`$HbA_{1c}$` PROJECT - NOVO NORDISK FARMA SHORT PUBLICATION

D. Cheta[1], *Emiliana Mocan*[2]

[1]INDNBM `N. Paulescu`, Bucharest, Romania
[2] Novo Nordisk Farma, Bucharest, Romania

Abstract

Type 2 diabetes is a progressive disease in which insulin secretion diminishes continuously in time. There is a strong correlation between glycaemic burden and late complications in type 1 and type 2 diabetes[2,3].

In order to avoid these complications, ADA currently recommends HbA_{1c} levels of < 7.0% and the IDF[6] and AACE[7] recommend a target of ≤ 6.5%[8-10].

Glycaemic control can be achieved initially by diet and exercise habits and/or the prescription of ≥1 OAD. Exogenous insulin therapy is required in addition to or as an alternative to OAD therapy as type 2 diabetes progresses.

Insulin therapy is often delayed due to concerns about injection, hypoglycaemia, and weight gain[13-14]. Insulin analogues, due its properties may improve patients adherence to initiating insulin therapy in an earlier stage of the disease.

Novo Nordisk initiated and conducted in May 2007 the `$HbA_{1c}$` Project in 13 diabetes centres in Romania.

The HbA_{1c} measurements in 9.000 type 2 diabetic patients diagnosed for 6-8 years on OADs and/or human insulin treatment showed that only 19% were < 7% and 81% were ≥ 7%.

ADA - American Diabetes Association; IDF - International Diabetes Federation AACE - American Association of Clinical Endocrinologists OAD - oral antidiabetic drug

Key words: type 2 diabetes, diabetes complications, HbA_{1c}, insulin initiation

Type 2 diabetes is a progressive disease in which insulin secretion, particularly in response to prandial stimuli, diminishes in the setting of insulin resistance.

Metabolic control deteriorates relentlessly as the duration of diabetes increases and beta-cell function is progressively lost.

Glucolipotoxicity has a very important role in this process[1-2] (fig. 1).

Findings from the U.K. Prospective Diabetes Study (UKPDS) showed that deterioration in beta-cell function occurred in the diet-only treatment group as well as in patients treated with sulfonylureas or metformin, suggesting that neither of these agents slowed the rate of decline[2].

Also, outcomes from the U.K. Prospective Diabetes Study (UKPDS) and the Diabetes Control and Complications Trial (DCCT) demonstrate a strong correlation between glycaemic burden and microvascular complications in both type 1 and type 2 diabetes. According to the Kumamoto Study, HbA_{1c} < 6.5%, fasting blood glucose

concentration <110 mg/dl, and 2-h postprandial blood glucose concentration <180 mg/dl constitute the glycaemic threshold to prevent the onset and progression of diabetic microvascular complications in type 2 diabetes[3].

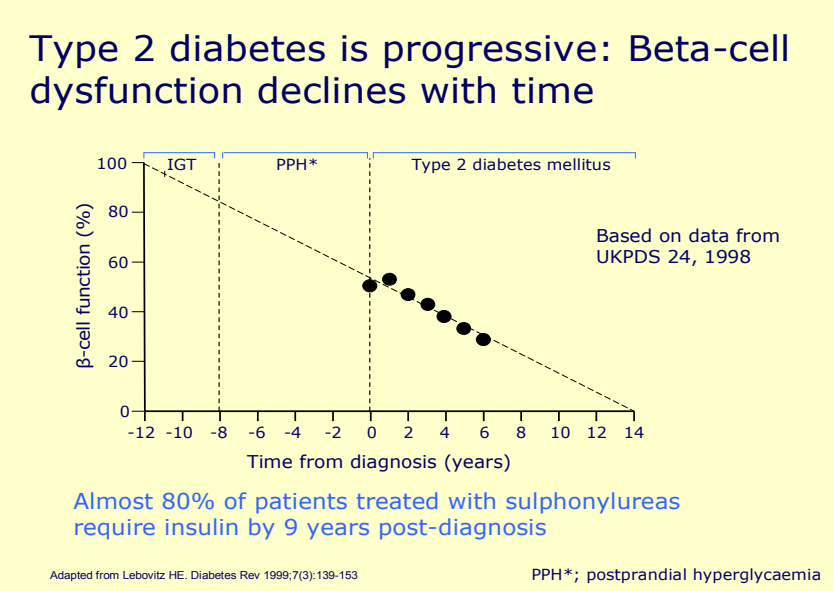

Fig. 1

Table 1

ADA and AACE glycaemic targets

	ADA	AACE
A1C (%)	< 7	≤ 6.5
Fasting/ preprandial* (mg/dl)	90–130	< 110
2-hour postprandial (mg/dl)	< 180†	< 140

*Plasma equivalent.
†Peak postprandial (~ 1 hour).

A stricter glycaemic control is necessary to prevent the macrovascular complications of diabetes.

Early glycaemic control is vital because of ‘‘glycaemic memory’’, as was shown in the EDIC (Epidemiology of Diabetes Interventions and Complications) Study[4]. Four years after the end of the DCCT trial, despite increasing hyperglycaemia, the reduction in the risk of progressive retinopathy and nephropathy persisted in the intensive therapy

group, showing us a ''legacy effect'' of improved glycaemia.

The American Diabetes Association currently recommends HbA_{1c} levels of < 7.0% The International Diabetes Federation[6] and American Association of Clinical Endocrinologists[7] recommend a target of ≤ 6.5% based on evidence that stricter glycaemic control might be necessary to prevent macrovascular complications[8-10] (table 1).

HbA_{1c} levels reflect overall glycaemic exposure over the past 2–3 months and are determined by both fasting and postprandial plasma glucose. Because postprandial hyperglycaemia has been implicated as a risk factor for macrovascular complications and cardiovascular disease, AACE has recommended aggressive treatment goals for 2-h postprandial glucose (140 mg/dl or less).

The American Diabetes Association estimates that the risk of diabetes-related mortality increases 25% for each 1% increase in HbA1c[11]. Each percentage point increase in HbA_{1c} has also been estimated to correspond to a 35% increase in the risk of microvascular complications and an 18% increase in the risk of myocardial infarction (fatal plus non-fatal).

Glycaemic control can be achieved initially by interventions to improve diet and exercise habits and/or the prescription of ≥1 oral antidiabetic drug (OAD), such as insulin secretagogue and/or metformin.

However, in patients in whom type 2 DM progresses as a result of declining beta-cell function, exogenous insulin therapy is required in addition to or as an alternative to OAD therapy. Recent guidelines and targets for glycaemic control published by the International Diabetes Federation[12] encourage the use of insulin at earlier stages in the disease process than has been conventional, but many patients and health care professionals delay insulin therapy due to concerns about injection-site pain, hypoglycaemia, and weight gain[13-14] (fig 2 and 3).

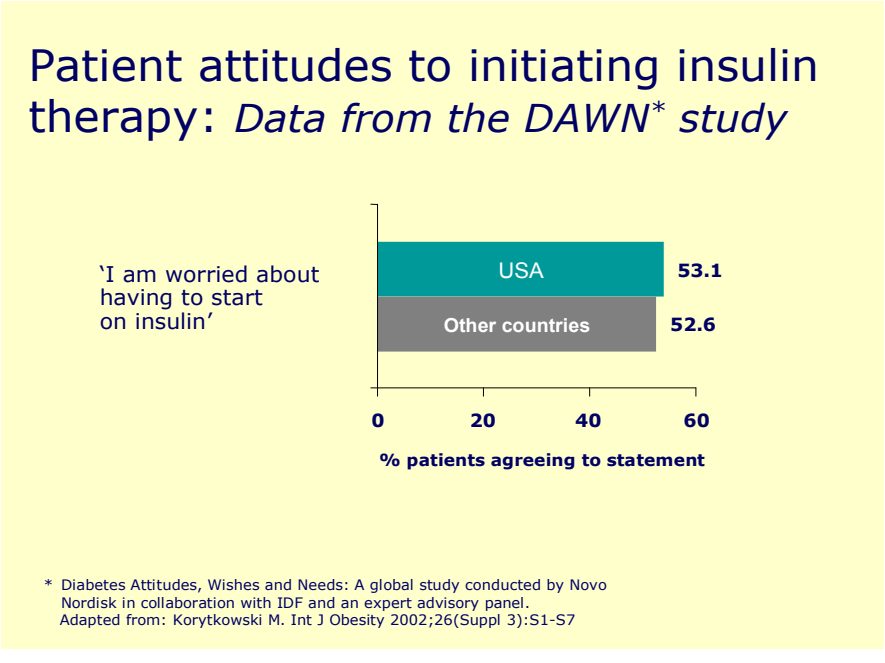

Fig. 2

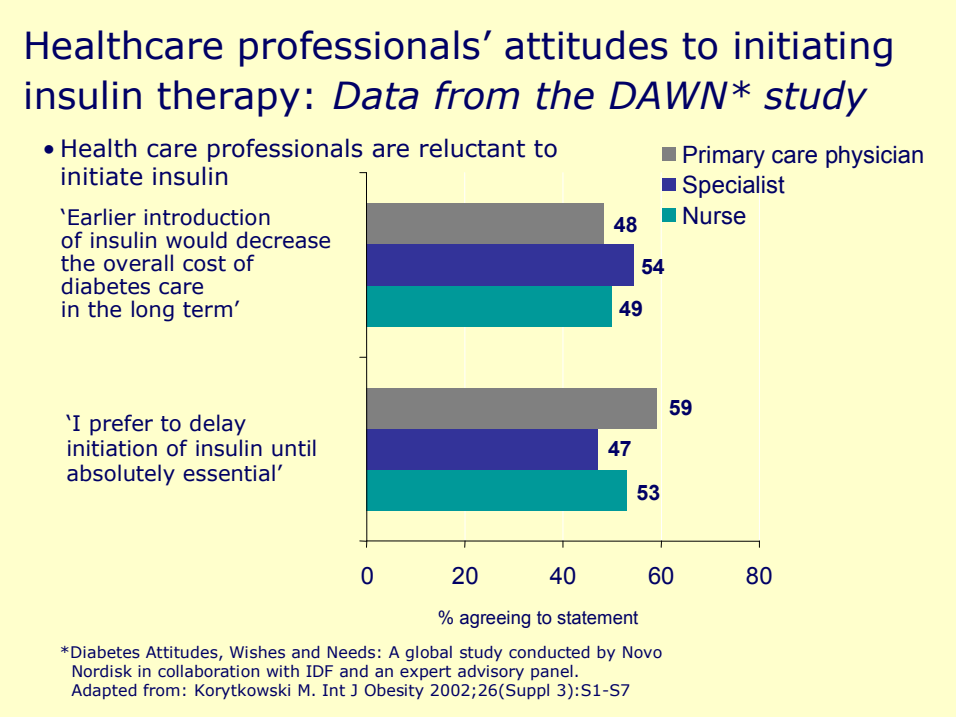

Fig. 3

There is no consensus concerning the best ways to overcome these barriers when initiating insulin therapy.

The addition of a QD or BID long-acting basal insulin formulation to an existing OAD regimen, followed by aggressive titration of the dose to achieve glycaemic targets has gained popularity in recent years. Treatment intensification through the subsequent addition of a mealtime insulin injection can be undertaken at a later stage, as needed, to achieve target levels of glycaemia if treatment with basal insulin plus OAD is not sufficient.

Insulin therapy is associated with increased risk of daytime and nocturnal hypoglycaemia, which has been attributed to the pharmacodynamic properties of traditional human insulin preparations[15]

Intermediate and long-acting human insulin preparations, such as NPH insulin, have pronounced insulin peaks 5 to 7 hours after injection, resulting in increased risk of nocturnal hypoglycaemia and duration of action that is too short to maintain glycaemic control throughout the night[16]. Furthermore, the dosing precision with NPH insulin is often highly variable due to inadequate resuspension [17-18].

Regular human insulin injected at mealtimes has a slower onset and a more prolonged action than endogenous insulin, and consequently the combination of these human insulin results in high postprandial blood glucose excursions and risk of hypoglycaemia between meals and overnight.

Insulin analogues have been developed to enable patients with diabetes mellitus to achieve near-normal glucose levels with decreased risk of hypoglycaemia and less variability.

A major deterrent to start insulin therapy is also the risk of weight gain, which is associated with poor cardiovascular outcomes[19]. Studies have shown that a 2.5% reduction in HbA_{1c} is associated with a 5 kg increase in weight, more commonly occurring in women than in men[20].

Insulin detemir has not been associated with a significant increase in body weight in patients with type 1 and type 2 diabetes mellitus. Significantly less weight gain was seen in patients with type 2 diabetes. These is a constant finding in all detemir interventional clinical trials and also, in the large observational study PREDICTIVE™ [21-34]

So, insulin analogues may significantly improve type 2 diabetes patient's adherence to initiating insulin therapy in an earlier stage of the disease.

In 2002, mean HbA_{1c} values in 8 Western European countries were above 7%[35] (fig. 4).

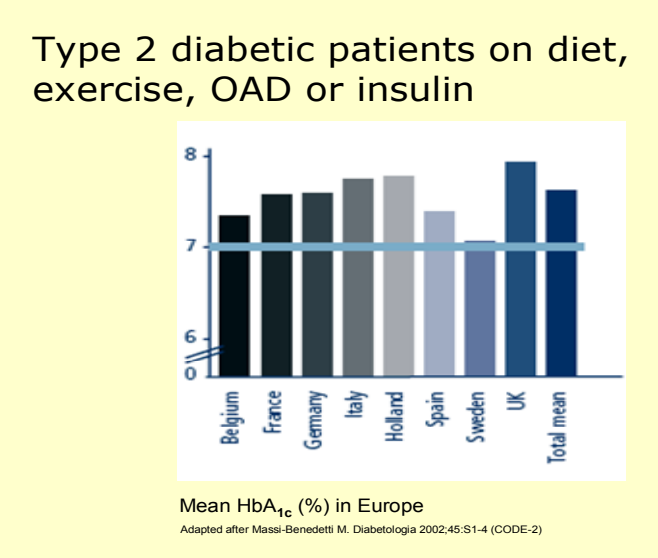

Fig. 4

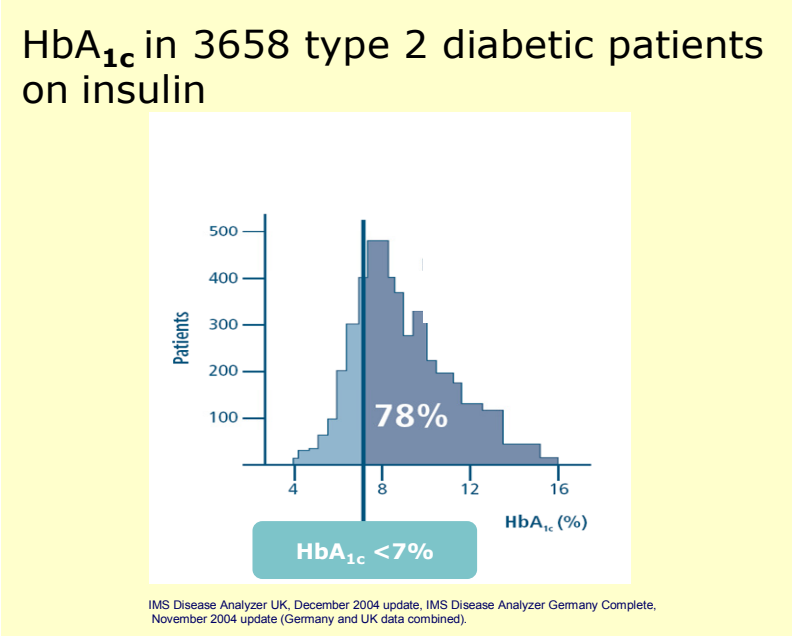

Fig. 5

Also, in 2004, combined data from IMS Disease Analyzer Germany and UK, showed that 78% of 3658 type 2 diabetic patients had mean HbA_{1c} values above ADA targets of <7%[36,37] (fig. 5).

Novo Nordisk, initiated and conducted the `HbA1c` Project in 13 diabetes centres in Romania, involving more than 200 diabetologists.

The objective of this project was to evaluate the current status of the metabolic control, determined though HbA_{1c} measurement in type 2 diabetes patients.

The project, which took part in May 2007 included HbA_{1c} measurements in 9.000 type 2 diabetic patients on OADs and/or human insulin treatment for 6-8 years

The data from this project shows that 83% of investigated type 2 diabetic patients had $HbA_{1c} \geq 7\%$ (table 2)

Table 2. Results of HbA1c measurements, May 2007

	Hb A1c < 7	Hb A1c between 7 - 9	Hb A1c > 9	Total HbA1c > 7%
OAD treatment				
1968	**512**	**807**	**649**	**1456**
	26%	40%	33%	74%
HM				
3703	**669**	**1305**	**1511**	**2816**
	19%	36%	45%	81%
HM+ OAD				
72	**11**	**23**	**38**	**61**

	15%	32%	53%	85%
Not specified				
3367	**503**	**1099**	**1765**	**2864**
	15%	33%	52%	85%
TOTAL				
9110	**1695**	**3234**	**3963**	**7197**
	19%	36%	45%	81%
Total excluding OHA treated patients				
7142	**1183**	**2427**	**3314**	**5741**
	17%	34%	49%	83%

In conclusion, type 2 diabetes is a progressive disease, in which the glycaemic burden is associated with the development of late complications. The development of these complications affects not only the progression and management of diabetes but also contributes to higher morbidity and mortality in patients with Type 2 diabetes. Complications have important effects on patient's quality of life as well as socio-economic implications. The treatment strategy implies measures to achieve metabolic control and to correct associated metabolic imbalances in order to prevent/delay progression of late diabetic complications and improve the quality of life.

But, the majority of type 2 diabetic patients do not reach and/or maintain glycaemic targets. There are some approaches which allow patients' empowerment to achieve glycaemic targets as:

- Modern insulins
- Improved insulin devices
- Simple titration guidelines for patients (home adjustments)
- Continuous Blood Glucose Monitoring (CBGM)

New and more comprehensive efforts are necessary in our country to improve the metabolic control of type 2 diabetes.

REFERENCES

1. UK Prospective Study Group, Prospective Diabetes Study 16. Overview of 6 years' therapy of type II diabetes: a progressive disease, Diabetes 44 (1995) 1249–1258.

2. Turner RC, Cull CA, Frighi V, Holman RR: Glycaemic control with diet, sulfonylurea, metformin, or insulin in patients with type 2 diabetes mellitus: progressive requirement for multiple therapies (UKPDS 49). *JAMA* 281:2005–2012, 1999)

3. M. Shichiri, H. Kishikawa, Y. Ohkubo, N. Wake, Long-term results of the Kumamoto study on optimal diabetes control in type 2 diabetic patients, Diabetes Care 23 (Suppl. 2) (2000) B21– B29)

4. DCCT/EDIC Research Group, Retinopathy and nephropathy in patients with type 1 diabetes four years after a trial of intensive therapy, N. Engl. J. Med. 342 (2000) 381–389

5. Standards of Medical Care in Diabetes, Diabetes Care 28 (2005) S4–S36

6. E. Standl, International Diabetes Federation European Policy Group standards for diabetes, Endocr. Pract. 8 (Suppl. 1) (2002) 37–40

7. American College of Endocrinology consensus statement on guidelines for glycaemic control, Endocr. Pract. 8 (Suppl. 1)(2002) 5–11

8. UK Prospective Diabetes Study (UKPDS) Group, Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33), Lancet 352 (1998) 837–853

9. M. Coutinho, H. Gerstein, Y. Wang, S. Yusuf, The relationship between glucose and incident cardiovascular events. A metaregression analysis of published data from 20 studies of 95,783 individuals followed for 12.4 years, Diabetes Care 22 (1999) 233–240.

10. K.-T. Khaw, N. Wareham, R. Luben, S. Bingham, S. Oakes, A. Welch, et al., Glycated haemoglobin, diabetes, and mortality in men in Norfolk cohort of European Prospective Investigation of Cancer and Nutrition (EPIC-Norfolk), BMJ 322 (2001) 15–18

11. American Diabetes Association. Implications of the United Kingdom Prospective Diabetes Study. Diabetes Care 2003; 26 (Suppl. 1): S28–S32

12. International Diabetes Federation. Clinical Guidelines Task Force. Global guideline for type 2 diabetes. Brussels, Belgium: IDF; 2005. Available at: http://www.idEorg. Accessed June 15, 2006

13. Korytkowski M. When oral agents Pail: Practical barriers to starting insulin. Int J Obes Relat Metab Disord. 2002; 26 (SuppI 3):18-24

14. Hinemann L Overcoming obstacles: New management options. Eur J Endocrinol. 2004; (SuppI 2):T23-T30

15. The Diabetes Control and Complications Trial Research Group (1997) Hypoglycaemia in the Diabetes Control and Complications Trial. Diabetes 46:271–286

16. Starke A, Heinemann L, Hohlmann A, Berger M The action profiles of human NPH insulin preparations. Diabet Med 6:239–244, 1989

17. Kølendorf K, Bojsen J, Deckert T (1983) Clinical factors influencing the absorption of 125I-NPH insulin in diabetic patients. Horm Metab Res 15:274–278

18. Jehle PM, Micheler C, Jehle CR, Breitig D, Boehm BO (1999) Inadequate suspension of neutral protamine Hagedorn (NPH) insulin in pens. Lancet 354:307–335

19. Fritsche A, Haring H. At last, a weight neutral insulin? Int J Obes Relat Metab Disord. 2004; 28 (suppl 2):S41-46

20. Hordern SV, Russell-Jones DL. Insulin detemir, does a new century bring a better insulin? Int J Clin Pract. 2005; 59:730-9

21. Philis-Tsimikas A et al. Study 1632. A comparison of once-daily insulin detemir with NPH insulin when added to oral antidiabetic drugs in poorly controlled type 2 diabetes. Clin Ther 2006; 28: 156981

22. Russell-Jones D, Bolinder J, Hylleberg B et al. Effects of QG Insulin Detemir or Neutral Protamine Hagedoen on Blood Glucose Control in Patiens with Type 1 Diabetes Mellitus Using a Basal-Bolus Regimen. Clinical Therapeutics 2004; 26(5): 724-736

23. Vague P, Selam JL, Skeie S et al. Insulin detemir is associated with more predictable glycafemic control and reduced risk of hypoglycaemia than NPH insulin in patiens with type 1 diabetes on a basal-bolus regimen with premeal insulin aspart. Diabetes Care 2003; 26(3): 590-596

24. De Leeuw I, Vague P, Selam JL et al. Insulin detemir used in basal-bolus therapy in people with type 1 diabetes is associated with a lower risk of nocturnal hypoglycaemia and less weight gain over 12 months in comparison to NPH insulin. Diabetes Obes Metab 2005; 7(1): 73-82

25. Pieber T, Grill V Kristensen A, Draeger E. Comparison of three multiple injection regimens for Type 1 diabetes: morning plus dinner or bedtime administration of insulin detemir vs. morning plus bedtime NPH insulin. Diabet Med 2005; 22(7): 850-857

26. Standl E, Lang H , Roberts A et al. The 12-Month Efficacy and Safety of Insulin Detemir and NPH Insulin in Basal-Bolus Therapy for the Treatment of Type 1 Diabetes. Diabetes Technology & Therapeutics 2004; 6(5): 579-588

27. Home P, Bartley P, Russell-Jones D et al. Insulin detemir offers improved control compared with NPH insulin in people with type 1 diabetes: a glycaemic

randomized clinical trial. Diabetes Care 2004; 27(5): 1081-1087

28. Hermansen K, Fontaine P, Kukolja KK et al. Insulin analogues (insulin detemir and insulin aspart) versus traditional human insulins (NPH insulin and regular human insulin) in basal-bolus therapy for patiens with type 1 diabetes. Diabetologia 2004; 47 (4): 622-629

29. Raslova K, Bogoev M, Raz I et al. Insulin detemir and insulin aspart: a promising basal-bolus regimen for type 2 diabetes. Diabetes Res Clin Pract 2004; 66(2): 193-201

30. Haak T, Tiengo A, Draeger E et al. Lower within-subject variability of fasting blood glucose and reduced weight gain with insulin detemir compared to NPH insulin in patiens with type 2 diabetes. Diabetes Obes Metab 2005; 7(1): 56-64

31. Hermansen K, et al. A 26-week, randomized, parallel, treat-to-target trial comparing insulin detemir with NPH insulin as add on therapy to oral glucose-lowering drugs in insulin-naïve people with type 2 diabetes. Diabetes Care 2006; 29(6):126974

32. Robertson K, Schonle E, Gucev Z, et al. Benefits of insulin detemir over NPH insulin in children and adolescents with Type 1 diabetes: Lower and more predictable fasting plasma glucose and lower risk of nocturnal hyploglycaemia. Diabet Med 2005; 22 (Suppl. 2): 45 (abstract P66)

33. Pieber TR, Treichel H-C, Robertson LI, et al. Insulin detemir plus insulin aspart is associated with less risk of major as well as nocturnal hypoglycaemia than insulin glargine plus insulin aspart at comparable levels of glycaemic control in type 1 diabetes. Diabetologia 2005; 48 (Suppl 1): A92

34. PREDICTIVE™: KST `07 European Regional Meeting (4)

35. Massi-Benedetti M. The Cost of Diabetes Type II in Europe. The CODE-2 Study Diabetologia 2002; 45:S1-4

36. IMS Disease Analyzer UK, December 2004 updatefff

37. IMS Disease Analyzer Germany Complete, November 2004 update