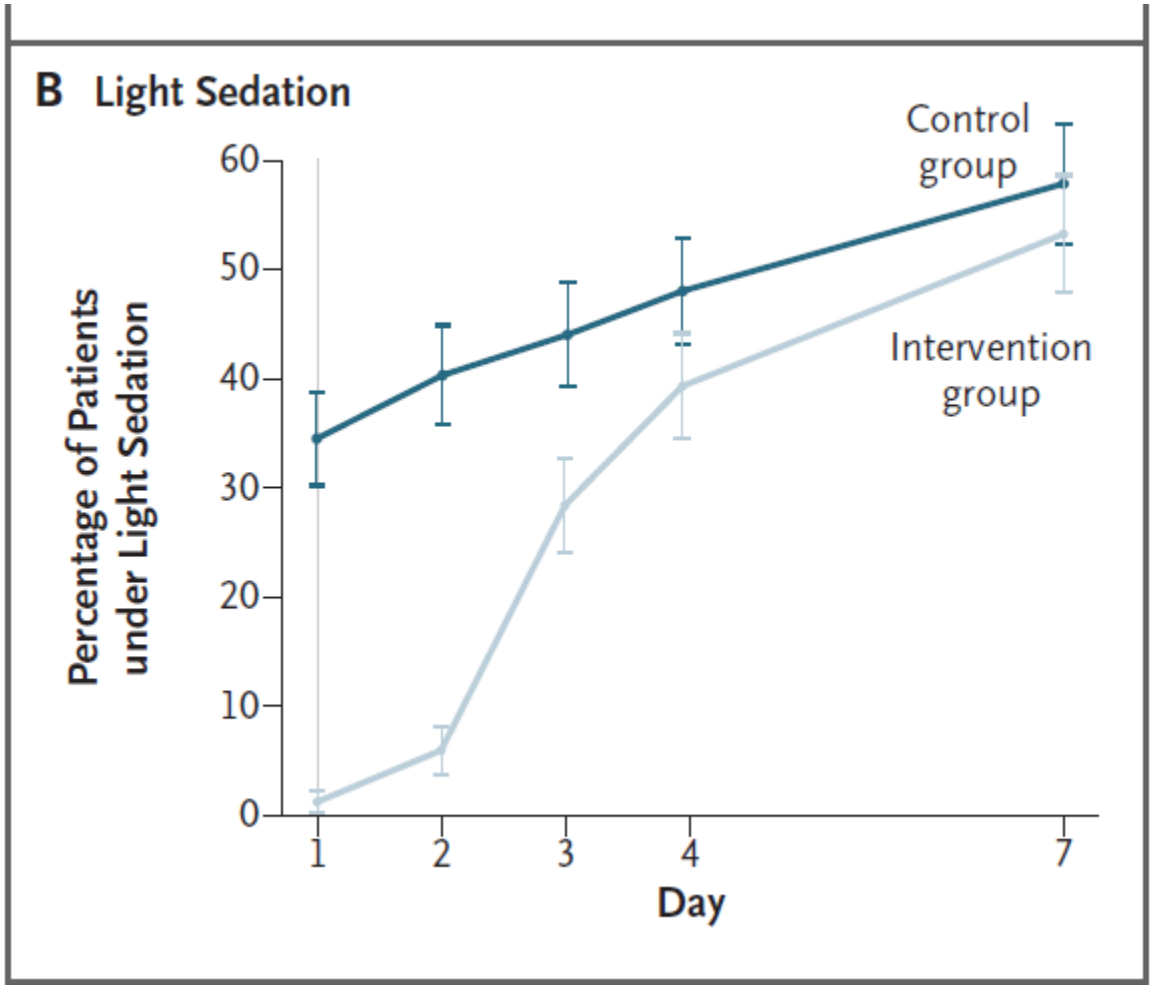
- Primary
  - 90-day in-hospital death
- Secondary
  - SOFA score
  - Organ failure free days
  - 28-day mortality
  - ICU acquired weakness

The POWER & The STATS

- 1408 patients in total
  - 90% power and alpha error of 0.05
  - Detect an absolute risk reduction in death of 8% (35% vs. 27%)

Main Outcomes

- Stopped for futi
- 1006pt recruite
  - 501 to Cisatracu
- Good adherer
- >80% complia



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Primary Outcome

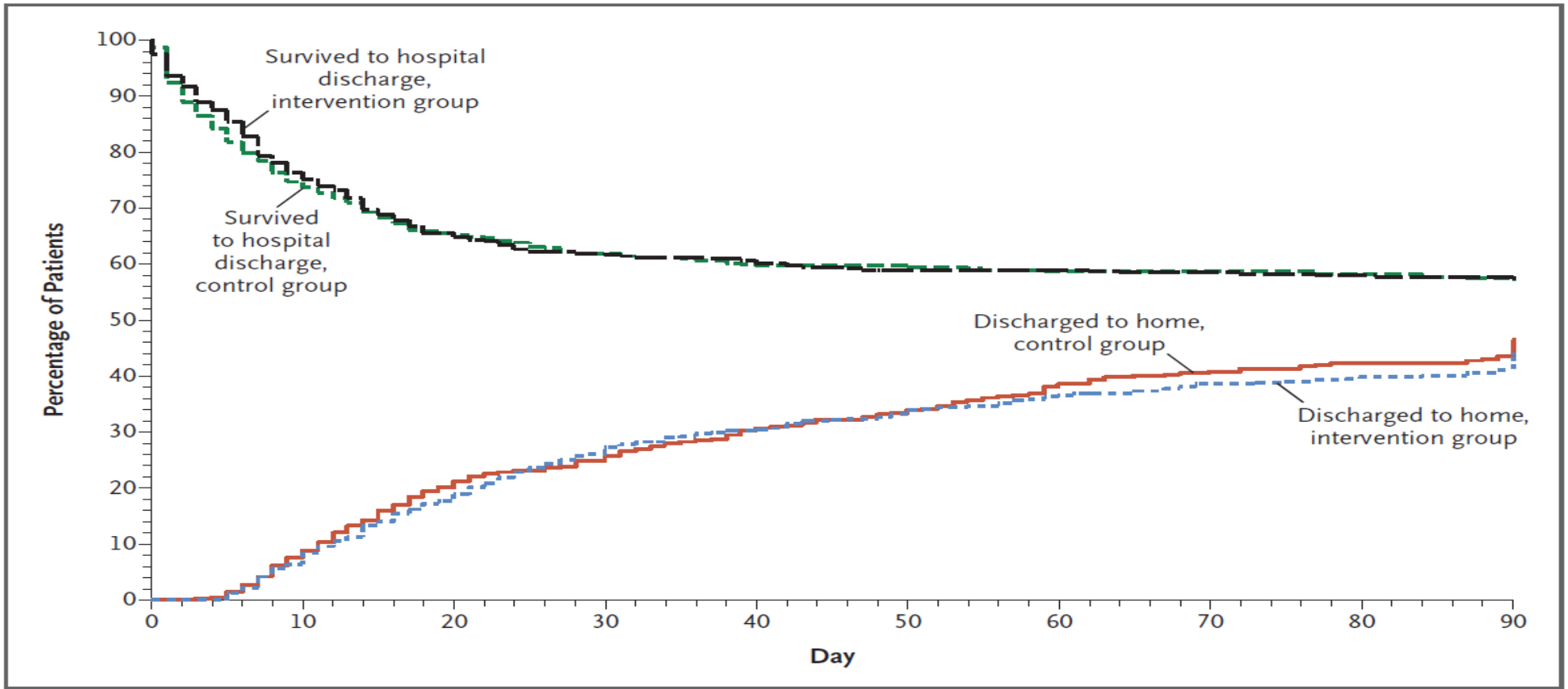

Figure 3. Patients Who Survived to Hospital Discharge and Were Discharged Home during the First 90 Days after Randomization.

The period of hospitalization included transfer to other health care facilities.

Other outcomes

- No differences in a whole host of secondary outcomes
- Increase in CVS events in intervention group
- Higher CVS SOFA score on days 1 & 2
- No increased ICU weakness
- No change in HRQOL at 3, 6 and 12-months

Conclusions

Cisatracurium doesn't lower 90-day mortality in patients with moderate to severe ARDS

Should this change what we do

- Depends
  - NMB is safe with no significant adverse effects
  - Trial protocol adherence in control group was poor
- What we focus on:
  - Use LPV
  - Use an individualised PEEP strategy
  - Prone
  - Not use beta-agonists

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JAMA | Original Investigation

Effect of Electroencephalography-Guided Anesthetic Administration on Postoperative Delirium Among Older Adults Undergoing Major Surgery

The ENGAGES Randomized Clinical Trial

JAMA February 5, 2019 Volume 321, Number 5

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Rationale

- Delirium is a problem post-operatively
- EEG guided anaesthesia may reduce delirium by 30-50%
  - Avoidance of burst suppression

- Aim:
  - Reducing anaesthetic administration & minimising burst suppression decrease incidence of delirium

Population & Setting

- Inclusions
  - Age ≥60years old
  - Major surgery with GA
- Exclusions
  - Blind or deaf
  - Dementia/Delirium
- Setting
  - Single centre in USA
  - 3 separate hospitals in Missouri

Interventions

	Usual Care	Intervention
Pre-operative	Delirium, Cognition and Frailty Assessment, Depression questionnaire and Health Survey (QOL)	
Intra-operative	BIS - clinician blinded	BIS guided intervention with EEG and derived measures displayed
Delirium Assessments	CAM or CAM ICU. Medical notes review	

Outcomes

- Primary Outcome:
  - Incidence of post-operative delirium day1-5.
- Secondary Outcomes
  - Delirium severity
  - EEG suppression
  - Anaesthesia doses
  - Adverse events
- Power
  - 1232pts needed for 90% power
  - Event rate of 25% with a reduction of 8%

Results

- Jan 2015 and April 2018
- 1232 randomised with 1213 assessed for primary outcome
- ETAA lower in the guided group (MAC 0.69 vs 0.8)
- Less burst suppression (7mins vs 13mins)
- Less time with BIS <40 (32mins vs.60mins)

No between group differences for baseline characteristics

Main Outcomes

Adverse events				
Undesirable intraoperative movement	137/614 (22.3)	95/618 (15.4)	6.9 (2.5 to 11.4)	.002
Intraoperative awareness	0/563 (0.0)	0/568 (0.0)	0 (−0.8 to 0.8)	NA
Postoperative nausea and vomiting	48/614 (7.8)	55/617(8.9)	−1.1 (−4.3 to 2.1)	.49
Perioperative serious adverse events[g]	124/614 (20.2)	130/618 (21.0)	−0.8 (−5.5 to 3.8)	.72
Mortality up to 30 days after surgical procedure	4/614 (0.7)	19/618 (3.1)	−2.42 (−4.3 to −0.8)	.004

Conclusions

This trial does not support the routine use of EEG to reduce the incidence of delirium in older adults undergoing major surgery

Should this change what we do?

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The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Volatile Anesthetics versus Total Intravenous Anesthesia for Cardiac Surgery

N ENGL J MED 380;13 NEJM.ORG MARCH 28, 2019

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Rationale

- CABG is common
- Anaesthesia provided as TIVA or combination of TIVA & Volatile
- Volatiles may be protective via ischaemia preconditioning
- Suggestion that volatiles reduce mortality after CABG

- Hypothesis:

Volatiles would reduce death after CABG vs. TIVA

Population & Setting

- Cardiac Surgery for elective isolated CABG
- Age >18

- International RCT in 36 centres in 13 countries
- Italian led

Interventions

Volatile	TIVA
Desflurane/Sevoflurane/Isoflurane GA	TCI or manual TIVA
Three strategies suggested MAC 1.0 for 30mins Stopping Volatile for 15min prior to CPB 3 wash-in wash out periods (MAC 0.5 for 10mins with 10min washout)	

Outcomes

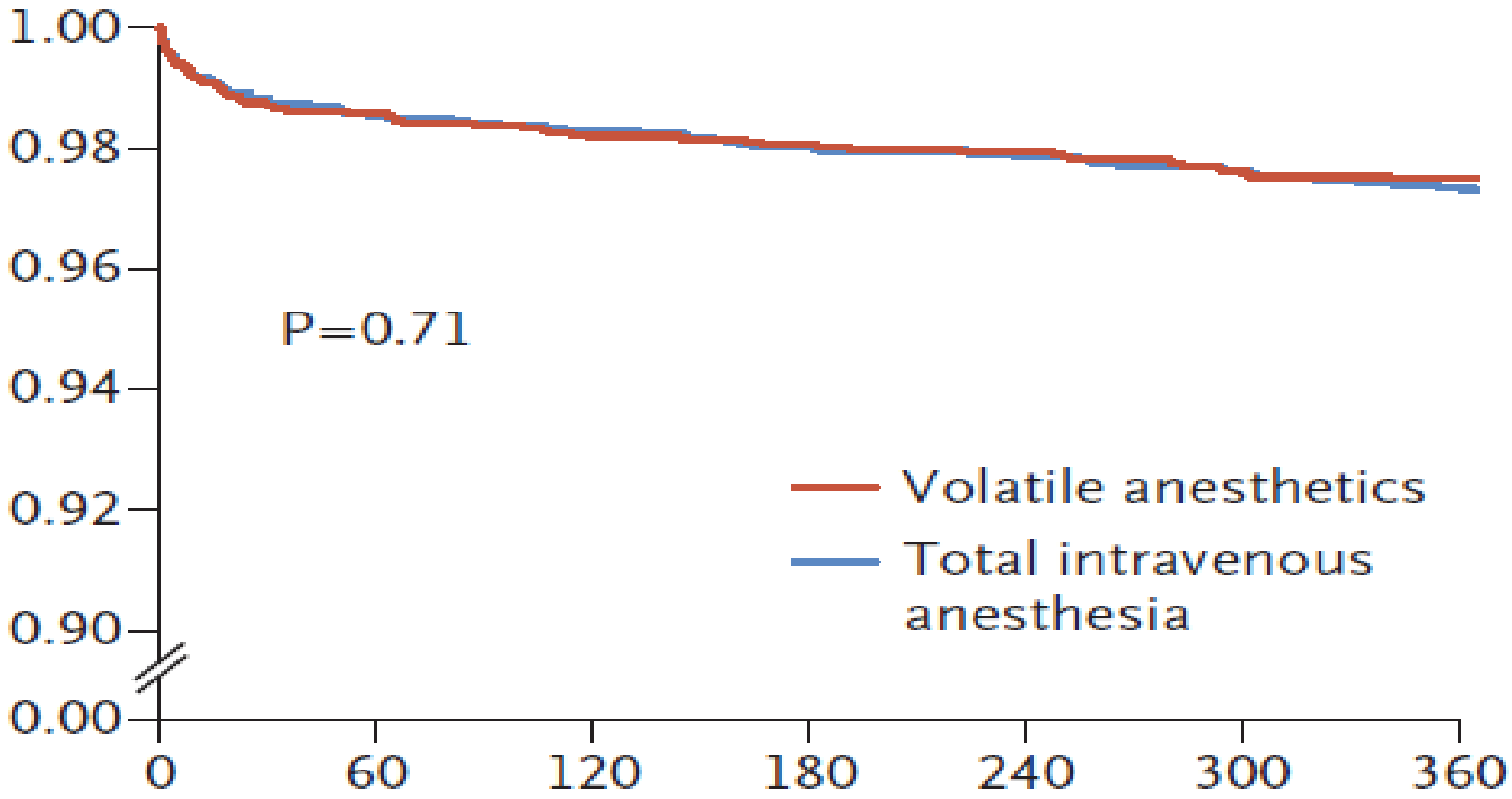
- Primary Outcome
  - All cause mortality at 1-year
- Secondary Outcomes
  - Mortality at 30-days – all cause
  - MI or cardiac death at 30-days and 1-year
  - Readmission
  - Duration of ICU LOS
  - Adverse events
- Power:
  - Detect a reduction in mortality of 1% (3% vs 2%)
  - 10600pts would give 90% Power

Results

- Multi-centre RCT- between 2014-2017
- Stopped for futility
- 5400pts enrolled
  - 2709 volatile vs 2691 TIVA
- Commonest Volatile = Sevo (83%)
- Commonest TIVA = Propofol

No between group differences for baseline characteristics

Main Outcomes



Considerations

- Not all the Cardio-protective strategies were employed
- Less Isoflurane used
  - Is there a specific drug effect

Conclusions

Volatile Anaesthesia in Patients undergoing CABG did not reduce deaths at 30-days or 1-year

Should this change what we do?

- No
- Reassuring that:
  - TIVA is safe
  - Volatiles are safe

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