UNIVERSITÉ DE NANTES

CENTRE HOSPITALIER UNIVERSITAIRE DE NANTES

Effets des corticoïdes sur la morbi-mortalité après chirurgie majeure

Karim Asehnoune
Laboratoire UPRES EA 3826 «Thérapeutiques cliniques et expérimentales des infections»
Service d'Anesthésie-Réanimation, CHU Nantes, F-44000 France

ATLANRÉA

Background

- PONV problématique majeure en post-opératoire
  - 25-30% des patients chirurgicaux
  - 80% des patients à risque

- Nausées : principal déterminant de durée de séjour en ambulatoire
  - 66% des patients
  - Première cause de ré-hospitalisation
  - Augmentation majeure des couts

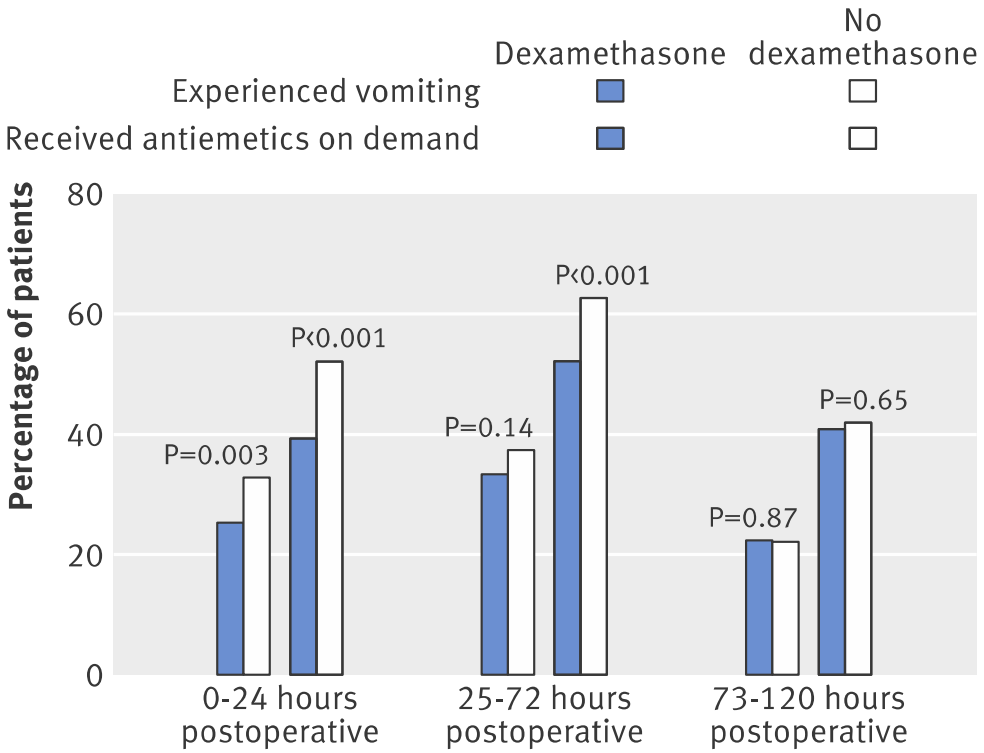
Efficace?

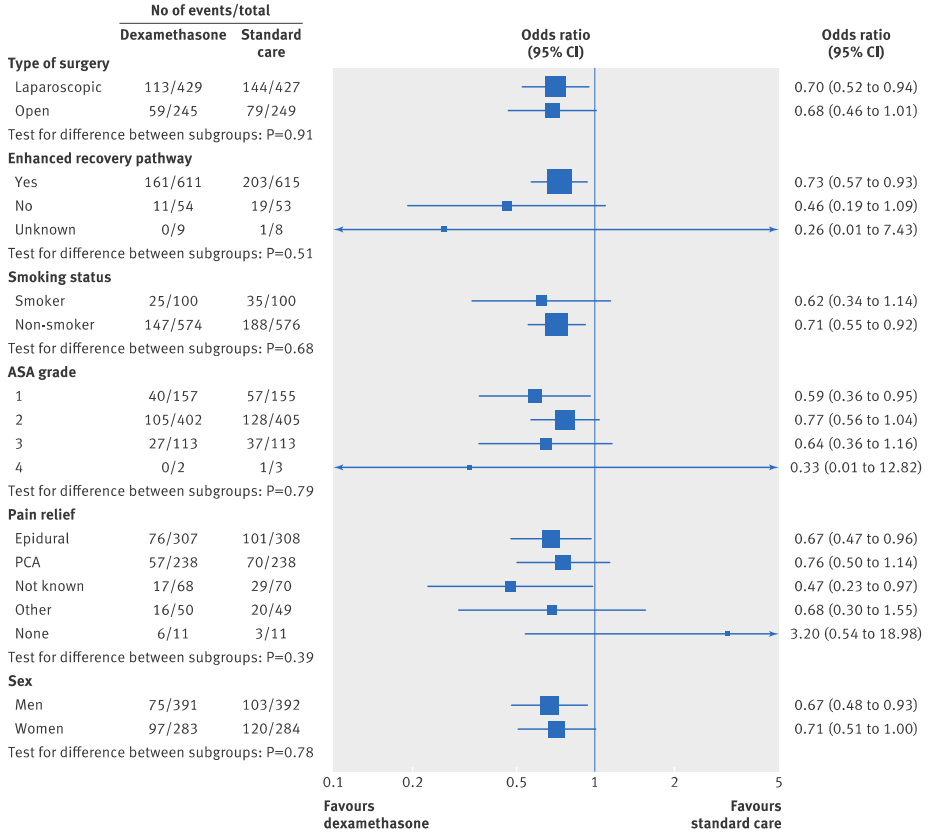
Dexamethasone versus standard treatment for postoperative nausea and vomiting in gastrointestinal surgery: randomised controlled trial (DREAMS Trial)

DREAMS Trial Collaborators and West Midlands Research Collaborative

the bmj | *BMJ* 2017;357:j1455 | doi: 10.1136/bmj.j1455

- **45 hopitaux (UK)**
- **1350 patients**
- **8mg DXM vs Placebo**





Enquete de pratique (ANZCA)

- 1000 envois, 333 questionnaires (33%)

- 71% DES PATIENTS
- 65% DXM
- Dose unique: 4-8 mg

Corcoran et al. Anaesth Intensive care 2015

Safety

Safety of Perioperative Glucocorticoids in Elective Noncardiac Surgery

A Systematic Review and Meta-analysis

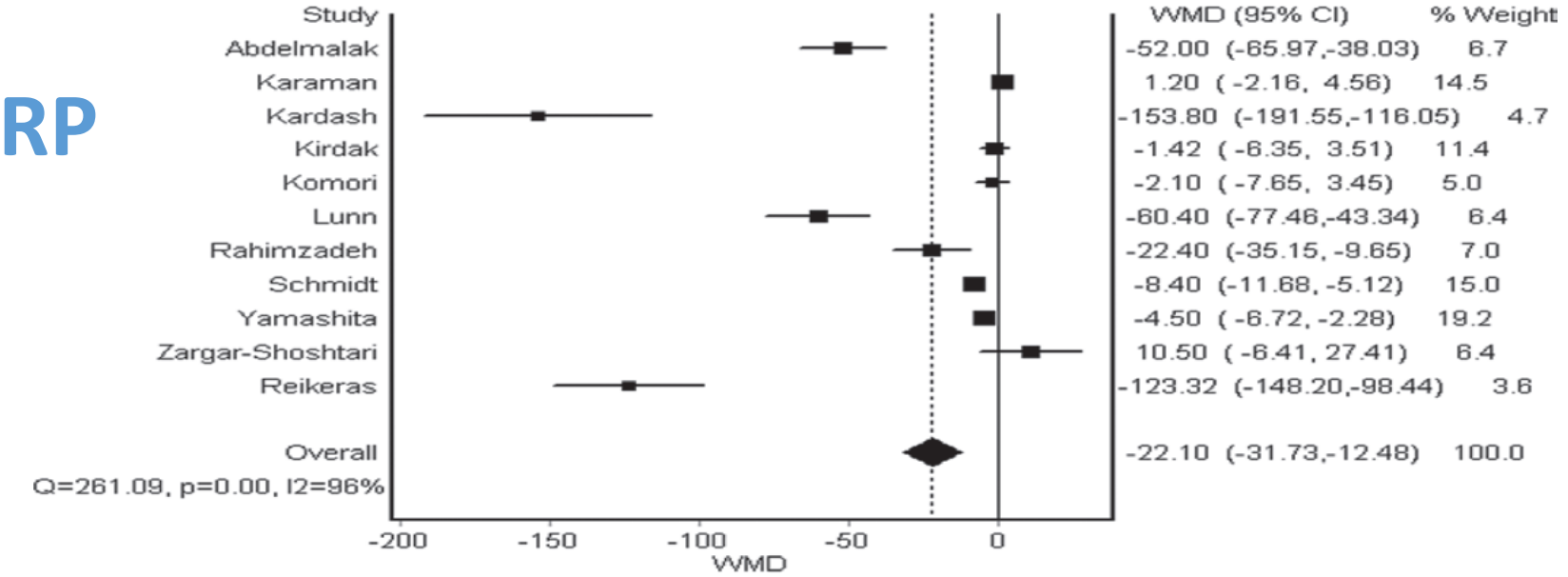
Andrew J. Toner, F.R.C.A., Vyhunthan Ganeshanathan, F.R.C.A., Matthew T. Chan, F.A.N.Z.C.A., Kwok M. Ho, Ph.D., Tomas B. Corcoran, M.D. (Res.)

(ANESTHESIOLOGY 2017; 126:234-48)

What We Already Know about This Topic

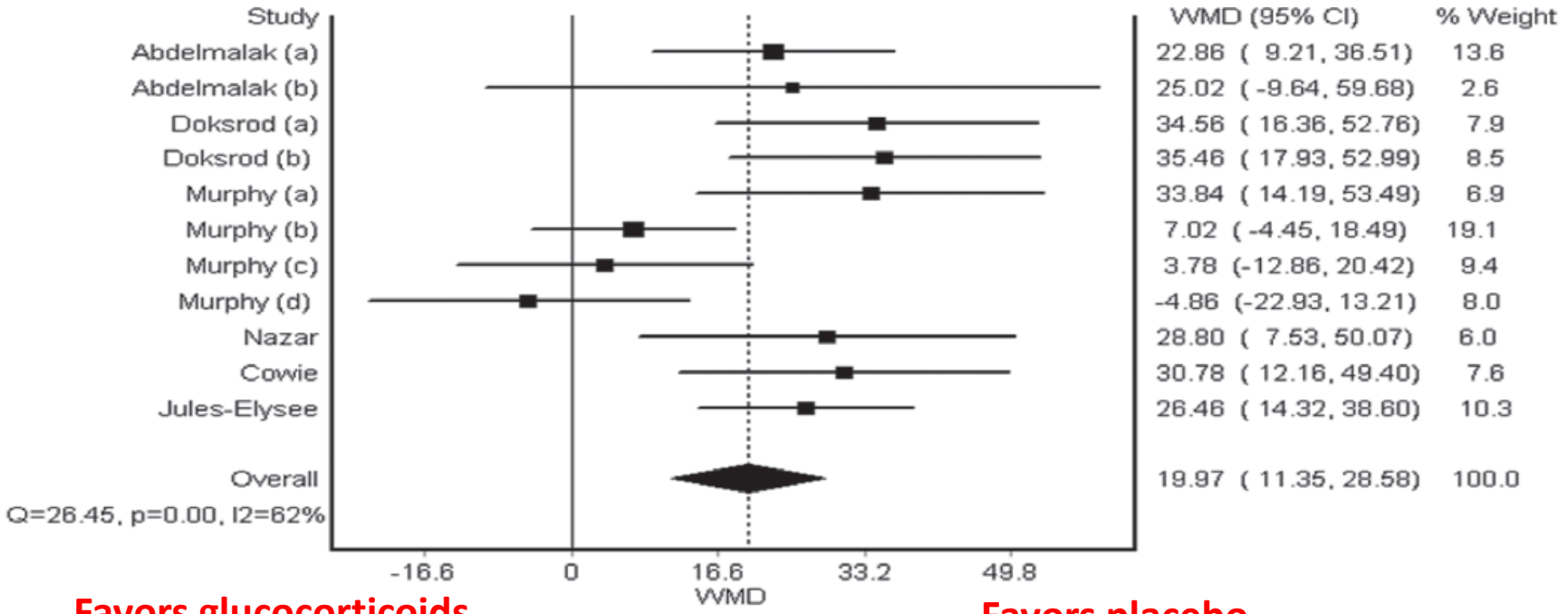
- Glucocorticoids are commonly given to prevent nausea and vomiting
- However, glucocorticoids are immunosuppressive and may promote infection
- The authors conducted a meta-analysis of 56 trials (n = 5,607) that evaluated infection, hospital duration, and intraoperative glucose concentration

CRP



Favors glucocorticoids **Favors placebo**

Glycémie



What This Article Tells Us That Is New

- Glucocorticoids did not impact on any wound infection (odds ratio, 0.84; 95% CI, 0.62 to 1.15) or length of stay (weighted mean difference, –0.27 days; CI, –1.37 to 0.84)
- Glucocorticoids slightly increased peak postoperative glucose concentrations by 20 mg/dl (CI, 11 to 29; $P < 0.001$), an amount that is probably not clinically important
- Single-dose steroid administration for prevention of nausea appears safe

N ENGL J MED 384;18 NEJM.ORG MAY 6, 2021

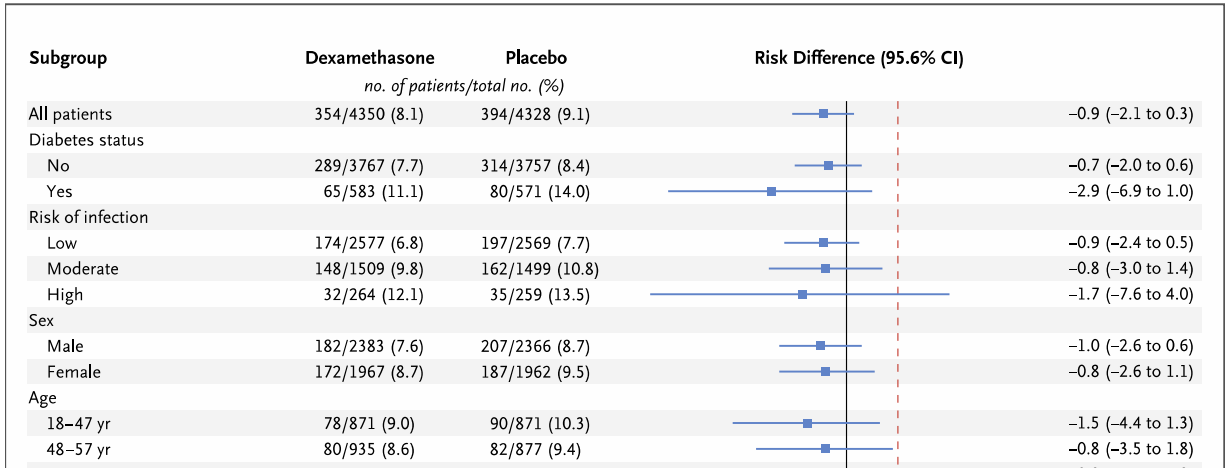
Dexamethasone and Surgical-Site Infection

Tomás B. Corcoran, M.D., Paul S. Myles, D.Sc., Andrew B. Forbes, Ph.D., Allen C. Cheng, Ph.D., Leon A. Bach, Ph.D., Edmond O'Loughlin, M.Clin.Res., Kate Leslie, M.D., Matthew T.V. Chan, Ph.D., David Story, M.D., Timothy G. Short, M.D., Catherine Martin, Ph.D., Pauline Coutts, P.Grad.Dip.N., and Kwok M. Ho, Ph.D., for the PADDI Investigators, the Australian and New Zealand College of Anaesthetists Clinical Trials Network, and the Australasian Society for Infectious Diseases Clinical Research Network*

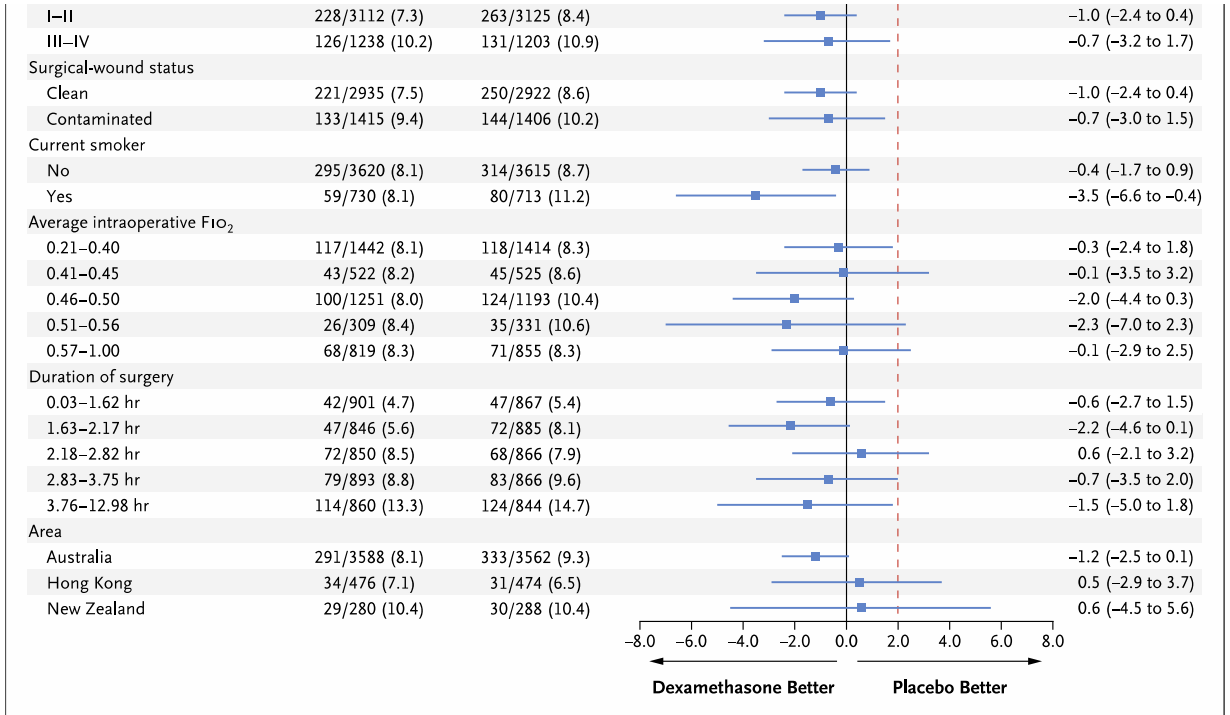
- **Chirurgie majeure (>2 heures)**
- **8725 patients**
- **8mg DXM vs Placebo**

Table 2. Outcomes in the Modified Intention-to-Treat Population.*

Outcome	Dexamethasone (N=4372)	Placebo (N=4353)	Risk Difference, Risk Ratio, or Median Difference (95% CI)
Primary			
Surgical-site infection at 30 days — no./total no. (%)†	354/4350 (8.1)	394/4328 (9.1)	
Risk difference			−0.89 (−2.11 to 0.29)‡
Risk ratio			0.89 (0.77 to 1.03)§
Secondary			
Deep or organ-space surgical-site infection with prosthetic material at 90 days — no./total no. (%)	26/1400 (1.9)	27/1363 (2.0)	0.94 (0.55 to 1.60)¶
Deep surgical-site infection at 90 days	13/1400 (0.9)	16/1363 (1.2)	0.79 (0.38 to 1.64)¶
Organ-space surgical-site infection at 90 days	13/1400 (0.9)	11/1363 (0.8)	1.15 (0.52 to 2.56)¶
Superficial surgical-site infection at 30 days — no./total no. (%)	284/4350 (6.5)	311/4328 (7.2)	0.91 (0.78 to 1.06)¶
Deep surgical-site infection at 30 days — no./total no. (%)	18/4350 (0.4)	16/4328 (0.4)	1.12 (0.57 to 2.19)¶
Organ-space surgical-site infection at 30 days — no./total no. (%)	57/4350 (1.3)	76/4328 (1.8)	0.75 (0.53 to 1.05)¶
Any infection at 30 days — no./total no. (%)	504/4366 (11.5)	544/4348 (12.5)	0.92 (0.82 to 1.03)¶
Urinary tract infection	194/4361 (4.4)	231/4347 (5.3)	0.84 (0.69 to 1.01)¶
Pneumonia	98/4364 (2.2)	94/4348 (2.2)	1.04 (0.79 to 1.38)¶
Infection associated with indwelling catheter	22/4361 (0.5)	13/4347 (0.3)	1.69 (0.85 to 3.34)¶
Sepsis at discharge	38/4370 (0.9)	65/4350 (1.5)	0.58 (0.39 to 0.87)¶
Other	211/4361 (4.8)	218/4347 (5.0)	0.97 (0.80 to 1.16)¶
Median QoR-15 score (IQR)‖			
Day 1	109 (93 to 123)	104 (87 to 118)	5.0 (3.8 to 6.2)**
Day 30	135 (123 to 143)	135 (122 to 144)	0.0 (−0.7 to 0.7)**
New-onset chronic postsurgical pain at 6 mo — no./total no. (%)	371/4254 (8.7)	300/4217 (7.1)	1.23 (1.06 to 1.42)¶
New-onset disability or death at 6 mo — no./total no. (%)	358/4233 (8.5)	338/4158 (8.1)	1.05 (0.90 to 1.21)¶



Pas de différence

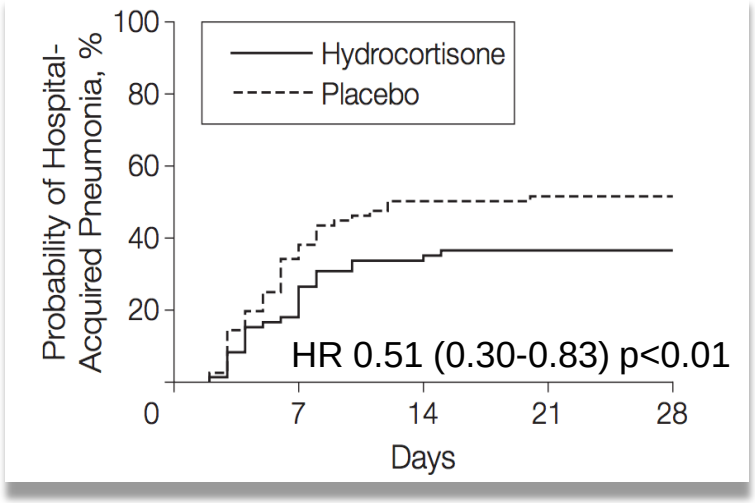


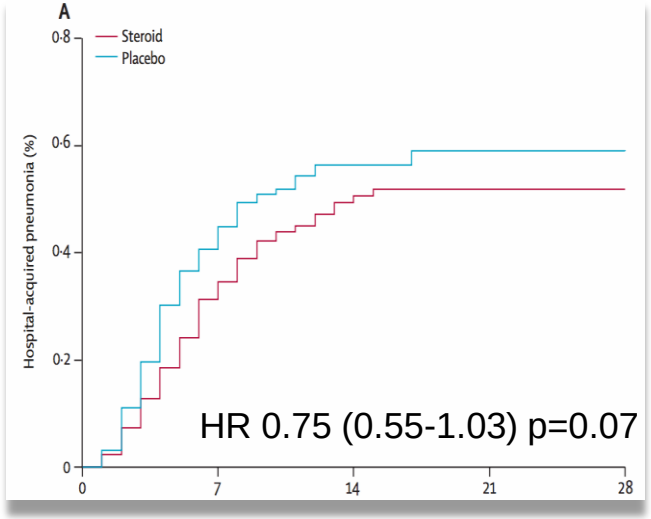
Corticosteroids

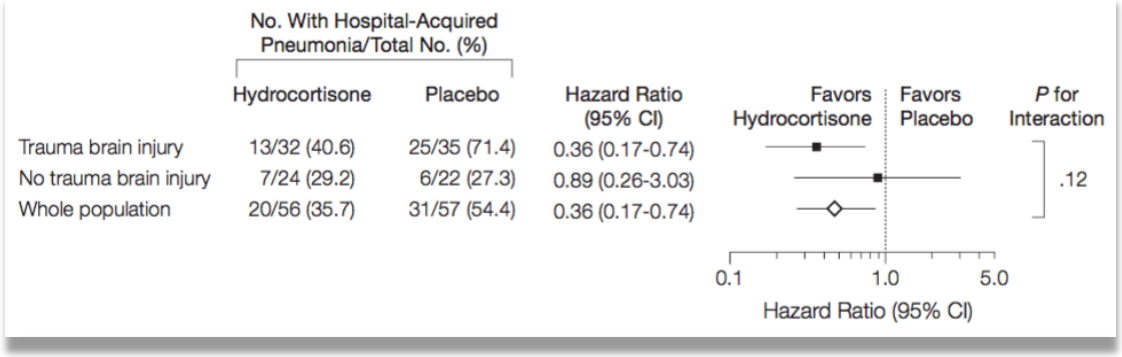
A new way of thinking

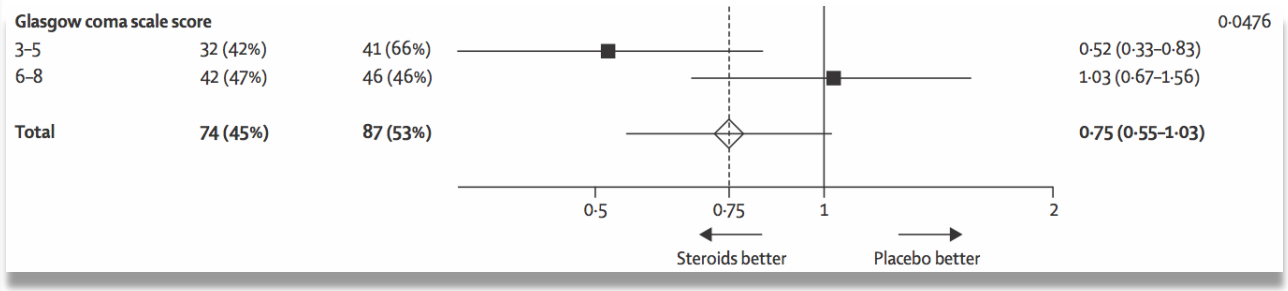
Moderate doses of steroids prevent infections in surgical critically ill patients

Steroids prevent pneumonia in severe trauma patients









Roquilly et al. JAMA 2011

Asehnoune et al. Lancet Respir Med 2014

And in surgical patients

FEATURE

Preoperative Glucocorticoid Use in Major Abdominal Surgery

Systematic Review and Meta-Analysis of Randomized Trials

Sanket Srinivasa, MBChB, Arman A. Kahokehr, MBChB, Tzu-Chieh Yu, MBChB, and Andrew G. Hill, MD, FRACS, FACS

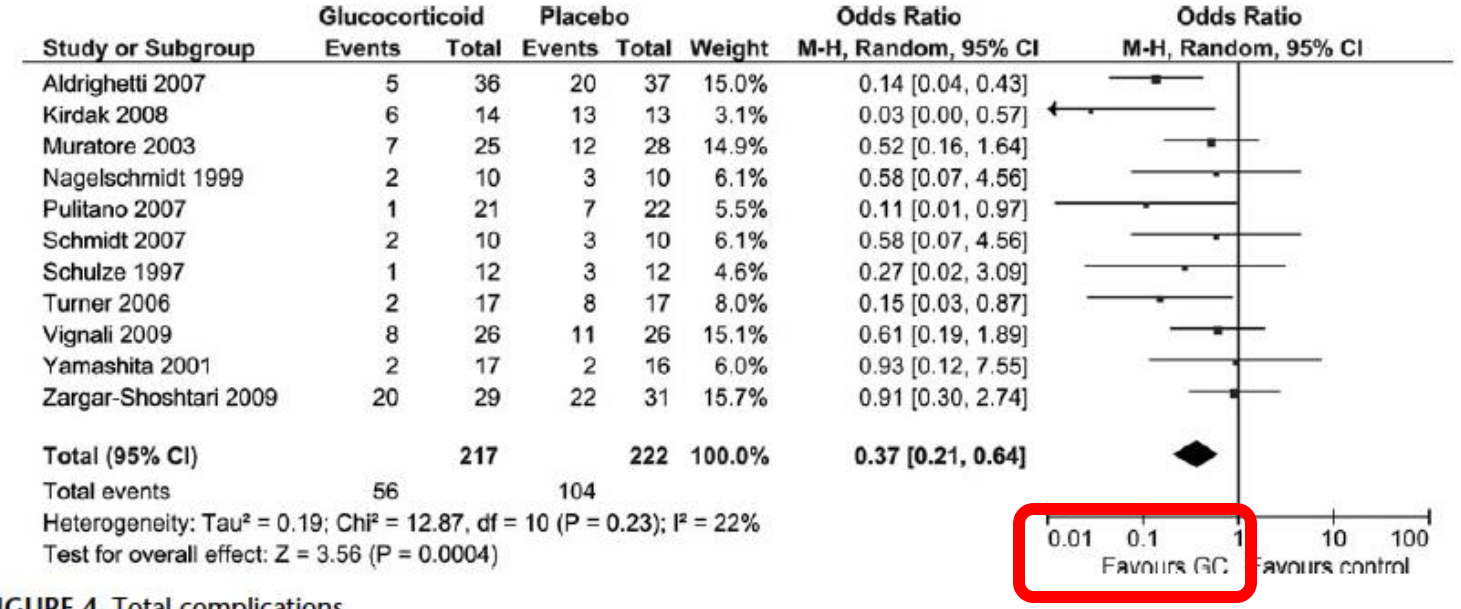


FIGURE 4. Total complications.

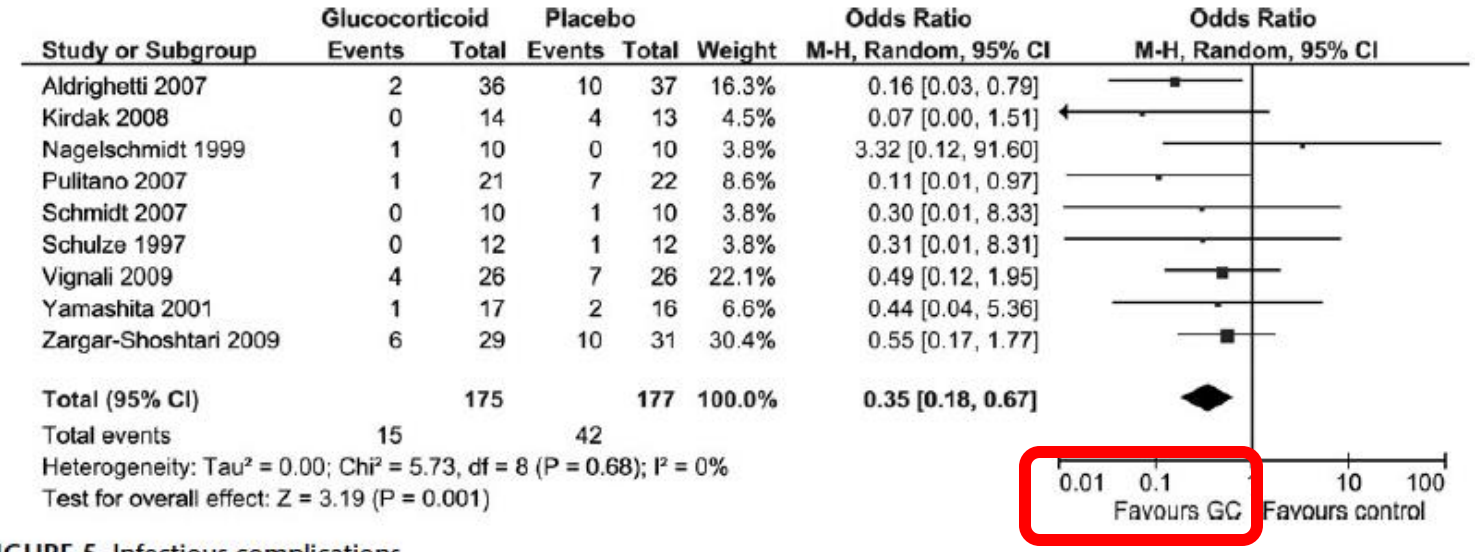


FIGURE 5. Infectious complications.

Effect of perioperative glucocorticoid administration on postoperative complications following esophagectomy: A meta-analysis

QIANG GAO[1,2*], HSIAO-PEI MOK[1*], WEN-PING WANG[2], XIAO-FEIZUO[2] AND LONG-QI CHEN[2]

[1]West China Medical School, Sichuan University; [2]Department of Thoracic Surgery, West China Hospital, Sichuan University, Chengdu, Sichuan 610041, P.R. China

Received April 2, 2013; Accepted October 16, 2013

Complications cardiaque

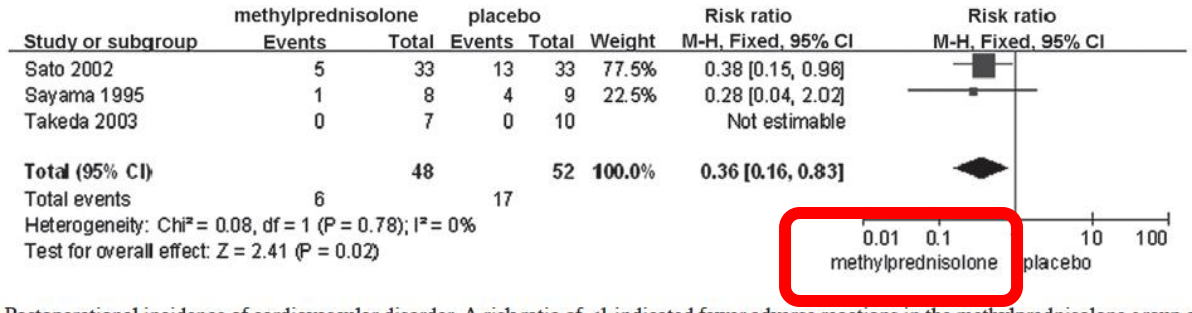


Figure 7. Postoperational incidence of cardiovascular disorder. A risk ratio of <1 indicated fewer adverse reactions in the methylprednisolone group compared with the control group. CI, confidence interval; df, degrees of freedom.

Complications pulmonaires

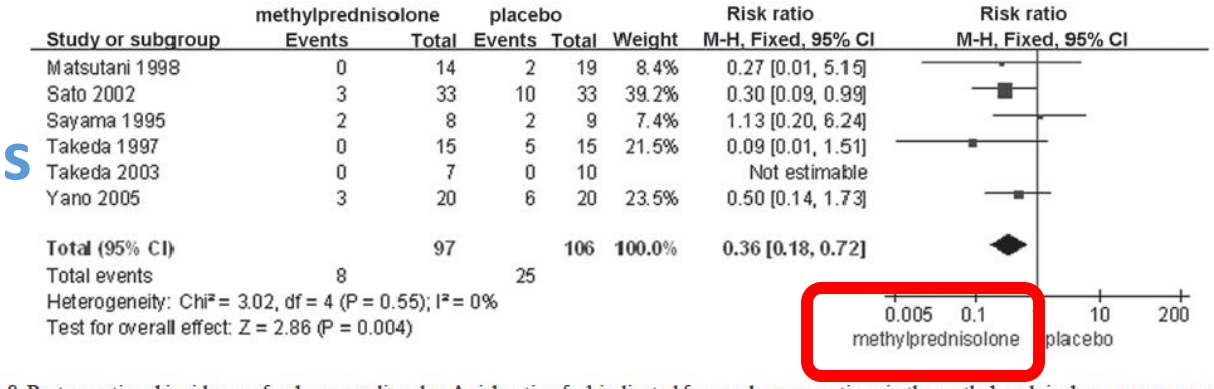
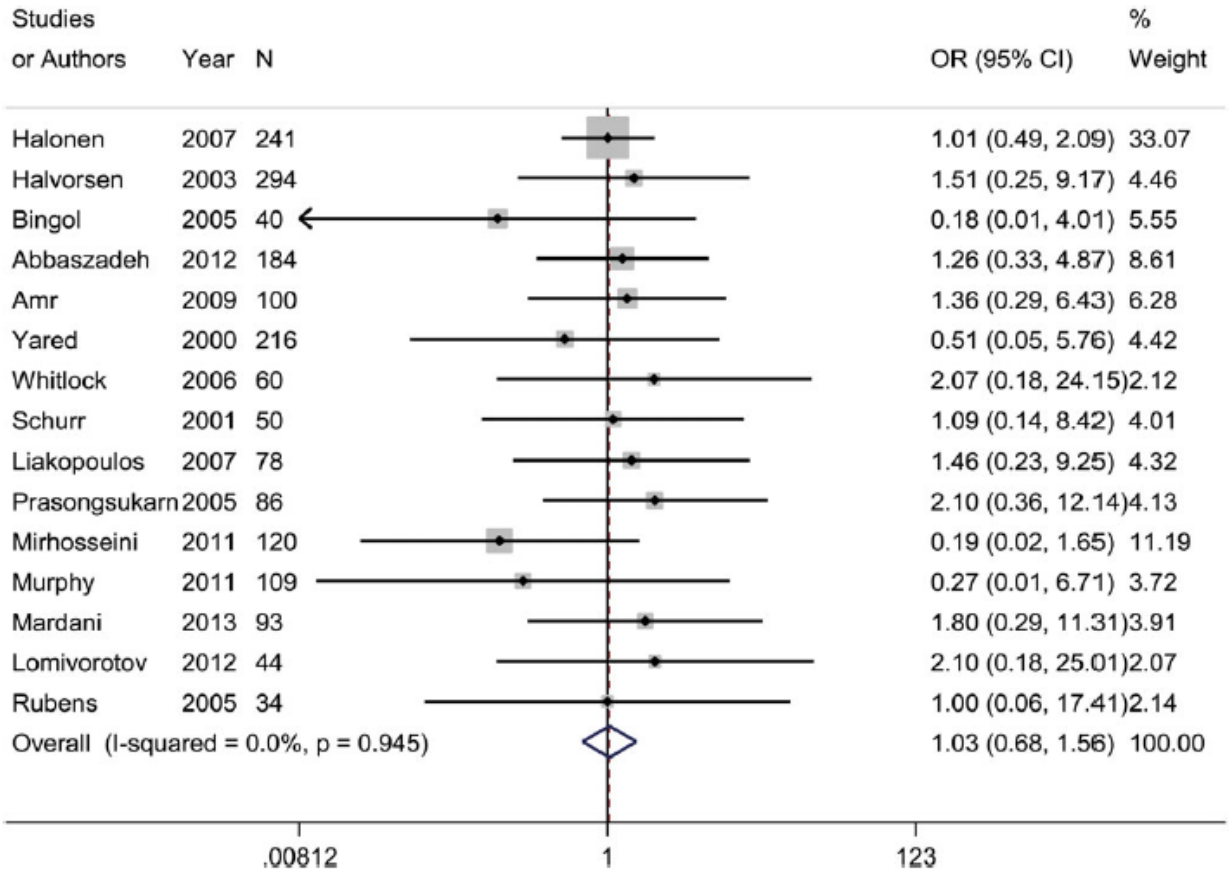


Figure 8. Postoperational incidence of pulmonary disorder. A risk ratio of <1 indicated fewer adverse reactions in the methylprednisolone group compared with the control group. CI, confidence interval; df, degrees of freedom.

Protective effects of corticosteroids in coronary artery bypass graft surgery alone or combined with valvular surgery: an updated and comprehensive meta-analysis and systematic review

Sadegh Ali-Hassan-Sayegh[a†*], Seyed Jalil Mirhosseini[a,b,†], Fatemeh Haddad[a], Ali Akbar Karimi-bondarabadi[a], Arezoo Shahidzadeh[a], Alexander Weymann[c], Aron-Frederik Popov[c] and Anton Sabashnikov[c]

- 1749 patients
- 5.4% vs 5.3%
- No increase of infection
  - in ages above and below 65 years
  - male and female,
  - Diabetic and non-diabetic patients



Incidence of post-operative infections

Moderate doses of steroids are well tolerated in critically ill patients

Corticosteroids in the Treatment of Severe Sepsis and Septic Shock in Adults

A Systematic Review

Corticosteroids did not increased the risk of

- Gastroduodenal bleeding (65/800 [8.1%] vs 56/764 [7.3%]; P=.50; I_2=0%),
- Superinfection (184/998 [18.4%] vs 170/ 950 [17.9%]; P=.92; I_2=8%),

Corticosteroids increased the risk of

- Hyperglycemia (363/703 [51.6%] vs 308/670 [46%]; P.001; I_2=0%)
- Hypernatremia (3 trials; 127/404 [31.4%] vs 77/401 [19.2%]; P.001; I_2=0%).

Doses faibles durée 7 jours OU doses très élevées durée courte (2 jours)

Safety is the key in surgical patients

Safety of very high doses Methylprednisolone > 5 mg/kg (x10 doses used in the PACMAN trial)

Methylprednisolone in patients undergoing cardiopulmonary bypass (SIRS): a randomised, double-blind, placebo-controlled trial

*Richard P Whitlock, P J Devereaux, Kevin H Teoh, Andre Lamy, Jessica Vincent, Janice Pogue, Domenico Paparella, Daniel I Sessler, Ganesan Karthikeyan, Juan Carlos Villar, Yunxia Zuo, Álvaro Avezum, Mackenzie Quantz, Georgios I Tagarakis, Pallav J Shah, Seyed Hesameddin Abbasi, Hong Zheng, Shirley Pettit, Susan Chrolavicius, Salim Yusuf, for the SIRS Investigators**

www.thelancet.com Vol 386 September 26, 2015

- 7507 patients under CPB
- No increased infection rate
- No increased surgical site infection

Take care of glucose/insuline

Safety outcomes	Methylprednisolone (n=3755)	Placebo (n=3752)	Relative risk (95% CI)	p value
Infection	465 (12%)	493 (13%)	0·94 (0·84–1·06)	0·33
Surgical site infection	151 (4%)	151 (4%)	1·00 (0·80–1·25)	0·99
Delirium	295 (8%)	289 (8%)	1·02 (0·87–1·19)	0·80
Gastrointestinal perforation or haemorrhage	55 (1%)	46 (1%)	1·19 (0·81–1·76)	0·37
Peak blood glucose (mmol/L)	12·7 (7·2)	12·1 (18·7)	..	0·04
Postoperative insulin (units)	50·3 (66·3)	32·6 (52·9)	..	<0·0001

Safety of High dose DXM 1 mg/kg (5 times higher than in the PACMAN trial)

Intraoperative High-Dose Dexamethasone for Cardiac Surgery

A Randomized Controlled Trial

JAMA. 2012;308(17):1761-1767

- 4494 patients under CPB
- Reduction of postoperative infection
- Reduction of mechanical ventilation
- Reuction of length of ICU and hospital stay

	Dexamethasone (n = 2235)	Placebo (n = 2247)	Relative Risk (95% CI)	*P* Value[a]
Gastrointestinal bleeding	13 (0.6)	11 (0.5)	1.19 (0.53-2.65)	.67
Any postoperative infection	212 (9.5)	333 (14.8)	0.64 (0.54-0.75)	<.001
Pneumonia	133 (6.0)	238 (10.6)	0.56 (0.46-0.69)	<.001
Urinary tract infection	50 (2.2)	60 (2.7)	0.84 (0.58-1.21)	.35
Wound infection	34 (1.5)	32 (1.4)	1.07 (0.66-1.72)	.79
Catheter-related infection	6 (0.3)	21 (0.9)	0.29 (0.12-0.71)	.004
Sepsis	18 (0.8)	26 (1.2)	0.70 (0.38-1.27)	.23

Take care of glucose/insuline

	Mean (SD)			
Highest serum glucose concentration in the ICU, mg/dL	195 (50)	177 (59)	NA	<.001

Safety

British Journal of Anaesthesia 110 (2): 191–200 (2013)
Advance Access publication 5 December 2012 · doi:10.1093/bja/aes431

BJA

Impact of perioperative dexamethasone on postoperative analgesia and side-effects: systematic review and meta-analysis

N. H. Waldron, C. A. Jones, T. J. Gan, T. K. Allen and A. S. Habib*
Department of Anesthesiology, Duke University Medical Center, Box 3094, Durham, NC 27710, USA

- 45 studies, 5796 patients (2997 received DXM)
- 1.25 to 20 mg DXM
- **Reduction in infection** RR 0.63 (95% CI:0.23, 1.69, P= 0.36; I^2=0%)
- **No increased risk of delayed healing :** RR 1.27 (95% CI:0.32, 4.96, P= 0.73; I^2=0%)
- **Higher blood sugar 24 hours postoperatively :** MD 0.39 (95% CI:0.04, 0.74, P= 0.03; I^2=10%

For numbered affiliations see end of article.

Correspondence to: K Asehnoune
karim.asehnoune@chu-nantes.fr
http://orcid.org/0000-0003-1899-3517

Cite this as: *BMJ* 2021;373:n1162
http://dx.doi.org/10.1136/bmj.n1162
Accepted: 05 May 2021

Effect of dexamethasone on complications or all cause mortality after major non-cardiac surgery: multicentre, double blind, randomised controlled trial

Karim Asehnoune,[1] Charlene Le Moal,[2] Gilles Lebuffe,[3] Marguerite Le Penndu,[1] Nolwen Chatel Josse,[4] Matthieu Boisson,[5] Thomas Lescot,[6] Marion Faucher,[7] Samir Jaber,[8] Thomas Godet,[9] Marc Leone,[10] Cyrus Motamed,[11] Jean Stephane David,[12] Raphael Cinotti,[13] Younes El Amine,[14] Darius Liutkus,[2] Matthias Garot,[3] Antoine Marc,[1] Anne Le Corre,[4] Alexandre Thomasseau,[5] Alexandra Jobert,[15] Laurent Flet,[16] Fanny Feuillet,[17] Morgane Pere,[15] Emmanuel Futier,[9] Antoine Roquilly[1], on behalf of the PACMAN study group

OBJECTIVE

To assess the effect of dexamethasone on complications or all cause mortality after major non-cardiac surgery.

PARTICIPANTS

1222 adults (>50 years) requiring major non-cardiac surgery with an expected duration of more than 90 minutes. The anticipated time frame for recruitment was 24 months.

INTERVENTIONS

Participants were randomised to receive either dexamethasone (0.2 mg/kg immediately after the surgical procedure, and on day 1) or placebo. Randomisation was stratified on the two prespecified criteria of cancer and thoracic procedure.

MAIN OUTCOMES MEASURES

The primary outcome was a composite of postoperative complications or all cause mortality within 14 days after surgery, assessed in the modified intention-to-treat population (at least one treatment administered).

Outcomes	Dexamethasone group (n=595)	Placebo group (n=589)	Estimate (95%CI)	P value
Primary outcome: complications and mortality at 14 days	101 (17.0)	117 (19.9)	0.81 (0.60 to 1.08)*	0.15
All cause mortality	6 (1.0)	7 (1.2)	0.84 (0.52 to 1.38)†	0.5
Postoperative pneumonia or sepsis, or both	78 (13.1)	94 (16.0)	0.82 (0.60 to 1.11)‡	0.2
Mechanical ventilation for respiratory failure	41 (6.9)	52 (8.8)	0.70 (0.53 to 0.93)‡	0.015

Decreased AKI with DXM

Subgroup	No of patients with event/ total No of patients (%)		Odds ratio (95% CI)	Odds ratio (95% CI)
	Dexamethasone group	Placebo group		
Cancer				
Yes	83/385 (21.6)	99/389 (25.5)		0.79 (0.56 to 1.11)
No	18/210 (8.6)	18/200 (9.1)		0.95 (0.47 to 1.88)
χ^2=0.23; P=0.63				
Intrathoracic procedure				
Yes	32/75 (42.7)	24/71 (33.8)		1.46 (0.74 to 2.85)
No	69/520 (13.3)	93/518 (18.0)		0.70 (0.50 to 0.99)
χ^2=3.54; P=0.06				

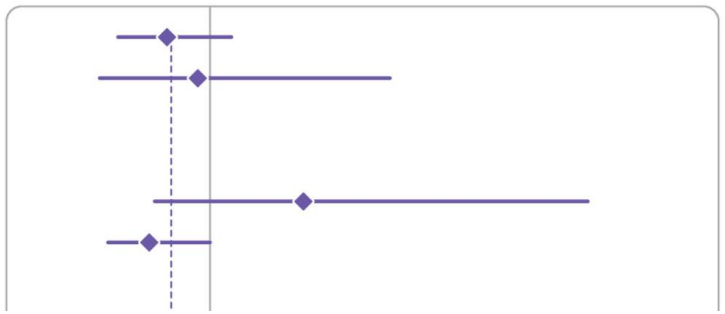


Table 3 | Safety outcomes in participants assigned to dexamethasone or placebo after major non-cardiac surgery. Values are numbers (percentages) unless stated otherwise

	Dexamethasone group (n=613)	Placebo group (n=609)	Estimate (95%CI)	P values
Adverse events	288 (47.0)	296 (48.6)	0.92 (0.74 to 1.15)*	0.46
Severe adverse events	106 (17.3)	103 (16.9)	1.03 (0.75 to 1.42)*	0.86
Anastomotic leakage	17 (2.8)	23 (3.8)	0.70 (0.38 to 1.31)*	0.27
Metabolic disorders†:				
Hypokalaemia	74 (12.4)	110 (18.8)	0.59 (0.43 to 0.81)*	0.001
Hyponatraemia	164 (27.4)	144 (24.6)	1.14 (0.89 to 1.45)*	0.31
Hypernatraemia	8 (1.3)	20 (3.4)	0.38 (0.17 to 0.86)*	0.02
Hypocalcaemia	159 (29.7)	190 (36.1)	0.71 (0.56 to 0.90)*	0.005
Healing:				
Normal	541 (89.6)	536 (89.9)	1.05 (0.72 to 1.54)*	0.79
Delayed	41 (6.8)	34 (5.7)	1.22 (0.64 to 2.33)*	0.50
Wound dehiscence	22 (3.6)	26 (4.4)	0.84 (0.46 to 1.55)*	0.58
Insulin treatment	166 (27.4)	131 (21.5)	1.36 (0.99 to 1.88)*	0.06
Median (interquartile range) total dose of insulin (IU/day):			−0.97 (−5.73 to 3.78)‡	0.69

Conclusion

- **No hazardous safety issue**
- **Potential great benefit (proven in critically ill patients)**
- **PACMAN: first «big study » to date in non-cardiac surgery**
- **Excellent cost/effectiveness**
- **Millions of patients treated around the world**