CSII from its beginning

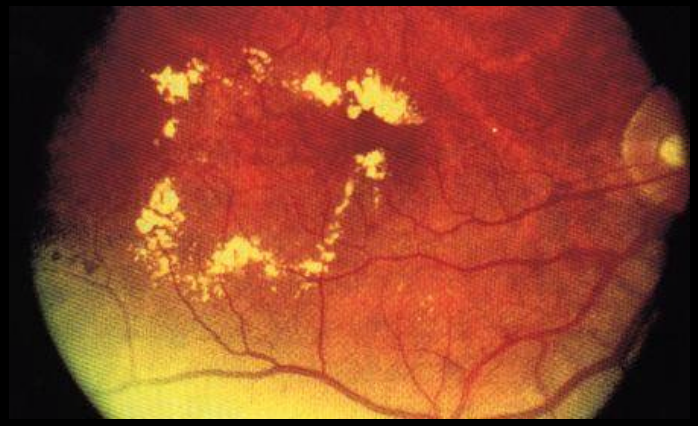
John Pickup
King’s College London School of Medicine
Guy’s Hospital, London

Why was CSII invented?

Back to the 1970s

Mysteries of the 1970s

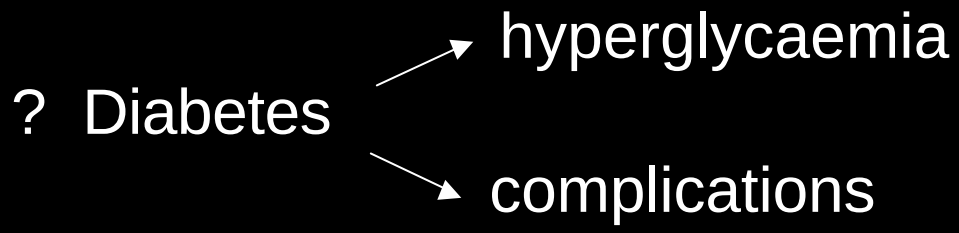
Why do people like John Travolta?



What causes diabetic Complications?

Views on diabetic complications in the 1970s

? Diabetes ? hyperglycaemia ? complications

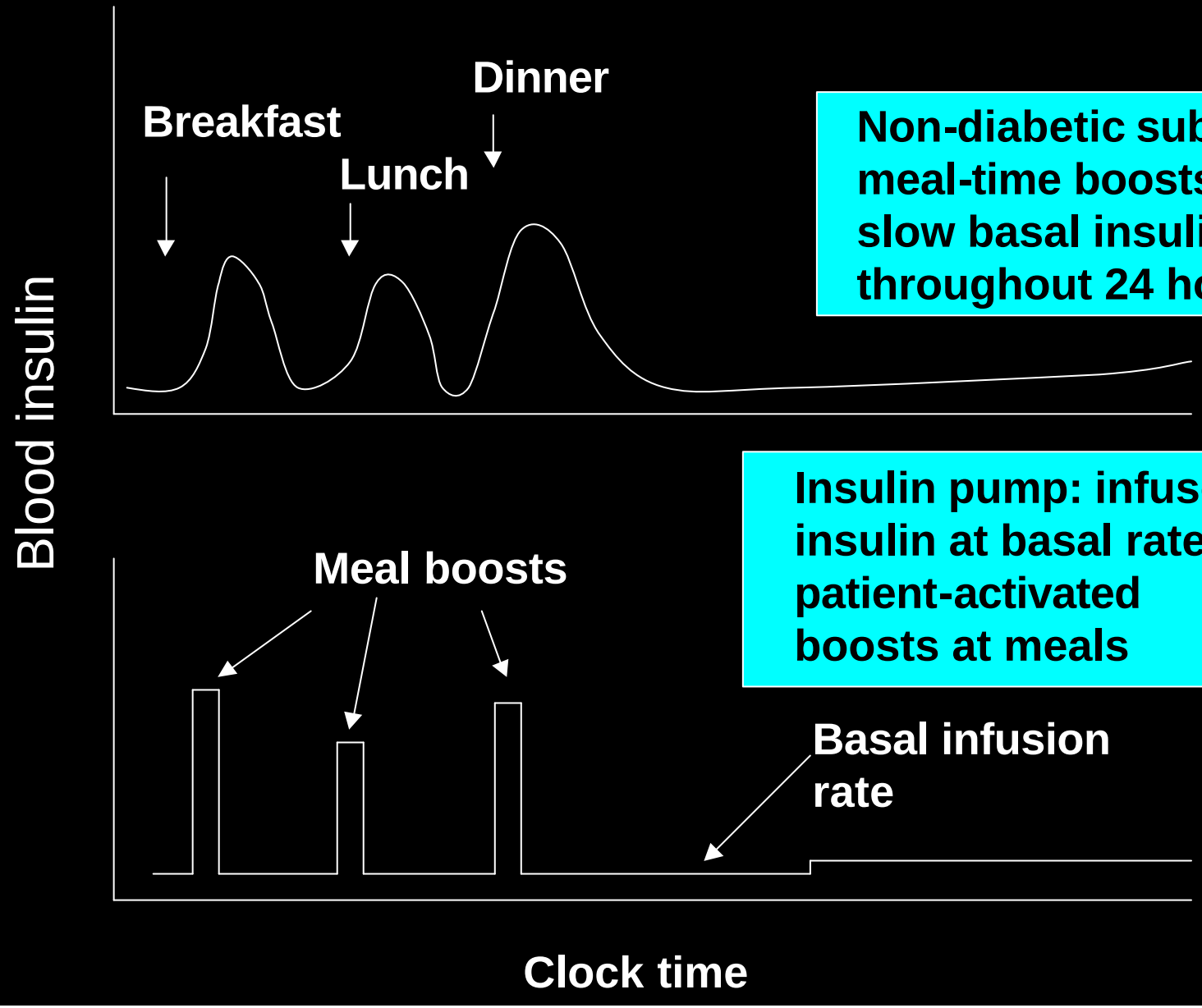


Testing the hypothesis:
allocate diabetic patients to near-normoglycaemia
for a prolonged period,
observe effect on complications

The problem

No way of maintaining strict glycaemic
control with insulin injections – need
new ways of improving control

Can we mimic non-diabetic insulin delivery by infusing insulin?



Slama, Hautecouverture, Assan, Tschobroutsky 1974

- 7 type 1 diabetic patients
- Regular insulin IV for 1-5 days from peristaltic pump in shoulder bag
- Basal rate and 15 fold higher prandial rate
- Prolonged insulin infusions feasible
- Very good glycaemic control possible without closing the loop but IV route has problems

Continuous subcutaneous insulin infusion (CSII)

The first insulin pump for CSII (Pickup et al., 1976/77)

- Developed as a research procedure to test effect of improved control on complications
- Basal and augmented preprandial insulin infusion given subcutaneously

What we asked 30 years ago

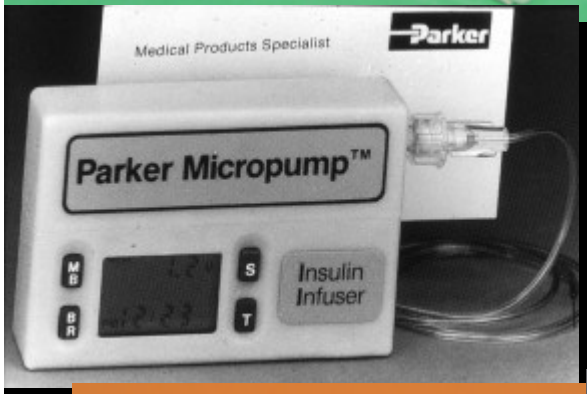
- Can technology for insulin infusion be improved?

  (Pumps were relatively unreliable and not programmable)

What we asked 30 years ago

- Can technology for insulin infusion be improved?
- Is CSII any better than best injection therapy, e.g. with pens?
- Is long term insulin infusion safe – what are the complications?
- Is CSII an experimental or routine treatment?
- If routine, what are the clinical indications?
- If experimental, does improved control influence diabetic complications?
- Is there a better pump insulin than regular insulin?
- Can closed-loop insulin delivery be a routine treatment?
- Are there advantages for alternative delivery routes – im, ip, intranasal, inhaled, oral?

The evolution pump technology



What we asked 30 years ago

- Is glycaemic control on CSII any better than best injection therapy?
- 30 years of controversy and confusion

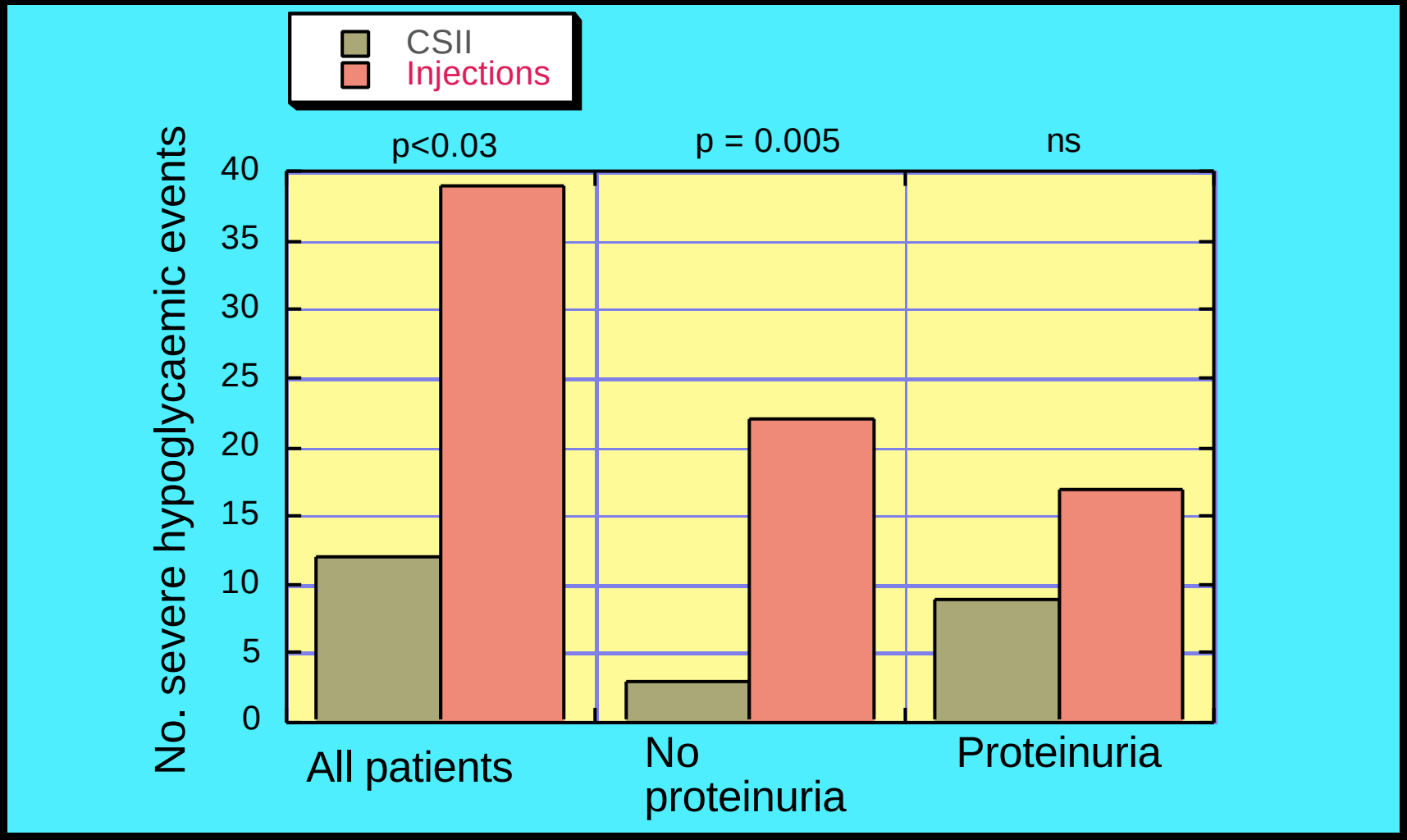
Best evidence for effectiveness of CSII

CSII reduces the frequency of hypoglycaemia compared to insulin injection therapy

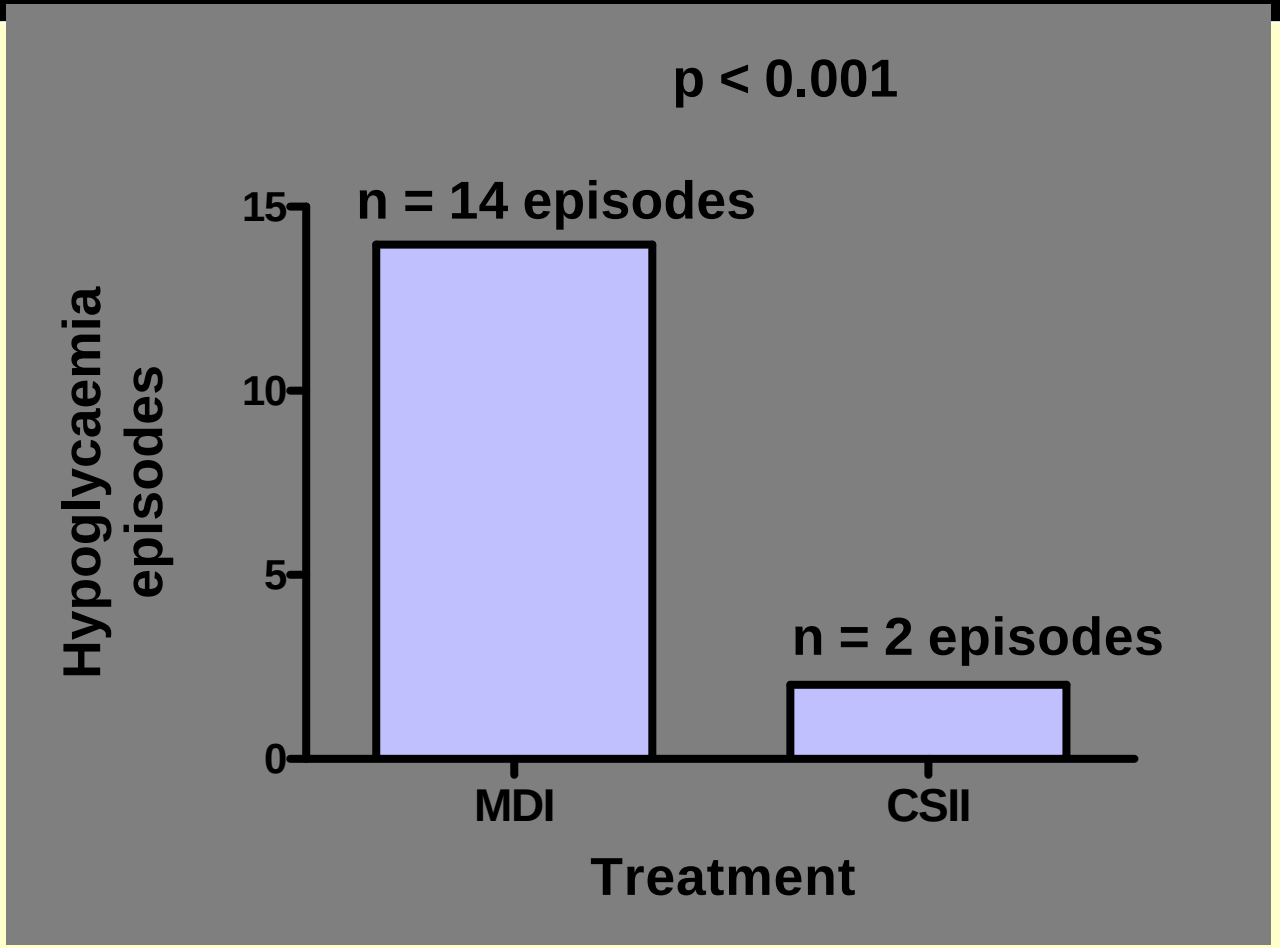
Known in mid 1980s but had to be rediscovered 10 years later

Severe hypoglycaemia CSII vs. insulin injection therapy (n=40, >6 mo treatment)

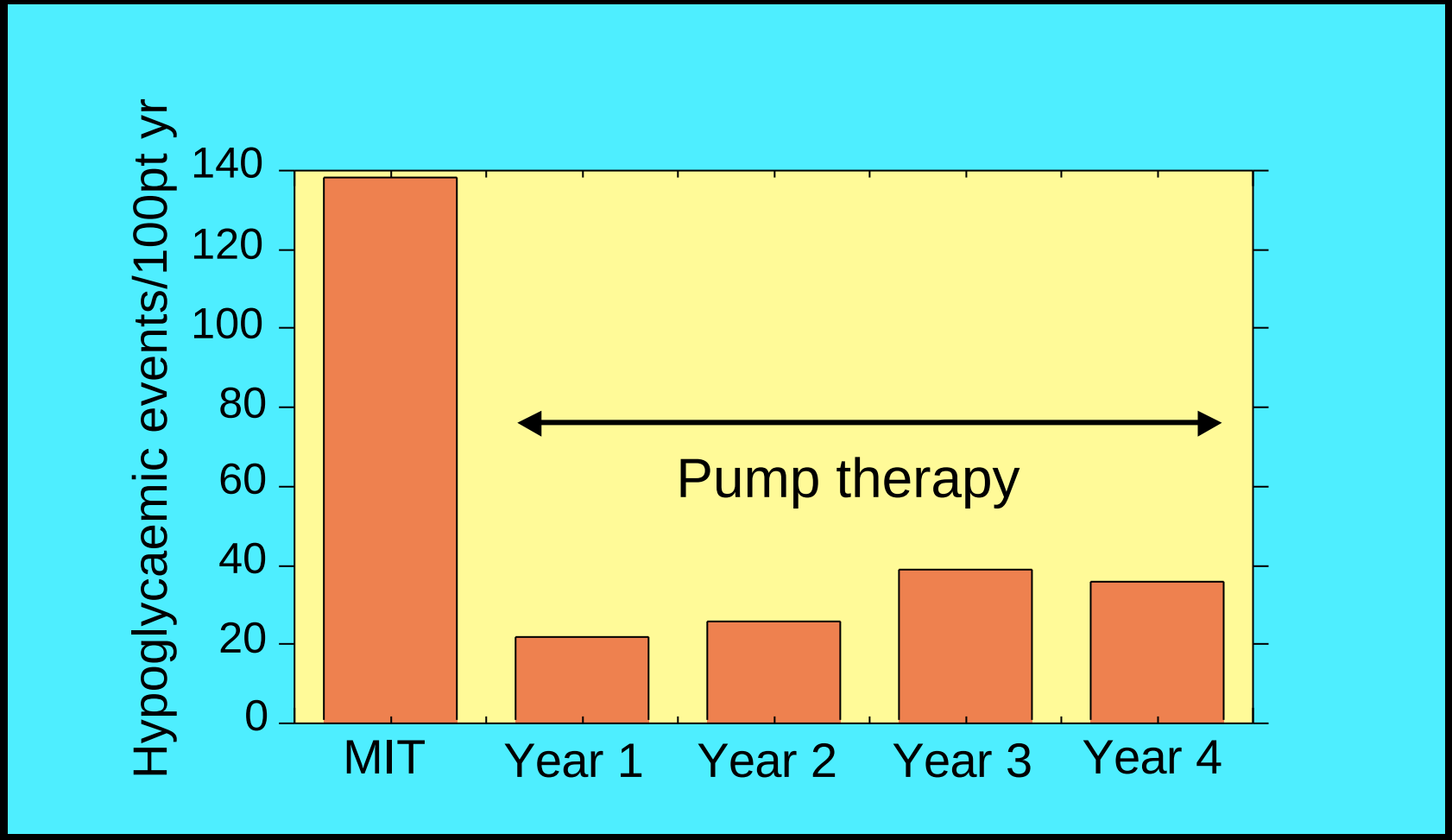
Bending, Pickup, Keen 1985



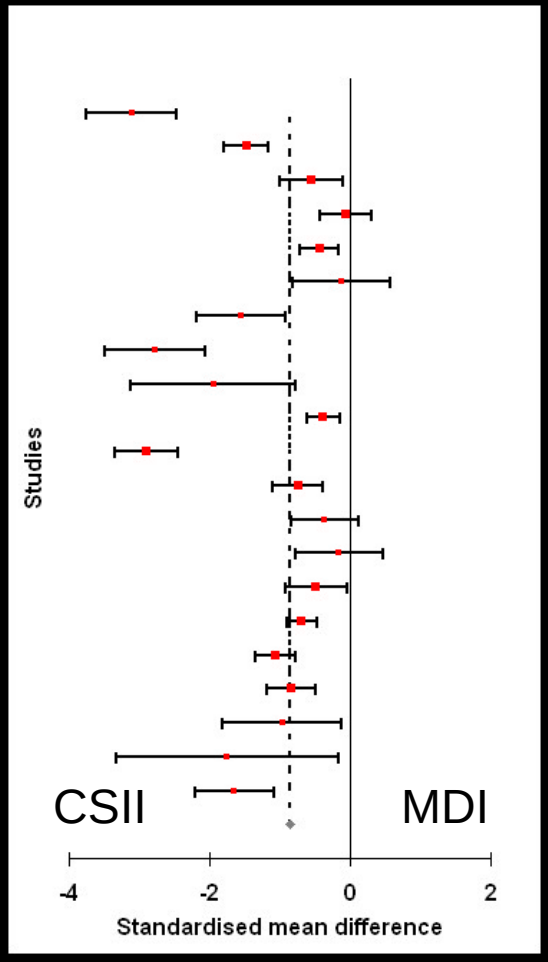
Reduction in severe hypoglycaemia in the Oslo Study (1986): RCT of MDI (and CIT) vs. CSII



Reduction in severe hypoglycaemia in 55 type 1 diabetic subjects: multiple insulin injections vs pumps Bode et al. 1996



Meta-Analysis of Severe Hypoglycaemia MDI vs CSII



- 21 trials
- Rate of severe hypoglycemia on MDI reduced by CSII from median 46 (23 - 81) to 12 (9 - 20) episodes / 100 patient-years

Pickup JC, et al. Unpublished Data

Severe hypoglycaemia is not improved by MDI with glargine or detemir vs. NPH regimens

Glargine

- Raskin et al Diabetes Care 2000; 23: 1666
- Warren et al Hlth Tech Assess 2004; 8: 1(systematic review)

Detemir

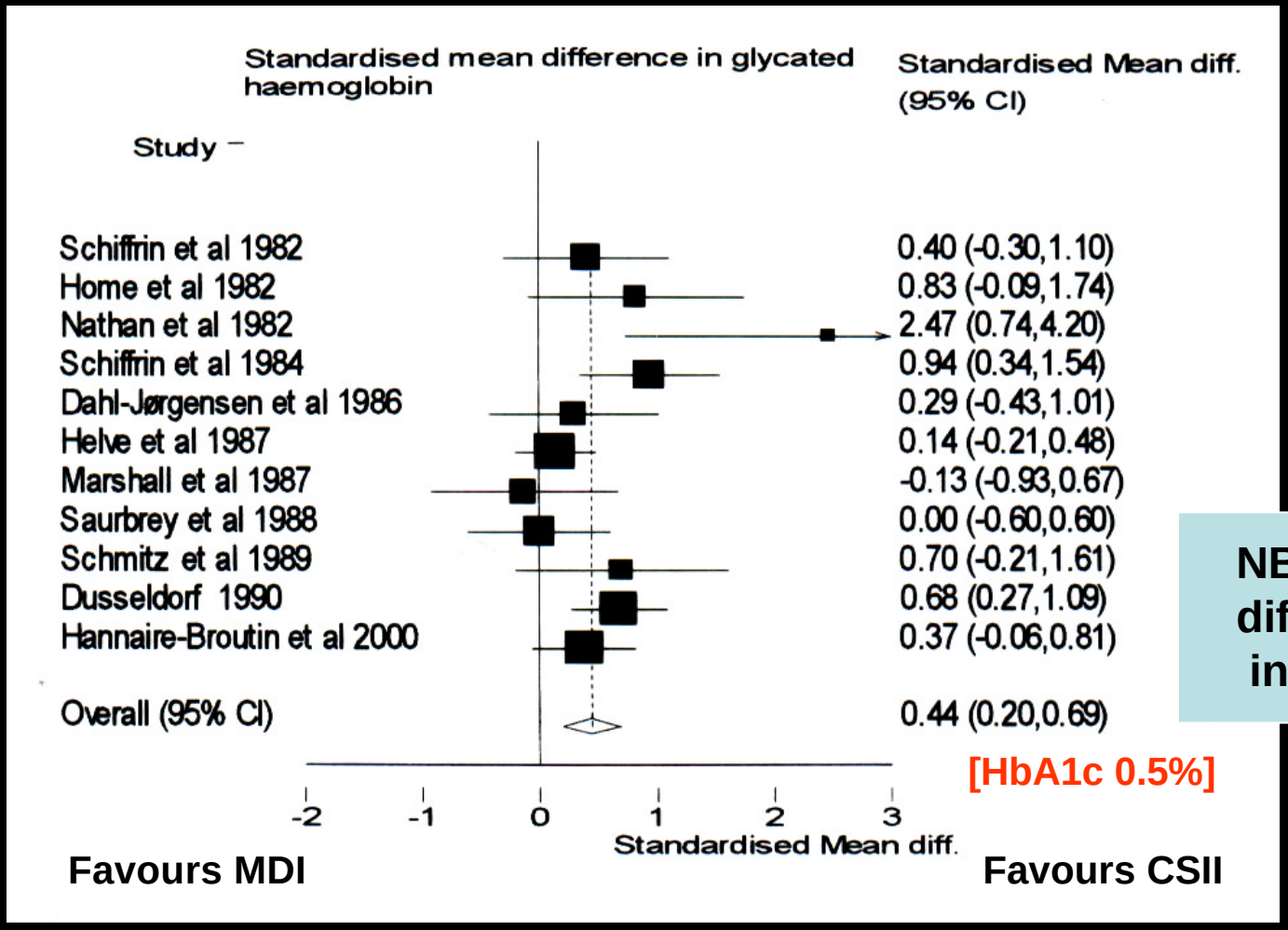
- Russell-Jones et al Clin Ther 2004; 26: 724
- Hermansen et al Diabetologia 2004; 47: 622
- Home et al Diabetes Care 2004; 27: 1081

What we asked 30 years ago

- Is HbA1c any better on CSII vs. best injection therapy?
- Many people still confused about pump effectiveness in 2006
- Had to discover that pumps are most effective for worst controlled patients (last year or so)

Meta-analysis in general diabetic patients

HbA1c in RCTs of MDI vs. CSII, Pickup et al., 2002



NB: small difference in HbA1c

[HbA1c 0.5%]

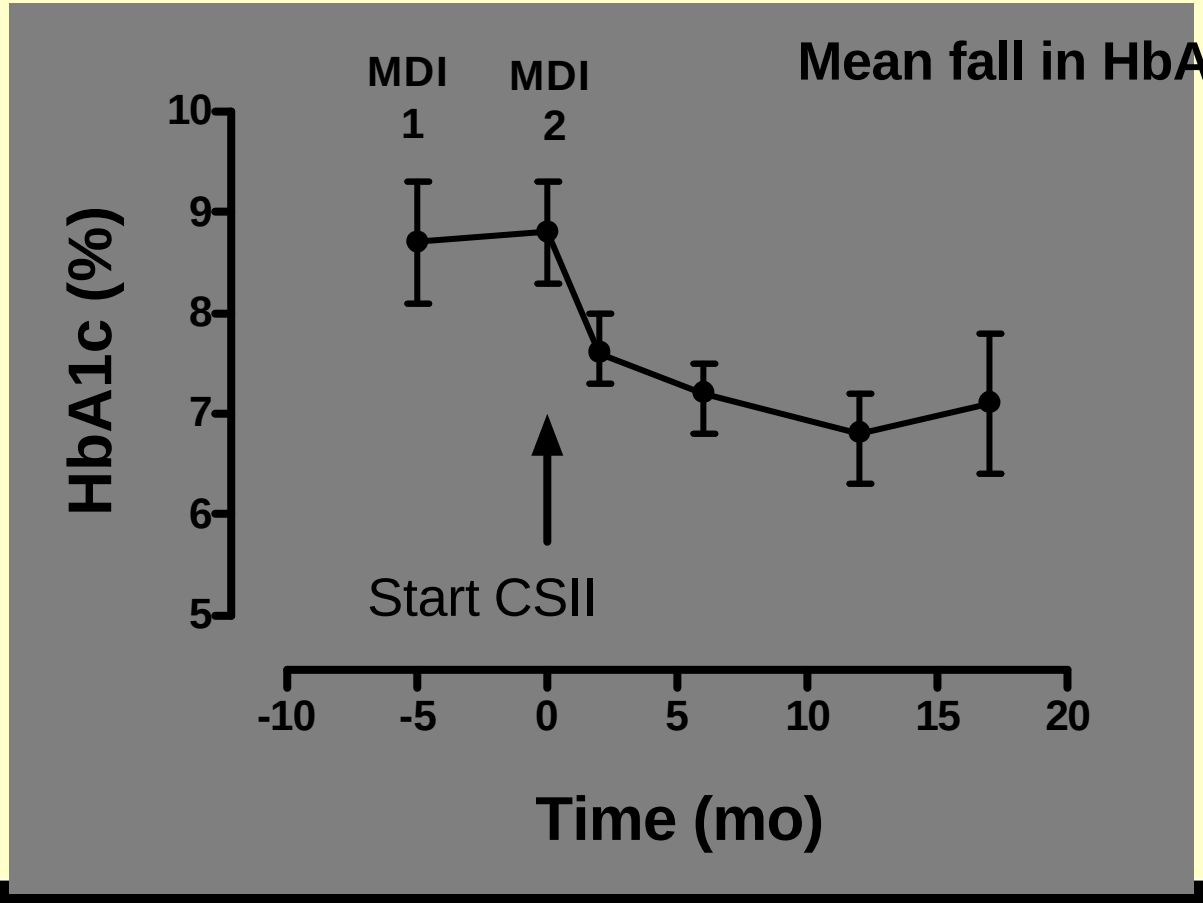
BUT

Reduction of HbA1c not well studied in (clinically-recommended) group of hypoglycaemia-prone type 1 diabetic patients

Reduction in HbA1c on switching to CSII is greater than expected in hypoglycaemia-prone type 1 diabetes

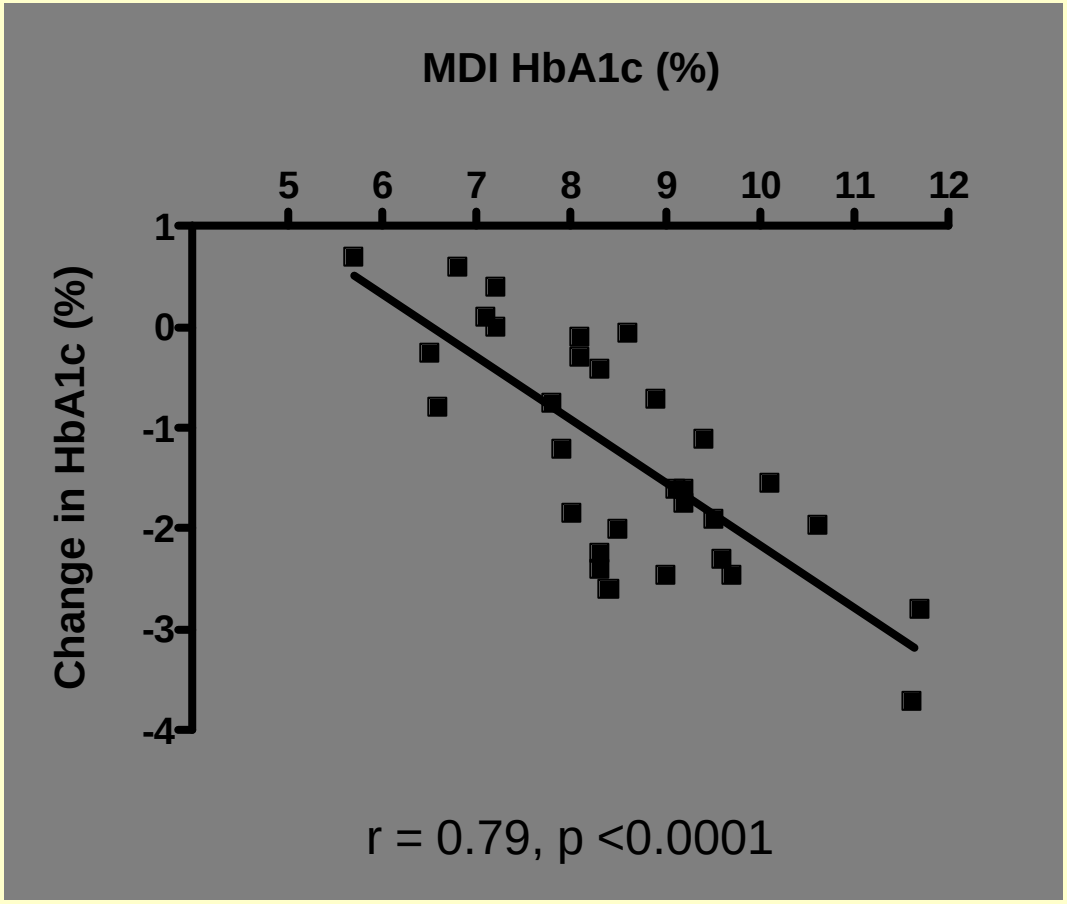
Switching to CSII in hypoglycaemia-prone type 1 diabetes (n=27),

Pickup et al Pract Diab Int 2005; 22: 10-14



Improvement in HbA1c on switching to CSII depends on HbA1c on MDI

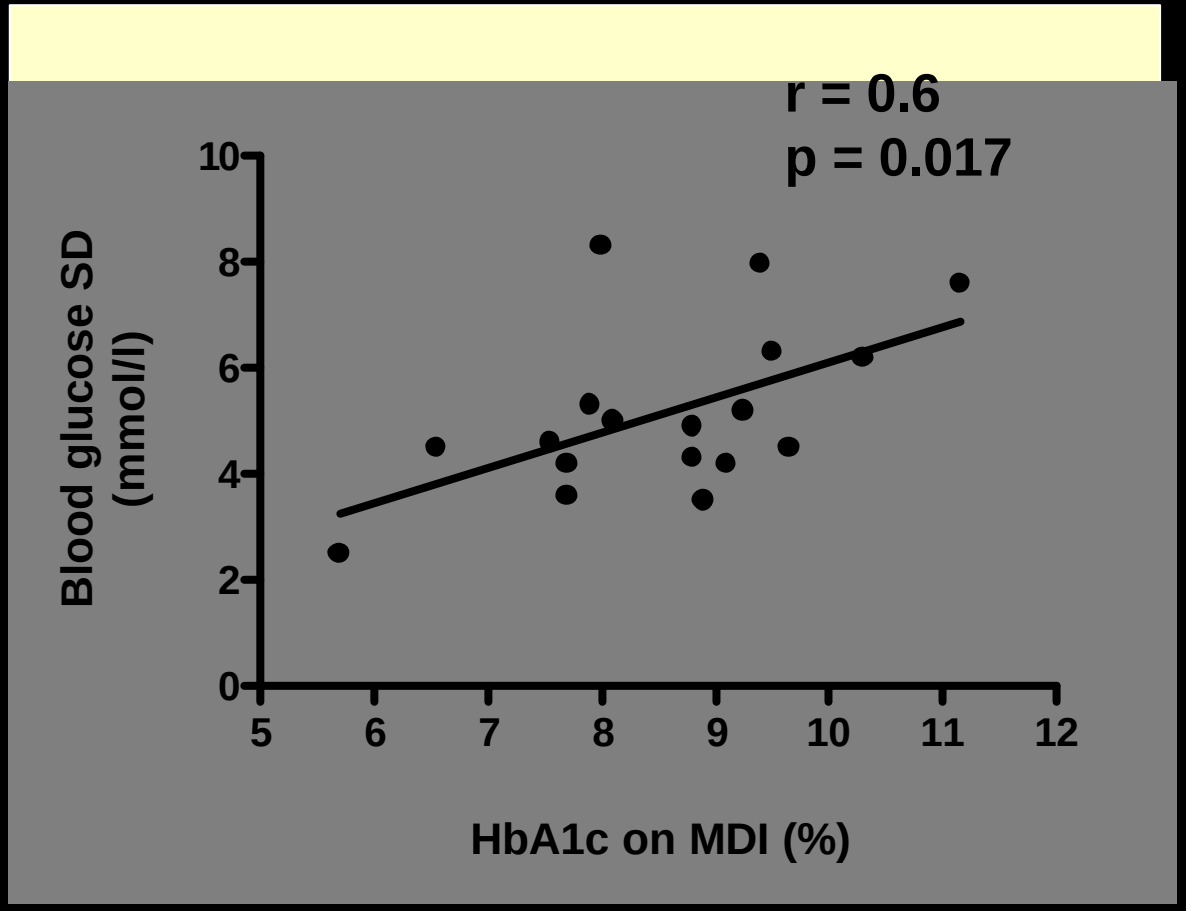
(Pickup et al Diab Metab Res Rev 2006; 22: 232-7)



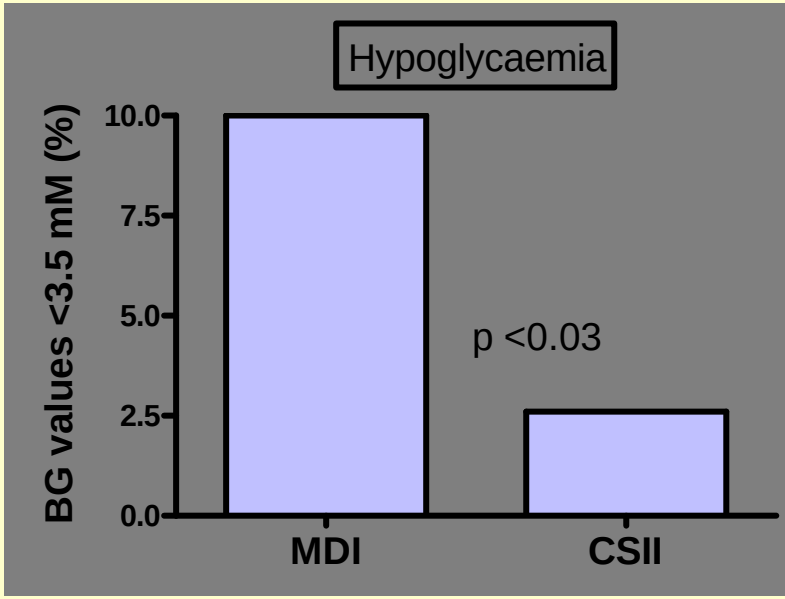
HbA1c achievable on MDI is related to blood glucose variability on MDI

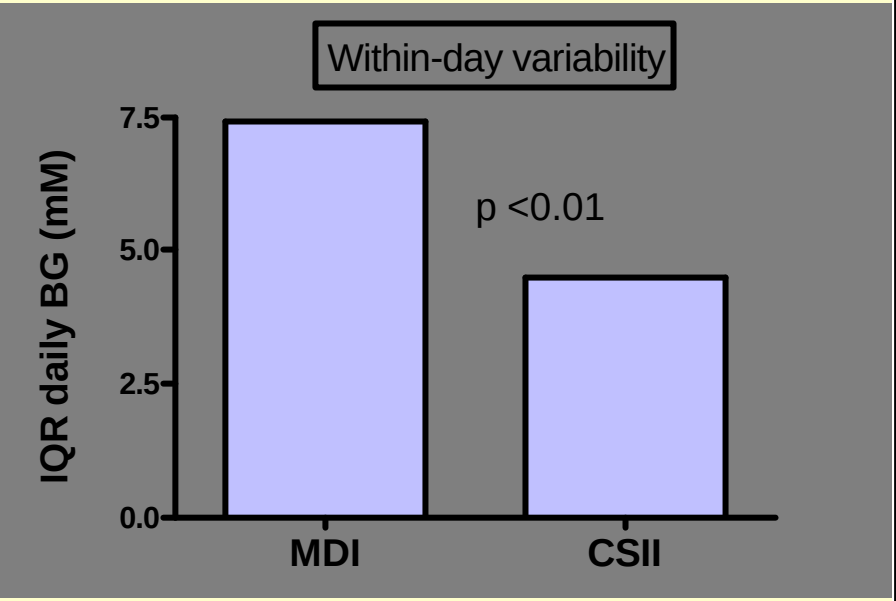
((Pickup et al Diab Metab Res Rev 2006; 22: 232-7))

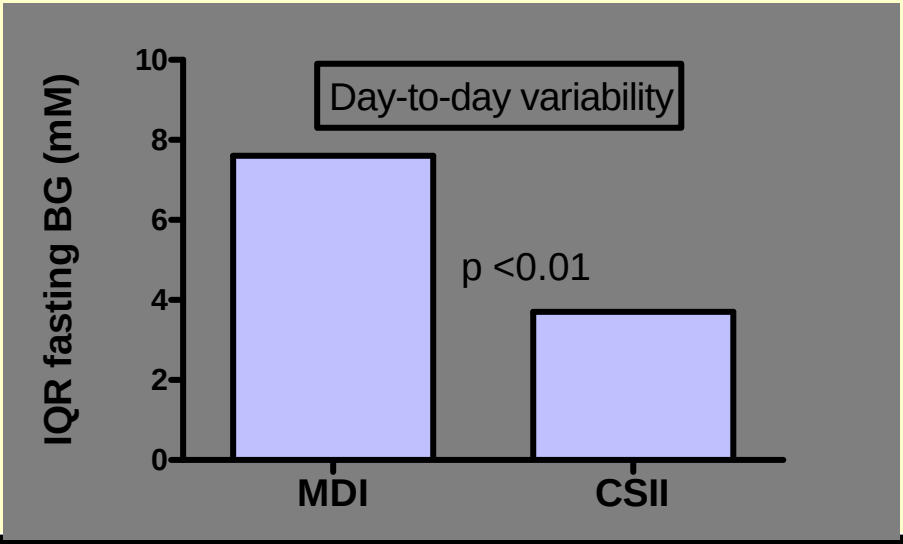
Subjects with high blood glucose variability on MDI resist improvement to avoid hypoglycaemia, thereby maintaining a high HbA1c



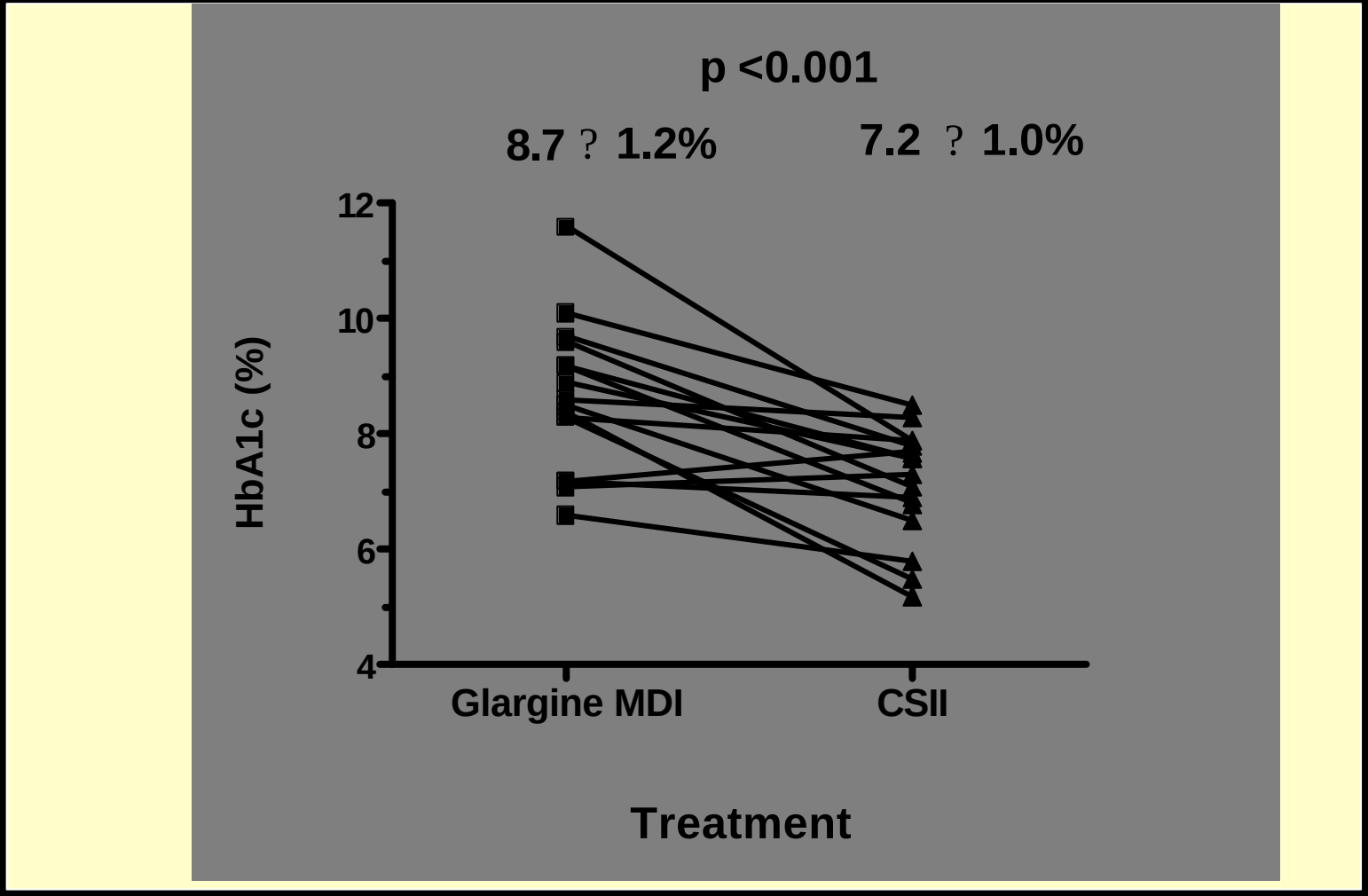
CSII reduces hypoglycaemia, and within- and between-day blood glucose variability (Pickup et al 2005)







HbA1c during glargine MDI is further improved by CSII (Pickup et al 2005)



What we asked 30 years ago

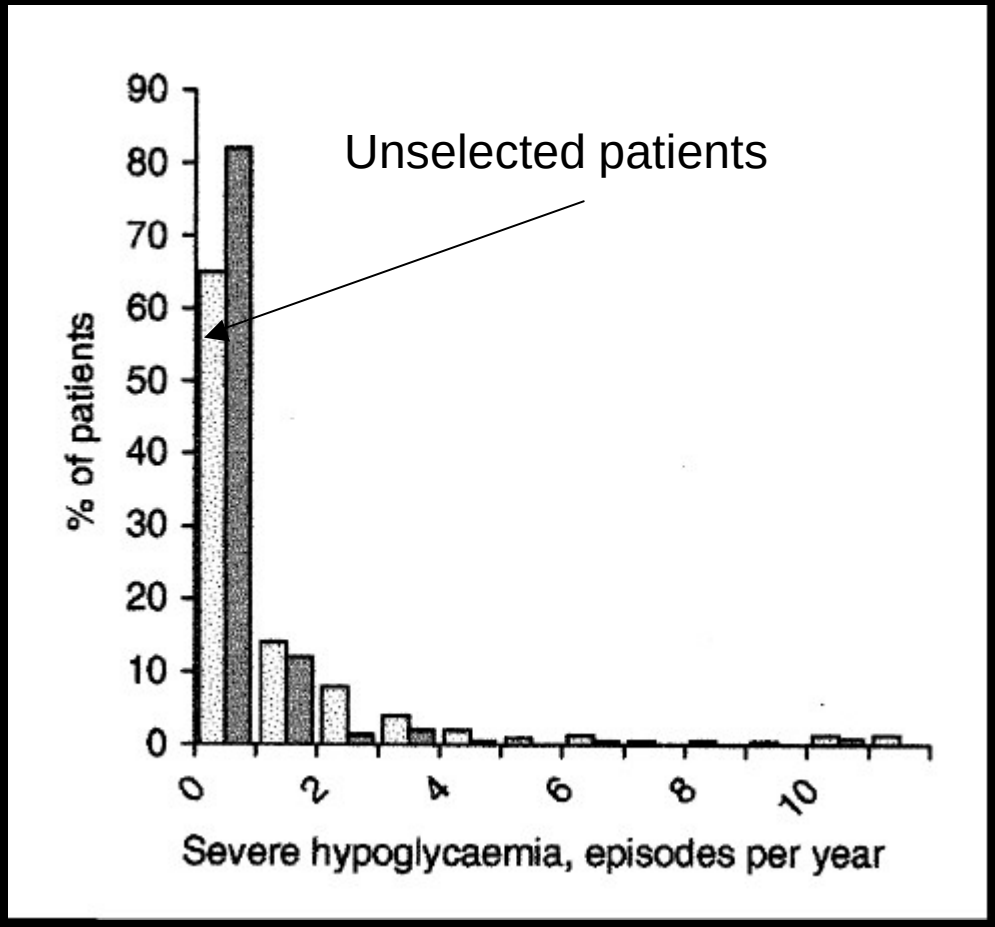
How many diabetic patients
should receive CSII?

Who should receive CSII?
Our changing views

- 1978 Research patients only
- 1980s Those with the dawn phenomenon
- 1990s Those with severe hypoglycaemia on MDI
- 2006 Those with elevated HbA1c and unpredictable glycaemic oscillations on MDI

How many type 1 diabetic patients have severe hypoglycaemia?

Distribution of Severe Hypoglycaemia on MDI



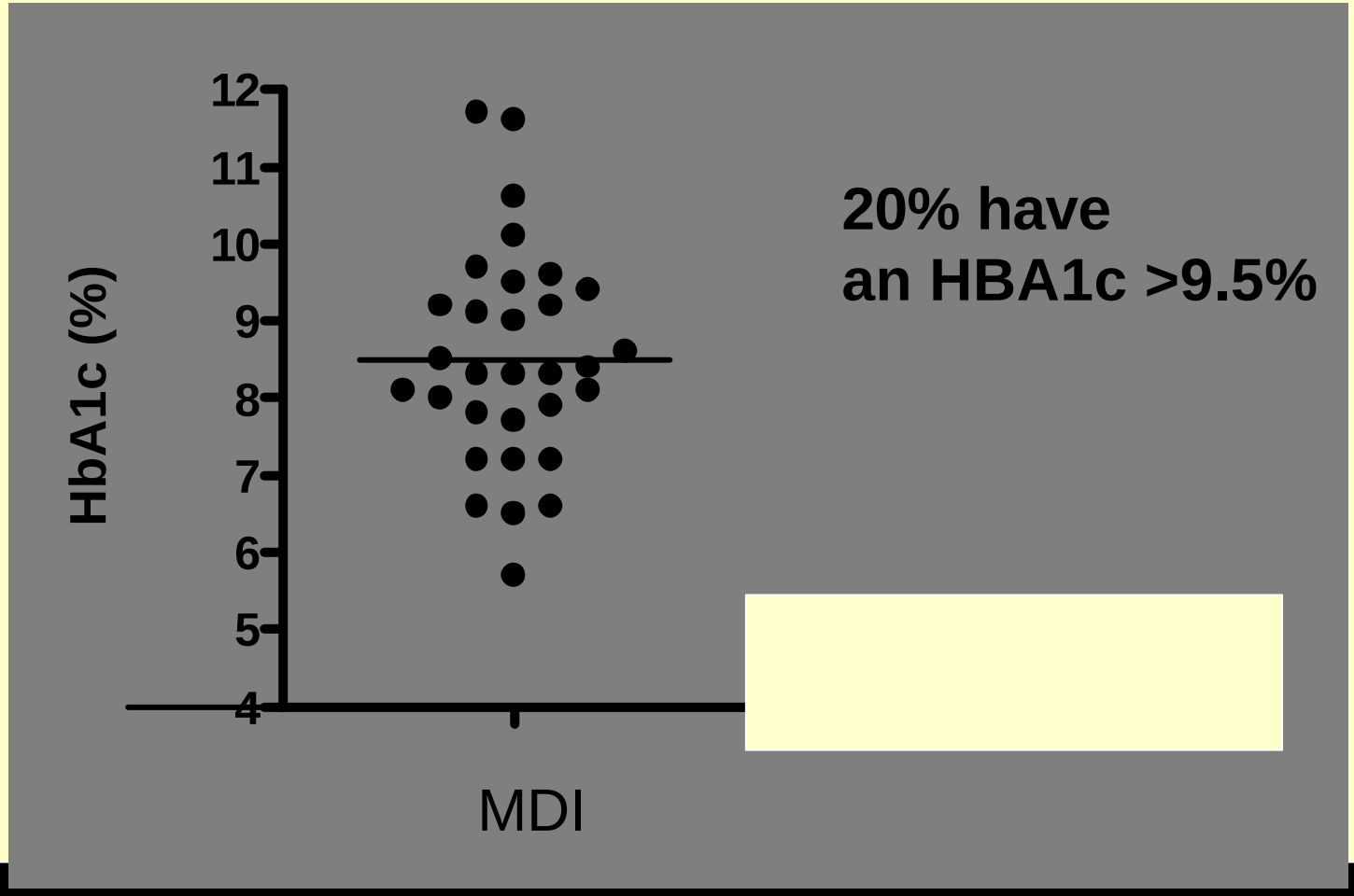
- 1076 adults with Type 1 DM in Denmark and UK
- 21% had 2 or more episodes in previous year
- Distribution very skewed: 5% of patients have >50% of episodes

Pedersen-Bjergaard U, et al. *Diabetes Metab Res Rev.* 2004;20:479-886.

How many type 1 diabetic patients have severely elevated HbA1c on best injection therapy?

30 type 1 diabetic subjects after an intensive MDI programme including glargine (median 5 mo)

(Pickup et al Diab Metab Res Rev 2006; 22: 232-7)



Efficacy of MDI regimens

- DAFNE (2002) HbA1c 8.4 ± 1.2% (no reduction in severe hypo vs. standard therapy)
  (17% HbA1c >9.5%)

- Hermansen et al (2004) detemir/aspart
  HbA1c 7.9 ± 0.9% (no reduction in severe hypo vs. NPH regimen)
  (15% HbA1c >9%)

Estimating the appropriate use of CSII

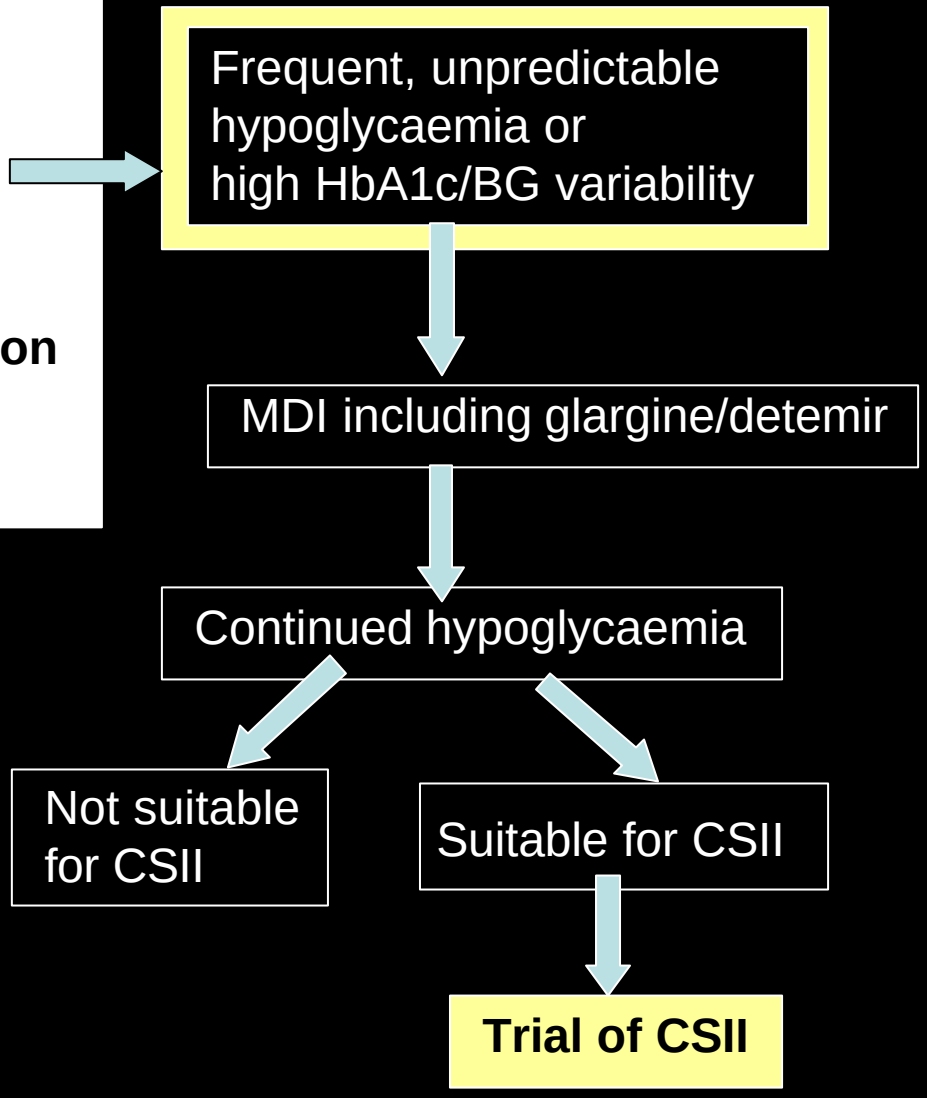
- Frequent severe hypoglycaemia on MDI 5%
- Severe hypoglycaemia lesser frequency on MDI 5%
- HbA1c >9 or 9.5% on MDI 15%
- Dawn phenomenon on MDI <5%

- Even if one quarter not suitable for CSII (decline CSII/prefer MDI, psychologically unsuitable)

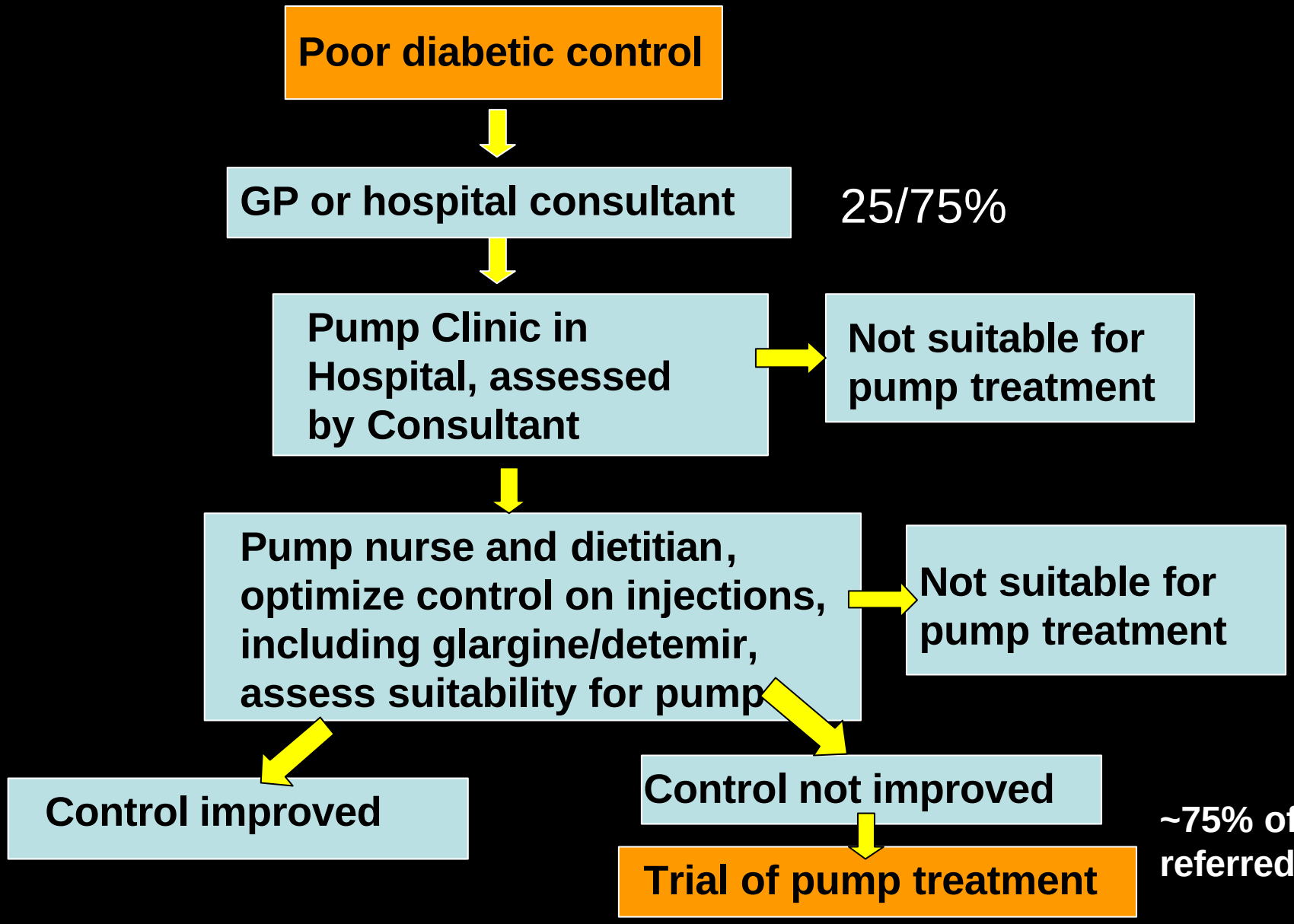
At least 15-20% of type 1 diabetic subjects should be offered a trial of CSII on clinical grounds alone

Clinical indications and treatment strategy for insulin pump therapy

Low insulin requirements
Dawn phenomenon
Hypoglycaemia unawareness
Erratic lifestyle
Pregnancy
Unpredictable insulin absorption/action
Attempts to correct BG swings
Attempts to lower HbA1c



Strategy for treating patients by CSII



The future of CSII

- Should choice of insulin delivery also be based on patient preference: the issue of quality of life?
- Technical improvements in pumps - ?smaller and cheaper
- Sensor-augmented pumps and closing-the-loop

CSII from the past to the future