Tip 2 Diyabette Erken İnsülin Tedavisi ve Bazal Insulin

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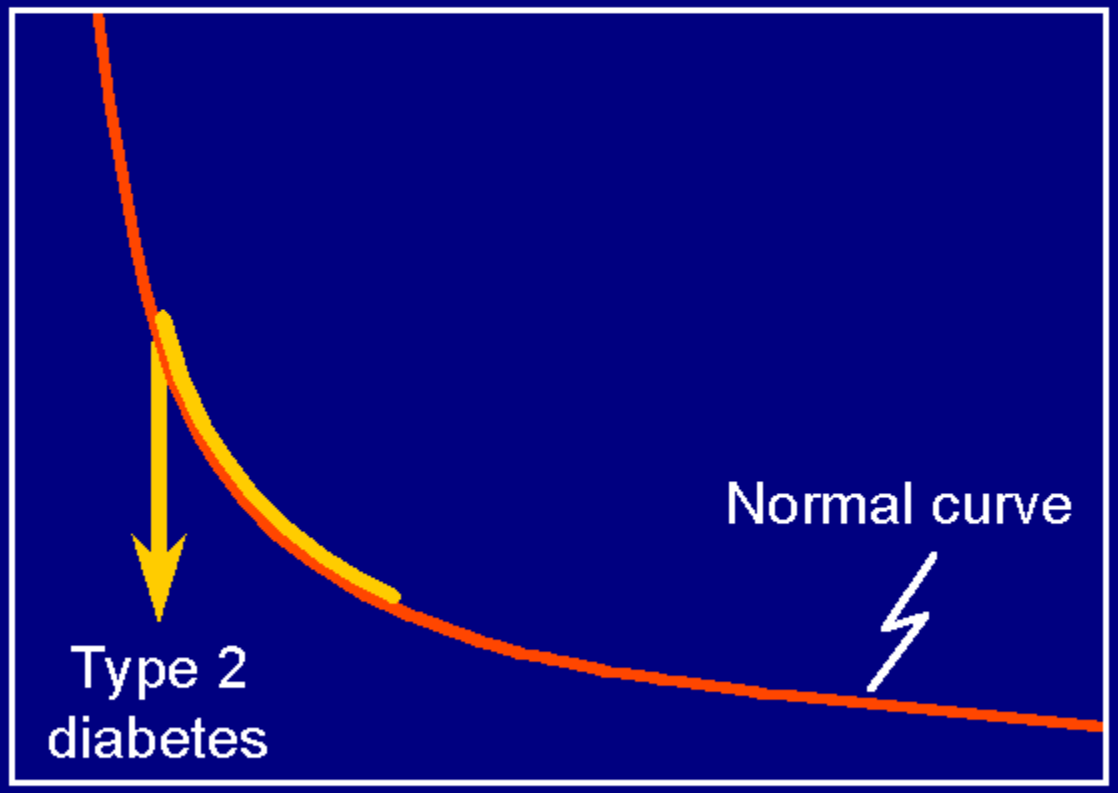
Pathogenesis of Type 2 Diabetes

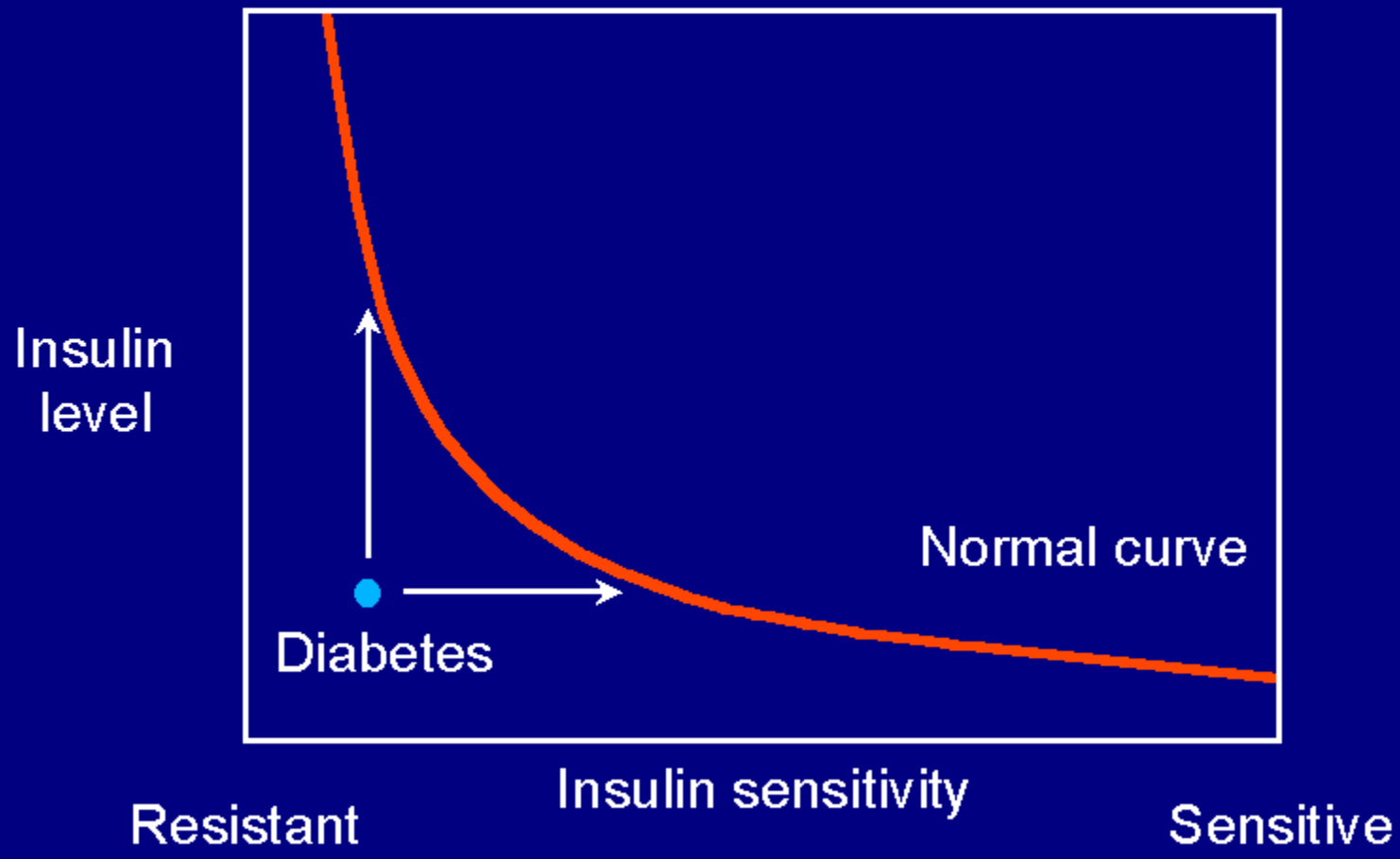
'Falling Off the Curve'



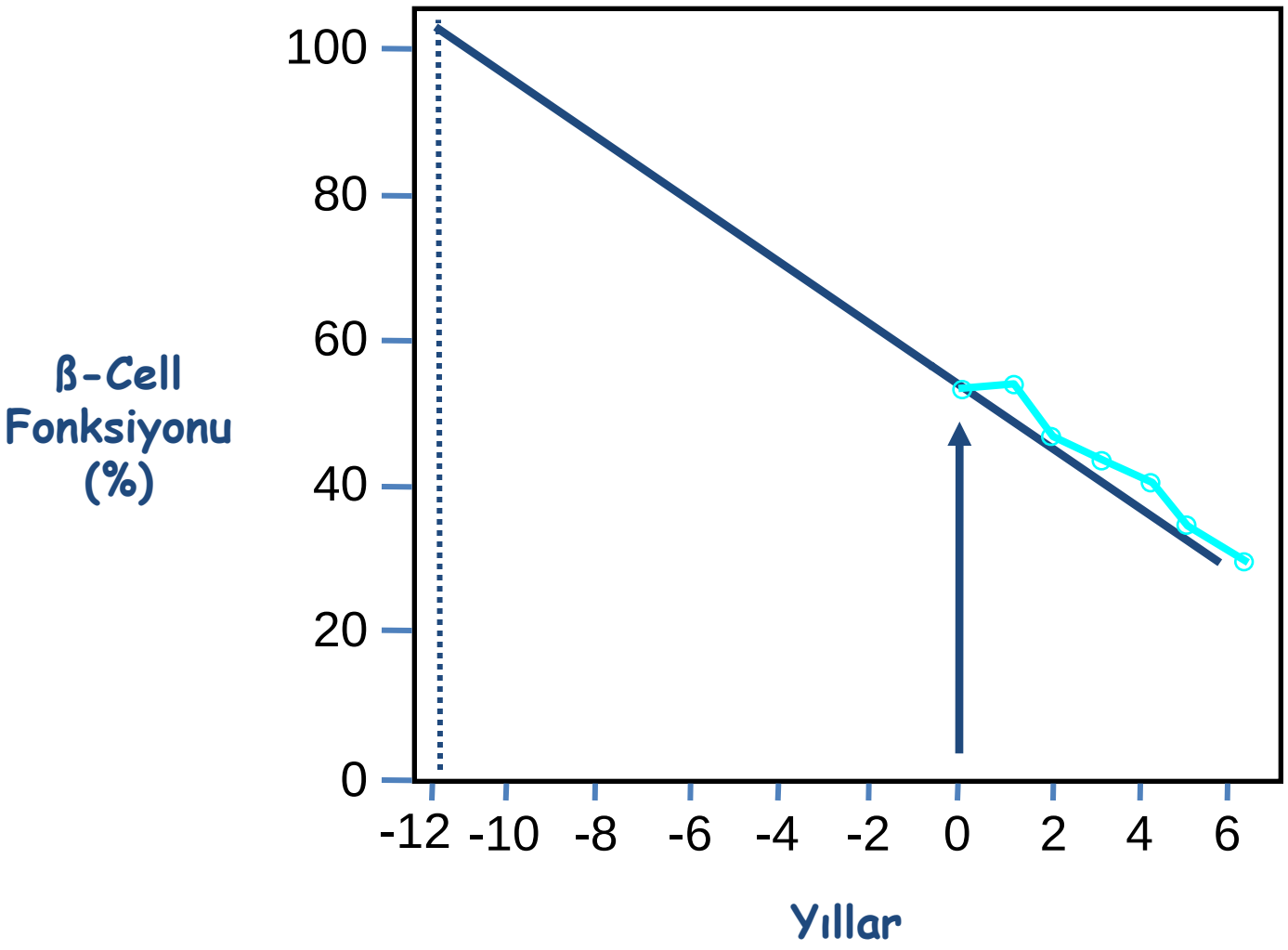
Bergman RN. *Diabetes*. 1989;38:1512-1527.

Treatment of Type 2 Diabetes

'Getting Back on the Curve'



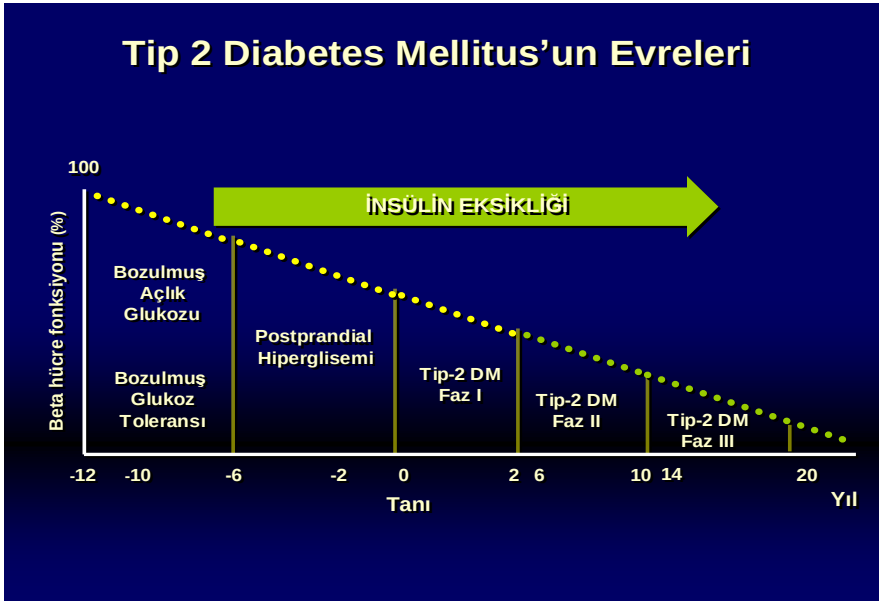
Beta hücre fonksiyonu



Holman RR. Diabetes Res Clin Pract 40 (Suppl l):S21-S25; 1998

T2DM - Beta Hücre Dekompansasyonu Evreleri

- İnsülin direncine adaptasyon
  1. Beta hücre hipertrofisi
  2. Beta hücre hiperplazisi
  3. Glikoza insülin yanıtı değişmesi
  4. Glikozla oluşan insülin sekresyonunun normal veya artmış olması
- Dekompansasyon: Hiperglisemi
  1. Glikoza insülin yanıtının kaybolması
  2. Arginine yanıtın normal olması
  3. İnsülin depoları normal
  4. Erken dönem beta hücre farklılaşması
     a. Gen ekspresyonu azalması (GLUT-2, GK, mGADPH, PK, VDCC, IP3R-II ve transkripsiyon faktörleri)
     b. LDH, HK, G-6-P ve c-myc gen transkripsiyonu artışı
- Dekompansasyon: Ciddi Hiperglisemi
  1. Glikoza bağlı insülin sekresyonunun kaybolması
  2. Arginine yanıtın kaybolması
  3. Proinsülin/insülin oranının artışı
  4. Degranülasyon (insülin deposu azalması)
  5. İleri derecede beta hücre farklılaşması
     a. Gen ekspresyonu azalması (İnsülin, IAPP, Kir6.2, SERCA2B ve transkripsiyon faktör Beta2)
     b. G-6-P, 12- lipoksigenaz, FA sentaz ve transkripsiyon faktör C/EBP β artışı



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Chronic Hyperglycemia Triggers Loss of Pancreatic β Cell Differentiation in an Animal Model of Diabetes*

(Received for publication, December 18, 1998, and in revised form, February 22, 1999)

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TABLE II

Changes in pancreatic islet gene mRNA levels in rats with different degree of hyperglycemia 4 weeks after Px

Px rats were classified according to their averaged 3- and 4-week blood glucose levels. The mRNA levels were compared in Px and sham by semiquantitative radioactive multiplex RT-PCR (Table I). After normalization of each product to the internal control gene level, mRNA levels were expressed in percent of sham levels observed in the same PCR. LPx, MPx, HPx, and SPx correspond to low, mildly, highly, and severely hyperglycemic Px rats. Values are means ± S.E. for the indicated number of independent determinations.

Group classification criteria	Sham, n = 11	LPx, <100 mg/dl, n = 18	MPx, 100–150 mg/dl, n = 10	HPx, 150–250 mg/dl, n = 4	SPx, >250 mg/dl, n = 6
Blood glucose (mg/dl)[a]	76 ± 2.4	84 ± 2.0	112 ± 2.7[b]	192 ± 11.3[b]	285 ± 11.4[b]
Islet hormones					
Insulin (I + II)	100 ± 3.0	92 ± 4.1	107 ± 12.5	50 ± 7.7[b]	51 ± 5.6[b]
IAPP	100 ± 3.7	121 ± 4.3[c]	112 ± 5.8	83 ± 7.1	71 ± 13.0[c]
Glucagon	100 ± 2.1	104 ± 7.1	139 ± 28.7	157 ± 37.0	122 ± 20.6
Somatostatin	100 ± 6.8	78 ± 3.1	83 ± 12.2	82 ± 21.5	82 ± 11.9
Metabolism enzymes					
GLUT2	100 ± 2.0	88 ± 3.6	75 ± 3.7[b]	53 ± 5.8[b]	53 ± 5.3[b]
GK	100 ± 0.7	83 ± 2.9	86 ± 9.8	57 ± 9.6[b]	61 ± 6.8[b]
HK I[e]	100 ± 2.8	189 ± 18[d]	184 ± 23[d]	258 ± 64.2[b]	342 ± 80[b]
mGPDH	100 ± 1.2	79 ± 4.1[c]	74 ± 9.9[c]	53 ± 5.4[b]	55 ± 6.7[c]
LDH-A	100 ± 8.3	249 ± 36.1[d]	278 ± 41.4[d]	480 ± 262[b]	535 ± 101[b]
Pyruvate carboxylase	100 ± 2.8	80 ± 3.9[c]	77 ± 10.5[c]	44 ± 7.6[b]	40 ± 6.6[b]
Ion channels/pumps					
Kir6.2	100 ± 1.7	91 ± 2.5	90 ± 5.1	64 ± 10.1[b]	62 ± 6.0[b]
SUR1	100 ± 2.2	74 ± 4.6	98 ± 15.8	86 ± 18.3	80 ± 14.4
VDCCα1D	100 ± 2.0	78 ± 3.3[b]	74 ± 7.8[b]	51 ± 7.3[b]	56 ± 6.2[b]
SERCA3	100 ± 3.1	90 ± 2.4	80 ± 5.2[b]	54 ± 7.3[b]	47 ± 7.3[b]
SERCA2B	100 ± 2.7	102 ± 3.5	97 ± 5.2	86 ± 7.2	76 ± 14[c]

Changes in transcription factor mRNA levels in rats with different degree of hyperglycemia 4 weeks after Px

Px rats were classified according to their averaged 3- and 4-week post-Px blood glucose levels (actual values are shown in Table II). The mRNA levels were compared between groups by semiquantitative radioactive multiplex RT-PCR (Table I). After normalization of each product to the internal control gene level, mRNA levels were expressed in percent of sham levels observed in the same PCR. LPx, MPx, HPx, and SPx correspond to low, mildly, highly, and severely hyperglycemic Px rats. Values are means ± S.E. for the indicated number of independent determinations.

Group classification criteria	Sham, n = 11	LPx, <100 mg/dl, n = 18	MPx, 100–150 mg/dl, n = 10	HPx, 150–250 mg/dl, n = 4	SPx, >250 mg/dl, n = 6
Blood glucose (mg/dl)[a]	76 ± 2.4	84 ± 2.0	112 ± 2.7[b]	192 ± 11.3[b]	285 ± 11.4[b]
Transcription factors					
PDX-1	100 ± 2.6	80 ± 3.5[c]	86 ± 8.8	60 ± 13.7[b]	59 ± 6.0[b]
Nkx6.1	100 ± 2.7	84 ± 3.6[c]	63 ± 4.7[b]	45 ± 6.9[b]	40 ± 6.1[b]
Pax6	100 ± 3.6	83 ± 4.3[c]	67 ± 3.5[b]	54 ± 7.0[b]	49 ± 8.5[b]
Beta2	100 ± 2.0	94 ± 4.1	95 ± 4.9	73 ± 13.6[c]	65 ± 7.3[b]
PAN1	100 ± 2.0	88 ± 2.8	85 ± 4.2[c]	80 ± 10[c]	74 ± 6.6[b]
IB1	100 ± 2.8	80 ± 4.3[c]	83 ± 8.1	74 ± 10.3[c]	67 ± 9.3[b]
HNF1α	100 ± 1.7	81 ± 4.6[c]	84 ± 7.7	56 ± 5.5[b]	49 ± 4.9[b]
HNF4α1	100 ± 2.7	77 ± 3.8[b]	78 ± 8.3[c]	60 ± 9.3[b]	58 ± 4.4[b]
HNF4α2/5	100 ± 2.4	70 ± 2.8[b]	66 ± 5.8[b]	54 ± 8.7[b]	51 ± 4.1[b]
HNF3β	100 ± 3.6	72 ± 2.7[b]	82 ± 12.8	62 ± 13.9[c]	56 ± 6.6[b]
SP1	100 ± 2.2	107 ± 3.8	94 ± 5.9	82 ± 2.8	105 ± 10.5

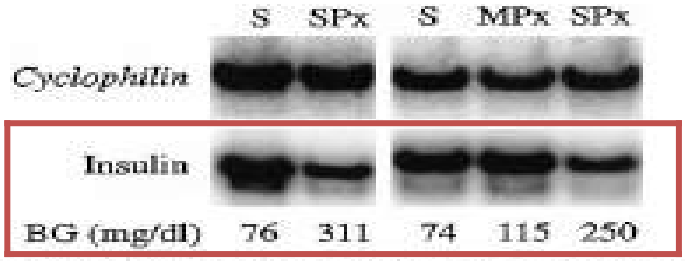


FIG. 3. **Comparison of insulin mRNA levels by semiquantitative RT-PCR in islets of representative sham (*S*), mildly hyperglycemic (MPx), and severely hyperglycemic (SPx) rats (*BG* represents the averaged blood glucose values 3 and 4 weeks post-Px). Insulin mRNA was decreased by ~50% in SPx islets but remained unaffected in MPx islets. Cyclophilin, used as internal control gene, did not change between groups. Mean changes of insulin mRNA levels in Px *versus* sham islets are indicated in Table II.**

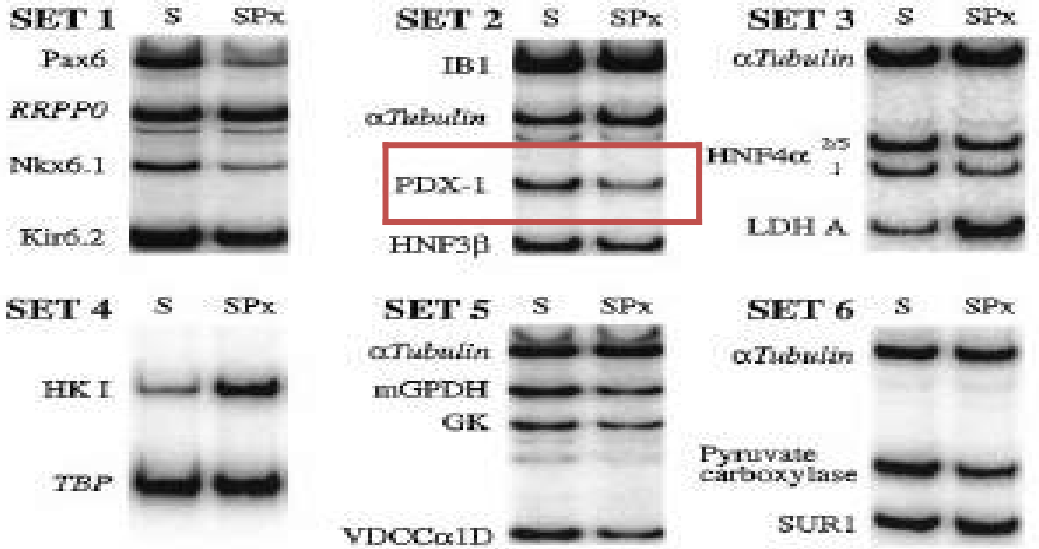


FIG. 4. **Semiquantitative multiplex RT-PCR sets used to compare the mRNA levels of several transcription factors, glucose metabolism genes, and ion channels in sham and Px islets. The internal control gene used in each particular set is highlighted in *italics*. The results were obtained with islets from a representative sham (*S*) and a severely hyperglycemic Px rat (*SPx*) 4 weeks after Px (averaged 3- and 4-week blood glucose levels were 76 and 311 mg/dl, respectively).**

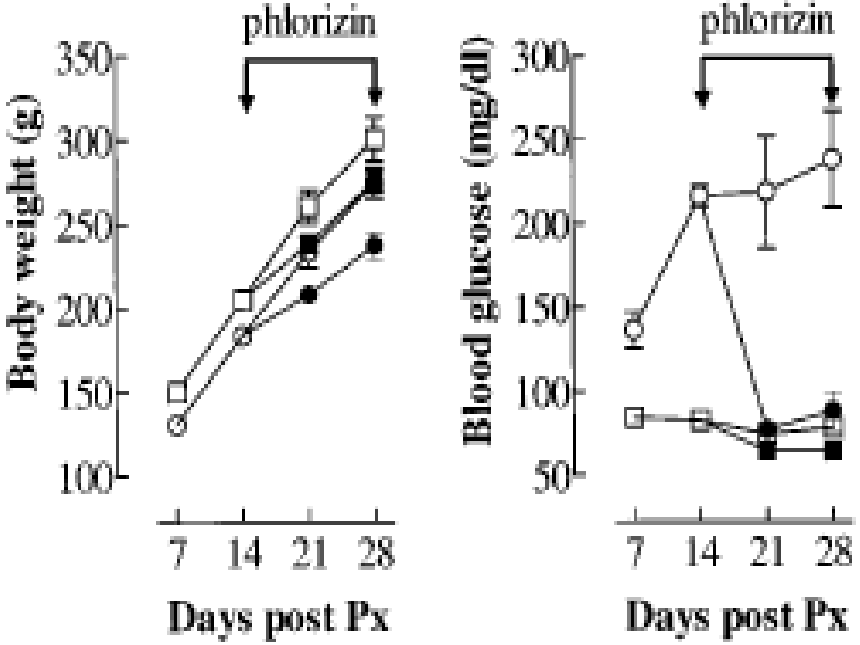
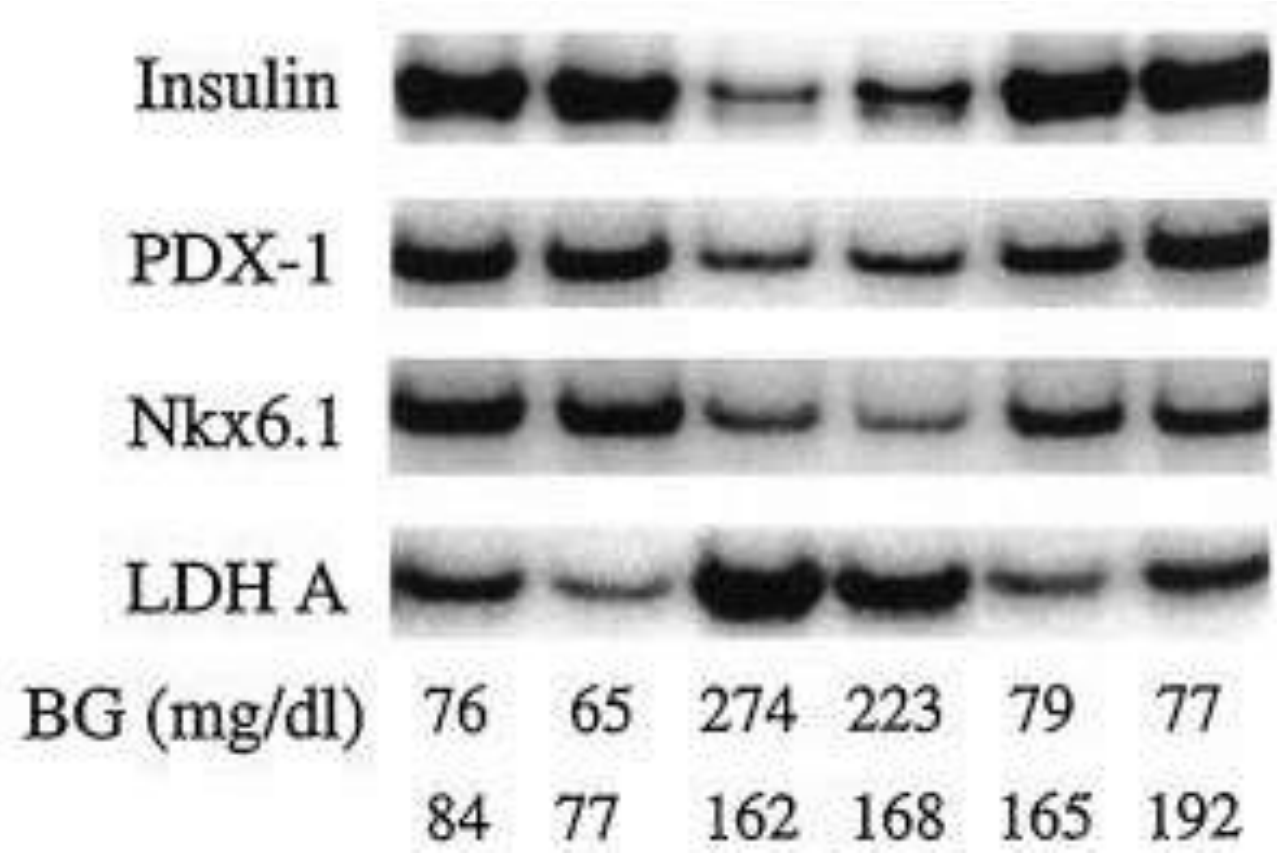


FIG. 5. **Effects of phlorizin treatment on body weight and blood glucose levels after Px.** Whole blood glucose levels were de-



Effect of 2-week normalization of blood glucose by phlorizin treatment on changes in islet gene mRNA levels after 90% Px. The different internal control genes used are highlighted in italics. The results were obtained 4 weeks after Px with islets from a representative sham (S), a sham injected with vehicle alone (SV), two severely hyperglycemic Px rats (Px), and two severely hyperglycemic Px rats treated with phlorizin for the last 2 weeks (PxP). BG shows the averaged blood glucose values 3 and 4 weeks post-Px on the upper line, and the averaged blood glucose values 1 and 2 weeks post-Px (before phlorizin treatment) on the bottom line.

Induction of Long-Term Glycemic Control in Newly Diagnosed Type 2 Diabetic Patients by Transient Intensive Insulin Treatment

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(3), a problem also faced with sulfonylureas (4). It is therefore considered preferable to control the disease with diet and exercise alone. However, these measures often fail to restore satisfactory metabolic control.

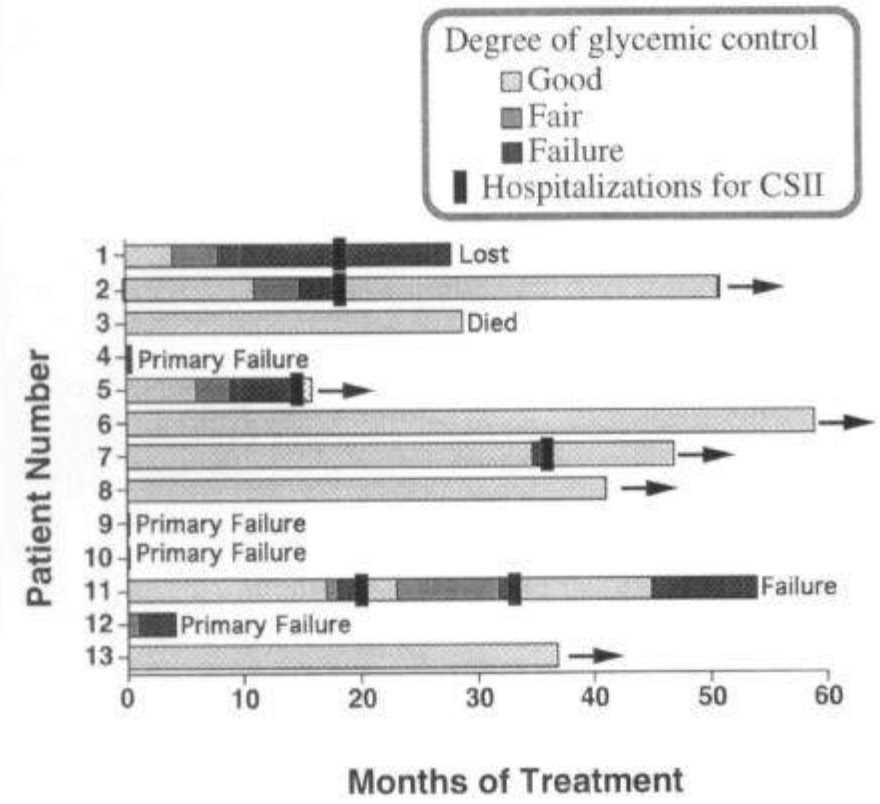

Figure 1—*Long-term follow-up of 13 patients. See results for a description of individual patients and Table 1 for a summary.*

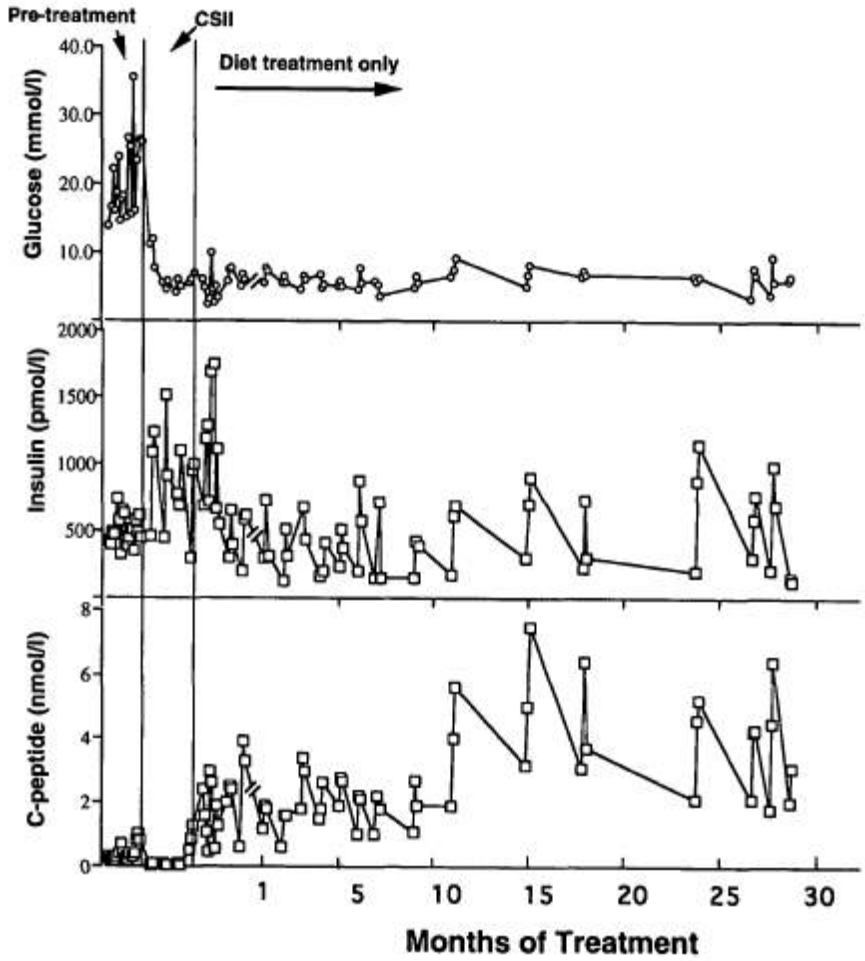

Figure 2—*Long-term follow-up in patient 8, showing pretreatment, CSII, and follow-up levels of glucose, insulin, and C-peptide. Data is for first 29 months of follow-up. At each visit, glucose, insulin, and C-peptide levels were determined before and 1 and 2 h after a standard breakfast. Glucose levels continued to be under excellent control for 15 additional months. However, insulin and C-peptide values were not available for this period.*

Induction of Long-term Glycemic Control in Newly Diagnosed Type 2 Diabetic Patients Is Associated With Improvement of β-Cell Function

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is affected by glucotoxicity generated by hyperglycemia and lipotoxicity due to lipolysis (2). The vicious cycle of elevated glucose further impairs and possibly destroys β-cells, finally stopping insulin production completely (3). Therefore,

Table 1—*Insulin and C-peptide concentrations of the patients during IVGTT in the whole group (n = 126)*

Item/time (min)	Before CSII	After CSII	P
Insulin concentration (pmol/l)			
0	102.8 ± 45.9	104.8 ± 91.0	0.836
1	98.3 ± 45.8	128.3 ± 60.7	<0.001
2	100.5 ± 63.9	139.4 ± 67.1	<0.001
4	84.3 ± 40.2	126.6 ± 62.9	<0.001
6	80.7 ± 38.2	123.6 ± 63.3	<0.001
10	90.8 ± 47.3	137.7 ± 67.7	<0.001
C-peptide concentration (pmol/l)			
0	0.8 ± 0.4	0.7 ± 0.3	0.023
1	0.7 ± 0.3	0.9 ± 0.4	<0.001
2	0.7 ± 0.3	0.9 ± 0.5	<0.001
4	0.67 ± 0.3	0.8 ± 0.4	<0.001
6	0.7 ± 0.3	0.9 ± 0.4	<0.001
10	0.7 ± 0.3	1.0 ± 0.5	<0.001

Data are means ± SD.

Table 2—*Clinical characteristics in the remission and nonremission groups*

Item	Remission	Nonremission	P
n	32	36	—
Age (years)	50.6 ± 10.4	51.6 ± 13.1	0.718
BMI before CSII (kg/m^2)	25.9 ± 4.3	24.3 ± 3.1	0.069
BMI after CSII (kg/m^2)	26.0 ± 4.2	24.3 ± 3.0	0.051
HbA_{1c} before CSII (%)	10.3 ± 1.9	10.0 ± 1.9	0.647
HbA_{1c} after CSII (%)	9.2 ± 2.0	8.6 ± 1.5	0.207
FPG before CSII (mmol/l)	14.9 ± 3.0	14.7 ± 5.0	0.852
FPG after CSII (mmol/l)	6.1 ± 1.2	6.7 ± 1.1*	0.035
PPBG before CSII (mmol/l)	21.7 ± 5.1	19.7 ± 5.5	0.141
PPBG after CSII (mmol/l)	8.8 ± 2.2	9.9 ± 2.4	0.064
Duration to achieve glycemic control (days)	8.5 ± 3.1	8.8 ± 3.9	0.757
Maximal total daily insulin dose to achieve glycemic control (units/kg)	0.7 ± 0.2	0.7 ± 0.2	0.744
lnHOMA-IR before CSII †	2.3 ± 0.5	2.1 ± 0.5	0.117
lnHOMA-IR after CSII †	1.3 ± 0.5	1.2 ± 0.5	0.456
lnHOMA-B before CSII †	3.3 ± 0.6	3.2 ± 0.5	0.631
lnHOMA-B after CSII †	4.8 ± 0.6	4.4 ± 0.7*	0.002
AUC of insulin before CSII ($pmol \cdot l^{-1} \cdot min^{-1}$)	834.8 ± 352.3	853.6 ± 365.4	0.837
AUC of insulin after CSII ($pmol \cdot l^{-1} \cdot min^{-1}$)	1,423.4 ± 523.2	1,159.5 ± 476.8*	0.044
AUC of C-peptide before CSII ($pmol \cdot l^{-1} \cdot min^{-1}$)	7.0 ± 3.2	6.3 ± 3.4	0.384
AUC of C-peptide after CSII ($pmol \cdot l^{-1} \cdot min^{-1}$)	9.9 ± 4.3	7.8 ± 3.4*	0.036
AIR before CSII ($pmol \cdot l^{-1} \cdot min^{-1}$)	−316.1 ± 214.9	−152.2 ± 311.2*	0.020
AIR after CSII ($pmol \cdot l^{-1} \cdot min^{-1}$)	326.45 ± 413.1	255.2 ± 307.7	0.447
ΔAIR ($pmol \cdot l^{-1} \cdot min^{-1}$)	621.8 ± 430.4	387.3 ± 428.8*	0.033

Data are means ± SD. *$P < 0.05$ vs. the remission group; †HOMA-IR and HOMA-B were nonnormally distributed, so the data were logarithmically transformed before analysis. PPBG, postprandial plasma blood glucose.

Effect of intensive insulin therapy on β-cell function and glycaemic control in patients with newly diagnosed type 2 diabetes: a multicentre randomised parallel-group trial

Jianping Weng*, Yanbing Li*, Wen Xu, Lixin Shi, Qiao Zhang, Dalong Zhu, Yun Hu, Zhiguang Zhou, Xiang Yan, Haoming Tian, Xingwu Ran, Zuojie Luo, Jing Xian, Li Yan, Fangping Li, Longyi Zeng, Yanming Chen, Liyong Yang, Sunjie Yan, Juan Liu, Ming Li, Zuzhi Fu, Hua Cheng

Methods 382 patients, aged 25–70 years, were enrolled from nine centres in China between September, 2004, and October, 2006. The patients, with fasting plasma glucose of 7·0–16·7 mmol/L, were randomly assigned to therapy with insulin (CSII or MDI) or oral hypoglycaemic agents for initial rapid correction of hyperglycaemia. Treatment was stopped after normoglycaemia was maintained for 2 weeks. Patients were then followed-up on diet and exercise alone. Intravenous glucose tolerance tests were done and blood glucose, insulin, and proinsulin were measured before and after therapy withdrawal and at 1-year follow-up. Primary endpoint was time of glycaemic remission and remission rate at 1 year after short-term intensive therapy. Analysis was per protocol. This study was registered with ClinicalTrials.gov, number NCT00147836.

Findings More patients achieved target glycaemic control in the insulin groups (97·1% [133 of 137] in CSII and 95·2% [118 of 124] in MDI) in less time (4·0 days [SD 2·5] in CSII and 5·6 days [SD 3·8] in MDI) than those treated with oral hypoglycaemic agents (83·5% [101 of 121] and 9·3 days [SD 5·3]). Remission rates after 1 year were significantly higher in the insulin groups (51·1% in CSII and 44·9% in MDI) than in the oral hypoglycaemic agents group (26·7%; p=0.0012). β-cell function represented by HOMA B and acute insulin response improved significantly after intensive interventions. The increase in acute insulin response was sustained in the insulin groups but significantly declined in the oral hypoglycaemic agents group at 1 year in all patients in the remission group.

Interpretation Early intensive insulin therapy in patients with newly diagnosed type 2 diabetes has favourable outcomes on recovery and maintenance of β-cell function and protracted glycaemic remission compared with treatment with oral hypoglycaemic agents.

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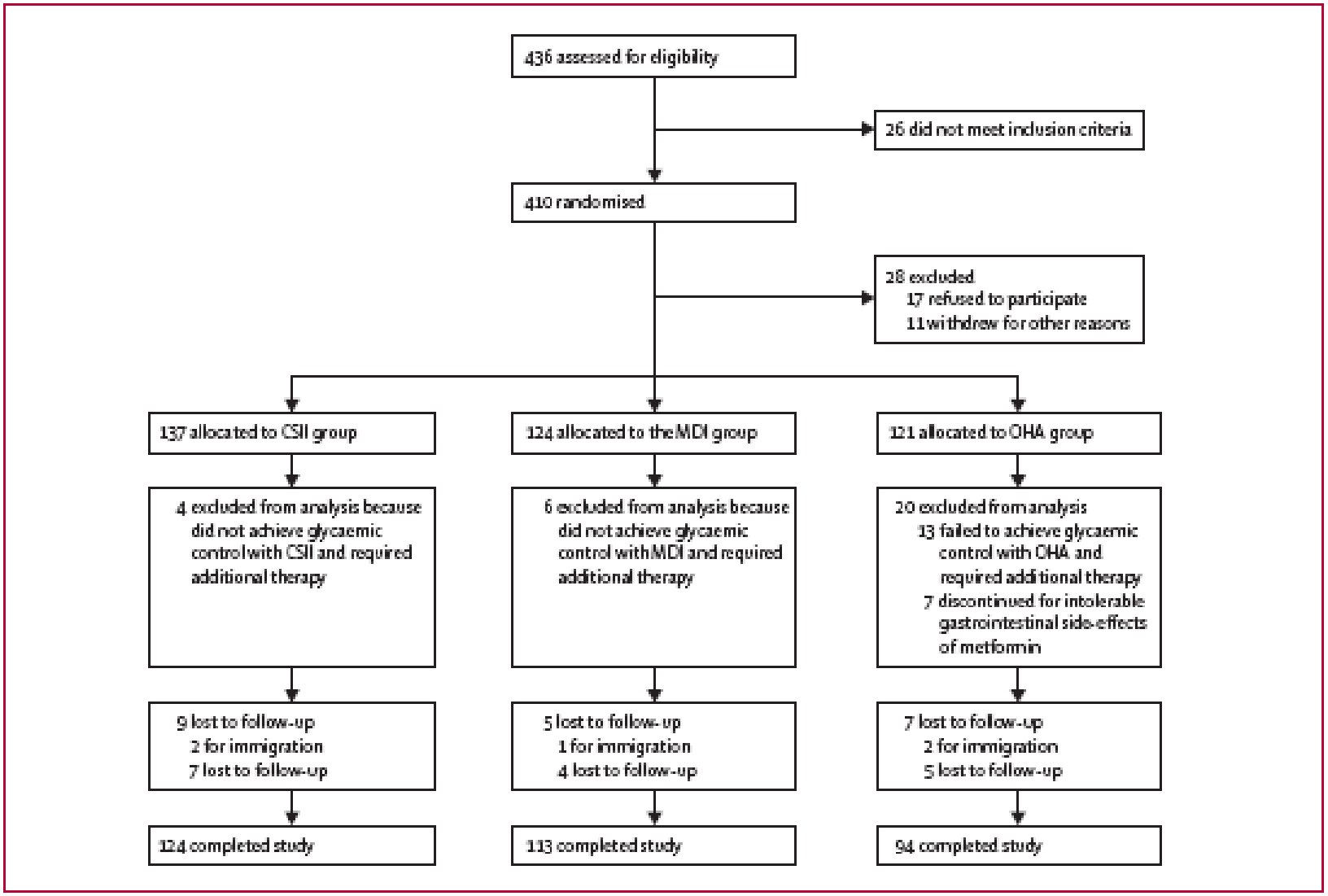

Figure 1: Trial profile

CSII=continuous subcutaneous insulin infusion. MDI=multiple daily insulin injections. OHA=oral hypoglycaemic agents.

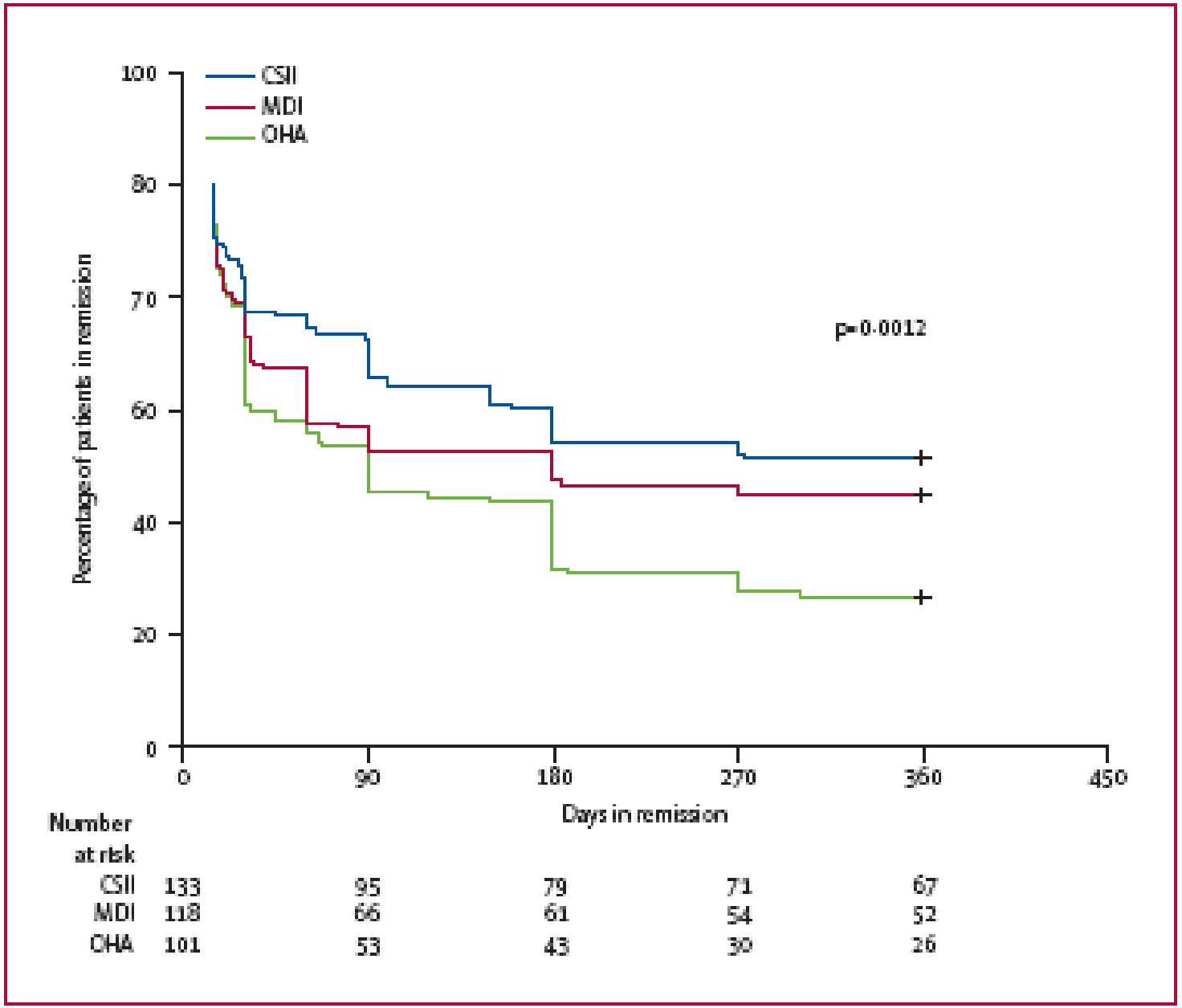

Figure 2: Kaplan-Meier estimates of time to primary endpoint

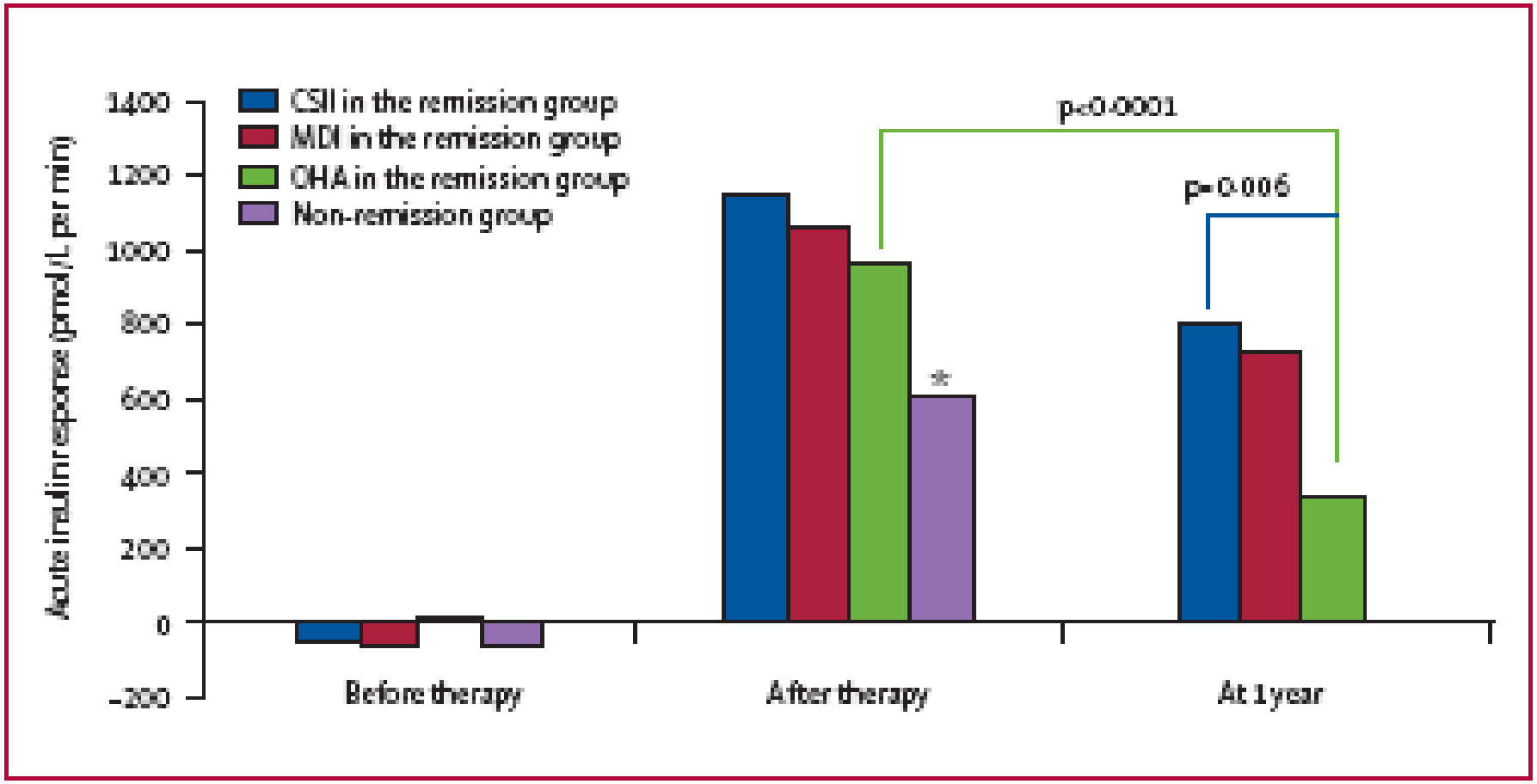

Figure 3: Acute insulin response (shown as median) before and after different interventions and at 1 year
*p<0·05 in the non-remission group compared with that in each intervention in the remission group (after treatment).

Early Insulin Treatment in Type 2 Diabetes

What are the pros?

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alike, compared with oral antidiabetic therapies (11). Patient resistance to the

Table 1—*Baseline characteristics and outcomes of patients with type 2 diabetes receiving temporary insulin therapy at disease diagnosis*

	n	Age	BMI	Baseline A1C (%)	Insulin dose (units · kg^{-1} · day^{-1})	Days to glycemic control	Duration insulin therapy (weeks)	% Early responders	% Sustained responders	Weight change
Ilkova et al. (17)	13	50	27	11.2	0.61	1.9	2	92	69 (26 months)	0.4 kg
Li et al. (16)	126	50	25	10.0	0.7	6.3	2	90	42 (24 months)	−0.04 kg/m^2
Ryan et al. (18)	16	52	31	11.8	0.37–0.73	<14	2–3	88	44 (12 months)	−0.5 kg/m^2

Early responders are subjects who achieved euglycemia with insulin treatment, and late responders are subjects who maintained long-term euglycemia without pharmacotherapy after the initial insulin treatment.

Table 2
Effects of intensive insulin therapy (IIT) at time of diagnosis on glycaemic control (GC).

	Treatment	*n*	Baseline HbA_{1c} (%)	HbA_{1c} after IIT (%)	Baseline FPG (mmol/L)	FPG after IIT (mmol/L)	Baseline PPG (mmol/L)	PPG after IIT	Days to achieve GC	Duration of IIT	% in GC (duration in months)[a]
Ilkova et al. (1997) [50]	CSII	13	11.0 ± 0.7	6.1 ± 0.5	12.1 ± 1.1	6.6 ± 0.4	16.9 ± 1.8	7.4 ± 0.4	1.9 ± 0.8	2 weeks	69 (26)[b]
Li et al. (2004) [51]	CSII	126	10.0 ± 2.2	8.7 ± 1.9	13.3 ± 4.4	6.3 ± 1.3	18.7 ± 6.1	8.6 ± 2.3	6.3 ± 3.9	2 weeks	42.3 (24)
Ryan et al. (2004) [52]	MDI	16	11.8 ± 0.3	N/A	13.3 ± 0.7	7.0 ± 0.4	N/A	N/A	N/A	2–3 weeks	44 (12)
Chen et al. (2007) [53]	CSII	138	11.9 ± 2.0	N/A	14.62 ± 1.68	6.62 ± 0.54	24.67 ± 8.03	N/A	3.15 ± 1.99	N/A	N/A
Weng et al. (2008) [49]	CSII	133	9.8 ± 2.3	8.0 ± 1.5	11.3 ± 3.3	6.6 ± 1.5	16.1 ± 5.5	7.5 ± 2.2	4.0 ± 2.5	N/A	51.1 (12)
	MDI	118	9.7 ± 2.3	8.0 ± 1.6	11.5 ± 3.2	6.8 ± 1.6	17.5 ± 5.5	8.1 ± 2.9	5.6 ± 3.8	N/A	44.9 (12)
Xu et al. (2009) [54]	CSII	84	9.91 ± 2.16	8.69 ± 1.78	13.73 ± 4.57	6.26 ± 1.16	19.36 ± 5.77	8.86 ± 2.49	N/A	2 weeks	50 (24)
Chon et al. (2010) [55]	MDI	61	10.7 ± 1.8	6.2 ± 1.1	11.8 ± 3.1	N/A	21.5 ± 4.1	N/A	2.6 months	N/A	8.7 (48)
Zeng et al. (2012) [48]	CSII	32	10.93 ± 2.23	10.03 ± 1.91	12.47 ± 3.70	5.89 ± 1.22	N/A	6.2 ± 0.9	3.8 ± 1.9	2 weeks	N/A
	BIM	27	10.78 ± 2.57	9.91 ± 1.95	13.27 ± 3.80	5.66 ± 1.09	N/A	10.2 ± 2.7	5.4 ± 1.4	2 weeks	N/A

GC: normoglycaemia without use of antiglycaemic therapy; FPG: fasting plasma glucose; PPG: postprandial glucose; CSII: continuous subcutaneous insulin infusion; MDI: multiple daily insulin injection; BIM: basal insulin monotherapy.

[a] Glycaemic remission is defined by normoglycaemia without use of antiglycaemic therapies.

[b] Median.

Table 2—*Baseline characteristics and clinical outcomes comparing subjects treated with insulin or oral agent therapies lasting for 2 weeks after achievement of normoglycemia*

	Continuous subcutaneous insulin infusion	Multiple daily injections	Oral agents
n	133	118	101
Age (yrs)	50	51	52
BMI (kg/m^2)	25	24	25
Baseline A1C (%)	9.8	9.7	9.5
% Achieving euglycemia	97	95	83
Time to euglycemia (days)	4	5.6	9.3
Daily drug doses	0.68 units/kg (mean)	0.74 units/kg (mean)	Glicazide 160 mg + metformin 1,500 mg (max median)
Δ in AIR* (pmol · l^{-1} · min^{-1})	951	800	831
AIR (median) in remission groups at 1 year	809	729	335†

From Weng et al. [21]. *Change in median AIR (acute insulin response) between baseline and treatment end. †$P < 0.05$ compared with continuous subcutaneous insulin infusion.

Changes in serum adiponectin concentrations and endothelial function after intensive insulin treatment in people with newly diagnosed type 2 diabetes: A pilot study

November 2011Volume 94, Issue 2,
Pages 186–192

Aims

We aimed to assess changes in serum adiponectin and endothelial function after intensive insulin treatment in patients with newly diagnosed type 2 **DIABETES** mellitus (T2DM).

Methods

Patients with newly diagnosed T2DM were randomly assigned to Group A (intensive insulin treatment) or Group B (conventional insulin treatment). Before treatment and 2 weeks after plasma glucose concentrations had been maintained at the specified concentrations, blood samples were obtained to measure serum adiponectin and nitric oxide (NO) concentrations. A total of 21 patients were randomized to each Group.

Results

Adiponectin, NO, endothelium-dependent vasodilation (EDD), and endothelium-independent vasodilation (EID) measures were significantly higher post-treatment than pre-treatment in Group A (all $P < 0.05$). Only EID was significantly higher in Group B ($P < 0.05$). Post-treatment adiponectin and NO concentrations, and EDD were significantly higher in Group A compared with Group B (all $P < 0.05$). Both treatment regimens were well tolerated (all patients completed the study). The most common adverse event was hypoglycemia. **Thus, early intensive insulin therapy can increase serum adiponectin and NO concentrations and improve endothelial function in patients with newly diagnosed T2DM.**

Conclusions

These effects may underlie the reduced incidence of microvascular and macrovascular in patients who receive early intensive hypoglycemic therapy.

Glucose Control Study Summary UKPDS

The intensive glucose control policy maintained a lower HbA_{1c} by mean 0.9 % over a median follow up of 10 years from diagnosis of type 2 diabetes with reduction in risk of:

12%	for any diabetes related endpoint	p=0.029
25%	for microvascular endpoints p=0.0099	
16%	for myocardial infarction	p=0.052
24%	for cataract extraction	p=0.046
21%	for retinopathy at twelve years	p=0.015
33%	for albuminuria at twelve years p=0.000054	

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.

- This trial was conducted to determine whether the reduction in microvascular risk and improved glycemic control that had been observed with medical therapy, as compared with conventional dietary treatment, in patients with newly diagnosed type 2 diabetes was sustained during 10 years of follow-up

- Despite an early loss of glycemic differences, continued microvascular risk reduction and emergent risk reductions for myocardial infarction and death from any cause were observed

N Engl J Med
Volume 359(15):1577-1589
October 9, 2008

The NEW ENGLAND JOURNAL of MEDICINE

Tip 2 Diyabette
Insulin tedavisinin baslanmasi

4-T Calismasinin Dayanaklari

- Hastalarin cogu insulin tedavisi gerektirecektir. Diyabetin ilerleyici ozelligi ve tani yasinin dusmesi bunu isaret etmektedir.
- Halen insulin tedavisinin hala nasil baslamasi gerektigi konusu tam olarak aydinlanmamistir
- Hangi insulin preparatinin kullanilmasi gerektigine iliskin bir fikir birligi bulunmamaktadir

4-T calismasi
Randomize controllu acik calisma
Insulin tedavi rejimlerini karsilastiran

Protokol: 1.YIL

Main inclusion criteria:

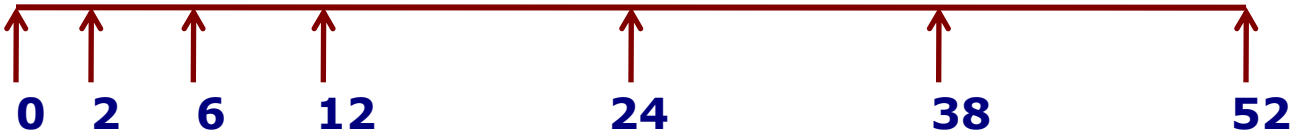
- Type 2 diabetes ≥ 1 year
- On maximum tolerated doses of metformin and SUs for ≥4 months
- HbA_{1c} >7.0 ≤10%

Basal insulin – insulin detemir OD or BD if required (n=234)

Biphasic insulin – biphasic insulin aspart 30 BD (n=235)

Prandial insulin – insulin aspart TD with meals (n=239)

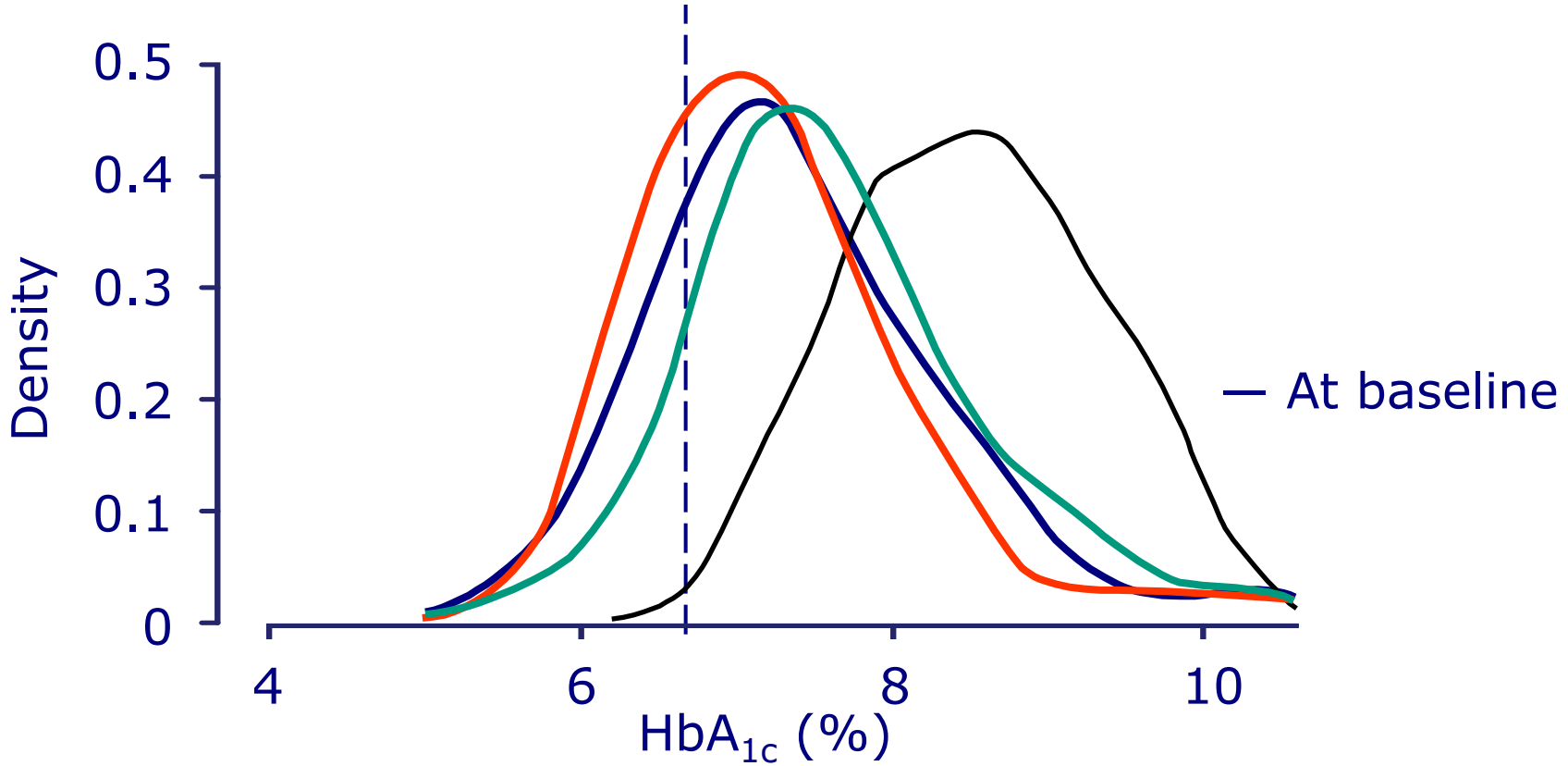
Existing OAD regimen continued



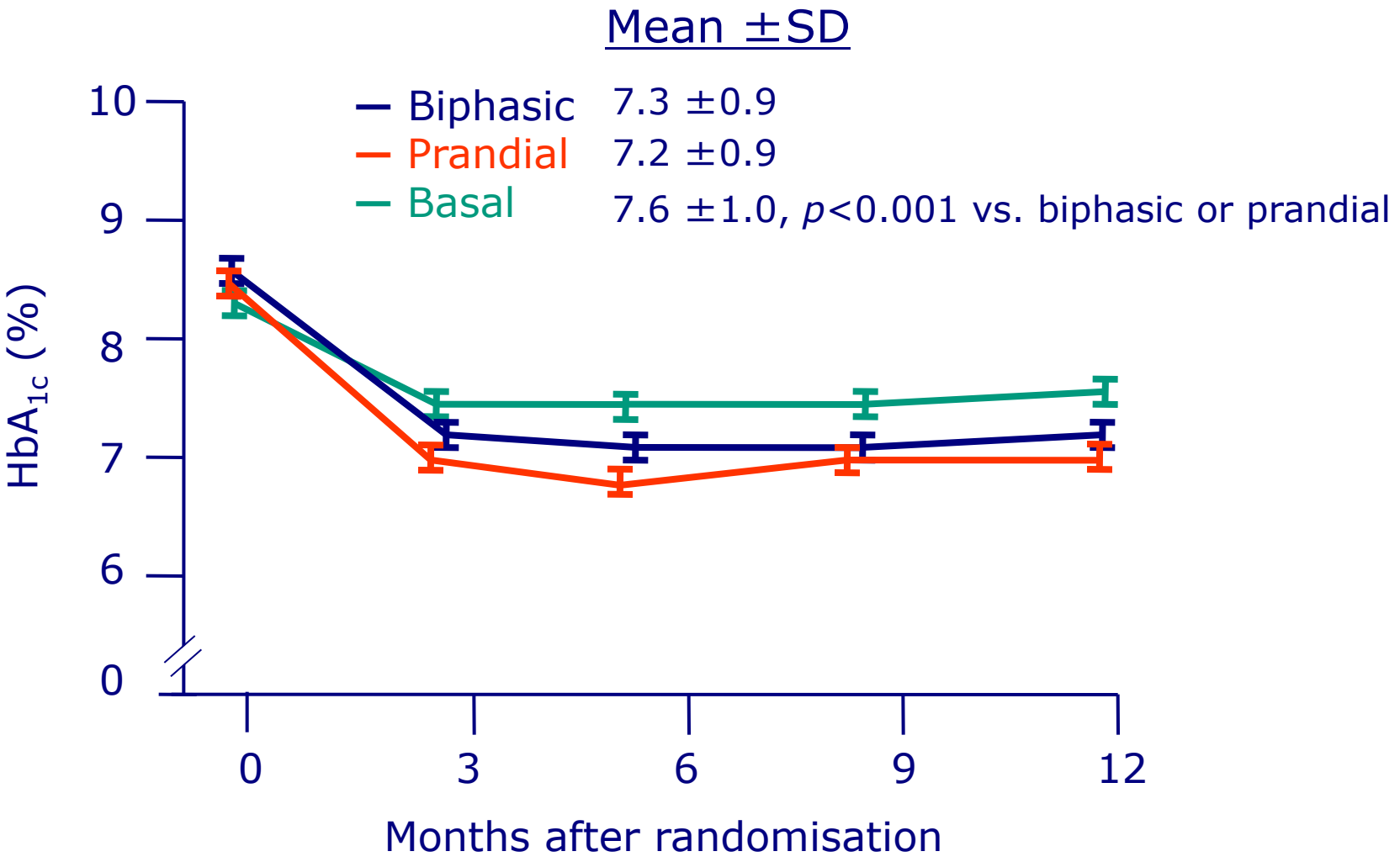
×6 visits and ×9 telephone calls

Hedefe ulasim-HbA_{1c}

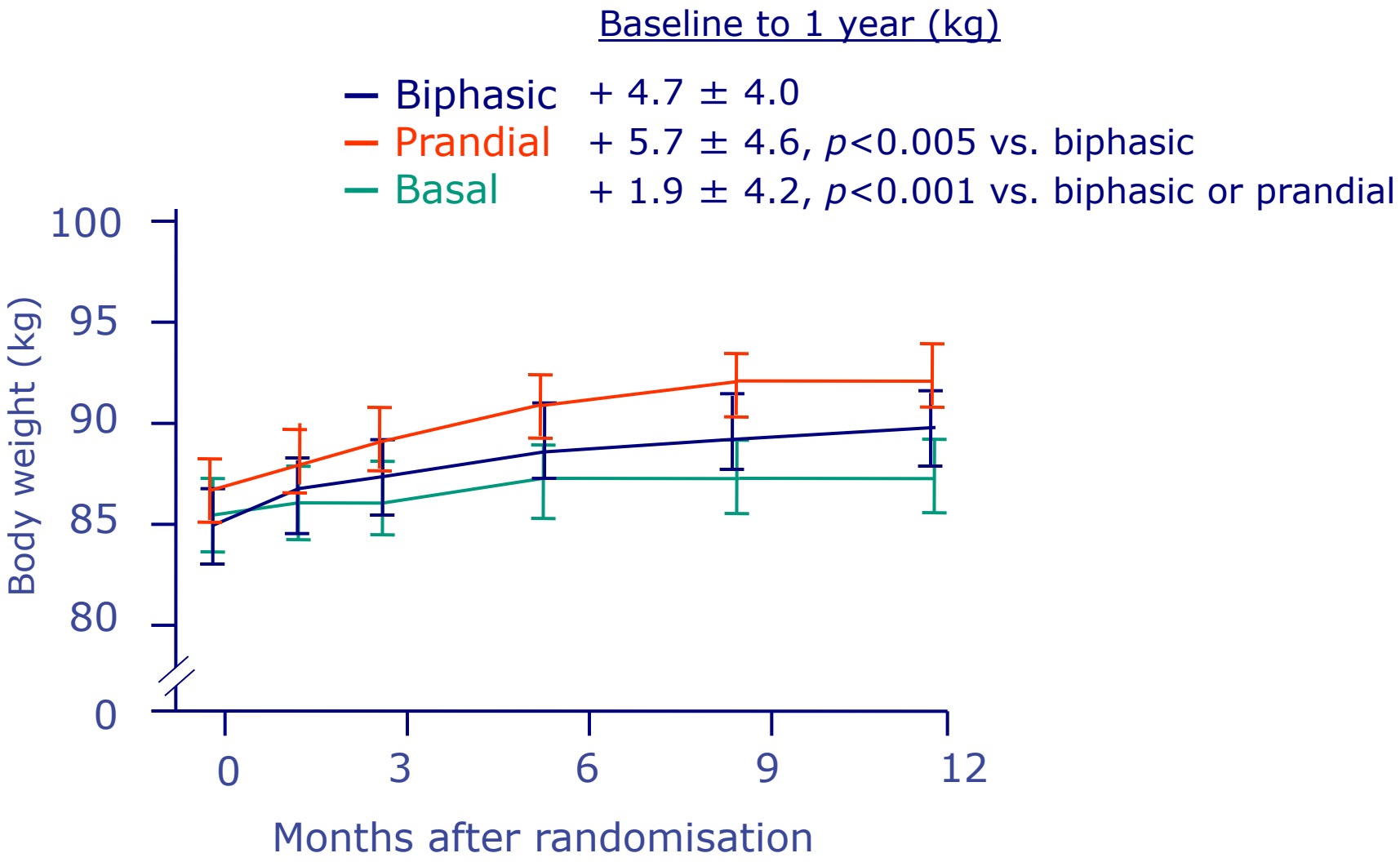
	Proportion <6.5%	Proportion <7.0%
Biphasic	17.0%	41.7%
Prandial	23.9%, (p=0.08 vs. biphasic)	48.7%
Basal	8.1%, (p=0.001 vs. biphasic, <0.001 vs. prandial)	27.8%



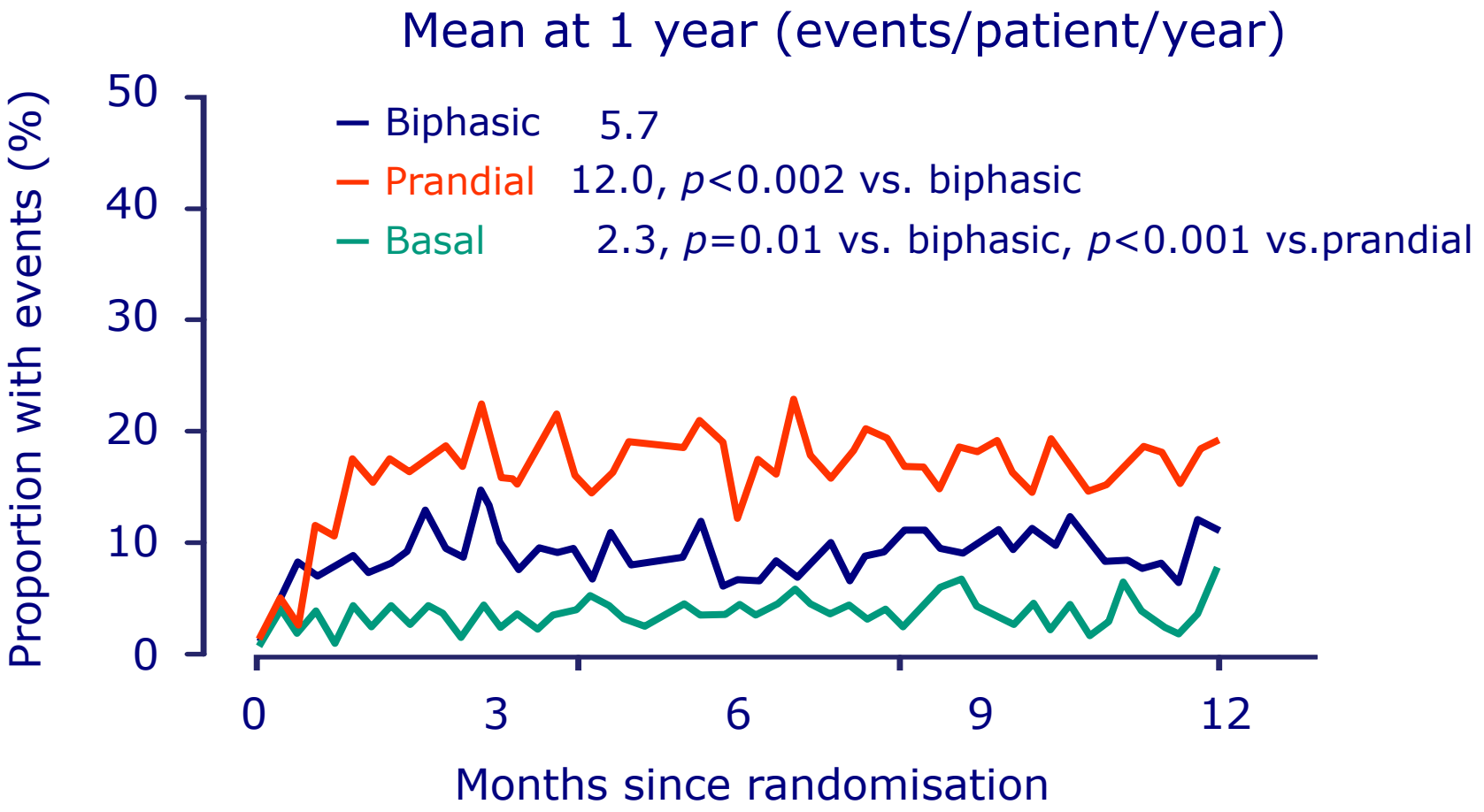
Primer sonlanim- HbA_{1c}



BEDEN AGIRLIGI



Hipoglisemi – 1 yillik sure icinde



4-T: Klinik degerlendirme

- Insulin rejimi secimi
  - Hasta icin belirlenen bireysel hedef
  - HbA1c spektrumunda hedef
  - Hipoglisemi riski
  - Kilo alma endisesi

Klinik te

Hasta A

- OAD alan ve HBA1c si %7.0-8.5 olanlar
- 4-T olgularinin % 50 si
- ADA/EASD kilavuzlarina gore insulin baslanmasi onerilen

Hasta B

- OAD alan ve HbA1c > % 8.5 olan
- 4-T olgularinin %50 si
- Komplikasyon riski tasiyan hastalar

Insulin tedavisine baslama
Hasta A (HbA1c <%8.5)

- **Bazal rejim**
  - Rejimler arasinda hedef olan HbA1c % 6.5 a ulasmada anlamli fark yok
  - Kilo alma ve hipoglisemi olasiligi dusuktur
  - Diyabetin ilerlemesi tedavide yogunlasmayi gerektirecektir- Hangi rejim? – Kanit YOK

Insuline baslama
Hasta B(HbA_{1c} >%8.5)

1 Bazal rejim

- <30% olasilikla %7.0 HbA_{1c} hedefine ulasilir
- Hafif kilo alimi (~2 kg) ve hafif ve az hipoglisemi
- Glukoz kontrolu ve
  - Hipoglisemi riski
  - Kilo alimi
  - Rejimin basitligi
  - Diyabetin ilerlemesi arasinda bir denge vardir

Insuline baslama: Hasta B (HbA_{1c} > %8.5)

2 Bifazik rejim

- <%50 olasilikla hedef HbA1c % 7 ye ulasma
- Hastalarin % 10-15 inde onemli hipoglisemi
- Kilo alimi : ~5 kg (fakat : SD 4.0 kg)
- Genel olarak basit bir rejim

Insuline baslama: Hasta B (HbA_{1c} >% 8.5)

3 Prandial rejim

- HbA_{1c} dususu ve hedefi tutturma bifazik rejimden daha iyi degil
- En fazla kilo alimi ve hipoglisemi

SONUC-Hangi Insulin Baslanmali?

- HbA1c si<%8.5 olan ve insulin gerektiren hastalar icin en uygun olan bazal insulin
- HbA1c si >%8.5 olan hastalarin cogunlugu prandiyal insulin tedavisini gerektirirler
- Bifazik insulin yanliz prandiyal insulin rejiminden daha etkilidir
- Insulin tedavi rejimi secimi bireysel olmalidir.

Insulin tedavisinin yogunlastirilmasi hastalarin bircogunda onerilen hedef glukoz degerlerine ulasmak icin gerekecektir

ORIGIN Glargine Trial: Primary and Secondary Outcomes

- Coprimary composite CV outcomes:
  - CV death, nonfatal MI, or nonfatal stroke
  - CV death, nonfatal MI, nonfatal stroke, revascularization (cardiac, carotid, or peripheral), or hospitalized heart failure
- Secondary outcomes:
  - Microvascular composite
  - New cases of type 2 diabetes among those without diabetes at baseline
  - New or recurrent cancer
  - All-cause mortality

ORIGIN=Outcome Reduction with Initial Glargine Intervention

ORIGIN Glargine Trial: Eligibility Criteria and Trial Profile

Eligible subjects:

- Aged ≥50 yrs
- History of type 2 diabetes* and using ≤1 OAD
- IGT, IFG, or newly detected diabetes
- Prior CV event (MI, stroke, or revascularization)
- Angina with documented ischemia
- Left ventricular hypertrophy
- ≥50% stenosis of coronary, carotid, or lower-limb artery on angiography
- Ankle–brachial index <0.9

10-day Run-in Period (N=13,765)

Randomized to

Insulin glargine (N=6,300)

or

Standard care (N=6,312)

Included in analysis

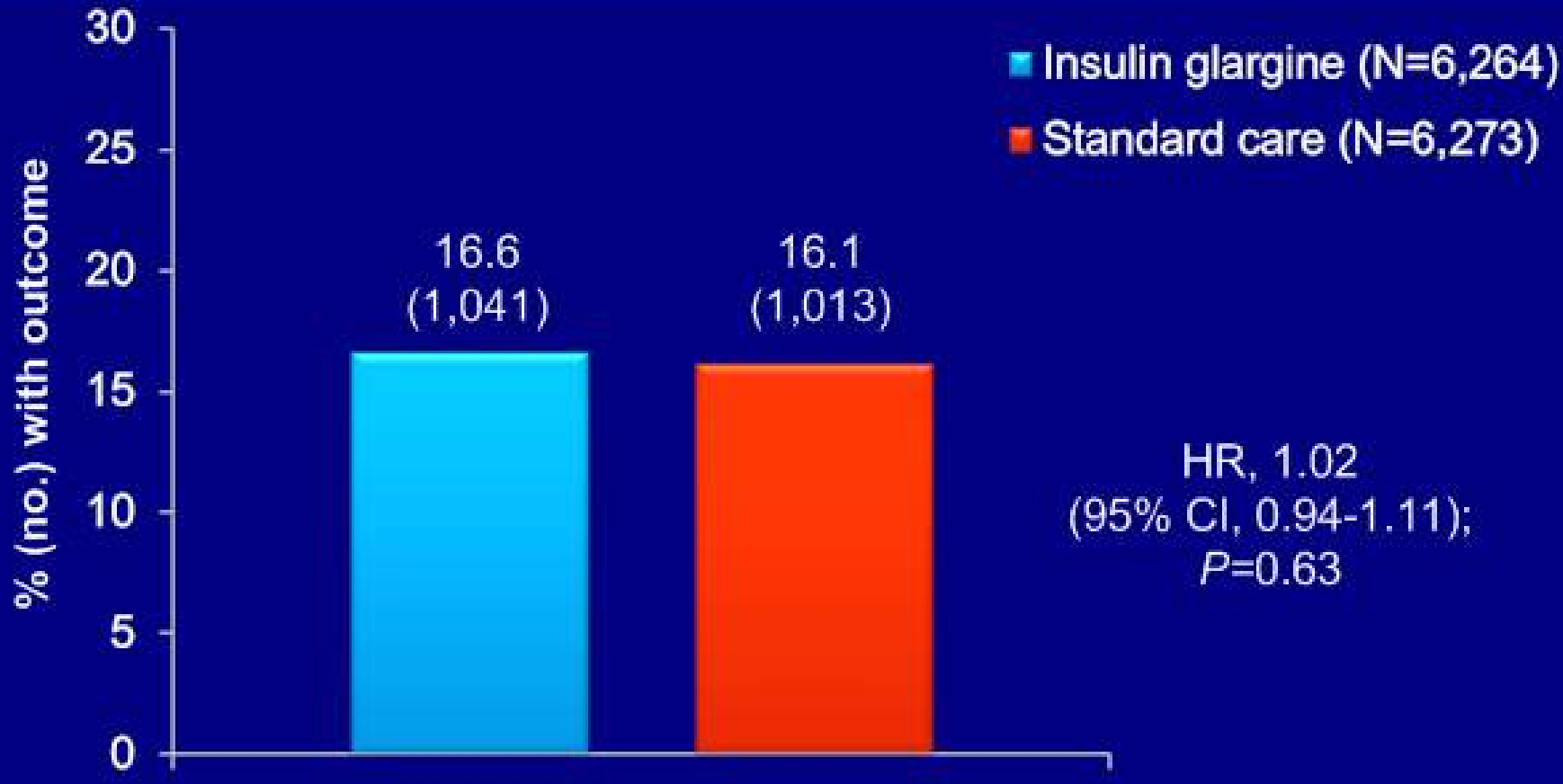
N=6,264

N=6,273

*A1C <9% if on 0 OAD, <8% if on half-maximum or a greater dose of OADs
ORIGIN=Outcome Reduction with Initial Glargine Intervention

ORIGIN Glargine Trial:
First Coprimary Composite CV Outcome—CV Death, Nonfatal MI, or Nonfatal Stroke

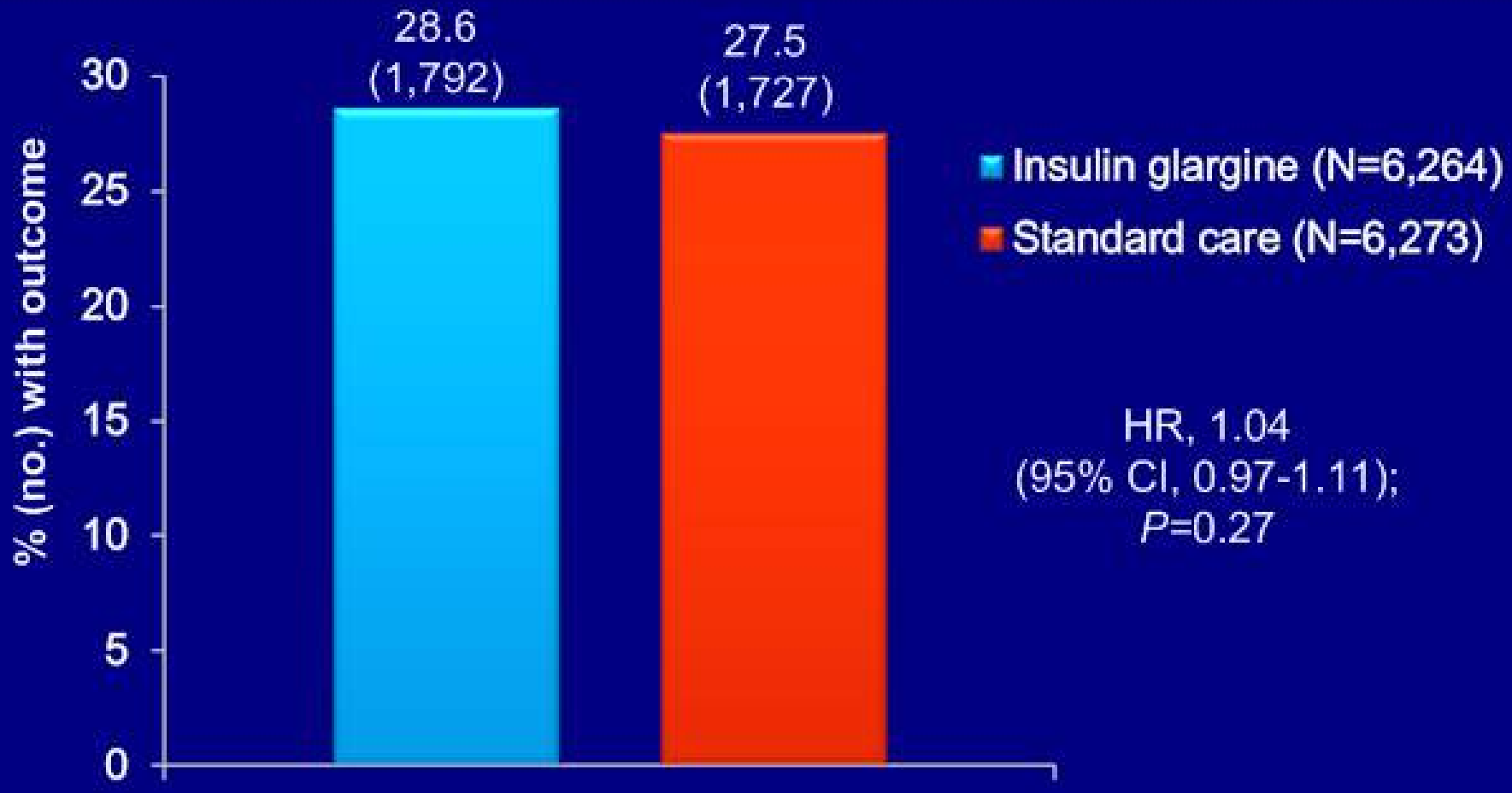
Continuous coverage of th
American Diabetes Associat
72nd Scientific Sessions



ORIGIN=Outcome Reduction with Initial Glargine Intervention

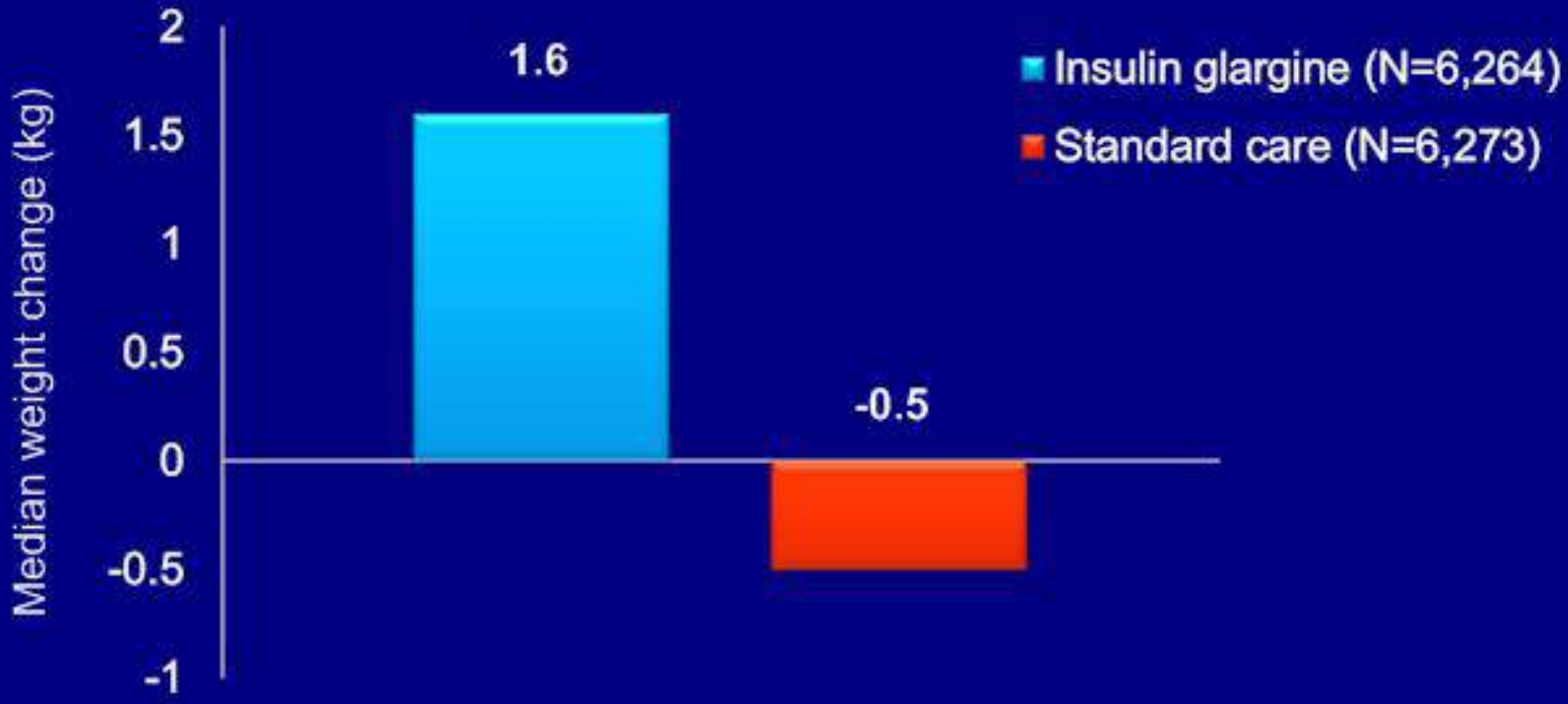
ORIGIN Glargine Trial:

Second Coprimary Composite CV Outcome—CV Death, Nonfatal MI, Nonfatal Stroke, Revascularization, or Hospitalized Heart Failure



ORIGIN=Outcome Reduction with Initial Glargine Intervention

ORIGIN Glargine Trial: Weight Change



ORIGIN=Outcome Reduction with Initial Glargine Intervention

ORIGIN Glargine Trial: Conclusions

- Treatment with insulin glargine vs standard care
  - Did not significantly reduce the coprimary composite CV outcomes CV death, nonfatal MI, or nonfatal stroke; and CV death, nonfatal MI, nonfatal stroke, revascularization, or hospitalized heart failure
  - Did not show an increase in cancer incidence
  - Showed a greater reduction in new-onset diabetes
  - Increased hypoglycemia and weight

ORIGIN=Outcome Reduction with Initial Glargine Intervention

Insulin as an Early Treatment for Type 2 Diabetes

ORIGIN or end of an old question?

Stefano Del Prato, md
Cristina Bianchi, md, phd
Angela Dardano, md, phd
Roberto Miccoli, md

DIABETES CARE, VOLUME 36, SUPPLEMENT 2, AUGUST 2013

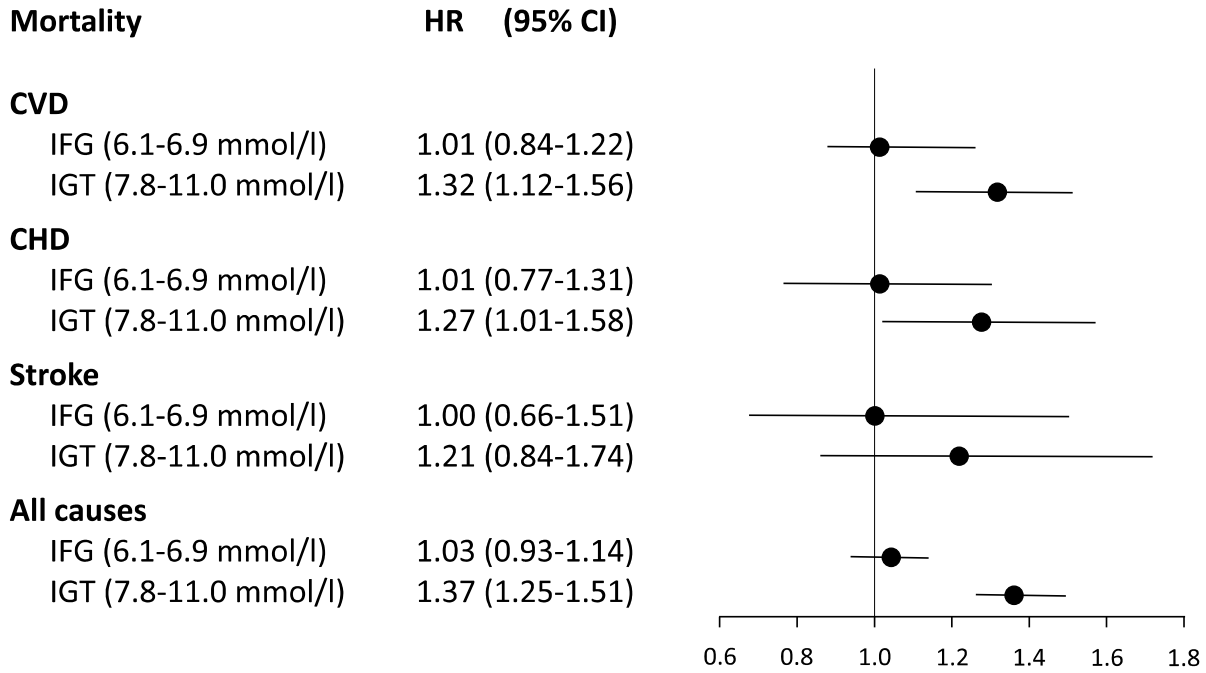


Figure 1—*Multivariate-adjusted HRs (95% CI) for deaths from CV disease (CVD), coronary heart disease (CHD), stroke, and all-cause mortality according to fasting and 2-h OGTT plasma glucose in the DECODE Study. Adapted from ref. 17.*

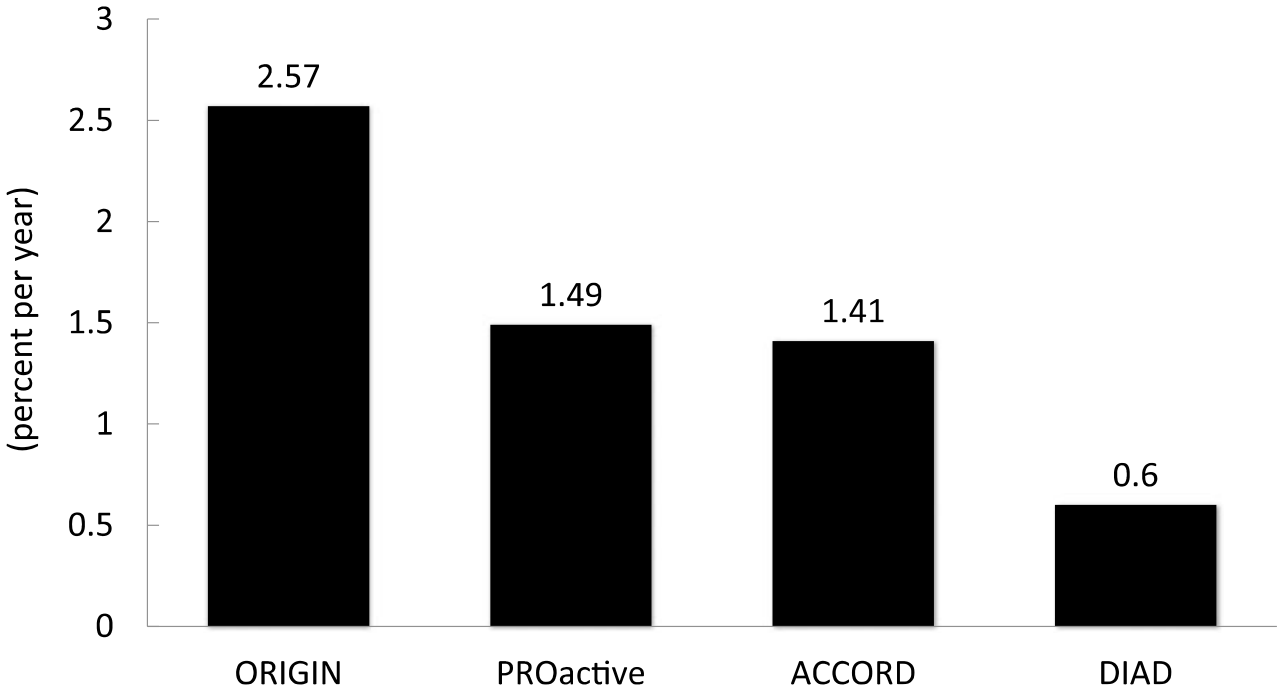


Figure 2—*Annual mortality rate in the ORIGIN, ACCORD, PROactive, and DIAD studies. The ACCORD trial was prematurely interrupted because of an excess of mortality in the intensively-treated arm (ref. 7). The PROactive trial included patients with some evidence of prior CV disease (ref. 28). The DIAD study reported annual mortality in asymptomatic patients (ref. 29).*

Table 1—*Summary of the main results of the ORIGIN trial*

	Insulin glargine	Standard care	*P*
A1C (%)*			
Baseline	6.4	6.4	NS
End of study	6.2	6.5	NS
Primary outcome (100 person-years)	2.94	2.85	NS
Secondary outcome (100 person-years)	5.52	5.28	NS
Hypoglycemia (100 person-years)			
Severe	1.0	0.31	<0.001
Confirmed nonsevere symptomatic	9.83	2.68	<0.001
Any nonsevere symptomatic	16.72	5.16	<0.001
Body weight changes from baseline (kg)*	1.6	−0.5	—
Cancer (100 person-years)			
Any cancer	1.32	1.32	NS
Death from cancer	0.51	0.54	NS

*Median values.

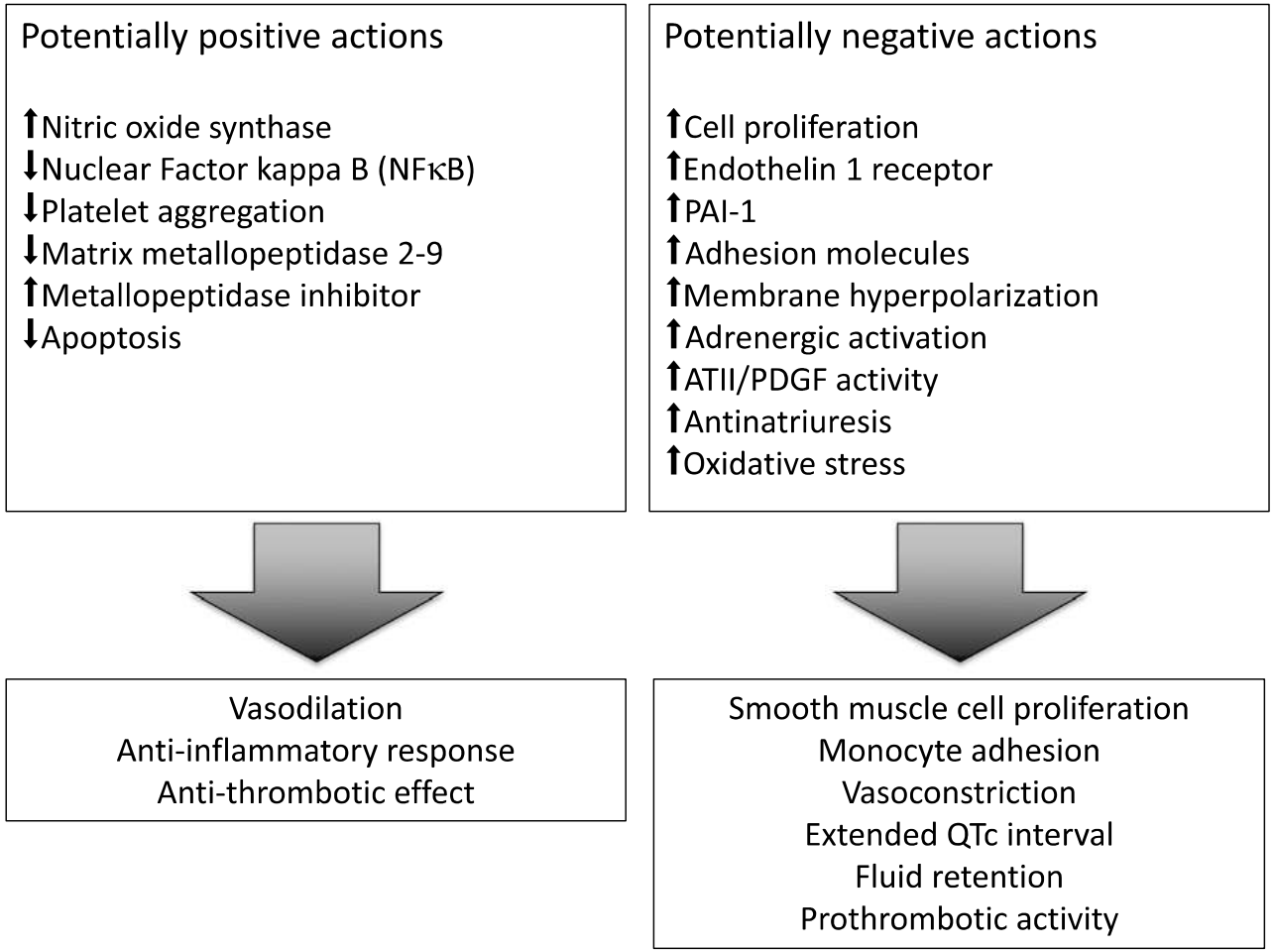
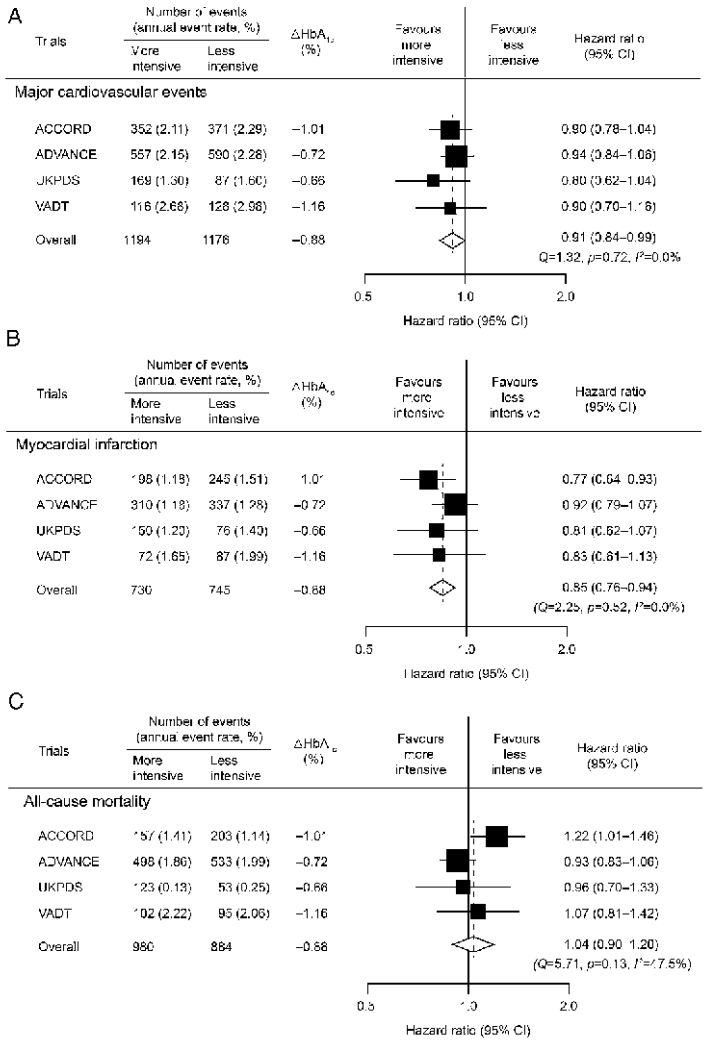


Figure 3—*Synopsis of potentially positive and potentially negative effects of insulin with respect to CV risk (adapted from ref. 30).*


A
Trials
Number of events (annual event rate, %)
More intensive
Less intensive
ΔHbA1c (%)
Favours more intensive
Favours less intensive
Hazard ratio (95% CI)
Major cardiovascular events
ACCORD 352 (2.11) 371 (2.29) −1.01 0.90 (0.78–1.04)
ADVANCE 557 (2.15) 590 (2.28) −0.72 0.94 (0.84–1.06)
UKPDS 169 (1.30) 87 (1.60) −0.66 0.80 (0.62–1.04)
VADT 116 (2.68) 128 (2.98) −1.16 0.90 (0.70–1.16)
Overall 1194 1176 −0.88 0.91 (0.84–0.99)
Q=1.32, p=0.72, I²=0.0%
0.5
1.0
2.0
Hazard ratio (95% CI)
B
Trials
Number of events (annual event rate, %)
More intensive
Less intensive
ΔHbA1c (%)
Favours more intensive
Favours less intensive
Hazard ratio (95% CI)
Myocardial infarction
ACCORD 198 (1.18) 245 (1.51) 1.01
ADVANCE 310 (1.18) 337 (1.28) −0.72
UKPDS 150 (1.20) 76 (1.40) −0.66
VADT 72 (1.65) 87 (1.99) −1.16
Overall 730 745 −0.88 0.85 (0.76–0.94)
(Q=2.25, p=0.52, I²=0.0%)
0.5
1.0
2.0
Hazard ratio (95% CI)
C
Trials
Number of events (annual event rate, %)
More intensive
Less intensive
ΔHbA1c (%)
Favours more intensive
Favours less intensive
Hazard ratio (95% CI)
All-cause mortality
ACCORD 257 (1.41) 203 (1.14) −1.01 1.22 (1.01–1.46)
ADVANCE 498 (1.86) 533 (1.99) −0.72 0.93 (0.83–1.06)
UKPDS 23 (0.13) 53 (0.25) −0.66 0.96 (0.70–1.33)
VADT 202 (2.22) 95 (2.06) −1.16 1.07 (0.81–1.42)
Overall 980 884 −0.88 1.04 (0.90–1.20)
(Q=5.71, p=0.13, I²=47.5%)
0.5
1.0
2.0
Hazard ratio (95% CI)

Sonuc-ORIGIN (Outcome Reduction with an Initial Glargin InterveNtion)

- **Erken insulin baslanmasi insanlara zarar vermemistir.(ateroskleroz,KV Risk, kanser, agir hipoglisemi,asiri kilo alma)**
- **Tedaviye uyum cok iyi olmustur**
- **Calisma boyunca (ort 6 yil) hiperglisemi cok etkili bir sekilde kontrol altinda tutulabilmistir.**
- **IGT ve disglisemisi olanlarda diyabetin ortaya cikmasi yavaslatilmis ve bir olcude engellenebilmistir.**

Neden insulin Tip 2 DM nin erken doneminde ORIGIN in olumsuz KV sonuclarina ragmen baslanmalidir?

CUNKU ORIGIN calışması göstermiştir ki:

- Insulin etkilidir ve etkisi uzun yillar devam etmektedir
- Emniyetlidir ve oral ajanlara gore daha az yan etkiye sahiptir
- Diyabete gidisi yavaslatmasi olasi beta hucresini koruma etkisinden oldugunu gostermektedir
- Erken tedavi olasi diyabetin dogal seyrini olumlu yonde degistirebilir

Yeni Tanı Konmuş Tip 2 Diyabette Komplikasyon Oranları

- %20–30 Diyabetik retinopati
- %10–20 Mikroalbuminüri (~%40 hiperfiltras.)
- %30–40 Hipertansiyon
- %50–80 Dislipidemi
- %80–100 Vasküler disfonksiyon

Başlangıçta bile yüksek komplikasyon oranları vardır ve kötü kontrol ile komplikasyon riski daha da artar !

Ne yapmalı?

“Erken agressif tedavi”

giderek daha fazla kabul görmektedir.