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Can technology produce worthwhile reductions in hypoglycaemia?

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Late 1970' s 2 seminal papers

- **Sonksen et al, Lancet 1978**
 - 64 patients measured blood glucose at home
 - 2/3 maintained tight glucose control for up to 18 months
 - Less hypoglycaemia
 - >70% preferred blood tests
- **Walford et al, Lancet 1978**
 - 69 patients measured blood glucose at home
 - Recorded profiles twice weekly
 - Very useful for hypoglycaemia and pregnancy
 - By the end 32/67 had profiles <10mM
 - ‘smaller and more portable machines will make technique more widely applicable’

Advent of SMBG

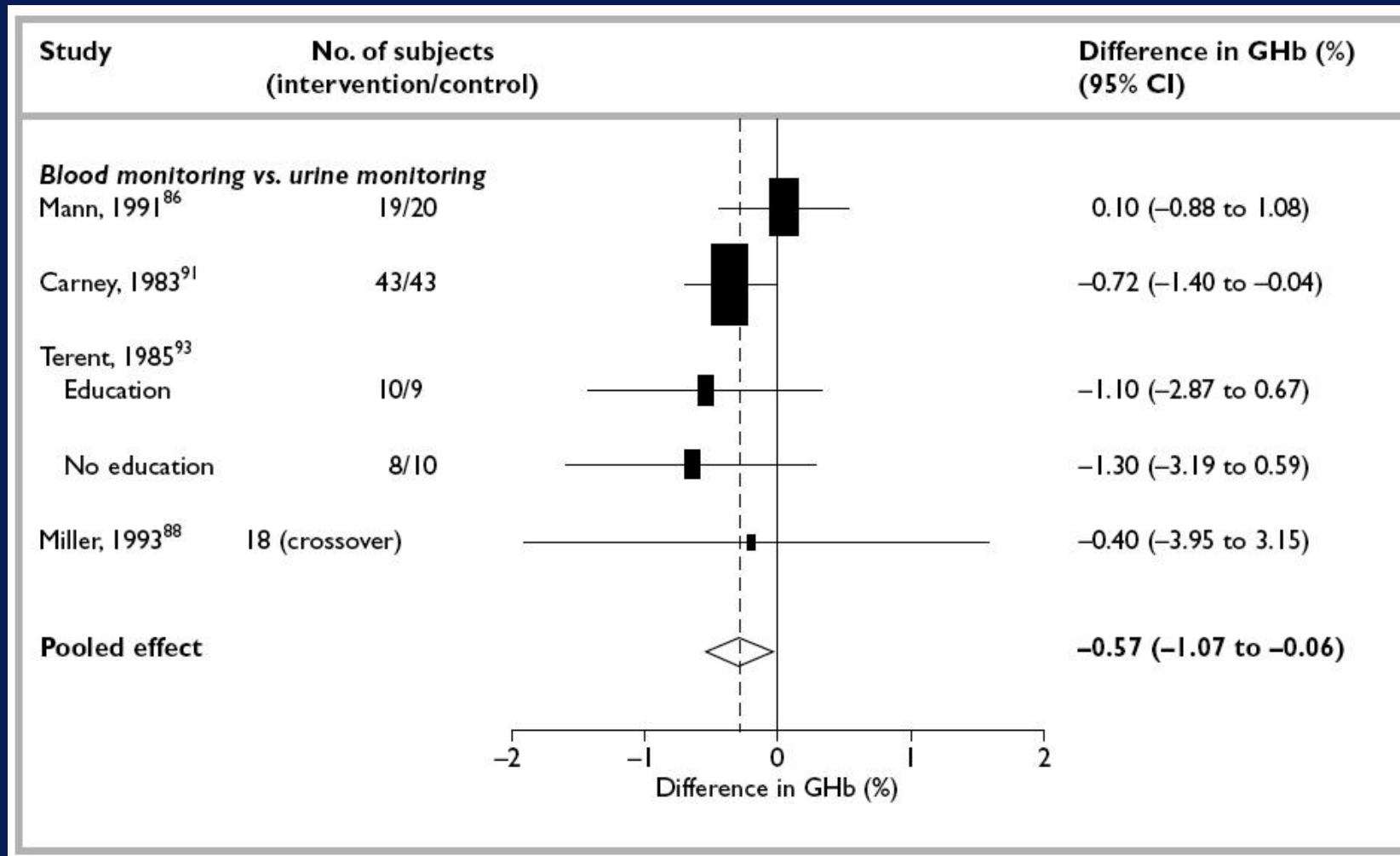
A technological revolution

- **Patients could control their diabetes more easily**
 - Adjust insulin more safely
 - Identify and treat hypoglycaemia at an early stage
- **Patients and clinicians learnt more about the variation in blood glucose during the day**
- **Motivating (for some)**

Meta-analysis of SMBG vs urine testing in Type 1 diabetes

4/24 studies with usable data

no differences in hypoglycaemia



Summary

- Blood glucose monitoring provided a technological revolution
- Ability of patients to identify hypoglycaemia and to contribute to self care has had major effects on QoL
- In practice modest improvement in HbA1c in Type 1 diabetes
- When compared to urine testing, no differences in hypoglycaemia suggesting limitations in RCTs/meta-analyses to establish benefit
- Variation in use and expense suggests we still don't know how best and in who to use this technology (particularly in Type 2 diabetes)

CSII

Potential benefits

- More precise basal insulin delivery
- Multiple boluses
- Adjustable basal insulin infusion, particularly at night
- Control of high fasting blood glucose
- In the UK, NICE recommends CSII in Type 1 diabetes with a high HbA1c and limited by hypoglycaemia

Systematic review, effects of CSII – RCT

- **20 studies comparing CSII with MDI**
 - Quality generally poor
 - In adults with Type 1 diabetes, HbA1c improved by 0.61% cw human insulin
- **Hypoglycaemic events did not differ between CSII and MDI in most trials**
 - some found fewer events with CSII
 - One found more hypoglycaemia with CSII

Updated systematic review

CSII vs NPH-based MDI in T1DM hypoglycaemia

- Trials in adults:
 - few patients
 - short durations
 - insufficient severe hypoglycaemic episodes to be conclusive
 - no significant differences in severe hypoglycaemia
- One trial in children:
 - a significant drop in severe hypoglycaemia, but based on five episodes on MDI vs two on CSII

Updated systematic review - hypoglycaemia

CSII versus NPH-based MDI in T1DM

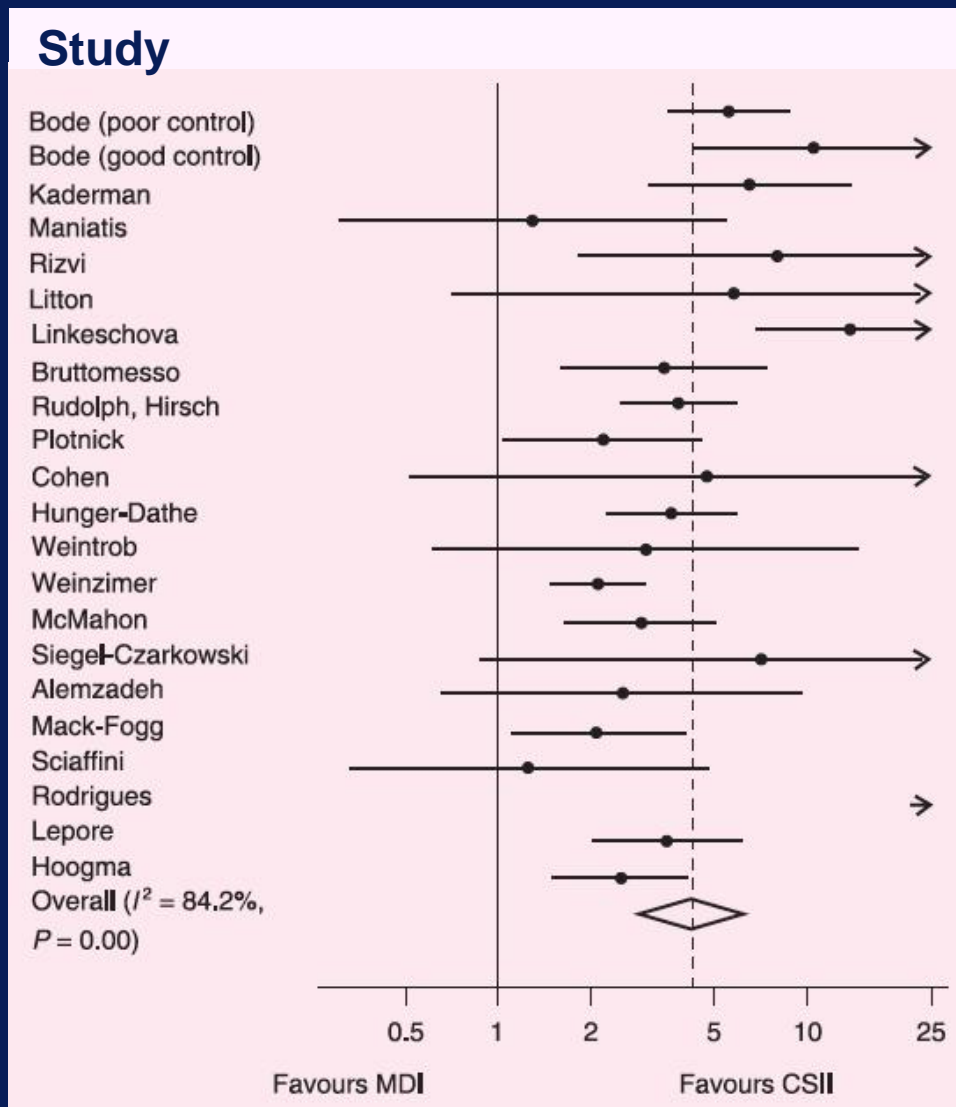
- Trials in adults
 - too few patients
 - too short durations
 - too few severe hypoglycaemic episodes to be conclusive

but reported no significant differences in the frequency of severe hypoglycaemia

- One trial in children -a significant drop in severe hypoglycaemia, but based on five episodes on MDI versus two on CSII

Meta-analysis comparing CSII vs human in those with high frequency of hypoglycaemia (>10 episodes a year)

22 studies, severe hypoglycaemia was reduced rate ratio of 2.89 for RCTs and 4.34 for before/after studies mean difference in HbA_{1c}, 0.2%



CSII and effects on hypoglycaemia

Summary

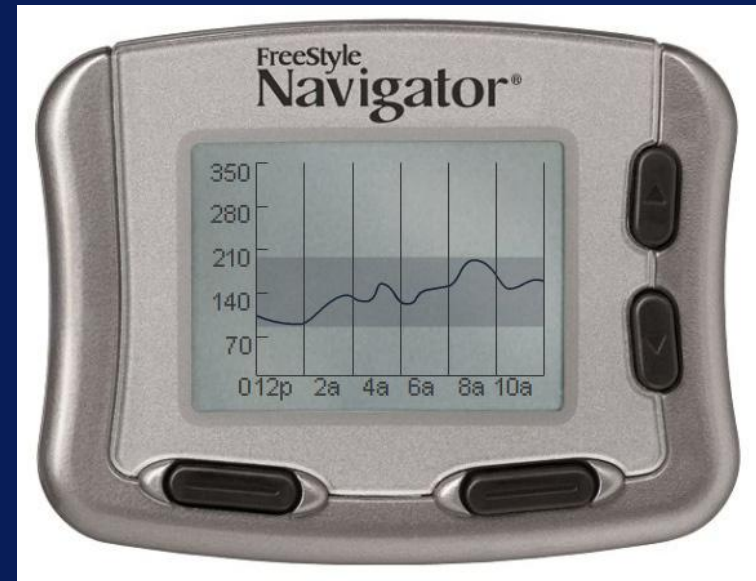
- Most trials compared to human insulin rather than analogues, small numbers, short duration
- Modest differences (although improved) in HbA_{1c}
- Minor difference in severe hypoglycaemia, but differing definitions limits meta-analysis
- When very common, reductions in hypoglycaemia
- No trial comparing pumps to high quality skills training in intensive insulin therapy

Differences between SMBG and continuous glucose monitoring (CMBG)

- SMBG provides only a brief snapshot of blood glucose profile mostly during the day and is inconvenient
- CMBG provides far more information
 - both a help and a hindrance
- CMBG has the potential to provide
 - Reliable warning of impending hypoglycaemia to many
 - If attached to a reliable pump, might cure Type 1 diabetes in a few

JDRF study of CGM

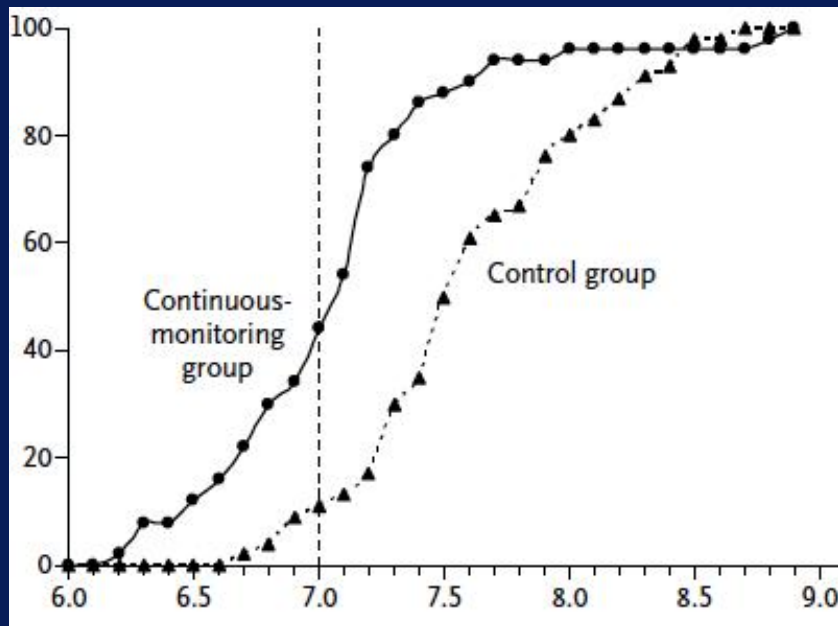
- 322 participants with Type 1 diabetes
- 3 age groups, adults, young adults, children
- HbA_{1c} 7-10%, primary outcome, HbA_{1c} at 6 months
- Participants issued with different CGM devices
- Insufficient numbers to measure severe hypoglycaemia



JRDF study of CGM

cumulative distribution of HbA1c

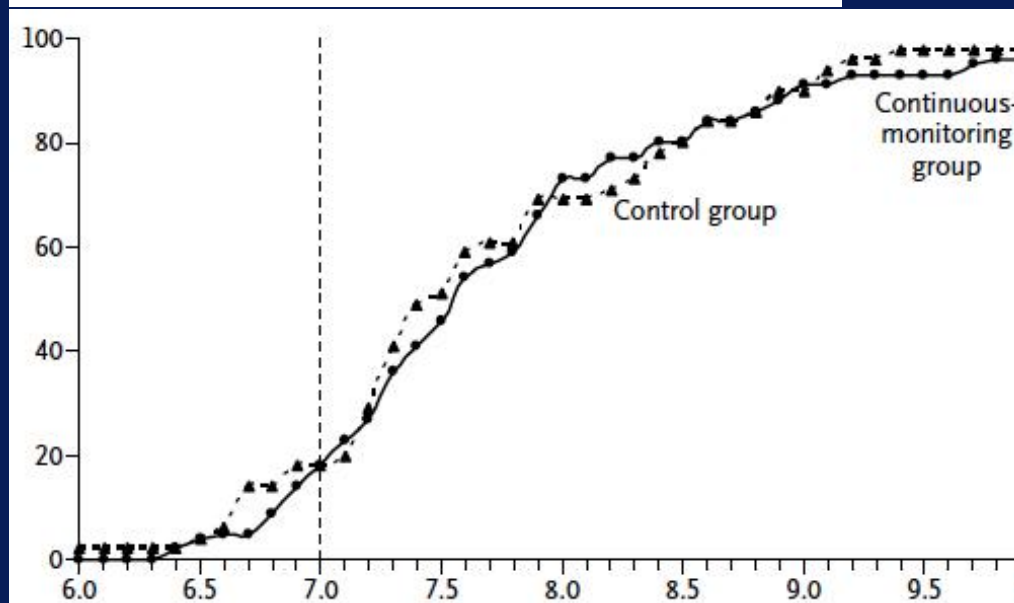
Age >25y



Differences in HbA1c only significant for adult group (and children)

Those using CGM >6 days a week, 83% in adults and 30% for young adults

Age 15-24y



JDRF study of CGM

Variable	≥25 Yr		P Value†	Age Group 15–24 Yr		P Value†
	Continuous-Monitoring Group (N=52)	Control Group (N=46)		Continuous-Monitoring Group (N=57)	Control Group (N=53)	
Severe hypoglycemic event ‡						
No. per patient — no. of patients (%)						
0 events	47 (90)	42 (91)		54 (95)	48 (91)	
1 event	3 (6)	3 (7)		1 (2)	4 (8)	
2 events	1 (2)	0		2 (4)	1 (2)	
3 events	0	1 (2)		0	0	
6 events	1 (2)	0		0	0	
Patients with ≥1 event — no. of patients (%)	5 (10)	4 (9)	1.0	3 (5)	5 (9)	0.48
Events per 100 person-yr — no.	43.4§	26.3	0.66	17.9	23.9	0.64

JDRF study of CGM

Conclusion

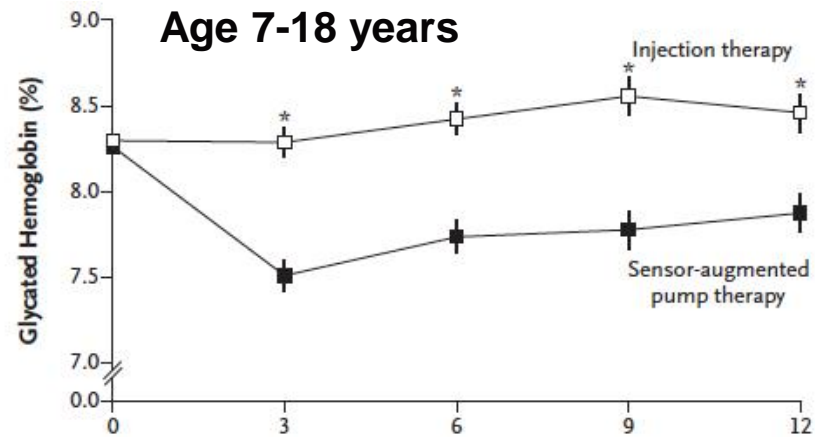
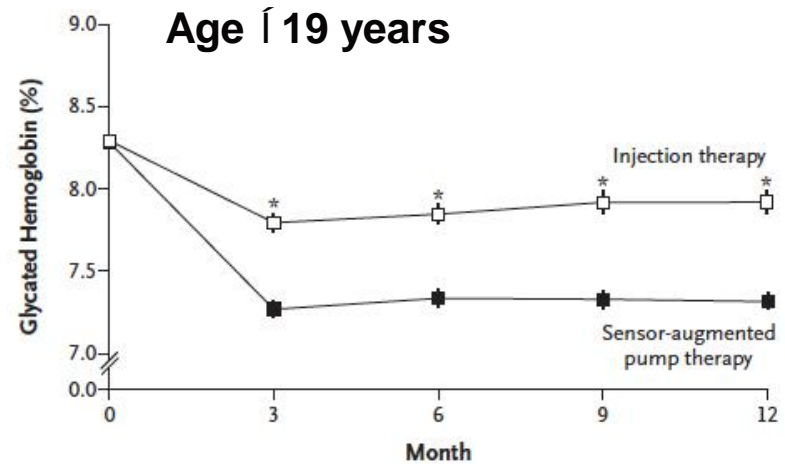
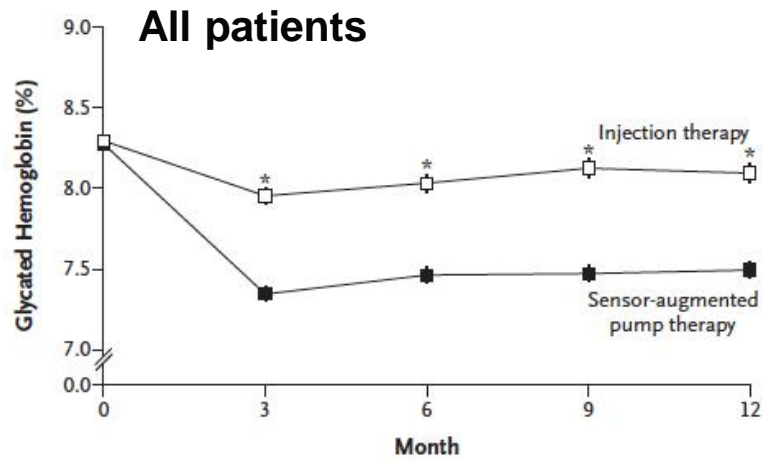
- CGM doesn't appear useful in less motivated patients
- CGM improves HbA_{1c} and may reduce hypoglycaemia in adults who are motivated and can incorporate it into diabetes self-management

Effectiveness of Sensor Augmented Insulin Pump Therapy in Type 1 Diabetes STAR3

- 485 patients
(adults and children)
- HbA_{1c} 7.5-9.5%
- 1 year measuring HbA_{1c}
- Using intensive insulin therapy
- No history of severe hypoglycaemia



STAR3 HbA_{1c} results in 3 groups



STAR3

Effect on severe hypoglycaemia

- Severe hypoglycemia rates in pump-therapy group (13.31 vs 13.48 per 100 person/years, $P = 0.58$)
(vs rates over 10 times higher in clinical practice)

Conclusions

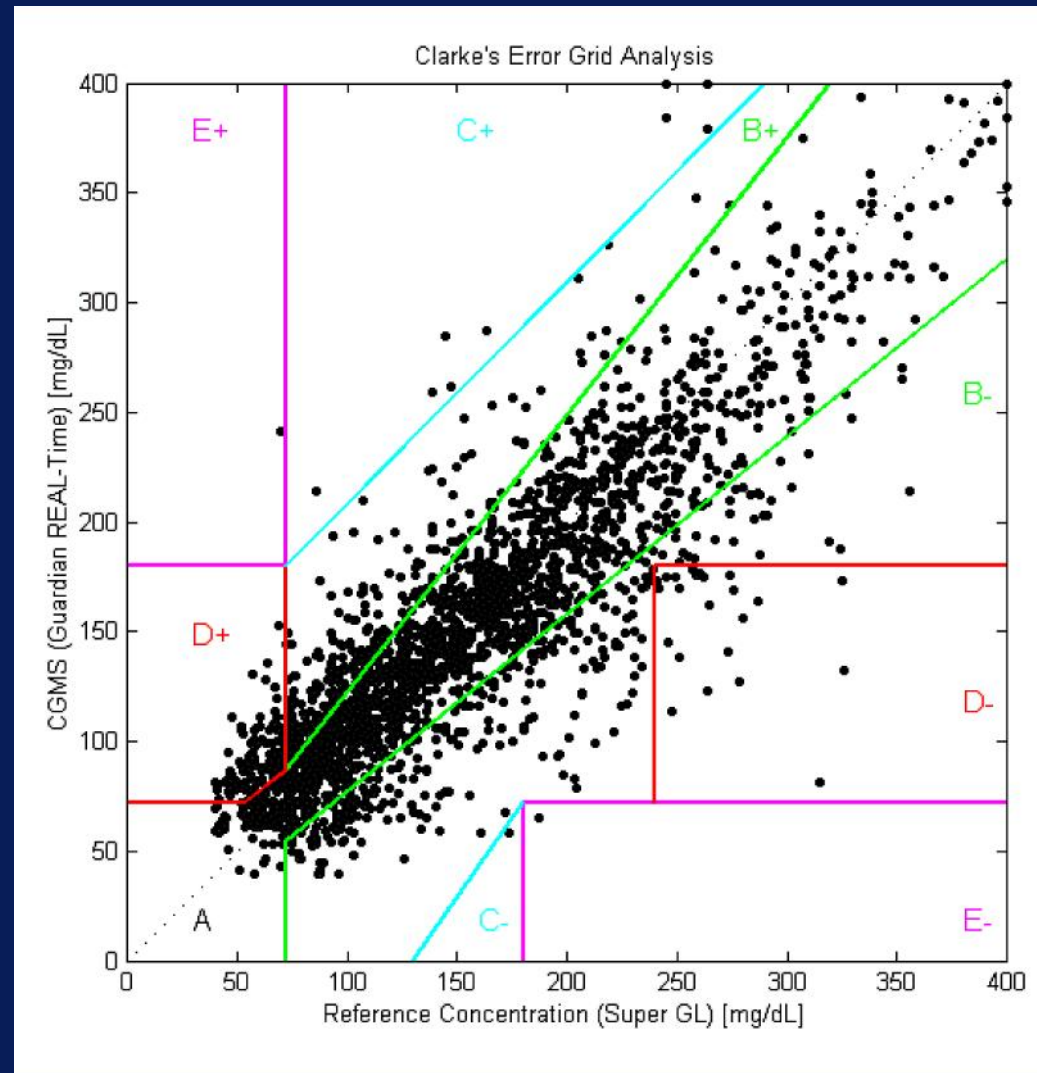
- In type 1 diabetes patients with suboptimal glycemic control, a sensor-augmented insulin pump vs MDI using insulin analogues led to
 - significant improvement in HbA_{1c}
 - no reduction in severe hypoglycaemia

Why has technology been relatively disappointing in reducing the risk of severe hypoglycaemia?

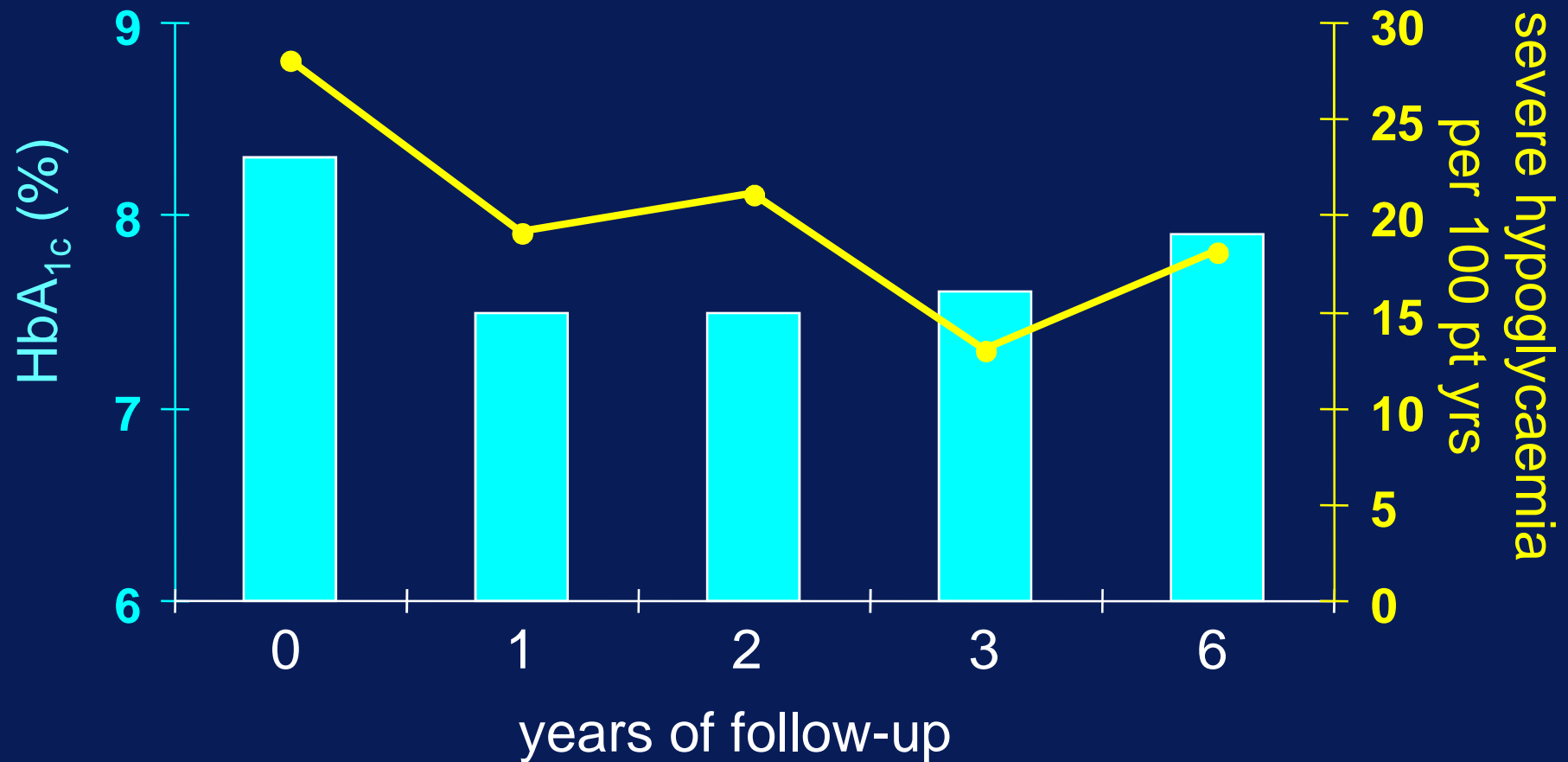
- RCTs, where severe hypoglycaemia is often confined to a few individuals may be an inappropriate design
- Different definitions of hypoglycaemia prevent robust metanalysis
- CGM is still insufficiently accurate in the low range to provide reliable hypoglycaemia alerts
- A continued failure to integrate the technology with other aspects of diabetes self management

Accuracy of a continuous glucose monitoring system (CGMS): still room for improvement

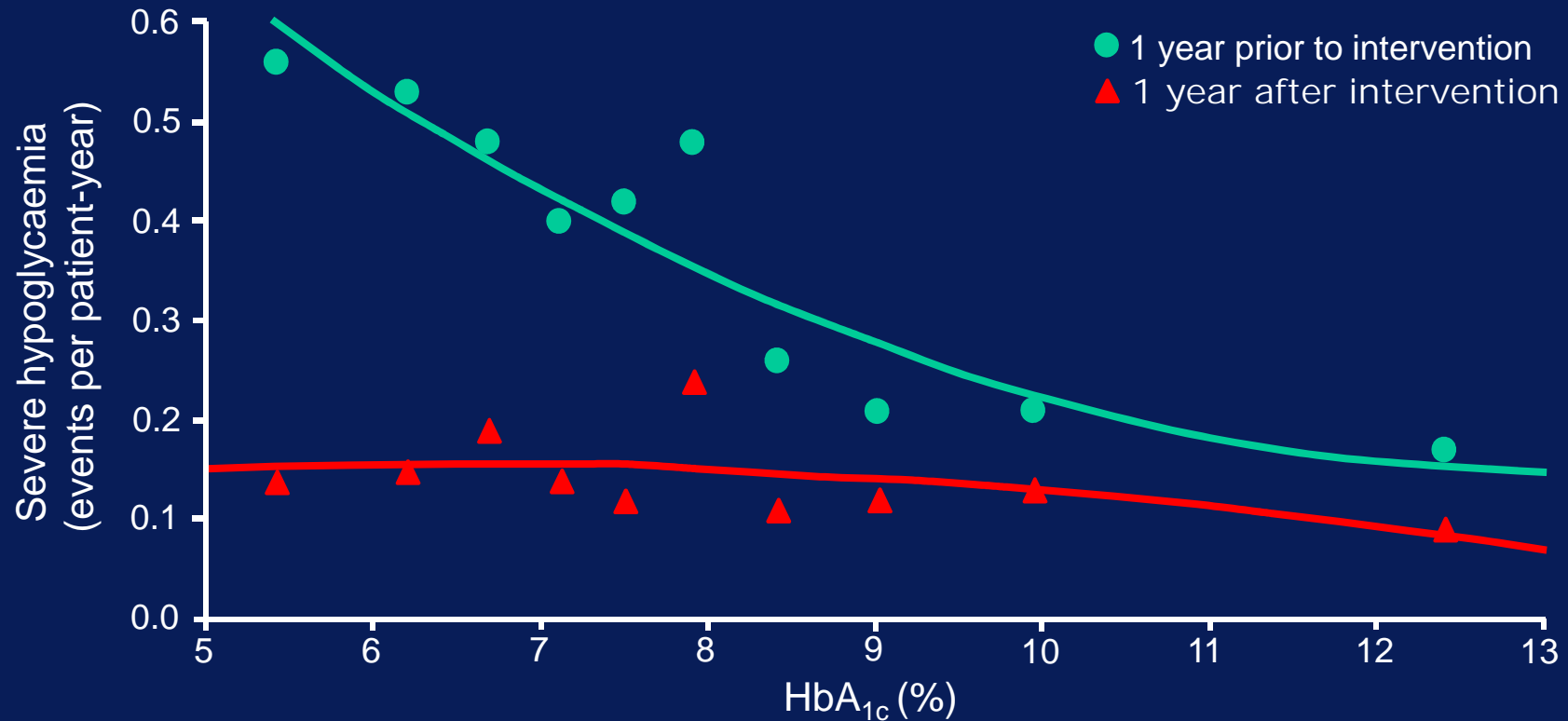
- 18 adults with Type 1 diabetes
- More than half true hypos (<4mM) undetected
- (sensitivity 38%)
- >half hypo alert alarms were false
- (false alert rate 53%)
- Median ref glucose concentration for alarm was 5mM



SMBG integrated into high quality training in insulin self management

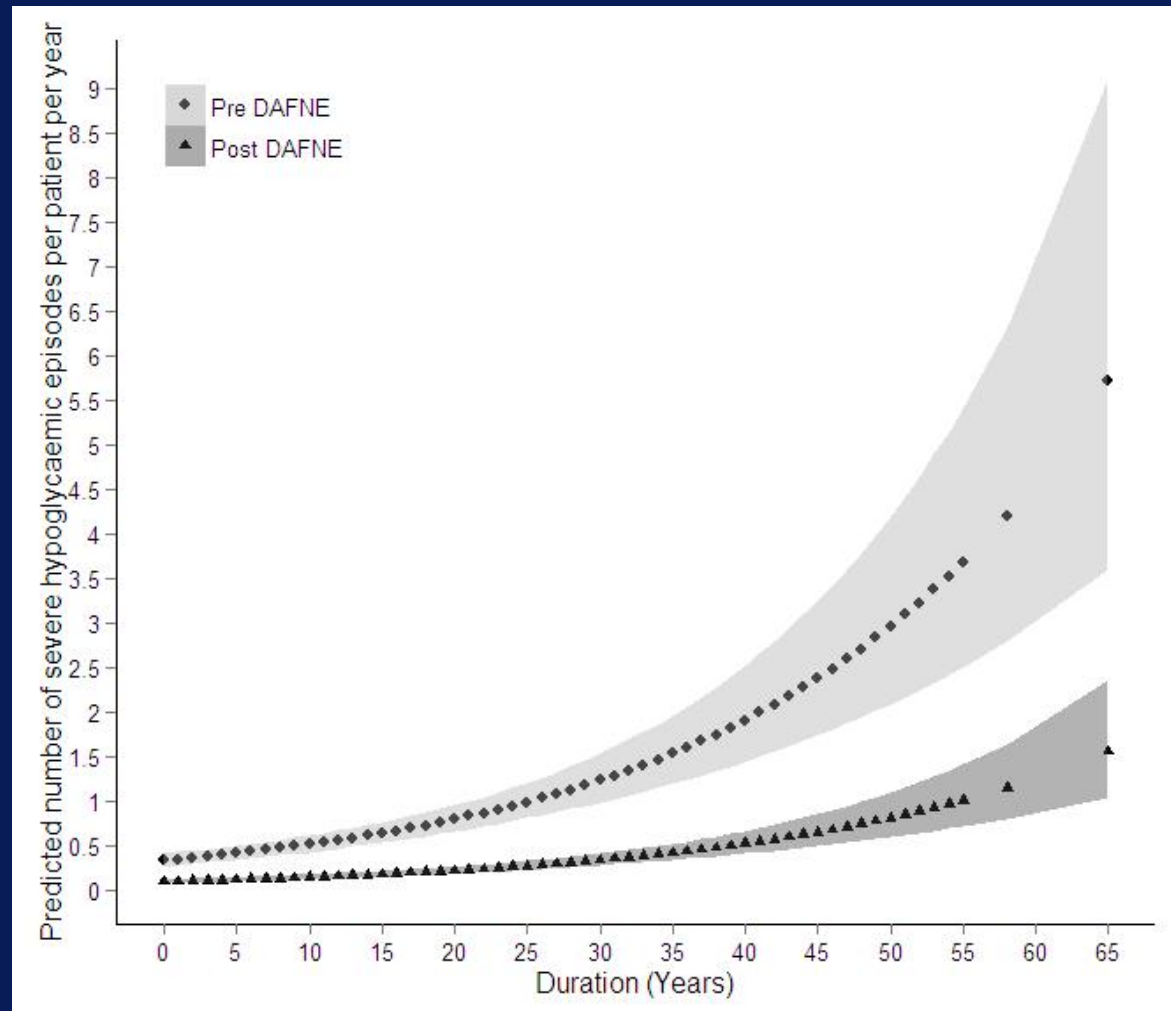


Effect of a structured training course alone on severe hypoglycaemia (coma or IV glucose) in over 9000 adults with type 1 diabetes



- 20-h inpatient training course
- Patients advised to measure blood glucose before main meals and at bedtime
- Insulin adjusted to actual blood glucose level and intended carbohydrate intake

Effect of duration of diabetes on rates of severe hypoglycaemia pre and post DAFNE training



Impact of skills training (DAFNE) in reducing hypoglycaemia risk (rates per pt year) in those with unawareness

Baseline	n	SH pre-DAFNE		SH post-DAFNE		Relative risk (95% CI)	p-value
		Mean	Range	Mean	Range		
Aware	528	0.4	0 - 17	0.2	0 - 12	0.52 (0.38 to 0.71)	<0.001
Impaired Awareness	406	1.4	0 - 50	0.3	0 - 10	0.20 (0.14 to 0.30)	<0.001
All	934	0.8	0 - 50	0.2	0 - 12	0.29 (0.22 to 0.39)	<0.001

Impact of skills training (DAFNE) in reducing hypoglycaemia risk (rates per pt year) in those with unawareness

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RCTs of technology vs evaluated roll-outs of structured training in self management

- RCTs select patients who want to use technology and may do worse in the control group
- RCTs usually underpowered to demonstrate benefit in severe hypoglycaemia
- Evaluated roll-outs reflect real-life with high rates of hypoglycaemia and large numbers but prone to bias and drop out in the absence of a control group

Current work incorporating technology and educational interventions

- **Hypo COMPaSS trial**

- 96 Type 1 adults with unawareness randomized to MDI or CSII; and to RT-CGM or SMBG
- 2x2 factorial design, duration of 24 weeks
- all receiving ‘hypoglycaemia’ self management education at start

- **REPOSE Trial**

- 280 Type 1 adults randomised to skills training (DAFNE) plus CSII or MDI
- Duration 2 years

The future (1)

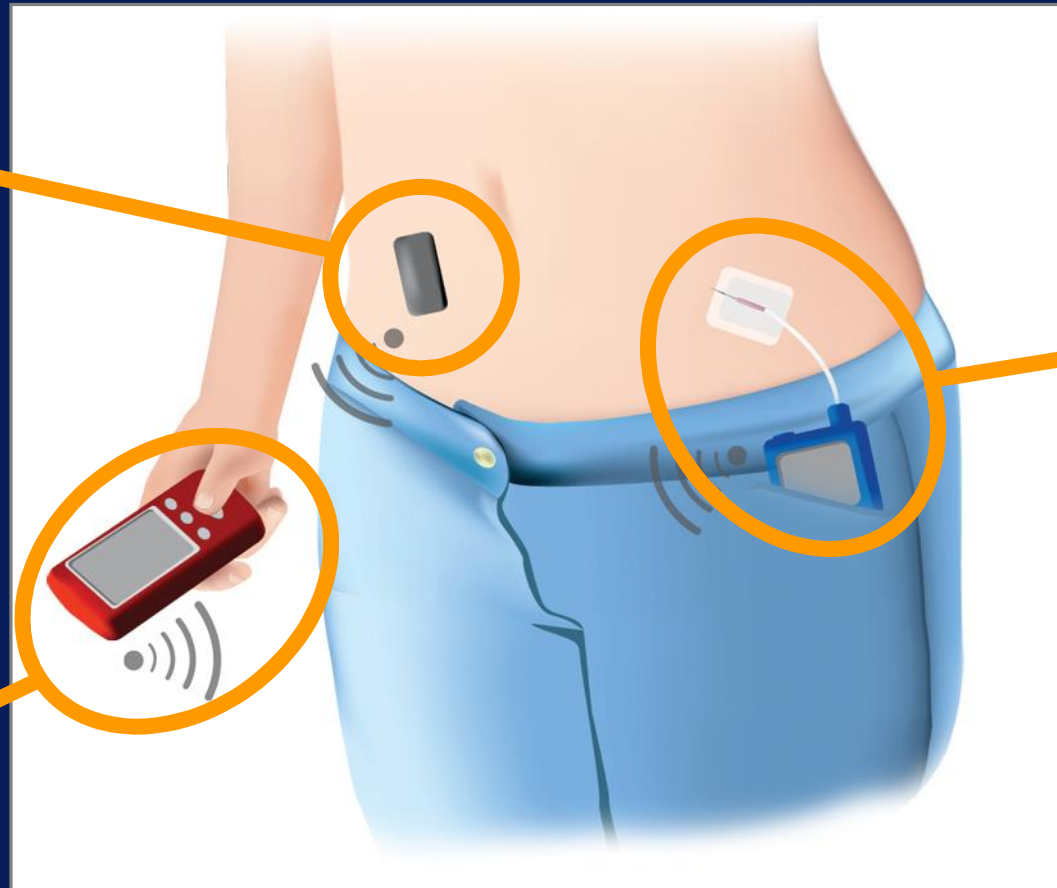


The artificial pancreas (Closed-loop)

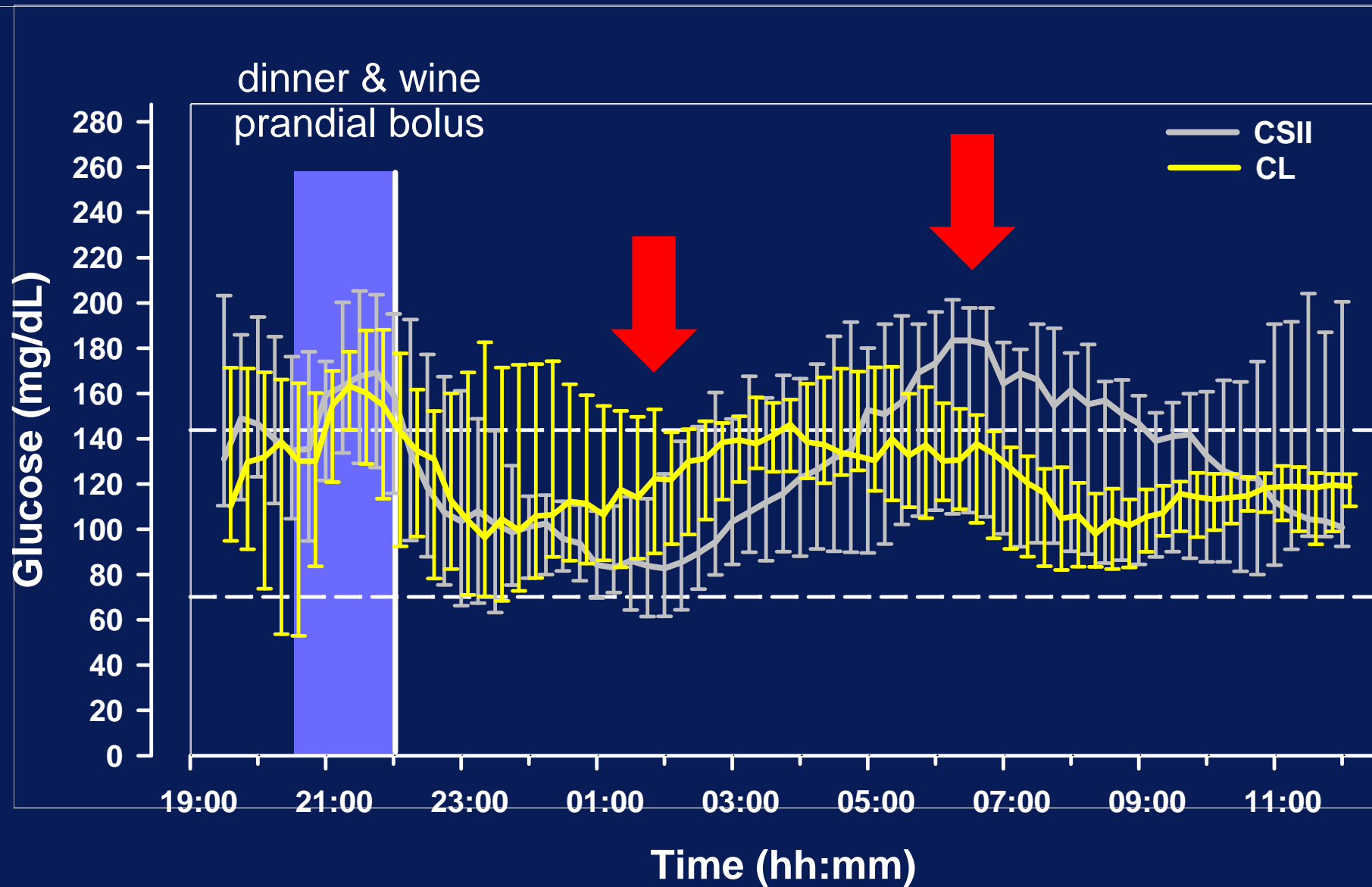
continuous
glucose
monitor

insulin
pump

control
algorithm



Median Plasma Glucose



Conclusions

- Despite use of SMBG in Type 1 diabetes, blood glucose control often poor and hypoglycaemia common as many patients self manage ineffectively
- Trials of CGM/CSII suggest modest benefit in reducing HbA_{1c} and hypoglycaemia
- Technology is one component of care and is expensive
- High quality self management training using conventional 'tools' may reduce the risk of severe hypoglycaemia as effectively as new technology
- Patients must integrate technology more effectively into self management if the full potential of reducing hypoglycaemia is to be realised