

Pharmacological management of pre-diabetes

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대구의 명소



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3.1 만세운동길



계산성당



이상화 고택



서상돈 고택



제일교회



종로 화교 협회



진골목



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대구근대역사관



삼성상회 옛터



달성공원

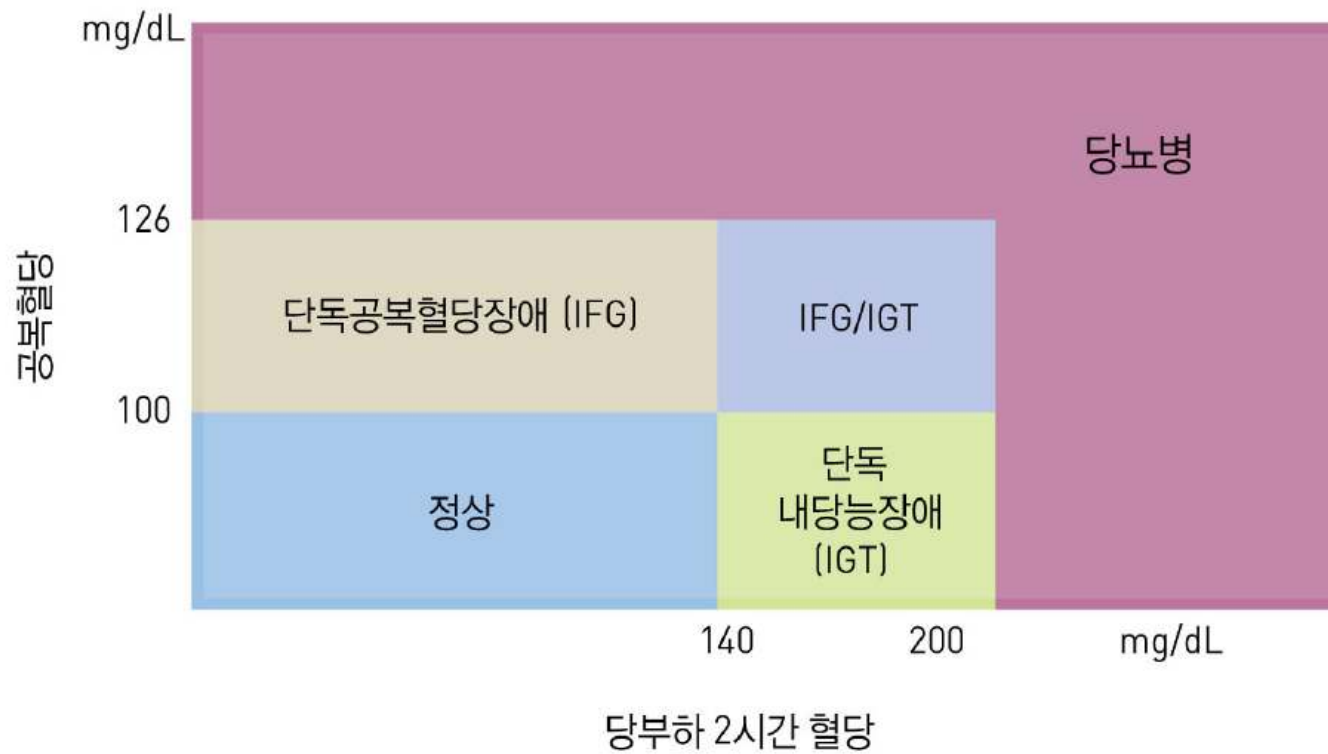
Definition of prediabetes

ADA (2012) Increased risk for diabetes	IFG	FPG 100-125 mg/dl (5.6- 6.9 mmol/liter)
	IGT	2hPG 141-199 mg/dl (7.8-11.0 mmol/liter) ; 2hr 75g-OGTT HbA1c 5.7 -6.4 %
Indian Health Service (2006)	IFG	FPG 100-125 mg/dl (5.6-6.9 mmol/liter)
	IGT	2hPG 141-199 mg/dl (7.8-11.0 mmol/liter)
Australian Diabetes Society (2007)	IFG	FPG 111-125 mg/dl (6.1-6.9 mmol/liter) with 2hPG <140 mg/dl (7.8 mmol/liter)
	IGT	FPG <126 mg/dl (7.0 mmol/liter) and 2hPG 141-199 mg/dl (7.8-11.0 mmol/liter)

Diabetes Care 35: suppl(1), 2012

J Clin Endocrinol Metab 93: 3259–3265, 2008

Definition of prediabetes



당뇨병 진료지침. 대한당뇨병학회 2011

Natural course of untreated prediabetes

- ♣ The risk of progressing to diabetes depends on
 - the degree of insulin resistance & insulin deficiency
 - other diabetes risk factors (age, family history, obesity, or GDM, PCO)
- ♣ Average annual risk of developing diabetes
 - Normoglycemia : approximately 0.7%/yr
 - Prediabetes (IFG or IGT) : 5~10%/yr
 - DPP : 11%/yr
- ♣ Over the lifetime, a majority of patients with IFG, IGT, or both would develop type 2 diabetes in the absence of intervention.

Prediction of Incident Diabetes Mellitus in Middle-aged Adults

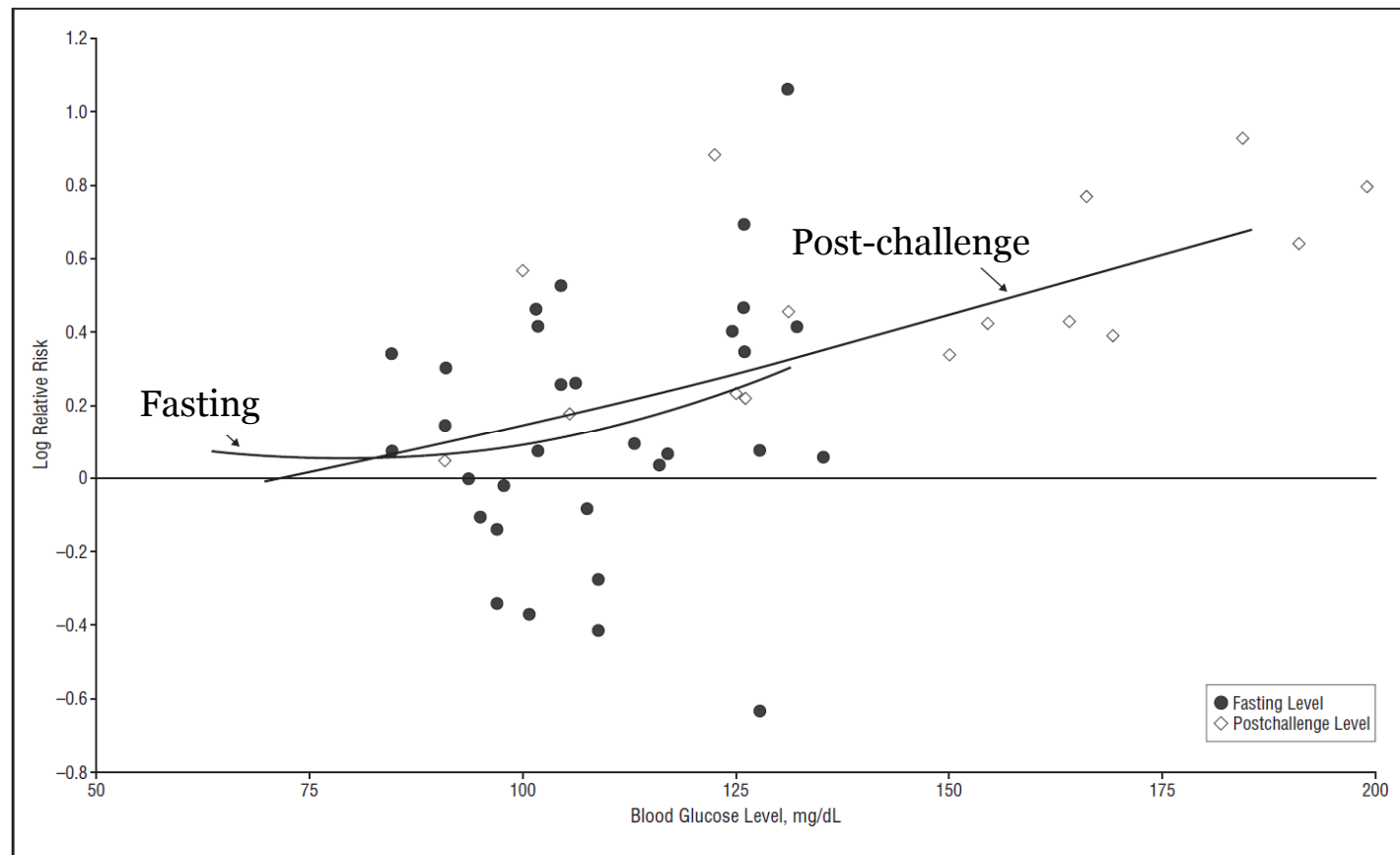
The Framingham Offspring Study

Items	Item Point Total	8-Year Risk of T2DM, %	Item Points
	≤10	≤3	
Fasting glucose level ≥126 mg/dL	11	4	10
BMI 25.0-29.9, yes/no	12	4	2
BMI ≥30.0, yes/no	13	5	5
HDL-C level <40 mg/dL, yes/no	14	6	5
Parental history of diabetes	15	7	3
Triglyceride level ≥150 mg/dL	16	9	3
Blood pressure ≥160/90 mmHg	17	11	2
Item Point Total	18	13	
	19	15	
	20	18	
	21	21	
	22	25	
	23	29	
	24	33	
	≥25	>35	

007;167:1068-1074

Dose-response relationship of cardiovascular disease with fasting and post-challenge blood glucose levels

Meta-analysis of 38 Prospective Studies





Treatment of Prediabetes

- Life style modification
- Pharmacologic management



Life style modification

- Finnish Diabetes Prevention Study
- Chinese Da Qing Diabetes Prevention Study
- Diabetes Prevention Program

1. Finnish Diabetes Prevention

- 핀란드 5개 센터
- 1993-1998년 (평균 3.2년)
- 대상자 – high risk (IGT, over weight)
- 522명 (남/여, 172/350)
- Intervention group (n=265)
- Control group (n=257)
- IGT : 1985년 WHO 기준

- Intervention group

“ 첫1년 동안 7회 임상영양사 상담
매3개월 식사요법 교육 반복

(지방 총열량 <30%, <포화지방 10%
식이섬유 >15g/1000Kal)

체중 5% 이상 감량 + 운동요법 (>4hr/주)”

- Control group

“ 당뇨병 예방을 위한 생활습관 관리의
일반적인 정보제공, 매년 센터 방문”

연구1년째 목표 도달 정도

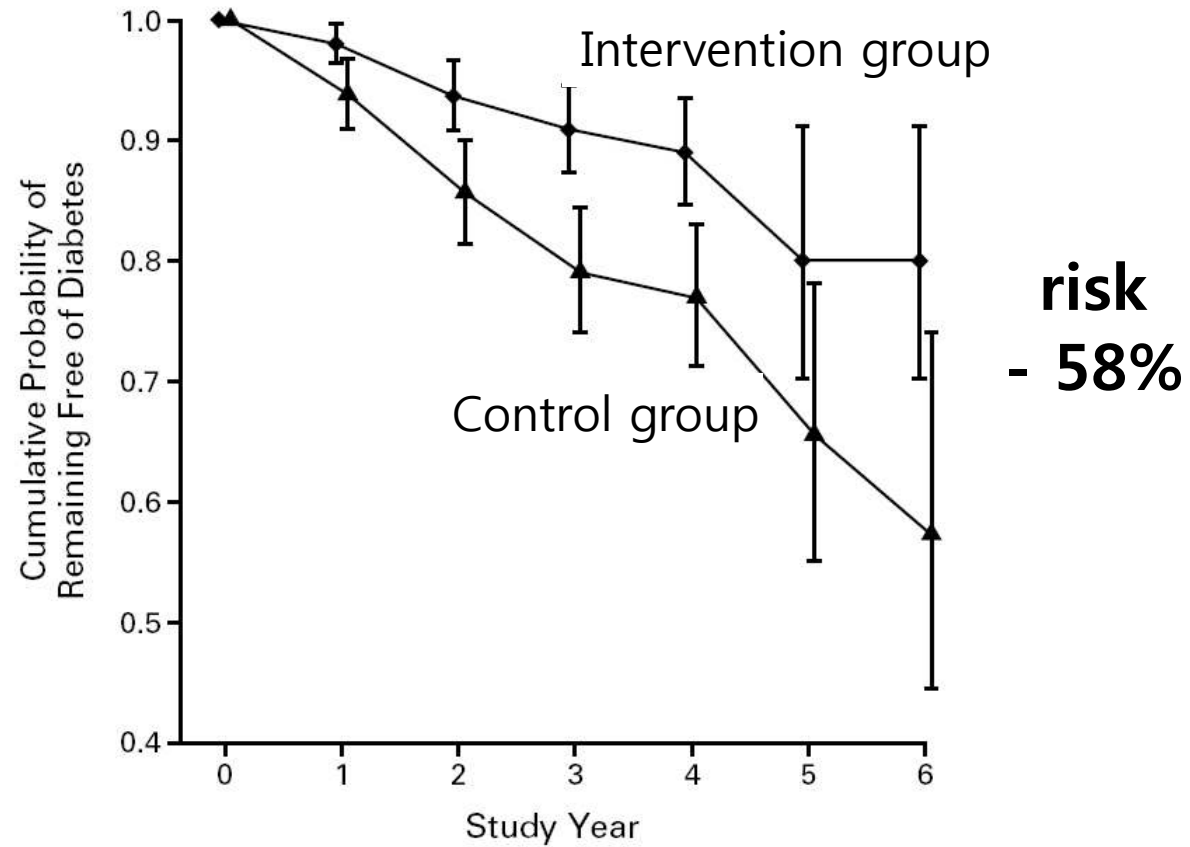
GOAL	INTERVENTION GROUP	CONTROL GROUP	P VALUE†
	% of subjects		
Weight reduction >5%	43	13	0.001
Fat intake <30% of energy intake	47	26	0.001
Saturated-fat intake <10% of energy intake	26	11	0.001
Fiber intake $\geq$ 15 g/1000 kcal	25	12	0.001
Exercise >4 hr/wk‡	86	71	0.001

* Nutrient intakes were calculated from three-day food records.

† P values were determined by the chi-square test for the difference between the groups.

‡ Exercise frequency was reported by the subjects who chose one of the four categories described in Table 3. The goal identified here was a frequency in category 2 or higher.

당뇨병 예방 효과



SUBJECTS AT RISK

Total no.	507	471	374	167	53	27
Cumulative no. with diabetes:						
Intervention group	5	15	22	24	27	27
Control group	16	37	51	53	57	59

Finnish Diabetes Study 요약

- 체중감소 (3.5 vs 0.8 kg ; 2년째)
- 4년간 당뇨병 누적발생률 (11 vs 23%)
- 당뇨병 발생 위험 - 58% 감소
- 목표달성0개: 당뇨병 발생 (38 vs 31%)
- 목표 4-5개 달성 : 당뇨병 발생(0 vs 0 %)
- 결론 : 식사 + 운동 당뇨병 예방, 효과적



2. 다칭 (大慶市, Da Qing) Study



2. Da Qing study

- 중국, Da Qing, 33개 진료소
 - 주민 87.3% (110,660) 중 IGT (577명)
 - 대상자 – 25세 이상, 6년 추적관찰
 - 식사요법군
 - 운동요법군
 - 식사+운동요법군
 - 대조군
- 

식사요법군 (n=141)

- BMI < 25kg/m²
 - ; 25-30Kal/kg/day,
(탄수화물/단백/지방 55-65/10-15/25-30%)
 - ; 야채섭취 권장, 술, 단순당 제한
- BMI ≥ 25kg/m²
 - ; reduce intake (목표 : BMI= 23kg/m²)
 - ; individual counseling

운동요법군 (n=130)

- 최소 1단위 leisure exercise
- <50세, 심질환(-), 관절질환(-) : 2 단위
- 첫1개월-매주, 이후 3개월-매월
이후에는 매3개월 마다 관리 및 교육
- 겨울- indoor activity ↑

식사+운동요법군 (n=126)

대조군 (n=133)

- 일반적인 정보제공
- 개별적인 교육 없음

1 단위 운동의 종류 및 시간

강도	시간(분)	운동 종류
약한	30	산보, 쇼핑, 집안 청소, 버스로 여행
중간	20	빨리걷기, 계단내려가기, 자전거타기, 빨래하기, 볼룸댄스
강한	10	천천히달리기, 계단오르기, 디스코, 배구, 탁구
아주 강한	5	농구, 수영, 줄넘기

Da Qing 연구 결과 (6년간 추적)

	당뇨병 누적발생률 (lean/overweight)	위험도 감소
대조군	67.7% (60.0 /72.3)	
식사요법군	43.8% (38.2 /48.0)	31%
운동요법군	41.1% (26.3 /51.2)	46%
식사+운동요법	46.0% (34.8 /52.5)	42%

식사+운동의 : additive effect 없음

3. DPP (Diabetes Prevention Program)

- 미국 27개 센터
- 1996-1999년 (평균 2.8년)
- 대상자 – IGT, BMI ≥ 24 , age > 25
- 3234명 (남/여, 172/350)
- placebo group (n=1082)
- metformin group (n=1073)
- Life-style group (n=1079)

- Intervention group

“ 첫6개월 동안 16회 이상 전문적 관리
이후 매달 전문적 관리를 받음
그룹지도 4-6주/매3개월, 전화상담 1회 이상/월
체중 감량 $\geq 7\%$ (500-1000Kal/day제한)
+ 운동요법 $> 150\text{min/week}$ ”

- Metformin group

“ 일반적인 정보제공 + 850mg bid/day

- Placebo group

“ 일반적인 정보제공 + placebo bid/day

당뇨병 누적 발생률

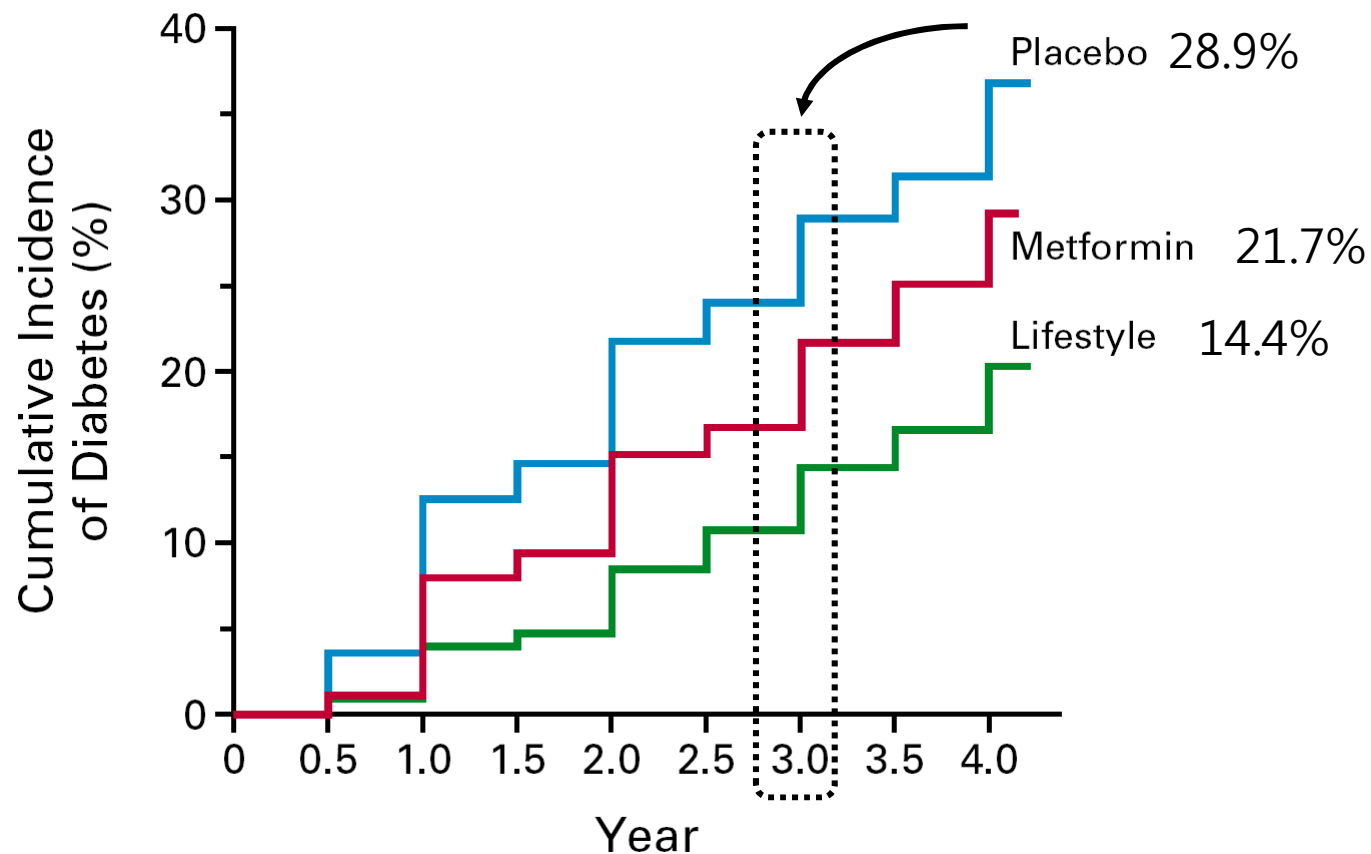
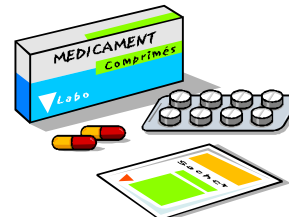


Figure 2. Cumulative Incidence of Diabetes According to Study Group.
The diagnosis of diabetes was based on the criteria of the American Diabetes Association. The incidence of diabetes differed significantly among the three groups ($P < 0.001$ for each comparison).

N Engl J Med 2002;346:393-403

DPP Study 요약

- 당뇨병발생률 (4.8 vs 7.8 vs 11.0%)
- 3년 누적발생률 (14.4 vs 21.7 vs 28.9)
- Diabetes risk ↓ : (58% vs 31%)
: 생활양식 중재 > **Metformin**
- 남녀, 인종별 차이 없음
- Metformin : 젊은연령, BMI 높은 경우 더 효과
- Lifestyle : 고령, BMI 상대적 낮은 경우 더 효과





Pharmacologic Intervention

- Metformin
- Thiazolidinedione
- Acarbose
- Sulfonylurea, glinides
- Orlistat
- ACEI, ARB
- Estrogen treatment

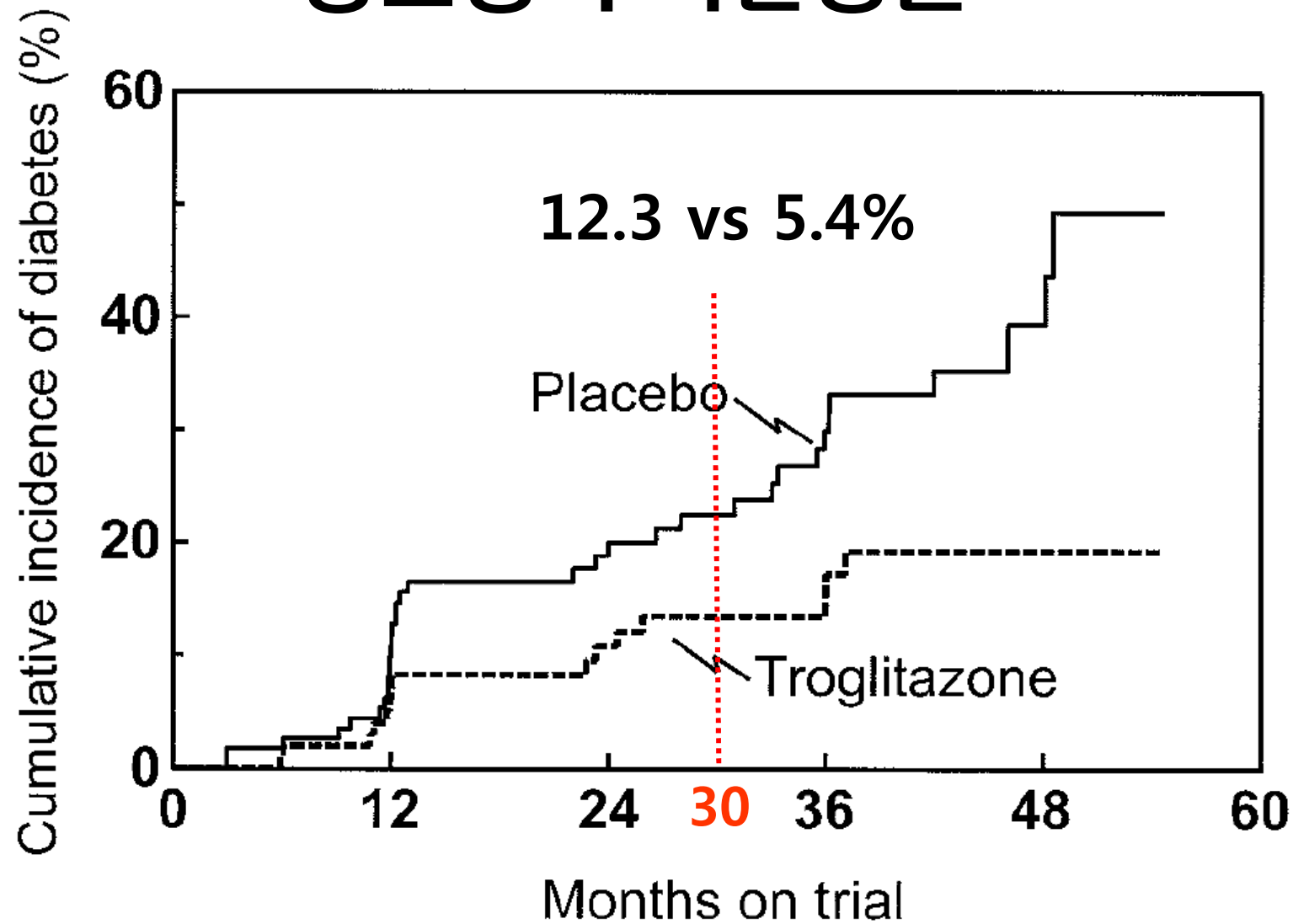
1. Thiazolidinedione

- **TRoglitzone** In the Prevention Of Diabetes (**TRIPOD**)
- Diabetes REduction Assessment with ramipril and **rosiglitazone** Medication (**DREAM, DREAM On**)
- **ACTos** NOW for the Prevention of Diabetes (**ACT NOW**)
- **Pioglitazone** In Prevention Of Diabetes (**PIPOD**)

TRIPOD [TRoglitazone In the Prevention Of Diabetes]

- 미국 1개 센터, 1995-1998 enroll
2000년 3월 중단 (간독성, 시판금지)
- 목적 : GDM(+) 여성에서 troglitazone이
인슐린저항성 개선, 당뇨병예방
- 대상 : 라틴계여성 235 (2.5년 연구)
75g OGTT (5회 혈당 $\geq 650\text{mg/dL}$)
- troglitazone group : 400mg/day
- placebo group :

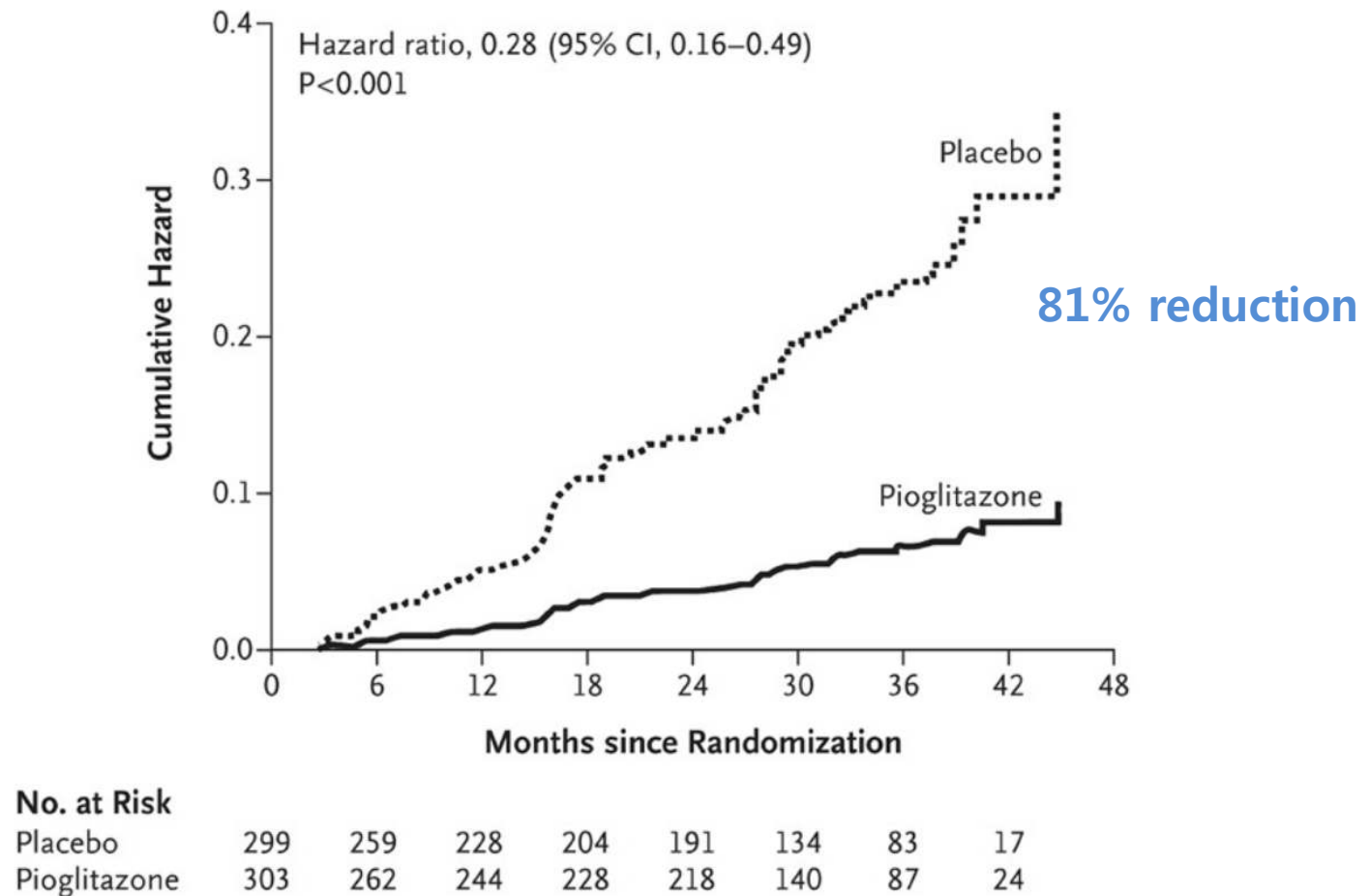
당뇨병 누적발생률



ACT NOW (pioglitazone)

- 미국 8개 센터, 내당능장애 602명 대상
- 목적 : pioglitazone이 내당능장애자에서
당뇨병 발생을 억제할 수 있는지
그외 : 인슐린 감수성/베타세포 기능개선
CVD risk 개선, IMT, microalbuminuria
- pioglitazone group : 45mg/day
- 48개월 관찰 연구

ACT NOW (pioglitazone)



PIPOD [Pioglitazone In the Prevention Of Diabetes]

- 목적 : β -cell function, 인슐린저항성, pioglitazone투약 시 당뇨병 발생률
- 대상 : 라틴계, GDM (+)여성으로 이전 TRIPOD 연구 참여(완료)자, 95명
- 3년간(30mg→45mg)투약, 6개월 wash out
- diabetes incidence rate ; 4.6%/yr
(대조군 없어 비교 곤란)

PIPOD [Pioglitazone In the Prevention Of Diabetes]

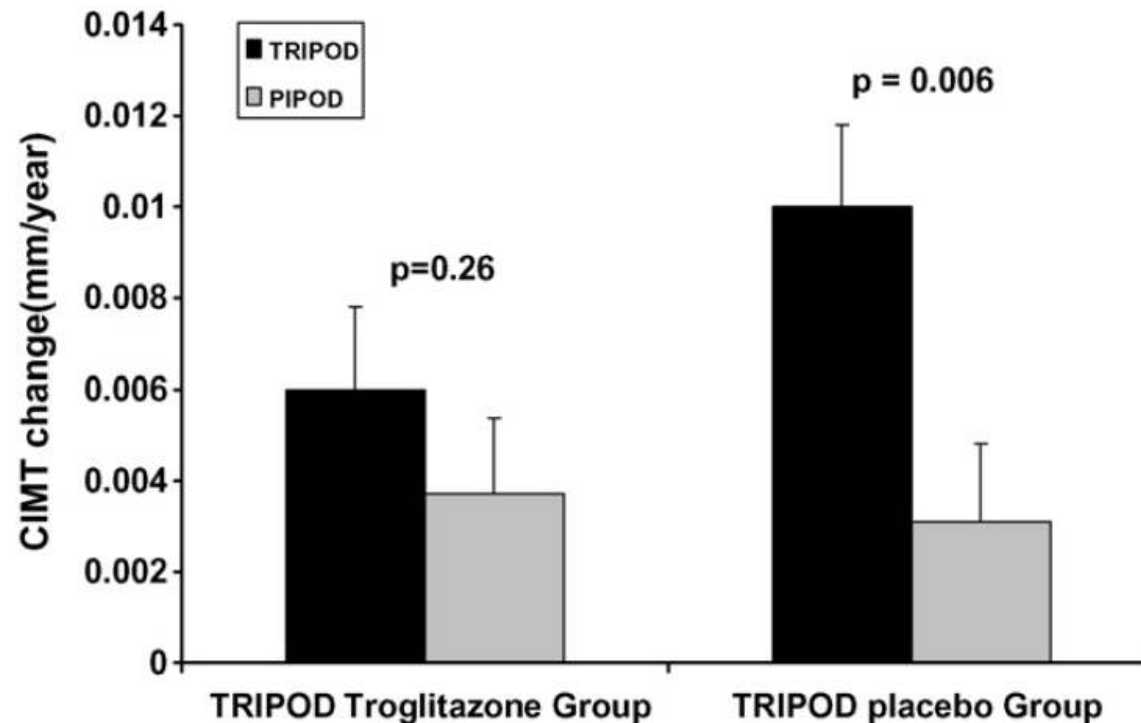
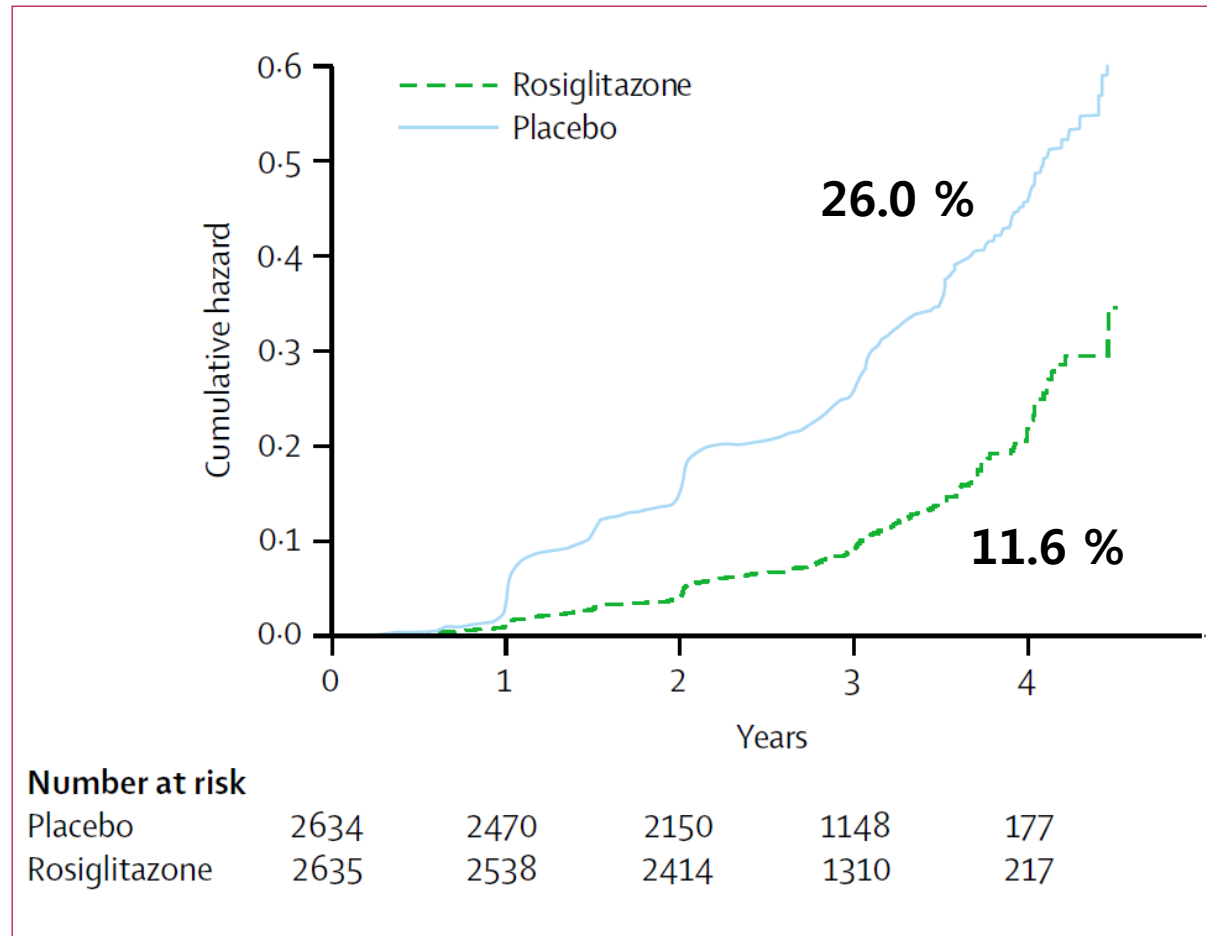


Fig. 1. CIMT progression rates during TRIPOD and PIPOD treatment periods for women who completed TRIPOD without diabetes and participated in PIPOD with at least one follow-up CIMT. Rates are presented as mean and S.E. by their initial TRIPOD randomization status: TRIPOD troglitazone group ($N= 31$) and TRIPOD placebo group ($N= 30$). p -Values are for differences between TRIPOD and PIPOD study periods, by random coefficients mixed-effect modeling.

DREAM [Diabetes REduction Assessment with ramipril and rosiglitazone Medicaiton]

- 목적 : rosiglitazone투약 시 당뇨병 예방효과
대상 : 30세 이상, IGT, IFG without CVD
21개국, 191센타 5269명
- rosiglitazone 8mg, 3년간 투약
- 11.6% vs 26.0% (HR 0.40) → T2DM
- 50.5% vs 30.3%, (1.71) →normoglycemia
- 심혈관 사건 빈도: 거의 비슷함
- Heart failure : 0.5% vs 0.1% ($p=0.01$)

Time to occurrence of primary outcome



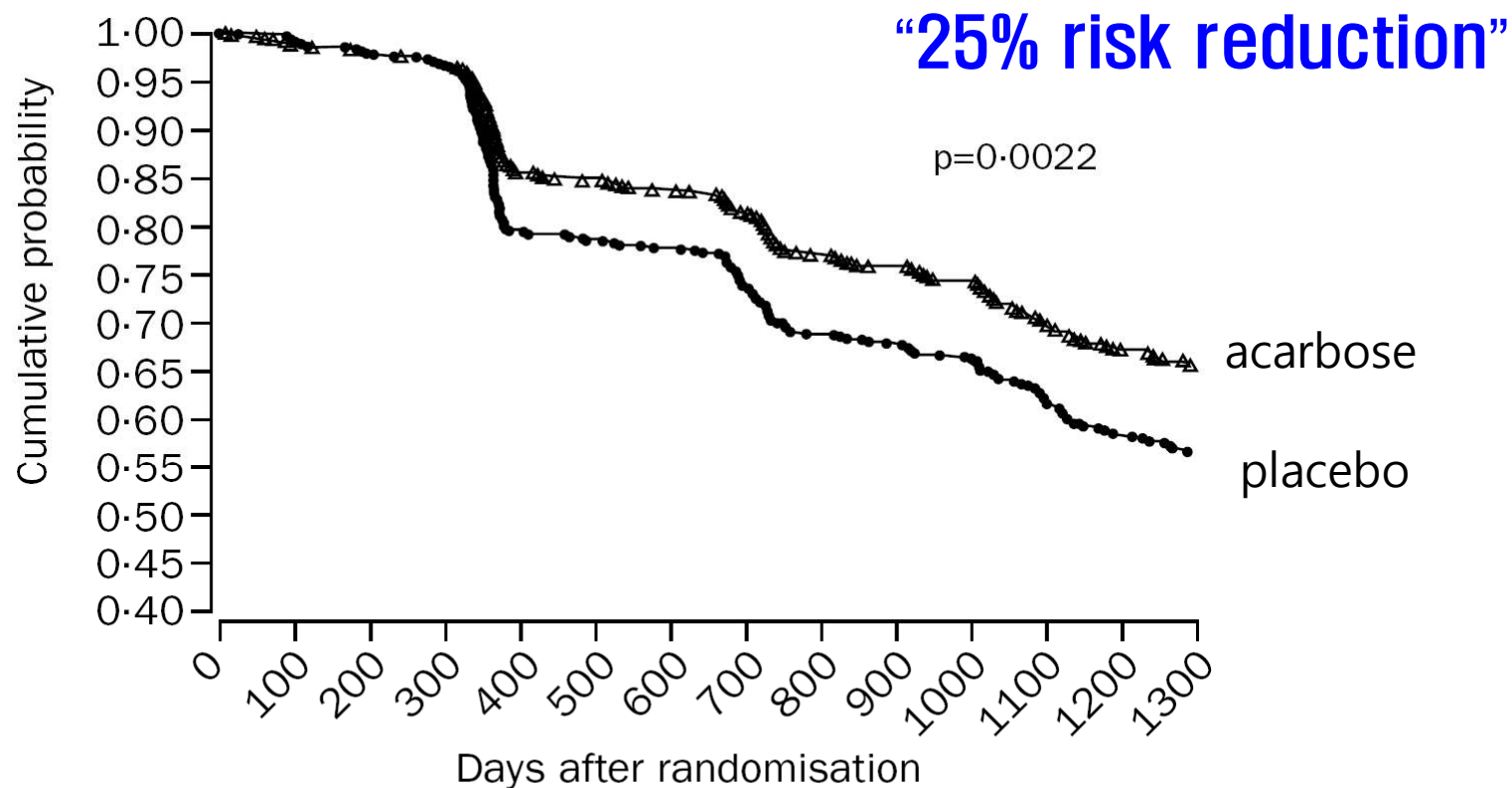
Lancet 368, 1096–1105, 2006

2. Acarbose [STOP-NIDDM]

- 유럽 8개국 + 캐나다
- 1998-2001년 (평균 3.3년)
- 대상자 ;
IGT, BMI ≥ 25 -40kg/m², age 40-70yr
- 1429명
- placebo group (n=715)
- acarbose group (n=714) : 100mg tid

STOP

Cumulative probability of remaining free of diabetes over time



Patients at risk

Acarbose	682	655	628	612	531	523	515	497	463	447	432	349	268	212
Placebo	686	671	655	640	512	505	497	470	434	427	414	331	255	208

3. Nateglinide (NAVIGATOR)

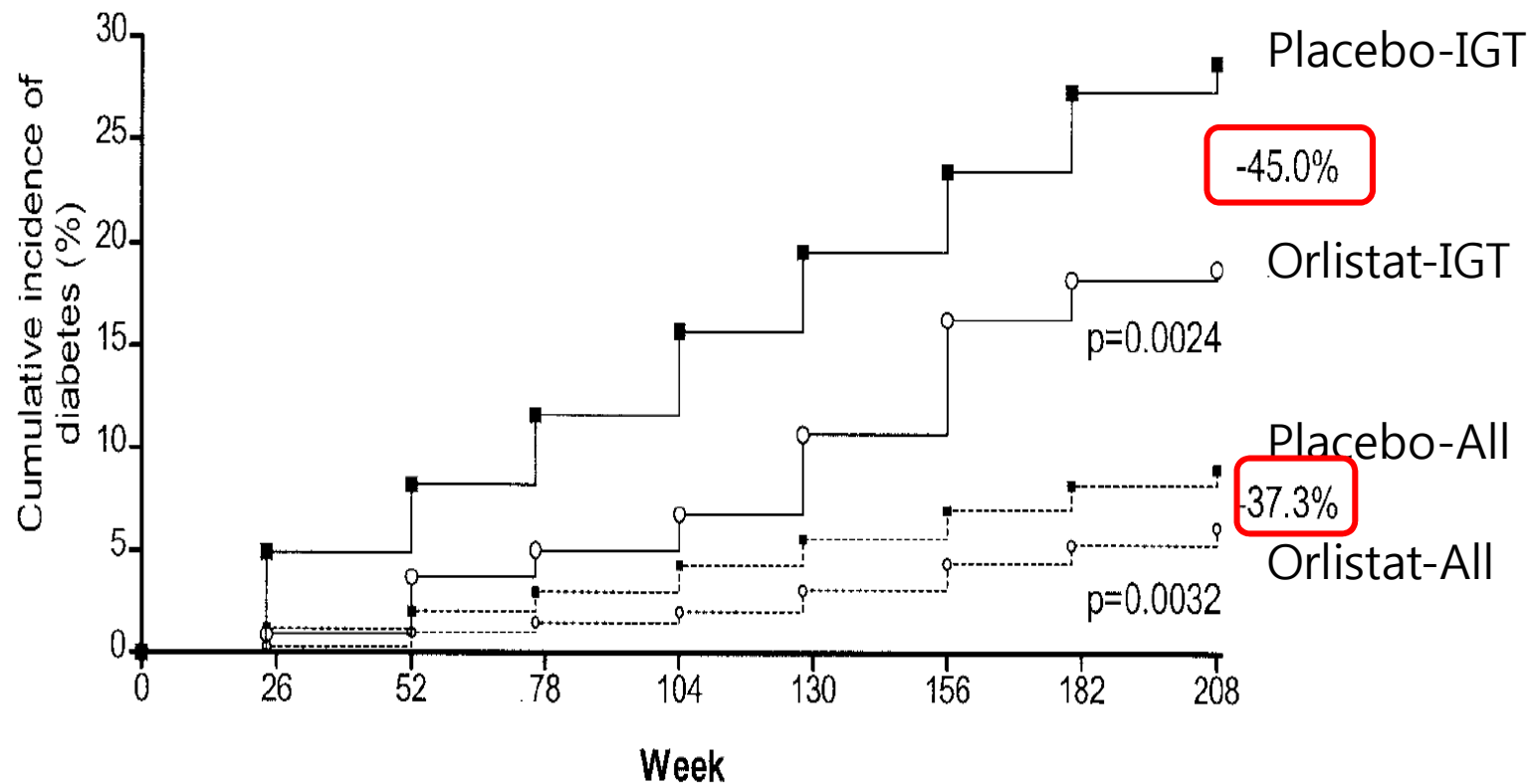
- ◆ Nateglinide (up to 60 mg tid) in subjects with IGT
 1. prevention of diabetes
 2. prevention of CVD or CVD risk.
- ◆ Followed up for a median of 5 years
- ◆ Nateglinide failed to reduce progression to diabetes rates.
; incidence of diabetes : 36% vs 34% (hazard ratio 1.07)
- ◆ Nateglinide also failed to reduce cardiovascular events,
whereas it increased the risk of hypoglycemia.

4. XENDOS [XENical in the prevention of Diabetes in Obese Subject]

- 스웨덴 22개 센터
- 1997-2002년 (평균 4 년)
- 대상자 – Obesity (BMI ≥ 30 kg/m²)
(IGT 79%, NGT 21%)
- 3305명
- Orlistat group (n=1650, 120mg tid)
- Placebo group (n=1655)
- All subjects - life style modification

당뇨병 누적 발생률

6.2% vs 9.0% (Orlistat : placebo)



5. Inhibition of Angiotensin II

- ◆ possible mechanisms of ACEI, or ARB on prevention
 - increased insulin sensitivity
 - protective effect on the pancreas via increased blood flow
- ◆ Most of the original data – secondary outcome
- ◆ incidence of newly diagnosed diabetes : 25%
- ◆ The available data suggest a relatively weak effect of ACE inhibitors or ARBs compared with lifestyle intervention or other effective medications for the prevention of diabetes.

Prevention of Type 2 Diabetes by ACE Inhibitors or ARBs

Trial (Ref. No.)	No. of Patients	Years of Follow-Up*	Percent of New Diabetics	Risk Ratio (95% Confidence Interval)†
CAPPP (15)	10,985	6.1	Captopril 337/5,183 (6.5%) Diuretic/beta-blocker 380/5,230 (7.3%)	0.79 (0.67–0.94)
STOP-2 (16)	6,614	5	Conventional drugs 97/1,961 (4.9%) ACE inhibitors 93/1,969 (4.7%)	0.96 (0.72–1.27)
HOPE (17)	9,297	5	Ramipril 102/2,837 (3.6%) Placebo 155/2,883 (5.4%)	0.66 (0.51–0.85)
LIFE (18)	9,193	4.8	Losartan 241/4,019 (6%) Atenolol 319/3,979 (8%)	0.75 (0.63–0.88)
ALLHAT (19)	33,357	4.9	Lisinopril 119/4,096 (8.1%) Chlorthalidone 302/6,766 (11.6%)	0.70 (0.56–0.86)
ANBP2 (20)	6,083	Median 4.1	Enalapril 138/2,800 (4.9%) HCTZ 200/2,826 (7.1%)	0.66 (0.54–0.85)
SCOPE (21)	4,937	3.7 Maximum 5	Candesartan 93/2,167 (4.3%) Placebo 115/2,175 (5.3%)	0.81 (0.61–1.02)
ALPINE (22)	392	1	Candesartan ± felodipine 1/196 (0.5%) Atenolol ± HCTZ 8/196 (4%)	0.13 (0.03–0.99)
CHARM (23)	7,599	3.2	Candesartan 163/2,715 (6%) Placebo 202/2,721 (7%)	0.78 (0.64–0.96)
SOLVD (24)	4,228	3.4	Enalapril 9/153 (5.9%) Placebo 31/138 (22.4%)	0.26 (0.13–0.53)
VALUE (25)	15,245	4.2	Valsartan 690/5,267 (13.1%) Amlodipine 845/5,152 (16.4%)	0.77 (0.69–0.86)
PEACE (26)	8,290	Maximum 7 Median 4.8	Trandolapril 335/3,432 (9.8%) Placebo 399/3,472 (11.5%)	0.83 (0.72–0.96)

6. Estrogen therapy

- ◆ Heart and Estrogen/Progestin Replacement Study (HERS)
cumulative incidence of type 2 diabetes ;
6.2 % vs 9.5 % (HR 0.6; 95% CI 0.5-0.9)
- ◆ Women's Health Initiative (WHI)
cumulative incidence of treated diabetes ;
3.5 % vs 4.2 % (HR 0.79; 95% CI 0.7-0.9)
- ◆ combined HRT may reduce the risk of type 2 diabetes mellitus. However, this effect is insufficient to recommend HRT as a diabetes prevention strategy in women.

Summary

TABLE II. LIFESTYLE INTERVENTIONS TO PREVENT DIABETES IN PATIENTS WITH PREDIABETES.

Study	Population	Study Protocol	Effect on Diabetes Incidence
Da Qing IGT and Diabetes Study ⁸	Patients with IGT (n = 577)	Diet; exercise; or diet plus exercise	Reductions: 31%, 46%, and 42%, respectively
Diabetes Prevention Program ⁹	Patients with IGT (n = 3234)	Intensive lifestyle intervention; or standard lifestyle intervention plus placebo or metformin	Reductions: intensive lifestyle 58% vs placebo, 39% vs metformin
Finnish Diabetes Prevention Study ¹⁰	Overweight patients with IGT (n = 522)	Lifestyle intervention; or control group	Reduction: lifestyle intervention 58% vs control group

TABLE III. ORAL AGENTS TO PREVENT DIABETES OR CARDIOVASCULAR (CV) EVENTS IN PATIENTS WITH PREDIABETES.

Study	Population	Intervention	Effect
DPP ⁹	Patients with IGT (n = 3234)	Metformin 850 mg BID or placebo	Reduced risk of diabetes: 31% with metformin vs placebo
TRIPOD ¹¹	Hispanic women with gestational diabetes (n = 266)	Troglitazone or placebo	Reduced incidence of diabetes: 55% with troglitazone vs placebo
DREAM ^{12,13}	Patients with IFG or IGT (n = 5269)	Rosiglitazone 8 mg/d or placebo, plus ramipril ≤15 mg/d or placebo	Reduced risk of diabetes: 60% with rosiglitazone; 9% with ramipril
STOP-NIDDM ¹⁴	Patients with IGT (n = 1429)	Acarbose 100 mg TID or placebo	Reduced relative risk of diabetes: 25% with acarbose vs placebo Reduced risk of CV events: 49% with acarbose vs placebo
Chinese Acarbose Study ¹⁵	Chinese patients with IGT (n = 261)	Acarbose 50 mg TID or placebo	Reduced conversion to diabetes: 7 vs 12 with acarbose vs placebo
XENDOS ¹⁶	Obese patients with or without IGT (n = 3305)	Orlistat 120 mg TID or placebo, plus lifestyle intervention	Reduced risk of diabetes: 37.3% with orlistat for all patients, 45% for patients with IGT vs placebo



ADA guidelines for Prediabetes

- ◆ Modest weight loss (5-10 percent of body weight)
- ◆ Moderate-intensity exercise (30 minutes daily)
- ◆ Smoking cessation
- ◆ Because of its effectiveness, low cost, and long-term safety, the ADA recommends consideration of metformin for prevention of diabetes in individuals at highest risk for developing diabetes.
- ◆ Patients treated with metformin require monitoring, including twice yearly A1C assessments.

감사합니다

