Treating Postprandial Hyperglycemia in Young with Type 2 Diabetes

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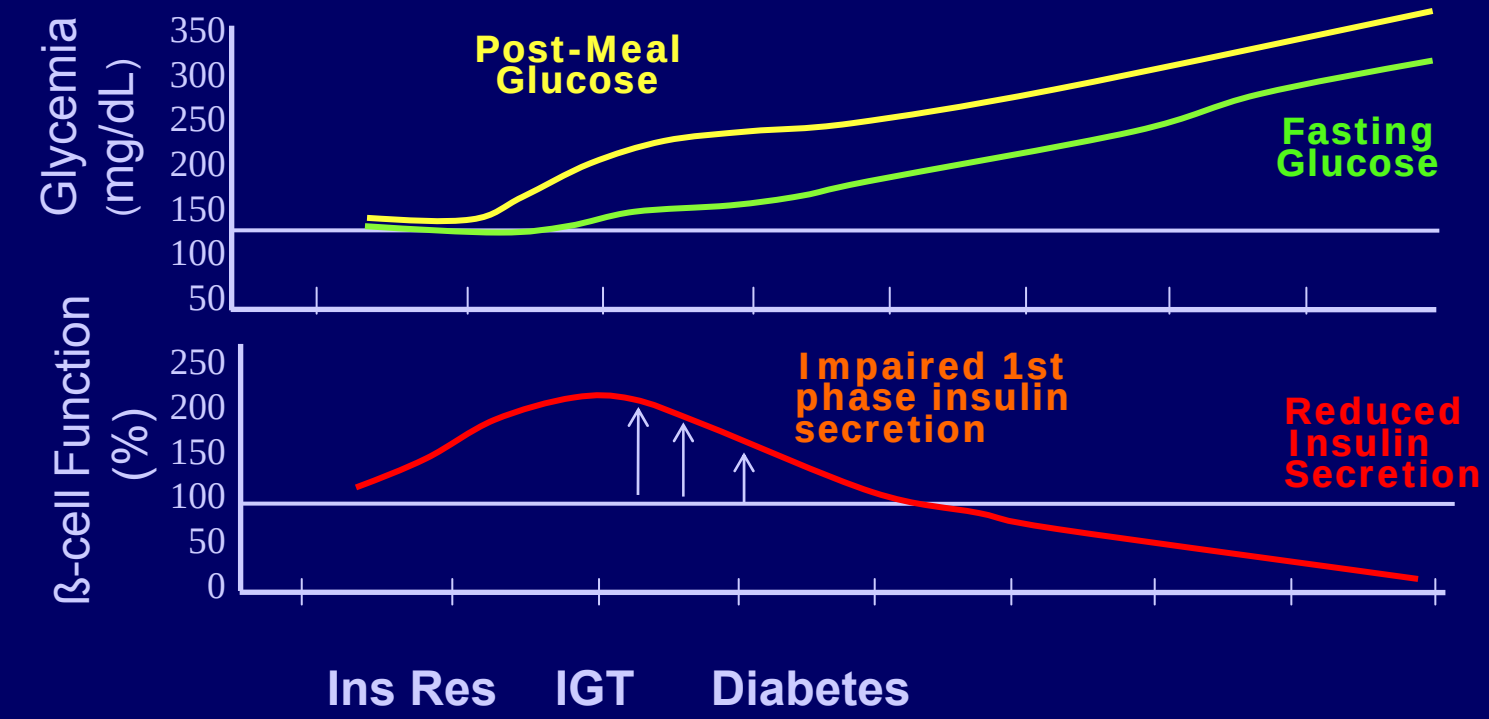
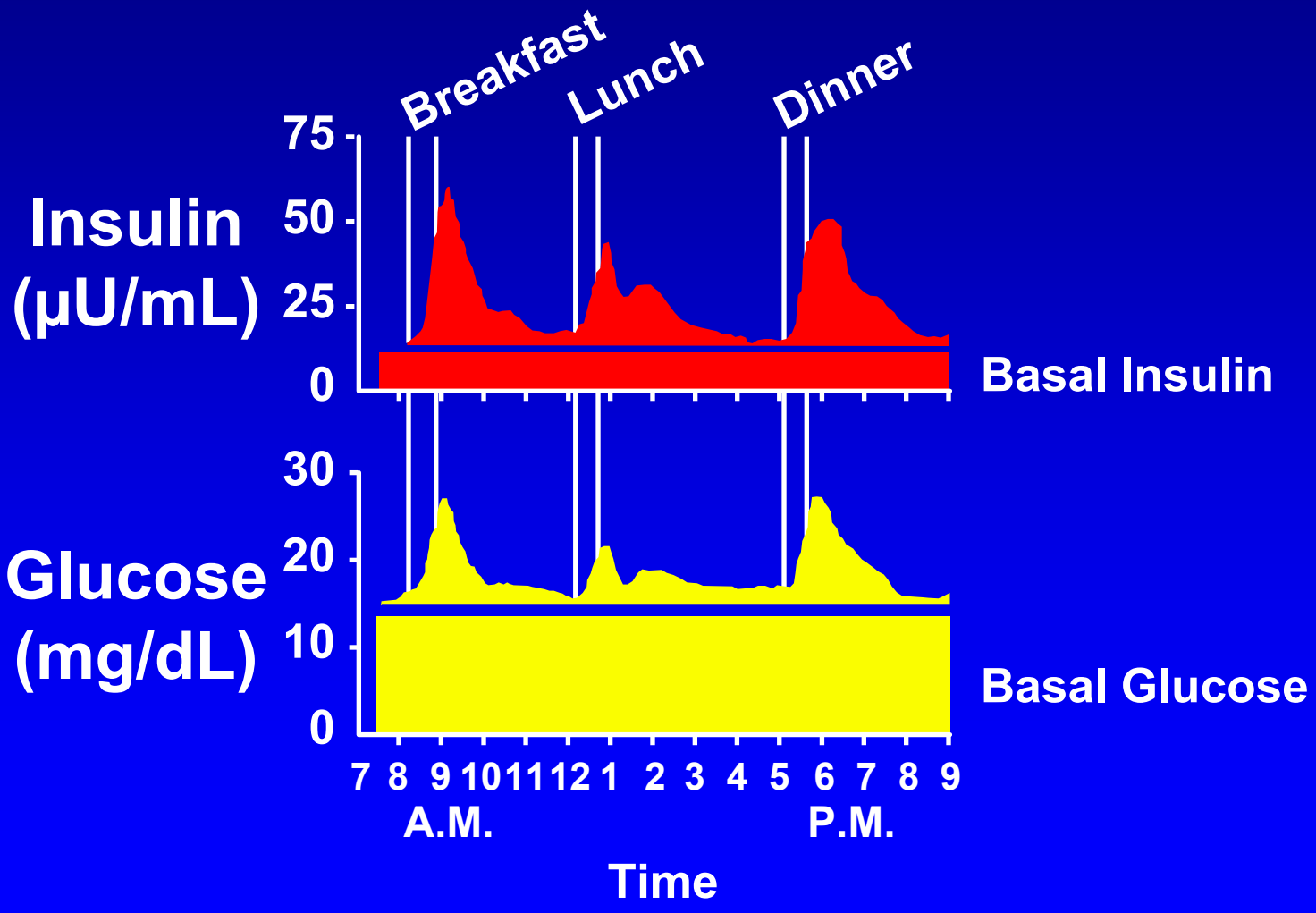
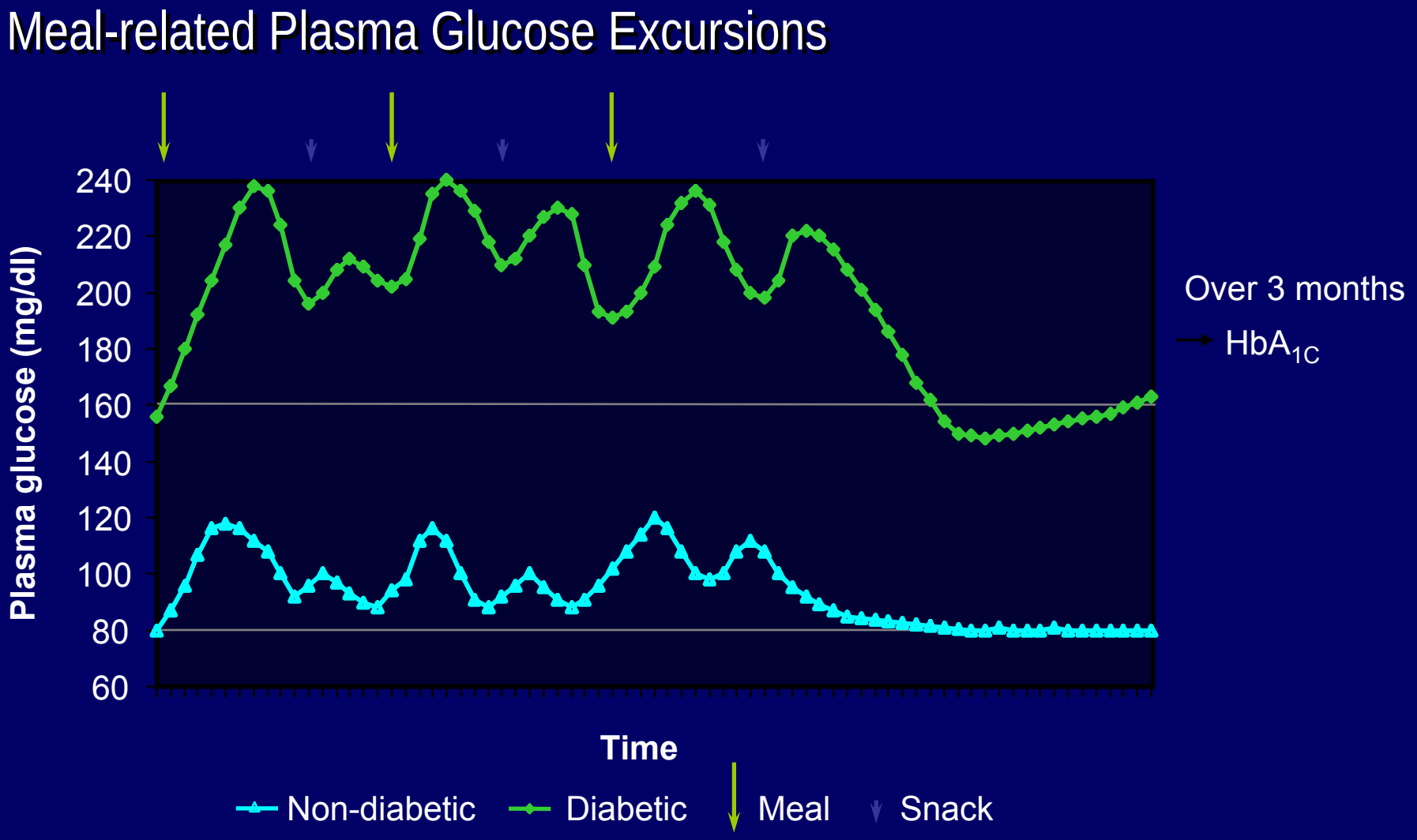
From Insulin Resistance to Diabetes



Insulin and Glycemia in Non-Diabetics



Blood Glucose Levels Over 24 Hours



International Diabetes Federation

The International Diabetes Federation Guideline for Management of Postmeal Glucose

September, 2007

Available at: www.idf.org

Methods: Key questions assessed

1) Is postprandial hyperglycaemia harmful?
2) Is treatment of postmeal hyperglycaemia beneficial?
3) Which therapies are effective in controlling postmeal plasma glucose?
4) What are the targets for postmeal glycaemic control and how should they be assessed?

Methods: Evidence-grading criteria

Level	Type of Evidence
1++	• High-quality meta-analyses, systematic reviews of randomized controlled trials (RCTs) or RCTs with a very low risk of bias
1+	• Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
1-	• Meta-analyses, systematic reviews of RCTs, or RCT with a high risk of bias
2++	• Highly-quality systematic reviews of case-control or cohort studies • Highly-quality case control or cohort studies with a very low risk of confounding bias and a high probability that the relationship is causal
2+	• Well-conducted case-control or cohort studies with a low risk of confounding bias or chance and a moderate probability that the relationship is causal • Well-conducted basic science with low risk of bias
2-	• Case-control or cohort studies with a high risk of confounding bias or chance and a significant risk that the relationship is not causal
3	• Non-analytic studies (for example case reports, case series)
4	• Expert opinion

Scottish Intercollegiate Guidelines Network. *Management of Diabetes: A national clinical guideline*. November, 2001.

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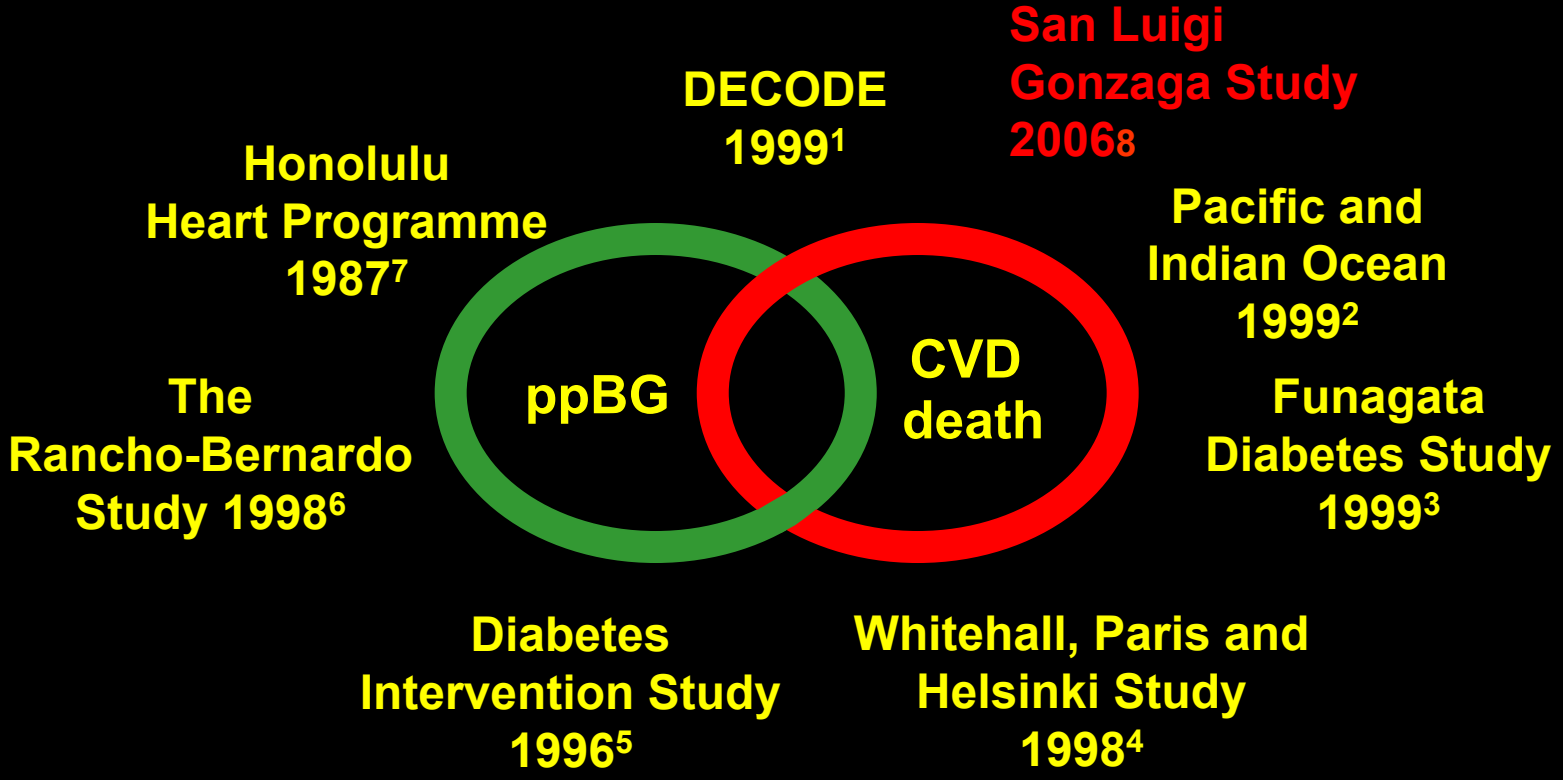
Question 1:
Is postprandial hyperglycaemia harmful?

Clinical Question #1
Is postprandial hyperglycaemia harmful?

Postmeal and postchallenge hyperglycaemia are independent risk factors for macrovascular disease	**[Level 1+]**
Postmeal hyperglycaemia is associated with: **Increased risk of retinopathy, increased CIMT, decreased myocardial blood volume/blood flow, increased risk of cancer, impaired cognitive function in the elderly** **Postmeal hyperglycaemia causes oxidative stress, inflammation and endothelial dysfunction**	**[Level 2+]**

CIMT = carotid-intima-media thickness

Relation between postprandial blood glucose levels and cardiovascular mortality



[1]DECODE Study Group. *Lancet* 1999;354:617. [2]Shaw JE et al. *Diabetologia* 1999;42:1050.
[3]Tominaga M et al. *Diabetes Care* 1999;22:920. [4]Balkau B et al. *Diabetes Care* 1998;21:360.
[5]Hanefeld M et al. *Diabetologia* 1996;39:1577. [6]Barrett-Connor E et al. *Diabetes Care* 1998;21:1236.
Cavalot F et al. J Clin Endocrinol Metabol 2006;

Postmeal glucose elevation independently predicts CV risk in T2DM

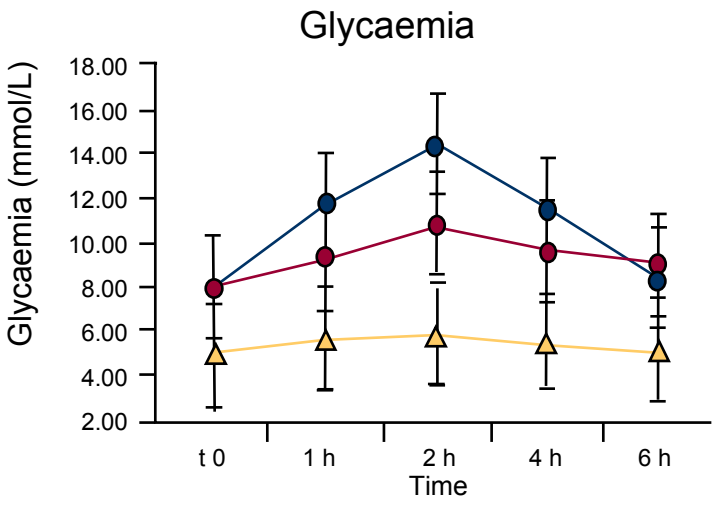
Model	Hazard ratio for 3rd tertile versus 1st and 2nd (95% CI)	
	Men	Women
Fasting plasma glucose	0.73 (0.35-1.54)	2.34 (0.66-8.20)
Postmeal glucose (2 hours after lunch)	2.12 (1.04-4.32)	5.54 (1.45-21.20)*
HbA_{1c}	1.11 (0.55-2.21)	1.35 (0.43-4.26)

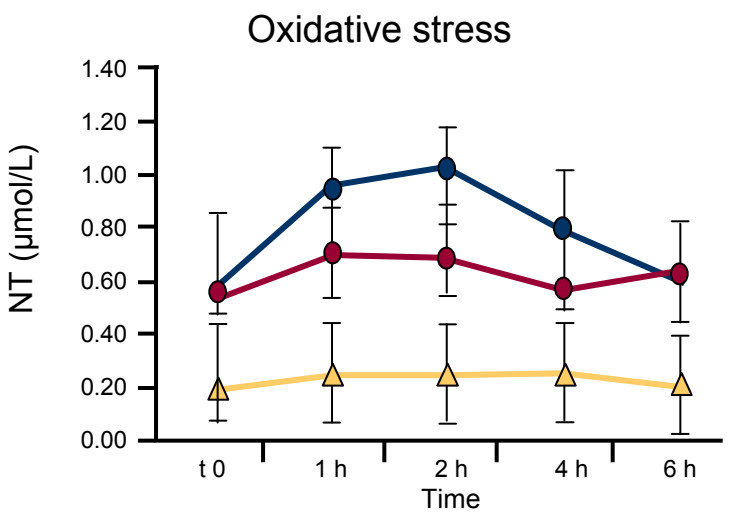
CI = confidence interval
HbA1c = glycated haemoglobin

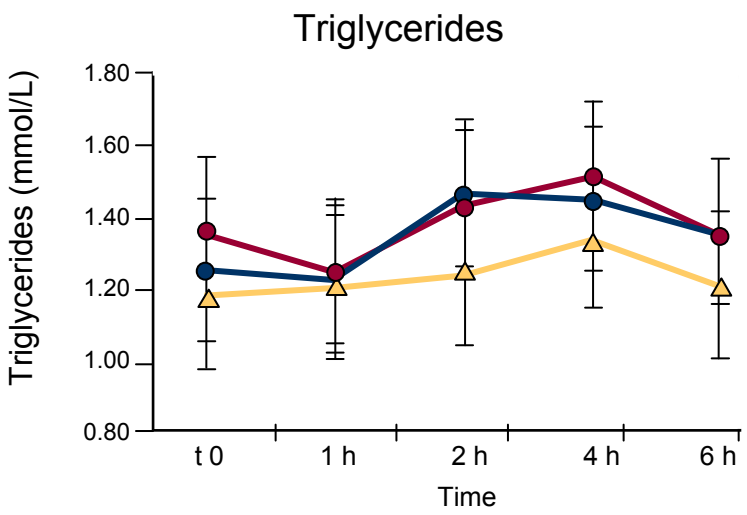
*P<0.01 for comparison between women and men (post lunch values)

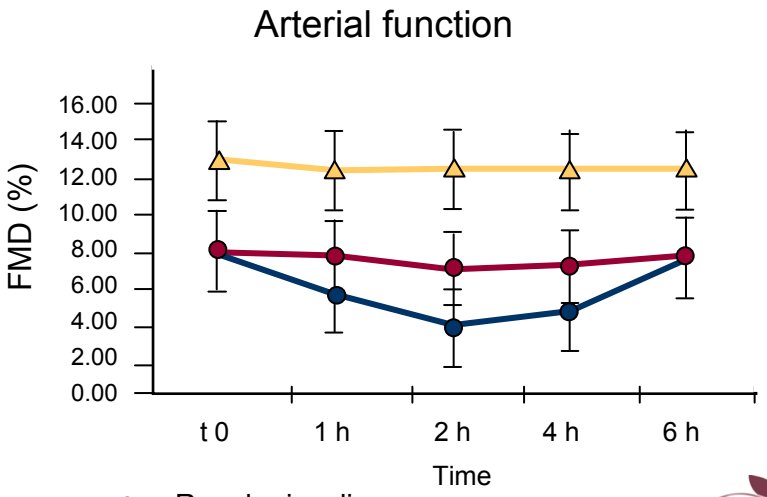
Adapted from Cavalot F et al. *J Clin Endocrn Metab* 2006; 91:813–819

Treatment to decrease postmeal glucose reduces oxidative stress and improves arterial function









Regular insulin
Insulin aspart
Controls

NT = nitrotyrosine
FMD = flow-mediated dilatation

Ceriello A et al. *Diabetes Care* 2002; 25:1439–1443.
Ceriello A et al. *Diabet Med* 2004; 21:171–175.

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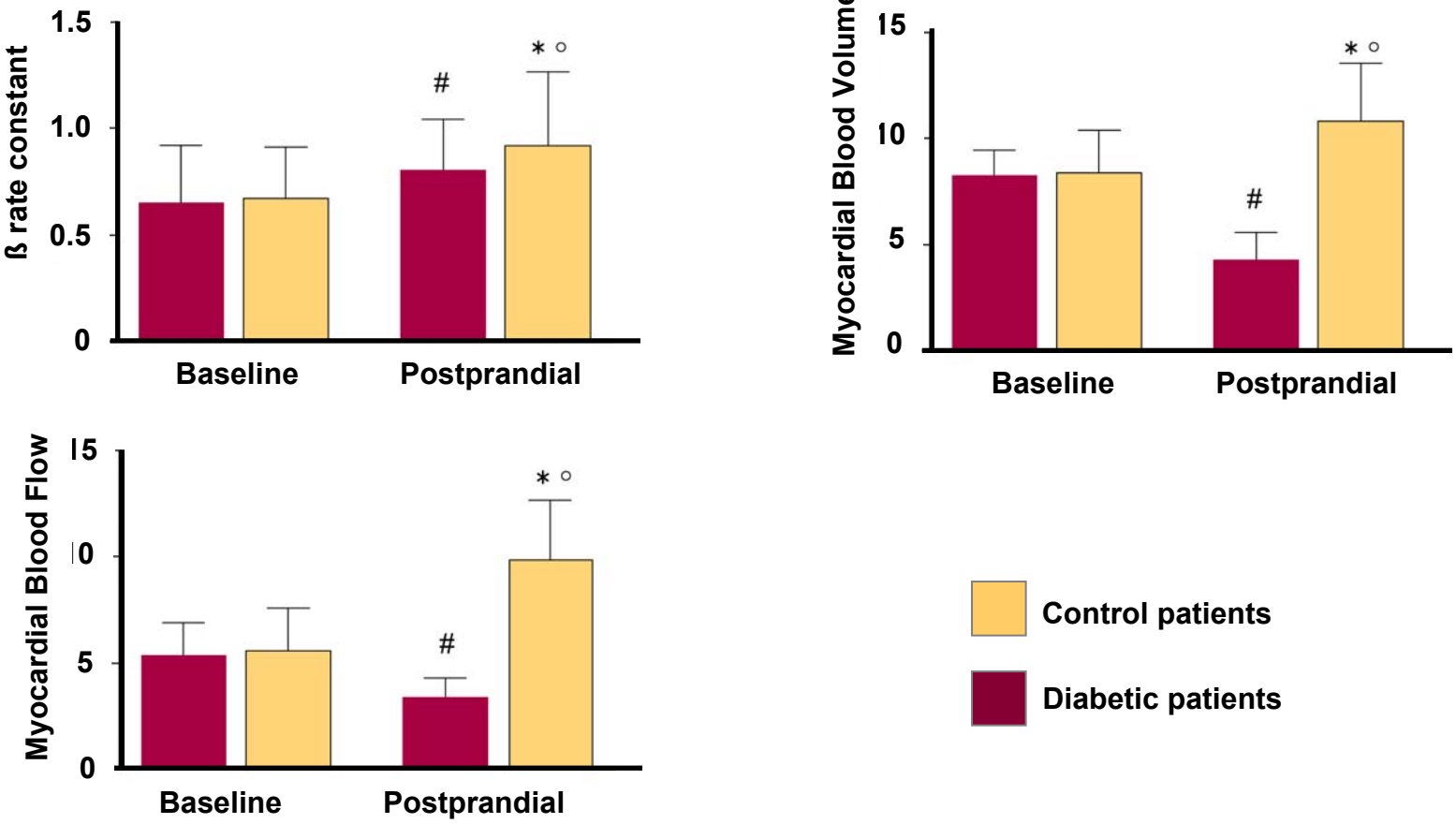
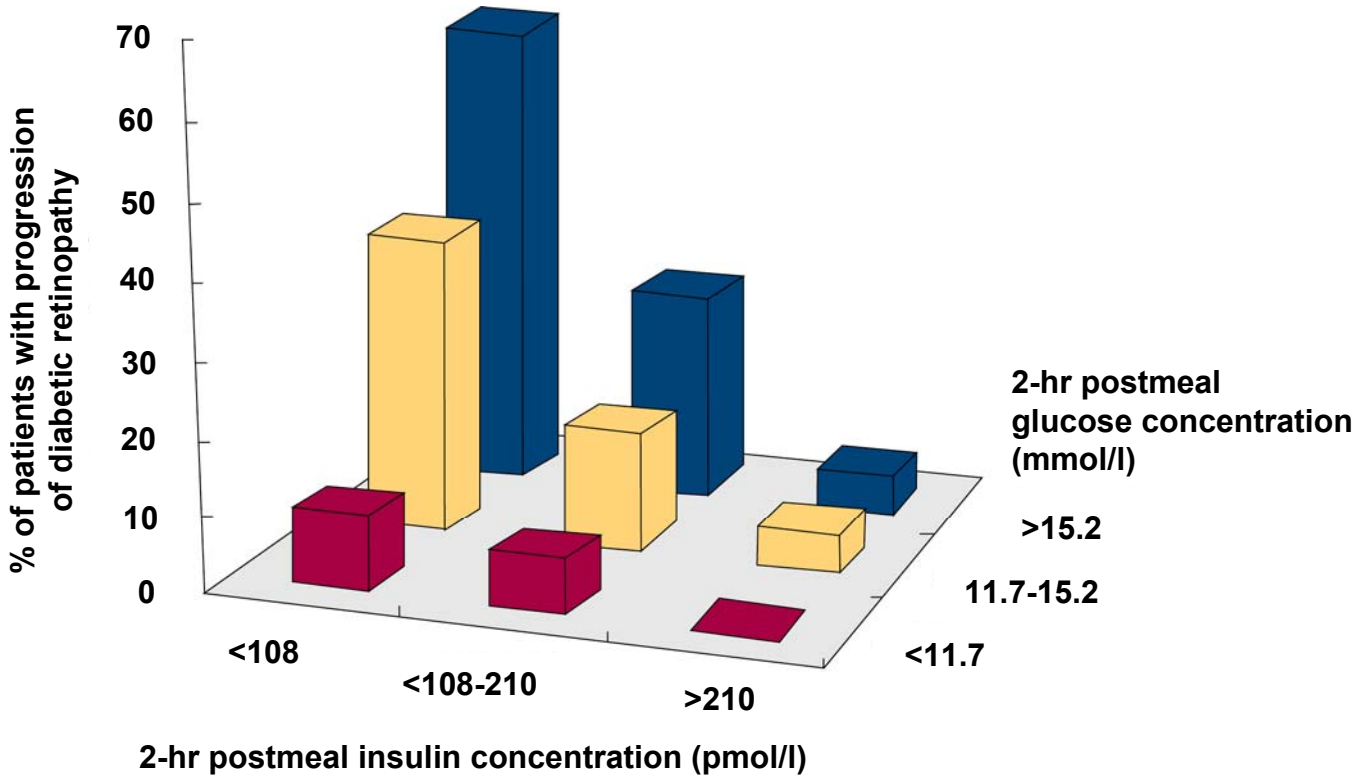
Myocardial perfusion deficits during the postprandial state in T2DM



* *P* <0.01, postprandial values (*ß*, MBV, and MBF) between controls and diabetic patients: °*P* <0.01, postprandial and fasting values in control subjects; #*P* <0.01, postprandial and fasting values in diabetic patients.

Scognamiglio R et al. Circulation 2005; 112(2):179-184.

Postprandial hyperglycaemia is associated with risk of retinopathy progression in T2DM



Shiraiwa T et al. Biochem Biophys Res Commun 2005; 336(1):339-345.

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Clinical Question #1
Is postprandial hyperglycaemia harmful?

Recommendation:

Postmeal hyperglycaemia is harmful and should be addressed.

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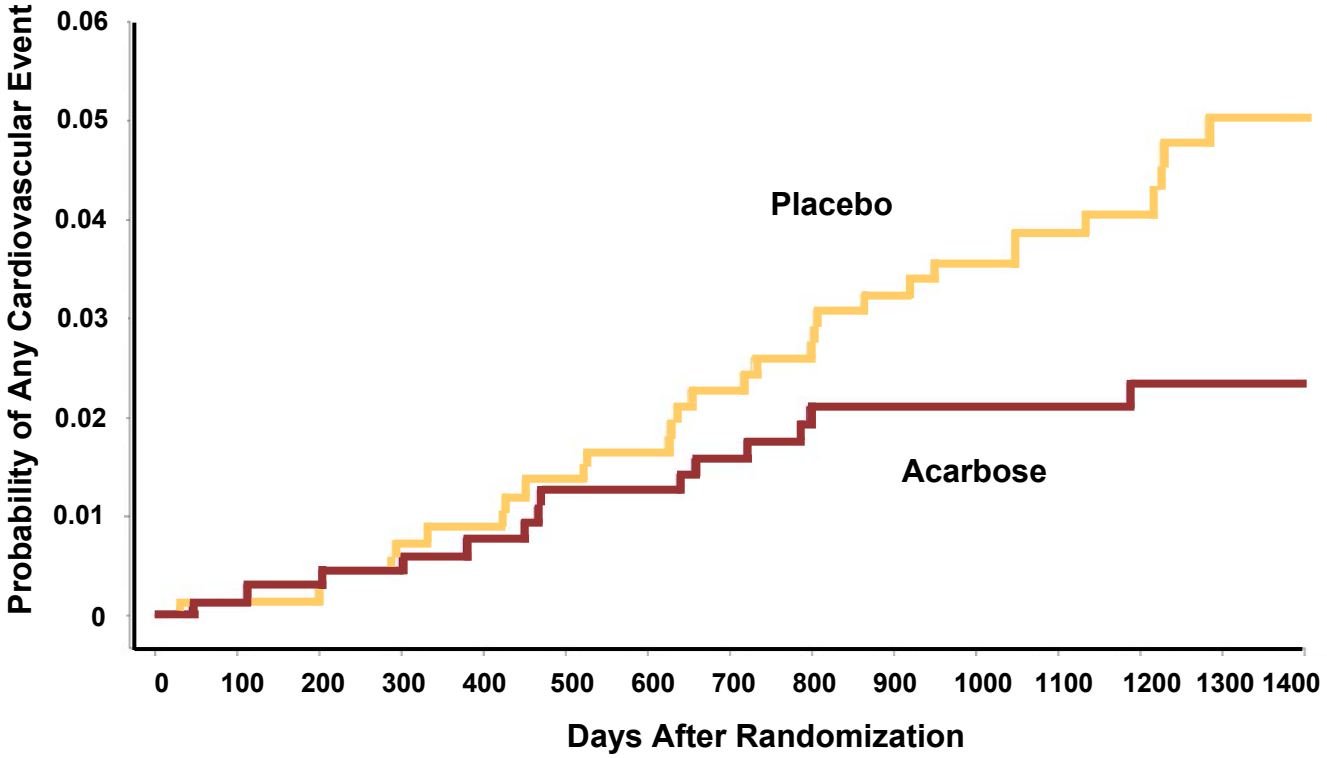
Question 2:
Is treatment of postmeal hyperglycaemia beneficial?

Clinical Question #2
Is treatment of postmeal hyperglycaemia beneficial?

Treatment with agents that target postmeal plasma glucose reduces vascular events	[Level 1-]
Targeting both postmeal and fasting plasma glucose is an important strategy for achieving optimal glycaemic control	[Level 2+]

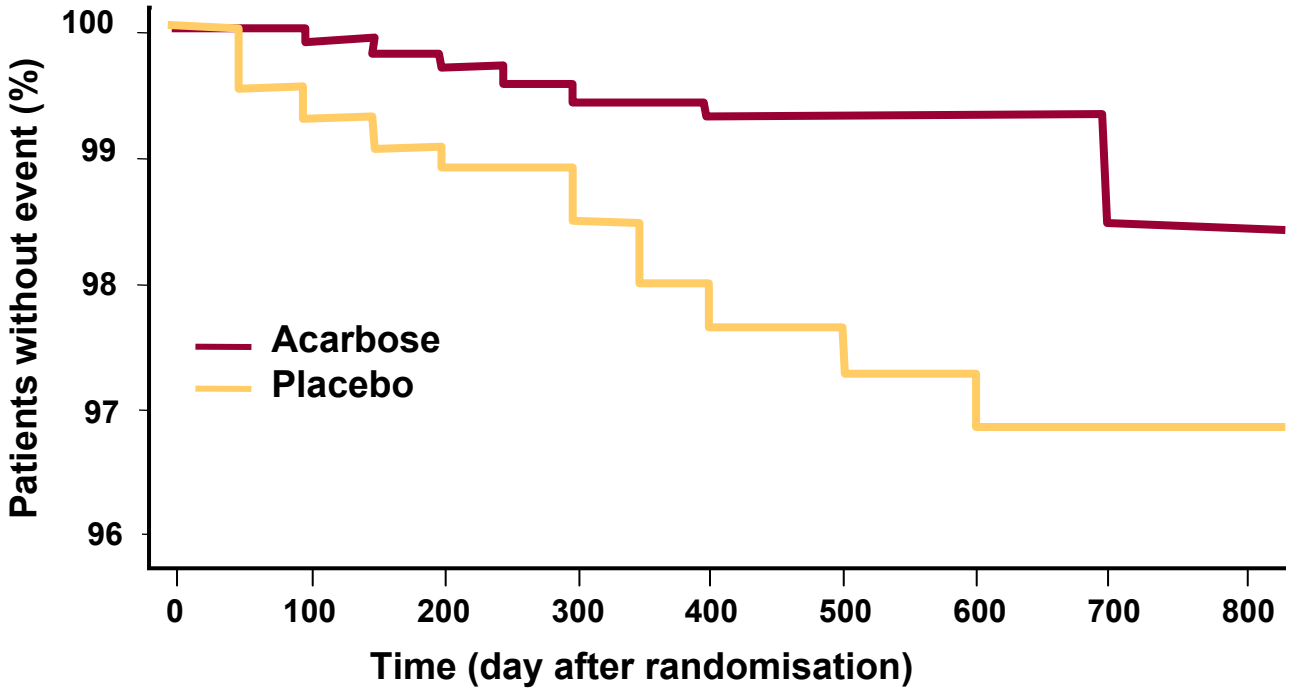
Targeting postmeal glucose reduces cardiovascular risk: The STOP-NIDDM Trial



P = .04 (Log-Rank Test)
P = .03 (Cox Proportional Model)

Chiasson JL et al. JAMA 2003;290:486–494.
Laube H. *Clin Drug Invest* 2002;22:141-56.

Targeting postmeal glucose significantly reduces cardiovascular events in T2DM



p=0.0087 (Log rank test)
p=0.0120 (Cox proportional model)

Hanefeld M et al. *Eur Heart J* 2004; 25(1):10-16.
LaubeH. *Clin Drug Invest* 2002;22:141-56.

Population and design of the HEART2D

Patients (1,115 type 2 diabetes, aged 30-75 years) were randomly assigned within 21 days after AMI to the

1) prandial strategy (PRANDIAL) (three premeal doses of insulin lispro targeting 2-h postprandial blood glucose <7.5 mmol/l)

or

2) basal strategy (BASAL) (NPH twice daily or insulin glargine once daily targeting fasting/premeal blood glucose <6.7 mmol/l).

The HEART2 D trial: Effects of Prandial Versus Fasting Glycemia on Cardiovascular Outcomes in Type 2 Diabetes

Raz I et al. Diabetes Care 2009; 32:381-389

- Risks of first combined primary CV events were similar in the PRANDIAL (31.2%) and BASAL (32.4%) groups (HR 0.98), but the observed events rates were lower than the expected of 40%
- The difference in postprandial glycemia between groups was only 1.3 mmol/l and not 2.5 mmol/l as projected and the HbA1c values were higher than 7.0% (7.7% vs. 7.8 %)
- When HbA1c was 8.0% on two consecutive visits the PRANDIAL treatment was intensified by adding NPH at bedtime, and the BASAL treatment was replaced with twice-daily human insulin 30/70
- Regimen intensification occurred more frequently in the PRANDIAL group (28%) versus the BASAL group (21%) (p= 0.005)
- In Summary, prandial versus basal insulin treatment strategies achieved no difference in secondary prevention in diabetes.

Effect of intensive control of glucose on cardiovascular outcomes and death in patients with diabetes mellitus: a meta-analysis of randomised controlled trials

Kausik K Ray, Sreenivasa Rao Kondapally Seshasai, Shanelle Wijesuriya, Rupa Sivakumaran, Sarah Nethercott, David Preiss, Sebhat Erqou, Naveed Sattar

Lancet 2009;373:1765–72

Background

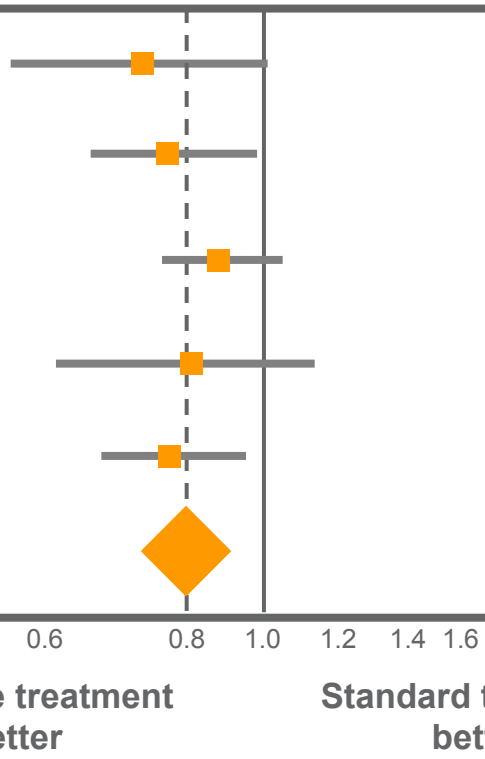
- Whether intensive control of glucose reduces macrovascular events and all-cause mortality in individuals with type 2 diabetes mellitus is unclear. We undertook a meta-analysis of randomised controlled trials to determine whether intensive treatment is beneficial.

N° of patients: 33,040

Lancet 2009;373:1765–72

Probability of events of coronary heart disease with intensive glucose-lowering versus standard treatment

	Intensive treatment/ standard treatment		Weight of study size	Odds ratio (95% CI)
	Participants	Events		
UKPDS	3071/1549	426/259	8.6%	0.75 (0.54-1.04)
PROactive*	2605/2633	164/202	20.2%	0.81 (0.65-1.00)
ADVANCE	5571/5569	310/337	36.5%	0.92 (0.78-1.07)
VADT	892/899	77/90	9.0%	0.85 (0.62-1.17)
ACCORD	5128/5123	205/248	25.7%	0.82 (0.68-0.99)
Overall	**17267/15773**	**1182/1136**	**100%**	**0.85 (0.77-0.93)**

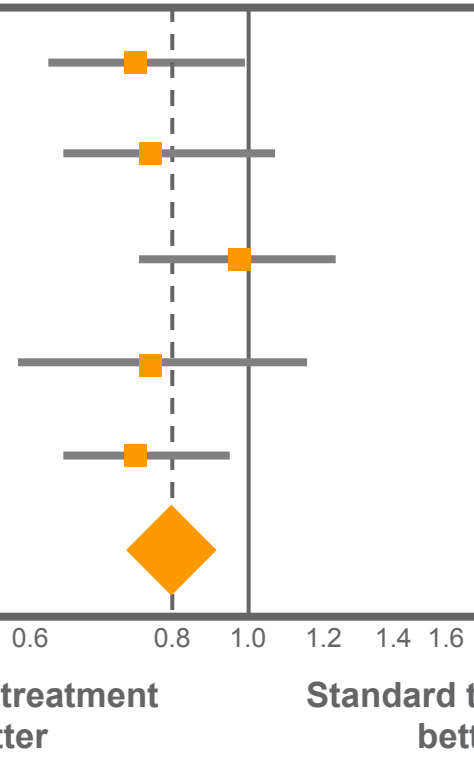


*Included non-fatal myocardial infarction and death from all-cardiac mortality

Lancet 2009;373:1765–72

Probability of events of non-fatal myocardial infarction with intensive glucose-lowering versus standard treatment

	Intensive treatment/ standard treatment		Weight of study size	Odds ratio (95% CI)	Odds ratio (95% CI)
	Participants	Events			
UKPDS	3071/1549	221/141	21.8%		0.78 (0.62-0.98)
PROactive	2605/2633	119/144	18.0%		0.83 (0.64-1.06)
ADVANCE	5571/5569	153/156	21.9%		0.98 (0.78-1.23)
VADT	892/899	64/78	9.4%		0.81 (0.58-1.15)
ACCORD	5128/5123	186/235	28.9%		0.78 (0.64-0.93)
Overall	**17267/15773**	**743/754**	**100%**		**0.83 (0.75-0.93)**



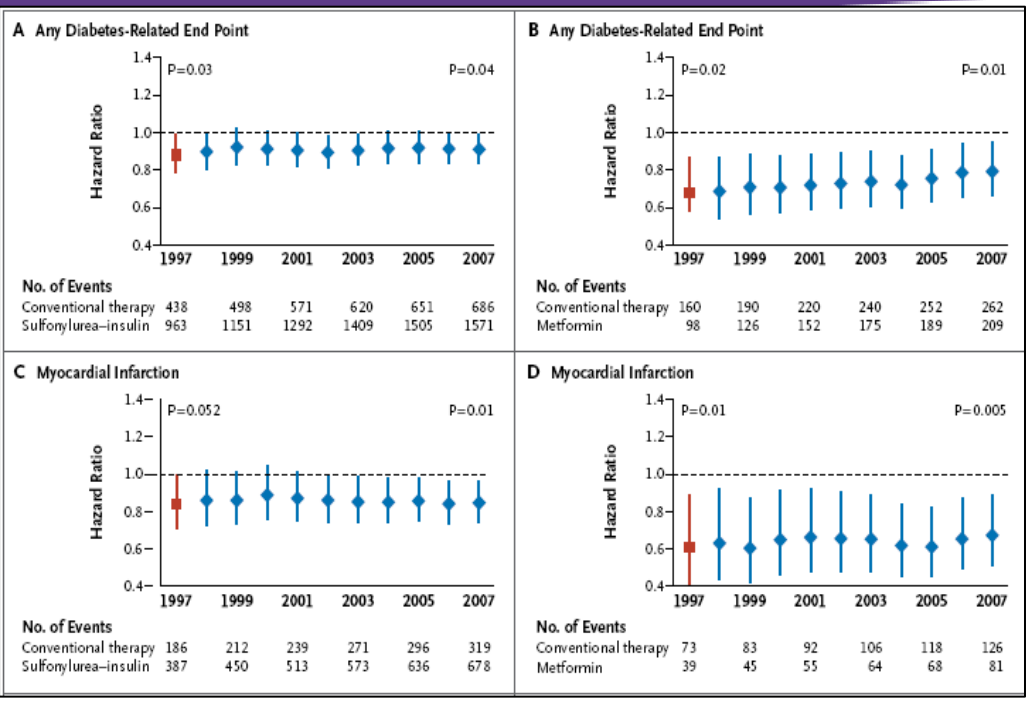
Lancet 2009;373:1765–72

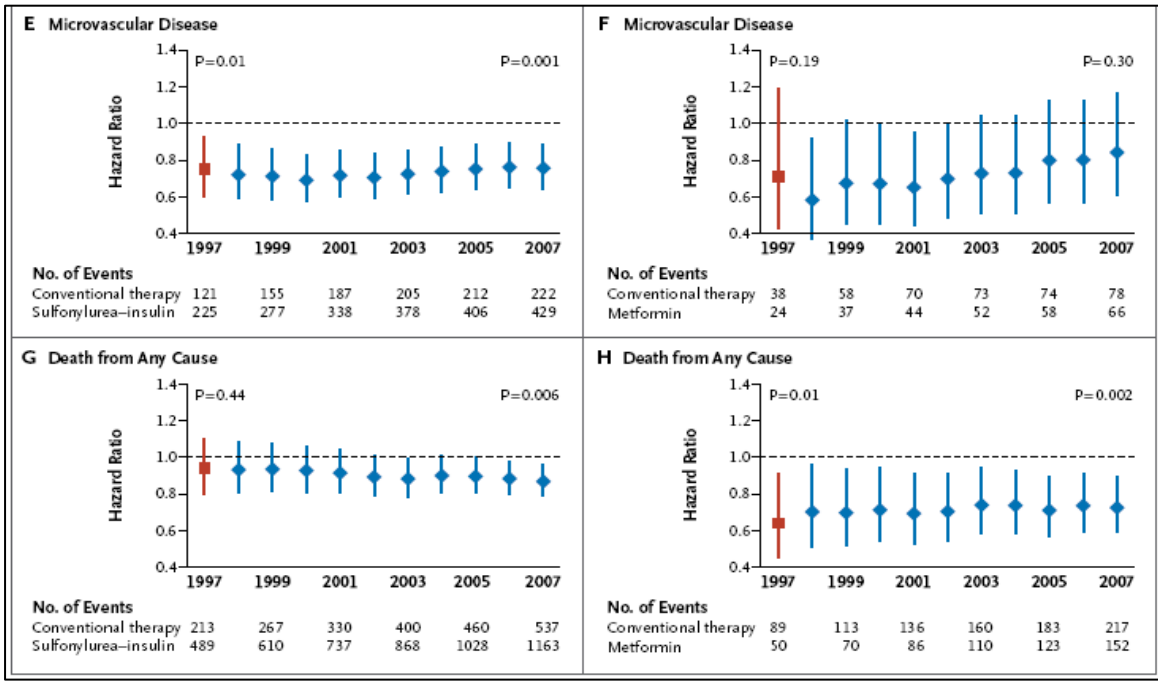
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

10-Year Follow-up of Intensive Glucose Control in Type 2 Diabetes

Rury R. Holman, F.R.C.P., Sanjoy K. Paul, Ph.D., M. Angelyn Bethel, M.D., David R. Matthews, F.R.C.P., and H. Andrew W. Neil, F.R.C.P.


A Any Diabetes-Related End Point
P=0.03
P=0.04
Hazard Ratio
1.4
1.2
1.0
0.8
0.6
0.4
1997 1999 2001 2003 2005 2007
No. of Events
Conventional therapy 438 498 571 620 651 686
Sulfonylurea–insulin 963 1151 1292 1409 1505 1571
B Any Diabetes-Related End Point
P=0.02
P=0.01
Hazard Ratio
1.4
1.2
1.0
0.8
0.6
0.4
1997 1999 2001 2003 2005 2007
No. of Events
Conventional therapy 160 190 220 240 252 262
Metformin 98 126 152 175 189 209
C Myocardial Infarction
P=0.052
P=0.01
Hazard Ratio
1.4
1.2
1.0
0.8
0.6
0.4
1997 1999 2001 2003 2005 2007
No. of Events
Conventional therapy 186 212 239 271 296 319
Sulfonylurea–insulin 387 450 513 573 636 678
D Myocardial Infarction
P=0.01
P=0.005
Hazard Ratio
1.4
1.2
1.0
0.8
0.6
0.4
1997 1999 2001 2003 2005 2007
No. of Events
Conventional therapy 73 83 92 106 118 126
Metformin 39 45 55 64 68 81


E Microvascular Disease
P=0.01
P=0.001
Hazard Ratio
1.4
1.2
1.0
0.8
0.6
0.4
1997 1999 2001 2003 2005 2007
No. of Events
Conventional therapy 121 155 187 205 212 222
Sulfonylurea–insulin 225 277 338 378 406 429
F Microvascular Disease
P=0.19
P=0.30
Hazard Ratio
1.4
1.2
1.0
0.8
0.6
0.4
1997 1999 2001 2003 2005 2007
No. of Events
Conventional therapy 38 58 70 73 74 78
Metformin 24 37 44 52 58 66
G Death from Any Cause
P=0.44
P=0.006
Hazard Ratio
1.4
1.2
1.0
0.8
0.6
0.4
1997 1999 2001 2003 2005 2007
No. of Events
Conventional therapy 213 267 330 400 460 537
Sulfonylurea–insulin 489 610 737 868 1028 1163
H Death from Any Cause
P=0.01
P=0.002
Hazard Ratio
1.4
1.2
1.0
0.8
0.6
0.4
1997 1999 2001 2003 2005 2007
No. of Events
Conventional therapy 89 113 136 160 183 217
Metformin 50 70 86 110 123 152

“The “Metabolic Memory”: Is More than Just Tight Glucose Control Necessary to Prevent Diabetic Complications?.”

A. Ceriello, J. Thorpe, M. Ihnat

J Clin Endocrinol Metabol, 2009;94:410-5

Postprandial Hyperglycaemia and Cardiovscular Disease: Is The HEART2D Study the answer?

Ceriello A, Diabetes Care 2009; 32:521-522

- The study could be criticized for several aspects. It is clearly under-powered, and this is confirmed by the low rate of the events. Otherwise, the patients were very well treated for cardiovascular disease.

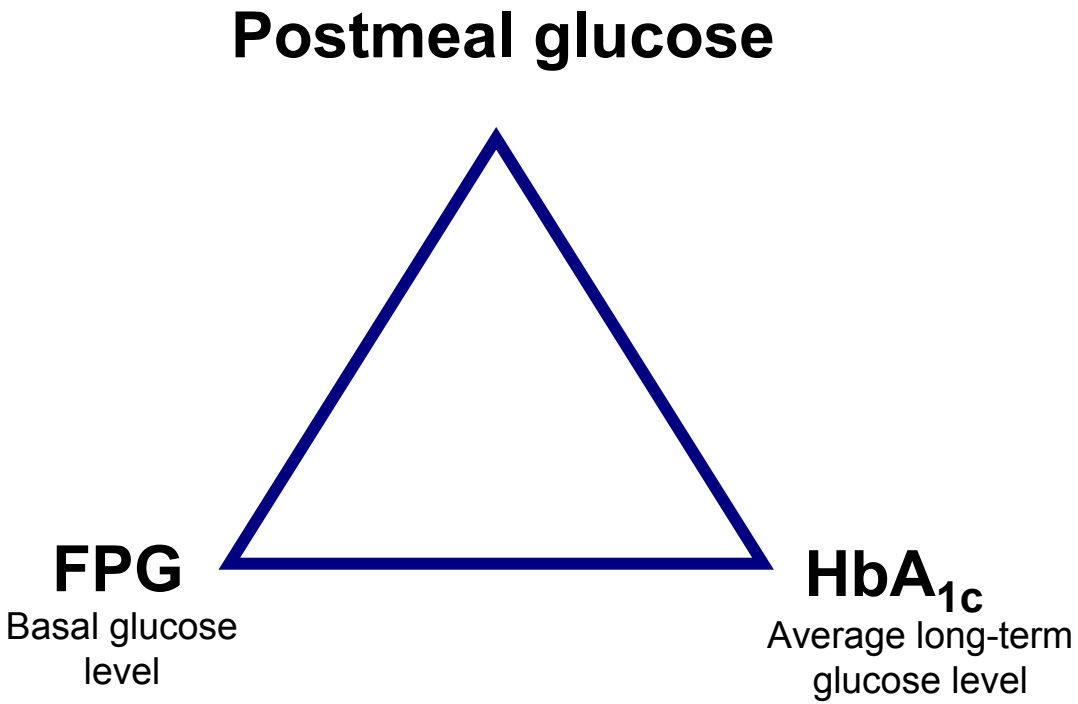
-The study also failed to reach the predetermined difference in postprandial hyperglycemia of 2.5 mmol/l, being the mean difference at the end of the study only 0.8 mmol/l, less than 1/3 of the goal.

Postprandial Hyperglycemia and Cardiovscular Disease: Is The HEART2D Study the answer?

Ceriello A, Diabetes Care 2009; 32:521-522

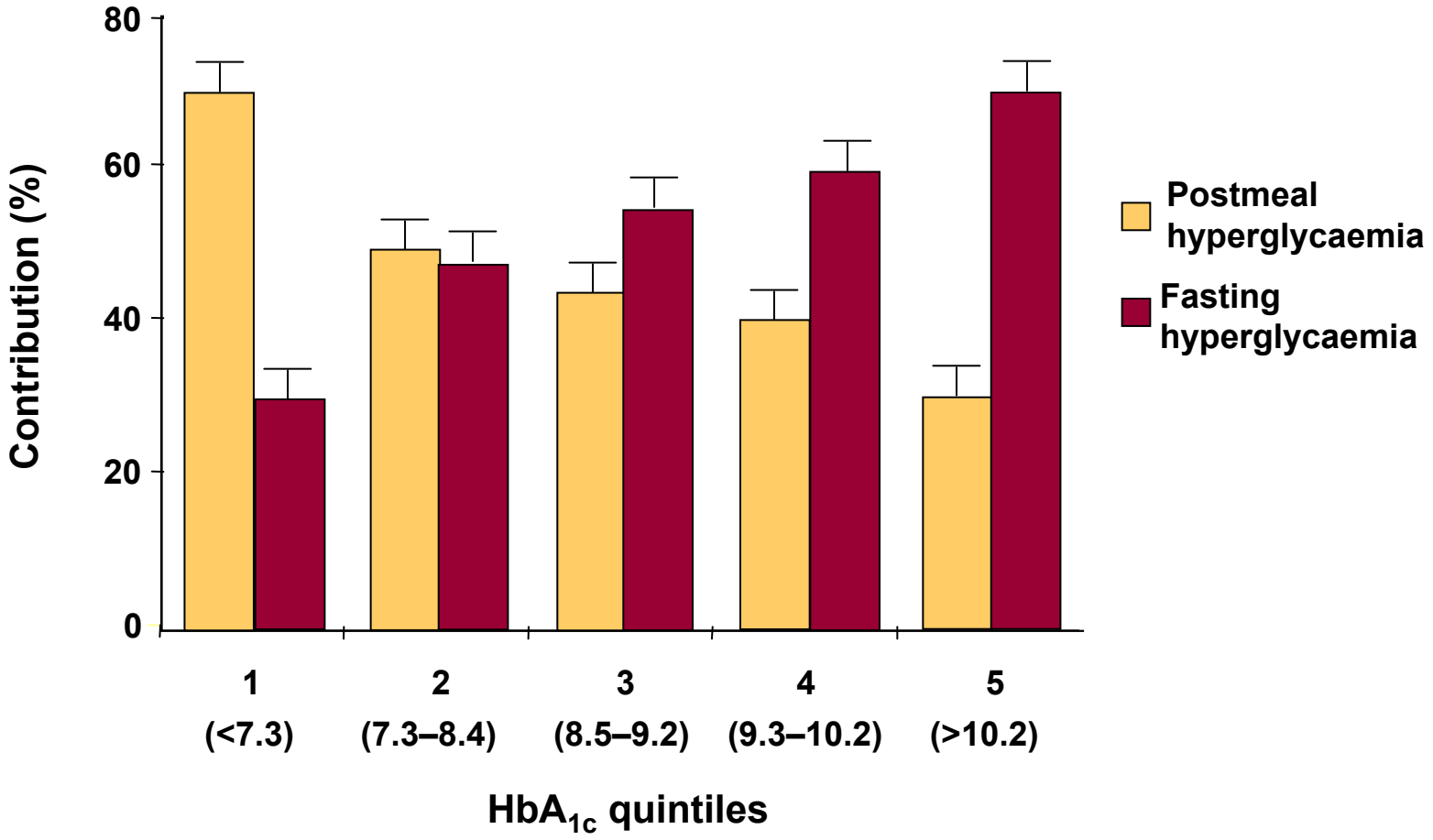
These differences seem to be too small in order to influence a so hard outcome, particularly in a very short time period.

‘Glucose triad’ of diabetes management



HbA_{1c} = glycated haemoglobin
FPG = fasting plasma glucose

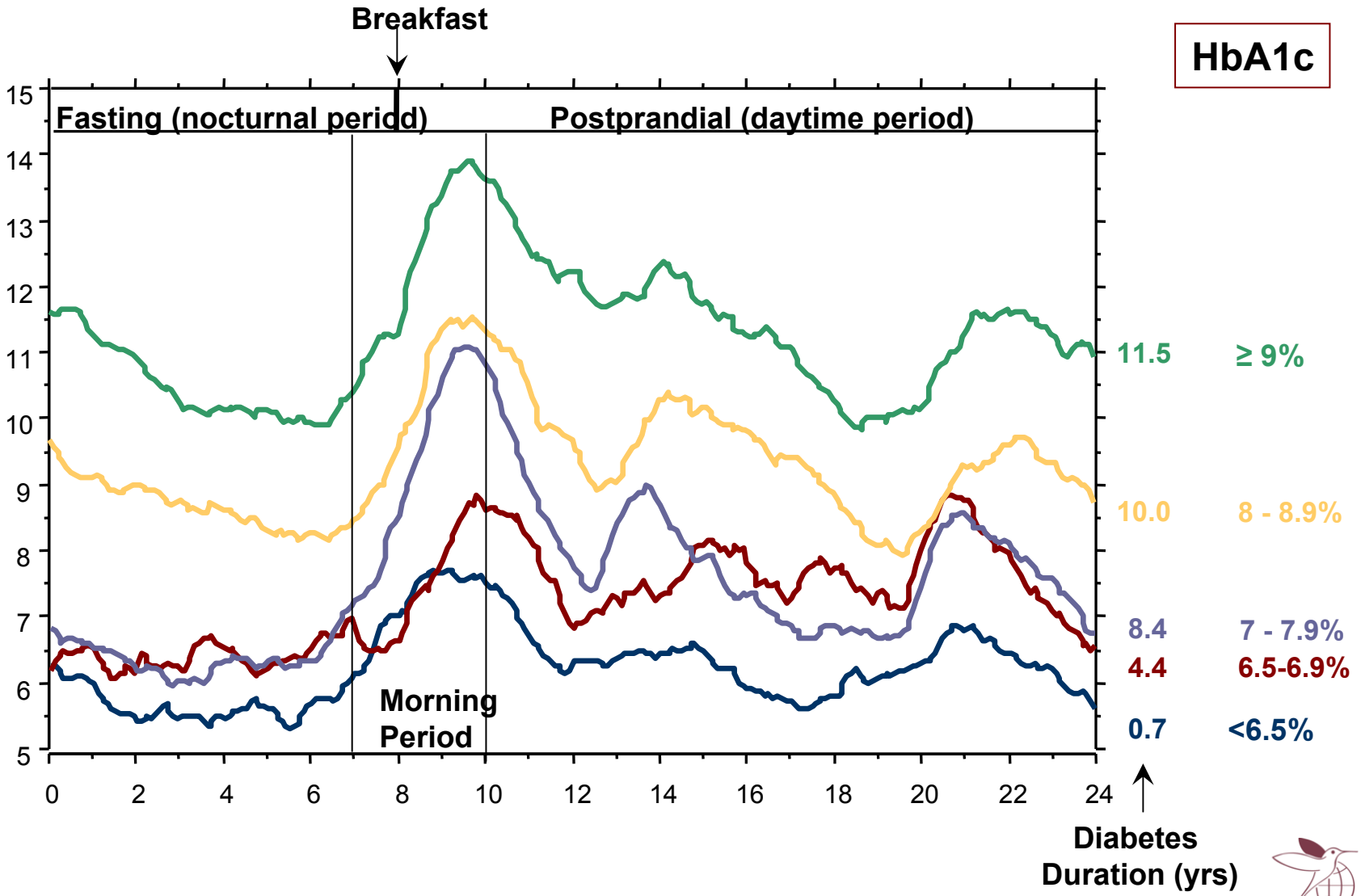
Postmeal glucose makes a major contribution to overall glycaemia across a range of HbA_{1c} values



Monnier L et al. Diabetes Care 2003; 26:881–885

International Diabetes Federation

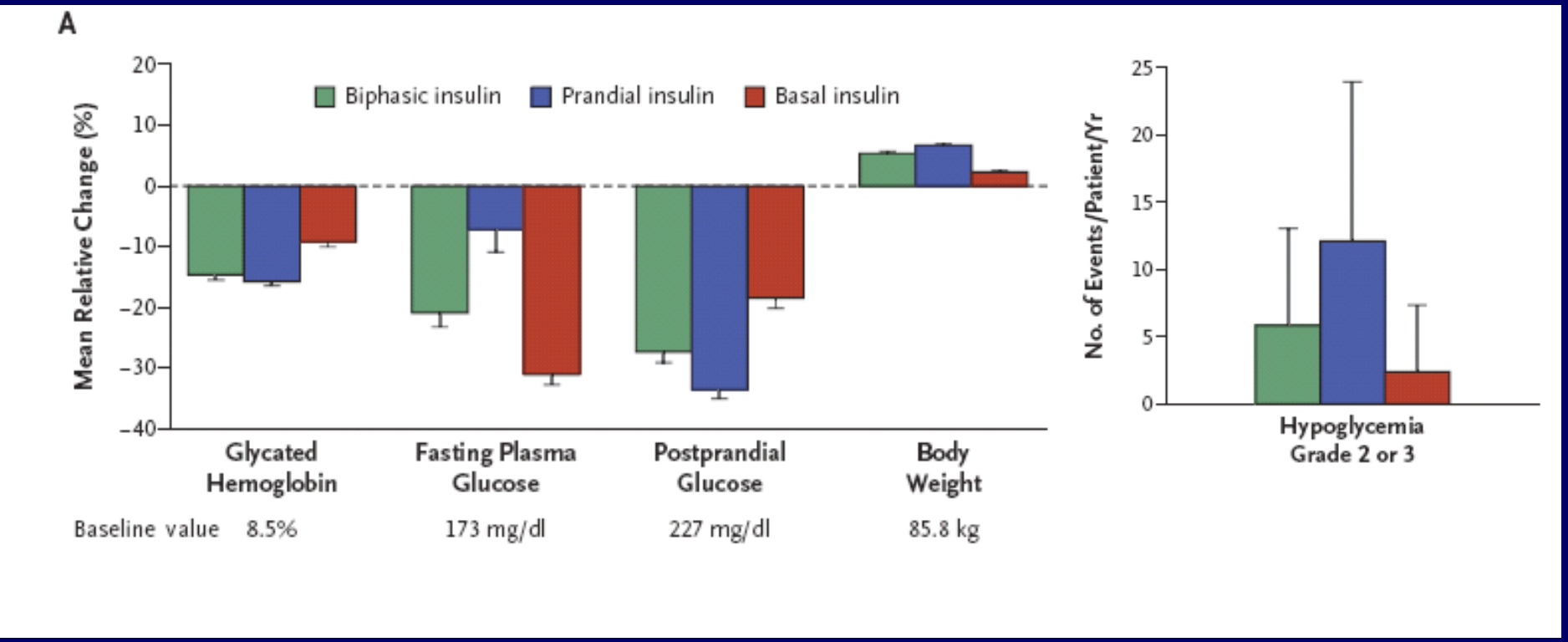
Daily glycemic variation (mmol/L) with worsening glycaemic control in type 2 diabetes



L Monnier ,C Colette, G Dunseath and D Owens, Diabetes Care 2007

International Diabetes Federation

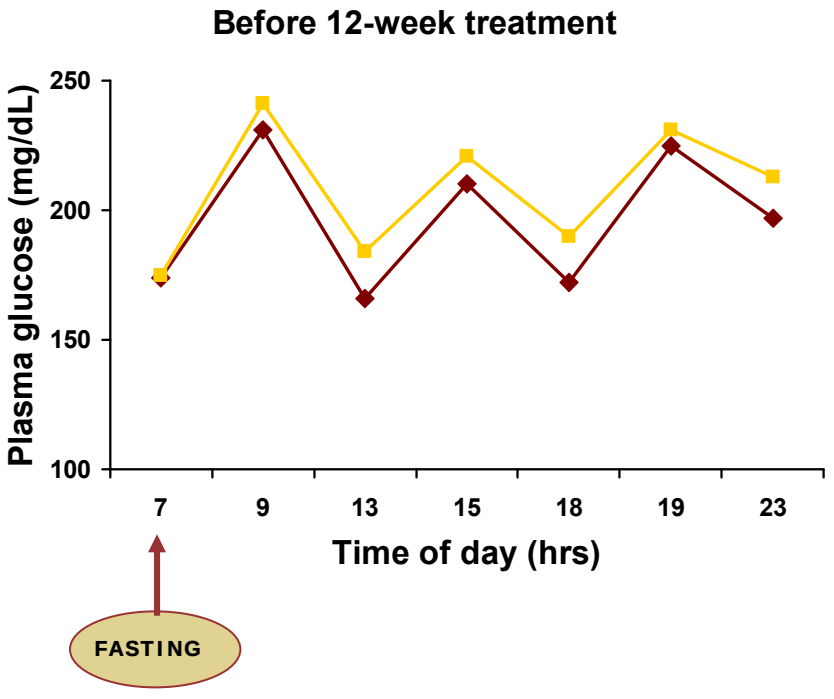
4T Trial

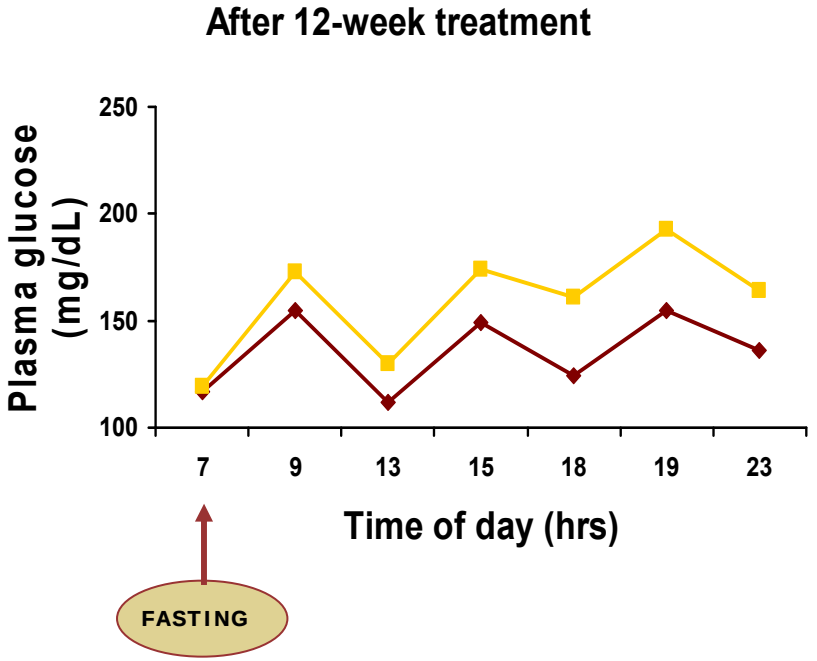


Percentage Change from Baseline to 1 Year in Glycated Hemoglobin, Fasting Plasma Glucose, Postprandial Glucose,and Body Weight (Panel A) and Mean (+SD) Hypoglycemic-Event Rate (Panel B).

N Engl J Med, 2007

Achieving HbA_{1c} target is dependent on postprandial glucose control





Failed to reach HbA_{1c} target after 12 weeks

Successfully reached HbA_{1c} target after 12 weeks

Woerle HJ et al. *Diabetes Res Clin Pract* 2007.

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Clinical Question #2
Is treatment of postmeal hyperglycaemia beneficial?

Recommendation:

Implement treatment strategies to lower postmeal plasma glucose in people with postmeal hyperglycaemia.

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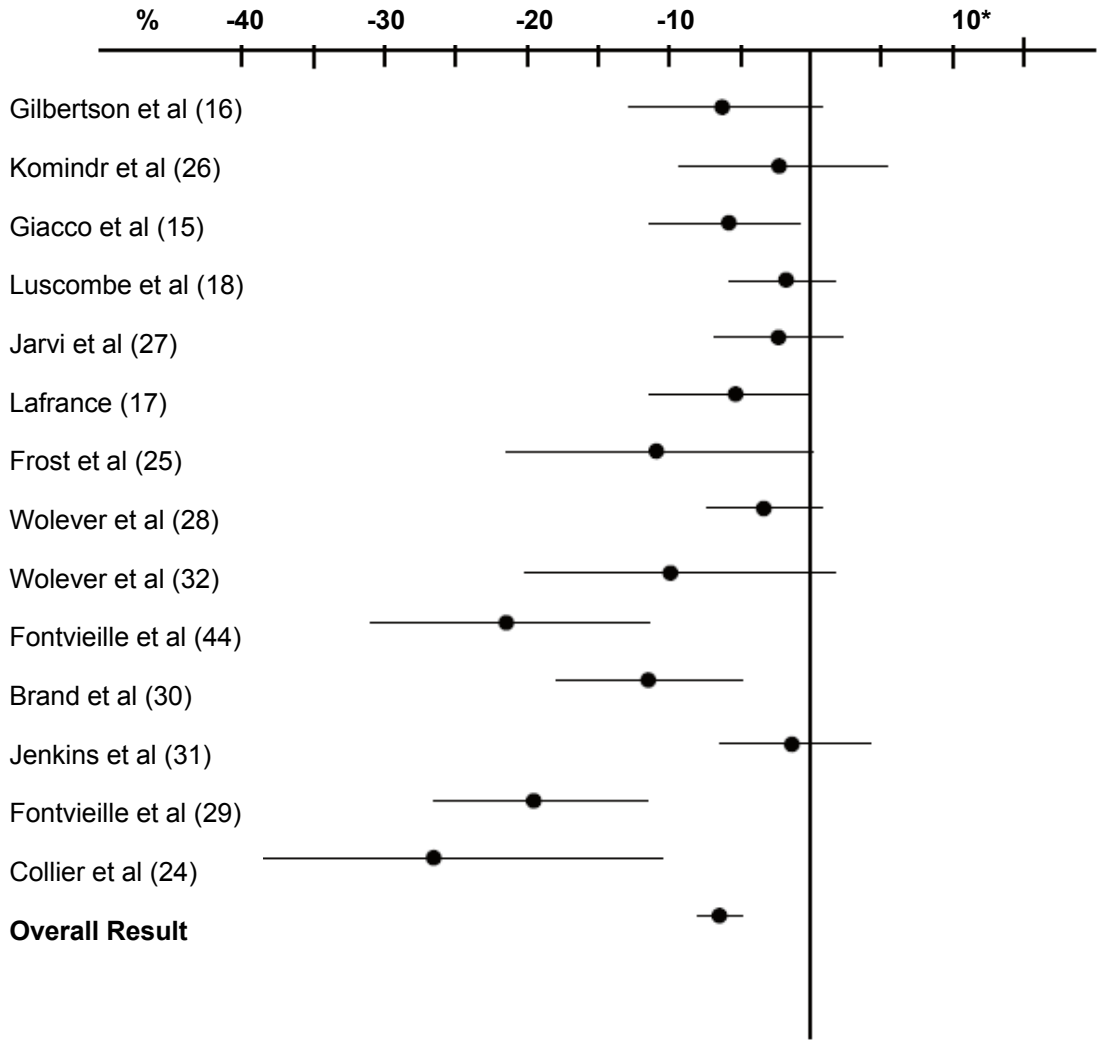
Question 3:
Which therapies are effective in controlling postmeal plasma glucose?

Clinical Question #3
Which therapies are effective in controlling postmeal plasma glucose?

Several pharmacologic agents preferentially lower postmeal plasma glucose	[Level 1++]
Diets with a low glycaemic load are beneficial in controlling postmeal plasma glucose	[Level 1+]

Glycaemic-lowering effect of low-GI foods in diabetes



A meta-analysis was performed using either the end point HBA1c or fructosamine data in all 24 studies. Because these factors have different units of measurement, the difference between the two diets has been expressed in percentage terms. *Points to the left of the vertical line indicate that the low-GI diet reduced values by x% over and above that seen with the high-GI diet. When final values were adjusted for differences at baseline, the mean difference was –7.4% (-8.8 to 6.0) in favor of the low-GI diet, assuming independence.

Brand-Miller J et al. Diabetes Care 2003;26:2261-2267.

Therapies that preferentially lower postmeal glucose

Drug class	Molecular action	Postmeal glucose lowering effect	Commercially available agents+
α-glucosidase inhibitors	Inhibits α-glucosidase enzyme in intestine	• Delays carbohydrate absorption	• Acarbose • Miglitol • Vogilbose
Amylin analogues	Synthetic analogues of human amylin	• Slows gastric emptying, lowers glucagon, increases satiety	• Pramlintide
DPP-4 inhibitors	Inhibits DPP-4 enzyme that degrades GLP-1	• Stimulates glucose-dependent insulin secretion, suppresses glucagon release, delays gastric emptying, increases satiety	• Sitagliptin • Vildagliptin
Glinides	Inhibits pancreatic β-cell K-ATP channels	• Stimulates rapid but short-lived insulin release	• Nateglinide • Repaglinide
GLP-1 derivatives	Degradation-resistant GLP-1-receptor agonists	• Stimulates glucose-dependent insulin secretion • Suppresses glucagon release • Slows gastric emptying • Enhances β-cell mass in rodent studies, weight loss and inhibition of food intake in humans	• Exenatide

+ Not all agents available in all regions. The table is current as of [INSERT DATE OF PUBLICATION OF SLIDE KIT]

Insulins that preferentially lower postmeal glucose

Insulins	Formulation	Commercially available agents+
Rapid-acting insulin analogues	Synthetic insulin	• Aspart • Glulisine • Lispro
Biphasic insulins	Combines rapid-acting insulin analogue with intermediate-acting insulin	• 75% insulin lispro protamine/25% lispro • 50% insulin lispro protamin/50% lispro • 70% insulin lispro protaimine/30% aspart
Inhaled insulin	Human insulin inhalation powder	• Exubera

+ Not all agents available in all regions.

Clinical Question #3
Which therapies are effective in controlling postmeal plasma glucose?

Recommendation:

A variety of both non-pharmacologic & pharmacologic therapies should be considered to target postmeal plasma glucose.

International Diabetes Federation

Question 4:
What are the targets for postmeal glycaemic control and how should they be assessed?

Clinical Question #4
What are the targets for postmeal glycaemic control and how should they be assessed (1)?

Postmeal plasma glucose levels seldom rise above 7.8 mmol/l (140 mg/dl) in people with normal glucose tolerance and typically return to basal levels 2-3h after food ingestion	**[Level 2++]**
IDF and other organizations define NGT as <7.8 mmol/l (140 mg/dl) 2h following ingestion of a 75-g glucose load	**[Level 4]**
The 2h timeframe for measurement of plasma glucose concentrations is recommended because it conforms to guidelines published by most of the leading diabetes organizations and medical associations	**[Level 4]**

Postmeal targets established by international organisations

Organisation	Postmeal Target values mmol/l (mg/dl)		Timing
IDF 2005[1]	<8.0 (<145)	T2DM	1-2h postmeal
ADA/EASD consensus statement 2006[2]	<10.0 (<180)	T2DM	1.5-2h postmeal
European Cardiovascular Prevention Guidelines 2007[3]	7.5-9.0 (135-160)	T1DM	"Peak"
	<7.5 (<135)	T2DM	
CDA 2003[4]	5.0-10.0 (90-180)	T1DM & T2DM	2h postmeal
ADA 2007[5]	<10.0 (180)	T1DM & T2DM	1-2h postmeal
AACE 2007[6]	<7.8 (140)	T1DM & T2DM	2h postmeal

1. IDF Global guidelines 2005. http://www.idf.org/webdata/docs/IDF%20GGT2D.pdf.
2. Nathan DM et al. Diabetes Care 2006;29:1963-1972.
3. Rydén L et al. *Eur Heart J* 2007;28:88-136.
4. CDA clinical practice guidelines. *Can J Diabetes* 2003;27:S1–S152.
5. ADA clinical practice recommendations. *Diabetes Care* 2007;30:S4–S41.
6. AACE Medical Guidelines for Clinical Practice for the Management of Diabetes Mellitus. *Endocr Pract* 2007; 13:5-68

Clinical Question #4
What are the targets for postmeal glycaemic control and how should they be assessed (1)?

Recommendation:

*Glycaemic goal for clinical management of diabetes:**

2h postmeal	***<7.8 mmol/l (<140 mg/dl)***

*Lower glucose parameters to as near normal as safely possible

Characterizing Glucose Exposure for Individuals with Normal Glucose Tolerance Using Continuous Glucose Monitoring and Ambulatory Glucose Profile Analysis

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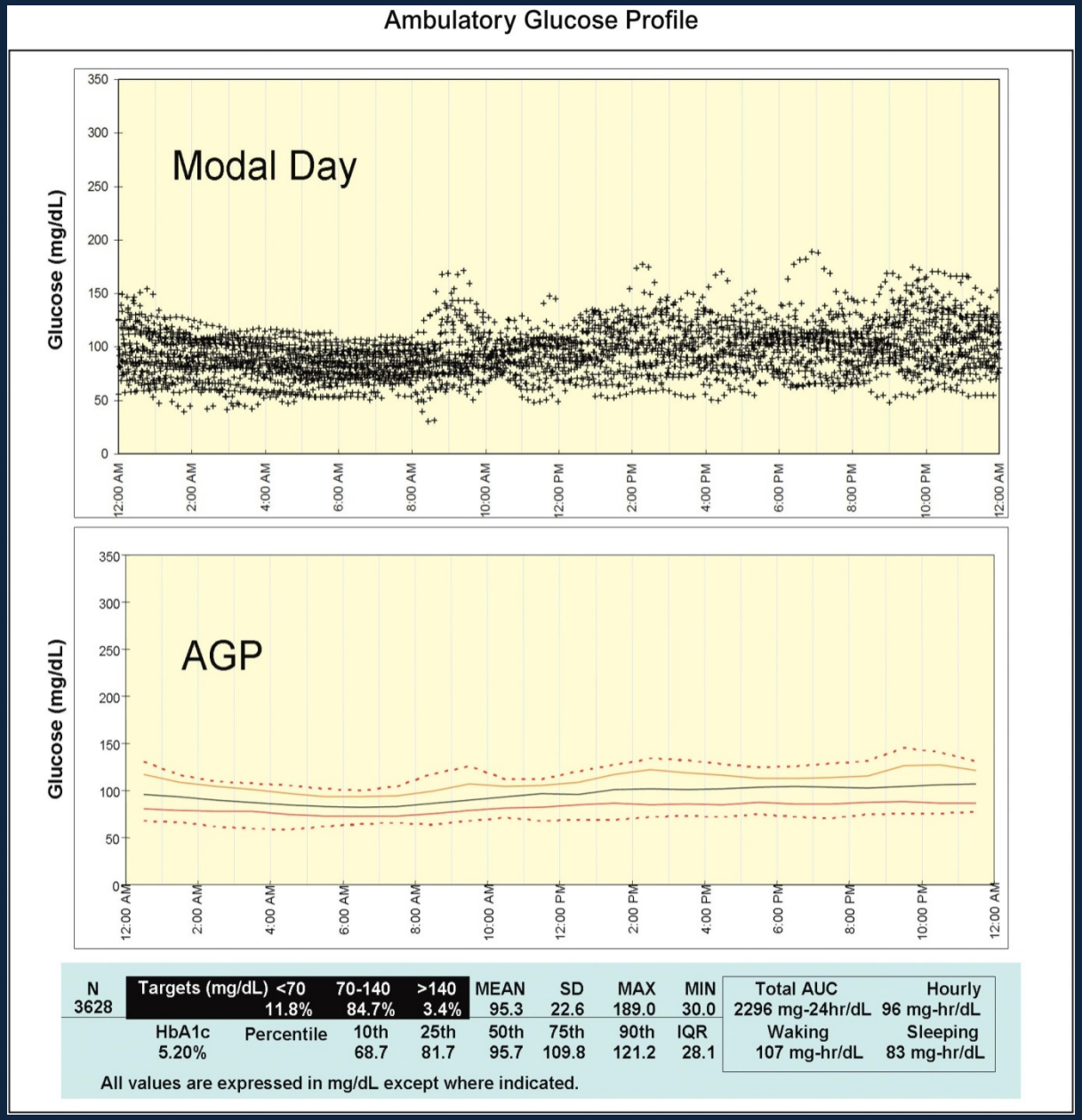

The modal day and the AGP depict 3,628 continuous glucose readings measured for 30 days. The modal day shows each data point graphed without regard to date. The AGP replaces the

Center solid line is the median, next two outer solid lines (25th and 75th percentiles) represent the IQR, the dotted lines depict the 10th and 90th percentiles

Clinical Question #4
What are the targets for postmeal glycaemic control and how should they be assessed (2)?

SMBG is currently the optimal method for assessing glucose levels	**[Level 1++]**
It is generally recommended that people treated with insulin perform SMBG ≥ 3X/day; SMBG frequency for people who are not treated with insulin should be individualized to each person's treatment regimen and level of glycaemic control	**[Level 4]**

Conclusions

- Postmeal and postchallenge hyperglycaemia are associated with cardiovascular (and other) risks
- Managing both postmeal and fasting glycaemia are needed to optimise glycaemic control
- Treatment of both should be initiated simultaneously at any HbA_{1c} level
- Subject to available therapies and technologies, 2h postmeal plasma glucose <7.8 mmol/l (140 mg/dl) is both reasonable and achievable