ABCD Debate Spring 2007

Inhaled insulin is an expensive waste of breath

Ian Gallen

Debating points

- Will people who delay or refuse insulin, start insulin because it can be inhaled?
- Do people already on insulin want to swap to inhaled insulin?
- Does it improve quality of life?
- Who can’t have it
- Safety concerns

Inhaled insulin devices

Lilly Alkermes

Exubera

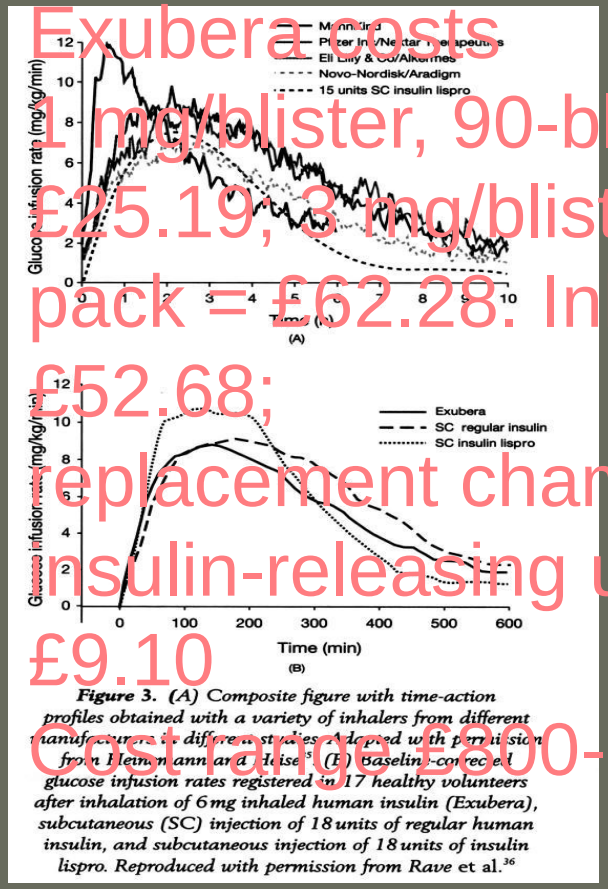


Figure 3. (A) Composite figure with time-action profiles obtained with a variety of inhalers from different manufacturers in different studies. Adapted with permission from Heinemann and Heise[5]. (B) Baseline-corrected glucose infusion rates registered in 17 healthy volunteers after inhalation of 6 mg inhaled human insulin (Exubera), subcutaneous (SC) injection of 18 units of regular human insulin, and subcutaneous injection of 18 units of insulin lispro. Reproduced with permission from Rave et al.[36]

MannKind

Novo-Nordisk Aer$_x$

Exubera costs 1 mg/blister, 90-blister pack = £25.19, 3 mg/blister, 90-blister pack = £62.28. Inhaler device = £52.68; replacement chamber = £10.11; insulin-releasing units 6-pack = £9.10

Cost range £800-2300 pa

Why inhaled insulin?

- Hypothesis 1
  - Fear of injection delays new or intensified insulin therapy
  - Inhaled insulin will improve glycaemic control with all the benefits that would come with this
- Hypothesis 2
  - People would prefer not to have to inject insulin
  - Quality of life is improved on inhaled insulin

- Do people reject insulin therapy because of injection?

Resistance to insulin therapy in the DAWN study

	Physicians		Nurses	
	n	Means ± SD or %	*n*	Means ± SD or %
Patient psychological problems¶	2,612	23.94 ± 16.74	1,040	30.97 ± 27.55
Patient attitudes toward insulin‖				
Worry	2,670	60.17 ± 30.56	1,092	62.40 ± 30.32
Self-blame	2,670	36.04 ± 29.53	1,077	38.90 ± 32.05
Attitudes toward insulin#				
Efficacy	2,566	3.60 ± 1.63	1,011	3.67 ± 1.60
Cost a barrier	2,649	2.80 ± 1.67	1,063	2.99 ± 1.69
Delay oral medication**	2,654	3.16 ± 1.73	1,048	3.45 ± 1.75
Delay insulin††	2,651	3.76 ± 1.72	1,057	3.66 ± 1.80

Resistance to Insulin Therapy Among Patients and Providers: Results of the cross-national Diabetes Attitudes, Wishes, and Needs (DAWN) study Peyrot et al. Diabetes Care. 2005. 28, 2673

Resistance to insulin therapy in the DAWN study

Duration of diabetes (years)	2,058	8.25 ± 7.69
Complications	2,061	1.34 ± 0.79
Adherence to recommendations*		
Medication	1,825	3.32 ± 1.15
Appointments	1,860	3.42 ± 0.96
SMBG	1,713	3.12 ± 1.12
Diet	2,012	3.08 ± 1.12
Exercise	1,962	2.96 ± 0.99
Perceived control†	2,048	2.54 ± 1.16
Diabetes distress‡	2,061	1.94 ± 0.70
Relationship with provider§	2,055	3.30 ± 0.67
Attitudes toward insulin initiation¶		
Efficacy	1,610	1.95 ± 1.01
Self-blame	1,818	2.54 ± 1.16

*Success following treatment recommendations (never = 1 to completely = 4). †Extent diabetes is in control (not at all = 1 to to a great extent = 4). ‡Four items: stressed because of diabetes, constant fear diabetes is getting worse, coping getting more difficult, and burned out by diabetes (fully disagree = 1 to fully agree = 4; measure = mean of all items [α reliability = 0.68]). §Three items: fully involved in treatment decisions, doctor spends enough time with me, and good relationship with diabetes care providers (fully disagree = 1 to fully agree = 4; measure = mean of all items [α reliability = 0.65]). ¶Taking insulin will help me manage diabetes better; starting insulin means not having followed treatment recommendations properly (fully disagree = 1 to fully agree = 4).

Resistance to Insulin Therapy Among Patients and Providers: Results of the cross-national Diabetes Attitudes, Wishes, and Needs (DAWN) study Peyrot et al. Diabetes Care. 2005. 28, 2673

Why do people refuse insulin treatment?

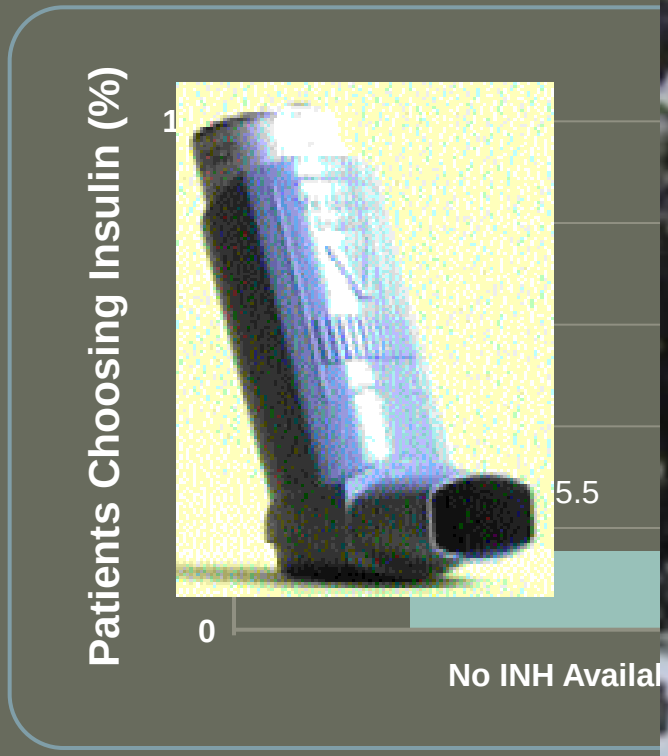
Table 1—*Attitudes about insulin therapy, unwilling vs. willing subjects*

	Unwilling	Willing	Total	*P**
Expected harm: Insulin therapy can cause problems, such as blindness	16.7	8.0	10.1	0.005
Illness severity: Taking insulin means my diabetes will become a more serious disease	46.7	35.4	38.1	0.000
Restrictiveness: Insulin therapy would restrict my life; it would be harder to travel, eat out, etc.	56.1	41.6	44.8	0.000
Lack of fairness: I've done everything I was supposed to; if I had to do insulin therapy, it just wouldn't be fair	41.5	21.9	26.8	0.000
Anticipated pain: I couldn't take the needle every day; it would be just too painful	50.8	30.2	34.7	0.000
Problematic hypoglycemia: Insulin therapy might cause serious problems with low blood sugar	49.3	37.9	40.6	0.021
Low self-efficacy: I'm not confident I could handle the demands of insulin therapy	58.1	39.7	43.9	0.000
Personal failure: Insulin therapy would mean I had failed, that I hadn't done a good enough job taking care of my diabetes	55.0	33.6	38.4	0.000
Permanence: Once you start insulin, you can never quit	53.1	42.6	44.9	0.000

Data are percentages of subjects who agree (either mildly, moderately, or strongly) with each barrier. **P* values compare differences between willing and unwilling subjects.

Polonsky WH, **Diabetes Care** 2005. 28, 10; 2543

Does inhaled insulin potentially increase insulin treatment?



Freemantle N et al. *Diabetes Care* 2005;28:427-428.

What about Type 1?
The Wycombe Experience

- Approximately 150 people expressed interest in inhaled insulin at AR Clinic
- 3 Education sessions
- 8 people initially wanted to go forward. No injection phobic person wanted to swap
- Only 2 followed through, both injection site/allergy problems
- 1 stopped due to device difficulty/poor technique, 1 other stopped because of poor control and too high dose.

- Do people reject insulin therapy because of injection?
- No, most rejection is based around other attitudes to diabetes and it’s treatment, and inhaled insulin makes little difference

Can you control diabetes on inhaled insulin alone?

- Given the scenario that a patient would not have insulin injection, can you manage without basal insulin?
- Is there data to compare TID inhaled insulin with OD basal insulin?

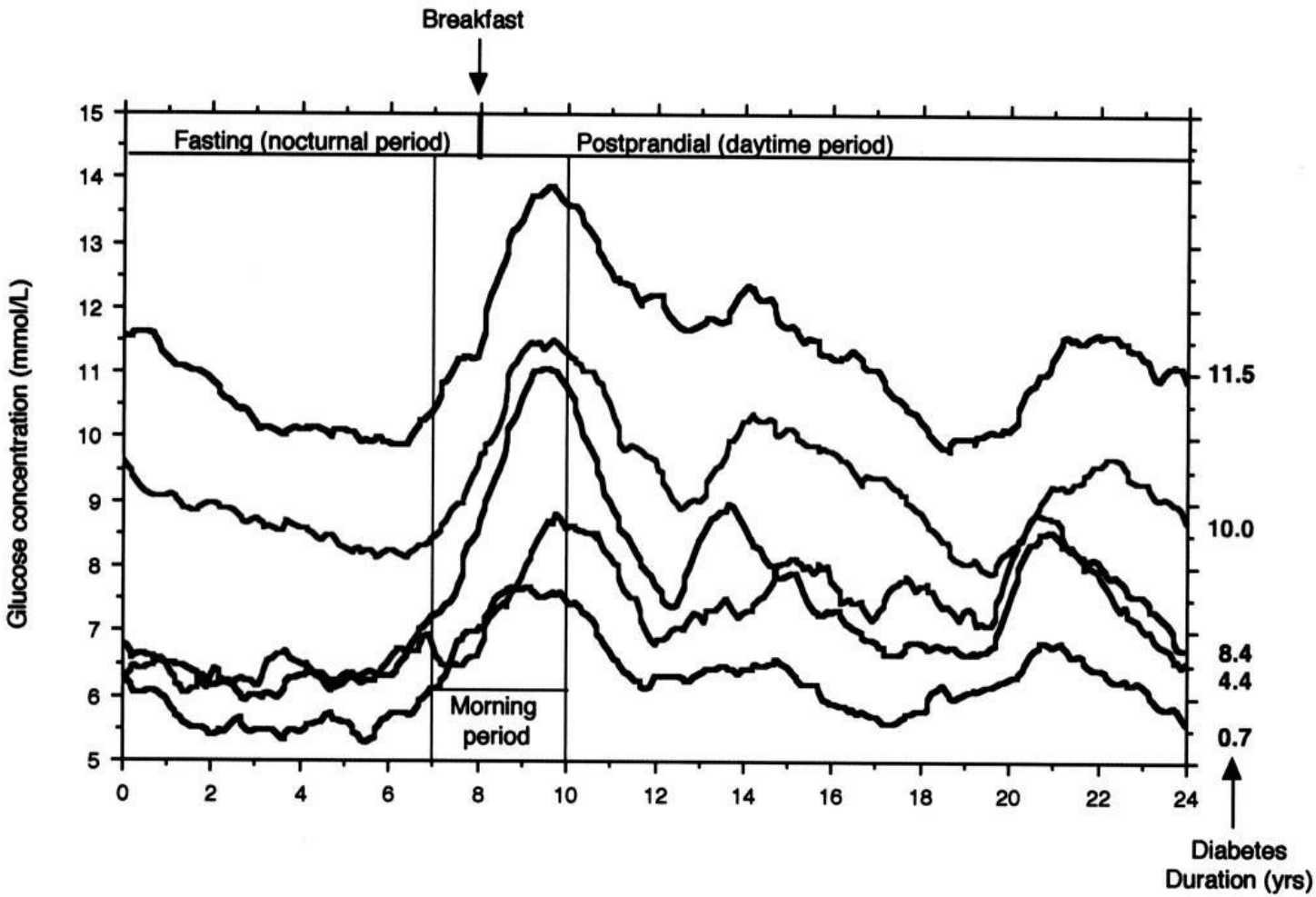


Figure 1—*Twenty-four hour recordings from the CGMS in the five groups of patients with type 2 diabetes. Curve 1 (blue): A1C <6.5%; curve 2 (red): ≤ 6.5% to <7%; curve 3 (green): ≤7% to <8%; curve 4 (orange): ≤8% to 9%; curve 5 (purple): ≥9%.*

Monnier, et al Diabetes Care. 2007.30,263,

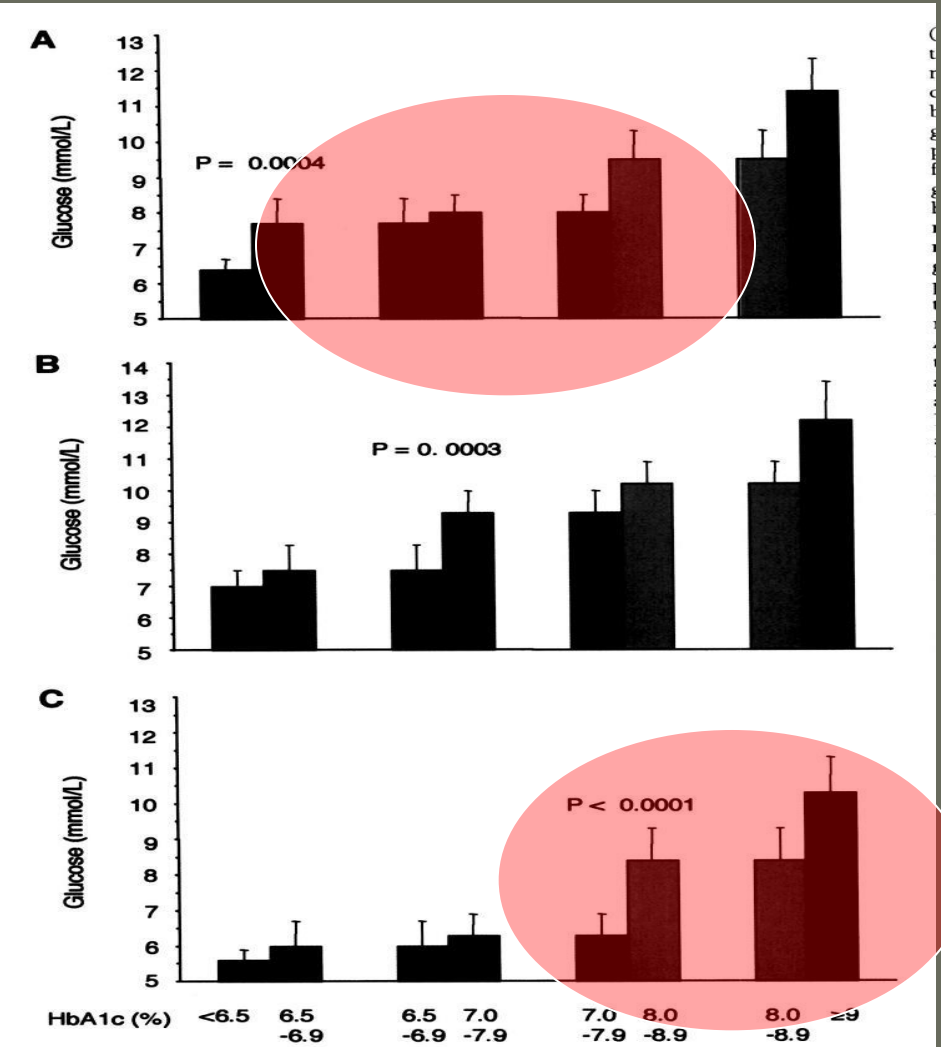


Figure 2—*Progressive deterioration of the glycemic profiles according to A1C levels in the three studied periods: daytime postmeal period (A), morning period (dawn phenomenon) (B), and nocturnal fasting period (C). Data are geometric means of glucose concentrations and superior value of 95% CI. Only the initial differences in mean glucose concentrations reaching statistical significance are indicated. Statistical comparisons were considered significant for* $P < 0.05/n$ *(n = comparison number, Bonferroni correction).*

Monnier, et al Diabetes Care. 2007.30,263,

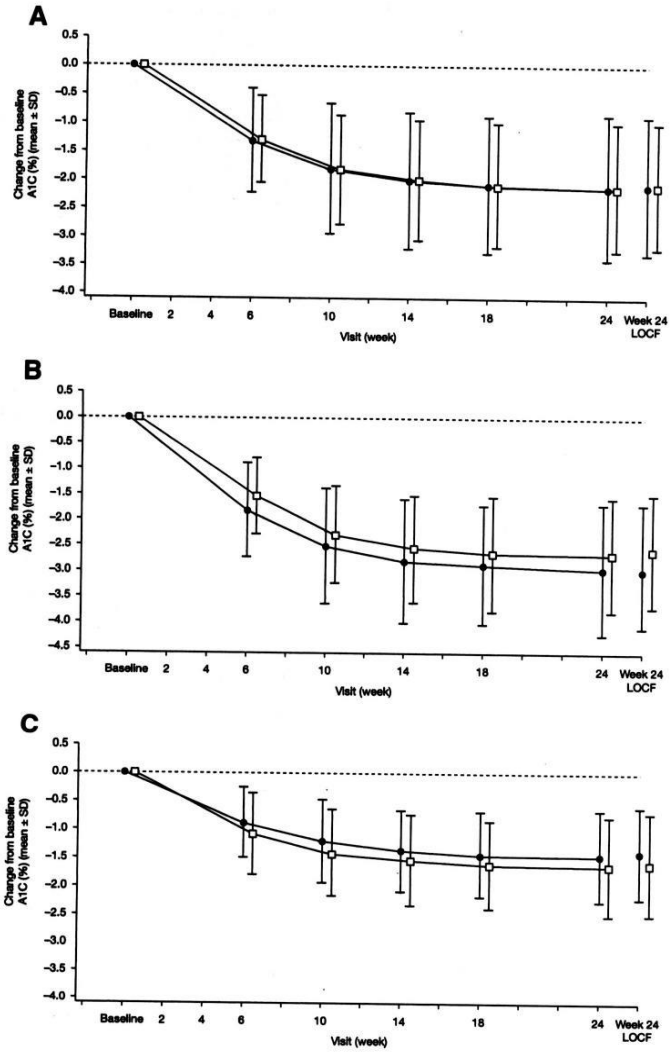


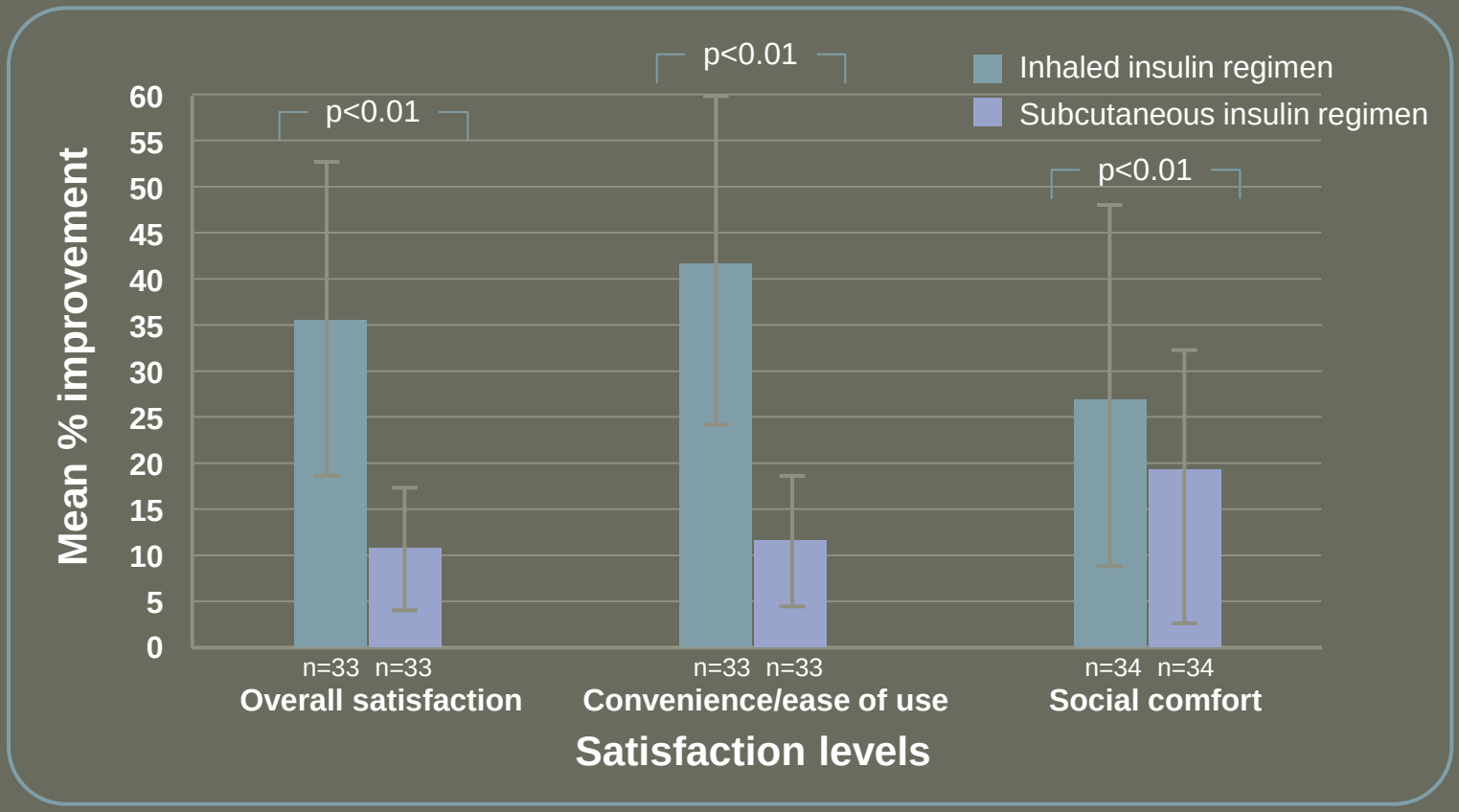
Figure 2—*Change from baseline in A1C (%) for patients with type 2 diabetes failing metformin therapy randomized to adjunctive INH or glibenclamide.* A: *Combined A1C arms.* ●, *metformin + INH* (n* = *234; 213*); □, *metformin + glibenclamide* (n* = *222; 201*). B: *Very high baseline A1C arm (>9.5 to ≤12%).* ●, *metformin + INH* (n* = *109; 96*); □, *metformin + glibenclamide* (n* = *103; 95*). C: *Moderately high A1C arm (≥8 to ≤9.5%).* ●, *metformin+ INH* (n* = *125; 177*); □, *metformin + glibenclamide* (n* = *119; 106*). n*, *number of subjects at baseline; number of subjects at week 24.*

Barnett AH, **Diabetes Care** 2006. Vol. 29, 8; 1818

Can you control diabetes on inhaled insulin alone?

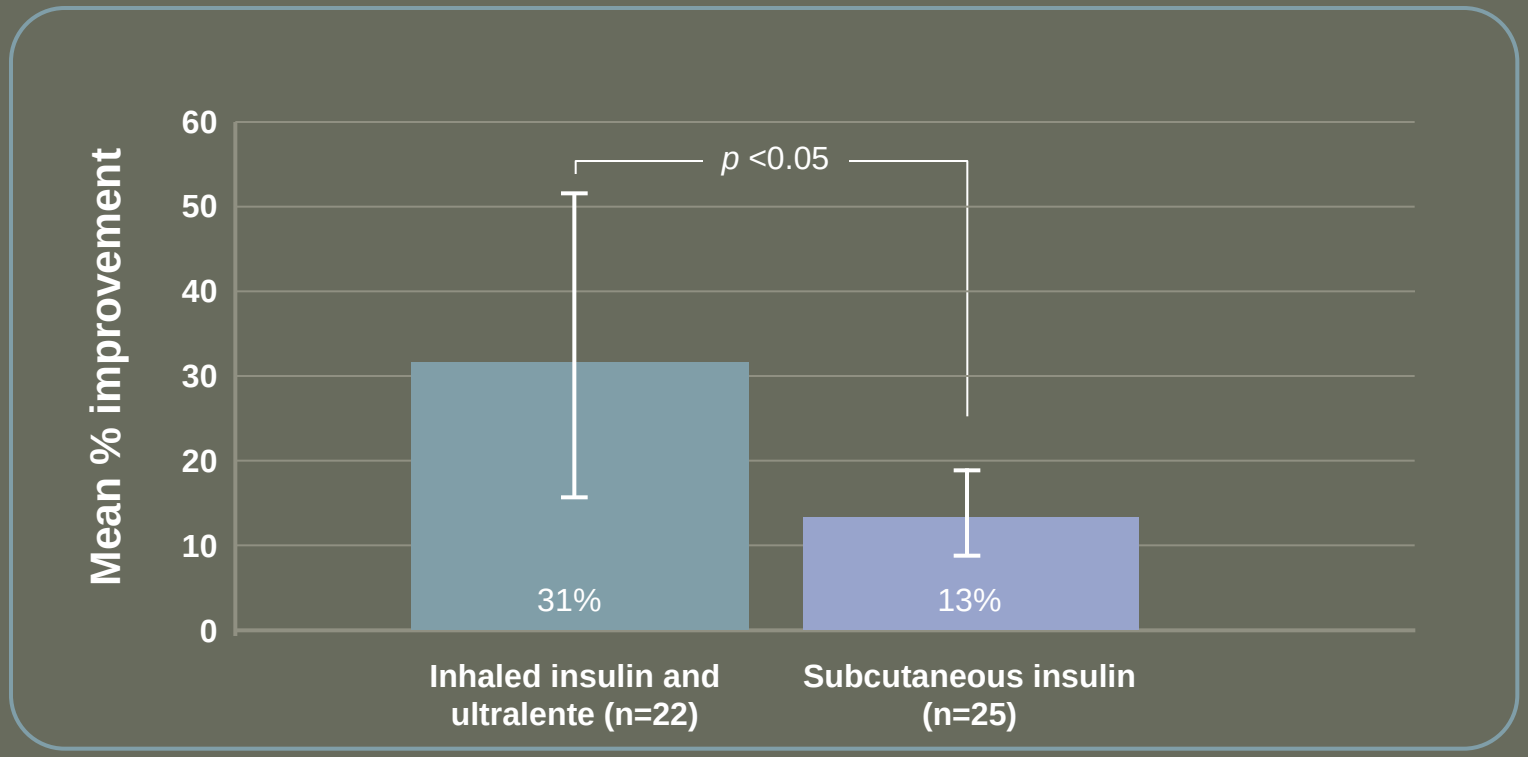
- Given the scenario that a patient would not have insulin injection, can you manage without basal insulin?
- Yes, but only if the HbA1c is low!, and is no better than Gliblenclamide
- Is there data to compare TID inhaled insulin with OD basal insulin?
- No Data

- Does inhaled insulin improve quality of life?
- If so, how does this compare with other interventions?



Gerber RA et al. Diabetes Care 2001;24:1556-1559.

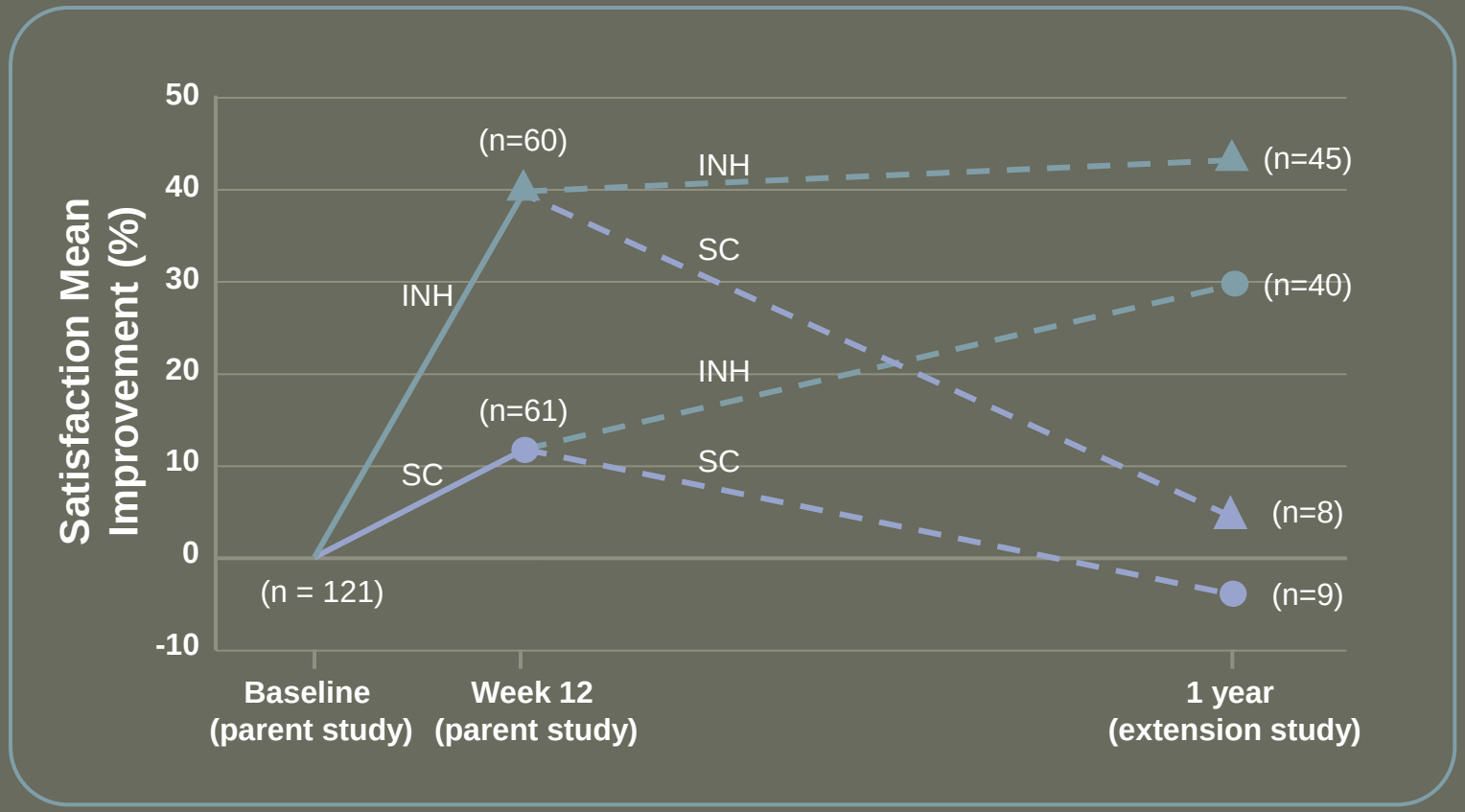
Satisfaction data T1DM



Cappelleri JC et al. *Clinical Therapeutics* 2002;24(2):552-564.

Satisfaction data T2DM

Overall satisfaction



INH = inhaled insulin regimen
SC = subcutaneous insulin regimen

Rosenstock J et al. Diabetes Care 2004;27:1318-1324.

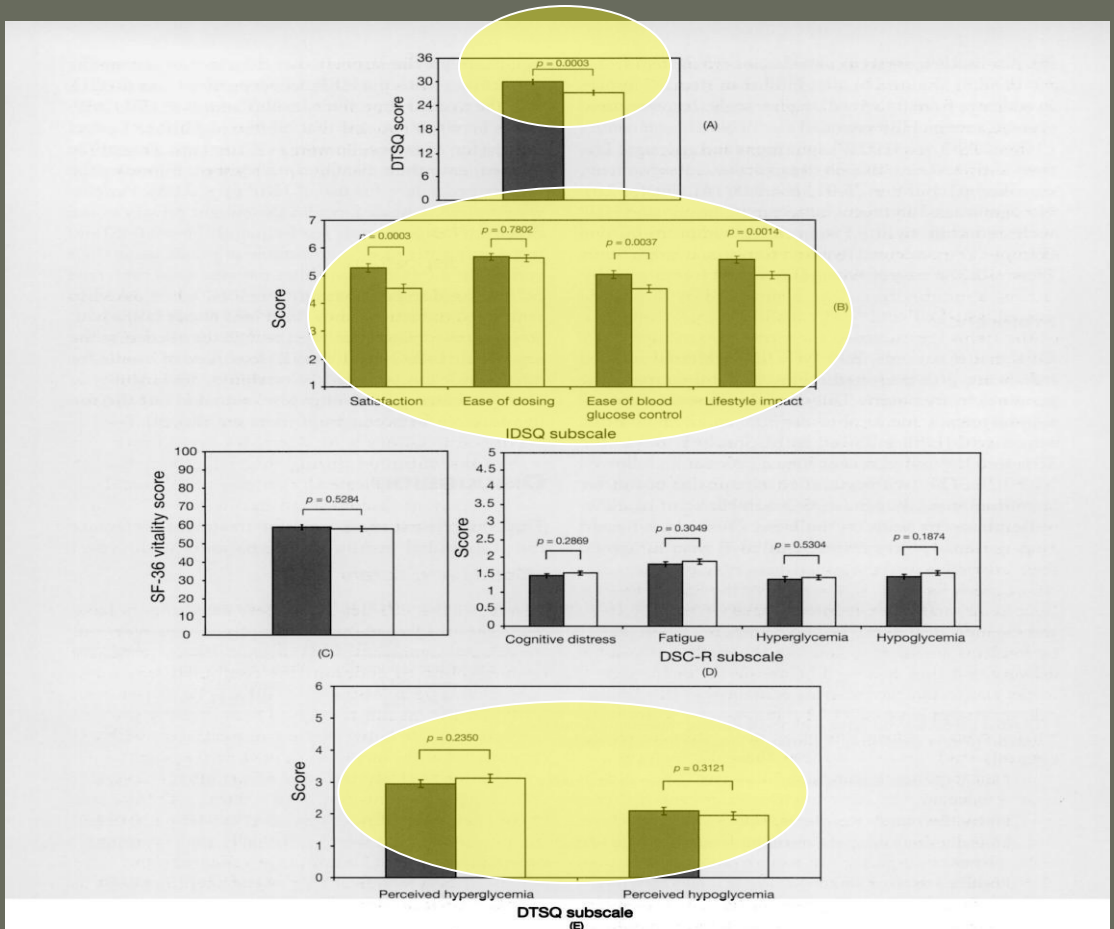


Figure 2. *Least square mean patient-reported outcome and insulin delivery system satisfaction scores for patients using HIIP and patients using SC insulin in a randomized, open-label, two-armed crossover study with 12 weeks on each treatment arm. Shaded bars: HIIP. Unshaded bars: SC insulin. Panel (A): Diabetes Treatment Satisfaction Questionnaire (DTSQ) Diabetes Treatment Satisfaction scores (n = 116). Scores range from 0 to 36; higher scores correspond to greater treatment satisfaction. Panel (B): Insulin Delivery System Questionnaire subscale scores (Satisfaction, n = 117; Ease of Dosing, n = 118; Ease of Blood Glucose Control, n = 119; Lifestyle Impact, n = 115). Scores range from 1 to 7; higher scores correspond to more positive evaluation of an insulin delivery system. Panel (C): SF-36 Vitality subscale scores (n = 119). Scores range from 0 to 100; higher scores correspond to greater vitality. Panel (D): Diabetes Symptom Checklist-Revised subscale scores (Cognitive Distress, n = 118; Fatigue, n = 119; Hyperglycemia, n = 116; Hypoglycemia, n = 116). Scores range from 0 to 5; Lower scores correspond to less symptom burden. Panel (E): Diabetes Treatment Satisfaction Questionnaire (DTSQ) Perceived Hyperglycemia (n = 117) and Perceived Hypoglycemia (n = 118) scores. Scores range from 0 to 6; higher scores correspond to greater perceived hyperglycemia and hypoglycemia*

Risa P. et al Current Medical Research and Opinion 2007 23 2 435

Table 2 Secondary outcomes: differences between immediate DAFNE and delayed DAFNE groups at six months. Values are means (SDs) unless stated otherwise

	W-BQ12	Diabetes treatment satisfaction questionnaire (DTSQ)			Cardiovascular risk factors			
			Perceived frequency† of:					
Group	Total wellbeing*	Total satisfaction*	Hyperglycaemia	Hypoglycaemia	Weight (kg)	Total cholesterol (mmol/l)	HDL cholesterol (mmol/l)	Triglycerides (mmol/l)
Immediate DAFNE:								
Baseline	20.94 (5.8)	22.88 (6.2)	3.57 (1.4)	2.04 (1.2)	80.5 (16.7)	5.2 (0.9)	1.5 (0.4)	1.5 (0.9)
6 months	24.34 (5.7)	31.58 (3.9)	2.90 (1.4)	2.16 (1.3)	81.5 (16.9)	5.1 (0.8)	1.6 (0.4)	1.4 (0.7)
Delayed DAFNE:								
Baseline	21.09 (5.8)	23.21 (5.8)	3.60 (1.6)	2.12 (1.4)	77.4 (13.4)	4.9 (0.8)	1.5 (0.5)	1.5 (0.9)
6 months	21.37 (5.5)	22.82 (6.0)	4.03 (1.3)	2.40 (1.3)	77.3 (13.4)	5.0 (1.0)	1.5 (0.3)	1.5 (0.9)
Difference between groups at six months								
Mean (95% CI)	2.98 (1.06 to 4.89)	8.75 (7.02 to 10.48)‡	−1.13 (−1.59 to −0.67)	−0.23 (−0.68 to 0.21)	4.18 (−0.90 to 9.27)	0.15 (−0.16 to 0.45)	0.09 (−0.01 to 0.22)	0.12 (−0.41 to 0.17)
Statistical values	t=3.1, P<0.01	t=−10.3, P<0.0001	t=−4.88, P<0.0001	t=−1.0, P=0.31	t=1.6, P=0.11	t=0.95, P=0.34	t=1.46, P=0.14	t=0.83, P=0.41

HDL=high density lipoprotein; W-BQ12=12-item wellbeing questionnaire.
*Scored from 0 to 36; a higher score indicates greater wellbeing or satisfaction.
†Scored from 0 to 6; a higher score indicates greater perceived frequency of hyperglycaemia or hypoglycaemia.
‡Confidence interval should be interpreted with caution as variable was transformed before parametric analysis was performed but natural data are reported.

Table 1 Primary outcomes: differences between immediate DAFNE and delayed DAFNE groups at six months. Values are means (standard deviations) unless stated otherwise

Group	Glycated haemoglobin (HbA_{1c}, %)	Proportion of participants experiencing severe hypoglycaemia in previous six months* (No (%))	Audit of diabetes-dependent quality of life (ADDQoL)		
			Weighted impact of diabetes on "freedom to eat as I wish"†	Average weighted impact of diabetes on quality of life†	Present quality of life‡
Immediate DAFNE:					
Baseline	9.4 (1.2)	15/68 (22)	−4.8 (2.9)	−2.0 (1.6)	1.0 (0.9)
Six months	8.4 (1.2)	12/67 (18)	−1.8 (2.3)	−1.6 (1.6)	1.3 (0.9)
Delayed DAFNE:					
Baseline	9.3 (1.1)	8/72 (11)	−4.0 (2.9)	−1.9 (1.3)	1.1 (0.8)
Six months	9.4 (1.3)	11/72 (15)	−4.0 (2.8)	−1.9 (1.4)	1.0 (1.1)
Difference between groups at six months					
Mean (95% CI)	1.0 (0.5 to 1.4)	–	2.2 (1.3 to 3.1)§	0.4 (−0.1 to 0.9)§	0.3 (−0.1 to 0.6)§
Statistical values	t=4.4, P<0.0001	χ^2=0.17, P=0.68	t=−5.4, P<0.0001	t=2.9, P<0.01	t=1.7, P=0.095

*Percent of participants: χ^2 test performed for differences between groups at six months.
†Scored from −9 (maximum negative impact) to +9 (maximum positive impact).
‡Scored from −3 (extremely bad) to +3 (excellent); 0=neither good nor bad, 1=good, 2=very good.
§Confidence interval should be interpreted with caution as variables were transformed before parametric analysis was performed but natural data are reported.

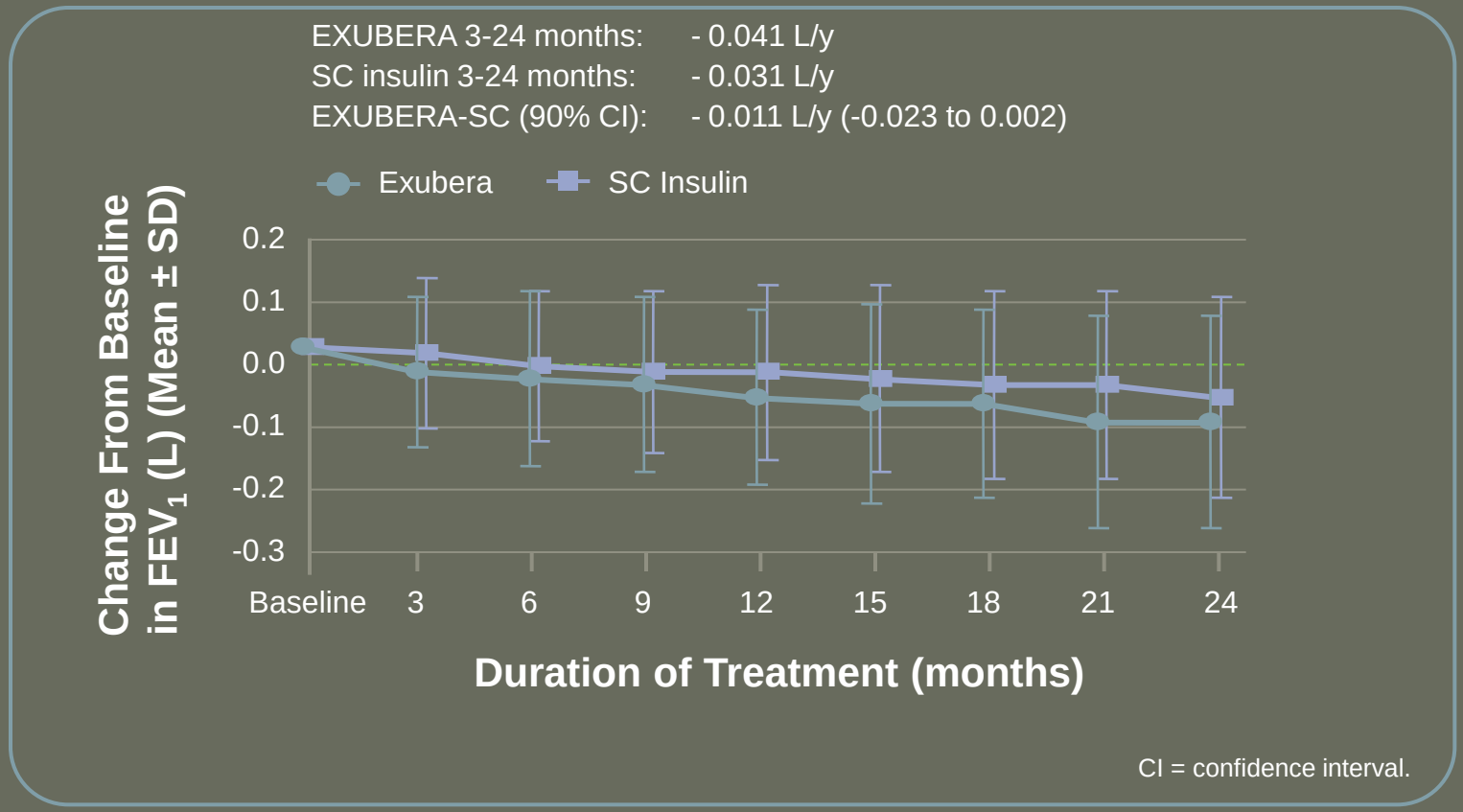
Do people want it?

- Patient preference data is weak
  - Comparison with older insulin/regimes
  - No comparison with pump treatment
  - There are ther cheaper/safer interventions which improve QoL
- Poor evidence of increase insulin treatment in insulin rejecters
  - Little of insulin refusal centred on injection itself
  - No evidence that these people would use inhaled insulin effectively
  - People would still need basal insulin
  - Many new treatments now available which can delay insulin therapy -(GLP1 agonists/DPPIV blockers)

Safety issues

- Why “Waste of breath”?

Change in lung function in Type 1 diabetes



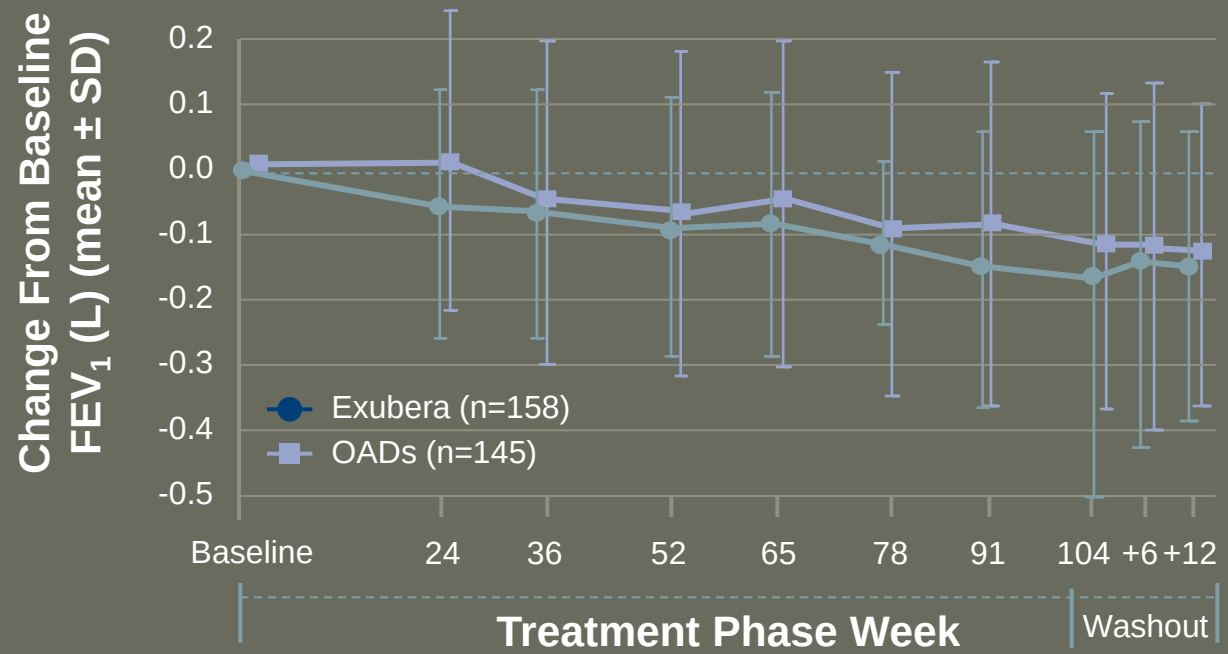
INH = inhaled insulin regimen SC = subcutaneous insulin regimen

Source: http://www.fda.gov/ohrms/dockets/ac/05/slides/2005-4169S1_00_Slide-Index.htm.

Change in lung function in Type 2 diabetes

Non-standardised Laboratories

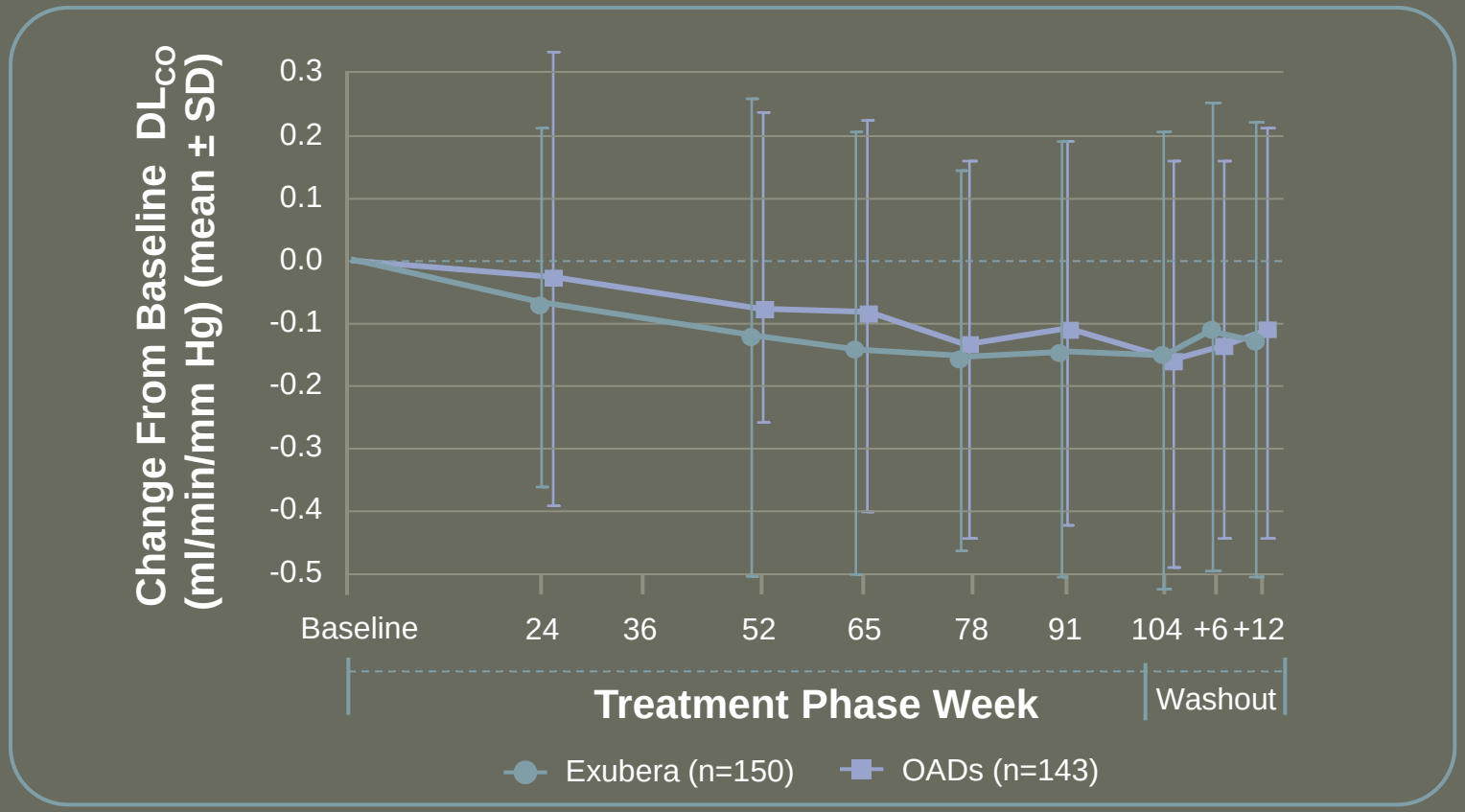
EXUBERA 6-24 months: - 0.075 L/y
Oral agents 6-24 months: - 0.075 L/y
EXUBERA-OAs (95% CI): 0.000 L/y (-0.032 to 0.033)



Exubera summary of product characteristics
Source: http://www.fda.gov/ohrms/dockets/ac/05/slides/2005-4169S1_00_Slide-Index.htm.

DL_{CO} – 2yr controlled data in Type 2 DM

Non-standardised Laboratories



Dreyer M et al. *Diabetologia.* 2004;47(suppl 1):A44.

Who does Pfizer think can use Exubera?

- Exubera is indicated for:
  - The treatment of adult patients with type 2 diabetes mellitus not adequately controlled with oral anti-diabetic agents and requiring insulin therapy
  - The treatment of adult patients with type 1 diabetes mellitus, in addition to long or intermediate acting subcutaneous insulin, for whom the potential benefits of adding inhaled insulin outweigh the potential safety concerns
- Exubera is contraindicated in:
  - Active smokers
  - Those who have stopped smoking less than 6 months ago
  - Moderate to severe underlying lung disease
- Exubera is not recommended for:
  - Patients with lung disease
  - Patients under 18 years of age
  - In pregnancy

Summary of Product Characteristics for Exubera.

Inhaled insulin in smokers and asthmatics

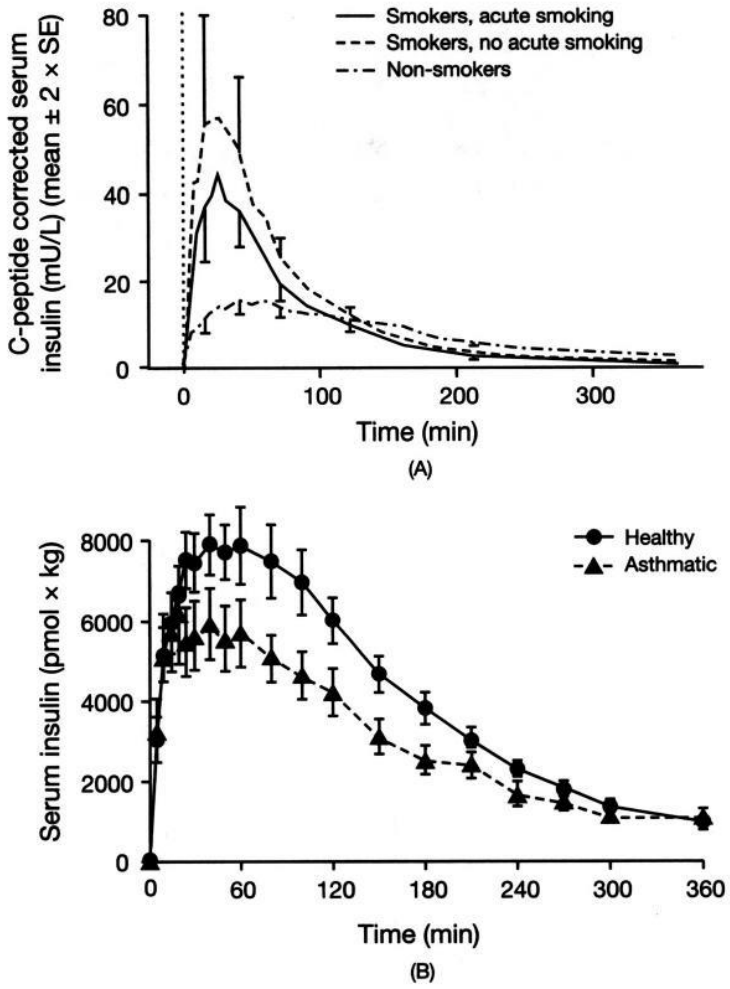


Figure 1. *Insulin pharmacokinetics in smokers (AERx, 33.8 IU [A]) and patients with asthma (AERx, 45 IU [B]). Adapted with permission from Himmelman* et al.[17] *and Henry* et al.[21]

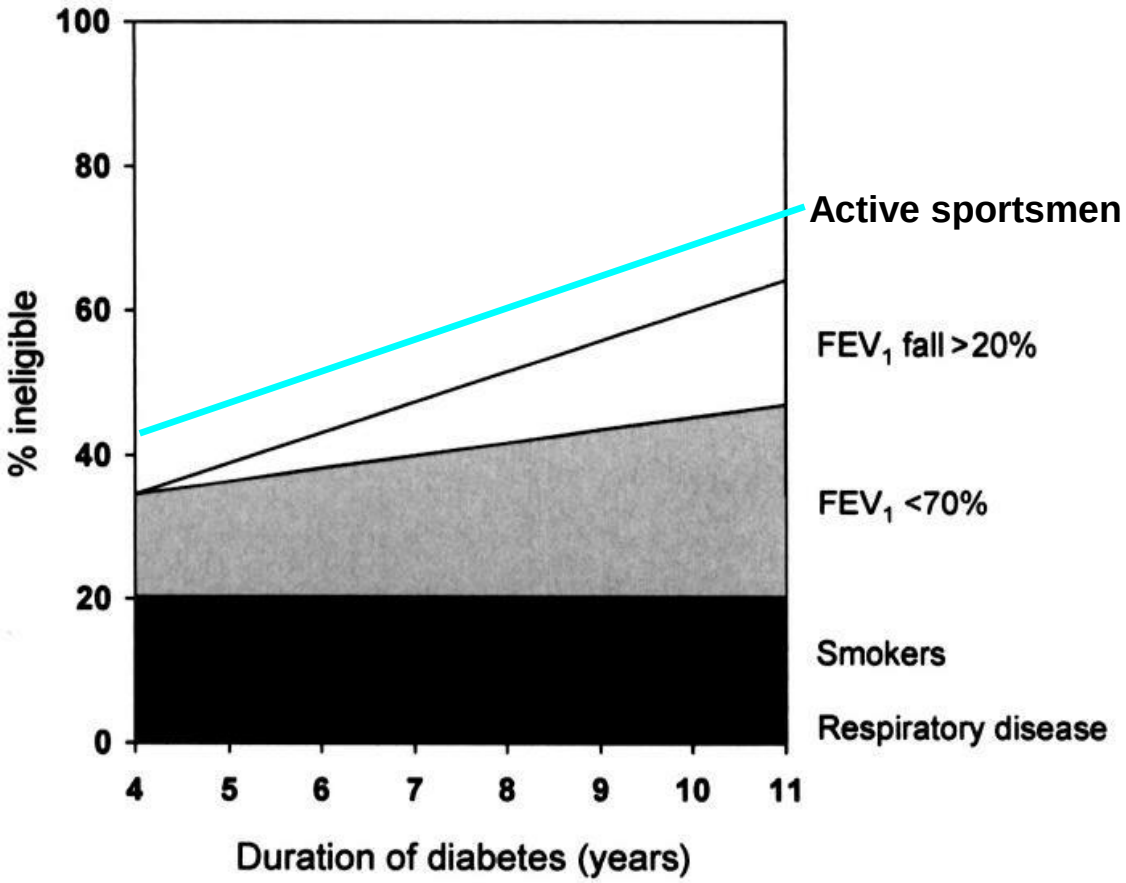


Figure 1—*Schematic representation of the percentage of type 2 diabetic patients ineligible for Exubera therapy between 4 and 11 years disease duration. Data are from cross-sectional and longitudinal FDS sources. The individual contraindications or precautions to Exubera use are represented by the shaded areas.*

Timothy M E Davis, Wendy A Davis. **Diabetes Care.** 2007. Vol. 30, Iss. 2; p. 360

Who does NICE think can use Exubera

- Inhaled insulin is not recommended for the routine treatment of people with type 1 or type 2 diabetes mellitus except
- An injection phobia diagnosed

- Severe persistent problems with injection sites (for example, as a consequence of lipohypertrophy).

Stock Market report April 2007

- **NEW YORK U.S. maker Novo Nordisk gained m nfidence in Pfizer's inhalable insulin**

- Analysts have bee tions of Exubera given prescription data. **a sales forecasts halved** for 2007 to res started coming in low**.**

- Recently, Merrill Ly r said the top reasons for Exubera's slow **about the long-term safety of inhaled** ck of reimbursement options because th onvenience; **and the complexity and size of the spray-can sized device.**

- In comparison, about **13 times as many new prescriptions of Januvia** diabetes medication in tablets form are being written on a weekly basis**.**

Jean-Francois Dehecq
CEO Sanofi-Aventis

Inhaled insulin

- **Expensive**
- Concept largely based on a flawed hypothesis
- Does not delivered the improvement in QoL hoped for
- Suitable at best for only a small proportion of patients
- Current device far from ideal
- Probably damages the lungs
- **waste of breath**

ABCD NICE Exubera audit

- Audit form