당뇨병 치료제의 임상연구

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주요 당뇨치료 임상연구

- Benefits of tight control
- reduce DM complicaions
  - microvascular and macrovascular
- Type I DM : DCCT
  - The Diabetes Control and Complication Trial
- Type II DM UKPDS
  - UK Prospective Diabetes Study

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DCCT

Diabetes Control and Complication Trial

제 **1**형 당뇨

N Engl J Med 2000;342:381-9

N Engl J Med 1993;329:977-86

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Patients

- Study duration: 1983-1989
- Type I DM, 13-39 year-old
- duration of DM: 1-15 year
- 1441 명의 type I DM-randomized to
  - Intensive therapy
  - conventional therapy

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Patients

- Primary prevention study: 726 명
  - no retinopathy
  - urinary albumin<40 mg/24 hrs
- Secondary prevention study: 715 명
  - min.-mod. Retinopathy
  - urinary albumin <200 mg/24hr

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Study Design

- Intensive insulin therapy
  - insulin pump or >3 injections of insulin
  - blood glucose/HbA1c in normal range
  - blood glucose measurement ~4/day
  - diet, exercise
- Conventional therapy
  - 1-2 insulin injections/day
  - 1 urine or blood glucose test/day

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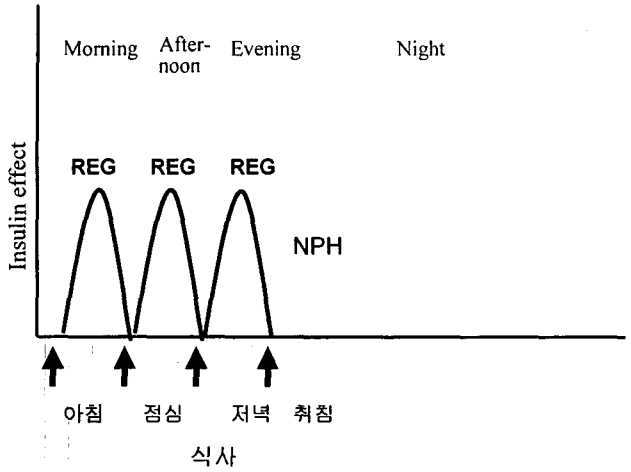
Multiple injections



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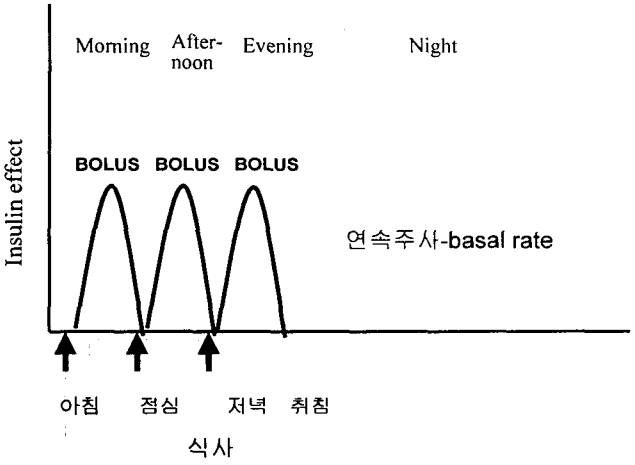
Insulin pump



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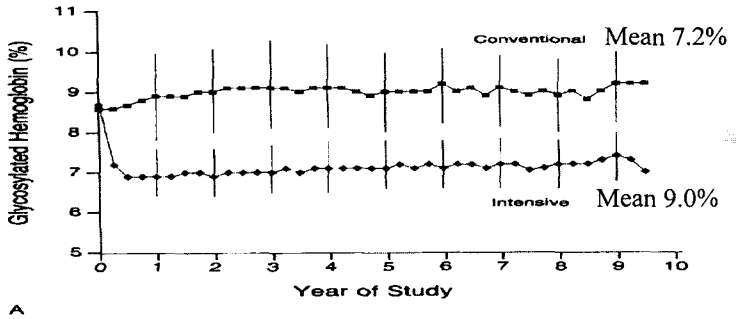

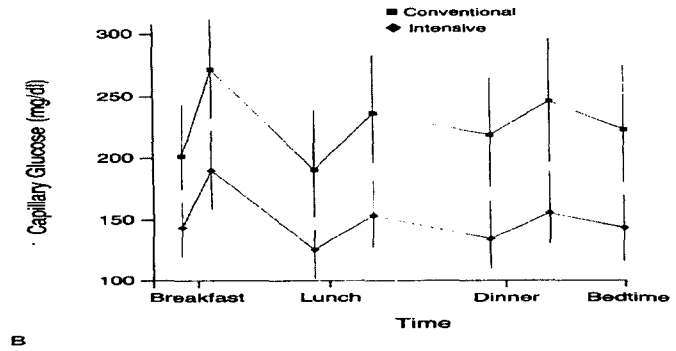

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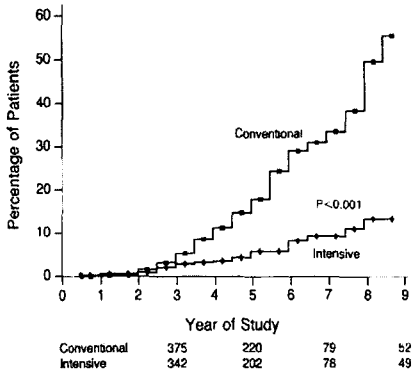
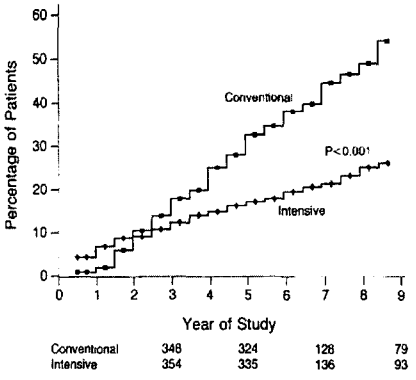
Retinopathy





Primary prevention
Risk Reduction 76%

Secondary prevention
54%

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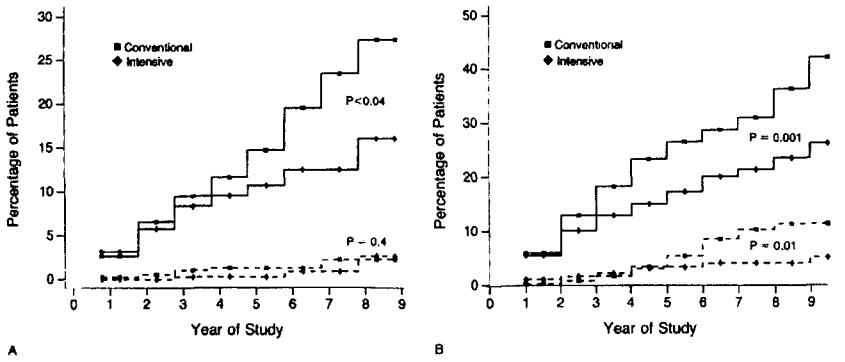
Retinopathy



Primay prevention — Secondary prevention

Urinary albumin >300 mg per 24 Hours (Dashed Line) 54%

Urinary albumin >40 mg per 24 Hours (Solid Line) 39%

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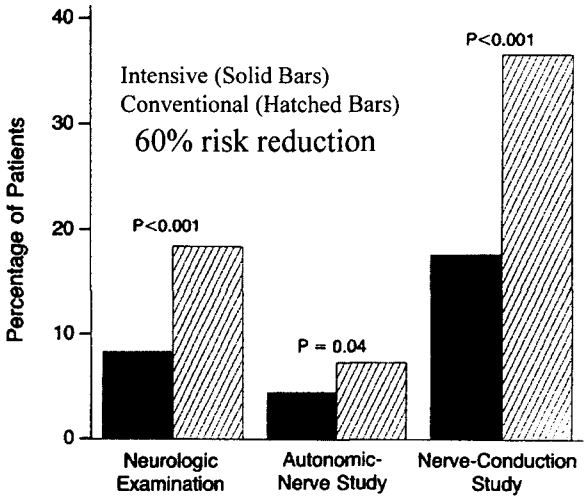
Nephropathy



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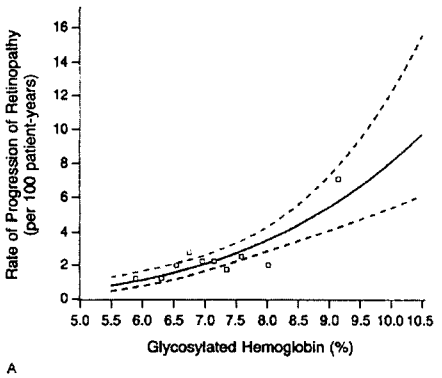
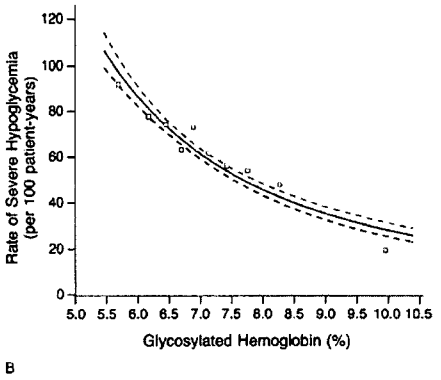
Complications





Progression of Retinopathy

Rate of Severe Hypoglycemia

Macrovascular disease

decrease by 41 % (0.5 event per 100 patient-years, vs. 0.8 event; 95 % CI, -10 to 68 %)

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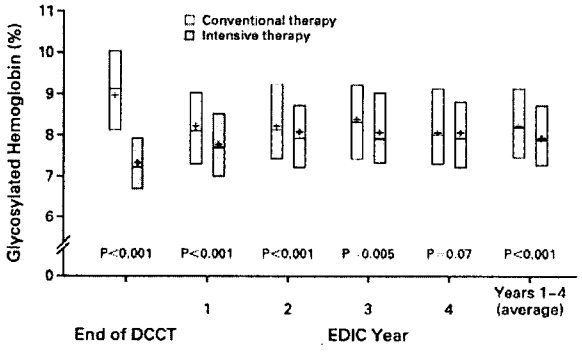
Four Years after DCCT

EDIC Epidemiology of Diabetes Intervention and Complications

- Median HbA1c between the conventional vs. intensive
  - the 6.5 years of the DCCT (9.1 % and 7.2 %, P<0.001)
  - 4 years follow-up (8.2 % and 7.9 %.; P<0.001).



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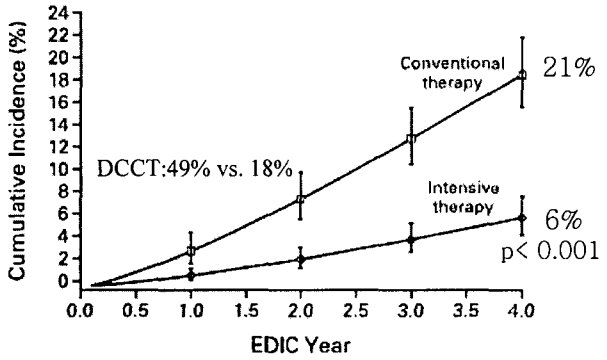
Retinopathy



Cumulative Incidence of Further Progression of Retinopathy
Microalbuminuria 11% vs 5%: p = 0.002

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residual beta-cell function

- intensive therapy maintained a higher stimulated C-peptide level and a lower likelihood of becoming nonresponders
- the importance of initiating intensive diabetic management

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Insulin Analogues

- Insulin: Pro(B28) , Lys(B29)
  - short acting
- Insulin Lispro: Lys(B28), Pro(B29)
  - rapid acting
- Insulin Aspart: Asp(28)
  - rapid acting
- Insulin Glargine:Gly(A21),Arg,Arg(B30)
  - long acting once daily for type I, II DM

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Alternative Treatment/prevention

- Insulin routes
  - Oral
  - Transdermal
  - Nasal
  - Sublingual
  - Inhaler
- Prevention for new DM
  - nicotinamide 3 g/d
  - Insulin ultralente bid
  - cyclosporine
  - azathioprine
- pancreas, islet transplantation

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UKPDS
UK Prospective Diabetes Study

UKPDS33 Lancet 1998;352:837-53
UKPDS34 Lancet 1998;352:854-65
UKPDS38 BMJ 1998;317:703-13
UKPDS39 BMJ 1998:317:713-719

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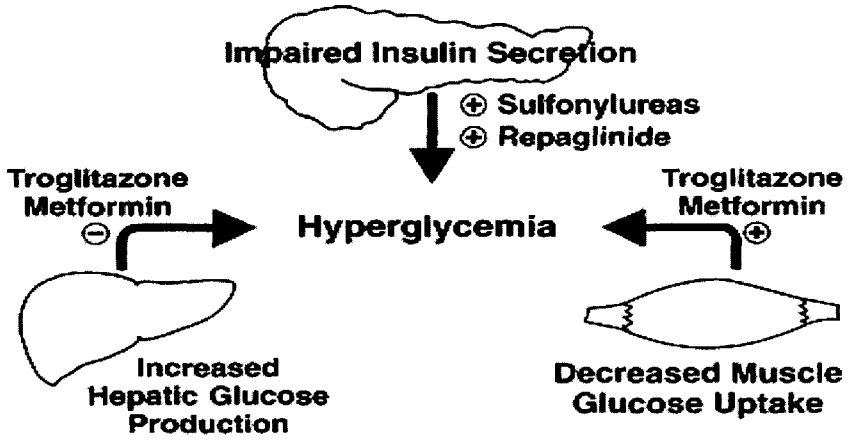
Pathogenesis of Type 2 DM



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Study design

- 20 년간 진행된 대규모 임상연구
  - Started in 1977-1991, 23 hospitals
- 주요 연구 목적
  - reduced the risk of macrovascular or microvascular complications with FPG<6 mmol/L
  - Diet, sulonylurea, Insulin, metformin

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Patients

- newly diagnosed diabetes aged 25-65 years
- Eligible Inclusion criteria
  - FPG > 6 mmol/L (108 mg/dL) on two am, 1-3 weeks apart
  - dietatary run-in
  - stratified by ideal bodyweight (IBW) (overweight was >120% IBW)

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Patients

- exclusion criteria
  - ketonuria > 3 mmol/L
  - serum creatinine > 175 mol/L (2.0 mg/dl)
  - myocardial infarction in the previous year
  - current angina or heart failure
  - more than one major vascular event retinopathy requiring laser treatment malignant hypertension

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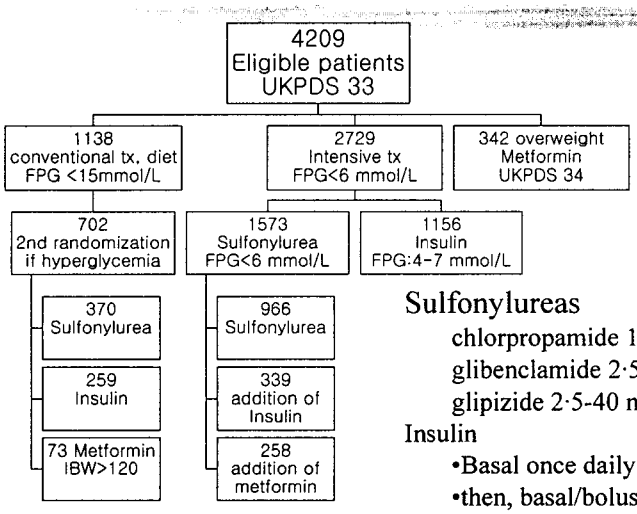
Study Design



Sulfonylureas

chlorpropamide 100-500 mg;
glibenclamide 2·5-20 mg;
glipizide 2·5-40 mg

Insulin

•Basal once daily ultralente insulin
•then, basal/bolus regimen
add regular insulin
if >14 units (U)/d or FPG> 7 mmol/L.

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Clinic Monitoring

- Every 3 month clinic visit
  - glucose, blood pressure, weight
  - hypoglycaemic episodes, home blood-glucose measurements, illness, time off work, admissions to hospital, general symptoms
- At entry, 6 months, 1 year, and annually
  - HbA1c, SrCr , TG, T-chol, LDL, HDL
  - insulin, insulin antibodies
- Every year: urinary albumin and creatinine

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DM related endpoints

- sudden death, stroke,
- death from hyperglycaemia or hypoglycaemia
- fatal or non-fatal myocardial infarction, angina
- heart failure, renal failure
- amputation [of at least one digit],
- vitreous haemorrhage, retinal photocoagulation, blindness in one eye, or cataract extraction

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UKPDS: Benefits of Glycemic control in Type 2 Diabetes

	Risk reduction over 10 years	
Any DM related endopoints	12 %	P=0.29
Microvascular endpoints	25%	P=0.0099
Myocardial infarction	16%	P=0.052
Cataract extraction	24%	P=0.046
Retinopathy at 12 years	21%	P=0.015
Microalbuminuria at 12 years	33%	P=0.000054

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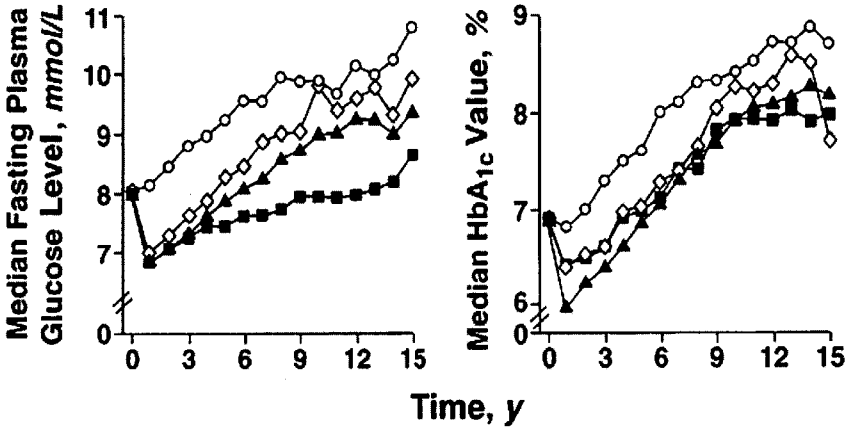
Fasting plasma glucose and HbA1c



○Diet ▲Sulfonyl urea ✧Metformin ■ Insulin

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Metformin in DM2: UKPDS 34

- To investigate intensive glucose control with metformin
- Dosage of metformin
  - one 850 mg tablet/day,
  - 850 mg twice daily,
  - 1700 mg in the morning and 850 mg with the evening meal (maximum dose=2550 mg)

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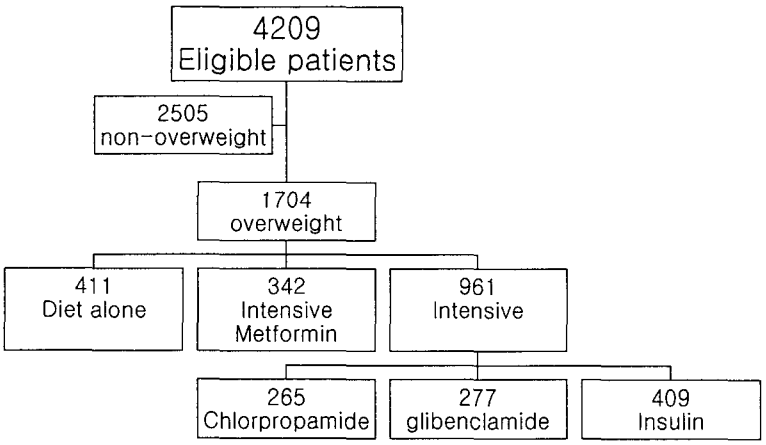
Study design



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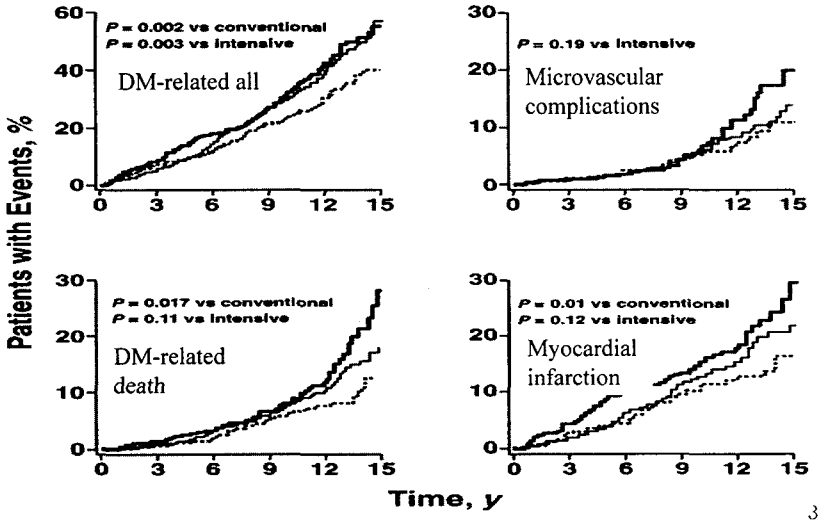
Metformin in reduction of CV events: UKPDS 34



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Hypertension in Diabetes Study (HDS)

- Objective: To determine whether tight control of blood pressure prevents macrovascular and microvascular complications in patients with type 2 diabetes.
- Setting: 20 hospital based clinics in England, Scotland, and Northern Ireland.
- Subjects: 1148 HTN patients with type 2 diabetes (mean age 56, mean BP at entry 160/94 mm Hg);
  - a median follow up of 8.4 years.

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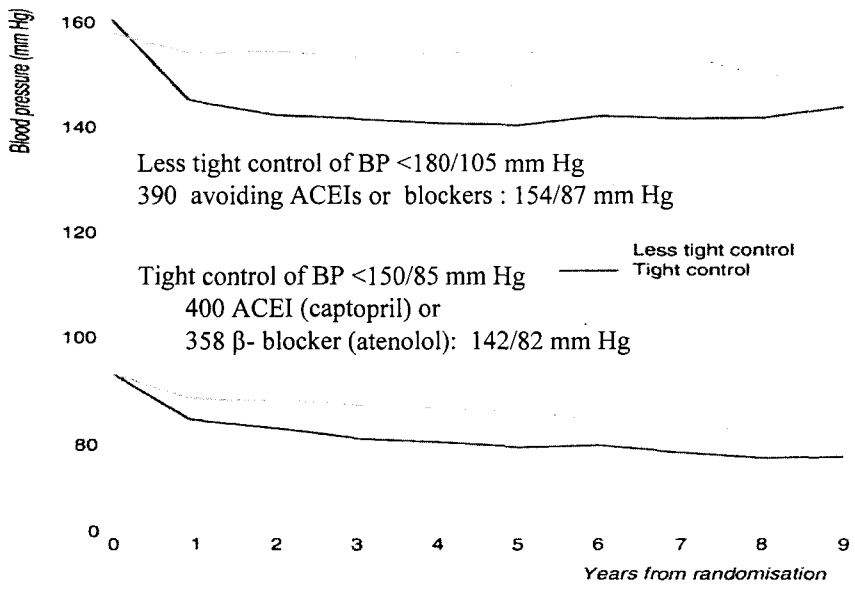

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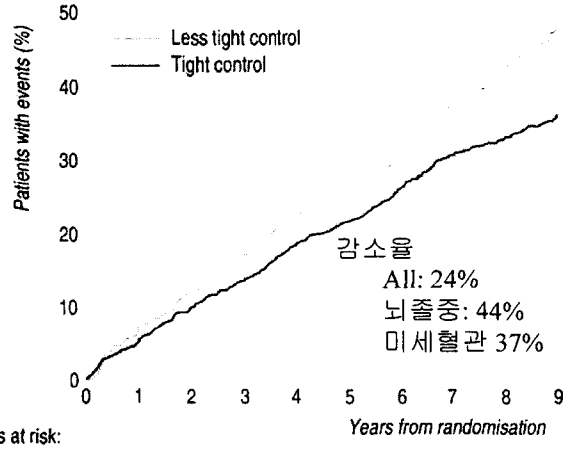
Any clinical end point, fatal or non-fatal, related to diabetes



No of patients at risk:

Less tight control	390	321	247	106
Tight control	758	640	494	235

Reduction in risk with tight control 24% (95% CI 8% to 38%)(P = 0.0046)

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Implications of UKPDS

- 혈당 및 혈압의 조절로서 위험률 감소
  - reduce 25% microvascular complications by 0.9% HbA1c
  - reduce macrovascular complications
- NS difference among treatments
- FPG 약 7% 유지
- Clincal use of metformin in obese: low weight gain, hypoglycaemic attacks
- Step-up treatments for glucose control

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Treatment algorithm

- at baseline
  - HbA1c, FPG
  - SrCr, microalbuminuria
  - BP, BMI, WH ratio
  - LFT, Lipid profile, CV risk, Eye exam
  - neuropathy, foot exam, BG test
  - aspirin/day
- Consider DM
  - duration, obesity, insulin resistance
  - cormorbid disease

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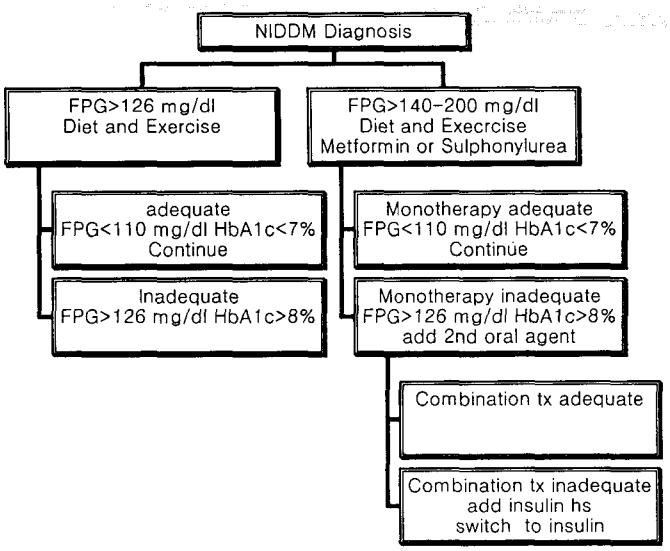
Treatment algorithm



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Treatment algorithm

- Diet and exercise >20 min 3/week
- Monotherapy for 3 months
- Combination therapy
  - SU/metformin
  - SU/acarbose or miglitol
  - Repaglinide/metformin
  - SU/Glitazone
  - Glitazone/metformin

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Treatment algorithm

- FPG >250-300 mg/dl: add insulin
  - SU am + NPH at bedtime
  - SU am + Insulin lispro before meals
  - Metformin + NPH insulin
  - Acarbose + NPH insulin
  - Glitazone + NPH insulin

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Thiazolidinediones-Rosiglitazone

- Addition of low-dose rosiglitazone to sulphonylurea therapy improves glycaemic control in Type 2 diabetic patients
- to test the efficacy and safety of low-dose rosiglitazone, a potent, insulin-sensitizing thiazolidinedione, in combination with sulphonylurea in Type 2 diabetic patients

Diabet Med 2000 Jan;17(1):40-7 40

Rosiglitazone

- phase IIIA, multicentre, double-blind, placebo-controlled, parallel-group
- 574 patients (59% male, mean age 61 years)
- 26 weeks of bid placebo (n=192), rosiglitazone 1mg (n=199) or rosiglitazone 2 mg (n= 183)
- in addition to existing sulphonylurea treatment with gliclazide (47.6% of patients), glibenclamide (41.8%) or glipizide (9.4%)
- Change in haemoglobin A1c (HbA1c), fasting plasma glucose (FPG), fructosamine, insulin, C-peptide, albumin, and lipids were measured, and safety was evaluated.

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Rosiglitazone

- Mean baseline HbA1c was 9.2% and FPG was 11.4 mmol/l.
- HbA1c (-0.59% and -1.03%, respectively; both $P < 0.0001$)
- FPG (1.35 mmol/l and 2.44 mmol/l, respectively; both $P < 0.0001$).
- The overall incidence of adverse experiences was similar in all three treatment groups, with no significant cardiac events, hypoglycaemia or hepatotoxicity.

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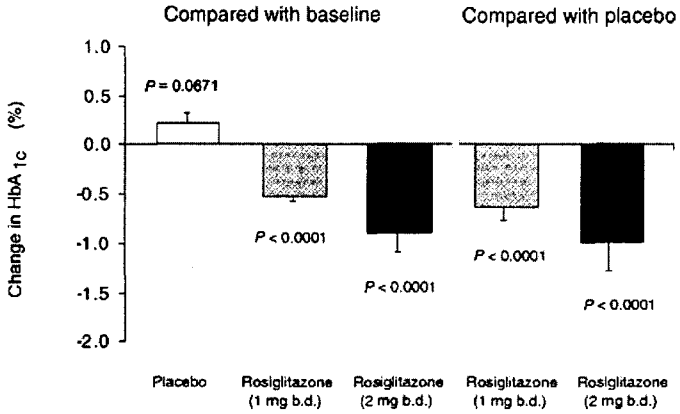
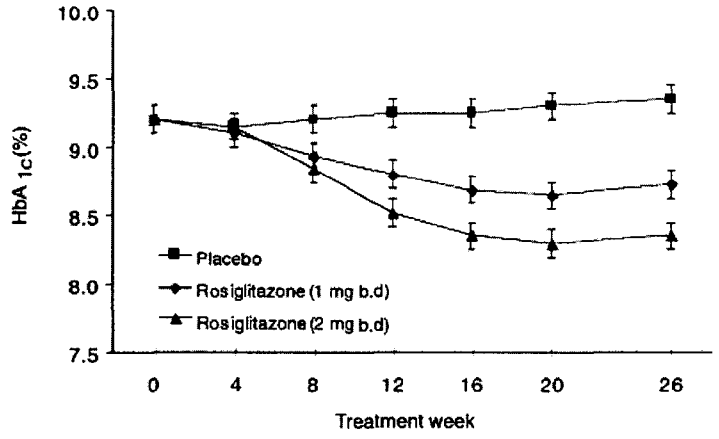
Rosiglitazone



Change in HbA1c at study end (week 26)

Rosiglitazone



Mean (±SE) HbA1c over time

Repaglinide

- To study assess efficacy and safety (with particular regard to body weight and hypoglycemia) of repaglinide when used in a flexible mealtime dosing regimen in a situation close to everyday clinical practice
- double-blind randomized placebo-controlled parallel group study
- 61 centers in 13 countries

Diabetes Care 2001 Jan;24(1):11-5 45

Repaglinide

- 408 patients with type 2 diabetes poorly controlled by diet, without a history of previous antidiabetic medication
- 0.5 mg repaglinide at mealtimes (increased to 1 mg after 4 weeks depending on blood glucose response) or placebo for 16 weeks
- one meal, one dose; no meal, no dose

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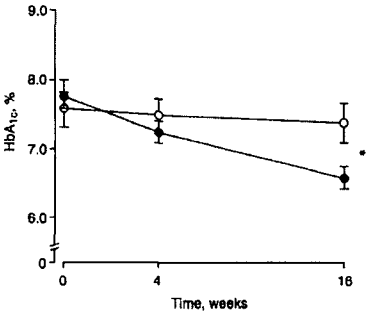
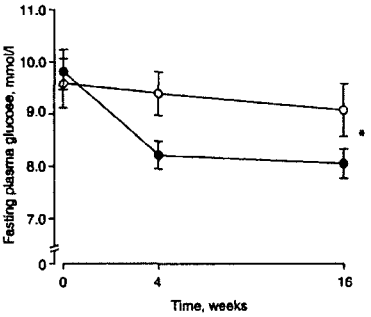
Repaglinide

- Reducing HbA1c by 1.14% from baseline
- Fasting plasma glucose by 1.8 mmol/l
- Mealtime dosing with repaglinide is effective





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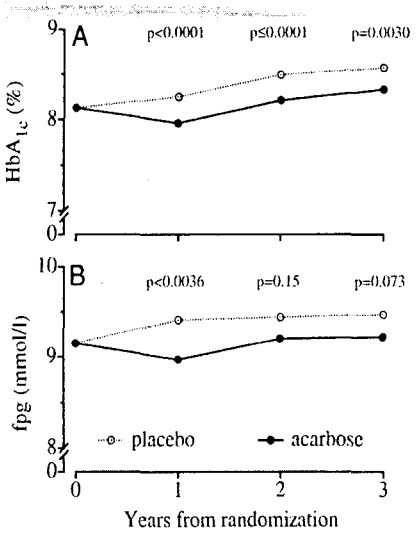
Acarbose vs. placebo

Patients: 1,946 patients (63% men)
Acarbose (n = 973) 25mg initial
max 100 mg three times per day
Matching placebo (n = 973)
3 year follow-up

Results
lower median HbA1c 0.7-1.0%
FPG reduced 0.5mmol/L
all clinical trials 1.4-1.7 mmol/L
Postprandial 2.2-2.8 mmol/L



Diabetes Care 22:960-964, 1999

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Hypoglycemic effects

Class	FPG 감소 mg/dl	HbA1c 감소 (%)
Sulfonylureas	50-70	1-2
Repaglinide		
Metformin	53, PPG 83	1.4
Pioglytazone	80	2.6
Rosiglitazone	62	1.5
Acarbose	30	0.7
SU/acarbose	30	0.9
SU/metformin	77	1.9
SU/glitazone	79	2.9
Repaglinide/met	40	1.4
Acarbose/met	23, 63 PPG	0.8
Pioglitazone/met	38	0.8
Pioglitazone/insulin	49	1.0

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New agents in clinical trials

Drugs	Phase of Trial	Comment
AERx inhaled insulin	Phase II (Aradigm)	Type I and II DM
Extendin-4	Phase II (Amylin)	DM II, analogue of lizard secertion, 39-amino acids
Extendin-(9-39)	Preclinical	Partial antagonist of the glucgon-like peptide I receptor
Nateglinide (Stalix®)	Novatis Recently approved	DM II
Pramintide (Symlin®)	Phase III (Amylin)	Amylin analog, regulate glucagon release
Pimagedine	Phase II/ III Alteon	DM nephropathy
Prosaptide TX14	Phase II	DM neuropathy
Zenarestat	Phase III	

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