Early and powerful DM control with combination therapy based on a multi-center trial in Korea

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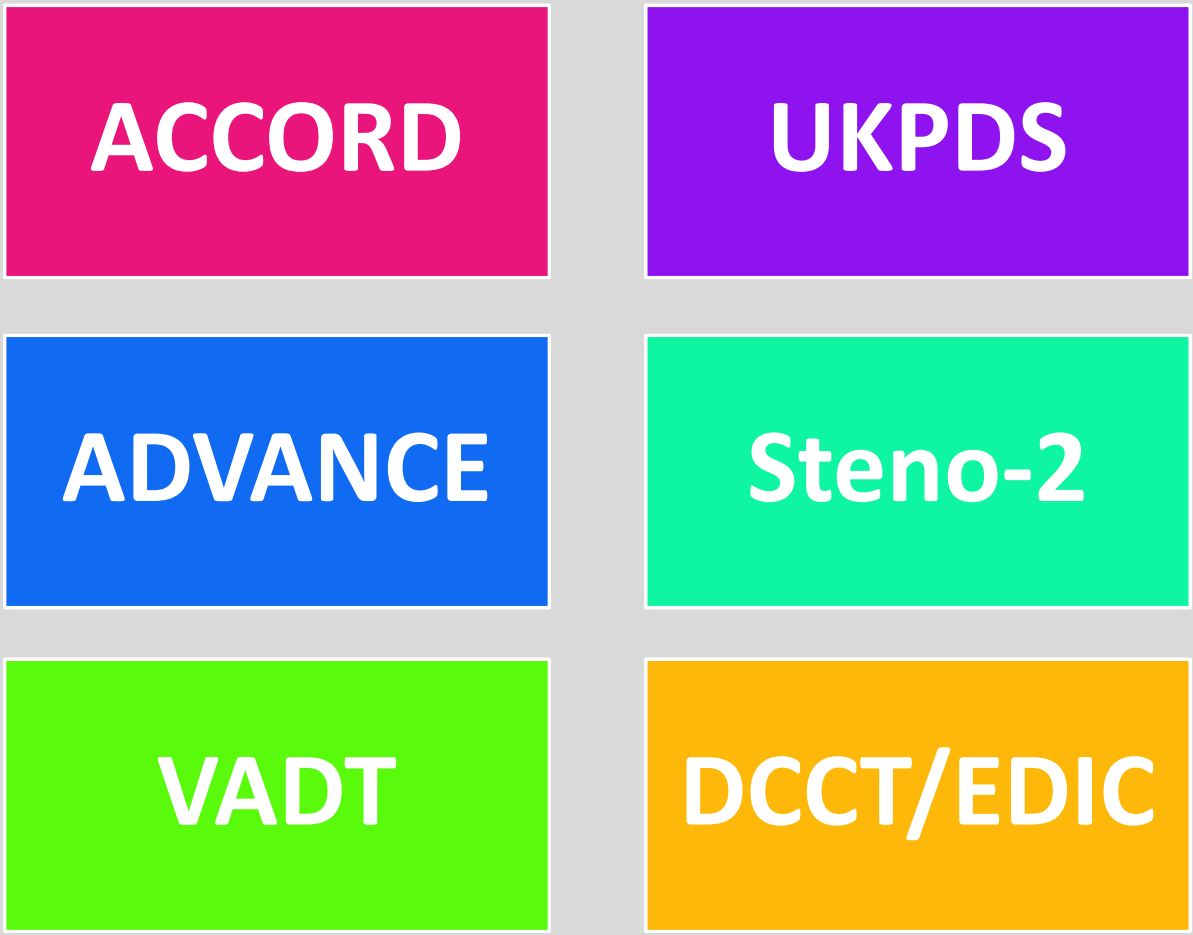
Needs for

Early & Intensive DM control

Intensive Glycemic Control



UKPDS 80 - Legacy Effect

- Method: Intensive treatment (SU, insulin, Metformin) vs. conventional treatment (diet)

Aggregate Endpoint		UKPDS 33 1997	UKPDS 80 2007
Any diabetes related endpoint	RRR	12%	9%
	P	0.029	0.040
Microvascular disease	RRR	25%	24%
	P	0.0099	0.001
Myocardial infarction	RRR	16%	15%
	P	0.052	0.014
All-cause mortality	RRR	6%	13%
	P	0.44	0.007

* RRR = Relative Risk Reduction, P = Log Rank

http://www.dtu.ox.ac.uk/index.php?maindoc=/ukpds/index.php,July 09, 2009

Meta analysis
- Intensive Therapy & CV disease Reduction

UKPDS ,PROactive, ADVANCE

VADT, ACCORD

33,040 patients, follow-up 4.95 years

Duration of T2DM 8 years

Mean HbA1c 7.8% at baseline

6.6%(INT) VS. 7.5%(STD) after follow-up

→ Intensive glucose control

: 17% reduction in non-fatal myocardial infarction

: 15% reduction in coronary heart disease

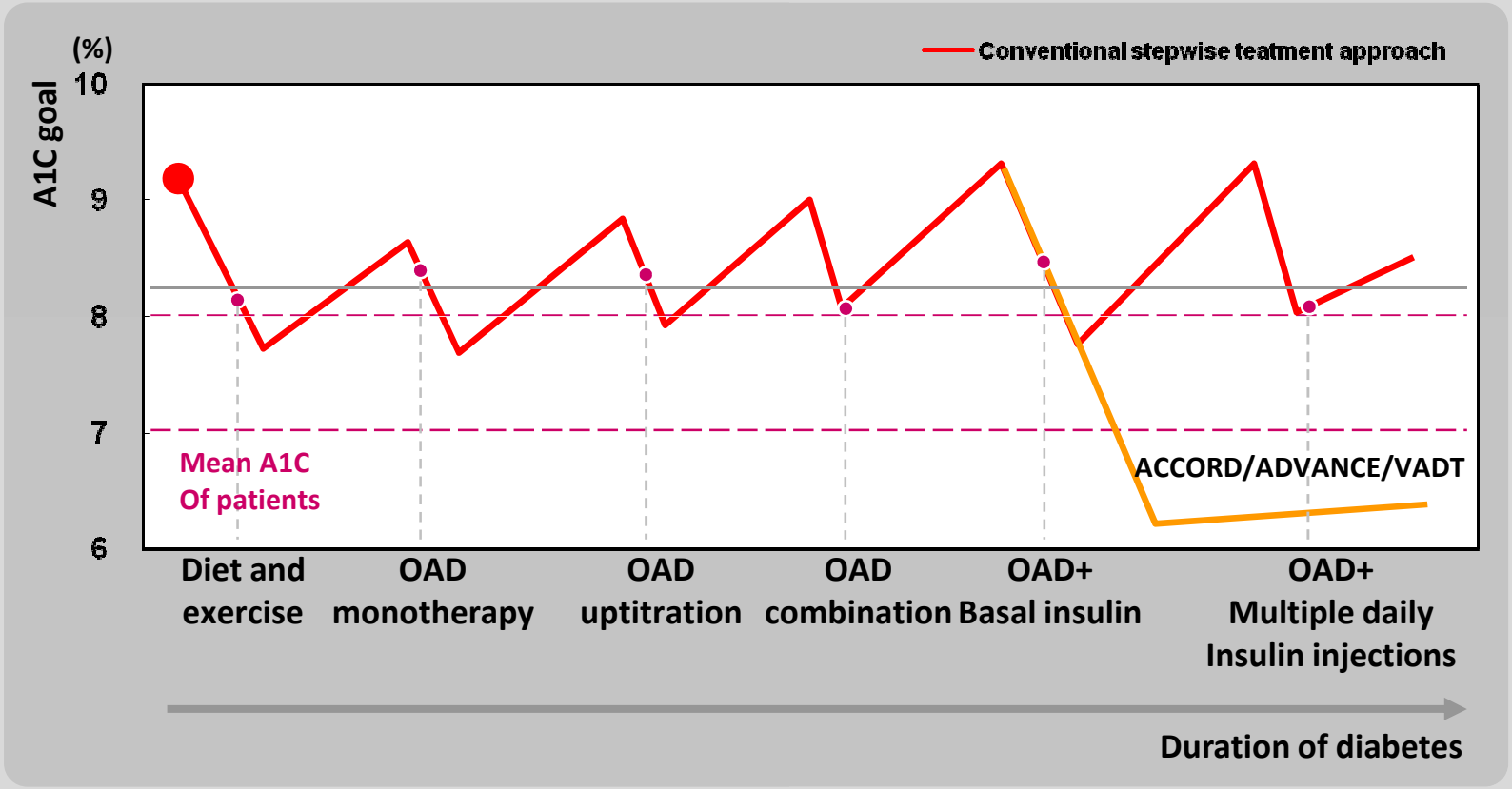
: 7% reduction in stroke (NS)

: no increase in all-cause mortality

*** INT: intensive therapy, STD: standard therapy**

Lancet 2009; 373: 1765–72

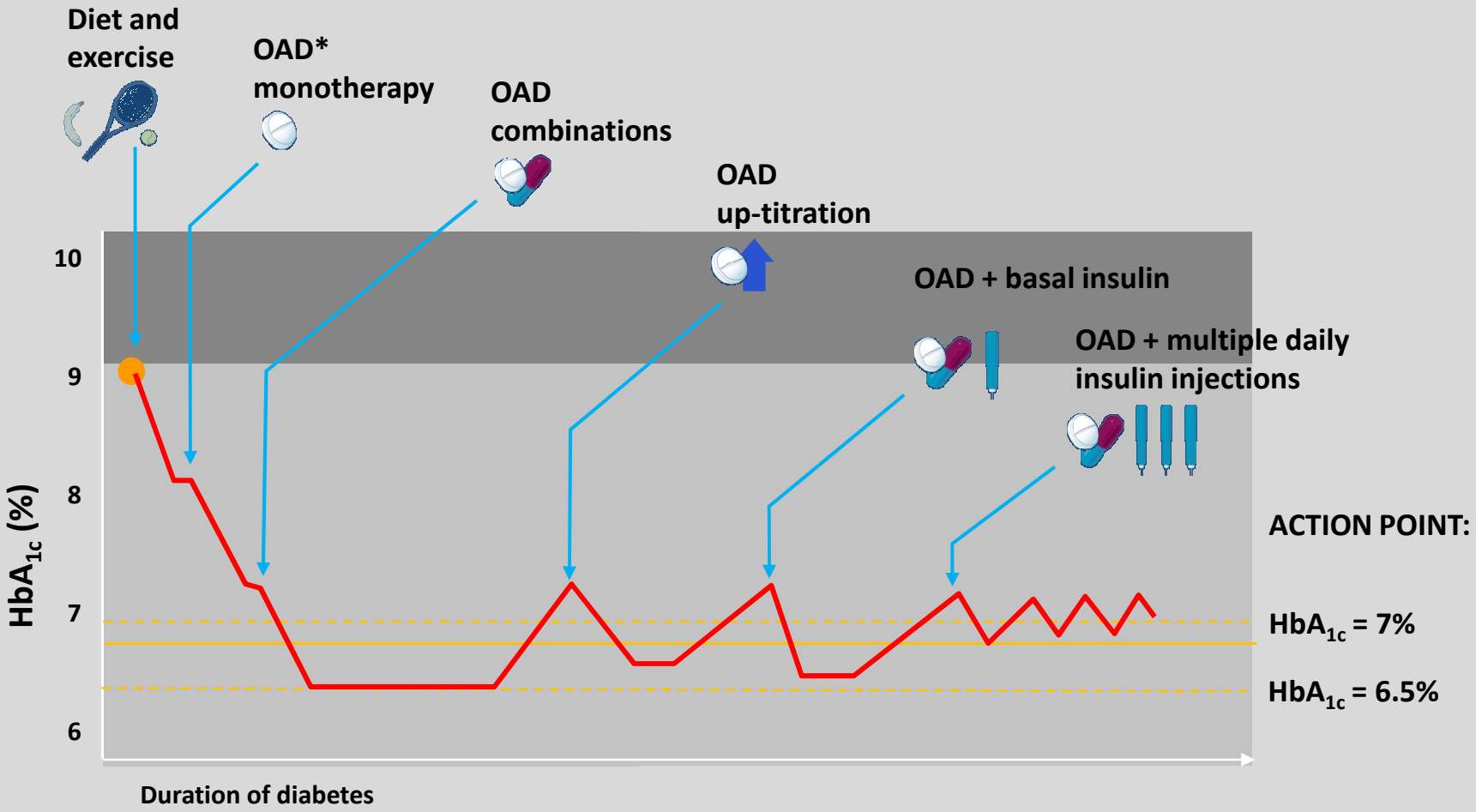
Traditional stepwise diabetes control



OAD=oral antihyperglycemic agent.

Adapted from Campbell IW. Br J Cardiol. 2007;7:625-631; Del Prato S et al. Int J Clin Pract 2005;1345-1355

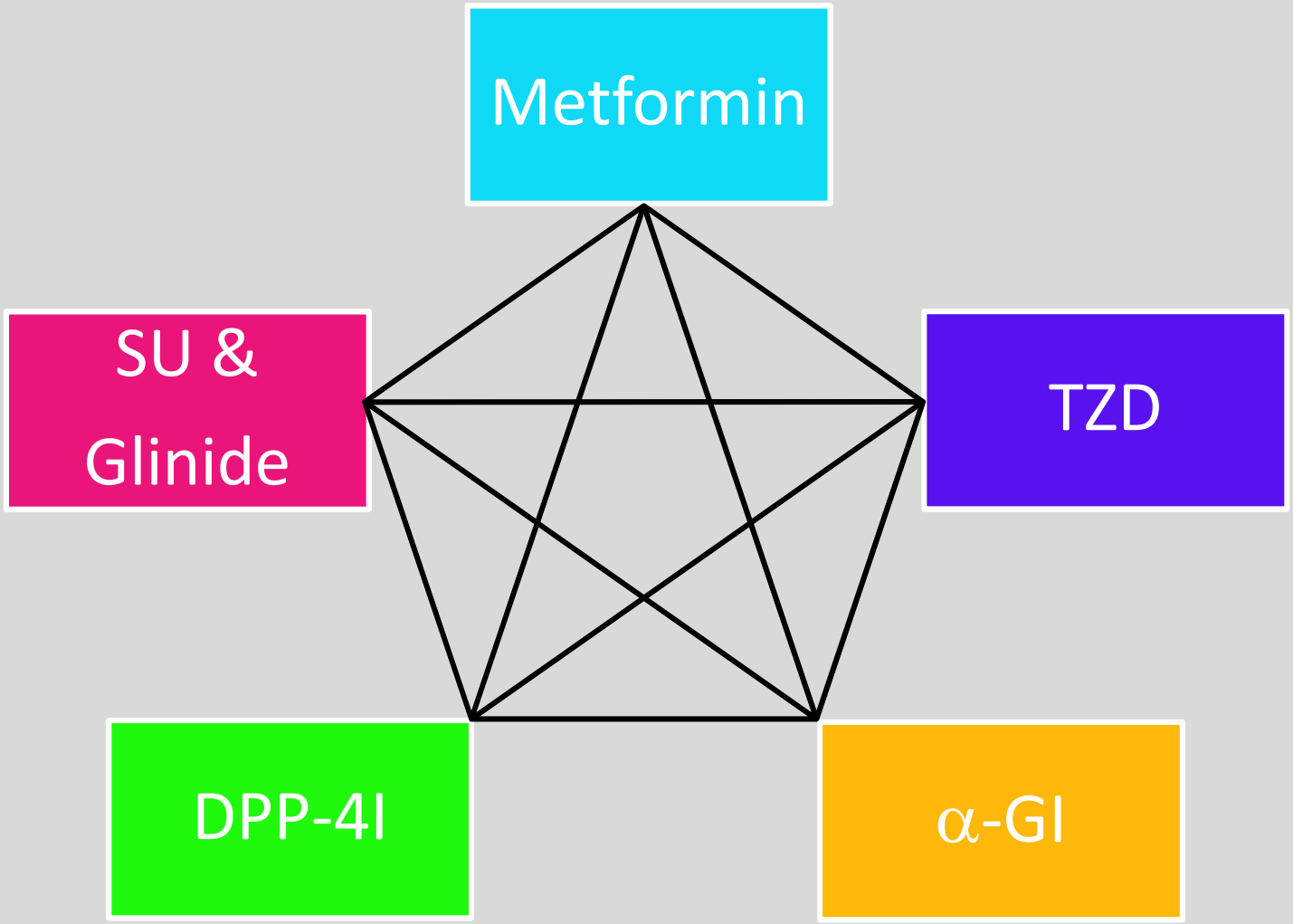
Early Combination Approach



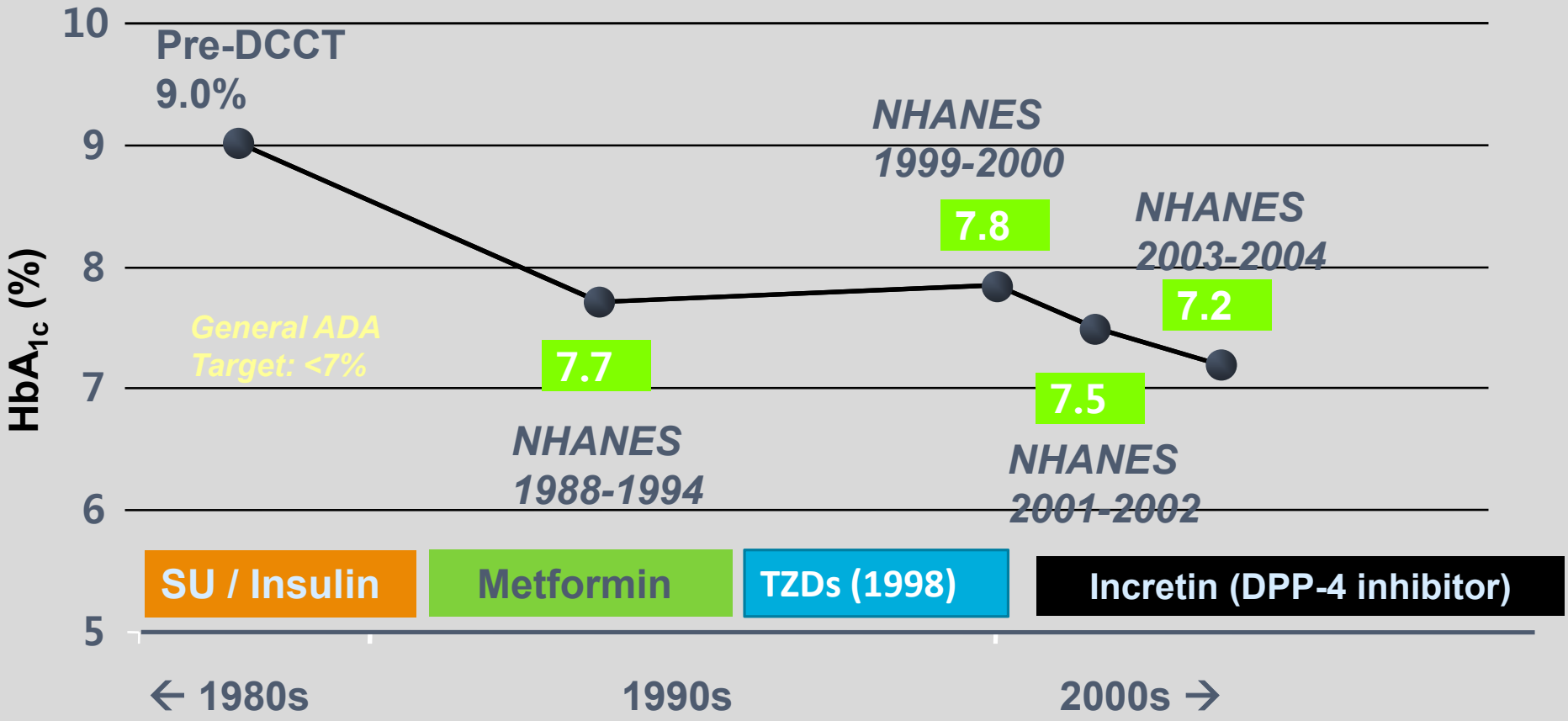
*OAD = oral antidiabetic

Adapted from Del Prato S et al Int J Clin Pract 2005;59:1345-1355

Possible OAD Dual Combinations



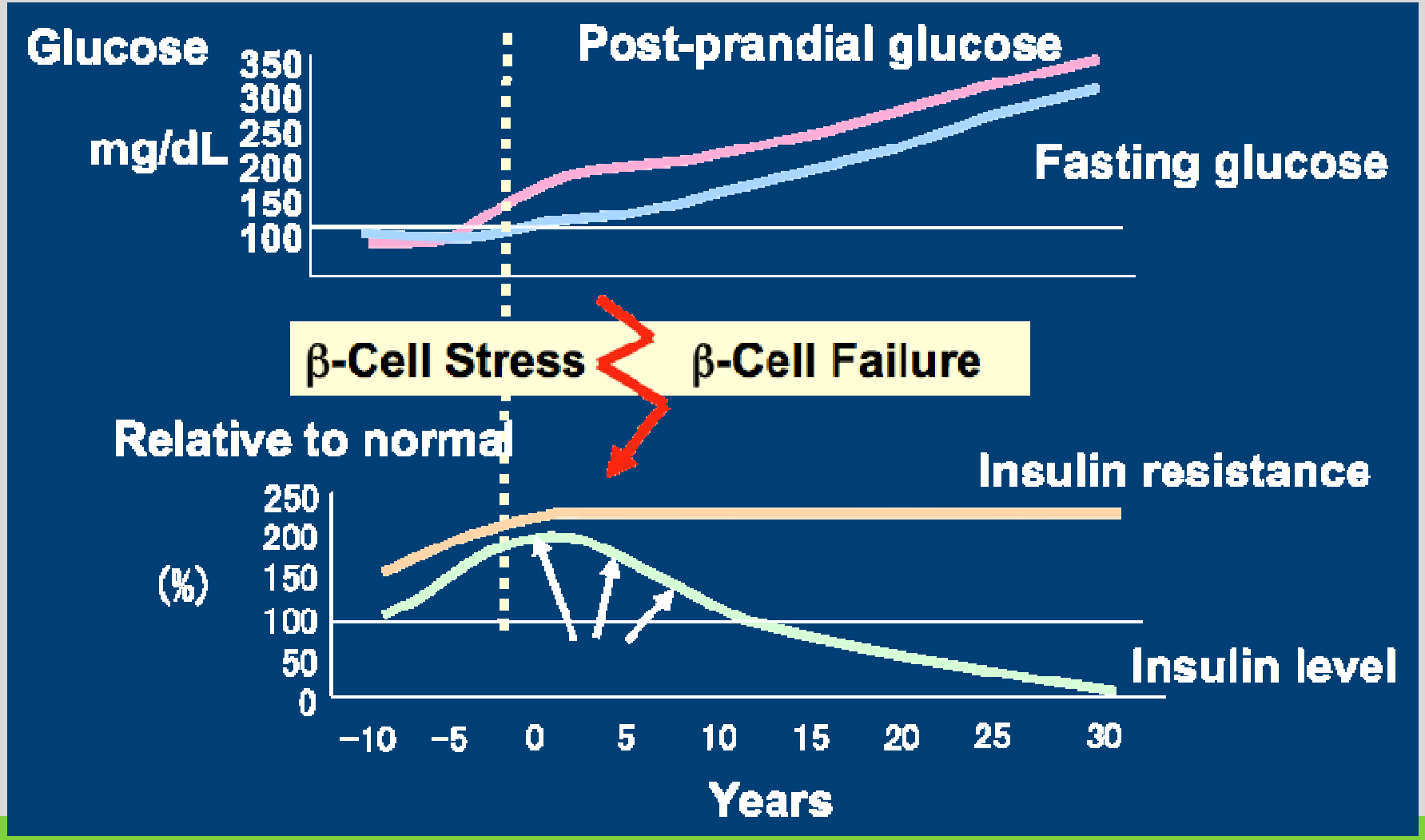
New Era of DM Treatment



SU=sulfonylurea; TZDs=thiazolidinediones; T2DM=type 2 diabetes.

Koro CE, et al. *Diabetes Care*. 2004;27:17-20; Hoerger TJ, et al. *Diabetes Care*. 2008;31:81-86.

Insulin Resistance and ß-cell Failure : Core Defects in Type 2 Diabetes



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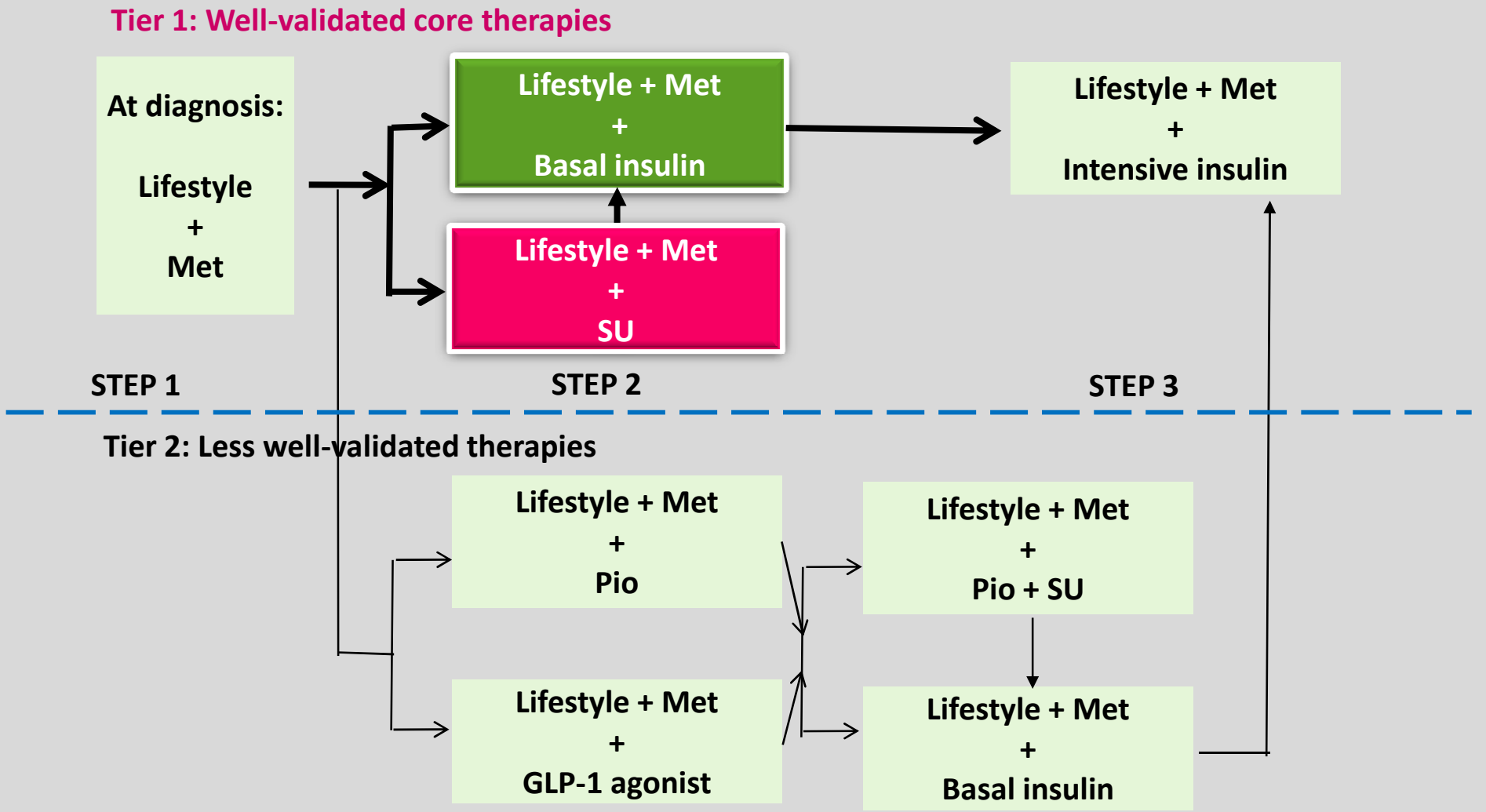
ADA/EASD Consensus Algorithm



Diabetes care 2009 32:193-203

AACE / ACE DIABETES ALGORITHM *For Glycemic Control*

LIFESTYLE MODIFICATION

A1C 6.5 - 7.5%**

Monotherapy

MET	TZD [2]	DPP4 [1]	AGI

2 – 3 Month ***

Dual Therapy

MET	+	GLP-1 or DPP4 [1]
		TZD [2]
		Glinide or SU [5]
TZD	+	GLP-1 or DPP4 [1]
MET	+	Colesevelam
		AGI [3]

2 – 3 Month ***

Triple Therapy

MET + GLP-1 or DPP4 [1]	+	TZD [2]
		Glinide or SU [4,7]

2 – 3 Month ***

INSULIN ± Other Agent(s) [6]

A1C 7.6 - 9.0%

Dual Therapy [9]

MET	+	GLP-1 or DPP4 [1,10] or TZD [2]
		SU or Glinide [4,5]

2 – 3 Month ***

Triple Therapy

MET	+	GLP-1 or DPP4 [1]	+ TZD [2]
		GLP-1 Or DPP4 [1]	+ SU [7]
		TZD [2]	

INSULIN ± Other Agent(s) [6]

2 3 Month ***

INSULIN ± Other Agents) [6]

A1C > 9.0%

Drug Naive *Under Treatment*

Symptoms *No Symptoms*

MET	+	GLP-1 or DPP4 [1]	± SU [7]	INSULIN ± Other Agent(s) [6]
		TZD [2]		
		GLP-1 or DPP4 [1]	± TZD [2]	

* May not be appropriate for all patients

** For patients with diabetes and A1C < 6.5% pharmacologic Rx may be considered

*** If A1C goal not achieved safely

1. DPP4 if ↑ PPG and ↑ FPG or GLP-1 If ↑↑ PPG
2. TZD if metabolic syndrome and/or nonalcoholic fatty liver disease (NAFLD)
3. AGI if ↑ PPG
4. Glinide if ↑ PPG or SU if ↑FPG
5. Low-dose secretagogue recommended
6. a) Discontinue insulin secretagogue with multidose insulin
   b) Can use pramlintide with prandial insulin
7. Decrease secretagogue by 50% when added to GLP-1 or DPP4
8. If A1C < 8.5% combination Rx with agents that cause hypoglycemia should be used with caution
9. If A1C > 8.5% in patients on Dual Therapy, Insulin should be considered
10. GLP-1 not approved for initial combination Rx

2010 ADA Debate
Will DPP-4 inhibitor replace Sulfonylurea?

NO

David R. Matthews, FRCP (Oxford Center for Diabetes, Endocrinology, and Metabolism, Oxford, UK) believes DPP-4 inhibitors will *not* replace sulfonylureas. While he readily admitted that DPP-4 inhibitors are useful agents with many advantages over sulfonylureas, he firmly believes sulfonylureas are a proven and safe therapy for type 2 diabetes. While the UGDP trial initially raised questions regarding the safety of SFUs, the UKPDS trial was specifically designed to better understand the long-term safety of these agents. Dr. Matthews referenced the strong evidence base of the use of sulfonylureas, which include long-term primary, secondary, and epidemiological studies. While he mentioned the lack of outcomes trials, Merck and BMS/AZ are both conducting such trials, as required by the FDA's guidance for diabetes drugs. He concluded by stating that DPP-4 inhibitors are unlikely to have a "cost or safety profile so superior that sulfonylureas will be relegated to history."

메트포르민으로 조절이 되지 않는 제2형 당뇨병 환자에서 아마릴®-M정의 조기 복합 요법과 메트포르민의 단일 증량 요법의 유효성 및 안전성을 비교 평가하기 위한 공개, 비교, 무작위배정, 병행군, 다기관 임상시험

A multicenter, randomized, parallel-group, open study to compare the efficacy and safety of early combination therapy with Amaryl®-M to Metformin HCl up-titration in Type 2 DM patients inadequately controlled on Metformin HCl

Data on file – Handok Pharm.

STUDY OVERVIEW

I. Study Objective
II. Inclusion/Exclusion Criteria
III. Study Design
IV. Titration Algorithm

Study Objective

메트포르민으로 조절이 되지 않는 제 2형 당뇨병 환자를 대상으로 아마릴®-M 정의 조기 복합 요법이 메트포르민의 단일 증량 요법에 비해 A1c의 변화가 우월함을 보여주기 위함이다.

Data on file – Handok Pharm.

Efficacy Variables

- **Primary Endpoint**
  - T0부터 M10/중도탈락 시까지 A1c 변화
- **Secondary Endpoints**
  - T0부터 M10/중도탈락 시까지 FPG, PPG2hr의 변화
  - M10/중도탈락 시 A1c 및 FPG에 대한 반응율

Data on file – Handok Pharm.

Safety Variables

- 저혈당의 발생빈도
  - 증상 있는 저혈당 (symptomatic hypoglycemia)
  - 중증 저혈당 (severe hypoglycemia)
- 이상반응
- 임상실험실검사 결과
  - Hematology (RBC, WBC, Hb, Hct, Platelet)
  - Biochemistry (BUN, Cr, Na, K, ALT/AST, Total-Cholesterol, LDL, HDL, Triglyceride)
  - Urinalysis (Protein, Glucose, Microscopic(WBC&RBC))
  - Urine Pregnancy Test
- 활력징후 및 신체검사

Inclusion Criteria

- 30세 ~ 75세의 남녀
- 제 2형 당뇨병으로 진단 받은 기간이 적어도 3개월 이상
- 최소 4주간 500 ≤ 메트포르민 ≤1000mg 단일 요법으로 치료 받은 환자
- 7% ≤ A1c ≤ 10%
- 21kg/m^2 ≤ BMI ≤ 40kg/m^2
- 임상시험절차 수행 전에 동의서에 서명
- SMBG 측정 후 결과를 피험자 일지에 기록할 능력과 의지가 있는 환자

Data on file – Handok Pharm.

Exclusion Criteria

- 스크리닝 전 3개월 이내에 Diabetic ketoacidosis, Hyperosmolar nonketotic coma 등과 같은 급성 대사성 합병증
- 스크리닝 전 4주 이내에 메트포르민 이외의 당뇨병 치료제의 복용, TZD의 경우 8주
- 시험 중 임상시험계획서 상의 병용금기약물의 투여가 예상되는 경우
- 임상적으로 의미 있는 신질환 또는 간질환
  - 신질환: Serum Creatinine > 1.5mg/dl(남), > 1.4mg/dl(여)
  - 간질환: ALT/AST > 2 x UNL
- 급성 신기능 변화를 야기할 수 있는 방사선 요오드 조영 물질의 정맥내 투여를 받고 있거나 임상시험 기간 중에 받을 것으로 예상되는 피험자
- 임상적으로 의미 있는 비정상적인 임상실험실 검사 결과 또는 시험의 완료나 결과에 영향을 미칠 수 있는 모든 의학적인 상태
- 임산부 또는 수유부
- 약물 또는 알코올 남용 병력
- 추적 관찰 방문에 비협조적인 경험이 있는 환자
- 글리메피리드, 메트포르민에 대한 과민 반응이 알려진 환자
- 수면 패턴이 일정하지 않은 환자(예: 야간 업무 종사자)
- 임상시험 참여 전 3개월 이내에 임상시험용 의약품으로 치료받은 환자
- 기타: 본 임상시험에 참여한 경험이 있는 환자

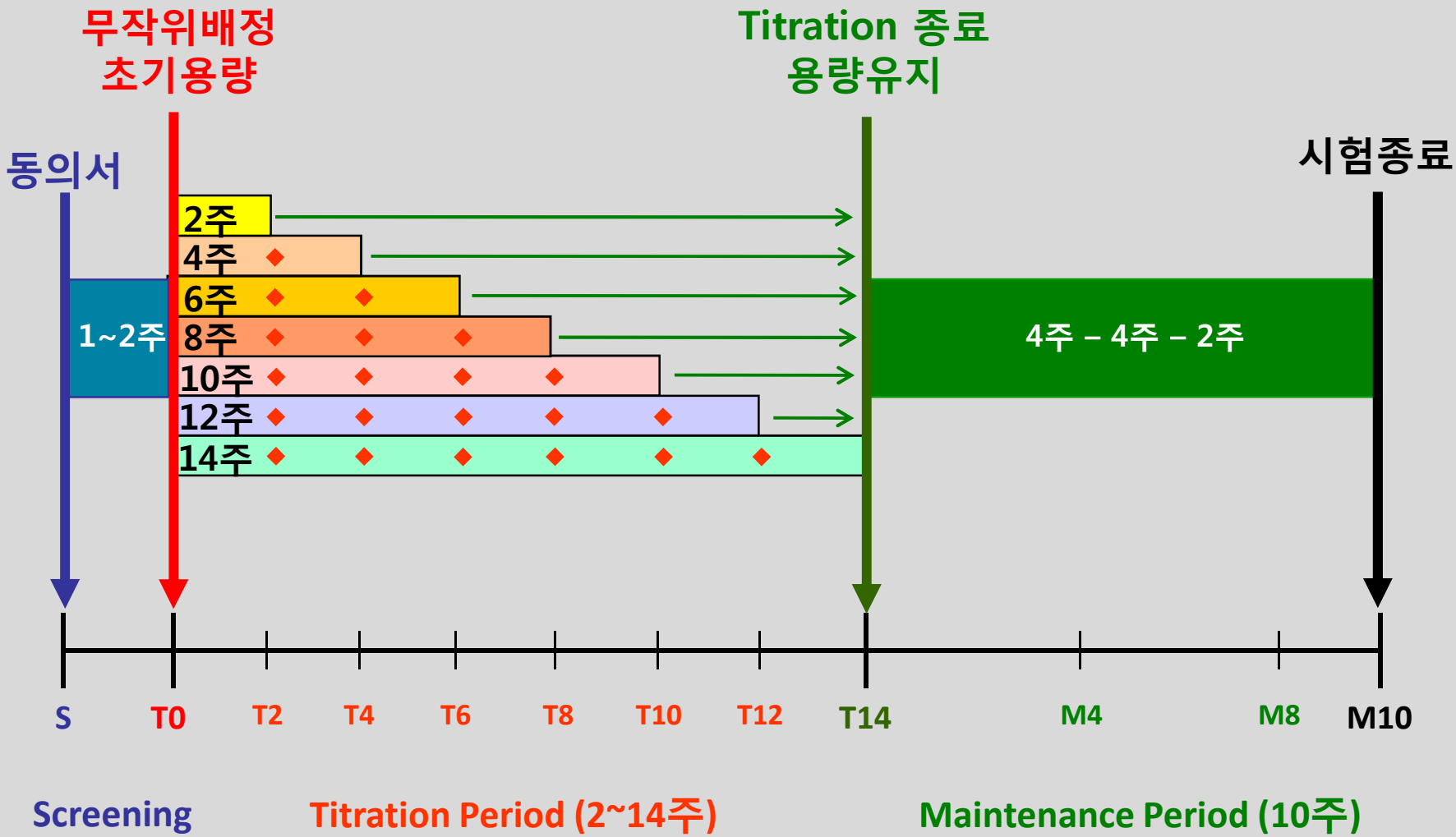
Study Design (1)

- **Target No. of subjects**
  - 무작위배정 피험자: 192명 (각 군당 96명) ➔ 탈락율 15% 예상
  - 평가 가능한 피험자: 162명 (각 군당 81명)
- **Study Period**
  - Screening 1~2주
  - Titration 2~14주 + Maintenance 10주 (총 최소 12~ 최대 24주)
- **Treatment group (Initial dose)**
  - 아마릴®-M 2/500mg: 1/250mg 1정 1일 2회 아침 및 저녁
  - 다이아벡스® 1000mg : 500mg 1정 1일 2회 아침 및 저녁

  → 식사와 함께 경구 투여

Data on file – Handok Pharm.

Study Design (2)



Data on file – Handok Pharm.

Study Drug

	Amaryl® - M	Diabex
Active Drug	Glimepiride/Metformin HCl	Metformin HCl
Formulation	Film coated tablet	
Usage	Twice a day with meal	
Dosage	2/500mg ~ 8/2000mg	1000mg ~ 2000mg
	Dose titration every 2 weeks	
Manufacturer	㈜한독약품	㈜대웅제약

Data on file – Handok Pharm.

Titration Algorithm

SMBG < 80 mg/dL의 증상 있는 저혈당이 2회 연속 나타나지 않고 중증의 저혈당이 없는 경우	평균 SMBG ≥200 mg/dL	아마릴®-M 2/500mg 증량(2단계) 다이아벡스® 500mg 증량(2단계)
	140 ≤평균 SMBG < 200 mg/dL	아마릴®-M 1/250mg 증량(1단계) 다이아벡스® 250mg 증량(1단계)
	80 ≤평균 SMBG < 140 mg/dL	이전 용량 유지
	평균 SMBG < 80 mg/dL	아마릴®-M 1/250mg 감량(1단계) 다이아벡스® 250mg 감량(1단계)
SMBG < 80 mg/dL의 증상 있는 저혈당이 2회 연속 나타난 경우 또는 중증의 저혈당이 있는 경우		아마릴®-M 1/250mg 감량(1단계) 다이아벡스® 250mg 감량(1단계)

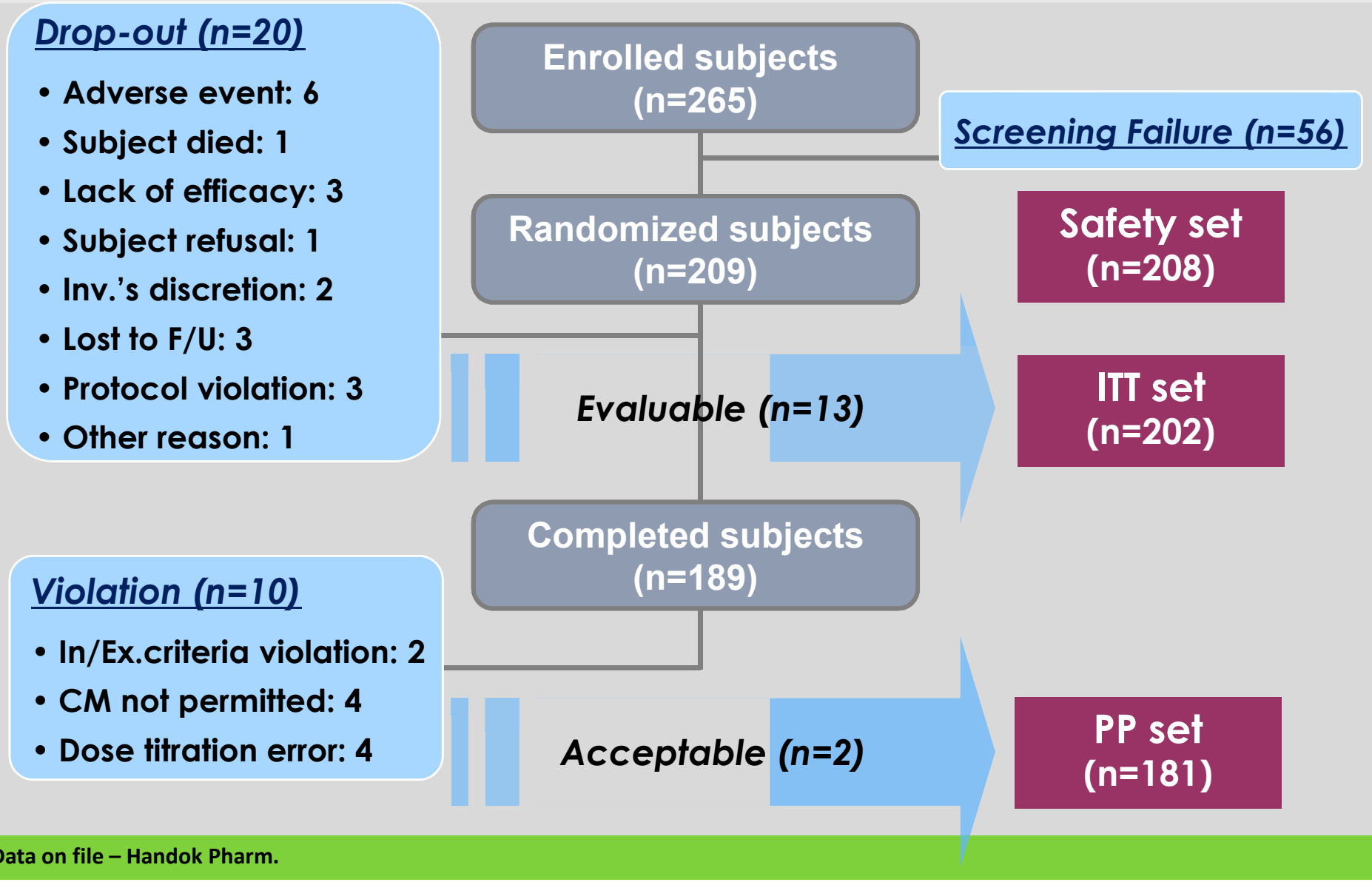
Data on file – Handok Pharm.

STUDY RESULTS

I. Study Results

II. Discussion

Patient Disposition (ITT & PP)



Data on file – Handok Pharm.

Early Study Termination

Reason	Amaryl®- M (n=101)		Metformin (n=108)	
	N	%	N	%
Adverse event	3	3.0	3	2.8
Subject died	1	1.0	0	0
Lack of efficacy	0	0	3	2.8
Subject refusal	0	0	1	0.9
Inv.'s discretion	1	1.0	1	0.9
Lost to F/U	0	0	3	2.8
Protocol violation	0	0	3	2.8
Other reason	1	1.0	0	0
Total	6	5.9	14	13.0

Data on file – Handok Pharm.

Analysis set

Reason	Amaryl®- M (n=101)	Metformin (n=108)	Total (n=209)
Safety set	100	108	208
Full anaysis set(ITT)	99	103	202
Per-Protocol set(PP)	90	91	181

Data on file – Handok Pharm.

Baseline Characteristics

Variables	Statistic	Amaryl®- M (n=101)	Met. (n=108)	Total (n=209)
Age (years)	Mean±SD	55.2±8.4	56.1±9.6	55.7±9.0
Gender(male/female)	%	51.5/48.5	47.2/52.8	49.3/50.7
Weight (kg)	Mean±SD	66.5±10.6	66.9±12.1	66.7±11.4
Height (cm)	Mean±SD	161.4±9.1	161.0±9.3	161.2±9.2
BMI (kg/m^2)	Mean±SD	25.5±3.5	25.7±3.2	25.6±3.3
Duration of diabetes	Mean±SD	4.4±4.3	4.7±4.7	4.6±4.5
Age at onset of diabetes	Mean±SD	51.2±8.5	51.8±8.7	51.5±8.6

No statistical differences.

Data on file – Handok Pharm.

Medical History- Diabetic Diseases

• Any previous diabetic disease/surgery

	Amaryl®- M (n=101)	Met. (n=108)	Total (n=209)
	5(5.0)	5(4.6)	10(4.8)
Diabetic retinopathy	1	1	2
Diabetic gastropathy	1	0	1
Gestational diabetes	1	0	1
Diabetic neuropathy	0	1	1
Diabetic nephropathy	0	1	1
Proteinuria	0	1	1
Cataract op.	0	1	1
Debridement	1	0	1
Haemorrhoid op.	1	0	1
Skin graft	1	0	1

• Any concomitant diabetic disease/surgery

	Amaryl®- M (n=101)	Met. (n=108)	Total (n=209)
	23(22.8)	34(31.5)	57(27.3)
Diabetic neuropathy	5	16	21
Dyslipidaemia	11	9	20
Diabetic retinopathy	5	5	10
Microalbuminuria	3	5	8
Diabetic nephropathy	1	2	3
Hyperlipidaemia	1	1	2
Neuropathy peripheral	1	1	2
Angina pectoris	0	1	1
Retinal artery occlusion	0	1	1
Retinopathy hypertensive	0	1	1
Hepatic steatosis	1	0	1
Diabetic foot infection	1	0	1
Pollakiuria	0	1	1
Proteinuria	1	0	1
Erectile dysfunction	1	0	1
Cataract operation	1	0	1

Data on file – Handok Pharm.

Medical History- Relevant Disease

• **Any previous relevant disease/surgery**

	Amaryl®-M (n=101)	Met. (n=108)	Total (n=209)
	48 (47.5)	52 (48.1)	100 (47.8)
Surgical & medical procedures	25	23	48
GI disorders	7	12	19
Infections & infestations	7	7	14
Nervous sys. disorders	6	8	14

* Relevant disease more than 5%.

• **Any concomitant relevant disease/surgery**

	Amaryl®-M (n=101)	Met. (n=108)	Total (n=209)
	80 (79.2)	87 (80.6)	167 (79.9)
Metabolism & nutrition disorders	37	38	75
Vascular disorders	49	42	91
Musculoskeletal & connective tissue disorders	15	12	27
Hepatobiliary disorders	10	17	27
Gastrointestinal disorders	11	11	22

* Relevant disease more than 10%.

Data on file – Handok Pharm.

Previous/ Concomitant Medication

• **Previous medication**

	Amaryl®-M (n=101)	Met. (n=108)	Total (n=209)
	100 (99.1)	108 (100.0)	208 (99.5)
Alimentary tract & metabolism	100	108	208
Cardiovascular system	9	9	18
Nervous system	2	6	8
Musculoskeletal system	2	5	7

* Previous medication more than 3%.

• **Concomitant medication**

	Amaryl®-M (n=101)	Met. (n=108)	Total (n=209)
	89 (88.1)	97 (89.8)	186 (89.0)
Cardiovascular system	77	78	155
Blood & blood forming organs	54	57	111
Alimentary tract & metabolism	38	41	79
Nervous system	14	21	35
Musculoskeletal system	15	19	34
Respiratory system	12	14	26

* Concomitant medication more than 10%.

Data on file – Handok Pharm.

Previous Medication: Metformin

	Amaryl®-M (n=101)	Metformin (n=108)
Duration (day)	262.3	275.1
Dosage (mg)	826.5	841.2

Data on file – Handok Pharm.

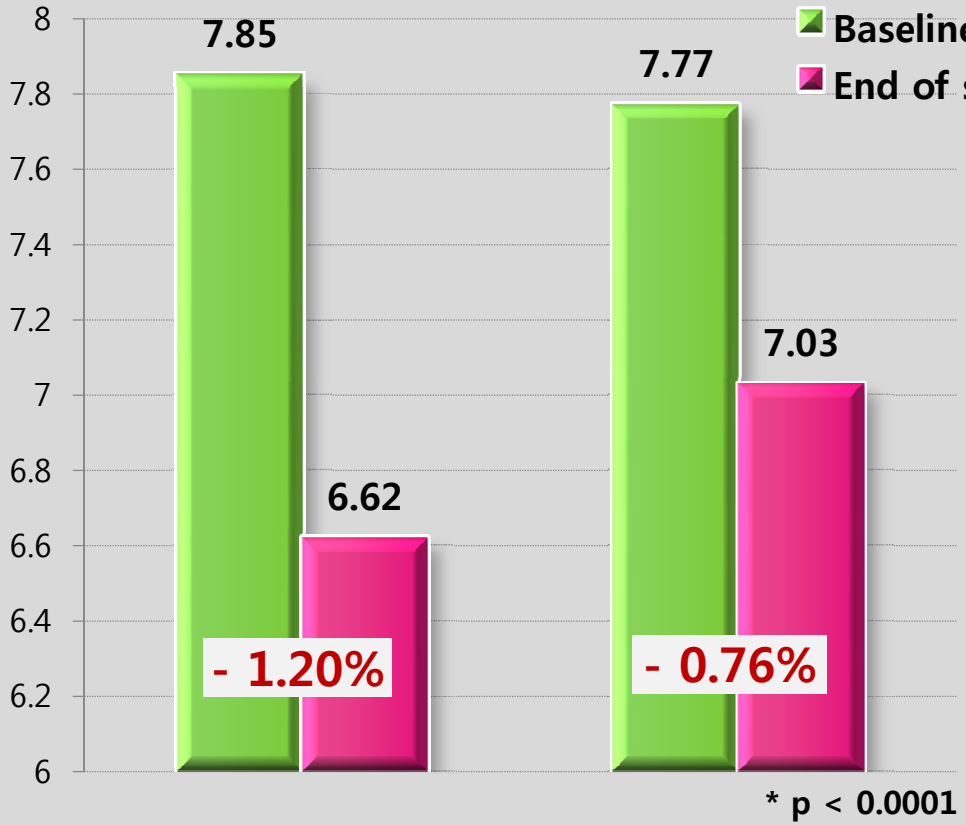
Maintenance Dose

	Amaryl®-M (n=101)	Metformin (n=108)
Morning (mg)	1.34/335	668.4
Evening (mg)	1.17/292	644.7
Total (mg/day)	2.51/627	1313.1

Data on file – Handok Pharm.

Change in HbA1c

- baseline to end of study (ITT set)

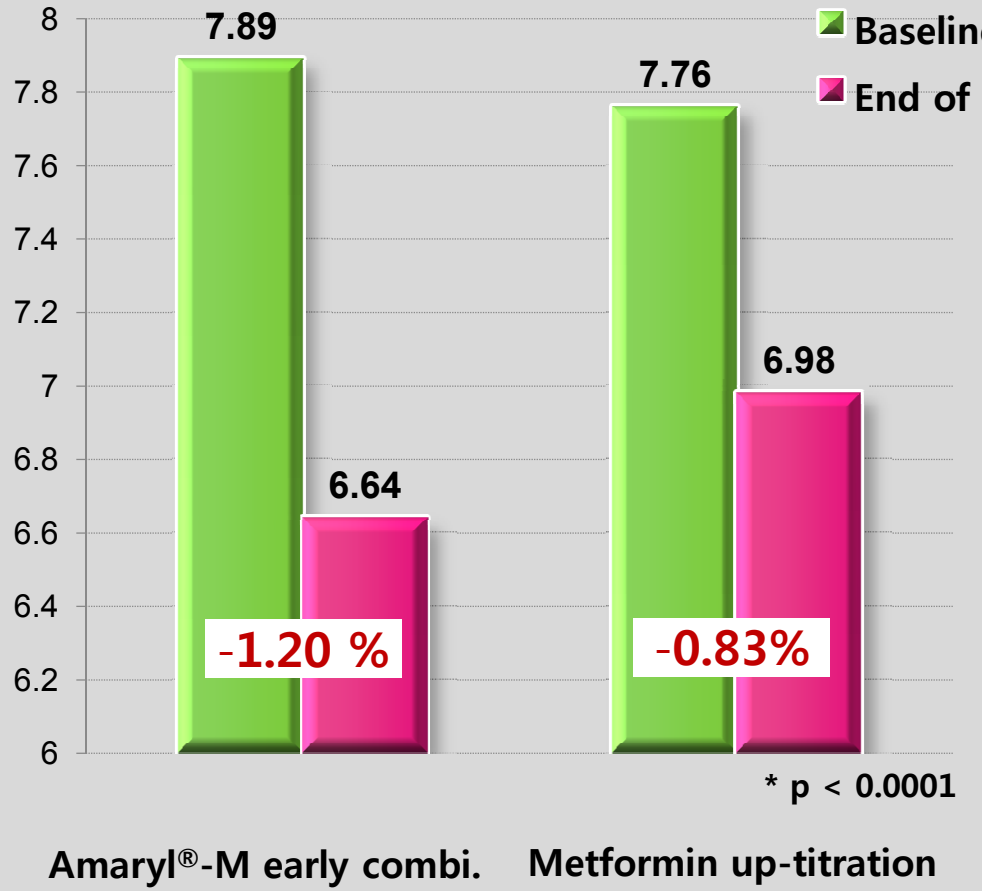


	Amaryl®-M (n=99)	Met. (n=103)
Baseline (mean)	7.85	7.77
End of study (mean)	6.62	7.03
Change (mean)	-1.23	-0.74
Change (adjusted mean)	-1.20	-0.76
Difference (adjusted means)	-0.44	
95% CI	(-0.61, -0.26)	
p-value (ANCOVA)	<0.0001	

Data on file – Handok Pharm.

Change in HbA1c

- baseline to end of study (PP set)

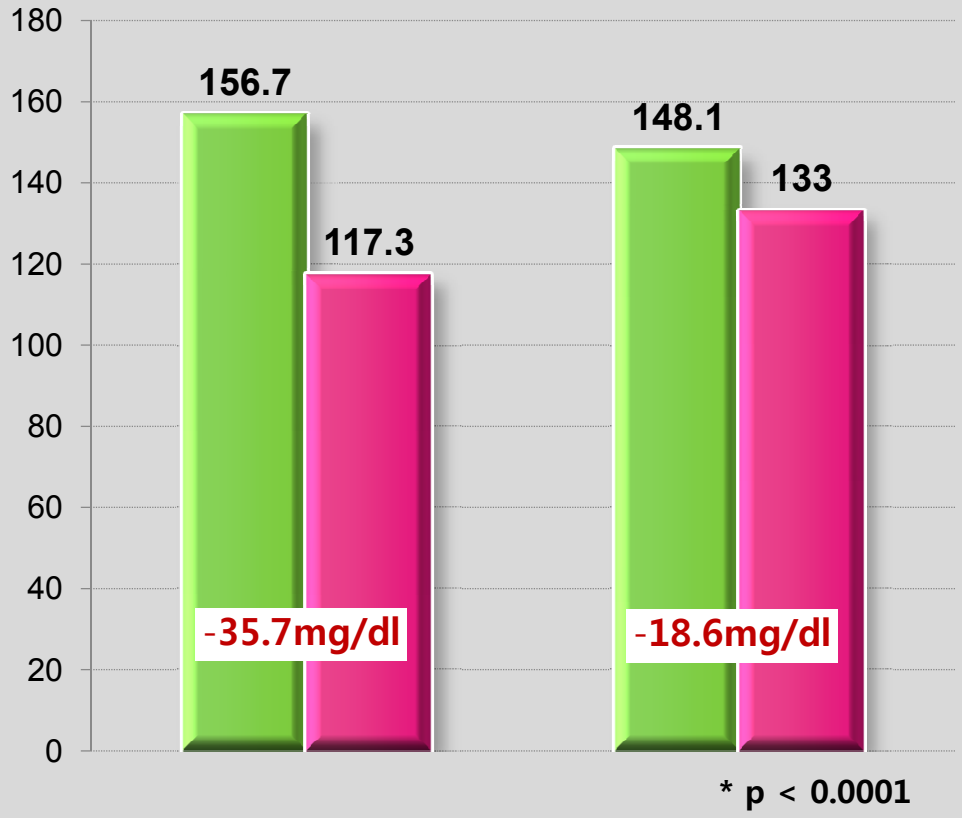


	Amaryl®-M (n=99)	Met. (n=103)
Baseline (mean)	7.89	7.76
End of study (mean)	6.64	6.98
Change (mean)	-1.25	-0.78
Change (adjusted mean)	-1.20	-0.83
Difference (adjusted means)	-0.38	
95% CI	(-0.56, -0.20)	
p-value (ANCOVA)	<0.0001	

Data on file – Handok Pharm.

Change in FPG

- baseline to end of study (ITT set)

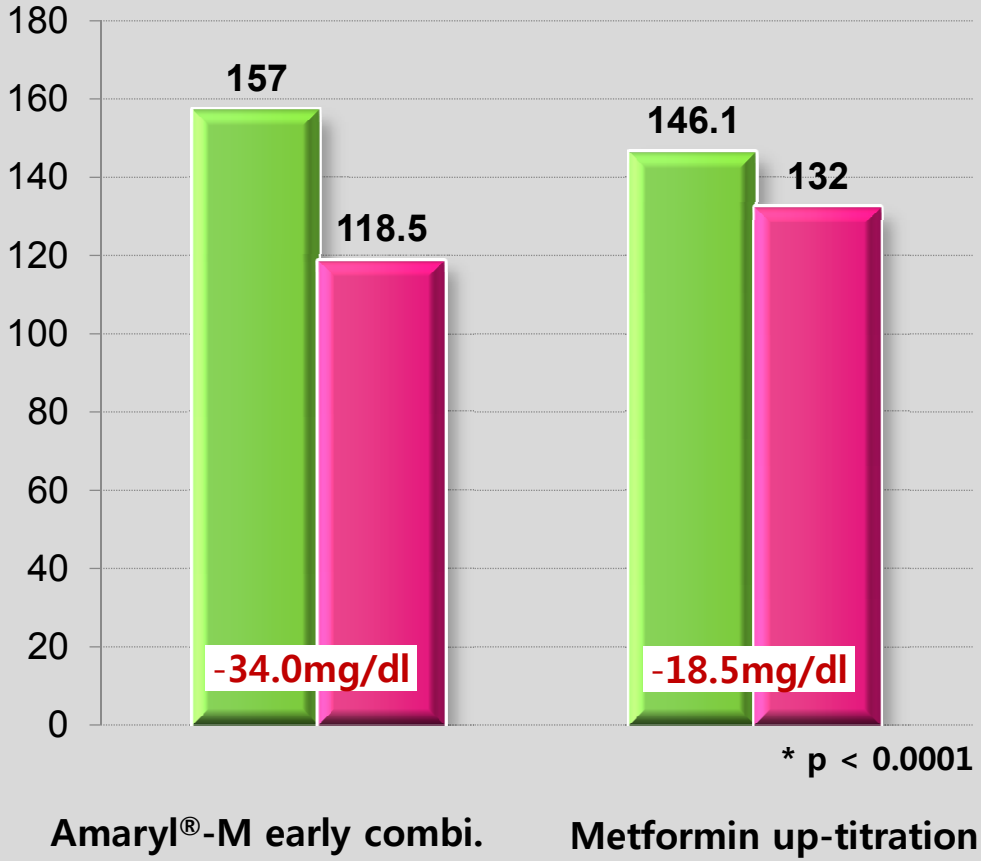


	Amaryl®-M (n=98)	Met. (n=103)
Baseline (mean)	156.7	148.1
End of study (mean)	117.3	133.0
Change (mean)	-39.4	-15.1
Change (adjusted mean)	-35.7	-18.6
Difference (adjusted means)	-17.1	
95% CI	(-22.8, -11.5)	
p-value (ANCOVA)	<0.0001	

Data on file – Handok Pharm.

Change in FPG

- baseline to end of study (PP set)

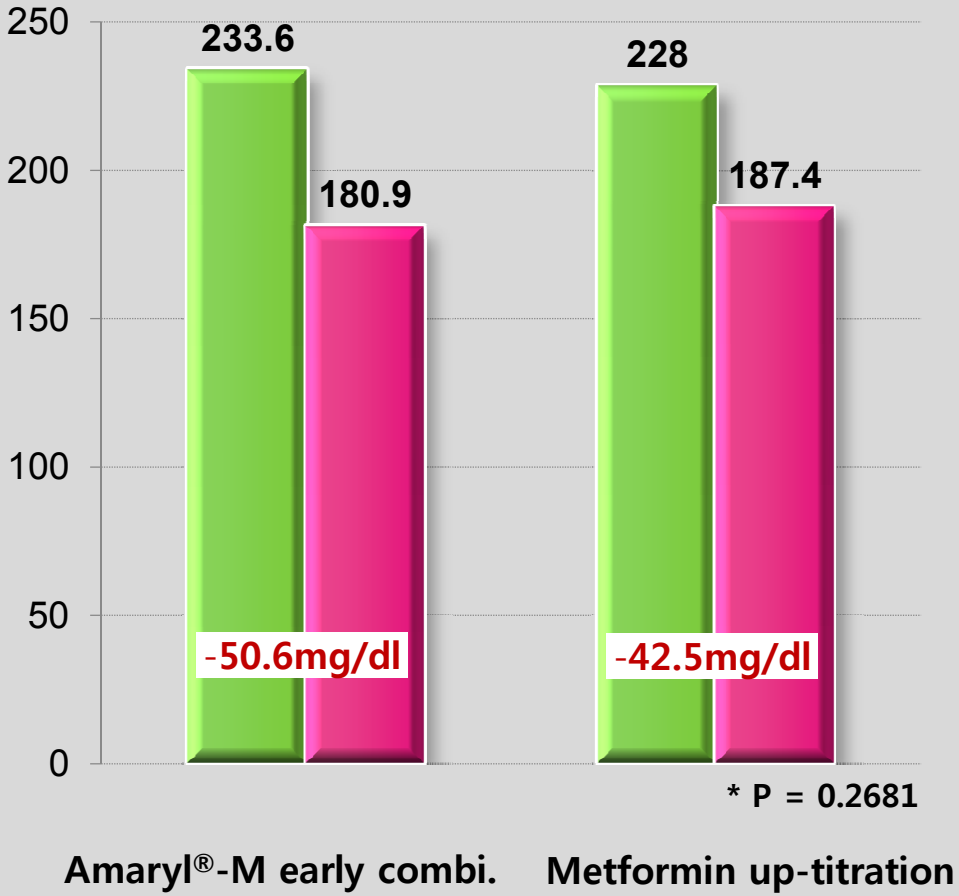


	Amaryl®-M (n=90)	Met. (n=91)
Baseline (mean)	157.0	146.1
End of study (mean)	118.5	132.0
Change (mean)	-38.5	-14.1
Change (adjusted mean)	-34.0	-18.5
Difference (adjusted means)	-15.5	
95% CI	(-21.3, -9.8)	
p-value (ANCOVA)	<0.0001	

Data on file – Handok Pharm.

Change in PPG2hr

- baseline to end of study (ITT set)

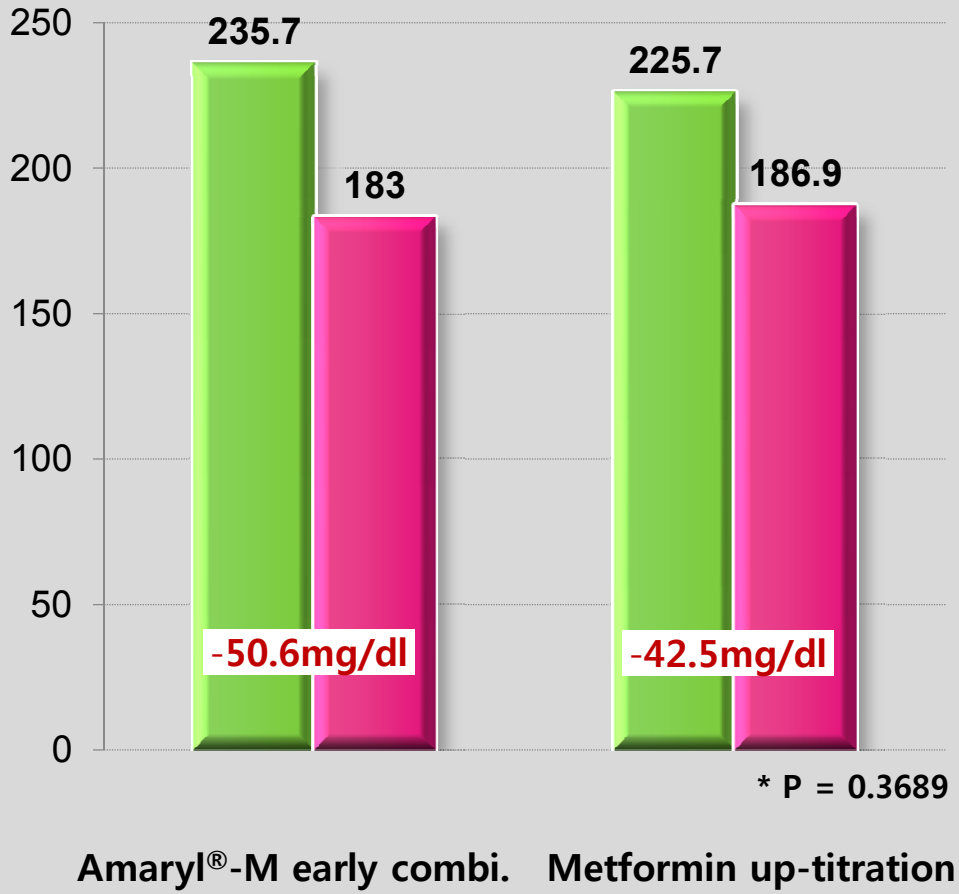


	Amaryl®-M (n=97)	Met. (n=102)
Baseline (mean)	233.6	228.0
End of study (mean)	180.9	187.4
Change (mean)	-52.6	-40.6
Change (adjusted mean)	-50.6	-42.5
Difference (adjusted means)	-8.1	
95% CI	(-22.4, 6.3)	
p-value (ANCOVA)	0.2681	

Data on file – Handok Pharm.

Change in PPG2hr

- baseline to end of study (PP set)



	Amaryl®-M (n=88)	Met. (n=90)
Baseline (mean)	235.7	225.7
End of study (mean)	183.0	186.9
Change (mean)	-52.7	-38.8
Change (adjusted mean)	-49.2	-42.2
Difference (adjusted means)	-7.0	
95% CI	(-22.3, 8.3)	
p-value (ANCOVA)	0.3689	

Data on file – Handok Pharm.

Response rate at study end (ITT set)

		Amaryl®-M	Metformin	p-value
HbA1c response (HbA1c <7%)	N n(%)	99 74(74.7)	103 48(46.6)	<0.0001
FPG response (FPG <140mg/dl)	N n(%)	98 83(84.7)	103 67(65.1)	0.0013
Combined response I (HbA1c <7% or FPG <140mg/dl)	N n(%)	99 88(88.9)	103 76(73.8)	0.0064
Combined response II (HbA1c <7% & FPG <140mg/dl)	N n(%)	98 69(70.4)	103 39(37.9)	<0.0001

Data on file – Handok Pharm.

Response rate at study end (PP set)

		Amaryl®-M	Metformin	p-value
HbA1c response (HbA1c <7%)	N n(%)	90 66(73.3)	91 42(46.2)	0.0002
FPG response (FPG <140mg/dl)	N n(%)	90 75(83.3)	91 62(68.1)	0.0168
Combined response I (HbA1c <7% or FPG <140mg/dl)	N n(%)	90 79(87.8)	91 69(75.8)	0.0410
Combined response II (HbA1c <7% & FPG <140mg/dl)	N n(%)	90 62(68.9)	91 35(38.5)	<0.0001

Data on file – Handok Pharm.

Hypoglycemia Definition

[증상 있는 저혈당]

- 저혈당으로 인해 임상적 증상을 느끼고 경구용 탄수화물 투여 후 즉각적으로 회복이 가능한 경우
- 증상은 없으나 혈당 수치가 60mg/dL 미만인 경우, 시험자의 판단 하에 '저혈당' 으로 기록(증례기록서 '저혈당'페이지)

[중증 저혈당]

- 저혈당으로 인해 타인의 도움을 필요로 하는 임상적 증상을 느끼며 다음 중 하나를 동반하는 경우
  - 혈당 수치가 < 36mg/dL 일 때 또는,
  - 탄수화물 경구 투여, 포도당 정맥 투여 또는 글루카곤 피하 투여 후 빠르게 회복되는 증상

[야간 저혈당]

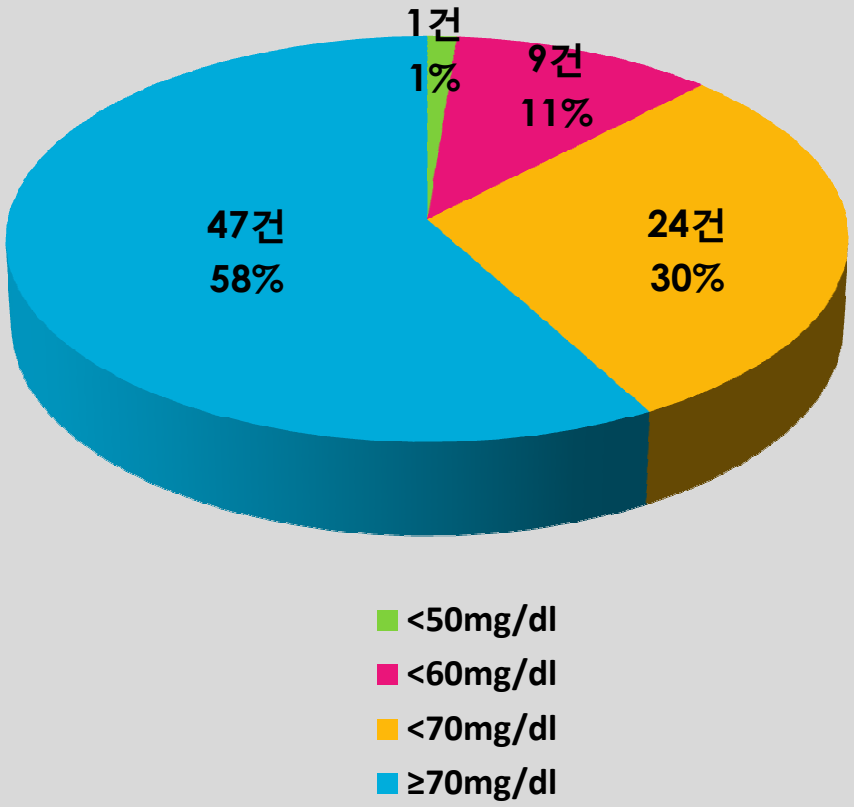
- 취침부터 아침 기상시간까지 수면 중에 발생한 저혈당

Hypoglycemia

	Amaryl®-M (n=100)		Metformin (n=108)		Total (n=208)		p-value (CMH)
	n(%)	event	n(%)	event	n(%)	event	
Any hypoglycemia	41(41.0)	100	6(5.6)	6	47(22.6)	106	<0.0001
titration period	19(19.0)	31	3(2.8)	3	22(10.6)	34	
maintenance period	29(29.0)	68	2(1.9)	2	31(14.9)	70	
Symptomatic hypoglycemia	39(39.0)	96	4(3.7)	4	43(20.7)	100	<0.0001
Nocturnal hypoglycemia	2(2.0)	2	0	0	2(1.0)	2	0.1484
Serious hypoglycemia	0	0	0	0	0	0	

Data on file – Handok Pharm.

Hypoglycemia Portion



	Amaryl®-M (n=81)	Metformin (n=4)	Total (n=85)
	n(%)	n(%)	n(%)
<50 mg/dl	1(1.2)	0(0.0)	1(1.17)
<60 mg/dl	9(11.1)	1(25.0)	10(11.7)
<70 mg/dl	24(29.6)	1(25.0)	25(29.4)
≥70 mg/dl	47(58.0)	2 (50.0)	49(57.6)

Data on file – Handok Pharm.

Adverse Event - Total

- During pre-treatment period (N=208, safety set)

	n (%)	event
Any pre-treatment AE	13 (6.3)	17
Pre-treatment SAE	0	0

- During treatment period (safety set)

		Amaryl®-M (n=100)	Metformin (n=108)	p-value
Treatment-emergent AEs	n(%)	34 (34.0)	34 (31.5)	0.7678
Possibly related AEs	n(%)	5 (5.0)	8 (7.4)	0.5725
Serious AEs	n(%)	1 (1.0)	3 (2.8)	0.6225
Study discontinuation due to AEs	n(%)	0	3 (2.8)	0.2475

Data on file – Handok Pharm.

Adverse Event - TEAE

SOC	Amaryl®-M (n=100)	Metformin (n=108)	Total (n=208)
Patient with AEs	34(34.0%)	34(31.5%)	68(32.7%)
Total adverse events	45	46	91
Gastrointestinal disorders	10(10.0%)	11(10.2%)	21(10.1%)
Infections and infestations	9(9.0%)	11(10.2%)	20(9.6%)
General disorders & administration site conditions	5(5.0%)	5(4.6%)	10(4.8%)
Nervous system disorders	5(5.0%)	2(1.9%)	7(3.4%)
Musculoskeletal & connective tissue disorders	2(2.0%)	4(3.7%)	6(2.9%)
Respiratory, thoracic & mediastinal disorders	3(3.0%)	3(2.8%)	6(2.9%)
Eye disorders	3(3.0%)	1(0.9%)	4(1.9%)
Skin & subcutaneous tissue disorders	2(2.0%)	1(0.9%)	3(1.4%)
Metabolism & nutrition disorders	1(1.0%)	1(0.9%)	2(1.0%)
Vascular disorders	0	2(1.9%)	2(1.0%)
Renal & urinary disorders	0	2(1.9%)	2(1.0%)
Investigations	0	1(0.9%)	1(0.5%)
Psychiatric disorders	1(1.0%)	0	1(0.5%)
Surgical & medical procedures	1(1.0%)	0	1(0.5%)
Injury, poisoning & procedural complications	1(1.0%)	0	1(0.5%)

Data on file – Handok Pharm.

Adverse Event- Possibly related AE

PT	Amaryl®-M (n=100)	Metformin (n=108)	Total (n=208)
Patient with possibly related AEs	5(5.0%)	8(7.4%)	13(6.3%)
Total possibly related AEs	5	9	14
Abdominal pain upper	2(2.0%)	1(0.9%)	3(1.4%)
Diarrhoea	0	3(2.8%)	3(1.4%)
Nausea	1(1.0%)	2(1.9%)	3(1.4%)
Constipation	0	1(0.9%)	1(0.5%)
Gastric ulcer	1(1.0%)	0	1(0.5%)
Gastrooesophageal reflux disease	1(1.0%)	0	1(0.5%)
Asthenia	0	1(0.9%)	1(0.5%)
Anorexia	0	1(0.9%)	1(0.5%)

Data on file – Handok Pharm.

Serious Adverse Events

- **Amaryl®-M early Combination**

SAE	Preferred term	Intensity	**Relation**	Outcome
Death	Road traffic accident	Severe	**No**	Died

- **Metformin Up-titration**

SAE	Preferred term	Intensity	**Relation**	Outcome
Required or prolonged inpatient hospitalization	Chest pain	Mild	**No**	Unknown
Required or prolonged inpatient hospitalization	Interstitial lung disease	Mild	**No**	Event not resolved
Required or prolonged inpatient hospitalization	Pyrexia	Moderate	**No**	Recovered

Data on file – Handok Pharm.

Summary of Lab. Result

- Shift from baseline to study end

	Amaryl®-M early comb.		Metformin uptitration	
	기초방문에서 정상인 피험자 N	BL에서 정상이면서 종료방문에서 비정상인 피험자 n(%)	기초방문에서 정상인 피험자 N	BL에서 정상이면서 종료방문에서 비정상인 피험자 n(%)
WBC	90	6(6.7)	96	5(5.2)
RBC	74	0(0.0)	80	11(13.8)
Hematocrit	73	2(2.7)	86	8(9.3)
Hemoglobin	87	3(3.4)	89	6(6.7)
Platelet count	92	4(4.3)	98	2(2.0)
Na	98	3(3.1)	103	1(1.0)
K	97	6(6.2)	95	9(9.5)
BUN	89	6(6.7)	98	8(8.2)
Creatinine	87	1(1.1)	91	3(3.3)
AST	88	4(4.5)	92	2(2.2)
ALT	76	8(10.5)	86	4(4.7)
Total cholesterol	85	7(8.2)	83	7(8.4)
LDL	90	7(7.8)	84	7(8.3)
HDL	67	11(16.4)	63	11(17.5)
Triglyceride	70	9(12.9)	75	8(10.7)

Data on file – Handok Pharm.

Other safety data

Variables	Treatment	Mean		
		Baseline	End of study	Change
Weight [kg]	Amaryl®-M early comb. (N=97)	66.8	67.7	0.91
	Metformin uptitration (N=104)	66.9	66.2	-0.72
Systolic blood pressure [mmHg]	Amaryl®-M early comb. (N=99)	124.7	123.4	-1.32
	Metformin uptitration (N=105)	124.5	122.5	-1.93
Diastolic blood pressure [mmHg]	Amaryl®-M early comb. (N=99)	75.3	74.9	-0.36
	Metformin uptitration (N=105)	75.6	74.3	-1.30
Pulse rate [beats/min]	Amaryl®-M early comb. (N=99)	77.8	79.5	1.68
	Metformin uptitration (N=105)	77.0	77.0	-0.01

Data on file – Handok Pharm.

Conclusion

- 1차 유효성 평가는 HbA1c의 변화로 Amaryl®-M early comb.군에서의 감소량이 Metformin uptitration군에서의 감소량보다 유의하게 큰 것으로 나타났다.
- 공복혈당의 경우도, Amaryl®-M early comb.군에서의 감소량이 Metformin uptitration군에서의 감소량보다 유의하게 높은 것으로 나타났다.
- HbA1c와 공복혈당으로부터 계산되는 모든 반응율의 경우 Amaryl®-M early comb. 군에서의 반응율이 Metformin uptitration군에서의 반응률보다 유의하게 높은 것으로 나타났다.
- 전반적인 저혈당의 경우, Amaryl®-M early comb.군에서 발현율이 Metformin uptitration군에서의 발현율에 비하여 상대적으로 매우 높았으나, 혈당수치가 60mg/dl 이하인 경우는 10건, metformin군에서는 1건이 발생하였다.
- Amaryl®-M early comb.군에서 baseline 대비 0.91kg이 증가되었다.
- 이상반응의 경우, Amaryl®-M early comb.군과 Metformin uptitration군간의 통계적 유의성은 없었다.

Metformin 500-1000mg 을 사용하지만 혈당 조절이 되지 않는 환자들의 경우, metformin up-titration보다 glimepiride 저용량을 추가하는 것이 목표혈당 도달에 더 효과적이다.

Data on file – Handok Pharm.