University of East Anglia | Norwich Medical School

Norfolk and Norwich University Hospitals NHS
NHS Foundation Trust

Diabetes and Steroids

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Glucocorticoids and Diabetes ?Issues

- Is it a problem?
- How to control hyperglycaemia associated with glucocorticoid use?

378 ANDREAE VESALII BRVXELLENSIS

QQ His characteribus sinistræ lateris membrana notatur, quæ illi correspondet, quam nuper O, O indicarunt.

R,S Vteri ceruicis anterior pars, inter R & S ea adhuc obducta tunica, quam peritonæi partes illi offerũt, quæ ipsi uasa exporrigunt, deducuntq;, ac illum peritonæo adnectunt. Cæterùm inter uallum inter R & S consistens, uteri ceruicis amplitudinem quodammodo significat. Rugæ uerò hic conspicuæ, illæ sunt quas uteri ceruix in se collapsa, neq; alias distenta, inter secandum commonstrat.

T Vesica, cuius posterior facies hic potissimum spectatur. ita enim in figuræ huius delineatione oculum direximus, ac si in corpore prostrato, posteriorem uesicæ sedem quæ uterum spectat, potissimum cernere uoluissemus. Si enim præsens muliebre corpus ita uti id quod modò subsequetur, erectum arbitrareris, etiam secus atq; res se habet, uteri fundum multo elatius ipsa uesica delineatum esse tibi persuaderes.

V Vmbilici est portio, à peritonæo inter secãdum liberata, & unà cum uasis fœtui peculiaribus hic deorsum reflexa.

X Portio uenæ ab umbilico iecur petentis.

Y Meatus à uesicæ fundi elatissima sede ad umbilicum pertinens, ac fœtus urinam inter secundum & intimum ipsius inuolucrum deducens.

Z, et & Duæ arteriæ ab umbilico huc secundùm uesicæ latera prorepentes, atq; hac sede magnæ arteriæ ramis pubis ossium foramina potissimum adeuntibus insertæ, seu continuæ.

VIGESIMAQVINTA QVINTI LIBRI FIGVRA

VIGE

A Bit Of Background

- At any one time, ~0.75% of the UK population is on oral glucocorticoids (0.2% in 20-29 year olds, 2.5% in 70-79 year olds)
- 40% of glucocorticoid use is for respiratory disease, with most of the rest being musculoskeletal and cutaneous diseases and conditions requiring immunosuppression
- Most use is for <5 days, but 22% is for > 6 months and 4.3% for > 5 years

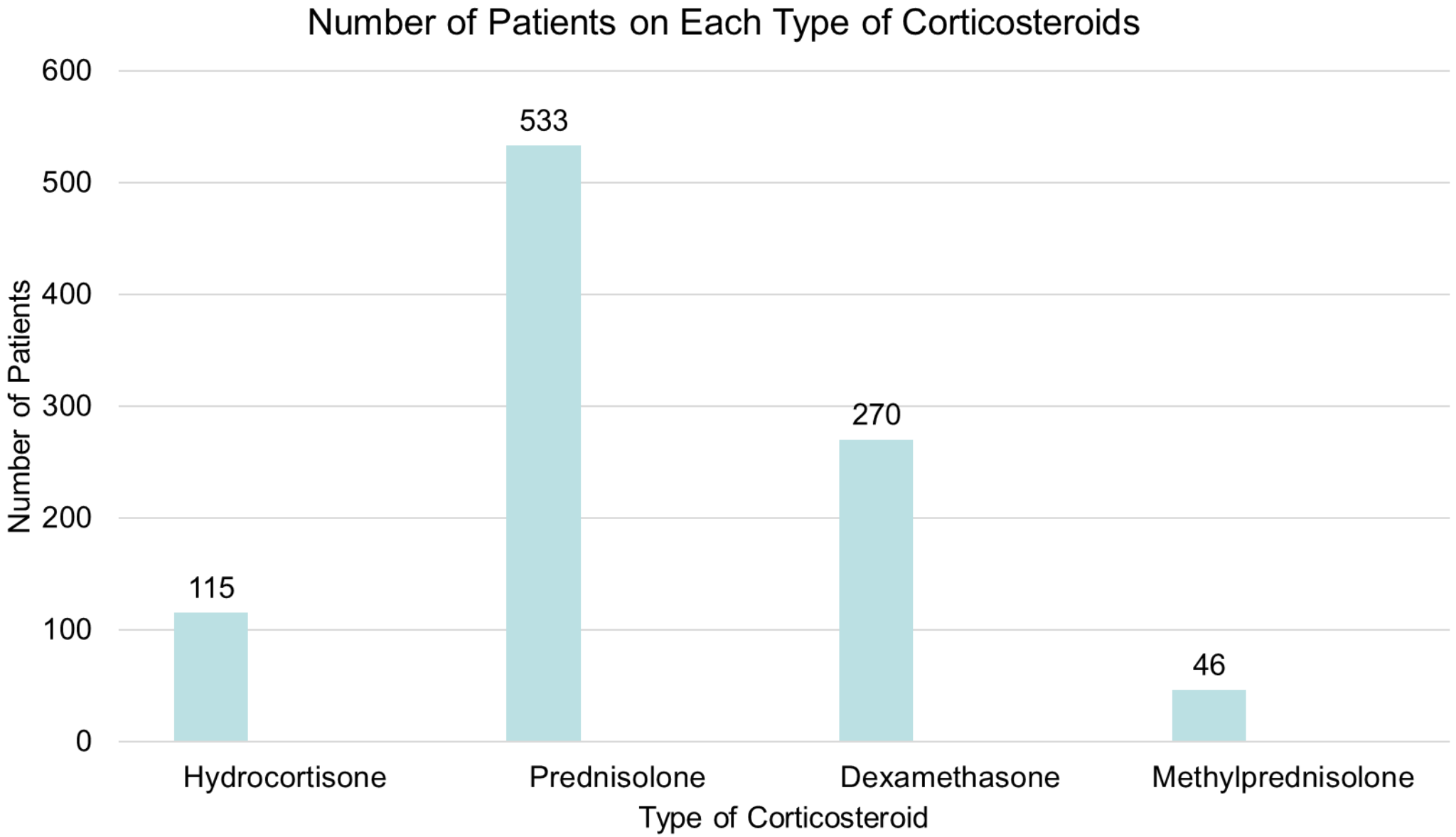
Royal College of Physicians Glucocorticoid guidelines 2002
Fardet L et al Rheumatology 2011;50(11):1982-1990

NNUH Audit

- Between 10th February 2021 and 10th September 2021
- 3260 inpatients received oral or IV corticosteroids
- 964 (30%) adult inpatients on Oral/IV steroids with blood glucose measurements

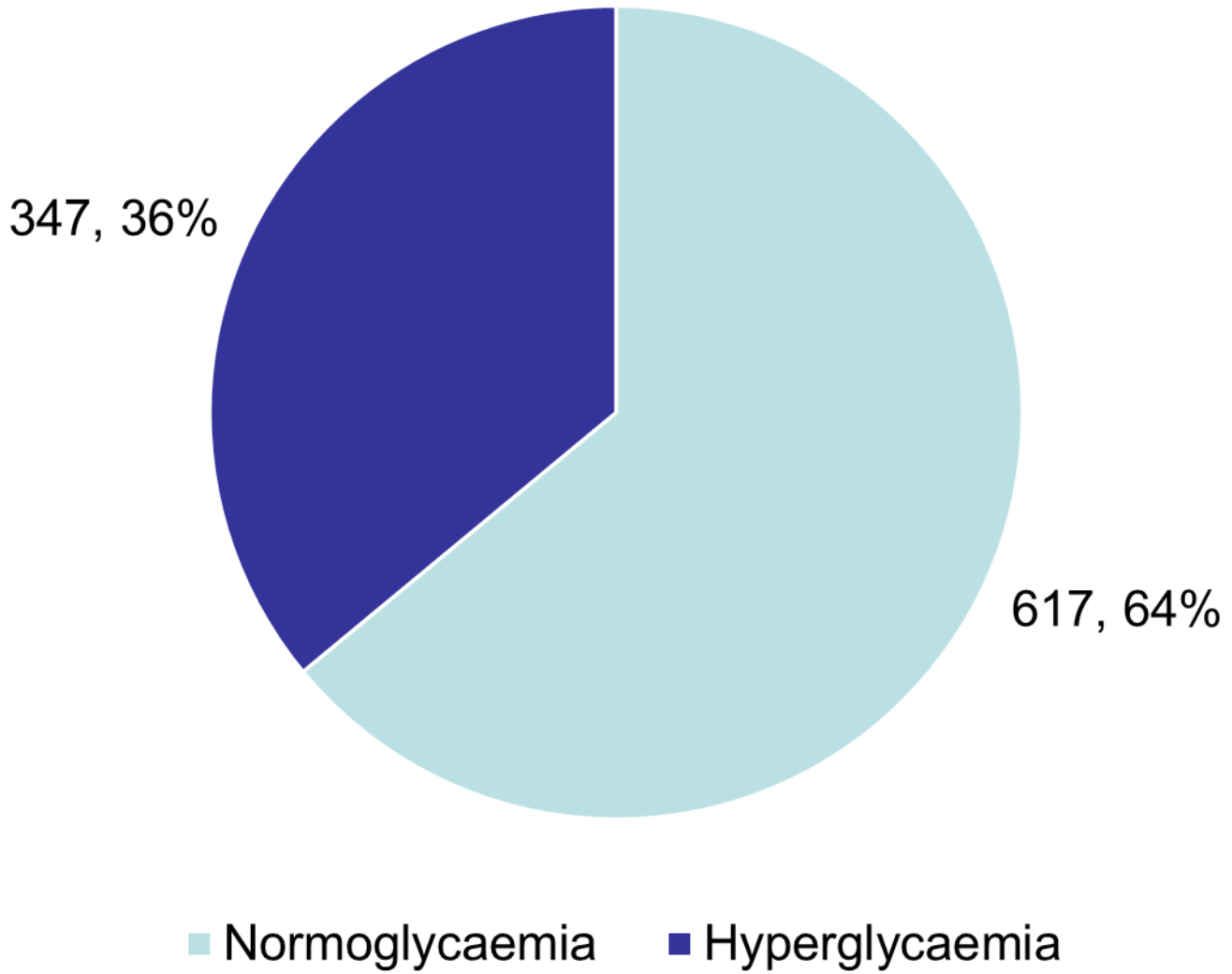
IV = Intravenous

Limbachia V et al Clin Med 2024 ;24(6):100249



Limbachia V et al Clin Med 2024 ;24(6):100249

Patients with Hyperglycaemia while on steroids



Limbachia V et al Clin Med 2024 ;24(6):100249

Mean differences in blood glucose concentrations of different steroid classes with 95% confidence interval across seven days

Study Drugs	Mean Difference, mmol/L	95% CI	P
Dexamethasone vs hydrocortisone	0.92	0.45 to 1.38	0.0007
Dexamethasone vs prednisolone	1.11	0.79 to 1.43	<0.0001
Dexamethasone vs methylprednisolone	–0.41	–1.02 to 0.21	0.7216
Hydrocortisone vs prednisolone	0.20	–0.22 to 0.61	0.9283
Hydrocortisone vs methylprednisolone	–1.33	–2.02 to –0.63	0.0011
Methylprednisolone vs prednisolone	1.52	0.91 to 2.13	<0.0001

CBG = Capillary Blood Glucose

Limbachia V et al Clin Med 2024 ;24(6):100249

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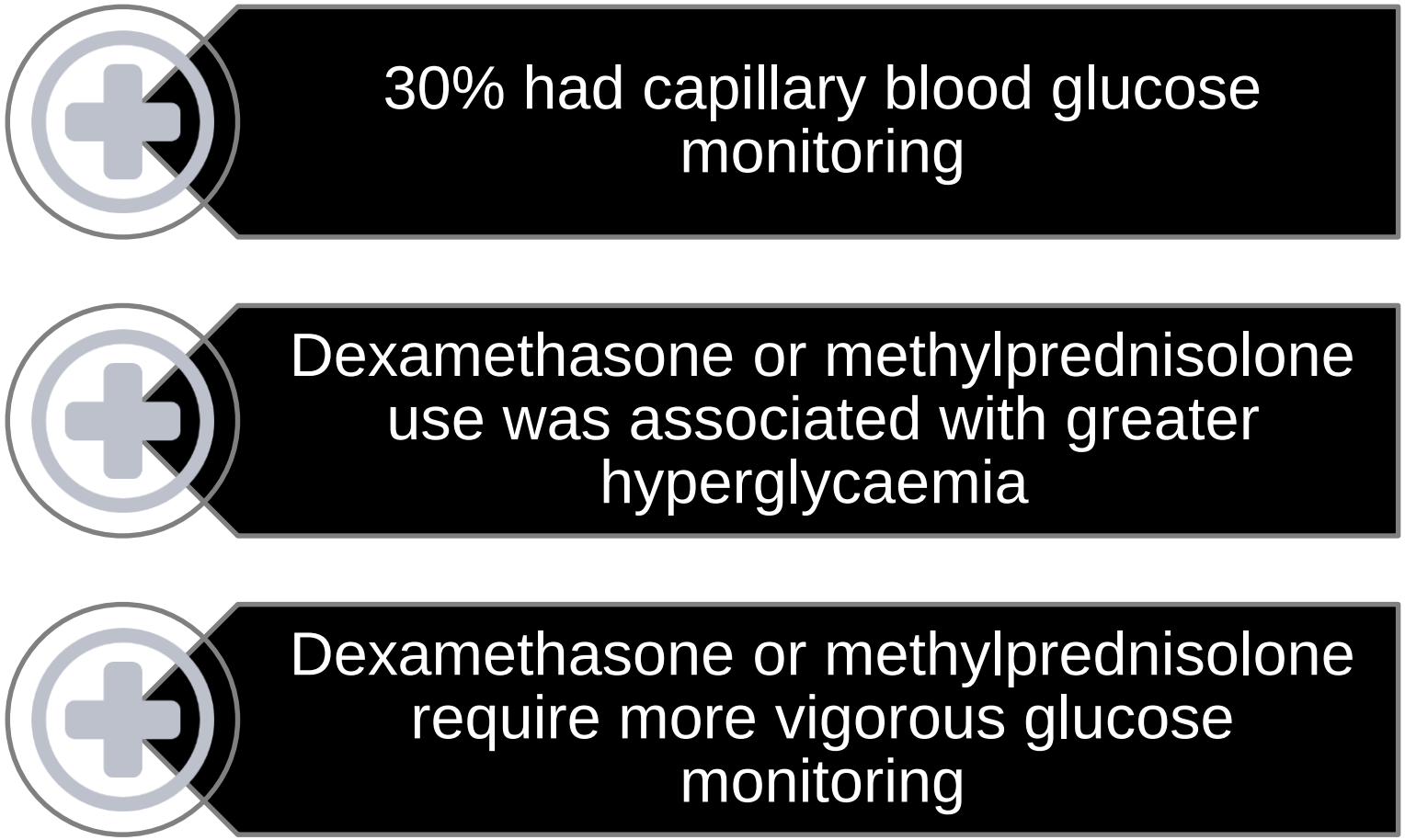
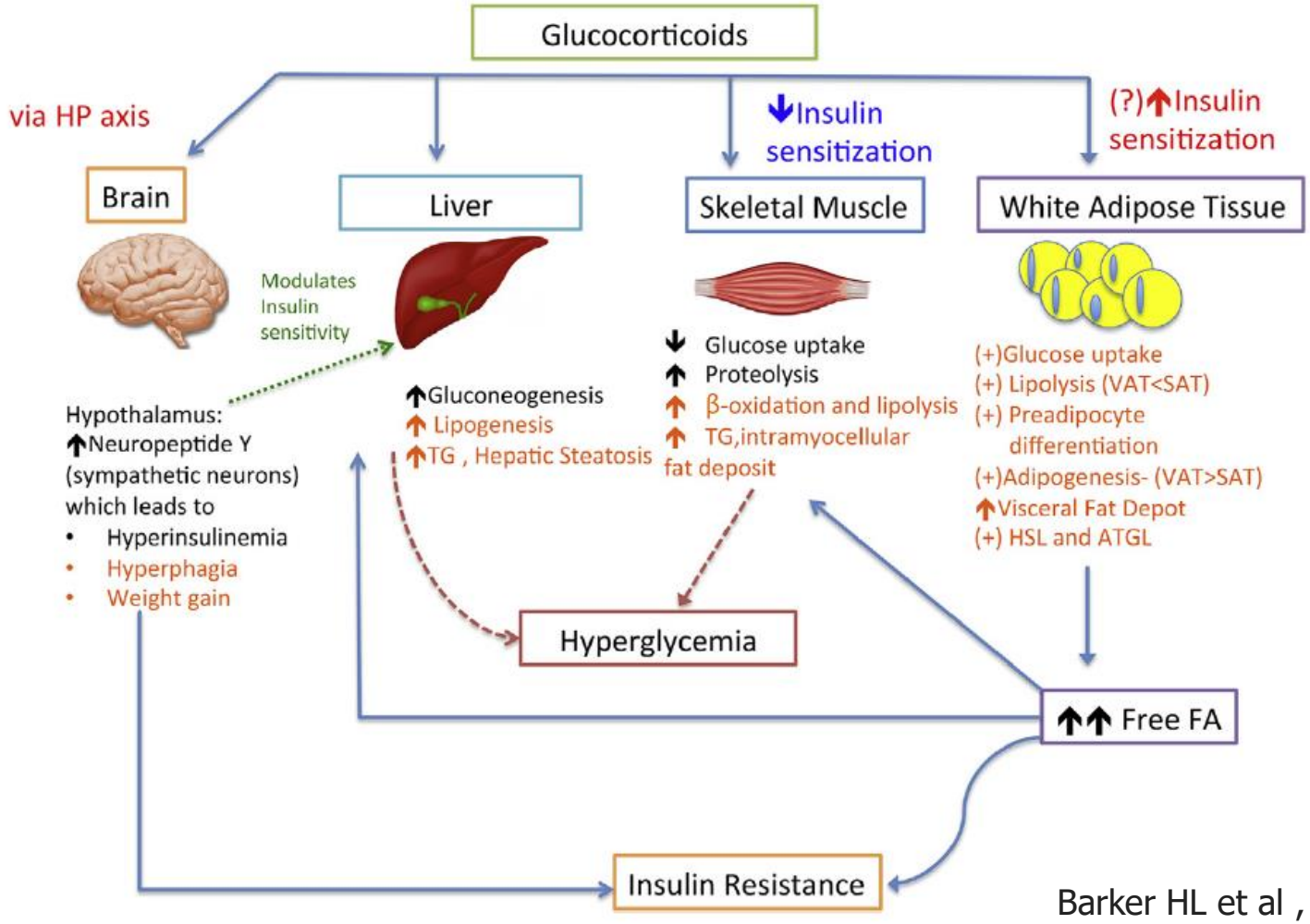
Limbachia V et al Clin Med 2024 ;24(6):100249



Limbachia V et al Clin Med 2024 ;24(6):100249

How do Glucocorticoids Affect Carbohydrate Metabolism?



Barker HL et al , Diabetes Ther 2023 14, 937–945
Geer EB et al Endocrinol Metab Clin North Am 2014;43(1):75-102

How do Glucocorticoids Affect Carbohydrate Metabolism?

- They promote visceral adipose tissue deposition
- Enhance lipolysis
- Alter levels of adipose tissue derived hormones and cytokines
- Acutely increases hepatic glucose production
- Complex effects on β-cell function

How do Glucocorticoids Affect Carbohydrate Metabolism?

- In the longer term induces insulin resistance
  - Diminished ability of insulin to initiate intracellular signalling mechanisms - in the liver, adipose, muscle
- Inhibits glucose uptake into muscle and reduced oxidative phosphorylation
- Induction of hyperinsulinaemia, dyslipidaemia and the metabolic syndrome

Saltiel AR et al Nature 2001;414:799-806
Hollingdal M et al Diabetologia 2002;45:49-55
Boyle PJ Diabetes Reviews 1993;1:301
Lambillotte C et al J Clin Invest 1997;99:414-423
Petersons CJ et al Diabetes Care 2013;36:2822-2829

Inhibition of Glucose Uptake

- Starts very early after glucocorticoid ingestion
- In (previously well controlled) inpatients the earliest manifestation of this is postprandial hyperglycaemia

Schacke H et al Pharmacol Ther 2002;96:23-43
Dimitriadis G et al Biochem J 1997;321:707–712
Petersons CJ et al Diabetes Care 2013;36:2822-2829

Spectrum of Disease

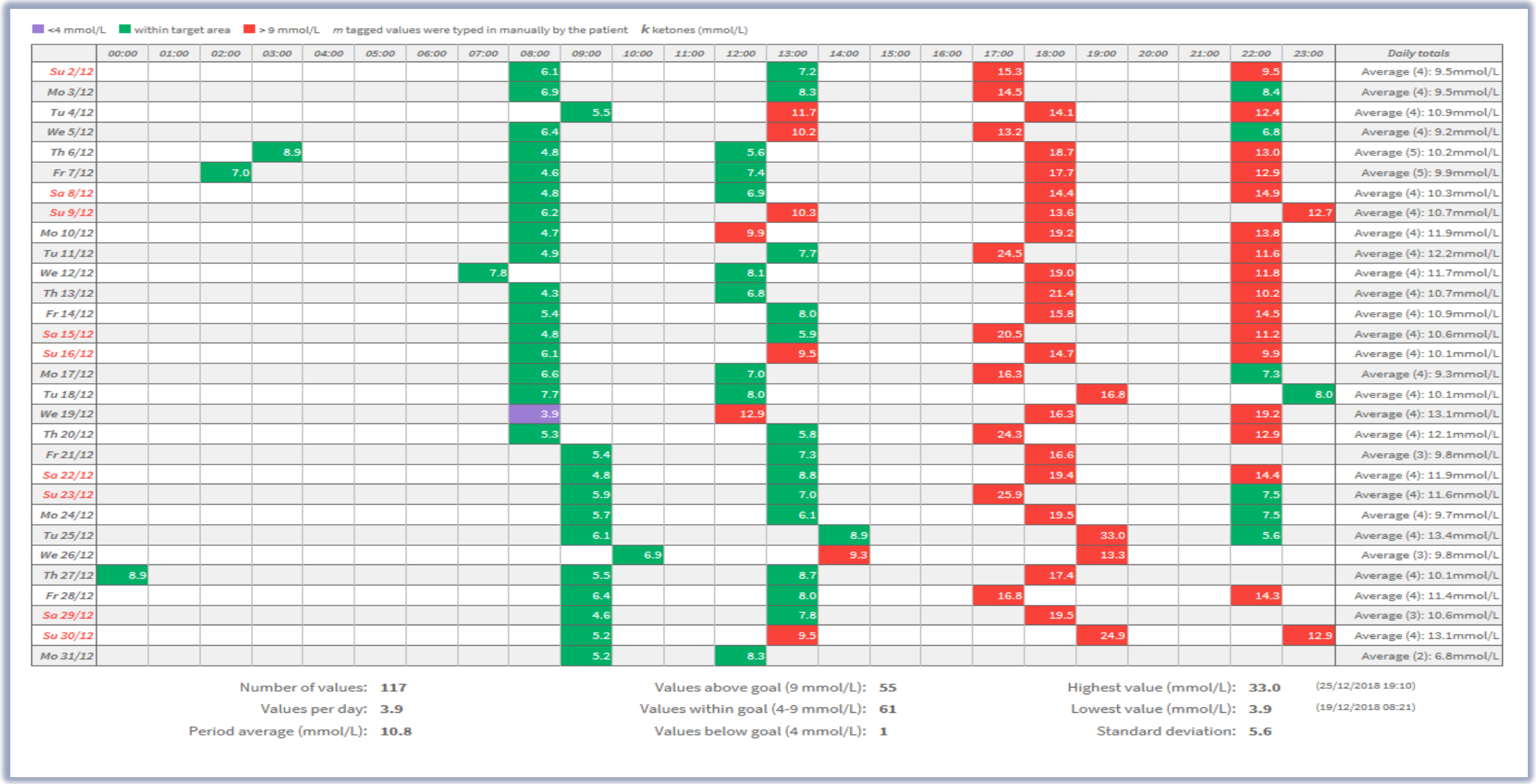
- The hyperglycaemia may be a transient rise of blood glucose levels or may result in HHS
- The best predictors of glucocorticoid-induced diabetes are family history of diabetes, increasing age, and glucocorticoid dose

Clement S Diabetes Care 2004;27(2):553-591

Back to Oral Steroids

- A 52 year old lady who had a liver transplant for antibiotic induced acute liver failure 1 month previously was on 30mg prednisolone as part of her immunosuppressive regimen. The dose had recently been reduced to 20mg
- Her HbA_1c was 50mmol/mol

Her Glucose Meter Download



<4 mmol/L | within target area | > 9 mmol/L | *m* tagged values were typed in manually by the patient | *k* ketones (mmol/L)

	00:00	01:00	02:00	03:00	04:00	05:00	06:00	07:00	08:00	09:00	10:00	11:00	12:00	13:00	14:00	15:00	16:00	17:00	18:00	19:00	20:00	21:00	22:00	23:00	Daily totals
Su 2/12									6.1					7.2				15.3					9.5		Average (4): 9.5mmol/L
Mo 3/12									6.9					8.3				14.5					8.4		Average (4): 9.5mmol/L
Tu 4/12										5.5				11.7					14.1				12.4		Average (4): 10.9mmol/L
We 5/12									6.4					10.2				13.2					6.8		Average (4): 9.2mmol/L
Th 6/12				8.9					4.8				5.6						18.7				13.0		Average (5): 10.2mmol/L
Fr 7/12			7.0						4.6				7.4						17.7				12.9		Average (5): 9.9mmol/L
Sa 8/12									4.8				6.9						14.4				14.9		Average (4): 10.3mmol/L
Su 9/12									6.2					10.3					13.6					12.7	Average (4): 10.7mmol/L
Mo 10/12									4.7				9.9						19.2				13.8		Average (4): 11.9mmol/L
Tu 11/12									4.9					7.7				24.5					11.6		Average (4): 12.2mmol/L
We 12/12								7.8					8.1						19.0				11.8		Average (4): 11.7mmol/L
Th 13/12									4.3				6.8						21.4				10.2		Average (4): 10.7mmol/L
Fr 14/12									5.4					8.0					15.8				14.5		Average (4): 10.9mmol/L
Sa 15/12									4.8					5.9				20.5					11.2		Average (4): 10.6mmol/L
Su 16/12									6.1					9.5					14.7				9.9		Average (4): 10.1mmol/L
Mo 17/12									6.6				7.0					16.3					7.3		Average (4): 9.3mmol/L
Tu 18/12									7.7				8.0							16.8				8.0	Average (4): 10.1mmol/L
We 19/12									3.9				12.9						16.3				19.2		Average (4): 13.1mmol/L
Th 20/12									5.3					5.8				24.3					12.9		Average (4): 12.1mmol/L
Fr 21/12										5.4				7.3					16.6						Average (3): 9.8mmol/L
Sa 22/12										4.8				8.8					19.4				14.4		Average (4): 11.9mmol/L
Su 23/12										5.9				7.0				25.9					7.5		Average (4): 11.6mmol/L
Mo 24/12										5.7				6.1					19.5				7.5		Average (4): 9.7mmol/L
Tu 25/12										6.1					8.9					33.0			5.6		Average (4): 13.4mmol/L
We 26/12											6.9				9.3					13.3					Average (3): 9.8mmol/L
Th 27/12	8.9									5.5				8.7					17.4						Average (4): 10.1mmol/L
Fr 28/12										6.4				8.0				16.8					14.3		Average (4): 11.4mmol/L
Sa 29/12										4.6				7.8					19.5						Average (3): 10.6mmol/L
Su 30/12										5.2				9.5						24.9				12.9	Average (4): 13.1mmol/L
Mo 31/12										5.2			8.3												Average (2): 6.8mmol/L

Number of values:	117	Values above goal (9 mmol/L):	55	Highest value (mmol/L):	33.0	(25/12/2018 19:10)
Values per day:	3.9	Values within goal (4-9 mmol/L):	61	Lowest value (mmol/L):	3.9	(19/12/2018 08:21)
Period average (mmol/L):	10.8	Values below goal (4 mmol/L):	1	Standard deviation:	5.6	

You May Have Seen This

Adjunct prednisone therapy for patients with community-acquired pneumonia: a multicentre, double-blind, randomised, placebo-controlled trial

Claudine Angela Blum, Nicole Nigro*, Matthias Briel, Philipp Schuetz, Elke Ullmer, Isabelle Suter-Widmer, Bettina Winzeler, Roland Bingisser, Hanno Elsaesser, Daniel Drozdov, Birsen Arici, Sandrine Andrea Urwyler, Julie Refardt, Philip Tarr, Sebastian Wirz, Robert Thomann, Christine Baumgartner, Hervé Duplain, Dieter Burki, Werner Zimmerli, Nicolas Rodondi, Beat Mueller, Mirjam Christ-Crain*

785 Patients were randomly assigned (1:1 ratio) to receive either prednisone 50 mg daily for 7 days or placebo.

The prednisone group had a higher incidence of in-hospital hyperglycaemia needing insulin treatment (76 [19%] *vs* 43 [11%]; OR 1·96, 95% CI 1·31–2·93, p=0·0010).

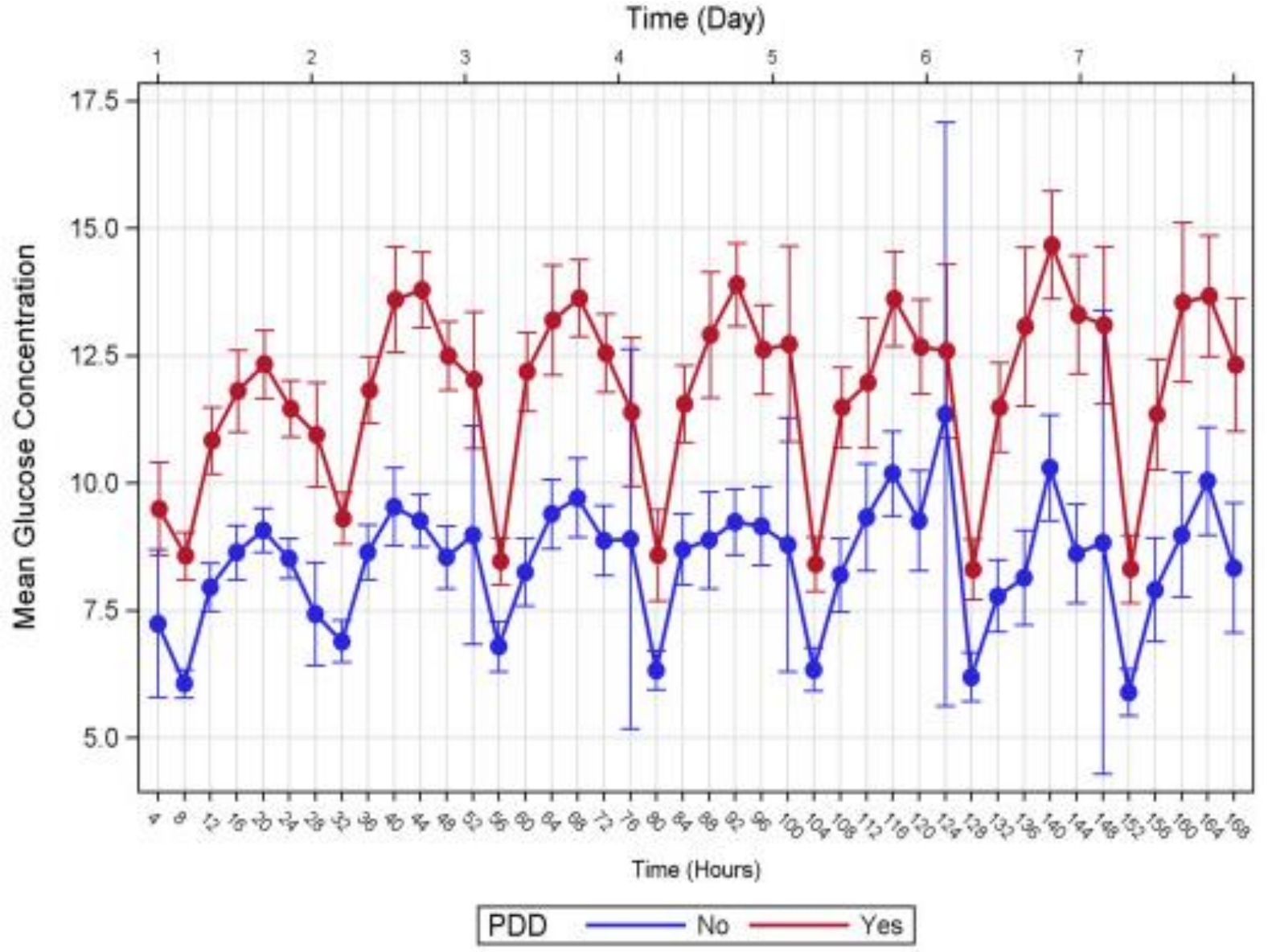
Lancet 2015;385:1511-1518

Some Evidence of Harm

- 433 patients admitted with an exacerbation of COPD from St George's in Tooting in 01/02
- Absolute risk of adverse outcomes (death or prolonged stay) increased ~15% per 1 mmol/L increase in glucose

Glucose level (mmol/L)	<6.0	6.0 - 6.9	7.0 - 8.9	>9.0
Mortality (%)	11.6	15.9	21.3	31.0

Baker EH et al Thorax 2006;61(4):284-289
Chakrabarti B Thorax 2009;64(10):857-862



PDD: Previous Diagnosis of Diabetes

Limbachia V et al Clin Therapeutics 2024;46(2):e59-63

Now We Know the Cause, What's the Treatment?

- Education and pre-empting the (almost) inevitable
- Letting teams know that when someone starts glucocorticoid treatment that blood glucose levels are very likely to rise and to watch for it
- When it happens, treat early

This is likely to meet with quite a lot of resistance – so be prepared!

Apart From That, What's the Treatment?

- There is work to shown that the hyperglycaemia associated with long term glucocorticoid use is amenable to treatment with glitazones
- There is a complex interaction between glucocorticoids and PPAR signalling pathways – these are the therapeutic targets for the glitazones

Willi SM et al Diabetes Res & Clin Pract 2002;58(2):87-96

But…..

- They work very slowly – so may have been useful in an outpatient setting
- Several controversies abound regarding the use of glitazones, thus their use is declining
  - Increased CV death rates
  - Increased fracture rates
  - Increased rates of macular oedema
  - Bladder cancer

Nissen SE NEJM 2007;356(24):2457-2471
Loke YK et al CMAJ 2009;180(1):32-39
Ryan EH et al Retina 2006; 26(5):562-70
Ferwana M et al Diabetic Med 2013;30(9):1026-1032

Sulphonylureas

- Little published evidence but widely used
- We asked for examples of guidelines used at different hospitals – and we got lots!
- All variations around a theme with some minor differences
- Most often used first line

Don't Incretins Prevent Postprandial Hyperglycaemia?

- They do, but GLP-1 use is limited by
  - Little experience in this setting
  - It makes people who are already unwell feel nauseated
  - Not appropriate for people who are NBM (??)
  - Safety concerns
- There are limited published data on the use of DPP-IV antagonists in this situation
  - e.g. Umpierrez using sitagliptin in 90 hospitalised patients

Umpierrez GE et al Diabetes Care 2013;36(11):3430-3435

The Best Treatment?

- Insulin is recommended in the US as the drug of choice for the treatment of glucocorticoid-induced hyperglycaemia
- Theoretically, prandial insulin should minimise the effects of the postprandial rise in glucose
- For patients receiving high-dose intravenous glucocorticoids, an intravenous insulin infusion may be appropriate

Hirsch IB et al Endocr Metab Clin North Am 1997;26:631–645

No Surprises There Then

- The dose needed is difficult to predict
- Intravenous infusions tend to achieve acceptable blood glucose concentrations quicker than MDI
- In hospital, an insulin infusion allows appropriate tapering of insulin infusion rates
  - Glycaemic control is not compromised
  - Hypoglycaemic risks can be minimised – especially with pulsed high dose glucocorticoids

What About Subcutaneous Insulin?

- Clearly iv insulin is not the answer for outpatients
- Subcutaneous insulin needs higher prandial doses than basal
- No work has been done to compare human with analogue insulin

Where's the Evidence?

- Naturally, there isn't any
- But there is evidence that hyperglycaemia in a hospital setting (for any cause) is associated with poor mortality, morbidity, and health economic outcomes
- Improving glycaemic control improves these outcomes

Umpierrez GE et al J Clin Endocrinol Metab 2002; 87:978–982
Bruno A et al Diabetes Care 2008;31(11):2209-2210
Dhatariya K BMJ 2013;346:f134

What Should the Targets Be?

- Targets similar to those of outpatients are unrealistic in hospital due to the effects of
  - Stress hyperglycaemia
  - Altered nutritional intake
  - Multiple interruptions to medical care
- Aiming for a range of 6.0 – 10.0 mmol/L with an acceptable range of 4.0 – 12.0 mmol/L if they can be safely achieved
- For end-of-life care, a range of 6.0 – 15.0 mmol/L is acceptable

DIABETICMedicine

DOI: 10.1111/dme.13675

Diabetes UK Position Statements

Management of hyperglycaemia and steroid (glucocorticoid) therapy: a guideline from the Joint British Diabetes Societies (JBDS) for Inpatient Care group

A. Roberts[1], J. James[2] and K. Dhatariya[3], on behalf of the Joint British Diabetes Societies (JBDS) for Inpatient Care*

[1]Cardiff and Vale University Local Health Board, Cardiff, UK, [2]University Hospitals Leicester NHS Trust, Leicester, UK and [3]Norfolk and Norwich University Hospitals NHS Foundation Trust, Norwich, UK

Accepted 12 May 2018

Roberts A et al Diabetic Medicine 2018;35(8):1011-1017

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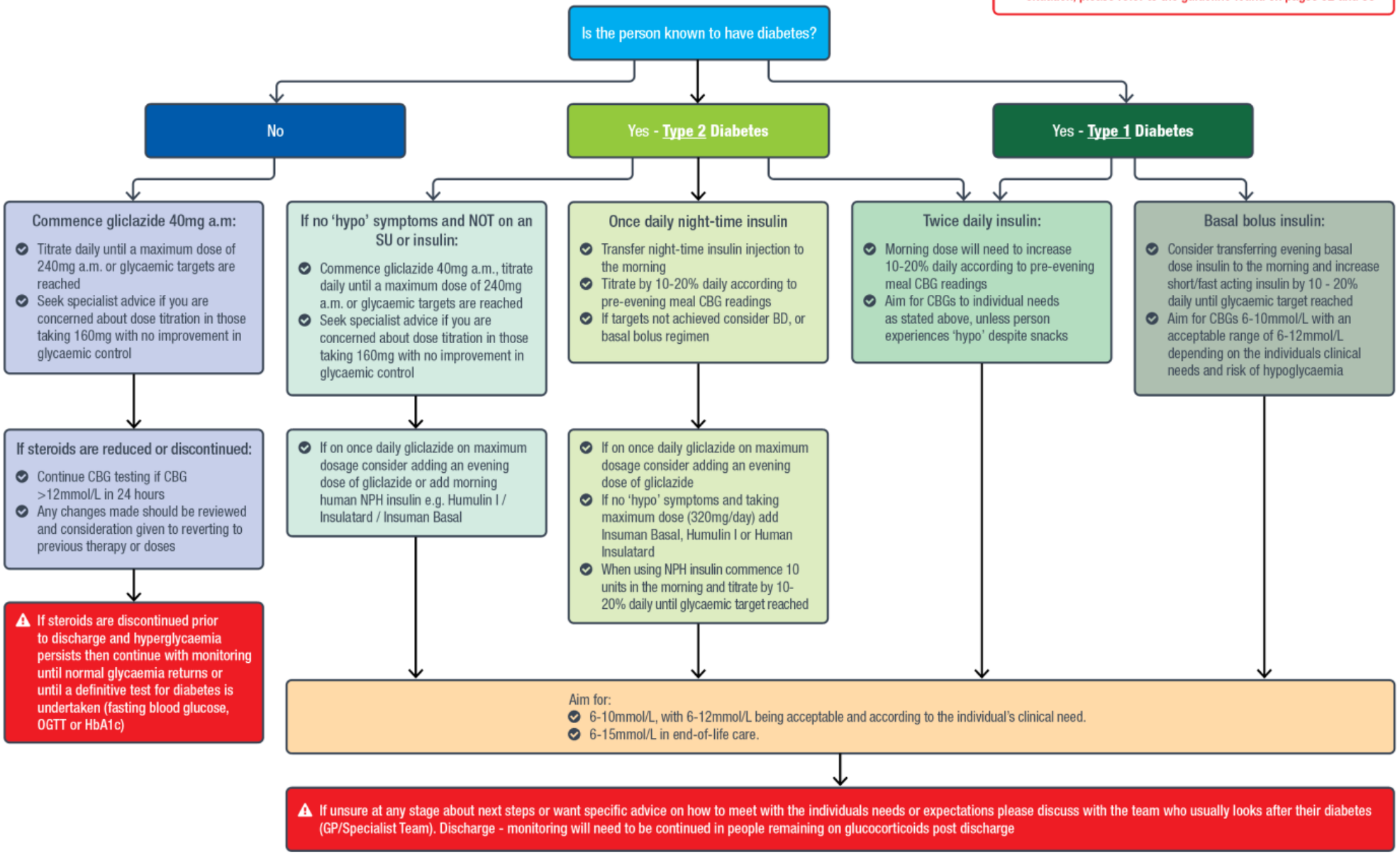
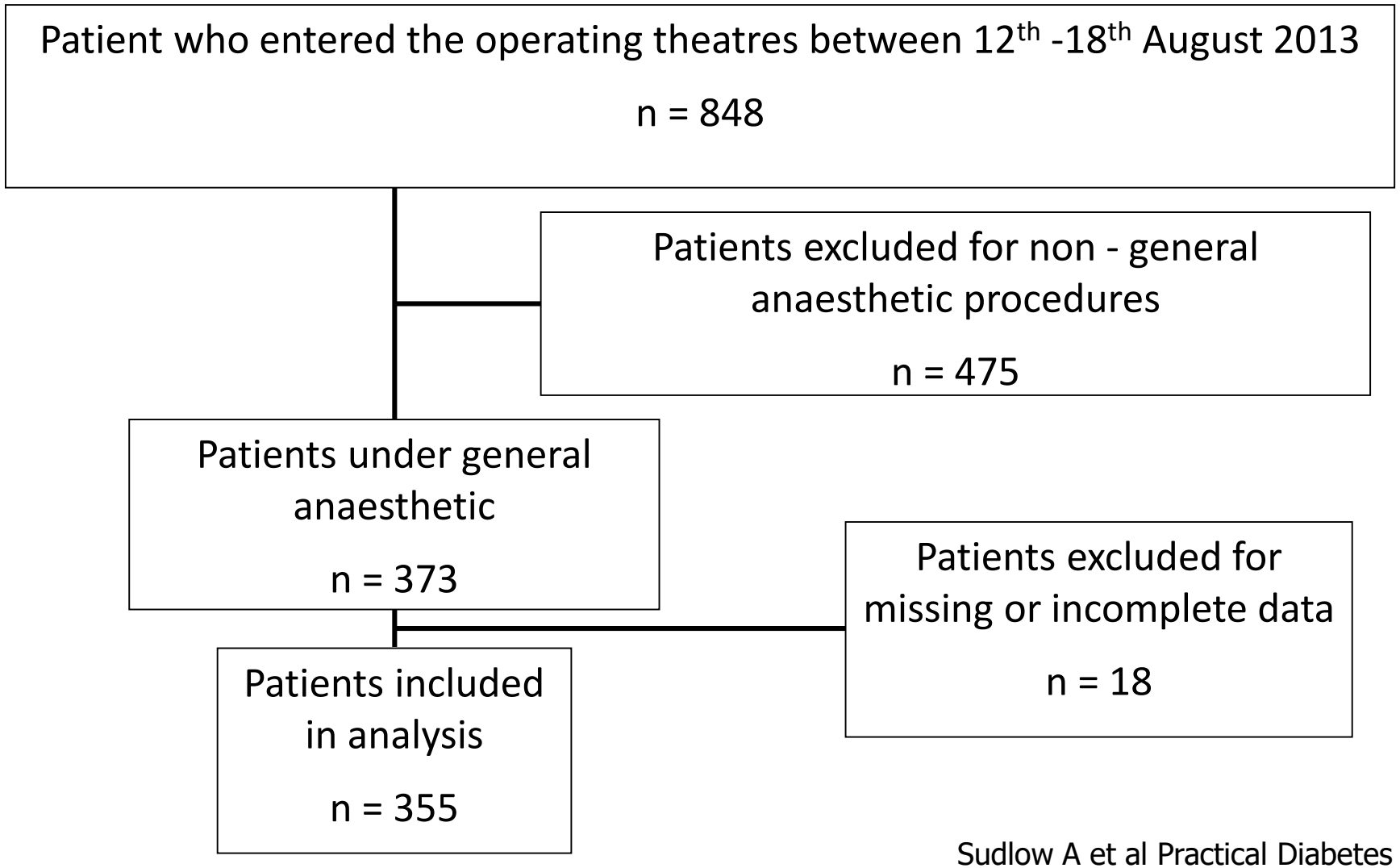
Norfolk and Norwich University Hospitals NHS
NHS Foundation Trust

Assessment of hyperglycaemia in people taking steroids: Algorithm

⚠ This algorithm should not be used for people with or without diabetes who have COVID-19 and are on dexamathasone. In that situation, please refer to the guideline found on pages 32 and 33



Patients



Sudlow A et al Practical Diabetes 2017;34(4):117-121

Specialties

Surgical speciality	Total number of cases	Number given dex (%)	Mean dose of dex (mg) (±SD)
General	91	66	7.1 (1.5)
Gynaecology	54	27	7.4 (1.0)
ENT	11	8	8.0 (0)
Vascular	20	9	7.1 (1.3)
Ortho	95	60	7.3 (1.4)
Dental	7	7	6.2 (2.3)
Urology	36	24	6.8 (1.8)
Thoracic	6	5	7.2 (0.8)
Paediatric	20	18	3.0 (1.5)
Plastics	11	10	6.9 (1.7)
Cardio	4	0	0 (0)
Totals	355	234 (66)	

Pre-operatively

- Only 14 of the 24 patients known to have diabetes had a pre-operative glucose level measured
- Only 15 of the 24 had a pre-operative HbA1c available within 3 months
  - 1 person who did not have diabetes had an HbA1c measured
- 11 patients were already on long term glucocorticoid therapy

Sudlow A et al Practical Diabetes 2017;34(4):117-121

Post-operatively

- Only 16 people (4.5%) had their blood glucose levels checked during the 24 hours post operatively
  - All of these patients had diabetes.
  - 2 patients who had diabetes and who were given dexamethasone did not have a glucose level measured
  - 8 patients with diabetes did not have a post-operative glucose level measured

Sudlow A et al Practical Diabetes 2017;34(4):117-121

One of My Favourite Subjects

Dexamethasone

Why?

- Possibly because a few years I wrote this…

British Journal of Anaesthesia **110** (5): 674–5 (2013)
doi:10.1093/bja/aet010

EDITORIAL II

Does dexamethasone-induced hyperglycaemia contribute to postoperative morbidity and mortality?

K. Dhatariya*

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* E-mail: ketan.dhatariya@nnuh.nhs.uk

Dhatariya K BJA 2013;110(5):674-675

Which Was Discredited by This

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Dexamethasone and Surgical-Site Infection

Or was it?

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*

Corcoran TB et al NEJM 2021;384(18):1731-1781

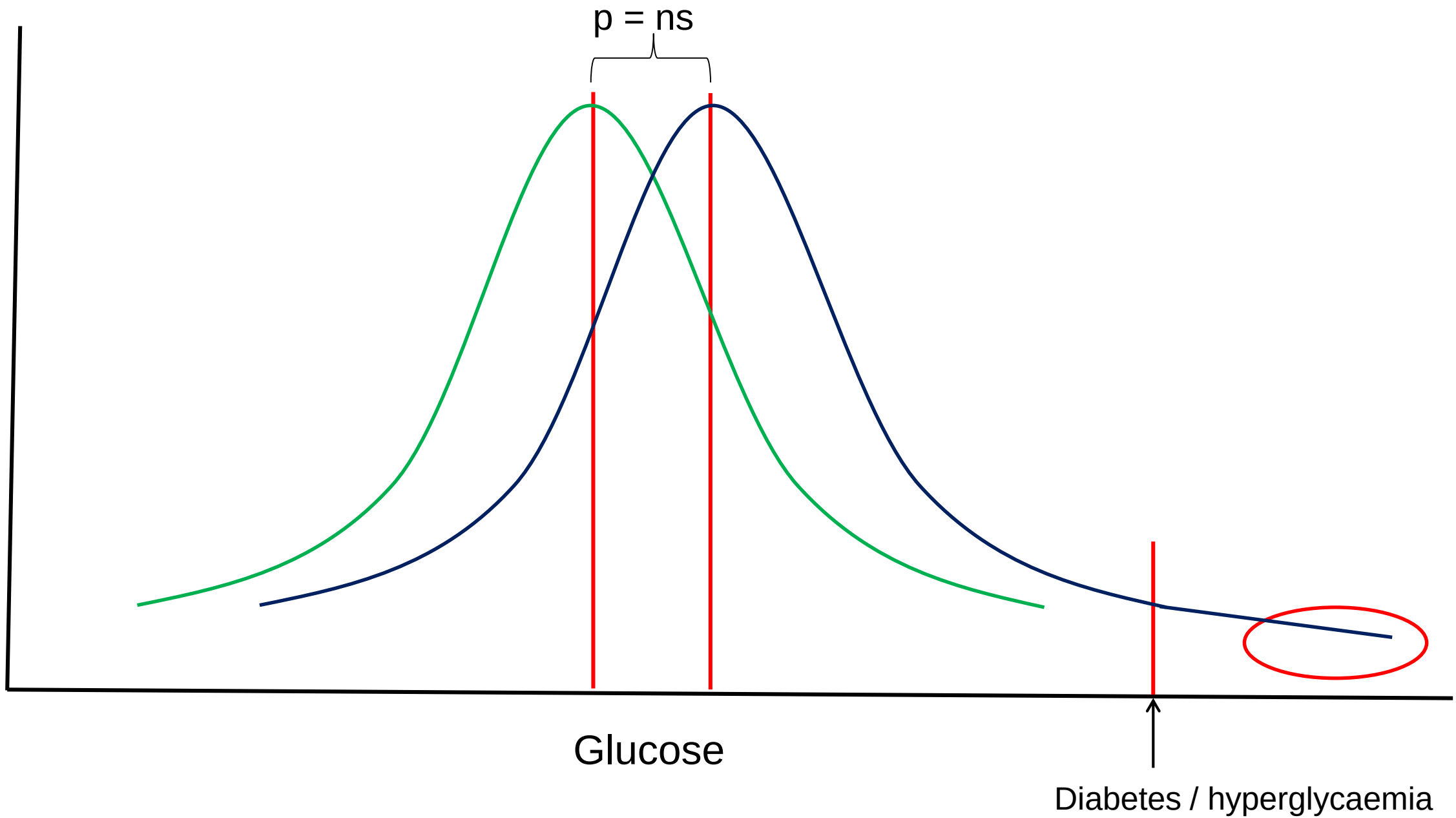
It Works!

- RR 0.48 for reducing PONV
  - 0.56 for ondansetron
  - 0.67 for cyclazine
  - 0.62 for droperidol
- Effect is additive when given with other anti-emetics
  - and it is long acting
- ↓Post-operative pain & swelling = earlier discharge

Carlisle J et al Cochrane Database. http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD004125.pub2/pdf.
Henzi I et al Anesthesia and Analgesia 2000;90(1):186-194
Kakodkar PS Anaesthesia 2013;68(9):889-891

But There May be Problems

- It may impair haemostasis and wound healing
- It is associated with psychological disturbance
- The hypothalamic – pituitary – adrenal axis may be affected for up to a week (it is a very long half life drug)
- It causes a rise in blood glucose


p = ns
Glucose
Diabetes / hyperglycaemia

Back to Corcoran

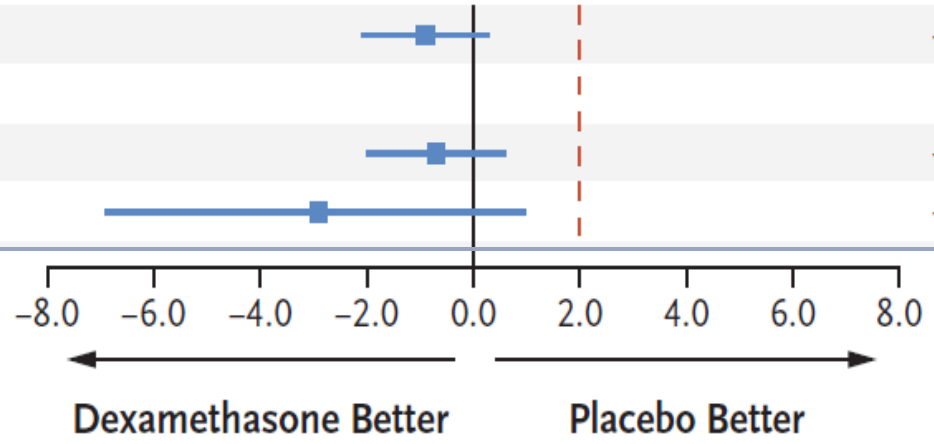
Of these 8725 patients, 1148 (13.2%) had diabetes mellitus, and 1116 (97.2%) had type 2 diabetes (Table 1).

Preoperative laboratory data		
Median glycated hemoglobin level (IQR) — %§		
Patients without diabetes	5.4 (5.2–5.7)	5.4 (5.2–5.7)
Patients with diabetes	6.8 (6.1–7.5)	6.6 (6.1–7.4)

Corcoran TB et al NEJM 2021;384(18):1731-1781

So Perhaps This Result is Unsurprising

Subgroup	Dexamethasone	Placebo	Risk Difference (95.6% CI)
	no. of patients/total no. (%)		
All patients	354/4350 (8.1)	394/4328 (9.1)	−0.9 (−2.1 to 0.3)
Diabetes status			
No	289/3767 (7.7)	314/3757 (8.4)	−0.7 (−2.0 to 0.6)
Yes	65/583 (11.1)	80/571 (14.0)	−2.9 (−6.9 to 1.0)



- They had good pre-op glycaemic control
- They were (probably) being attended to more often

Corcoran TB et al NEJM 2021;384(18):1731-1781

Have I Been Maliciously Maligning Dexamethasone Unnecessarily?

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2018 Cochrane Review – Wound Infection

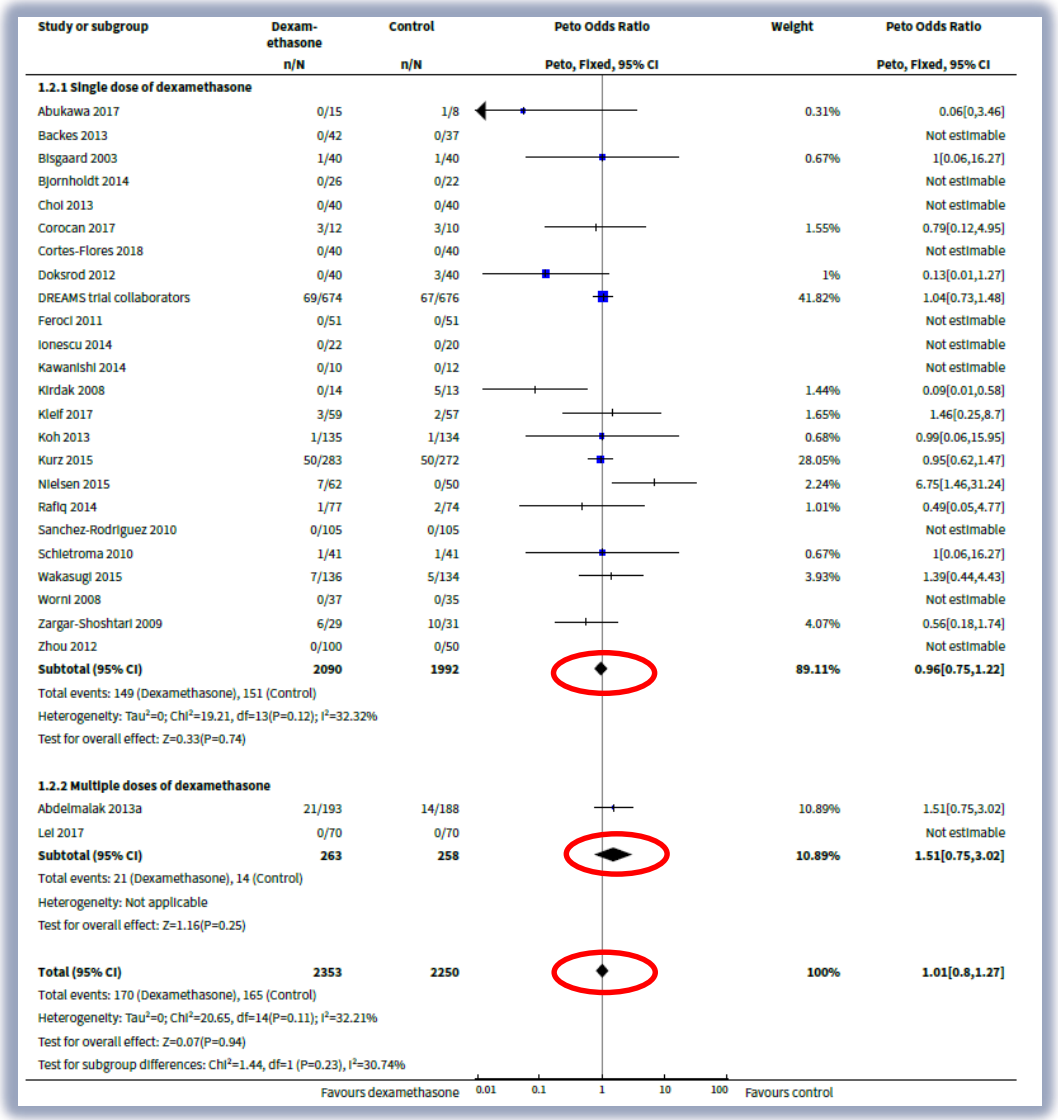
Single dose →

Multiple doses →

Total →

Favours dexamethasone ←

Favours placebo →



Study or subgroup	Dexamethasone n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
1.2.1 Single dose of dexamethasone					
Abukawa 2017	0/15	1/8		0.31%	0.06[0,3.46]
Backes 2013	0/42	0/37			Not estimable
Bisgaard 2003	1/40	1/40		0.67%	1[0.06,16.27]
Bjornholdt 2014	0/26	0/22			Not estimable
Choi 2013	0/40	0/40			Not estimable
Corocan 2017	3/12	3/10		1.55%	0.79[0.12,4.95]
Cortes-Flores 2018	0/40	0/40			Not estimable
Doksrod 2012	0/40	3/40		1%	0.13[0.01,1.27]
DREAMS trial collaborators	69/674	67/676		41.82%	1.04[0.73,1.48]
Feroci 2011	0/51	0/51			Not estimable
Ionescu 2014	0/22	0/20			Not estimable
Kawanishi 2014	0/10	0/12			Not estimable
Kirdak 2008	0/14	5/13		1.44%	0.09[0.01,0.58]
Kleif 2017	3/59	2/57		1.65%	1.46[0.25,8.7]
Koh 2013	1/135	1/134		0.68%	0.99[0.06,15.95]
Kurz 2015	50/283	50/272		28.05%	0.95[0.62,1.47]
Nielsen 2015	7/62	0/50		2.24%	6.75[1.46,31.24]
Rafiq 2014	1/77	2/74		1.01%	0.49[0.05,4.77]
Sanchez-Rodriguez 2010	0/105	0/105			Not estimable
Schietroma 2010	1/41	1/41		0.67%	1[0.06,16.27]
Wakasugi 2015	7/136	5/134		3.93%	1.39[0.44,4.43]
Worni 2008	0/37	0/35			Not estimable
Zargar-Shoshtari 2009	6/29	10/31		4.07%	0.56[0.18,1.74]
Zhou 2012	0/100	0/50			Not estimable
Subtotal (95% CI)	**2090**	**1992**		**89.11%**	**0.96[0.75,1.22]**
Total events: 149 (Dexamethasone), 151 (Control)					
Heterogeneity: Tau^2=0; Chi^2=19.21, df=13(P=0.12); I^2=32.32%					
Test for overall effect: Z=0.33(P=0.74)					
1.2.2 Multiple doses of dexamethasone					
Abdelmalak 2013a	21/193	14/188		10.89%	1.51[0.75,3.02]
Lei 2017	0/70	0/70			Not estimable
Subtotal (95% CI)	**263**	**258**		**10.89%**	**1.51[0.75,3.02]**
Total events: 21 (Dexamethasone), 14 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.16(P=0.25)					
Total (95% CI)	**2353**	**2250**		**100%**	**1.01[0.8,1.27]**
Total events: 170 (Dexamethasone), 165 (Control)					
Heterogeneity: Tau^2=0; Chi^2=20.65, df=14(P=0.11); I^2=32.21%					
Test for overall effect: Z=0.07(P=0.94)					
Test for subgroup differences: Chi^2=1.44, df=1 (P=0.23), I^2=30.74%					

Favours dexamethasone 0.01 0.1 1 10 100 Favours control

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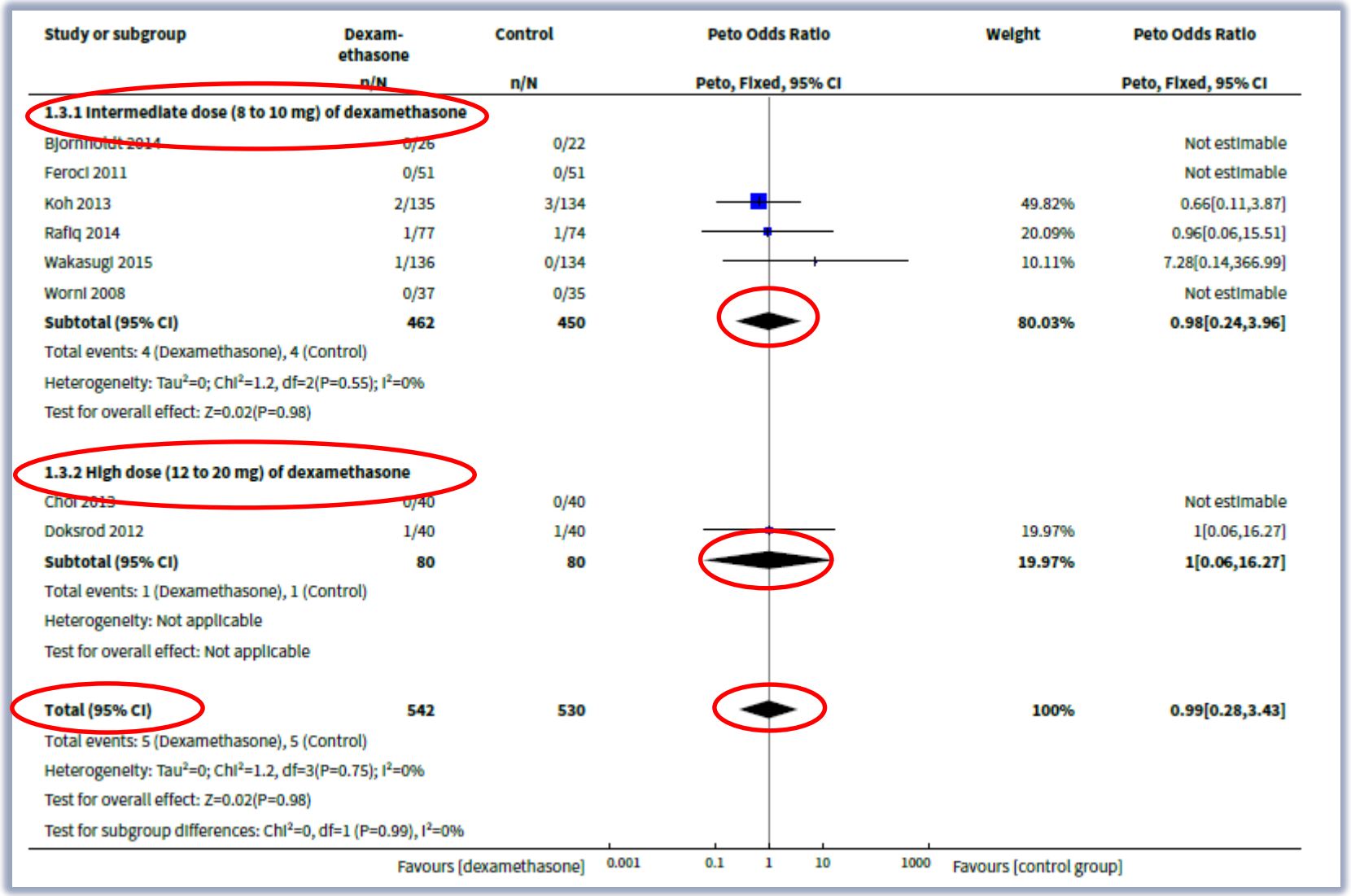
2018 Cochrane Review – Wound Healing

Favours dexamethasone



Favours placebo

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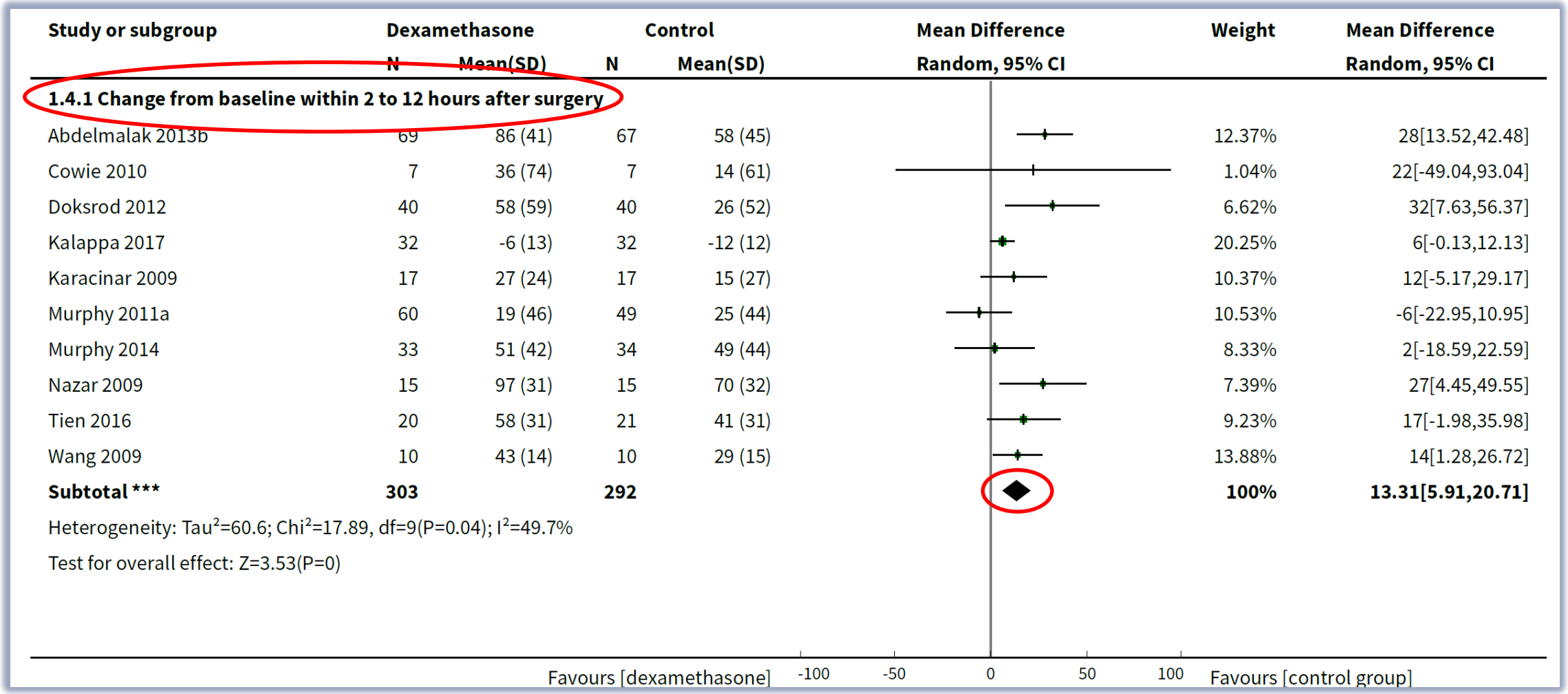
2018 Cochrane Review – Glucose (1)



Study or subgroup	Dexamethasone N	Dexamethasone Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
1.4.1 Change from baseline within 2 to 12 hours after surgery							
Abdelmalak 2013b	69	86 (41)	67	58 (45)		12.37%	28[13.52,42.48]
Cowie 2010	7	36 (74)	7	14 (61)		1.04%	22[-49.04,93.04]
Doksrod 2012	40	58 (59)	40	26 (52)		6.62%	32[7.63,56.37]
Kalappa 2017	32	-6 (13)	32	-12 (12)		20.25%	6[-0.13,12.13]
Karacinar 2009	17	27 (24)	17	15 (27)		10.37%	12[-5.17,29.17]
Murphy 2011a	60	19 (46)	49	25 (44)		10.53%	-6[-22.95,10.95]
Murphy 2014	33	51 (42)	34	49 (44)		8.33%	2[-18.59,22.59]
Nazar 2009	15	97 (31)	15	70 (32)		7.39%	27[4.45,49.55]
Tien 2016	20	58 (31)	21	41 (31)		9.23%	17[-1.98,35.98]
Wang 2009	10	43 (14)	10	29 (15)		13.88%	14[1.28,26.72]
Subtotal ***	**303**		**292**			**100%**	**13.31[5.91,20.71]**

Heterogeneity: Tau^2=60.6; Chi^2=17.89, df=9(P=0.04); I^2=49.7%

Test for overall effect: Z=3.53(P=0)

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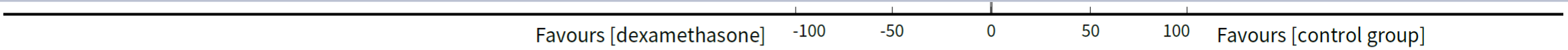
2018 Cochrane Review – Glucose (2)

1.4.2 Change from baseline 24 hours after surgery

Study or subgroup	Dexamethasone N	Dexamethasone Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Corocan 2017	16	22 (23)	15	23 (22)		18.48%	-1[-16.84,14.84]
Cowie 2010	7	27 (64)	7	10 (70)		6.38%	17[-53.26,87.26]
Kalappa 2017	32	40 (21)	32	-11 (12)		19.94%	51[42.62,59.38]
Murphy 2014	33	23 (31)	34	20 (31)		18.71%	3[-11.85,17.85]
Tien 2016	20	91 (43)	21	49 (31)		16.6%	42[18.96,65.04]
Zhang 2016	103	14 (37)	130	1 (29)		19.89%	13[4.29,21.71]
Subtotal ***	**211**		**239**			**100%**	**21.19[-0.17,42.55]**

Heterogeneity: Tau^2=577.32; Chi^2=65.03, df=5(P<0.0001); I^2=92.31%

Test for overall effect: Z=1.94(P=0.05)



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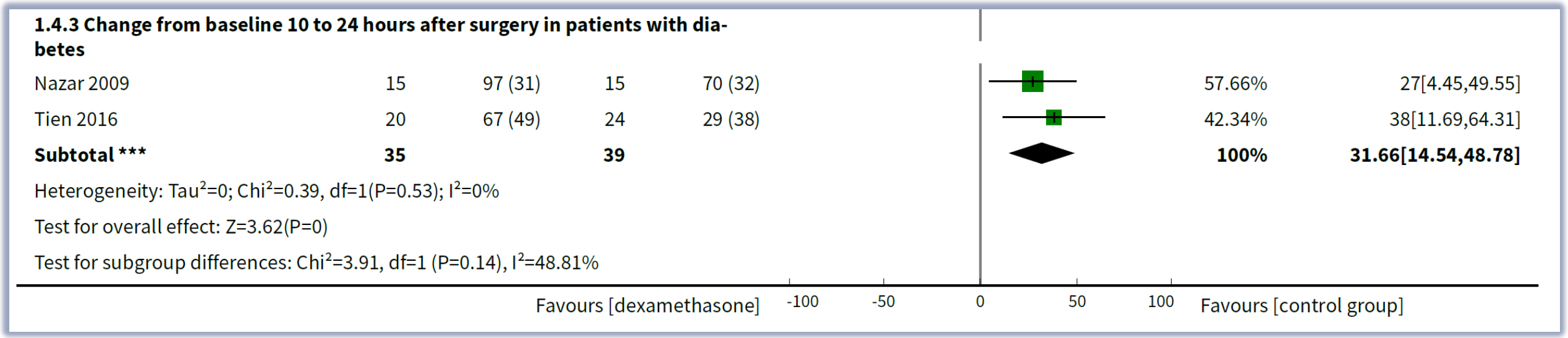
2018 Cochrane Review – Glucose (3)



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So Is Dexamethasone Safe?

- I'd still argue not necessarily

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with control	Risk with dexamethasone				
Postoperative wound or systemic infection Follow-up: mean 30 days	Study population 80 per 1000	81 per 1000 (65 to 100)	OR 1.01 (0.80 to 1.27)	4603 (26 RCTs)	⊕⊕⊕⊖ Moderate[a]	
Delayed wound healing Follow-up: mean 30 days	Study population 70 per 1000	69 per 1000 (21 to 205)	OR 0.99 (0.28 to 3.43)	642 (8 RCTs)	⊕⊕⊖⊖ Low[b]	
Glycaemic response - change from baseline to 2 to 12 hours postoperatively in patients without diabetes Follow-up: 1 day	Mean glycaemic response - change from baseline to 2 to 12 hours postoperatively in patients without diabetes: 48 mg/dL	MD 13 mg/dL higher (6 higher to 21 higher)	-	595 (10 RCTs)	⊕⊕⊖⊖ Low[c]	
Glycaemic response - change from baseline to 10 to 24 hours after surgery in patients with diabetes Follow-up: 1 day	Mean glycaemic response - change from baseline to 10 to 24 hours after surgery in patients with diabetes: 80 mg/dL	MD 32 mg/dL higher (15 higher to 49 higher)	-	74 (2 RCTs)	⊕⊖⊖⊖ Very low[d]	

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **MD:** mean difference; **OR:** odds ratio; **RCT:** randomized controlled trial.

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I'd Argue The Wrong Question Was Asked

- What they asked was "is dexamethasone use is associated with harm?"
- What they should have asked was "is dexamethasone induced hyperglycaemia associated with harm"
- I'd also suggest that sample sizes have been too small to get a definitive answer

A Quote to Sum it Up

- If an inpatient is on glucocorticoids… “the design of insulin therapy depends on the timing of the glucocorticoids and challenges the creativity of the caregiver”

Thompson CL et al Diabetes Spectrum 2005; 18:20-27

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