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Translating Nutritional Science to Good Health

Glycaemia in ICU

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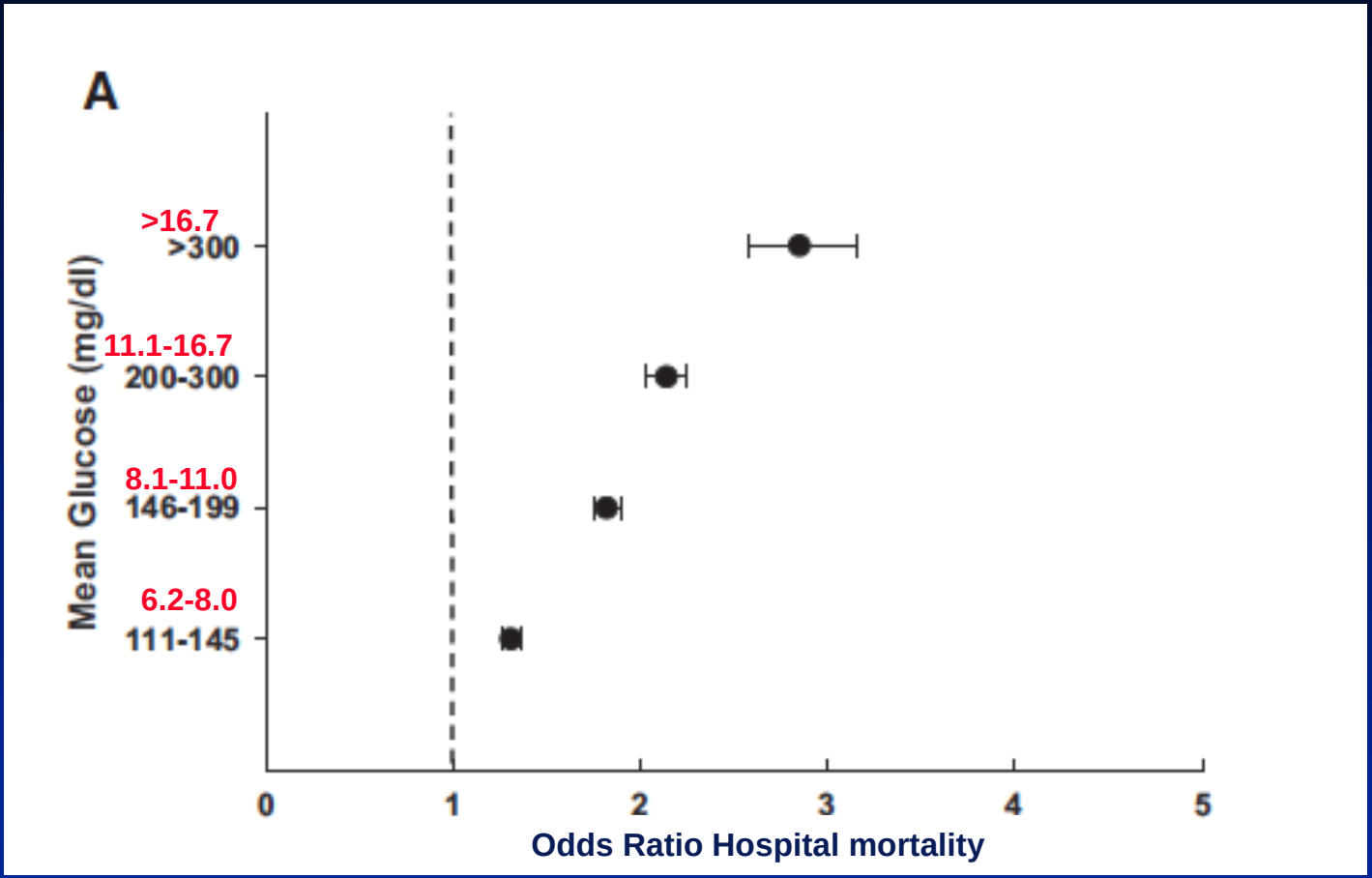
Outline

1. Glycaemic control in ICU
   - Observational studies
   - Intervention studies
2. Current guidelines for glycaemic control in ICU and in hospital
3. Critical illness associated hyperglycaemia vs. pre-existing T2DM
   - Definition
   - Prevalence
   - Implications – short and long term

Is hyperglycaemia harmful or a physiological response to critical illness?

Hyperglycaemia and mortality



n = 259,040

Falciglia, et al. Crit Care Med (2009)

Outline

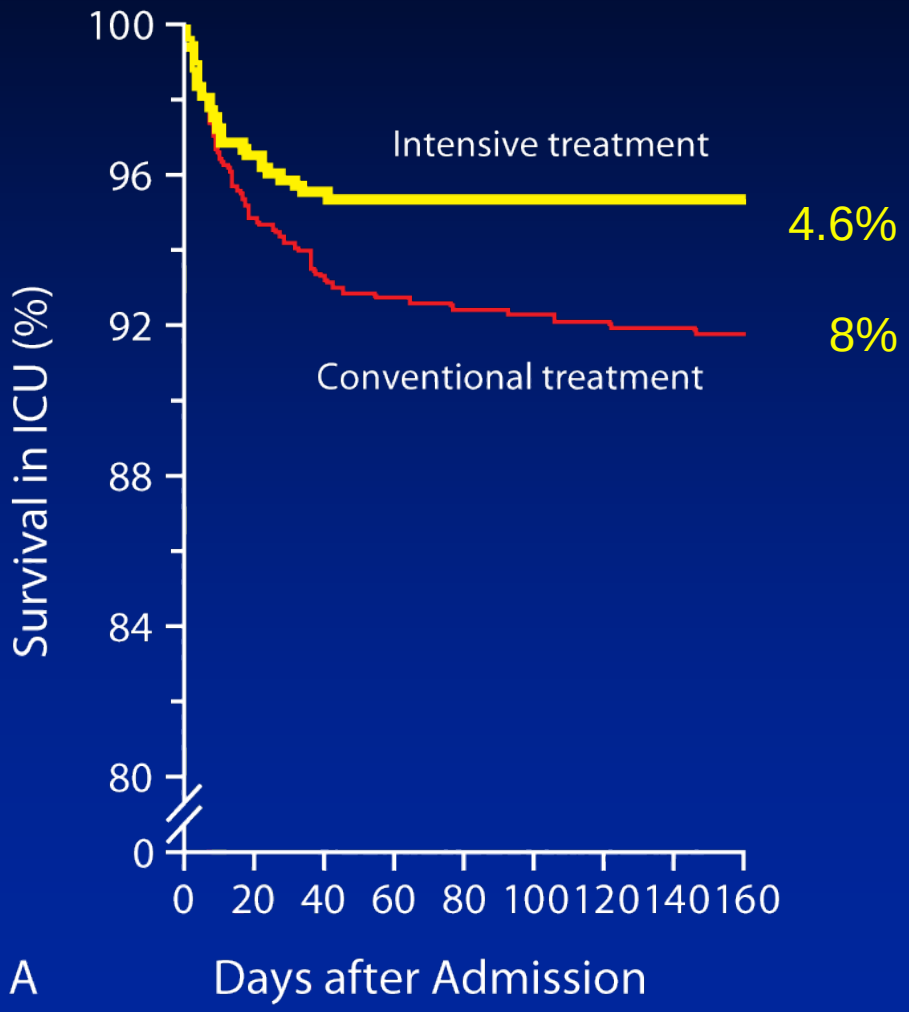
1. Implications of glycaemic control in ICU
   - Observational studies
   - Intervention studies

Intensive insulin treatment in ICU
Leuven surgical trial

- Prospective randomised controlled study (n=1,548)
- Admitted to surgical ICU and receiving mechanical ventilation
- Mean age 63 years; 71% males; post-cardiac surgery (63%)
- Treatment:
  - intensive insulin treatment (IIT): BSL target 4.4-6.1 mmol/L
  - conventional treatment: insulin if BSL > 11.9 mmol/L; target 10.0-11.1 mmol/L

Van den Berghe, et al. NEJM (2001)

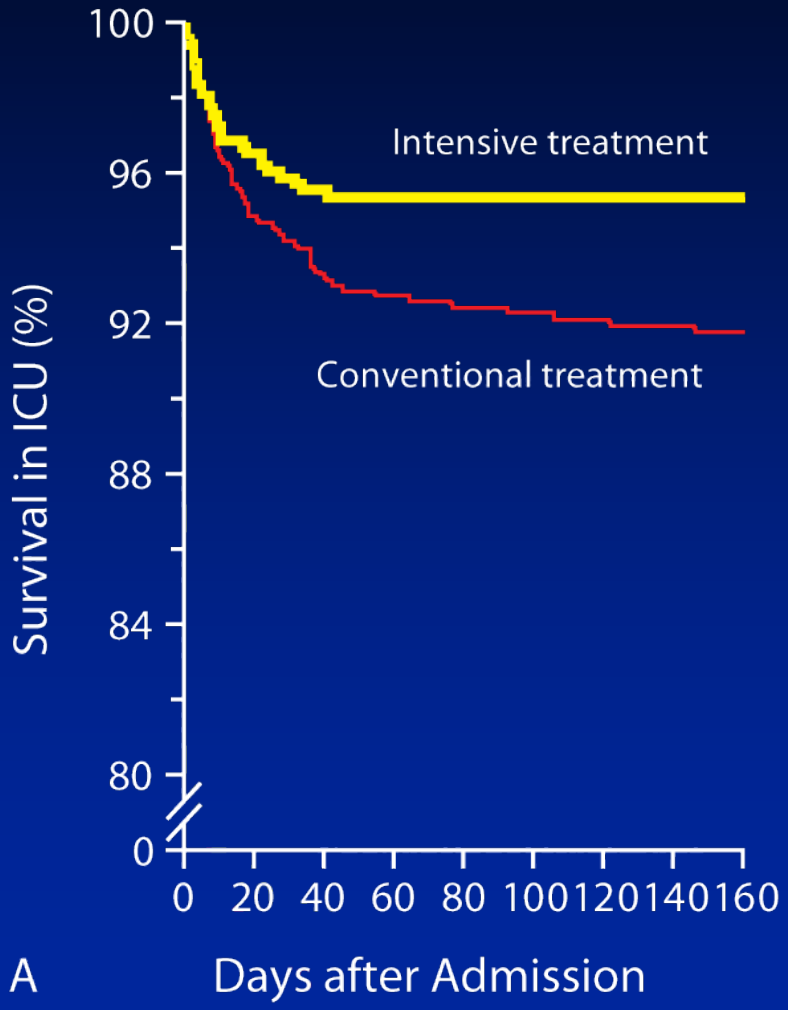
Intensive insulin treatment in ICU
Leuven surgical trial

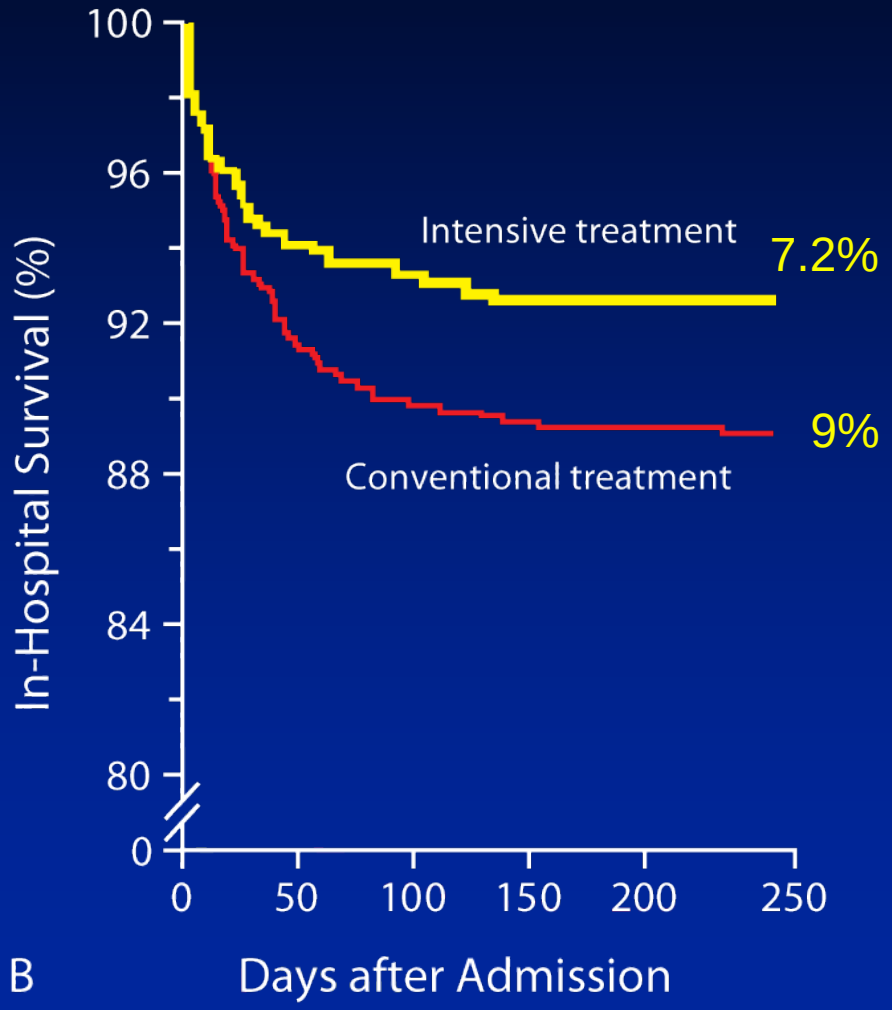


Van den Berghe, et al. NEJM (2001)

Intensive insulin treatment in ICU

Leuven surgical trial





Van den Berghe, et al. NEJM (2001)

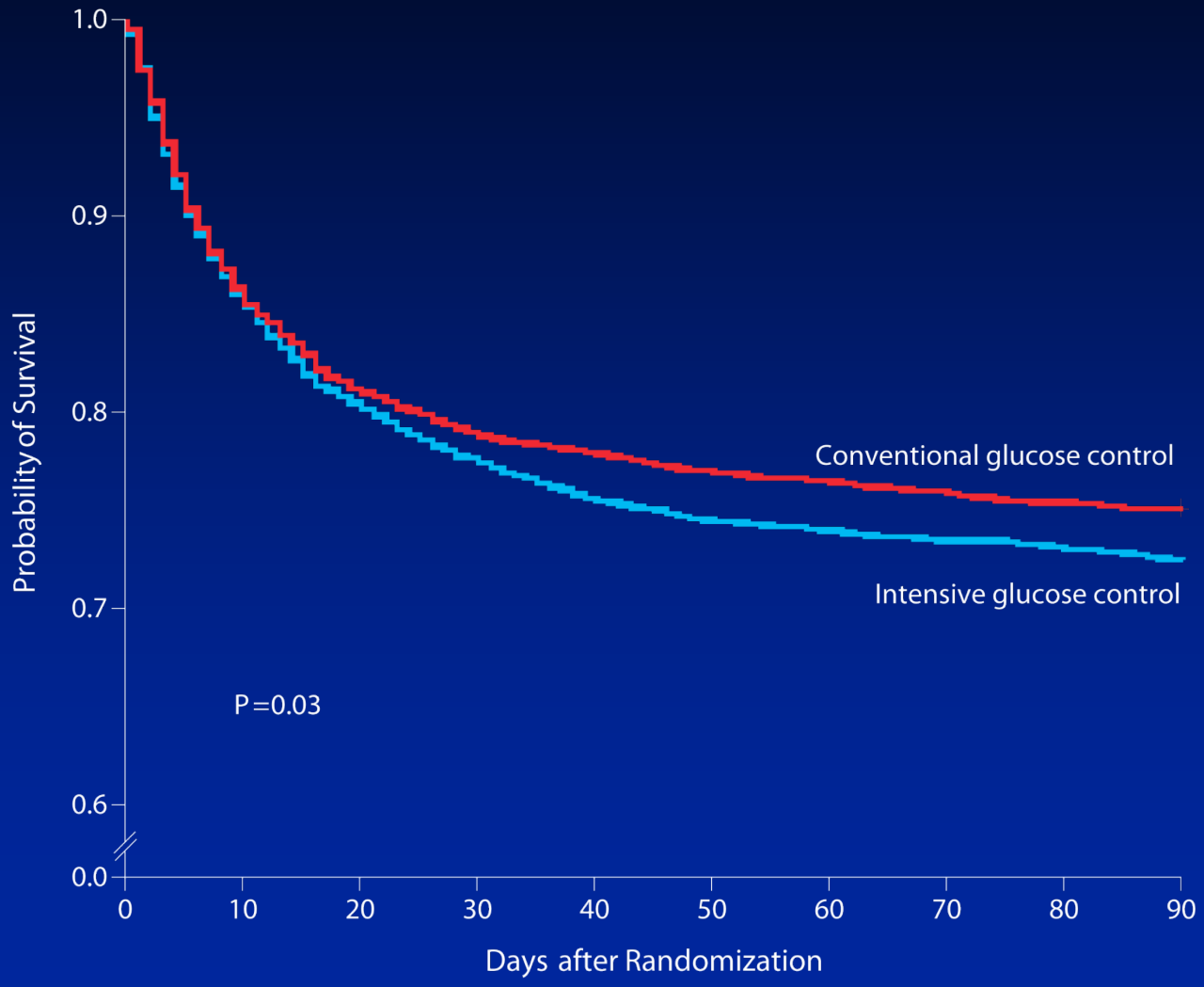
Acute hyperglycaemia is harmful and should be aggressively treated?

Intensive insulin therapy in ICU
NICE-SUGAR

- Multicentre Normoglycaemia in Intensive Care Evaluation Survival Using Glucose Algorithm Regulation (NICE-SUGAR)
- Mixed surgical/medical ICU
  - IIT (4.5 – 6 mmol/L)
  - Conventional (< 10mmol/L); insulin infusion ceased if BSL < 8 mmol/L

NICE SUGAR Investigators NEJM (2009)

Intensive insulin therapy causes harm

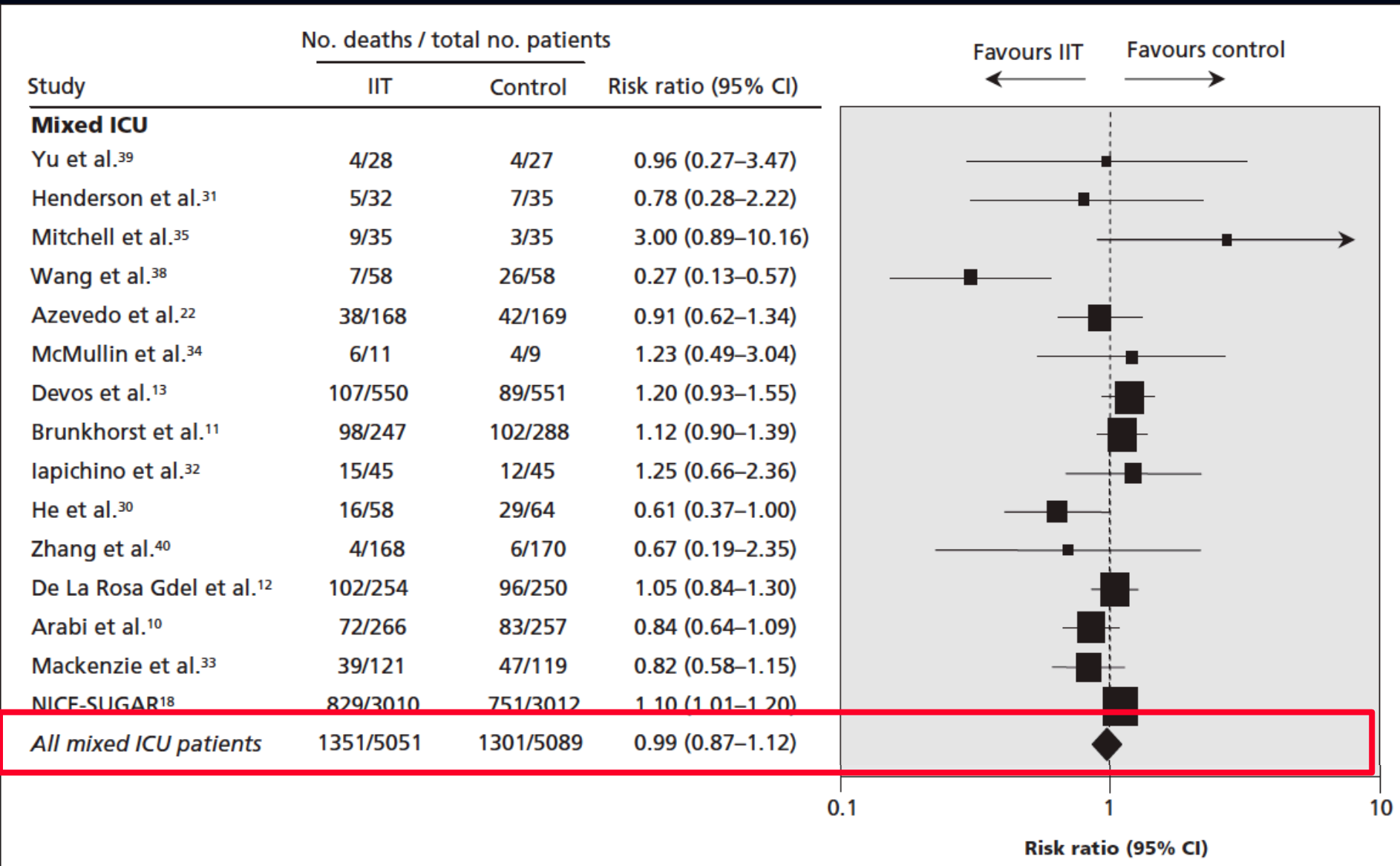


24.9%

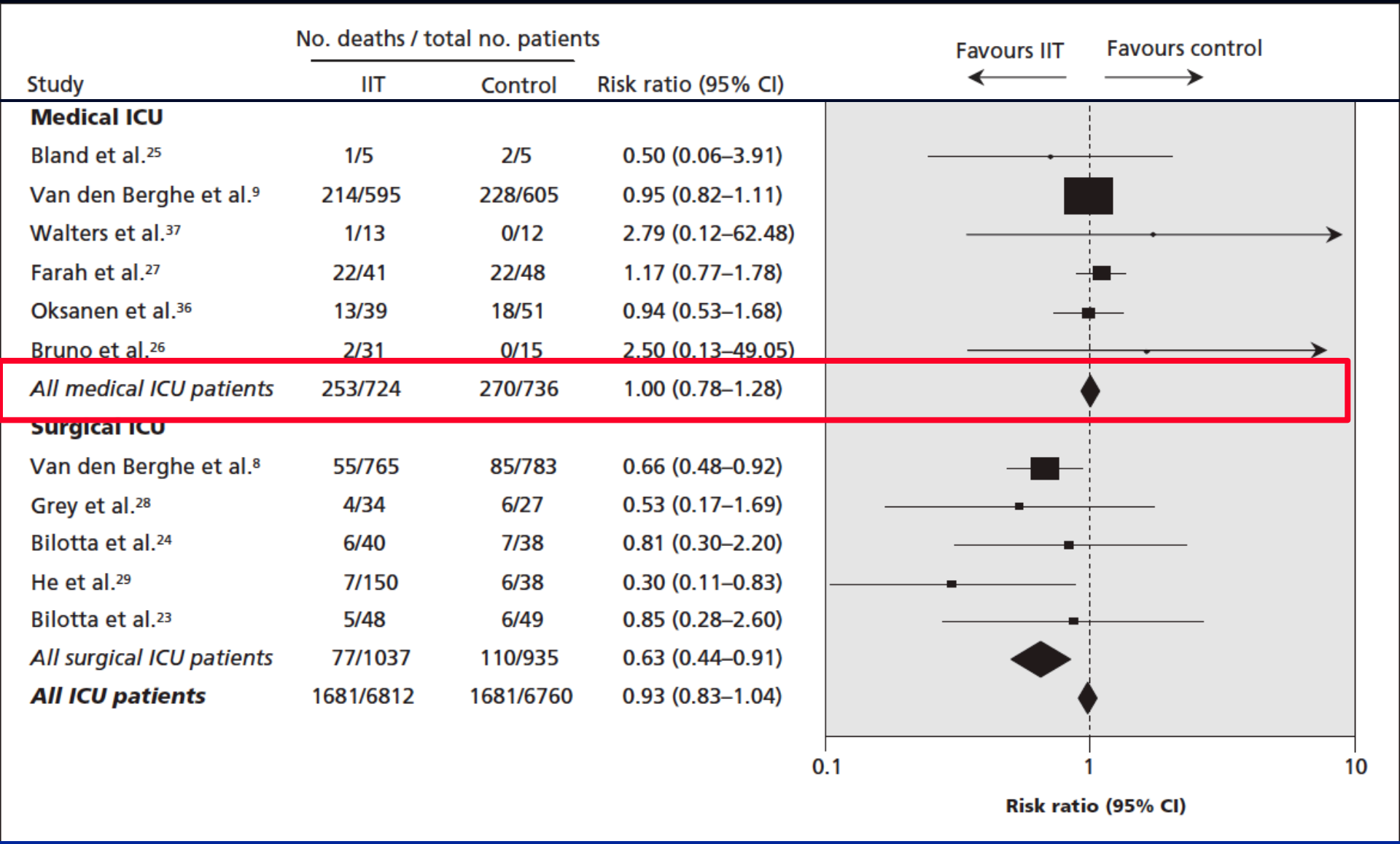
27.5%

NICE SUGAR Investigators NEJM (2009)

Other trials?



Griesdale D et al CMAJ 2009



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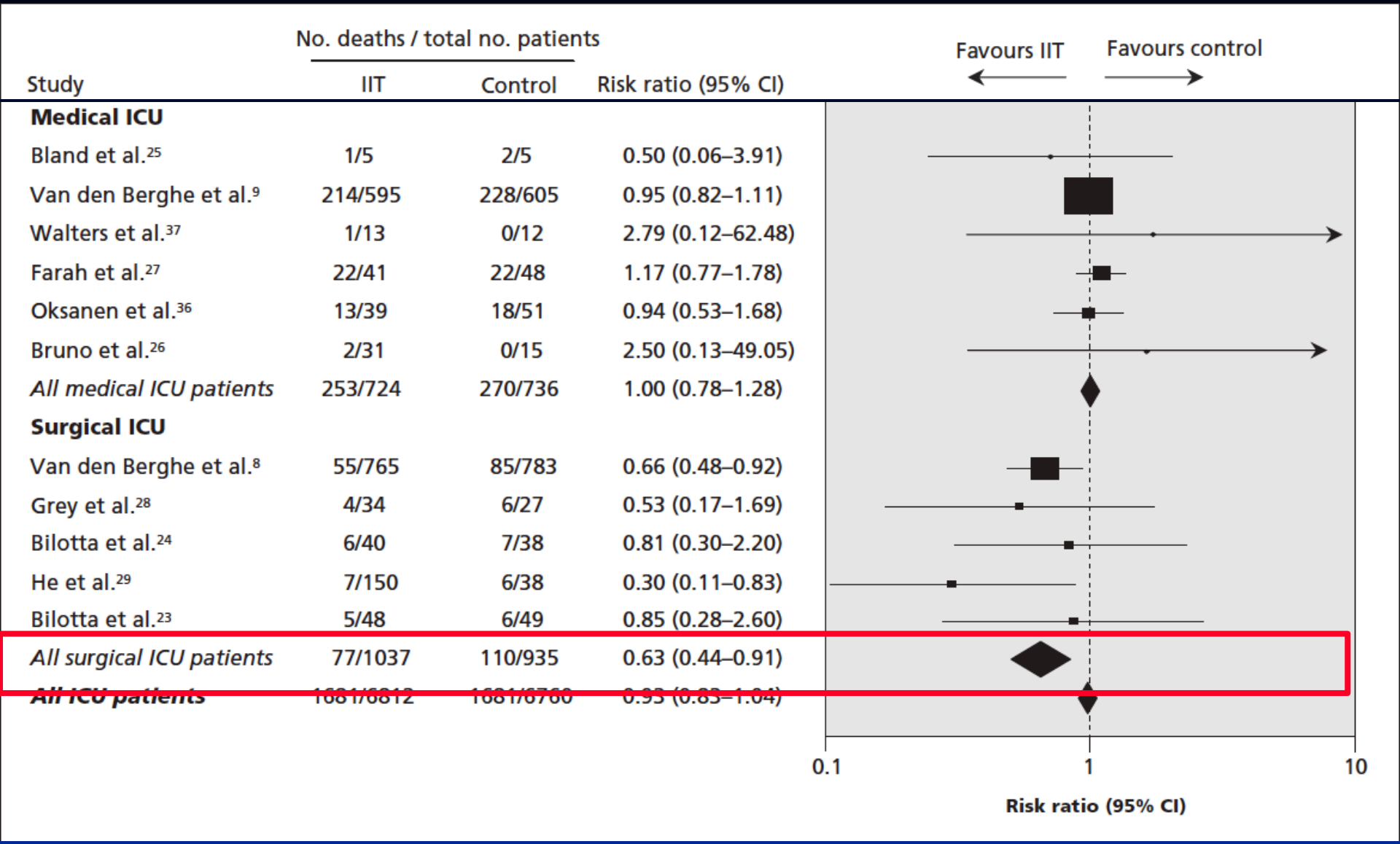

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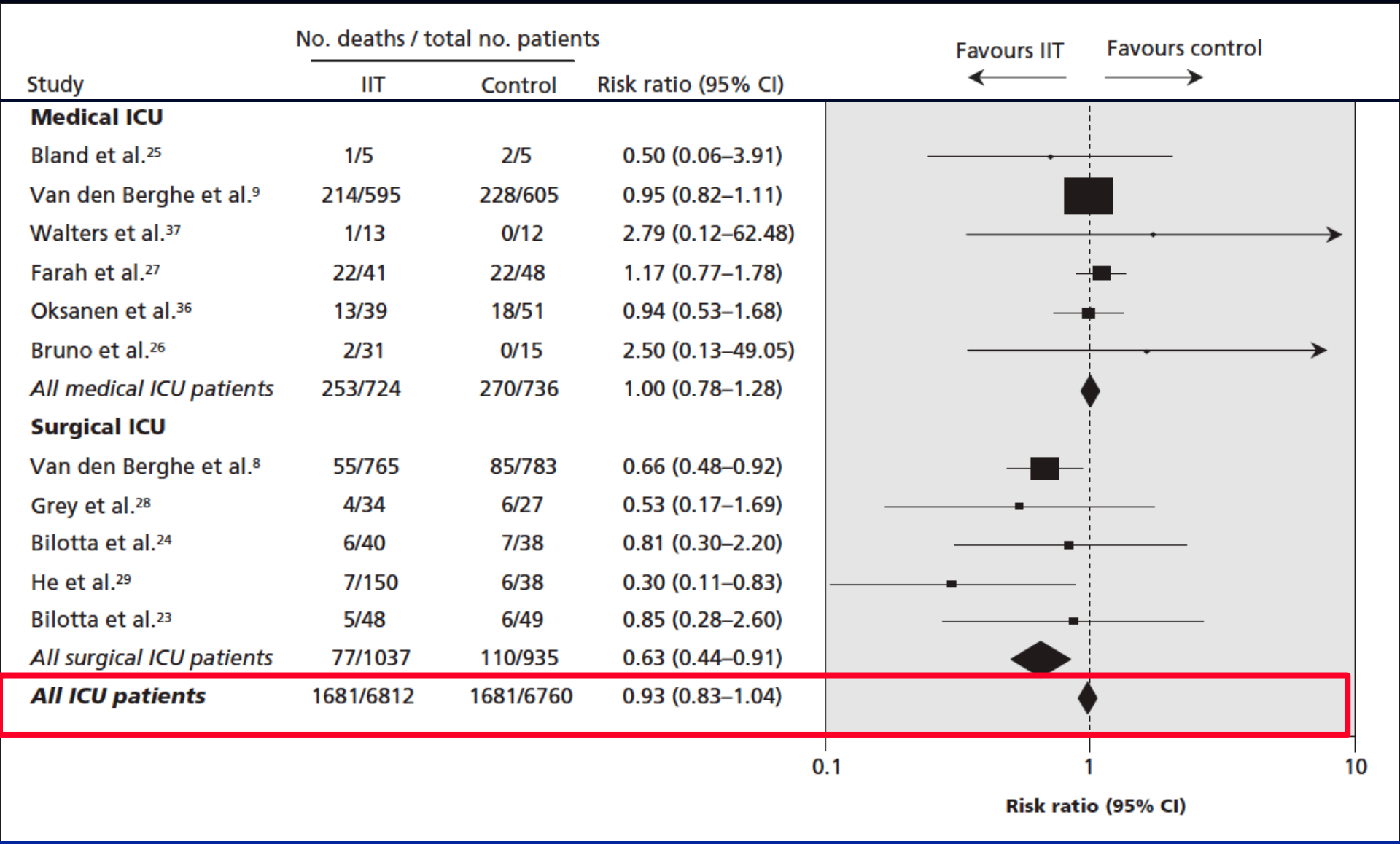


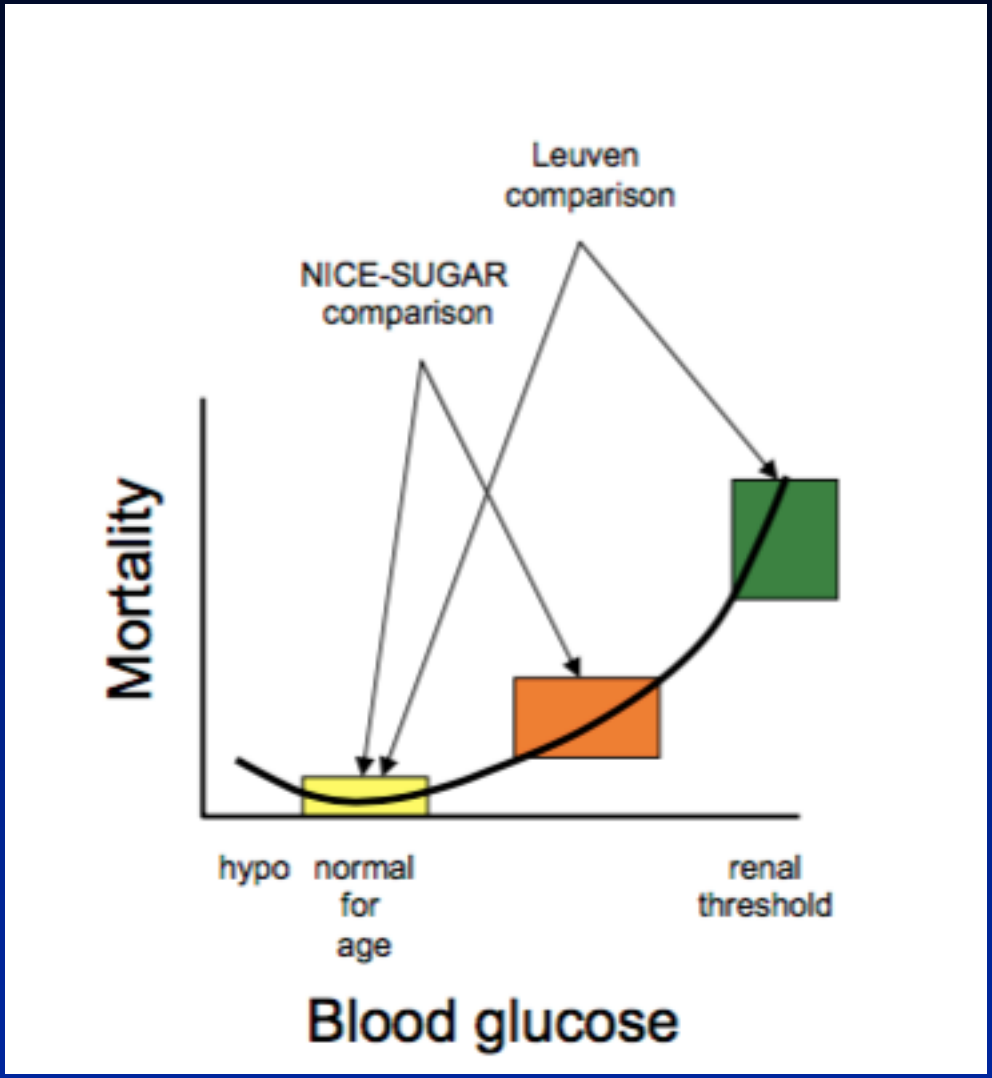
Griesdale D et al CMAJ 2009

Reason for differential findings

Reason for differential findings

- Heterogeneous population
- Different targets/protocols/expertise
  - Leuven surgical trial high mortality rate in control group - ?due to large glucose load: patients given glucose 200-300 g / 24 h glucose with early introduction of parenteral/enteral feeding
  - issues with potential accuracy of glucose measurements (glucometer), potassium balance, centre experience with protocols

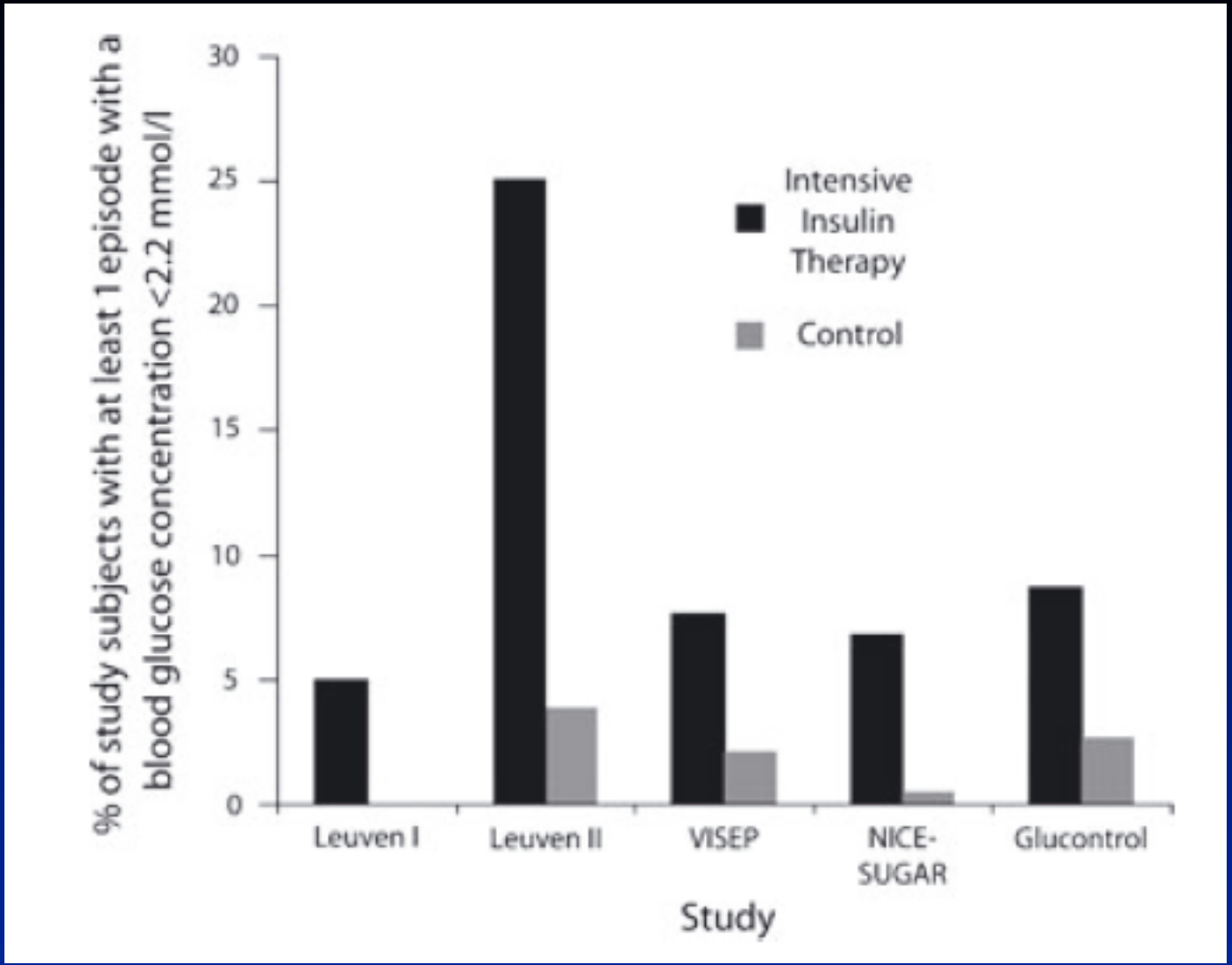
J shaped curve glycaemia and mortality



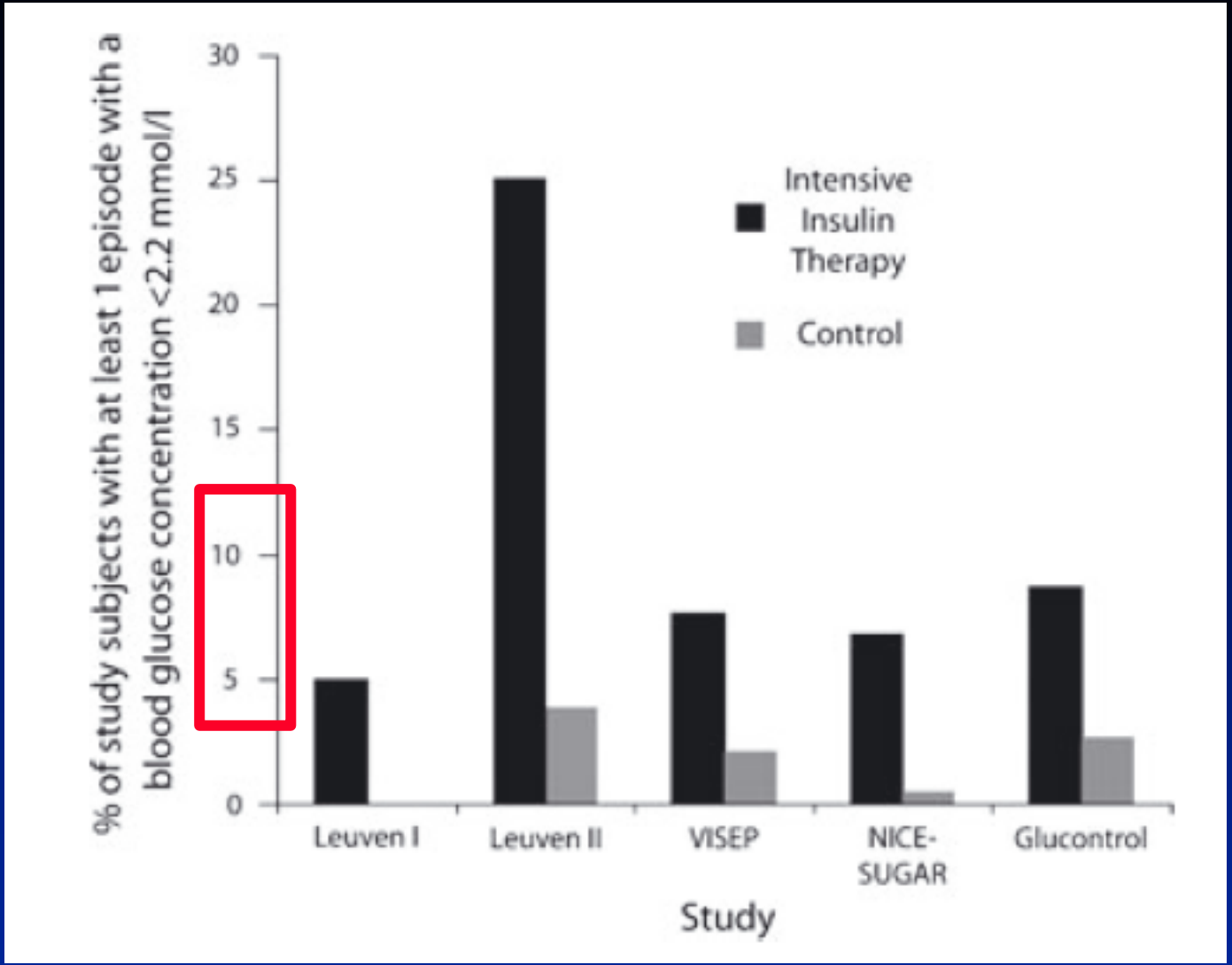
Van den Berghe G et al JCEM 2009

Mechanism of harm

- Hypoglycaemia
  - Acute effects (arrhythmia)
  - Alterations in physiological response to subsequent hypoglycaemia
  - Legacy effect – metabolic memory
  - ?autonomic dysfunction
- Glycaemic variability



Deane & Horowitz M, DOM 2013



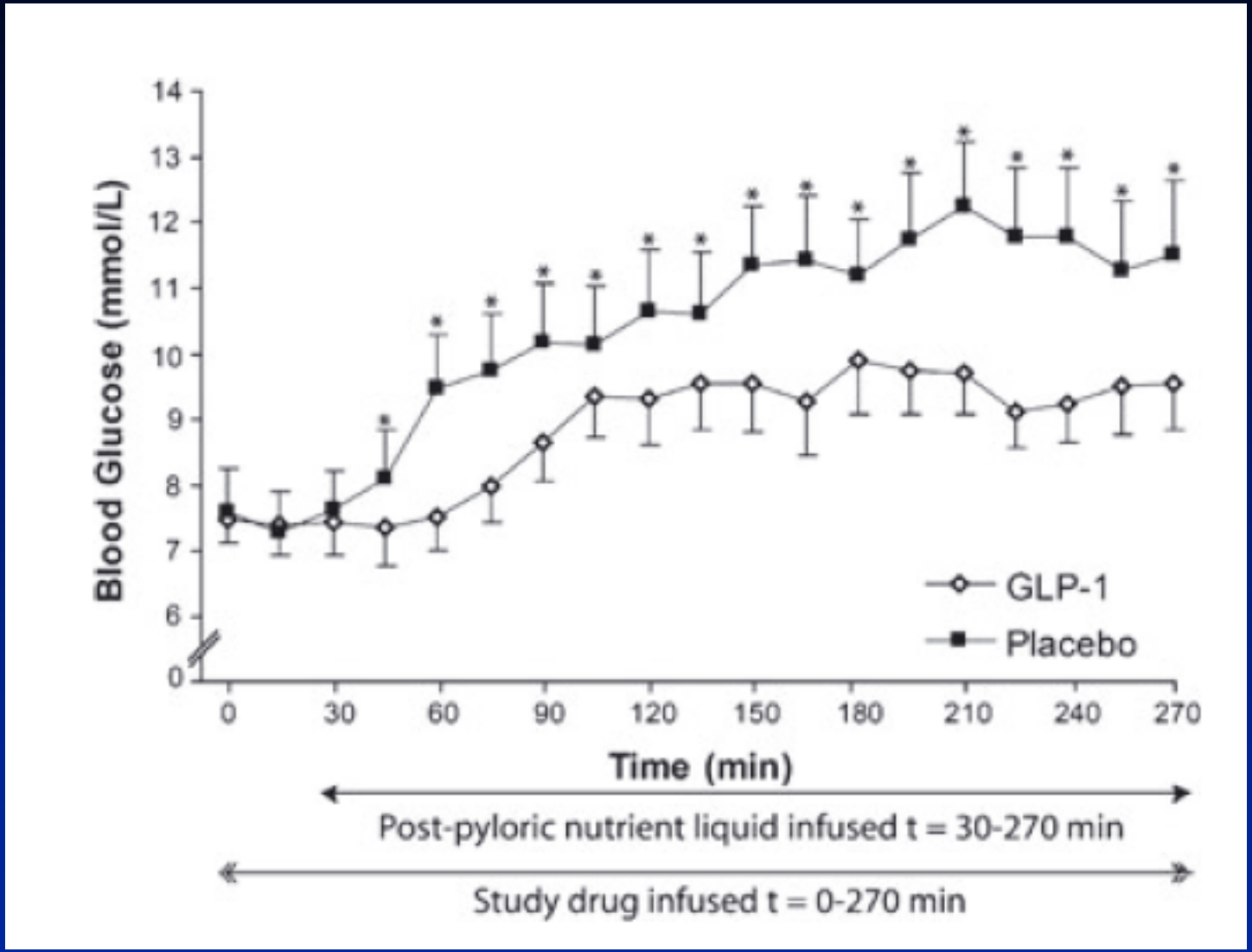
Deane & Horowitz M, DOM 2013

Novel approaches?

Novel approaches?

- GLP-1 based therapy
  - glucose independent

GLP-1 in ICU



Deane A et al Critical Care 2009

Outline

1. Implications of glycaemic control in ICU
   - Observational studies
   - Intervention studies
2. Current guidelines for glycaemic control in ICU and in hospital

Guidelines - ICU

- Ideal glucose range in ICU unknown
- Targeting BSL < 6 mmol/L avoided
- Optimal range is controversial
  - ? 7.8 – 10 mmol/L
  - ? 6.0 – 10 mmol/L
  - ? 6.1-7.8 mmol/L

Glycemic Targets for Critically Ill Individuals

Insulin is the preferred method for achieving glycemic control for diabetes care in the hospital

Critically ill individuals

Persistent hyperglycemia:

- Initiate insulin starting at ≤180 mg/dL (10.0 mmol/L)
- Once insulin started, a target glucose range of 140-180 mg/dL (7.8-10.0 mmol/L) is recommended for most patients

More stringent targets may be appropriate for certain patients providing no increased hypoglycemia risk

- 110-140 mg/dL (6.1-7.8 mmol/L)

Hypoglycemia management protocol should be established for each patient

- Plan for prevention and treatment
- Episodes should be documented and tracked
- Review and change treatment regimen when glucose is <70 mg/dL (3.9 mmol/L)

Guidelines – general hospital

We sought to achieve concordance in our recommendation to a single target glucose level for the majority of clinical situations, although there are some differences in the limited data for different scenarios. The overall recommendation is that for most hospital patients with hyperglycaemia, treatment should be instituted to achieve and maintain blood glucose (BG) levels below 10 mmol/L, but because of the potential dangers of hypoglycaemia, treatment should not aim to lower glucose levels below 5 mmol/L.

Australian Diabetes Society Guidelines for Routine Glucose Control in Hospital, 2012

Guidelines – general hospital

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   - Prevalence
   - Implications – short and long term

Critical illness associated hyperglycaemia

- Definition: blood glucose concentrations that, in health, would lead to a diagnosis of diabetes, but occur in critically ill patients without diabetes

Critical illness associated hyperglycaemia

- Prevalence = ~50%
  - 1000 consecutively admitted patients to ICU*
  - Pre-existing diagnosed and unrecognised T2DM excluded by contacting GP/care giver and obtaining HbA1c
  - vs. 12-40% with T2DM

*Plummer M et al Intensive Care Medicine 2014

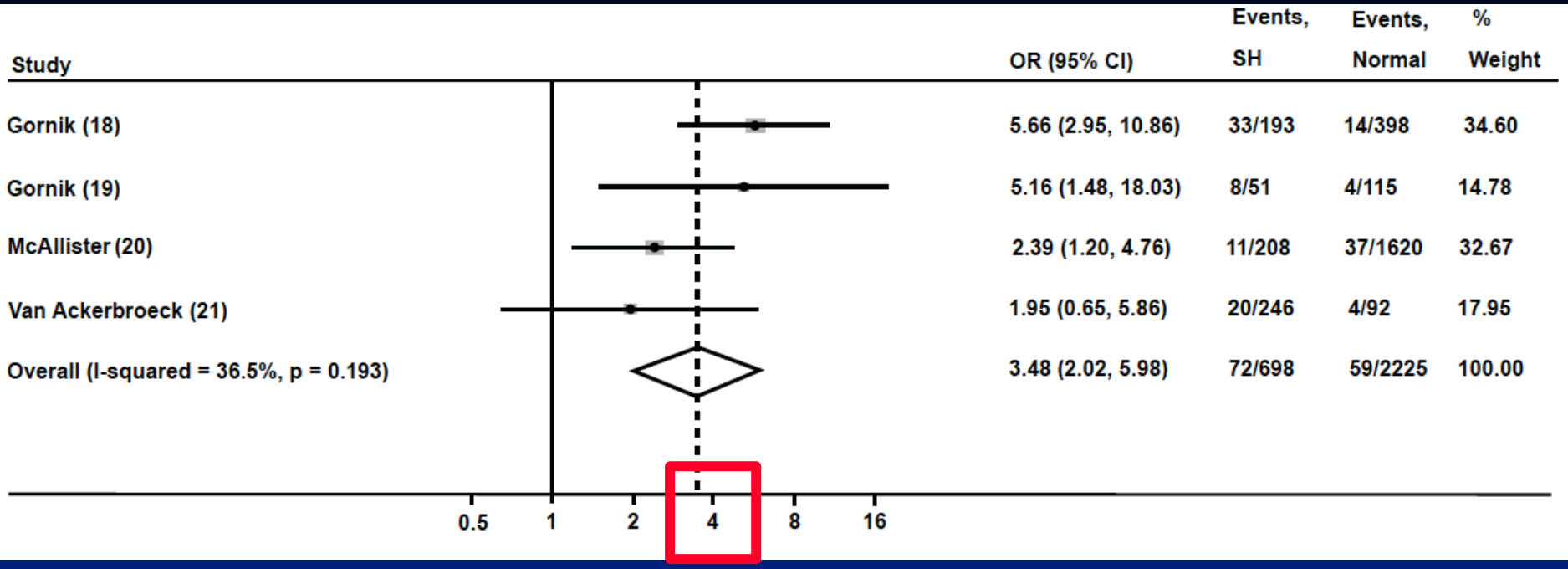
Critical illness associated hyperglycaemia

- Pathophysiology
  - temporary insulin resistance, insulin deficiency, glucagon
  - counter-regulatory hormones, inflammatory mediators
  - medical intervention (glucocorticoids, nutrition, pressors)

***Plummer M et al Intensive Care Medicine 2014**

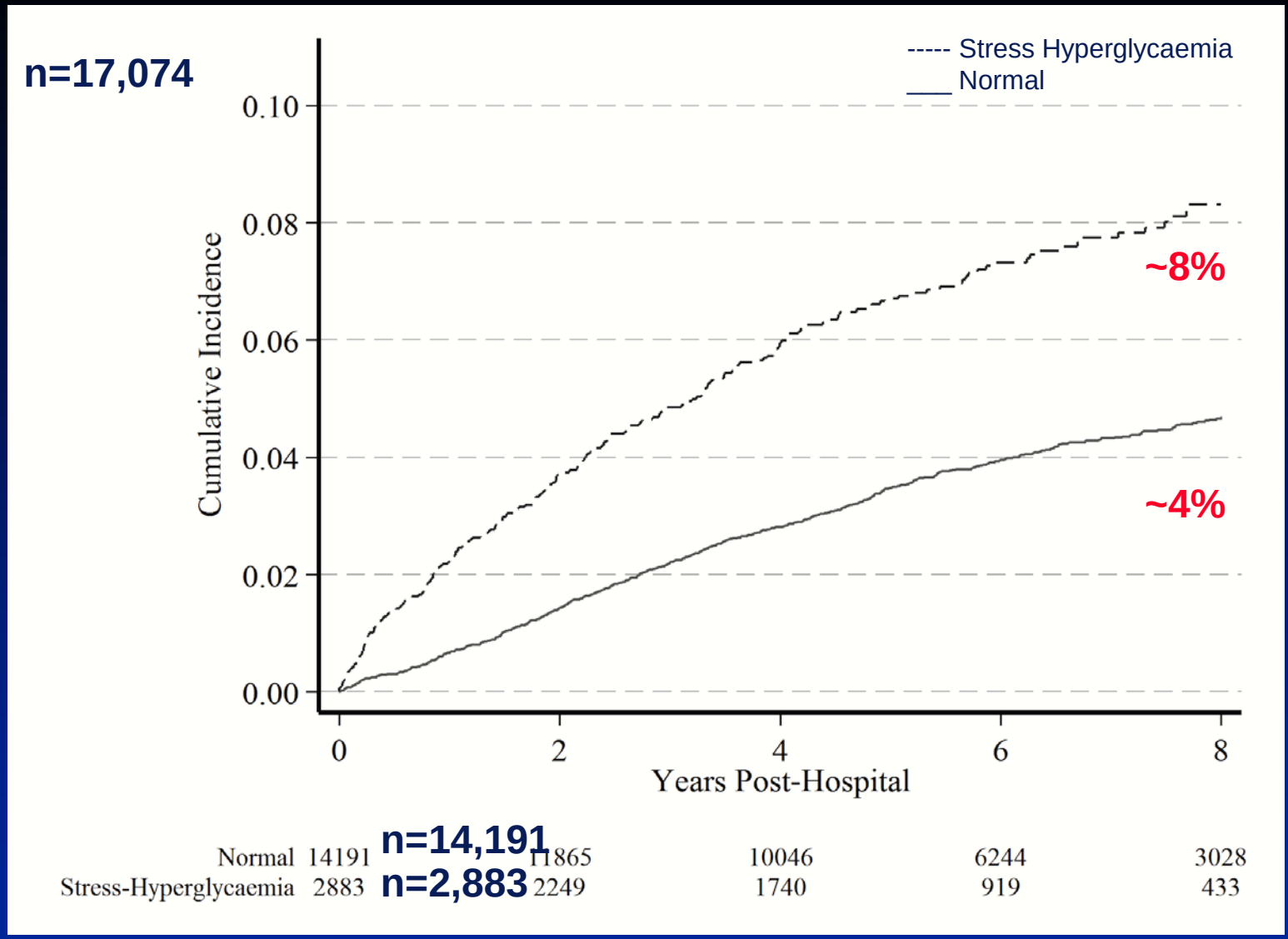
Critical illness associated hyperglycaemia

- Does it predict subsequent T2DM?



Gornik I et al, Crit Care, 2010;14:R130
Gornik I et al, Acta Diabetol, 2010;47:29-33
McAllister DA et al, Plos Med 2014;11:e1001708
Van Ackerbroeck S, et al Crit Care 2015;19:355

AliAbdelhamid Y, unpublished data



Plummer M et al, unpublished data

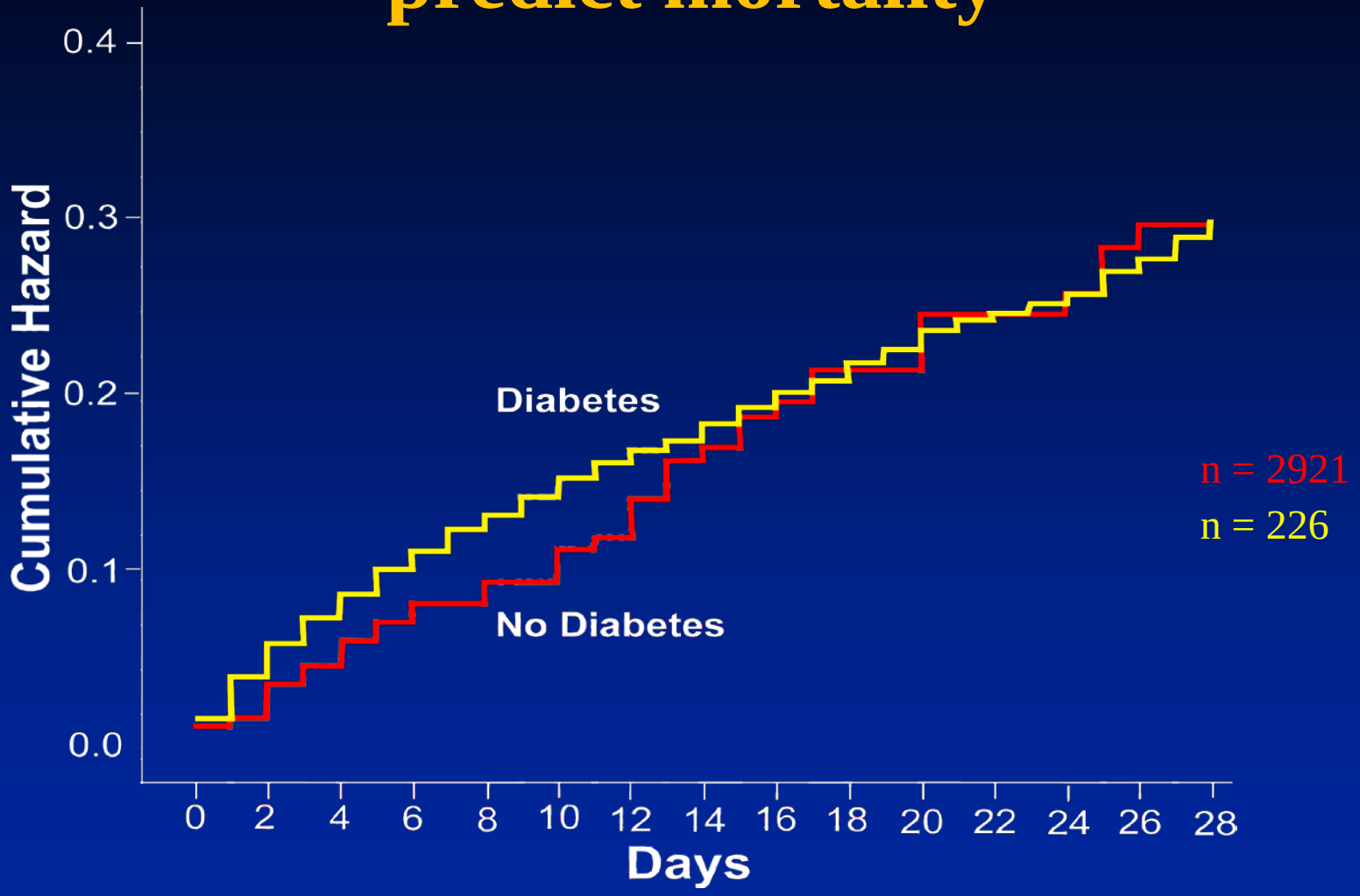
Stress hyperglycaemia

- Does it predict subsequent T2DM?
  - prospective studies
  - may identify group who derive particular benefit from screening/primary prevention

Implications of T2DM

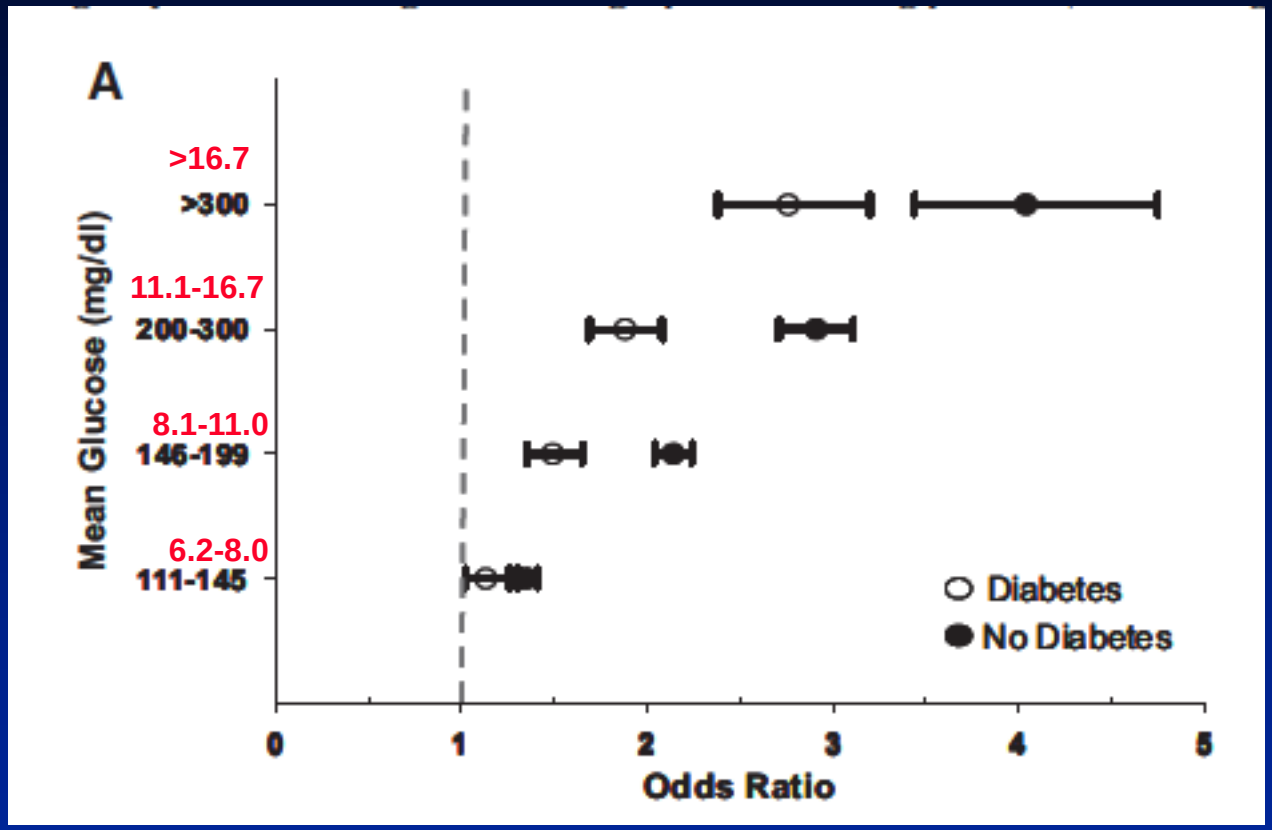
- Impact on short-term mortality
- In-hospital glycaemic targets?
- Follow up?

Diabetes on admission does not predict mortality



Vincent JL, et al. Crit. Care (2010)

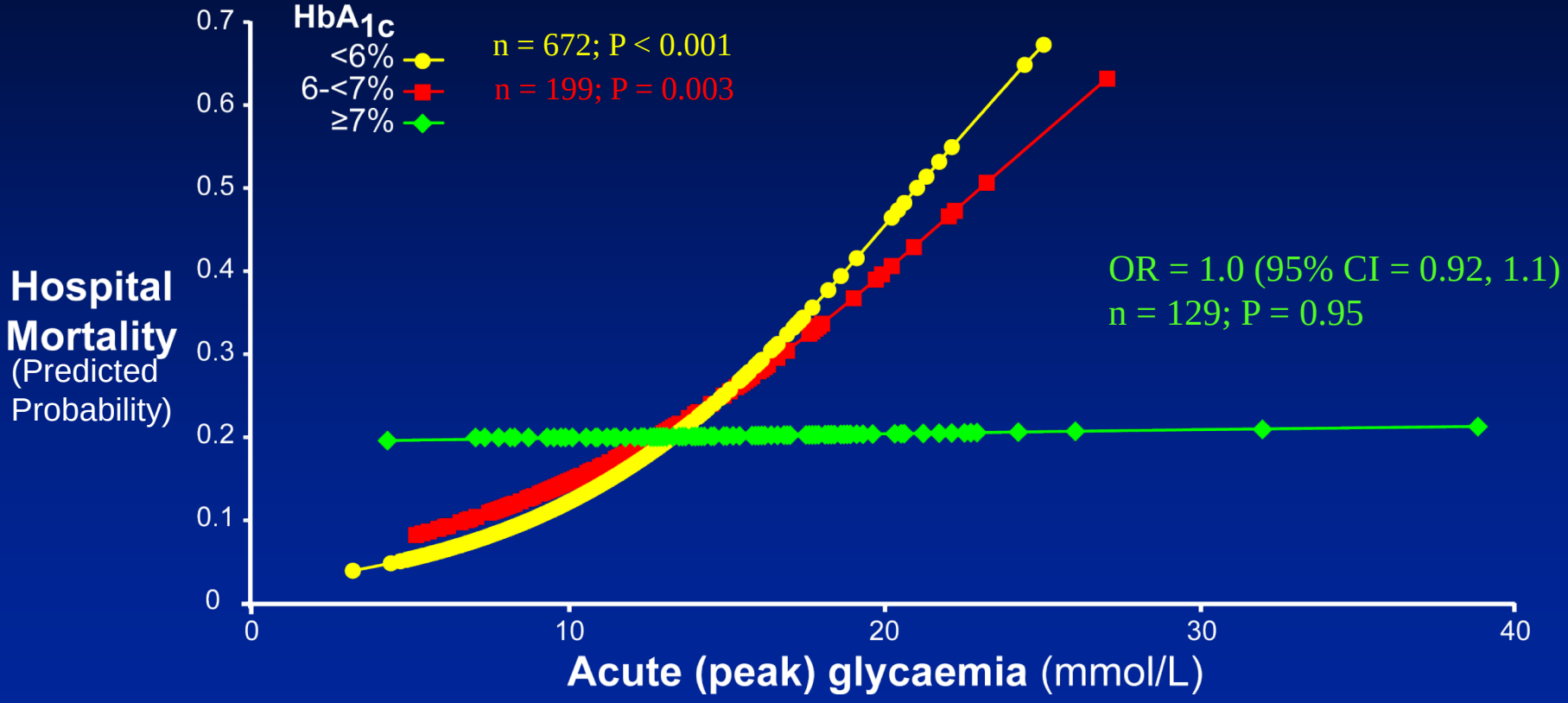
Hyperglycaemia mortality T2DM



n = 259,040

Falciglia, et al. Crit Care Med (2009)

Acute hyperglycaemia in patients with chronic hyperglycaemia

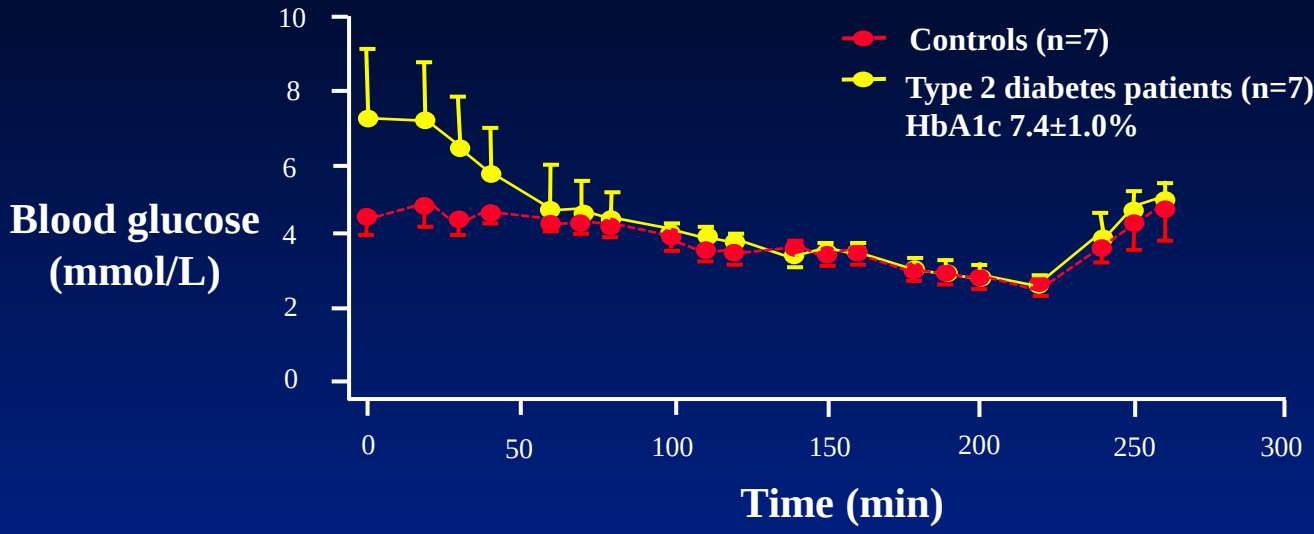


Plummer, et al. Intensive Care Medicine 2014

Implications of T2DM

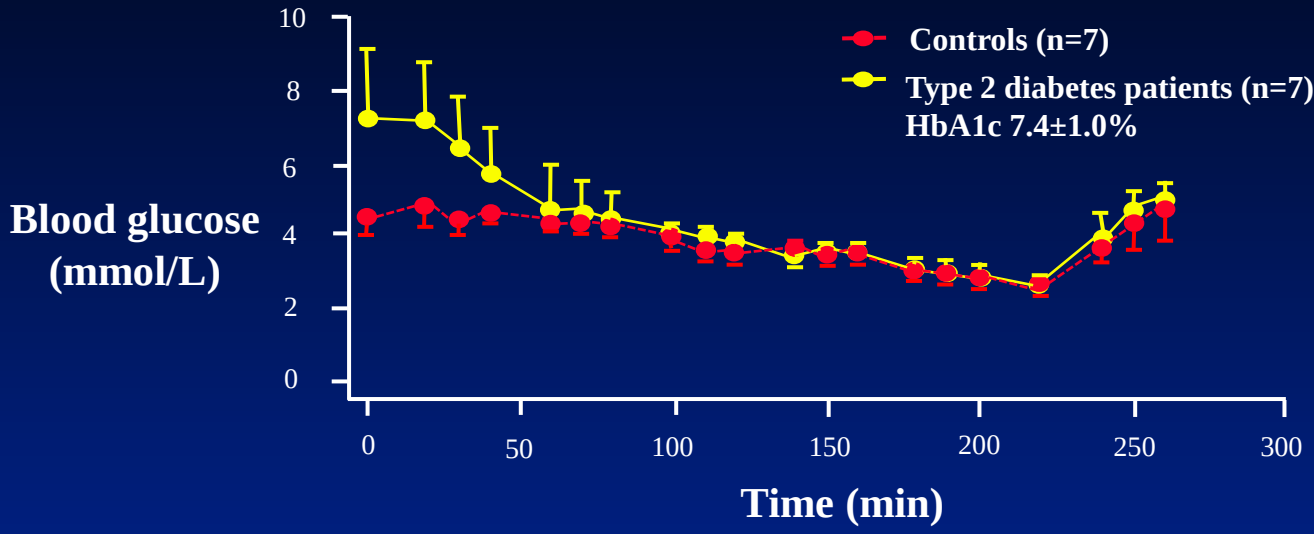
- In-hospital glycaemic targets?

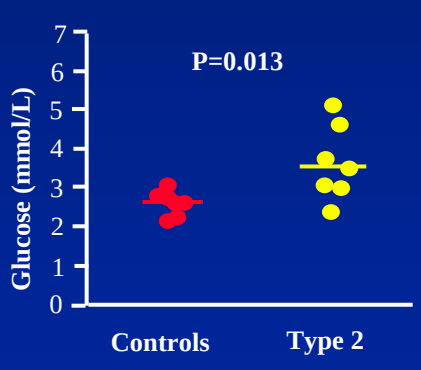
Threshold for hypoglycaemia occurs at higher glucose concentrations patients with T2DM



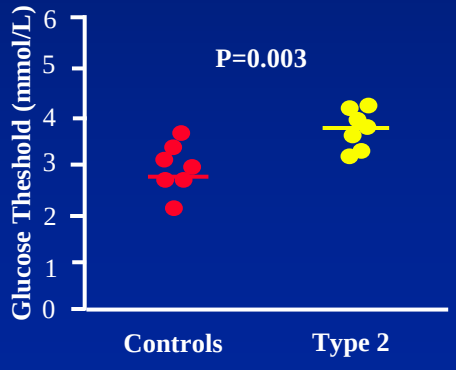
Spyer, et al. Lancet (2000)

Threshold for hypoglycaemia occurs at higher glucose concentrations patients with T2DM

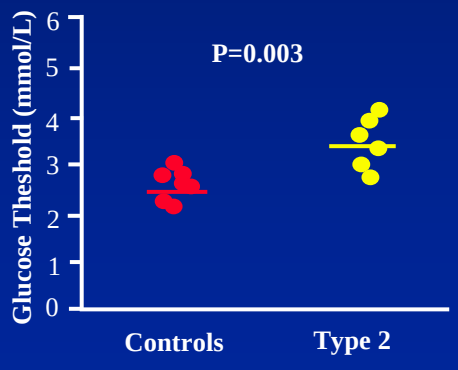




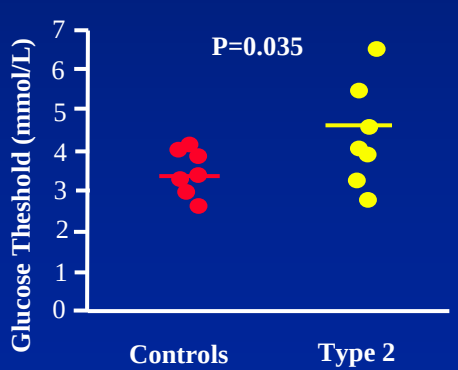
Symptoms



Adrenaline



Noradrenaline



Plasma Cortisol

Spyer, et al. Lancet (2000)

Concept of the glucose continuum

Patients with critical illness associated hyperglycaemia

HARMFUL → potentially harmful → optimal range → potentially harmful → HARMFUL

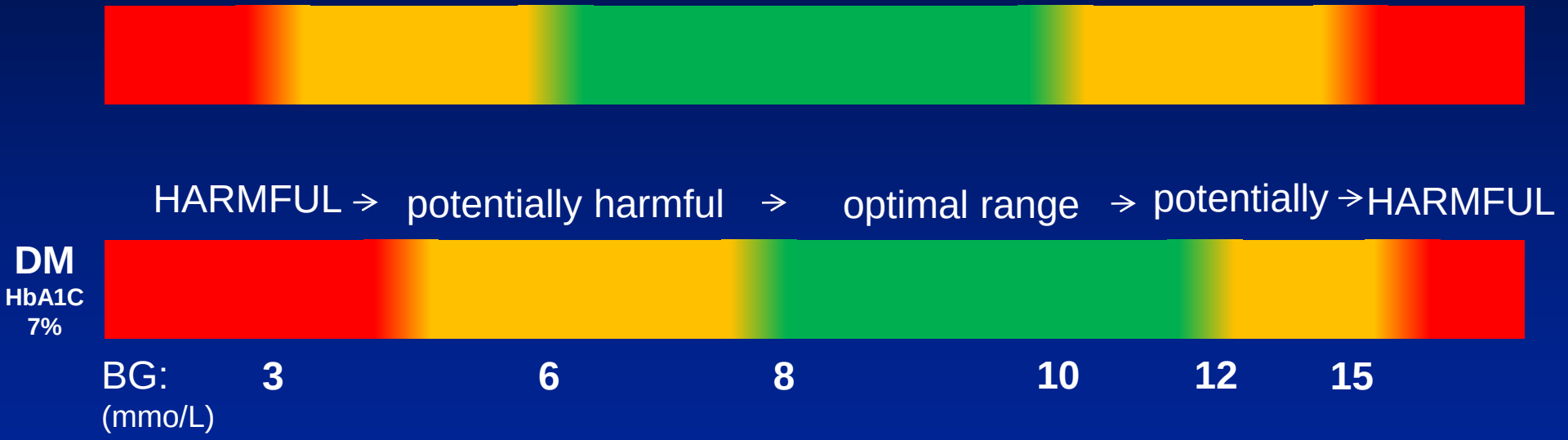
BG: (mmo/L)

3 **6** **10** **15**

Deane A & Horowitz M Diab. Obes. Metab. (2013)

Concept of the glucose continuum

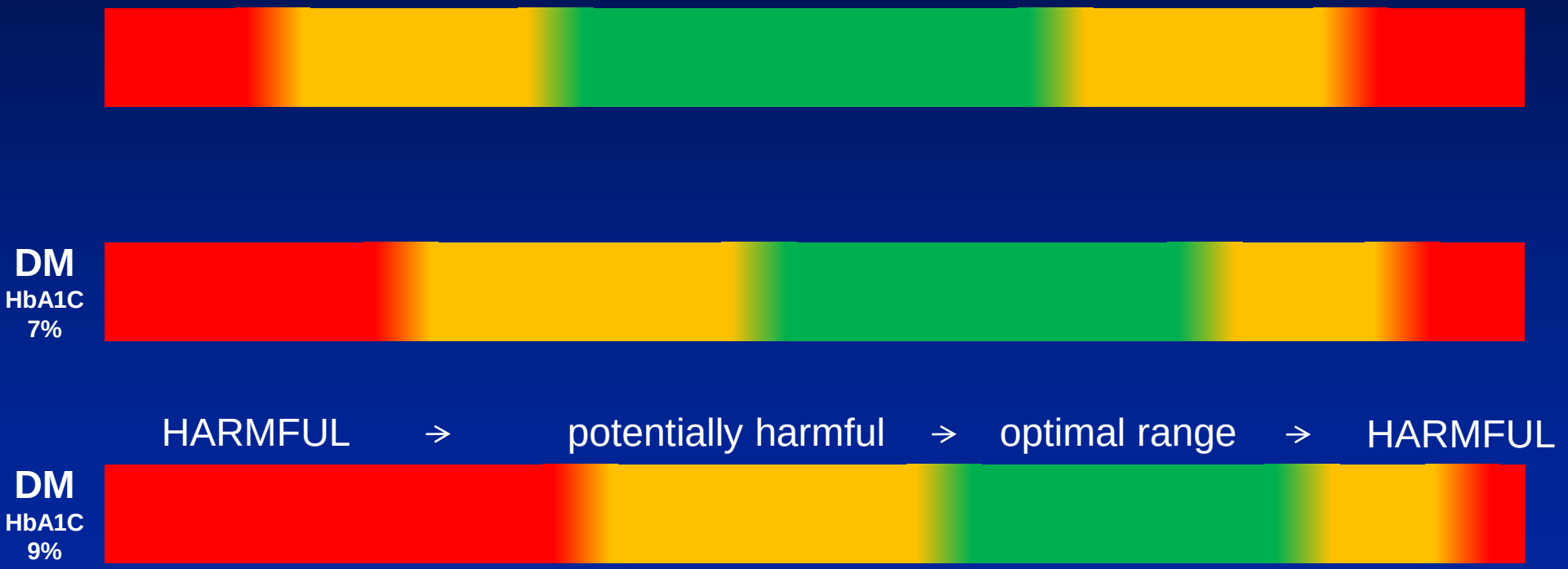
Patients with diabetes and chronic ‘moderate’ hyperglycaemia



Deane A & Horowitz M Diab. Obes. Metab. (2013)

Concept of the glucose continuum

Patients with diabetes and chronic ‘severe’ hyperglycaemia



Deane A & Horowitz M Diab. Obes. Metab. (2013)

T2DM in critically ill

- Modify targets based on glycaemic control
- Impact of ICU follow up clinics
  - targeted follow up clinic post discharge
  - evaluate “shared-care” follow up with intensivist and diabetologist after discharge from ICU

Summary

1. Hyperglycaemia associated with increased mortality
   - In those without diabetes
   - Intervention studies have **not** consistently supported euglycaemic targets, particularly in those with diabetes
2. Current guidelines for glycaemic control in ICU
   - < 10 mmol/L; avoid hypoglycaemia
   - ?role novel treatment
3. Critical illness associated hyperglycaemia vs. pre-existing diabetes
   - Stress hyperglycaemia is likely to predict those at risk of incident diabetes
   - May identify group for primary prevention/screening
   - Glucose continuum - individualise glycaemic targets for those with diabetes

Table 1 Prevalence of diabetes in hospital population (chronological order)

Ref.	Year	R-D	UR-D	Total study patients	Location	Diabetes diagnosed by	Unrecognised diabetes diagnosed by
Umpierrez *et al*[14]	2002	495 (26%)	223[1] (12%)	1886	Atlanta, United States	Admission history	Fasting blood glucose ≥ 7 mmol/L Random blood glucose ≥ 11.1 mmol/L × 2
Wallymahmed *et al*[15]	2005	126 (11%)	13[1] (1%)	1129	Liverpool, United Kingdom	Admission history Hospital records	Random blood glucose ≥ 11.1 mmol/L
Wexler *et al*[17]	2008	136 (19%)	33 (5%)	695	Boston, United States	Admission history Hospital records	HbA1c > 6.5
Mazurek *et al*[18]	2010	342 (35%)	152 (16%)	971	New York, United States	Admission history Hospital records Medication review	HbA1c ≥ 6.5
Feldman-Billard *et al*[16]	2013	355 (17%)	156[1] (7%)	2141	Multicentre (France)	Admission history	Fasting blood glucose ≥ 7 mmol/L

[1]May include patients with stress hyperglycaemia/critical illness associated hyperglycaemia. R-D: Recognised diabetes; UR-D: Unrecognised diabetes.

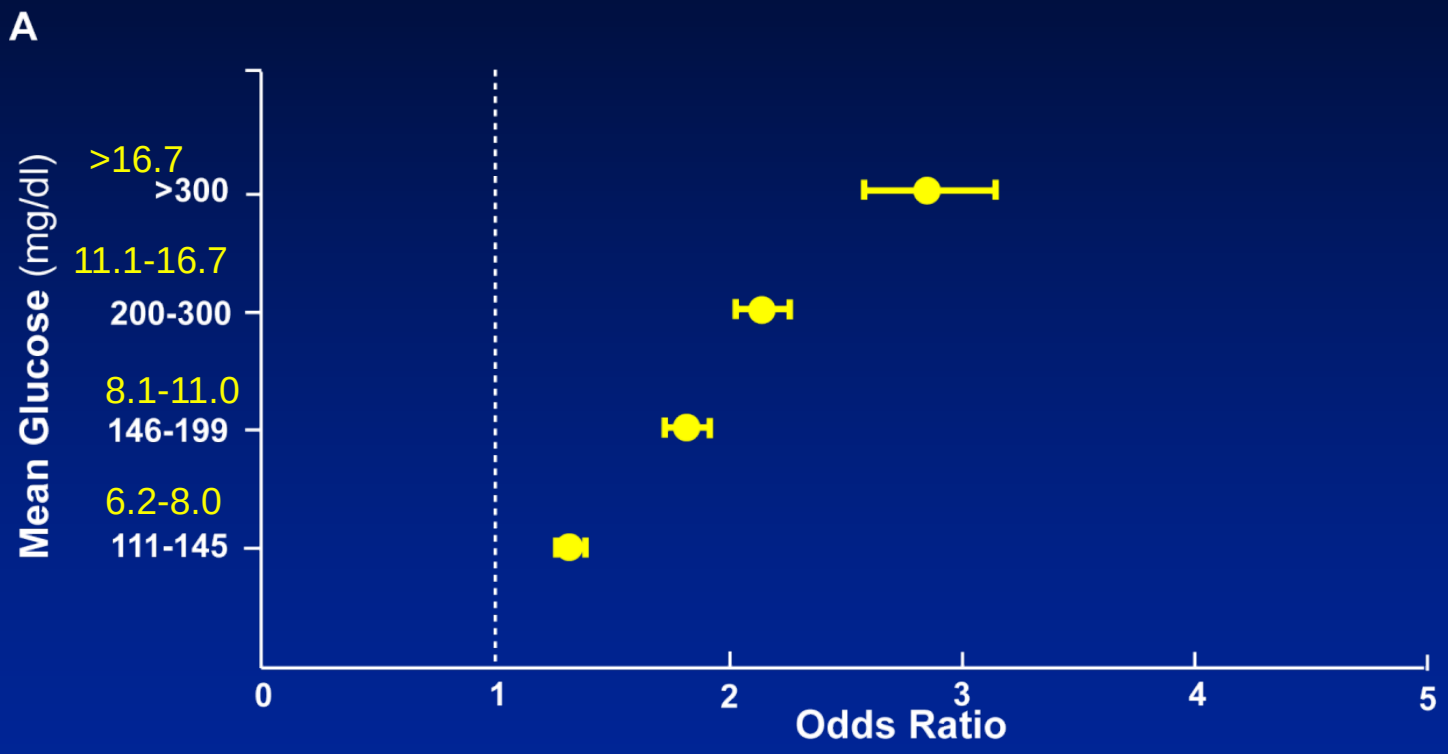
Table 2 Prevalence of diabetes in the intensive care unit population (chronological order)

Ref.	Year	Study type	R-D	UR-D	Total study patients	Location	Recognised DM diagnosis	Unrecognised diabetes diagnosed by
Van den Berghe *et al*[36]	2001	Interv	204 (13%)	N/A	1548	Leuven, Belgium	Admission history	N/A
Finney *et al*[27]	2003	Observ	86 (16%)	N/A	523	London, United Kingdom	Unknown	N/A
Whitcomb *et al*[23]	2005	Observ	574 (21%)	395[1] (15%)	2713	Baltimore, United States	Admission history	Hyperglycaemia without a history of DM
Van den Berghe *et al*[37]	2006	Interv	203 (17%)	N/A	1200	Leuven, Belgium	Admission history	N/A
Krinsely[24]	2006	Observ	1110 (21%)	N/A	5365	Stamford, United States	Hospital records (ICD-9 codes) for the first 2 yr then all available info	N/A
Egi *et al*[28]	2008	Observ	728 (15%)	N/A	4946	Multicentre (Australia)	Hospital records	N/A
Treggiari *et al*[25]	2008	Observ	1361 (13%)	N/A	10456	Seattle, United States	Hospital records	N/A
Arabi *et al*[39]	2008	Interv	208 (40%)	N/A	523	Riyadh, Saudi Arabia	Admission history Hospital records	N/A
Bronkhurst *et al*[38]	2008	Interv	163 (30%)	N/A	537	Multicentre (Germany)	Unknown	N/A
Del La Rosa *et al*[42]	2008	Interv	61 (12%)	N/A	504	Medellin, Colombia	Admission history	N/A
Finfer *et al*[41]	2009	Interv	1211 (20%)	N/A	6029	Multicentre (Australia, NZ, Canada)	Admission history	N/A
Preiser *et al*[40]	2009	Interv	203 (19%)	N/A	1078	Multicentre (Europe)	Admission history	N/A
Falciglia *et al*[26]	2009	Observ	77850 (30%)	N/A	259040	Multicentre (United States)	Hospital records (ICD-9 codes)	N/A
Stegenga *et al*[30]	2010	Observ	188 (23%)	N/A	830	Multicentre (Worldwide)	Admission history	N/A
Hermanides *et al*[29]	2010	Observ	699 (12%)	N/A	5961	Amsterdam, Netherlands	Hospital records (computerised system)	N/A
Krinsely *et al*[33]	2011	Observ	669 (21%)	N/A	3263	Multicentre (United States, Europe)	Hospital records (ICU clinical database)	N/A
Krinsley *et al*[32]	2013	Observ	12880 (29%)	N/A	44964	Multicentre (Worldwide)	Admission history	N/A
Plummer *et al*[34]	2014	Observ	220 (22%)	55 (6%)	1000	Adelaide, Australia	Admission history Phone call to GP HbA1c ≥ 6.5	HbA1c ≥ 6.5 without a history of DM

[1]May include patients with stress hyperglycaemia/critical illness associated hyperglycaemia. Interv: Interventional; Observ: Observational; R-D: Recognised diabetes; UR-D: Unrecognised diabetes; NZ: New Zealand; N/A: Not available.

Kar P et al World Journal Diabetes 2015

Hyperglycaemia and mortality



n = 259,040

Falciglia, et al. Crit Care Med (2009)

Leuven surgical trial

- Mean age 63 years; 71% males; post-cardiac surgery (63%)
- Mean BSL 5.7 mmol/L (IIT) vs 8.5 mmol/L (conventional)
- Reduction ICU and in-hospital mortality
  - especially for those in ICU > 5 days
  - critical illness polyneuropathy, acute renal failure, transfusion, bacteraemia
- Hypoglycaemia (BSL < 2.2 mmol/L): 5.1 vs 0.8%

Van den Berghe, et al. NEJM (2001)

Table 1

Hospital use of native GLP-1 in medical and surgical patients and GLP-1RAs in critical care

Hospital use of native GLP-1 in medical and surgical patients

Author	Design	Population, *n*	Intervention	Findings	Adverse events
Nikolaidis 2004 (15)	Single-center, nonrandomized controlled pilot study	Acute MI and LV systolic dysfunction	72-h IV GLP-1 (1.5 pmol/kg/min) following successful angioplasty	GLP-1 improved LV function and global wall motion scores indices	GLP-1 group: nausea ($n = 4$), vomiting ($n = 2$), constipation ($n = 2$), reduced appetite ($n = 3$);
		GLP-1, $n = 10$ (DM = 5) Control subjects, $n = 11$ (DM = 4)	Control subjects received standard therapy alone	No differences in glucose between groups	Hypoglycemia: 2 events (52 and 58 mg/dL)
Meier 2004 (13)	Single-center, randomized, placebo-controlled trial	8 patients with T2D, 2–8 days postmajor surgery	8-h IV GLP-1 infusion (1.2 pmol/kg/min) vs. placebo	GLP-1 reduced BG levels, increased insulin, C-peptide ($P < 0.001$), and suppressed glucagon ($P = 0.041$)	No recorded hypoglycemic events or other adverse reactions
Sokos 2006 (17)	Single-center, open-label, nonrandomized pilot study	CHF on stable medications	6-week SC GLP-1 infusion, started at 1.25 pmol/kg/min for 1 week, followed for 4 weeks at 2.5 pmol/kg/min	GLP-1 improved LVEF, 6-min walk test, and improvement in BG compared with control subjects	GLP-1 group: nausea and constipation in 5 patients and increase in HR (~5 bpm);
		GLP-1, $n = 12$ (DM = 8) Control subjects, $n = 9$ (DM = 5)			Hypoglycemia: 9 episodes in 4 GLP-1 patients, 4 episodes in 2 control patients
Sokos 2007 (16)	Single-center, randomized, double-blind, placebo-controlled pilot study	Elective CABG; GLP-1, $n = 10$ (DM = 2)	48-h IV GLP-1 infusion started 12-h preoperative and continued for 48-h postoperative vs. standard IV insulin therapy	GLP-1 improved glycemic control pre- and intraoperatively, but no difference in postoperative period;	Rescue insulin therapy required in 5 GLP-1 subjects
		Insulin infusion, $n = 10$ (DM 3)		No group differences in LVEF at baseline, 48 h, or at discharge	Hypoglycemia: 1 event with GLP-1 (BG 43 mg/dL) and 2 with standard therapy (43 and 56 mg/dL)

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Müssig 2008 (14)	Single-center, randomized, open-label, controlled trial	Insulin-naive patients with T2D after elective CABG; GLP1, n = 10 (DM = 10) Insulin infusion, n = 10 (DM = 10)	12-h IV GLP-1 infusion (3.6 pmol/kg/min) after transfer from the operating room to the ICU vs. standard IV insulin therapy	Glycemic control was comparable in the 2 groups Higher insulin requirement in control group; Fewer insulin dose adjustments during hours 0–6 with GLP-1, but similar dose adjustments hours 6–12	Rescue therapy with insulin required for several GLP-1 patients; No adverse events or hypoglycemia reported
Halbirk 2010 (18)	Single-center, double-blinded placebo-controlled crossover design	Ischemic heart failure in non-DM subjects GLP-1, n = 10; Placebo, n = 10	48-h IV GLP-1 (1.0 pmol/kg/min) or placebo in random orders 14 days apart Infusion rate reduced 0.7 pmol/kg/min because of high frequency of hypoglycemia	GLP-1 had no effect on LVEF, diastolic function, exercise capacity, or regional myocardial contractile function GLP-1 resulted in 9 episodes of hypoglycemia in 8 patients (nadir 40 mg/dL) vs. no hypoglycemia in placebo group	Nausea and vomiting in half of GLP-1 group

Hospital use of GLP-1RAs in critical care

Author	Design	Population, n	Intervention	Findings	Adverse events
Abuannadi 2013 (20)	Single-center, nonrandomized open-label, pilot study	T2D in cardiac ICU Exenatide, n = 40 (DM = 40); Historic control subjects treated with insulin infusion (n = 133)	24–48-h IV exenatide infusion (0.025 μg/min)	No differences in mean steady-state BG between exenatide and IV insulin therapy	Nausea with exenatide; 6 patients (15%) excluded because of severe nausea; Hypoglycemia reported in 10% with exenatide and 15–20% during insulin infusion
Mecott 2010 (19)	Single-center, open-label, controlled study	Severely burned pediatric patients in a burned unit SC exenatide, n = 6; insulin infusion (n = 18)	SC exenatide 5–10 μg every 12 h vs. IV or SC insulin therapy	No differences in mean steady-state BG or glycemic variability between exenatide and insulin; Lower insulin requirement in the exenatide group	Hypoglycemia 0.38 events/patient/month in each group

DM, diabetes; HR, heart rate; LV, left ventricular; LVEF, left ventricular ejection fraction; MI, myocardial infarction; T2D, type 2 diabetes.

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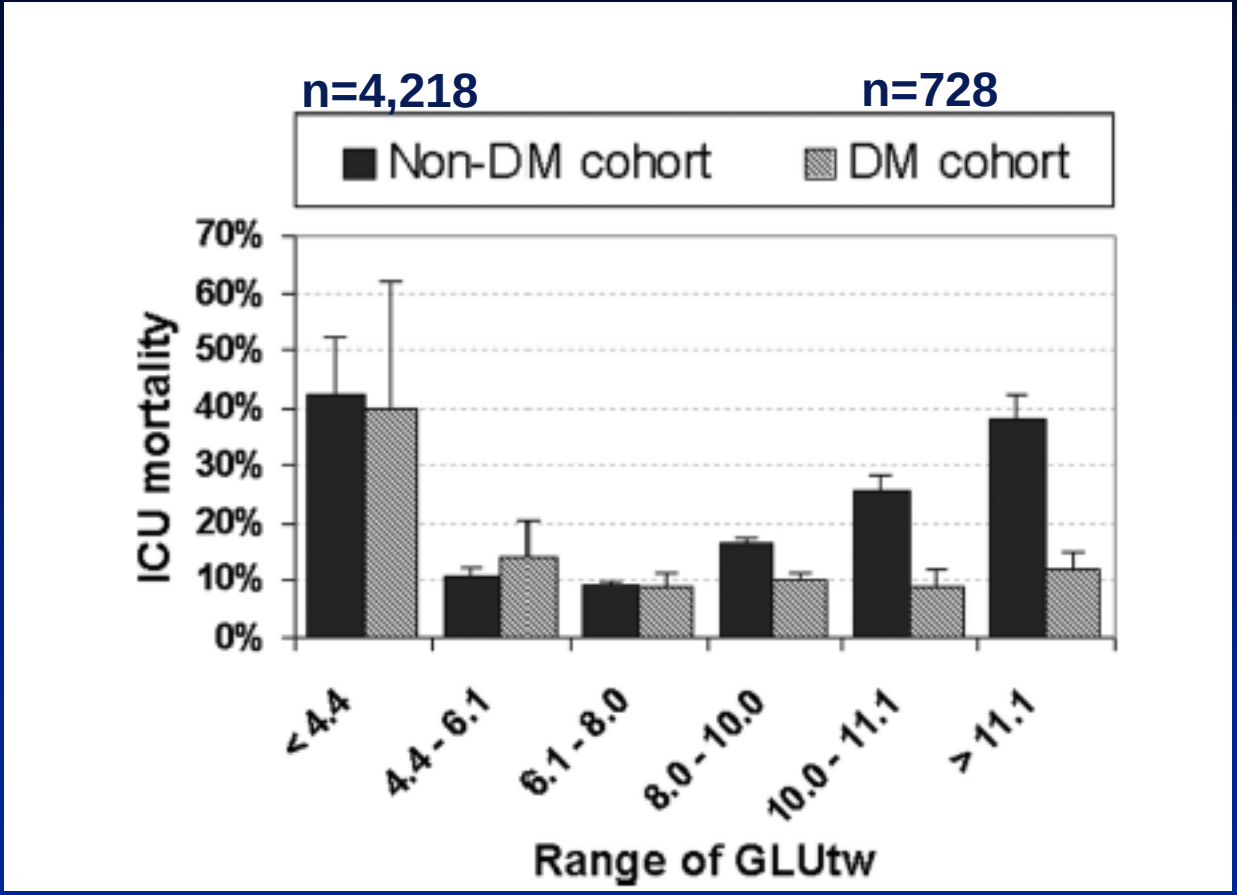
Hyperglycaemia mortality T2DM



Blood glucose (mmol/L time weighted)

Egi, et al. Crit. Care Med (2008)