Norfolk and Norwich University Hospitals NHS
NHS Foundation Trust

Diabetes, Dexamethasone and Death

or Peri-operative Glucose Control - Is it Important?

Dr Ketan Dhatariya MSc MD MS FRCP
Consultant in Diabetes and Endocrinology
Norfolk and Norwich University Hospitals

Who is This Strange Man?

- I qualified in 1991
- I trained in D&E and GIM in South Thames
- I did general practice for 2 years
- I did ITU / anaesthetics for a year
- I did research at Mayo Clinic
- I have been in Norwich since 2004
- Currently my national roles are
  - ABCD meetings secretary
  - Secretary of the SCE in D&E
  - JBDS – IP Group member (inpatient diabetes guidelines)
    - Peri-operative, DKA, Hypo, HHS, enteral feeding, self management, e-learning on safe use of IV insulin, etc, etc, etc

Recent Data

- People with diabetes are
  - Less likely to be offered day case surgery
  - More likely to have emergency surgery
  - Have a longer LOS following surgery
  - Have higher rates of 28-day readmissions following surgery

http://www.yhpho.org.uk/resource/view.aspx?RID=105866

Do Peri-Operative High Glucose Levels Cause Harm?

- High pre-operative glucose or HbA1c has been related to adverse outcomes following
  - spinal surgery
  - vascular surgery
  - colorectal surgery
  - cardiac surgery
  - trauma
  - mastectomies
  - foot and ankle
  - neurosurgery
  - transplant surgery
  - HBP surgery
  - cholecystectomy
  - cardiac surgery

Walid MS et al 2010 J Hosp Med 5:E10-E14
O'Sullivan CJ et al 2006 Europ Jl of Vasc Endovasc Surg 32:188-197
Gustafsson UO et al 2009 Brit J Surg 96:1358-1364
Halkos ME et al 2008 Ann of Thorac Surg 86:1431-1437
Kreutziger J et al 2009 J Trauma 67(4):704-8
Vilar-Compte et al 2008 Am J Infect Control 36(3):192-198
Park C et al Transplantation 2009 87(7):1031-1036
Ambiru S et al J Hosp Infect 2008 68(3):230-233
Chaung SC et al J Formos Med Ass 2004 103(8):607-612
Shibuya N et al J Foot Ankle Surg 2013 52(2):207-211

Excess Mean Length of Stay in Diabetes Inpatients Aged 18 – 60 Years

269,265 Diabetes Discharges and 4,411,593 Matched Controls

	Mean LOS (days)			Excess LOS (days)		n		
	E10	E11	C	E10	E11	E10	E11	C
Surg.	5.4 (0.1)	5.1 (0.1)	4.2 (0.2)	1.2	0.9	18,032	32,135	1,501,453
T &O	4.8 (0.1)	5.3 (0.2)	4.6 (0.1)	0.2	0.7	8,178	12,203	885,606
GM	4.8 (0.2)	5.4 (0.2)	4.4 (0.1)	0.4	1.0	70,988	82,446	1,709,553
Card.	4.2 (0.1)	4.2 (0.1)	3.8 (0.1)	0.4	0.4	5,307	15,009	229,784
MFE	4.8 (0.2)	5.6 (0.2)	4.7 (0.1)	0.1	0.1	2,444	4,549	85,197

E10 = Type 1 diabetes E11 = Type 2 diabetes c = controls

English Hospitals, 4 consecutive years of discharges 2000-2004

Sampson MJ et al Diabetes Research & Clinical Practice 2007;77(1):92-98

Day Case Avoidance

	Admissions for males with diabetes	Admissions per 1000 males with diabetes	Admissions per 1000 males without diabetes	Diabetes admissions/non-diabetes admissions	Excess admissions in diabetes
0-15	956	99	50	1.99	475
16-24	1,633	51	43	1.20	274
25-34	3,289	70	57	1.24	627
35-44	10,014	93	79	1.18	1,511
45-54	27,487	122	118	1.04	994
55-64	60,788	210	203	1.04	2,148
65-74	87,207	241	355	0.68	-41,187
75+	77,832	328	413	0.79	-20,344
All male	269,206	205	123	0.82 (age adjusted)	-55,501

	Admissions for females with diabetes	Admissions per 1000 females with diabetes	Admissions per 1000 females without diabetes	Diabetes admissions/non-diabetes admissions	Excess admissions in diabetes
0-15	975	106	40	2.63	604
16-24	1,986	58	62	0.94	-136
25-34	3,708	79	91	0.87	-567
35-44	10,390	190	118	1.61	3,942
45-54	23,708	172	160	1.08	1,736
55-64	42,589	202	207	0.97	-1,184
65-74	61,743	233	288	0.81	-14,657
75+	62,924	213	279	0.76	-19,748
All female	208,023	197	137	0.87 (age adjusted)	-30,011
Total (male and female)	477,229	202	130	0.85 (age-adjusted)	-85,512

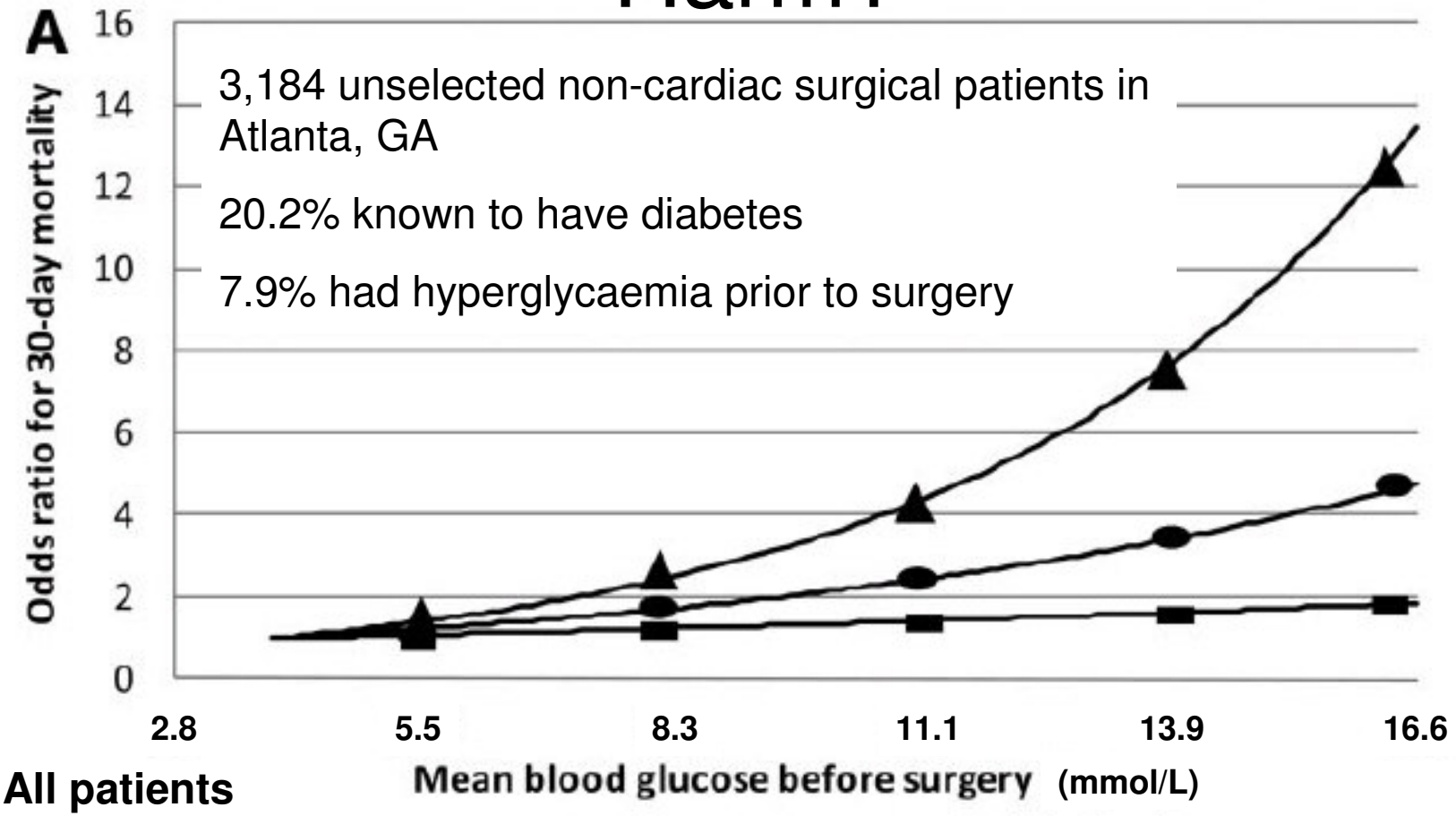
Men

In 2009-10, 85,512 people with diabetes were denied day case surgery. If 1 bed day costs £300, then this equates to £25.6m

Women

Kerr M, *'Inpatient Care for People with Diabetes: the Economic Case for Change'*. NHS Diabetes 2012

Do High Glucose Levels Cause Harm?



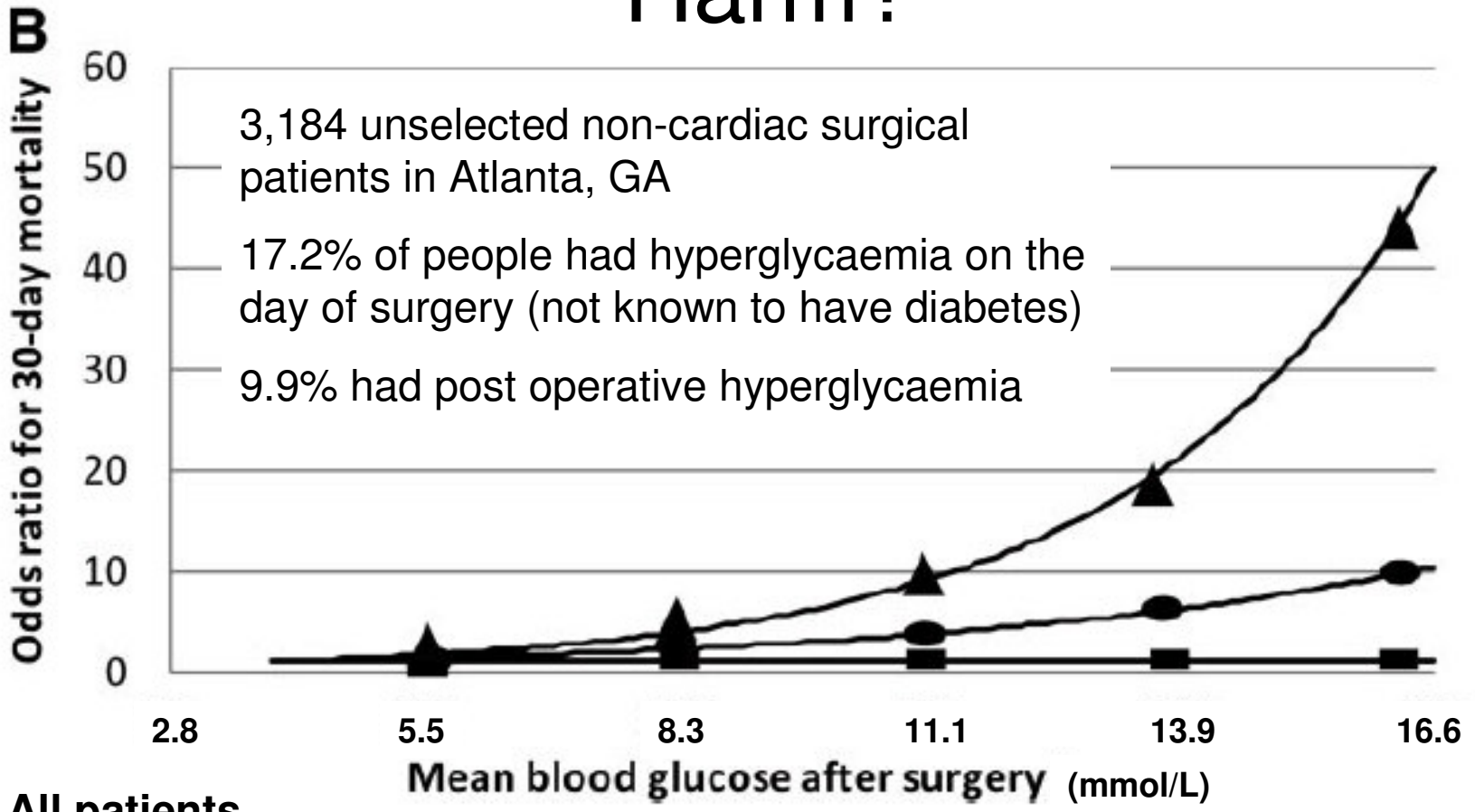
All patients

Patients with diabetes

Patients without diabetes

Frisch A et al Diabetes Care 2010;33(8):1783-1788

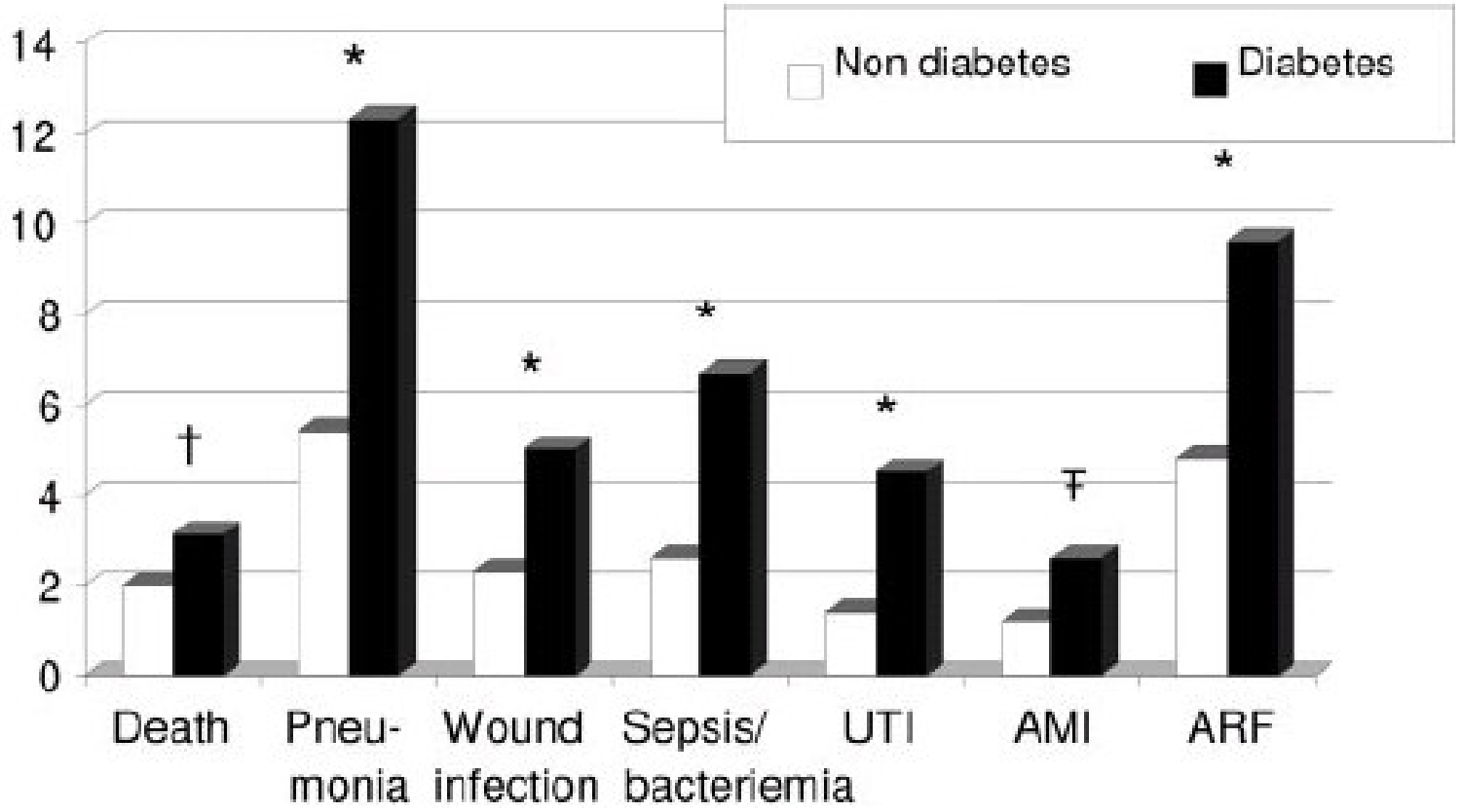
Do High Glucose Levels Cause Harm?



- **All patients**
- **Patients with diabetes**
- **Patients without diabetes**

Frisch A et al Diabetes Care 2010;33(8):1783-1788

Do High Glucose Levels Cause Harm?



Frisch A et al Diabetes Care 2010;33(8):1783-1788

More Observational Data

- Observational data from 55 US hospitals over 5 years looked at the outcomes of 18,278 patients 11,633 of whom who had a BG measured pre op, on day 1 post op or day 2 post op
- 55.4 ± 15.3 years
- 65.7% women

Kwon S et al Ann Surgery 2013;257(1):8-14

Hyperglycaemic Individuals

- Were more likely to be
  - Older
  - Heavier
  - More comorbidities
  - Have longer operations
  - Have diabetes (but not always)

Kwon S et al Ann Surgery 2013;257(1):8-14

Outcomes

TABLE 2. Adjusted Multivariate Logistic Regression Analysis on the Effect of Perioperative Hyperglycemia (>180 mg/dL at Any Point on the Day of Surgery, Postoperative Day 1, or Postoperative Day 2) on Outcomes Presented as Odds Ratio and 95% Confidence Intervals (Within Parenthesis)

	Composite Infections (n = 491)	Deaths (n = 48)	Reoperative Interventions (n = 257)	Anastomotic Failures (n = 43)	Myocardial Infarctions (n = 13)
Hyperglycemia	2.0 (1.63–2.44)	2.71 (1.72–4.28)	1.8 (1.41–2.3)	2.43 (1.38–4.28)	1.15 (0.43–3.1)

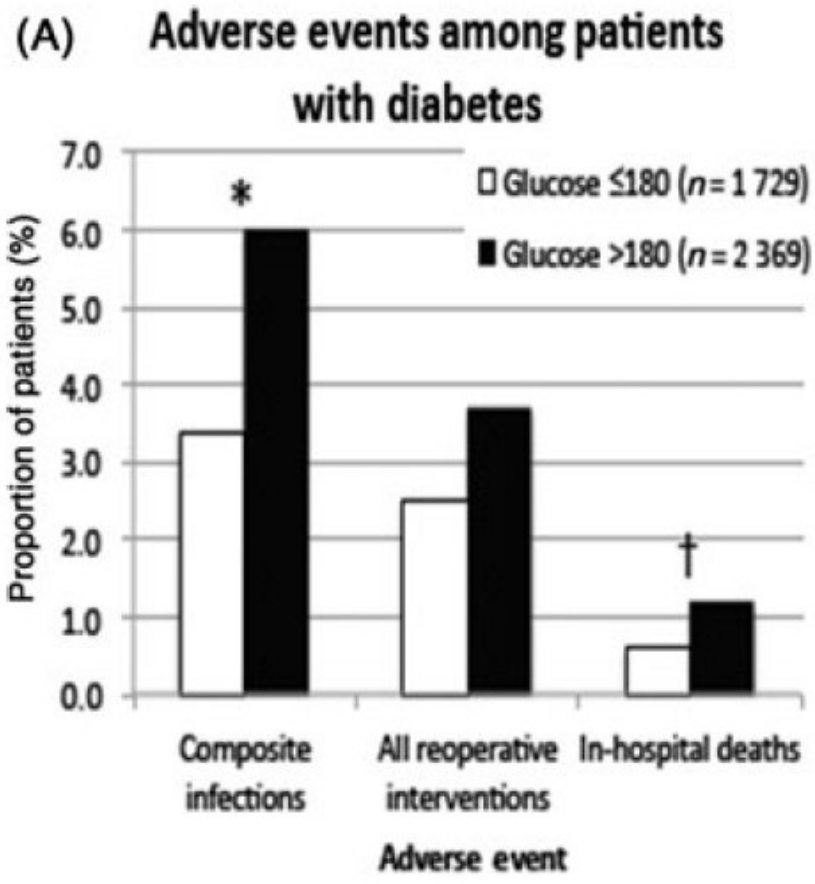
High glucose levels were associated with poor outcomes

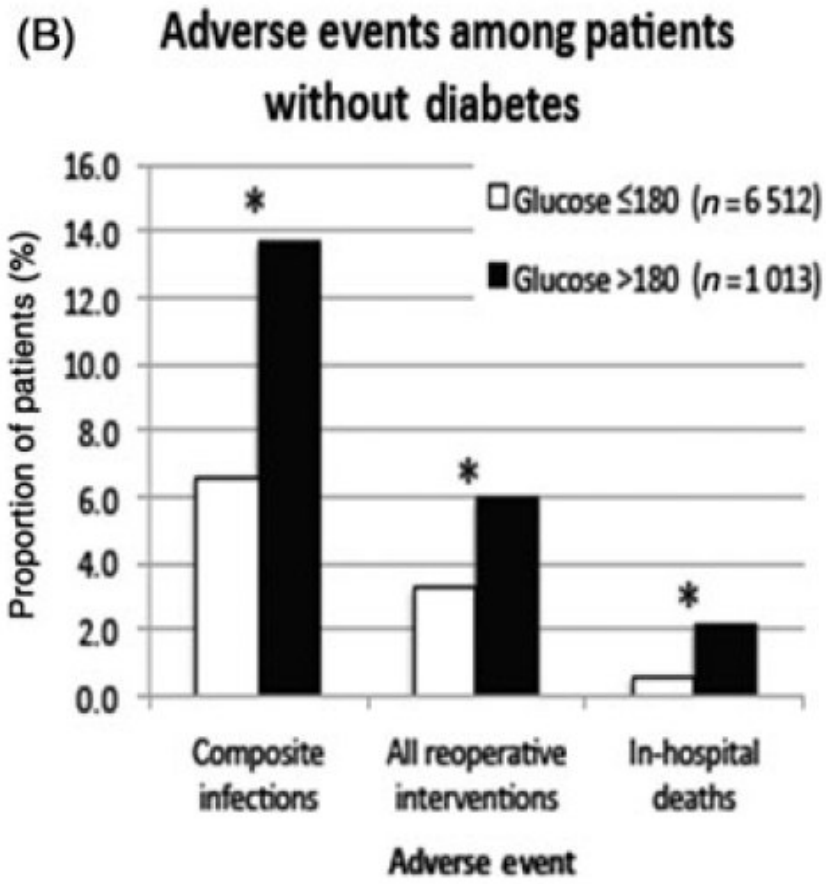
Diabetes[§]					
Noninsulin-dependent	0.51 (0.37–0.69)	0.48 (0.25–0.93)	0.63 (0.44–0.9)	0.45 (0.21–0.99)	0.77 (0.15–4.08)
Insulin-dependent	0.52 (0.35–0.76)	0.78 (0.36–1.68)	0.54 (0.35–0.85)	0.49 (0.18–1.32)	1.66 (0.26–10.71)

But – having diabetes was protective (?increased vigilance)

Kwon S et al Ann Surgery 2013;257(1):8-14

Outcomes





180 mg/dl = 9.72 mmol/L $^{*}P < 0.01$; $^{\dagger}P < 0.05$

Kwon S et al Ann Surgery 2013;257(1):8-14

Colorectal Surgery

- Single centre, 2 year retrospective analysis of outcomes in 2447 patients without diabetes undergoing elective colorectal surgery and 181 with diabetes

Non diabetic (n=2447 (93.1%))	Diabetic (n=181 (6.9%))
Normoglycaemic (<6.7 mmol/L) 816 (33.3%)	Normoglycaemic (<6.7 mmol/L) 63 (34.8%)
'Mild' hyperglycaemia (6.8-10.7 mmol/L) 1289 (52.7%)	'Mild' hyperglycaemia (6.8-10.7 mmol/L) 98 (54.1%)
'Severe' hyperglycaemia (>10.8 mmol/L) 342 (14%)	'Severe' hyperglycaemia (>10.8 mmol/L) 20 (11%)

66.7% of the 'non-diabetics' developed hyperglycaemia

Kiran RP et al Annals of Surgery 2013;258(4):599-605

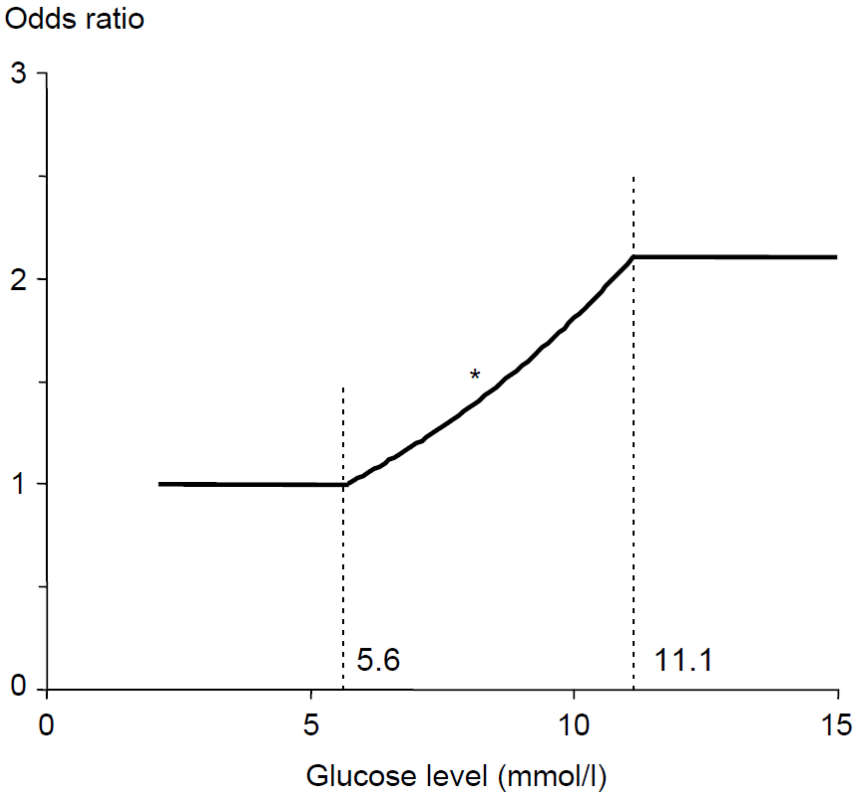
Outcomes

- In patients with or without a previous diagnosis of diabetes, a high blood glucose was found to be associated with
  - Estimated blood loss
  - Length of surgery
  - Transfusion
  - Diverting ostomy
  - AKI
  - Anastomotic leak
  - Arrythmia
  - Reintubation
  - Sepsis
  - SSI
    - Deep
    - Superficial
    - Organ / space
  - UTI
  - LOS
  - Reoperation
  - Mortality

Kiran RP et al Annals of Surgery 2013;258(4):599-605

In Addition…..

- Other data has confirmed the harm of high pre-operative glucose levels in non-cardiac, non vascular surgery



30 day mortality rates for 989 patients with diabetes – for each mmol/L increase in blood glucose, OR for mortality rose by 1.19 (CI 1.1 - 1.3)

Noorddij PG et al EJE 2007;156(1):137-142

Thus….

- Whilst there is data to show that poor glycaemic control is associated with poor outcomes
- There is no consistent data to show that improving control also improves outcomes

(A bit like diabetes care in general until the mid 1990's)

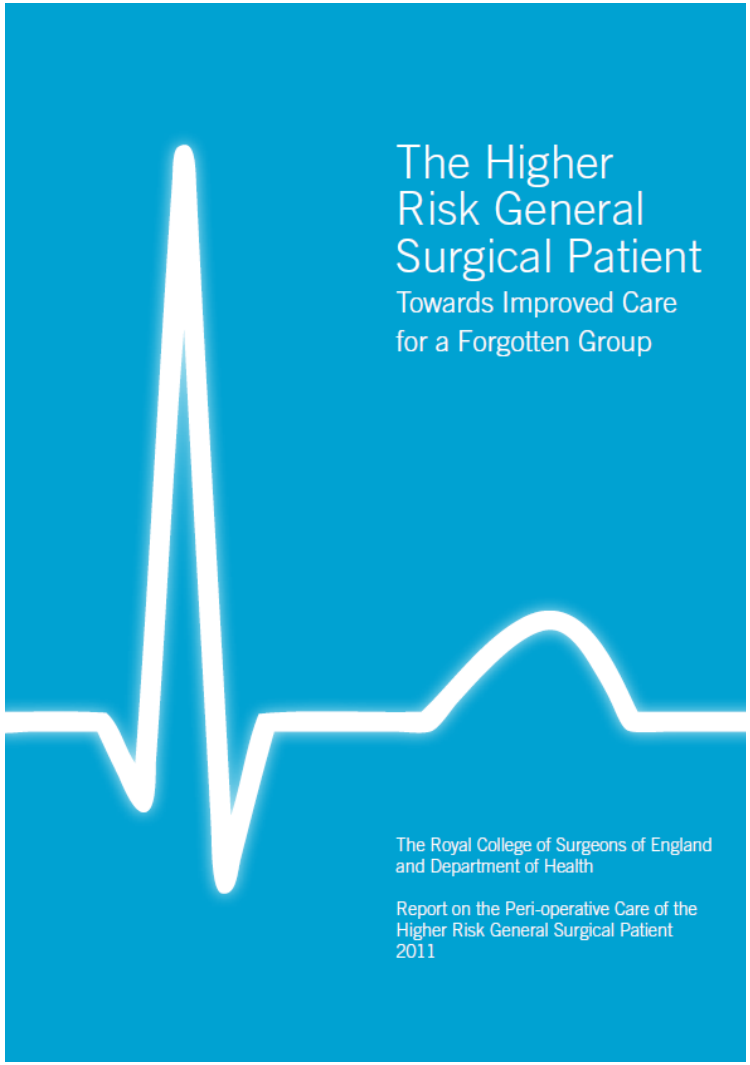
The ITU Story

- 2001 Leuven (Surgical) 1548 Positive
  Van den Berghe G et al NEJM 2001;345:1359-1367
- 2006 Leuven (Medical) 1200 Neutral / Positive
  Van den Berghe G et al NEJM 2006;354:449-461
- 2008 VISEP (Septic) 537 Stopped early
  Brunkhorst FM et al NEJM 2008;358:125-139
- 2008 De la Rosa (General) 504 Neutral
  De La Rosa G et al Critical Care 2008;12:R120
- 2009 GluControl 1078 Stopped early / Neutral
  Preiser J-C et al Intensive Care Medicine 2009 35:1738-1748
- 2009 Leuven (PICU) 700 Positive
  Vlasselaers D et al Lancet 2009;373:547-556
- 2009/12 NICE-SUGAR 6104 Harmful (especially hypos)
  The NICE-SUGAR Study Investigators NEJM 2009;360:1283-1297
  NEJM 2012;367:1108-1118
- 2012 Boston Children's 980 Neutral
  Agus MS et al NEJM 2012;367(13):1208-1219

"The jury is still out"

Van den Berghe G Intensive Care Med 2013;39(5):823-825

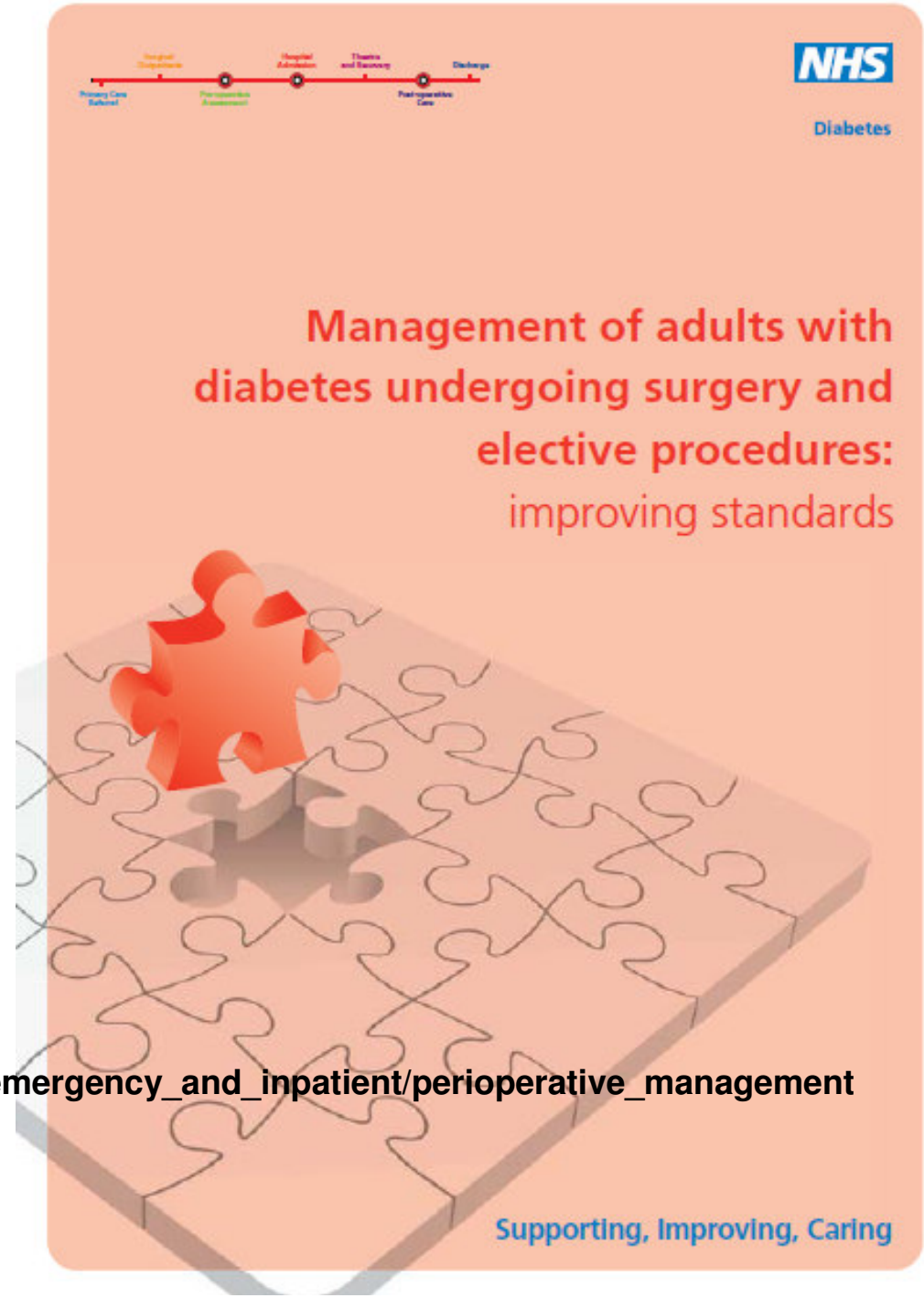
Something Some of You May Have Seen



- Disappointingly, the word ‘diabetes’ appears only once, ‘hyperglycaemia’ and ‘glucose’ do not appear at all in this document

http://www.rcseng.ac.uk/publications/docs/higher-risk-surgical-patient/

Along Came This…..



http://www.diabetes.nhs.uk/areas_of_care/emergency_and_inpatient/perioperative_management

And This…..

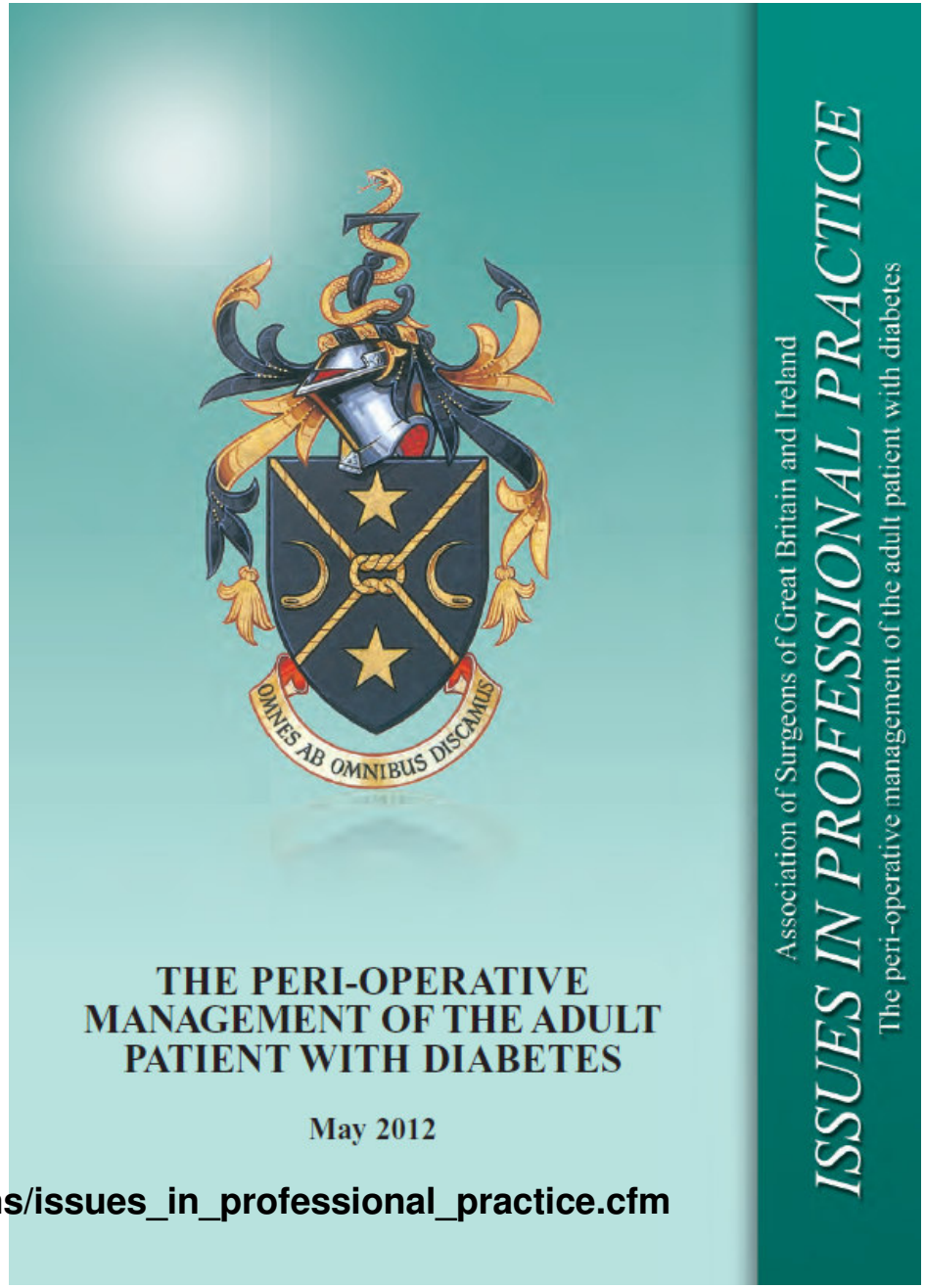
Diabetes UK Position Statements and Care Recommendations

NHS Diabetes guideline for the perioperative management of the adult patient with diabetes*

K. Dhatariya[1], N. Levy[2], A. Kilvert[3], B. Watson[4], D. Cousins[5], D. Flanagan[6], L. Hilton[7], C. Jairam[8], K. Leyden[3], A. Lipp[1], D. Lobo[9], M. Sinclair-Hammersley[10] and G. Rayman[11] for the Joint British Diabetes Societies

Diabetic Medicine 2012;29(4):420-433

And This…..



http://www.asgbi.org.uk/en/publications/issues_in_professional_practice.cfm

National Guidelines

- Document divided into sections:
  - Primary care
  - Surgical outpatients
  - Pre-operative assessment clinic
  - Hospital admission
  - Theatre and recovery
  - Post-operative care
  - Discharge

Dexamethasone

It Works!

- RR for reducing PONV - 0.48
  - 0.56 for ondansetron
  - 0.67 for cyclazine
  - 0.62 for droperidol
- Effect of dexamethasone is additive when given with other anti-emetics – and it is long acting
- Less post-operative pain and swelling, and earlier hospital discharge

Carlisle J et al Cochrane Database. http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD004125.pub2/pdf. Last accesses 14th November 2013
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

Norfolk and Norwich University Hospitals NHS
NHS Foundation Trust

September 2013

Anaesthesia 2013, 68, 889–898 Editorial

Editorial

Routine use of dexamethasone for postoperative nausea and vomiting: the case against

R. Bartlett
Specialist Registrar in Anaesthetics
A. J. Hartle
Consultant Anaesthetist and Intensivist
St Mary's Hospital Imperial College Healthcare NHS Trust

Anaesthesia 2013, 68, 889–898

Editorial

Routine use of dexamethasone for postoperative nausea and vomiting: the case for

P. S. Kakodkar
Consultant Anaesthetist
Northampton General Hospital

BJA May 2013

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

EDITORIAL II

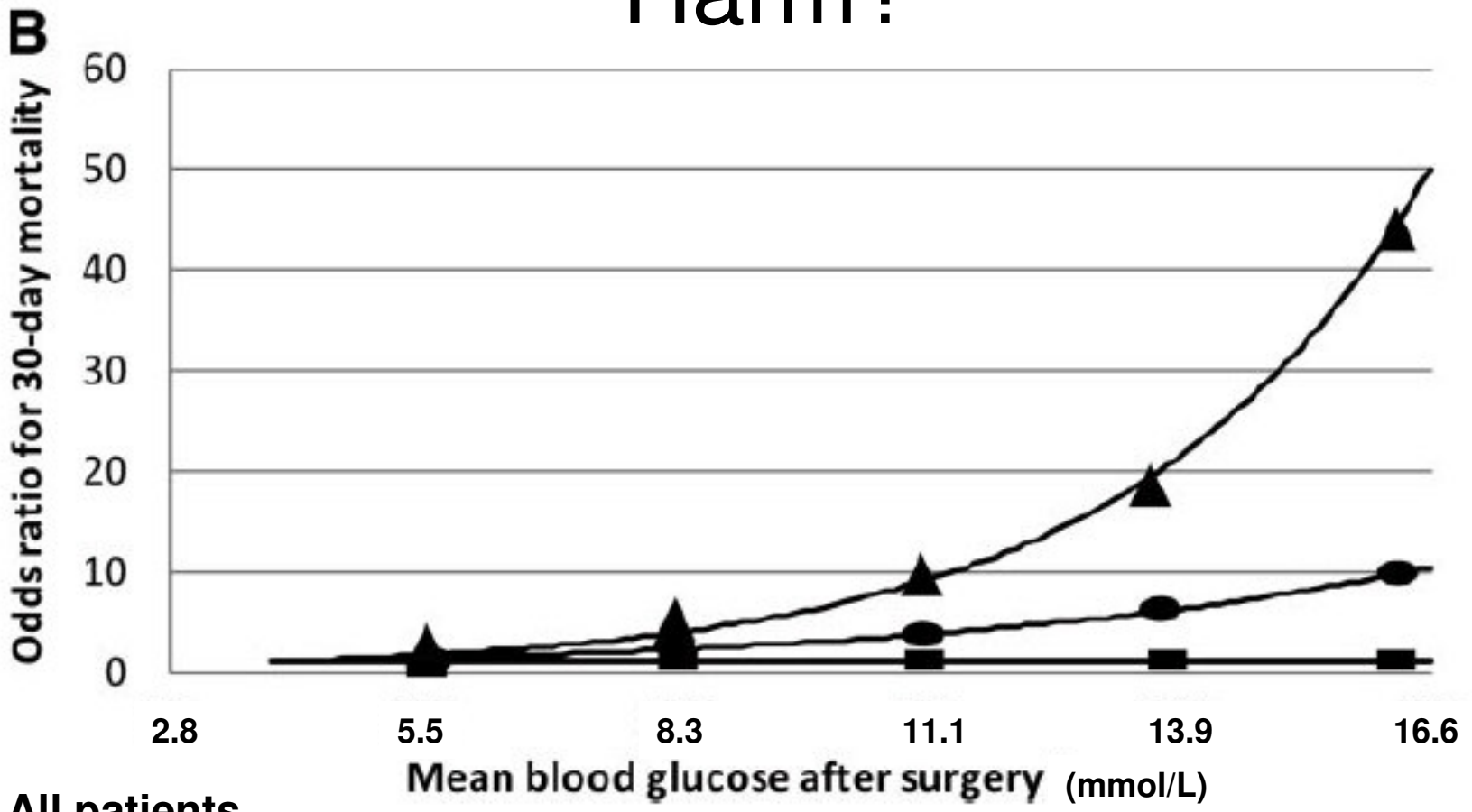
Does dexamethasone-induced hyperglycaemia contribute to postoperative morbidity and mortality?

K. Dhatariya*

- You know the world is getting heavier
- You know that BMI is associated with the risk of hyperglycaemia
- You know that dexamethasone use is associated with (transient) hyperglycaemia
- You (now) know that hyperglycaemia is bad for the post-op patient

Whose responsibility is it?

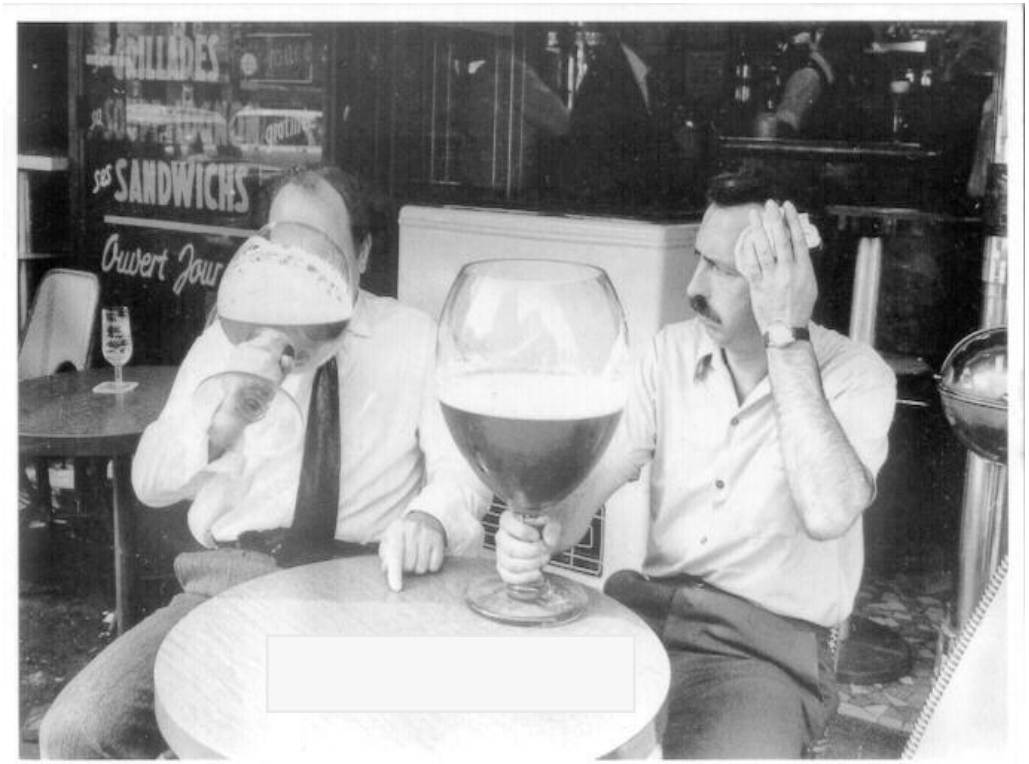
Do High Glucose Levels Cause Harm?



- All patients
- Patients with diabetes
- Patients without diabetes

Frisch A et al Diabetes Care 2010;33(8):1783-1788

Intermission or Stop?



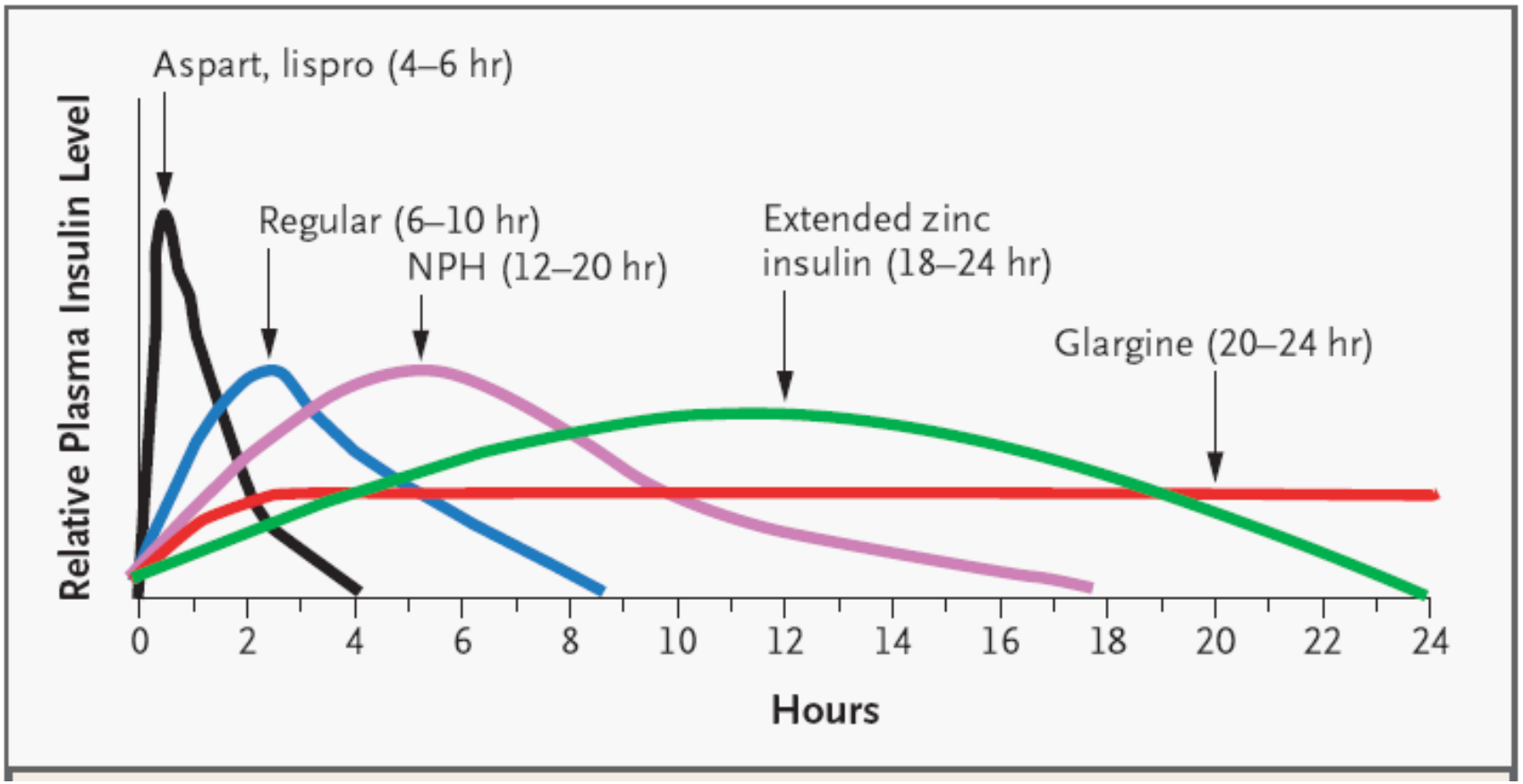
The Peri-Operative Management of Diabetes Drugs

Hypoglycaemic Agents

- α glucosidase inhibitors
- Metaglinides
- Metformin
- Sulphonylureas
- Thiazolidindiones
- GLP – 1 analogues
- DPP IV inhibitors
- (SGLT2 inhibitors)

Tablets	Day prior to admission	Day of surgery	
		Patient for AM surgery	**Patient for PM surgery**
Acarbose	Take as normal	Omit morning dose if NBM	Give morning dose if eating
Meglitinide (repaglinide or nateglinide)	Take as normal	Omit morning dose if NBM	Give morning dose if eating
Metformin (procedure not requiring use of contrast media*)	Take as normal	Take as normal	Take as normal
Sulphonylurea (e.g Glibenclamide, Gliclazide, Glipizide, etc.)	Take as normal	Once daily AM omit Twice daily omit AM	Once daily AM omit Twice daily omit AM and PM
Pioglitazone	Take as normal	Take as normal	Take as normal
DPP IV inhibitor (e.g. Sitagliptin, Vildagliptin, Saxagliptin)	Take as normal	Omit on day of surgery	Omit on day of surgery
GLP-1 analogue (e.g. Exenatide, Liraglutide)	Take as normal	Omit on day of surgery	Omit on day of surgery

Insulin Durations

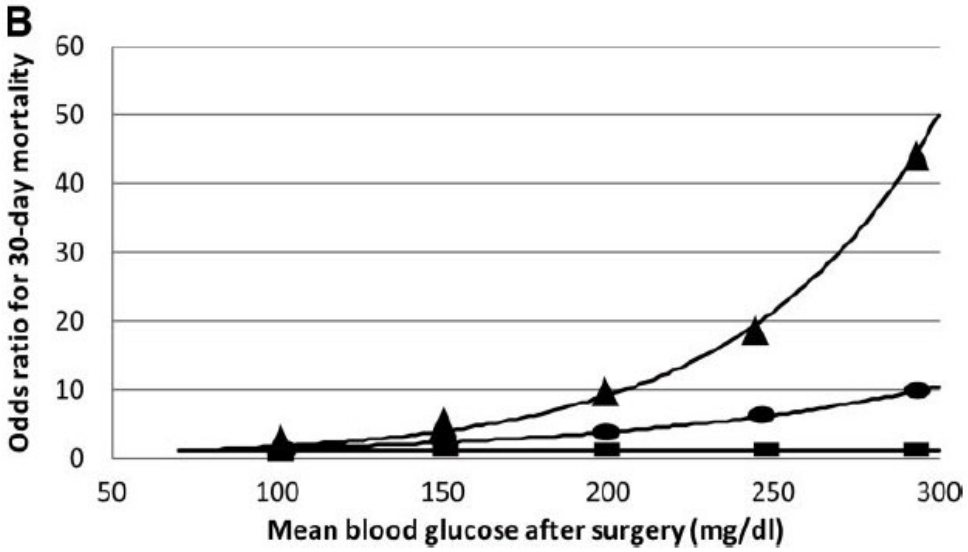


Hirsch I NEJM 2005;352(2):174-183

Insulins	Day prior to admission	Day of surgery	
		Patient for AM surgery	Patient for PM surgery
Once daily (evening) (e.g. Lantus® or Levemir®. Insulatard®, Humulin I®, Insuman®)	No dose change*	Check blood glucose on admission	Check blood glucose on admission
Once daily (morning) (Lantus® or Levemir® Insulatard®, Humulin I®, Insuman®)	No dose change	No dose change*. Check blood glucose on admission	No dose change*. Check blood glucose on admission
Twice daily (e.g. Novomix 30®, Humulin M3® Humalog Mix 25®, Humalog Mix 50®, Insuman® Comb 25, Insuman® Comb 50 twice daily Levemir® or Lantus®)	No dose change	Halve the usual morning dose. Check blood glucose on admission. Leave the evening meal dose unchanged	Halve the usual morning dose. Check blood glucose on admission. Leave the evening meal dose unchanged
Twice daily - separate injections of short acting (e.g. animal neutral, Novorapid® Humulin S®) Apidra® **and intermediate acting** (e.g. animal isophane Insulatard® HumulinI® Insuman®)	No dose change	Calculate the total dose of both morning insulins and give half as intermediate acting only in the morning. Check blood glucose on admission. Leave the evening meal dose unchanged	Calculate the total dose of both morning insulins and give half as intermediate acting only in the morning. Check blood glucose on admission. Leave the evening meal dose unchanged
3, 4, or 5 injections daily	No dose change	**Basal bolus regimens:** omit the morning and lunchtime short acting insulins. Keep the basal unchanged.* **Premixed AM insulin:** halve the morning dose and omit lunchtime dose Check blood glucose on admission	Take usual morning insulin dose(s). Omit lunchtime dose. Check blood glucose on admission

It's a Minefield

- Remember, if you knew that without you even TOUCHING the patient you could *potentially* reduce their peri-operative mortality by 40 fold would you do that first?



Norfolk and Norwich University Hospitals NHS
NHS Foundation Trust

Diabetes, Dexamethasone and Death

or Peri-operative Glucose Control

- Is it Important?

www.norfolkdiabetes.com