Glycaemic control in ACS

Will TITAN-ACS answer the question?

Maggie Sinclair Hammersley
Consultant Physician
Oxford University Hospitals

In collaboration with Dr John Birkhead, Chair MINAP

On behalf of: Trial of Intravenous Insulin Therapy to Achieve Normoglycaemia in ACS Steering Group

Outline

- Hyperglycaemia in ACS
  - Prevalence
  - Mortality and morbidity
  - Hyperglycaemic harm in ACS
  - Mechanisms of harm
- Evidence from interventional trials
- Oxford pilot of VRIII
- TITAN-ACS
  - Aims
  - Methods
  - Results

Background

- 85% of patients presenting with ACS have some degree of dysglycaemia at presentation
- The admission blood glucose level is a powerful predictor of in-hospital morbidity and mortalit
- For a 1 mmol/L increase in blood glucose above the normal range there is a
  - 4% increase in mortality patients with no known diabetes
  - 5% for known patients with diabetes

1.Stranders I, et al. Admission blood glucose level as risk indicator of death after myocardial infarction in patients with and without diabetes mellitus. Arch Intern Med 2004;164:982–8.

Prevalence of hyperglycaemia in ACS

- **20% ≥ 11.0 mmol/L**
  - **(20% raised HbA1c)**

  Oswald & Yudkin. *Diabetes Medicine* 1987

- **25% > 9.4 mmol/L**
  - **(22% self-reported diabetes)**

  Petursson *et al. Int J Cardiol* 2007

- **19.8% 9.6-13.3 mmol/L (42% known DM)**
  20.5% > 13.3 mmol/L (74% known DM)

  Kosiborod *et al. Circulation* 2005

- **16.4% 7.88-9.27 mmol/L**
  16.7% > 9.27 mmol/L

  Kadri *et al. Heart* 2006

- **9.9% troponin-positive ≥ 11.1 mmol/L**
  - (excluding self-reported DM)

  Weston *et al. Heart* 2007

Determinants and importance of stress hyperglycaemia in non-diabetic patients with myocardial infarction

G A OSWALD, C C T SMITH, D J BETTERIDGE, J S YUDKIN

No	311
Age (SD)	64·9 (11·9)
No (%) of women	86 (27·7)
No (%) who died with plasma glucose concentrations (mmol/l) on admission of:	
<8	12/112 (10·7) CI 5·0 - 16·4%
8-11	13/52 (25·0) CI 12·2 - 36·8%
>11	13/21 (61·9) CI 41·1 - 82·7%
χ^2	29·27 p<0·001
Kendall τ -c	0·285 p<0·001
No (%) who died with no plasma glucose estimation	36/126 (28·6) CI 20·7-36·5%

HbA1C <6.9%

Admission Glucose and Mortality in Elderly Patients Hospitalized With Acute Myocardial Infarction

Implicatic (*Circulation*. 2005;111:3078-3086.) **)iabetes**

Mikhail Kosiborod, MD; Saif S. Rathore, MPH; Silvio E. Inzucchi, MD; Frederick A. Masoudi, MD; Yongfei Wang, MS; Edward P. Havranek, MD; Harlan M. Krumholz, MD, SM

After multiple adjustments, raised admission glucose is associated with a graded increased mortality risk in patients not known to have DM

In contrast only very high levels of admission BG are associated with increased risk in known diabetes

n = 14,1680 (30.4% diabetes)

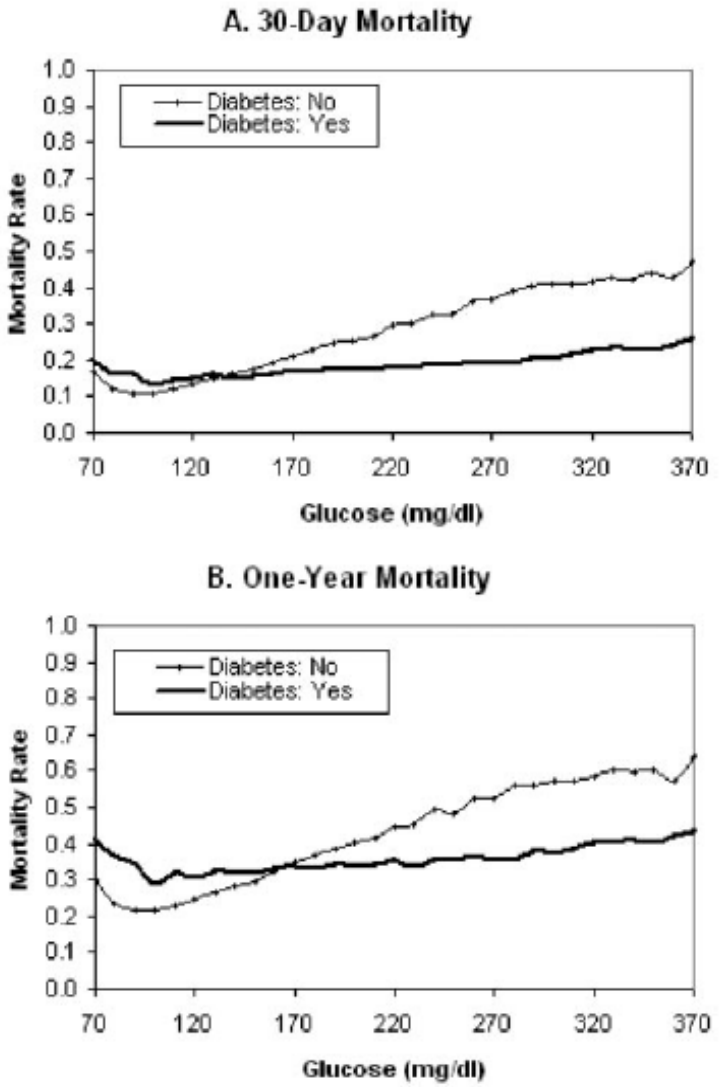
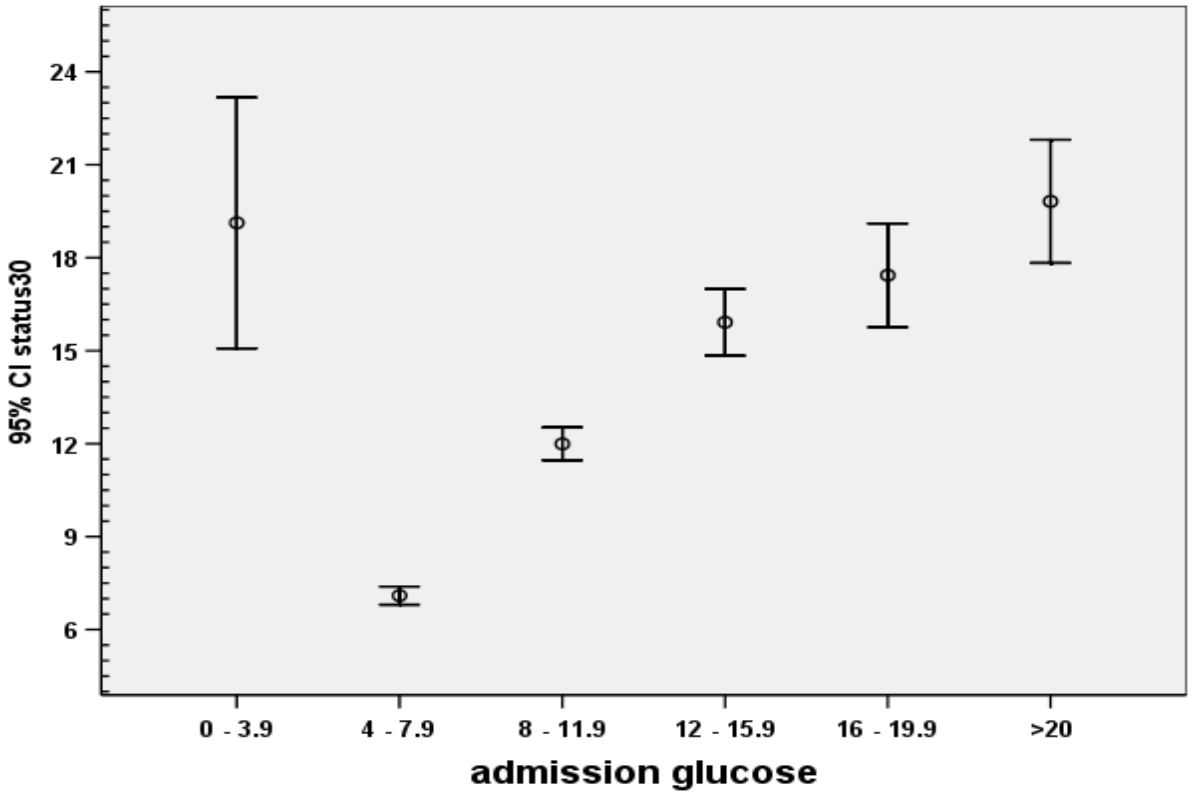


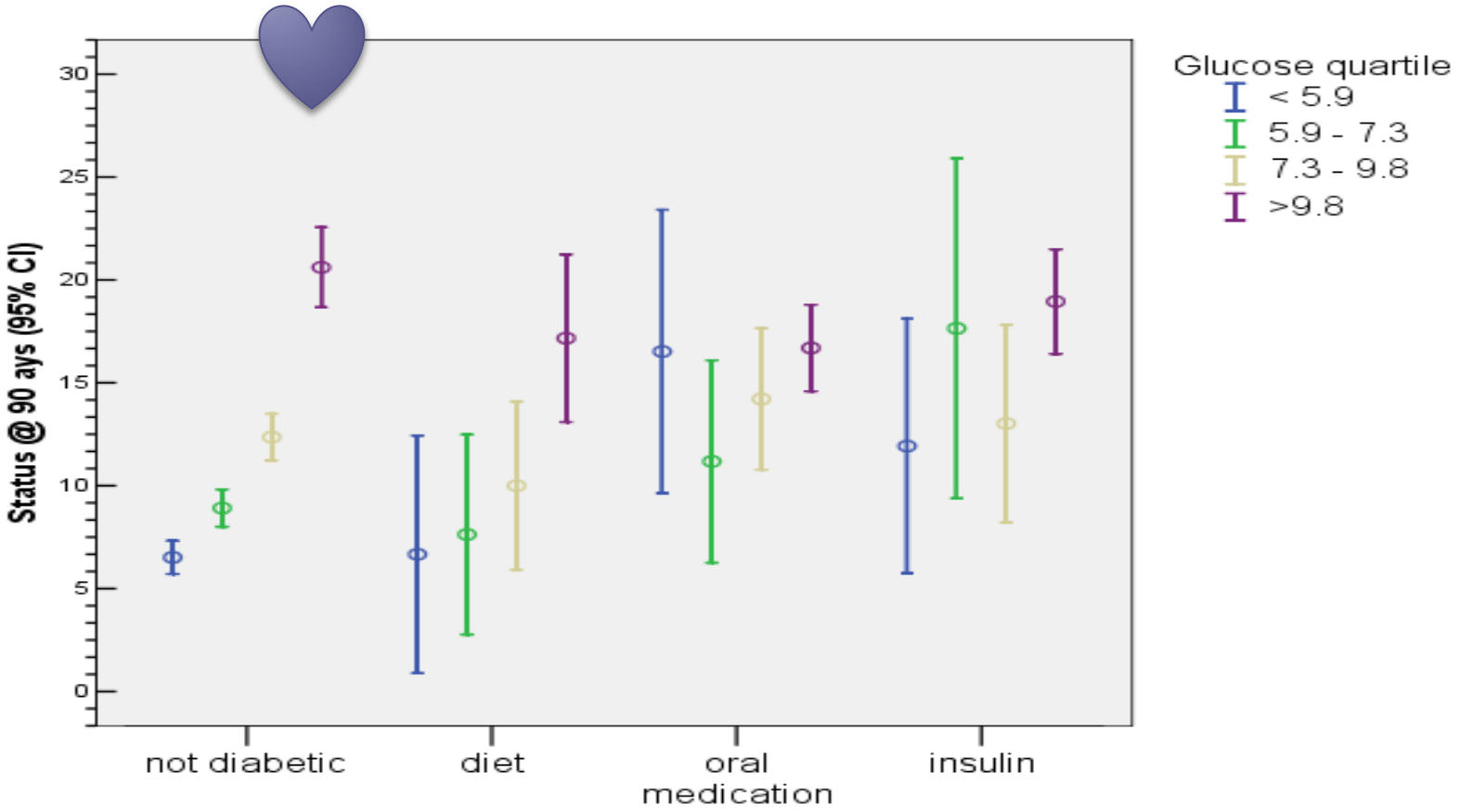
Figure 4. Direct comparison of risk-adjusted 30-day mortality (A) and 1-year mortality (B) in patients with and without recognized diabetes across range of glucose values.

30 day Mortality MINAP database 2007



Mortality at 90 days after ACS

diabetes = 4500, not known diabetes =14500



MINAP RCP website 2005

Mechanisms of hyperglycaemia harm in ACS

- Predicts incomplete resolution of ST elevation after thrombolysis
  - L'Hullier *et al.* Am J Cardiol 2006
- Is associated with poor flow in infarct-related artery before primary PCI (unlike HbA1c or DM)
  - Timmer *et al.* J Am Coll Cardiol 2005
- Is associated with the 'no-reflow' phenomenon after successful primary PCI
  - Iwakura *et al.* J Am Coll Cardiol 2003
  - Ishihara *et al.* Am Heart J 2005
  - Shen *et al.* Chin Med J 2006
  - esp if the glucose level remains elevated (≥ 8.9 mmol/L) through the first 24 hrs
    - Kosuge *et al.* Circ J 2005

Possible mechanisms for glucose ‘toxicity’

- Prolongation of QT interval
  - Marfella *et al.* Diabetologia 2000
- Impaired ischaemic preconditioning
  - Kersten *et al.* Am J Physiol 2000
  - Ebel *et al.* Pflugers Arch 2003
  - Ishihara *et al.* Am J Cardiol 2003
- Reduced effectiveness of collaterals
  - Kersten *et al.* Am J Physiol 2001

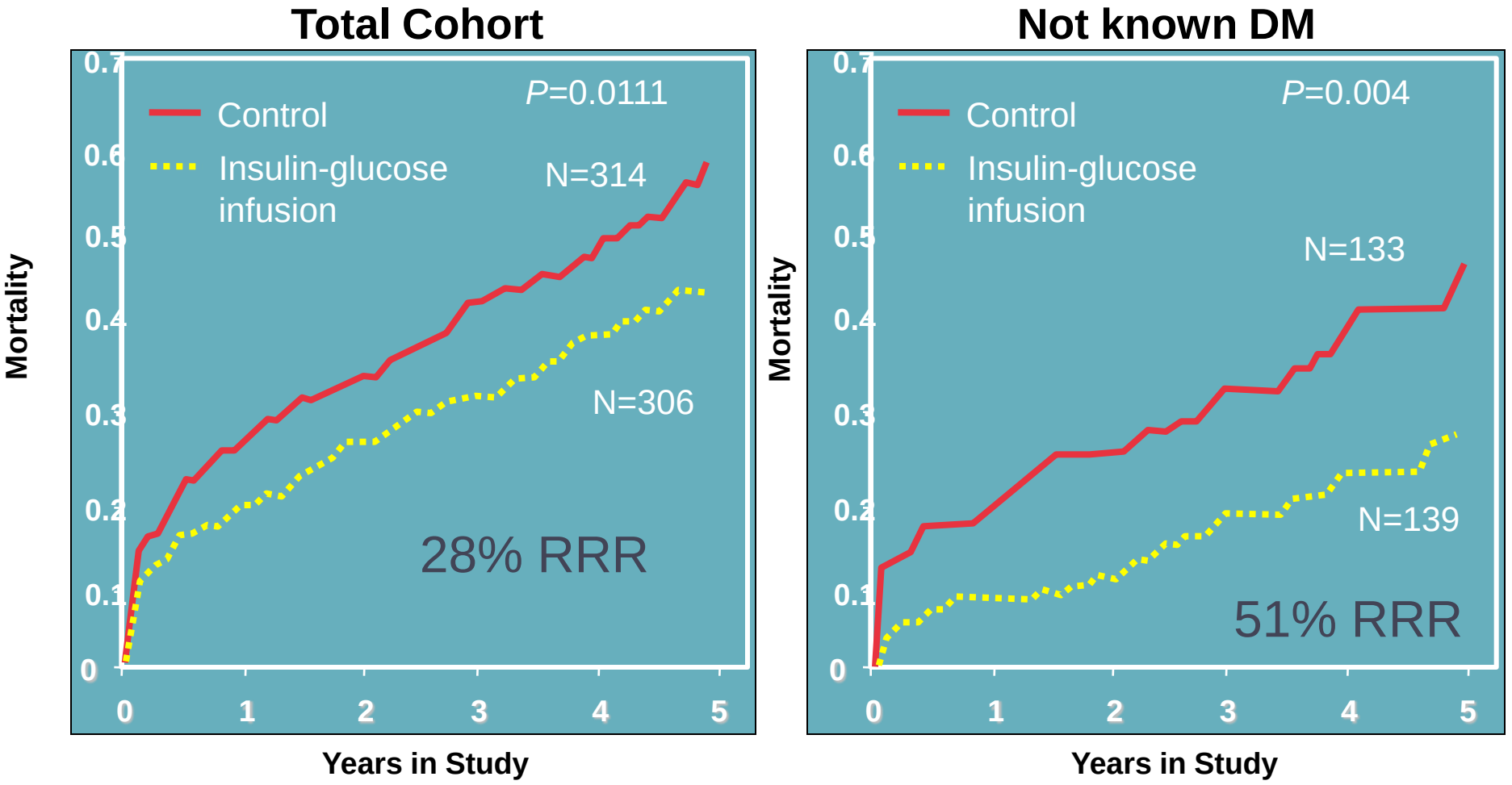
Intravenous insulin treatment

	Insulin infusion	GIK (Glucose-Insulin-Potassium)
Underlying aim	Reduce toxic effects of hyperglycaemia	Suppression of FFA utilisation and provision of glucose to myocytes
Focus	‘Glycaemic focus’	‘Insulin focus’
Insulin infusion rate	Variable related to blood glucose level	Predetermined by protocol
Effect on glucose level	Rapid reduction	Variable - and not of primary concern

Trial Glycaemic focus	n	% non-diabetes	Admission glucose (mmol/L)	Achieved glucose during infusion (mmol/L)	Difference in achieved glucose (C - I)
DIGAMI-1 [1]	620	11%	I: 15.4 C: 15.7	I: 9.6 at 24 hr C: 11.7 at 24 hr	2.1 mmol/L at 24 hr
DIGAMI-2 [2]	1253		Ii: 12.8 Iii: 12.5 C: 12.9	Ii: 9.1 at 24 hr Iii: 9.1 at 24 hr C: 10.0 at 24 hr	0.9 mmol/L at 24 hr (no difference between intervention groups)
HI-5 [3]	240	51.7%	I: 10.8 C: 11.1	I: 8.3 at 24 hr C: 9.0 at 24 hr	0.7 mmol/L at 24 hr
Insulin focus					
CREATE-ECLA [4]	20,201	I: 82.4% C: 82.2%	I: 9.0 C: 9.0	I: 10.4 at 6 hr 8.6 at 24 hr C: 8.2 at 6 hr 7.5 at 24 hr	–1.8 mmol/L at 6 hr – 0.7 mmol/L at 24 hr

[1] Malmberg *et al* Circulation 1999 [2] Malmberg *et al* Eur Heart J 2005
[3] Cheung *et al* Diabetes Care 2006 [4] CREATE-ECLA JAMA 2006

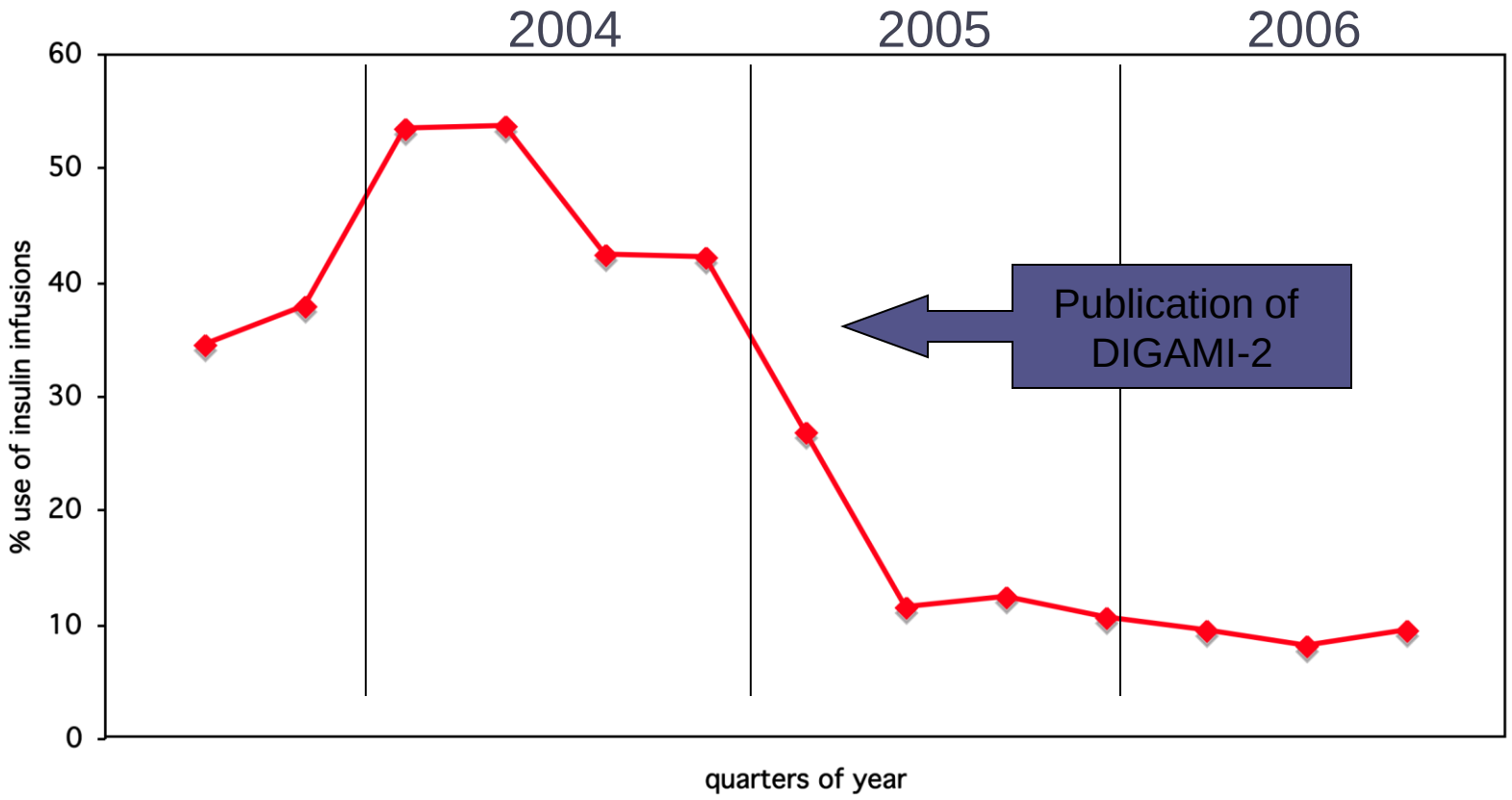
DIGAMI: Intensive glycaemic control included IV insulin for 48 hr and s.c. insulin qid for 3 months



DIGAMI=Diabetes Mellitus, Insulin Glucose Infusion in Acute Myocardial Infarction.

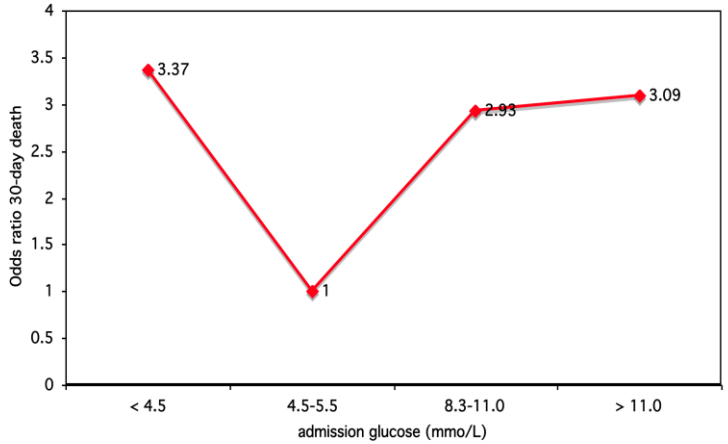
Malmberg K et al. *BMJ.* 1997;314:1512-1515.

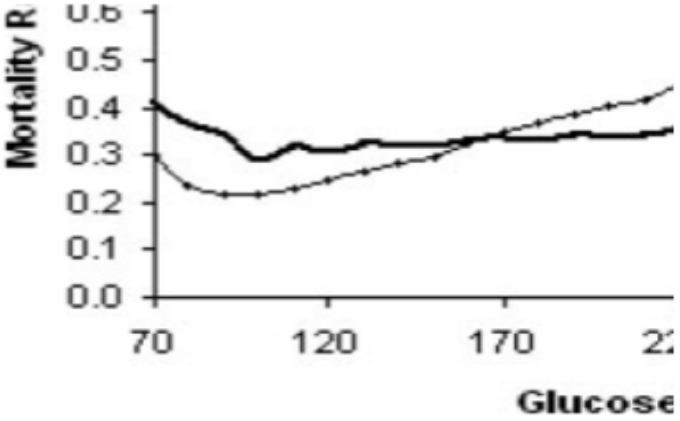
MINAP Use of an insulin infusion in non-diabetes with admission glucose ≥ 11.1 mmol/L



Myocardial Ischaemia National Audit Project (MINAP) database

Hypoglycaemia in ACS (<3.0 mmol/L)





Odds ratio of 30-day mortality in diabetes/non-diabetes with STEMI

Pinto *et al* J Am Coll Cardiol 2005

With nSTEMI associated with increased 2 yr mortality (increased hazard ratio of 1.93)

Svensson *et al* Eur Heart J 2005

What was happening in UK? ABCD audits

- 2007 Sampson audit of inpatient care (MI care)
  - Use of 'DIGAMI protocol' in 177/223(79%) responding centres
  - 39% of centres stated that 'negative results' of DIGAMI-2 had altered practice
  - Interpreted as 60% had never used DIGAMI (? = insulin) or altered practice after DIGAMI 2
- 2008 ABCD ACS audit
  - 4 centres
  - Norwich, Portsmouth, Oxford and Herts
  - Widely different practice

Current guidelines

- Evidence of improved outcomes with treatment of hyperglycaemia remains thin on the ground and uncertainty still prevails
- In the absence of robust evidence to guide clinical practice the current consensus guidelines recommend the use of intravenous insulin in the first 24-48 hours to reduce hyperglycaemia

It became apparent……

- There was little guidance about the optimal method to lower blood glucose in ACS.
- Data from the Myocardial Ischaemia National Audit Project (MINAP) shows that many patients with ACS and dysglycaemia are commenced on a VRIII for the first 24 hours
- There is no current standardised methodology for administering a safe and effective VRII for patients with ACS in UK hospitals.

NICE CG 130

NHS
National Institute for
Health and Clinical Excellence

Hyperglycaemia in acute coronary syndromes

Management of hyperglycaemia in acute coronary syndromes

Issued: October 2011

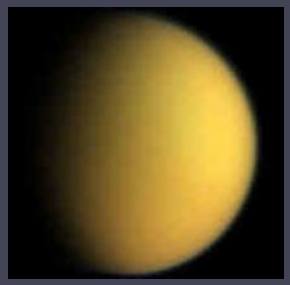
1 Recommendations

Managing hyperglycaemia in inpatients within 48 hours of ACS

Recommendations in this section partially update recommendation 1.12.3.6 in 'Type 1 diabetes'. Recommendation 1.12.3.6 is updated for the treatment of patients with threatened or actual myocardial infarction, but not stroke.

1.1.1 Manage hyperglycaemia in patients admitted to hospital for an acute coronary syndrome (ACS) by keeping blood glucose levels below 11.0 mmol/litre while avoiding hypoglycaemia. In the first instance, consider a dose-adjusted insulin infusion with regular monitoring of blood glucose levels.

1.1.2 Do not routinely offer intensive insulin therapy (an intravenous infusion of insulin and glucose with or without potassium) to manage hyperglycaemia (blood glucose above 11.0 mmol/litre) in patients admitted to hospital for an ACS unless clinically indicated.



MINAP and ABCD Collaborative ACS and Hyperglycaemia Audit The TITAN-ACS Study

Evaluating the effectiveness of an intensified intravenous insulin infusion to achieve normoglycaemia in patients admitted with acute coronary syndrome and hyperglycaemia: An Observational Study

Dr John Birkhead
Dr Maggie Sinclair Hammersley

TITAN-ACS Patients

- The study group determined, on the basis of evidence from the MINAP database to limit recruitment to those patients presenting with an admission glucose ≥ 10mmol whether known to have diagnosed diabetes or not.
- Patients were excluded if
  - Had severe non cardiac co-morbidities and a prognosis of 6 months or less
  - Patients had complex metabolic disorders likely to have an impact on glycometabolic control eg Cushings disease
  - Pregnant females

TITAN-ACS AIMS

- To identify and treat at the earliest opportunity all patients having troponin positive ACS presenting with an admission glucose ≥10 mmol (approximately 15% of all ACS).
- To evaluate effectiveness of an intravenous insulin regime with concomitant dextrose and potassium infusion for patients with ACS presenting with an admission glucose of ≥ 10 mmol.
- To use the information derived from these data develop a guideline for management of hyperglycaemia that would be applicable for use nationally.

TITAN-ACS Primary Outcomes

- To confirm that use of a standardised insulin regime
- Was effective in achieving normoglycaemia – time to reach 8 mmol
- Was effective in maintaining normoglycaemia
  - Mean BG within target range throughout 24 hour period.
- Was not associated with
  - Increased frequency of either mild hypoglycaemia BG < 4mmol or moderate hypoglycaemia BG < 3 mmol
  - Hypokalaemia +/- excess arrythmias

Secondary Outcomes

- To use the MINAP audit data to examine whether there was a mortality benefit for those receiving a standardised intravenous insulin regime titrated to achieve normoglycaemia
- Comparison of treated and untreated hyperglycaemic patients using matched propensity analyses with analyses performed separately for those with known diabetes and those without diagnosed diabetes
- Comparison of outcome for groups of hospitals based on previous insulin use, before and after introduction of the insulin regime.
- Comparison of mortality between patients receiving the standardised insulin infusion within 0-4, 4-8 and ≥ 8 hours after onset of symptoms.

TITAN-ACS Methods

- Patients were recruited from 40/228 centres participating in the MINAP in England and Wales.
- This database collects comprehensive data on all patients presenting with troponin positive ACS.
- An additional dataset was developed to capture glucometrics for the participants of the TITAN-ACS study.
- All patients within the study received a validated VRIII and a low dose 5% dextrose infusion with potassium for the first 24 hours in hospital.

Oxford Pilot Protocol for VRIII

- 50 patients recruited with BG >8.0 mmol/L
- Only troponin positive patients were included
- Included known diabetes and stress hyperglycaemia
- Standardised variable rate intravenous insulin infusion was used and titrated to achieve normoglycemia
- Target glycaemic range defined as 4 to 8 mmol/L
- Intravenous infusion of 5-10% glucose with potassium at 15-30 ml/hr

Oxford Pilot Protocol Results

- 80% BG results over the 1st 24 hours were within the target range.
- Mean BG over the 1st 24 hours was 7.3mmol/L (SD = 1.37).
- No difference between the mean BG for patients on medical wards and those on CCU.
- Rates of hypoglycaemia were low
  - 2.53% rate of mild hypoglycaemia (3 - 4 mmol/L)
  - 0.63% rate of moderate hypoglycaemia (< 3 mmol/L).

TITAN-ACS Statistical analysis

- Adjusted all cause mortality data for insulin treated patients in those centres participating in TITAN.
- This group will be compared with patients in the remaining MINAP centres who are currently receiving 'standard treatment' which includes a large percentage of patients who do not receive any insulin treatment.
- Statistical analysis will be undertaken using a variety of techniques including matched historical controls from the same hospitals, and matched propensity analyses against contemporary untreated patients.
- Mortality outcome will be examined against a variety of indicators of glucometric control
- Mortality outcome will be examined against the delay from onset of symptoms to treatment with insulin.
- Mortality outcome will be examined against the delay from onset of symptoms to achievement of normoglycaemia (glucose < 8 mmol).

TITAN-ACS Data collection

- Data collected from patients presenting to CCUa with ACS (STEMI and NSTEMI) and admission blood glucose (BG) = and > 10 mmol/l.
- There will be no restriction in terms of severity of the presenting ACS, or of proposed treatment modality, including pPCI. Data items include:
  - Admission capillary glucose
  - Hourly capillary glucose measurements – as appropriate – up to 24 h.
  - Plasma potassium levels at admission, at the time of any arrhythmia, and at 24 hours.
  - HbA1c.

TITAN-ACS Exclusions

- Patients having severe non cardiac co-morbidities and a prognosis of 6 months or less
- Patients having complex metabolic disorders likely to have an impact on glycometabolic control eg Cushings disease
- Pregnant females

TITAN-ACS Patient characteristics

- All patients *known to have diabetes or not to have diabetes* with BG ≥ 10 mmol

With the following:

- Suspected acute coronary syndrome
- Dynamic ECG changes (ST elevation, ST depression, T wave inversion)
- Raised Troponin

ABCD
Association of British Clinical Diabetologists

Myocardial
Ischaemia
National
Audit
Project

Evidence of absence of harm

1. Mellbin LG, Malmber**g** K, Waldenström A, *et al.* Prognostic implications of hypoglycaemic episodes during hospitalisation for myocardial infarction in patients with type 2 diabetes: a report from the DIGAMI 2 trial. *Heart* 2009;**95**:721-7.

2. Kosiborod M, Inzucchi SE, Goyal A, *et al* Relationship between spontaneous and iatrogenic hypoglycemia and mortality in patients hospitalized with acute myocardial infarction. *JAMA.* 2009;**301**:1556-64.

Results Primary Outcomes

- Demographics
- Efficacy
- Safety

Demographics

Number of patients	744 (66% male)
Known DM:Not known	72:28 %
Admission BG	15.6 (5.09) mmol/L
nSTEMI:STEMI	404:311
Age nSTEMI:STEMI	70:66 yrs
Admission K^+	4.39 (0.64)
K^+ at 24 hours	4.29 (0.60)

Diabetes treatment on admission

Treatment	Frequency	Percent
Not known DM	211	28.4%
Diet only	62	8.3%
OHs	284	38.2%
Insulin	148	19.9%
Insulin + OHs	31	4.2%

Achieved glucose 6 hours in TITAN-ACS

		SerumGlucose	@5hours	@6hours
N	Valid	741	587	560
	Missing	16	170	197
Mean		15.373	8.999	8.874
Std. Deviation		5.5735	3.8013	3.8518
Percentiles	25	11.300	6.200	6.200
	50	14.000	8.400	8.200
	75	18.000	10.800	10.900

DIGAMI 1

Admission glucose was 15.4 mmol/L SD 4.1,
6 hour glucose was 7.1 mmol/L SD 3.1,

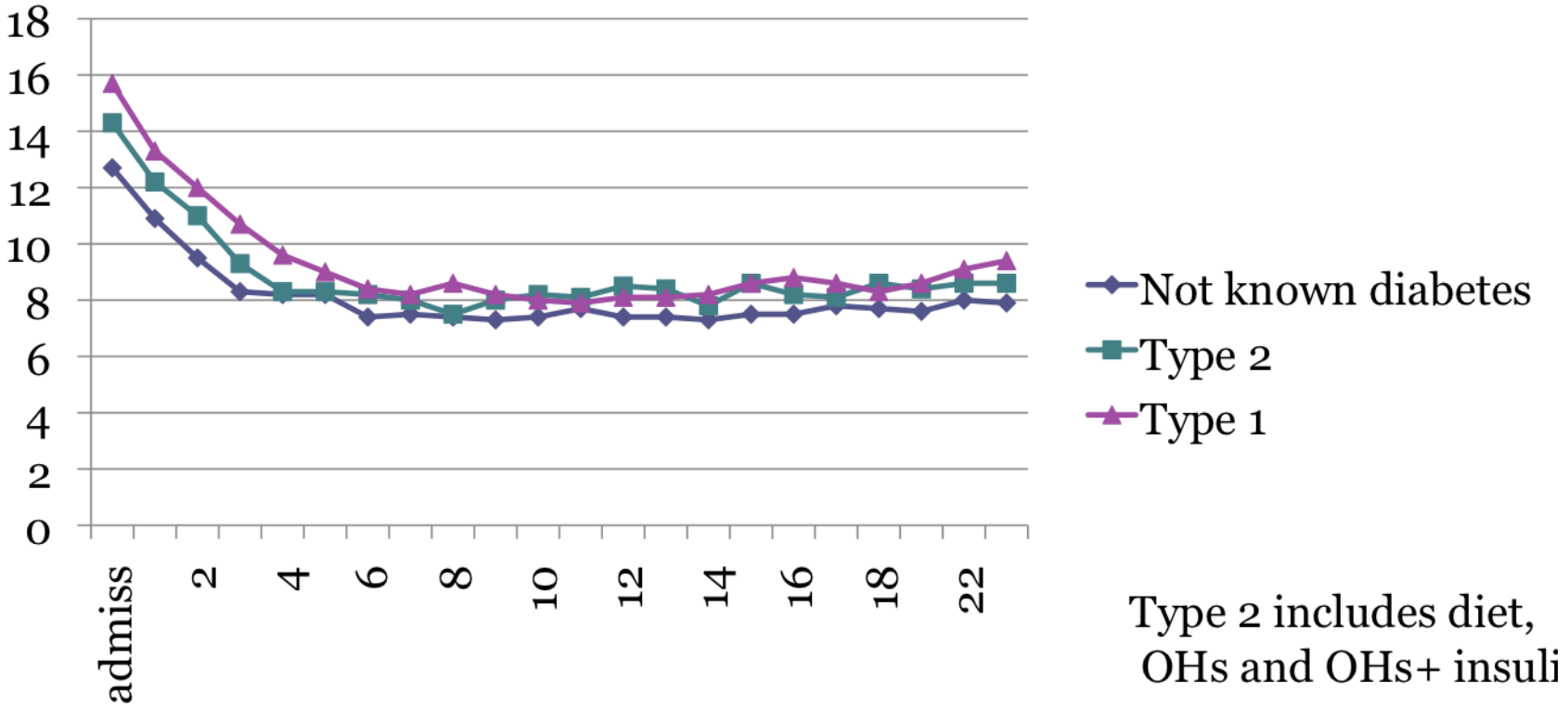
Achieved glucose at 24 hours TITAN-ACS

		@22hours	@24hours
N	Valid	389	440
	Missing	368	317
Mean		9.241	9.313
Std. Deviation		3.7365	3.6920
Percentiles	25	6.500	6.500
	50	8.600	8.400
	75	11.200	11.400

DIGAMI 1

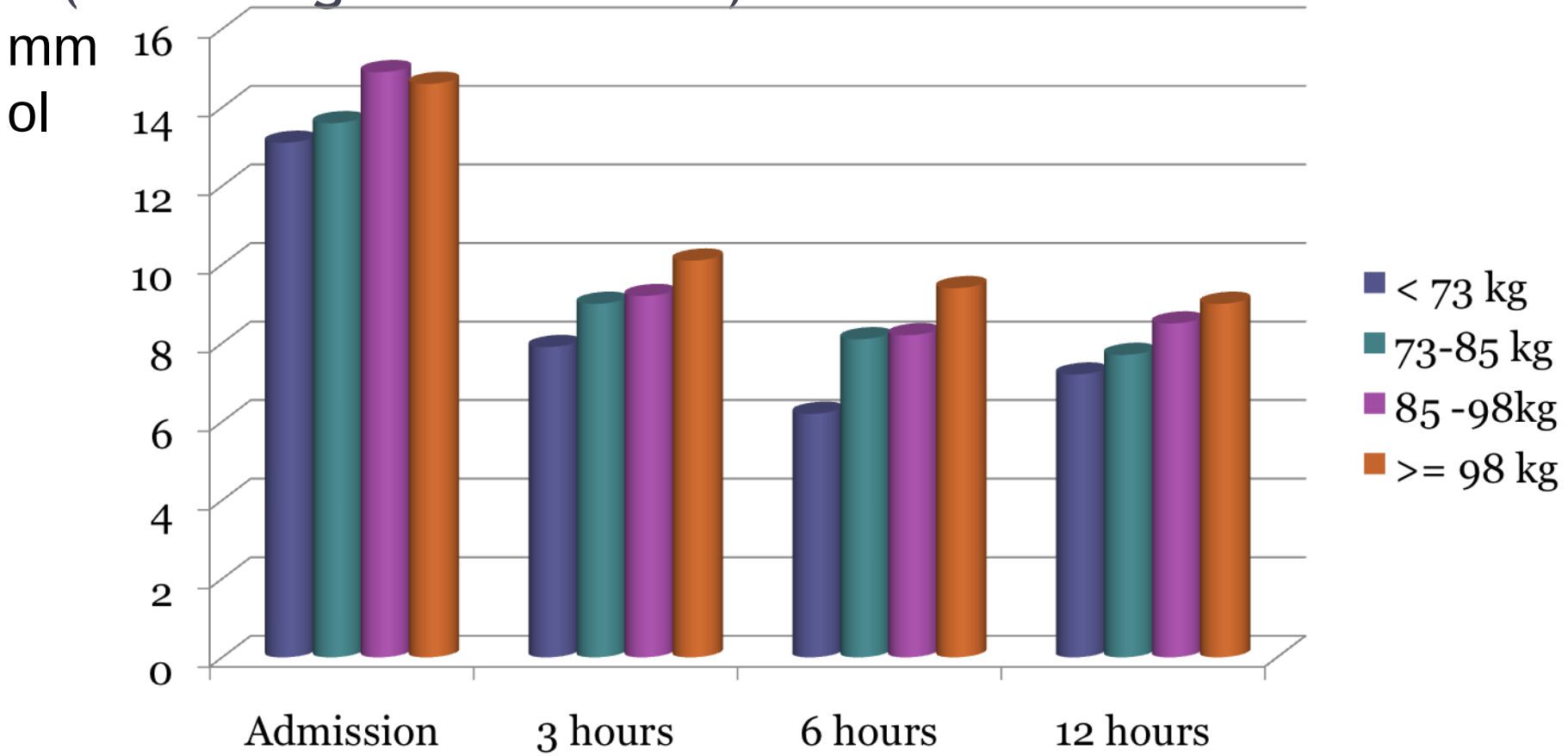
24 hour mean BG was 9.1 mmol,

Median glucose values during TITAN regime



Type 2 includes diet, OHs and OHs+ insuli

Response to insulin in relation to body weight (median glucose values)



Complications of VRIII

Complications of VRIII	Numbers (%)
Mild hypoglycaemia (3-4 mmol/L)	129 (16.3)
Moderate hypoglycaemia (<3mmol/L)	33 (4.3)
Arrhythmias	60 (12.4)

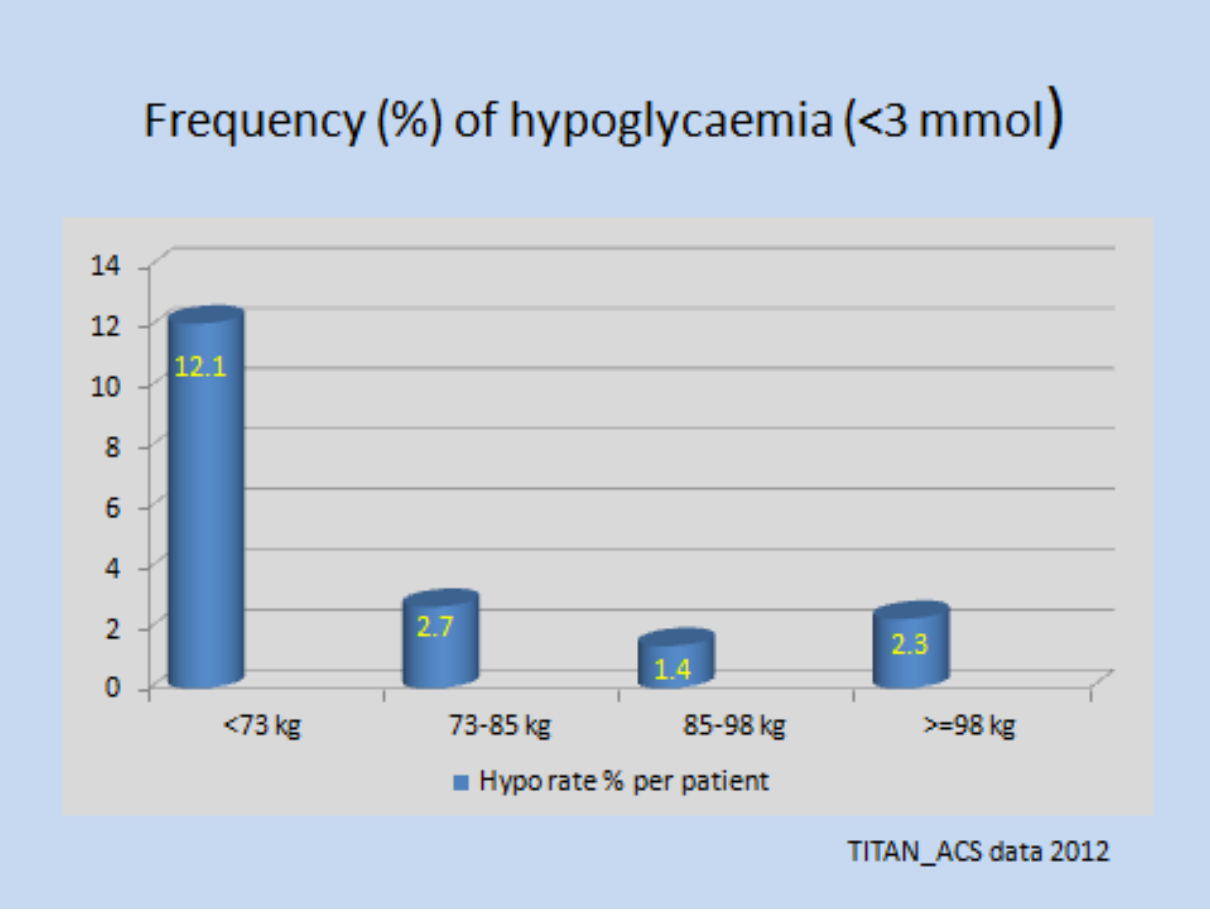
Moderate hypoglycaemia in TITAN-ACS

- 4.4 % (33 patients) had BG < 3 mmol/L
  - 22 had single episode
  - 6 had 2 episodes
  - 5 had 3 episodes
- There were no in-hospital deaths in the hypoglycaemic group

Hypoglycaemia rates (< 3.0 mmol/L) in major ACS trials

Trial	Number in trial	Hypo rates in %
DIGAMI-1	620	15
DIGAMI-2	1253	11.5
HI-5	240	10.3
TITAN-ACS	757	4.4

Hypoglycaemia rates by body weight



Hypokalaemia

Admission K^+ mmol/L	**4.4 (0.63)**
K^+ at 24 hours mmol/L	4.3 (0.60)

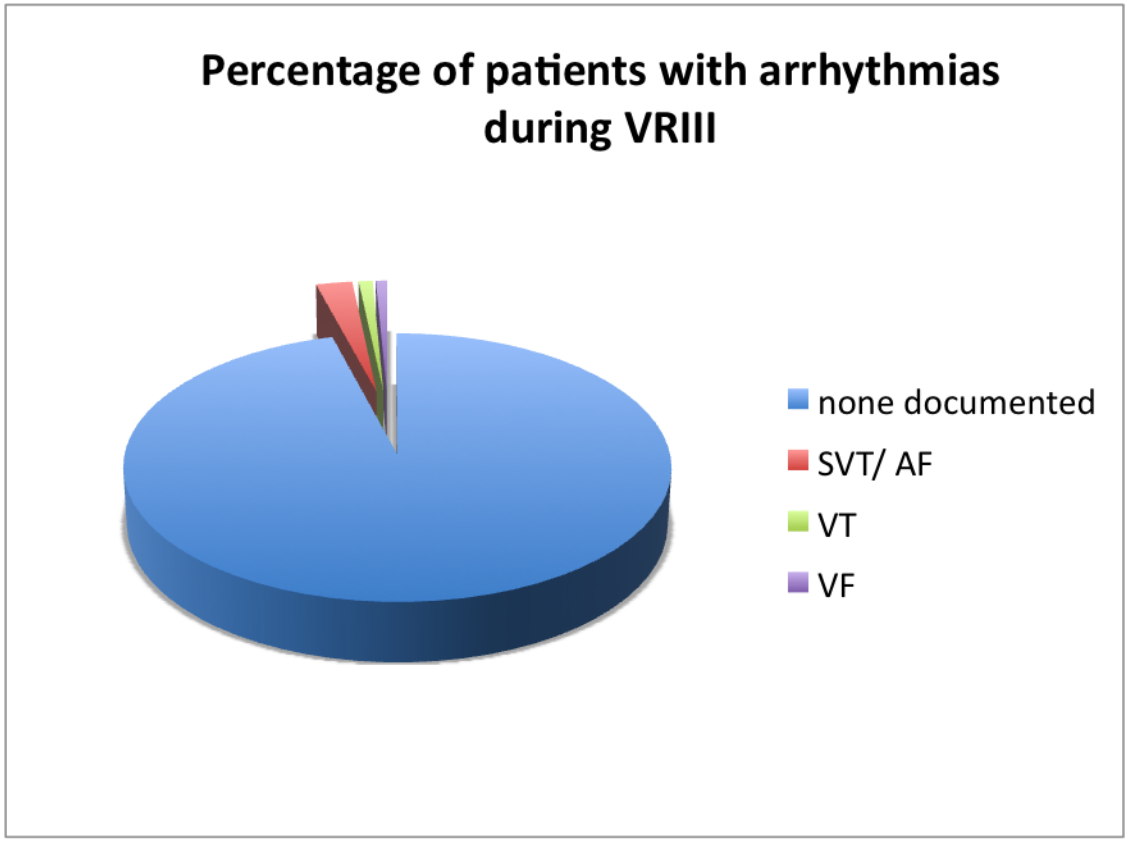
Admission K^+ and arrhythmia K^+ cross tabulation

		ArrhythmiaPotassium								Total
		2.2	3.1	3.3	3.6	3.7	3.8	3.9	4.0	
Admission Potassium	2.2	1	0	0	0	0	0	0	0	1
	3.1	0	3	0	0	0	0	0	0	3
	3.3	0	0	1	0	0	0	0	0	1
	3.6	0	0	0	2	0	0	0	0	2
	3.7	0	0	0	0	1	1	0	0	2
	3.8	0	0	0	1	0	2	0	0	3
	3.9	0	0	0	0	0	0	1	0	1
	4.0	0	0	0	0	0	0	1	2	3
	4.1	0	0	0	0	1	0	0	0	1
	5.3	0	0	0	0	0	1	0	0	1
Total		1	3	1	3	2	4	2	2	18

The above table shows that the potassium at the time of arrhythmia generally reflects the admission potassium and is not the product of the TITAN regime

Type of arrhythmia and admission K^+

		Arrhythmia				
		None	AF/SVT	VT	VF	Total
ArrhythmiaPotassium	2.2	0	0	1	0	1
	3.1	0	0	1	2	3
	3.3	0	0	0	1	1
	3.6	0	2	1	0	3
	3.7	0	1	1	0	2
	3.8	0	3	0	1	4
	3.9	0	2	0	0	2
	4.0	0	0	0	2	2
	4.1	0	2	1	0	3
	4.2	2	2	1	2	7
	4.3	0	2	0	4	6
	4.4	0	3	1	0	4
	4.6	0	1	1	0	2
	4.7	1	0	1	0	2
	4.8	2	1	0	0	3
	4.9	0	1	1	0	2
	5.0	0	1	1	0	2
	5.1	0	1	0	0	1
	5.2	0	1	1	0	2
	5.8	0	1	0	0	1
	6.0	0	1	1	0	2
	6.4	0	1	0	0	1
	6.5	1	0	0	0	1
Total		7	26	13	12	57


Percentage of patients with arrhythmias during VRIII
none documented
SVT/ AF
VT
VF

Admission K^+ and in-hospital deaths from ACS

		Frequency	Percent
Valid	3.0	1	2.9
	3.2	1	2.9
	3.6	1	2.9
	3.7	2	5.9
	3.8	1	2.9
	3.9	1	2.9
	4.0	2	5.9
	4.2	2	5.9
	4.3	2	5.9
	4.4	2	5.9
	4.5	2	5.9
	4.6	1	2.9
	4.7	2	5.9
	4.8	2	5.9
	5.0	2	5.9
	5.2	2	5.9
	5.5	1	2.9
	5.6	3	8.8
	Total	30	88.2
Missing	System	4	11.8
Total		34	100.0

Conclusions: Efficacy

- The standardised VRIII used in the TITAN-ACS study was effective in achieving and maintaining defined target glucose range in patients with hyperglycaemia and ACS.

Conclusions: Safety

- There were low rates of both mild and moderate insulin-induced hypoglycaemia in TITAN-ACS
- The rates of moderate hypoglycaemia are considerably lower when compared with similar studies
- There was no fall in potassium during the 24 hour period on VRIII

Acknowledgments

- Steering Group
  - Dr John Birkhead
  - Dr Clive Weston
  - Dr Iain Squires
  - Dr Bernard Prendergast
  - Dr Peter Winocour and Dr Chris Walton
  - Professor S Gough
  - Dr Gerry Rayman
- Funders
  - Association of British Clinical Diabetologists
  - NHS Diabetes