Rediscovering the One Insulin you know:

Latest update focused on CV risk & New clinical trial

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Eun Seok Kang, MD
Yonsei University College of Medicine
Severance Hospital Diabetes Center

Disclaimer

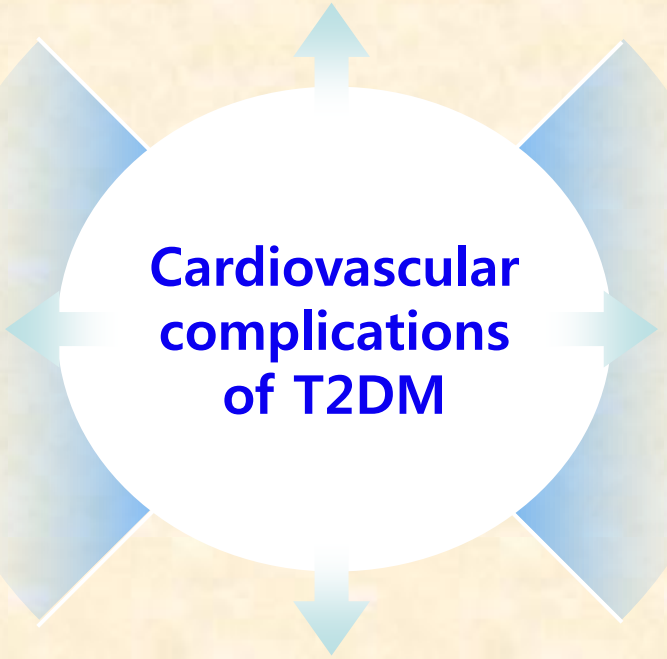
Glargine is not approved for patients with IFG or IGT.
This slide deck is provided
for scientific and medical exchanges only.

Before prescribing Glargine always refer to the prescribing information available in your country. Sanofi does not recommend the use of its products in any manner inconsistent with that described in the full prescribing information available in Korea

CONTENTS

Diabetes and Cardiovascular disease

~65% of deaths are due to CV disease



Coronary heart disease deaths ↑2- to 4-fold

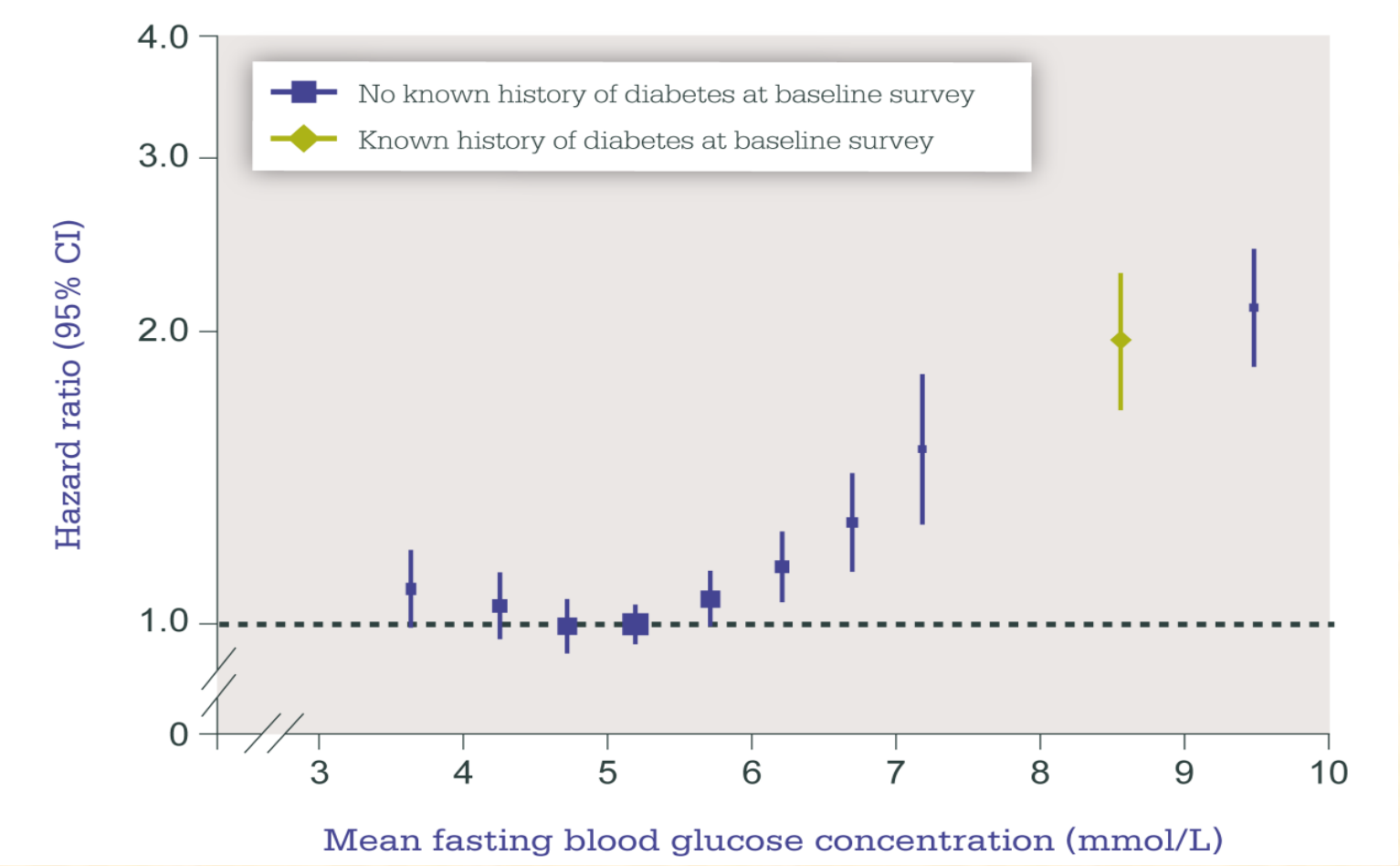
Stroke risk ↑2- to 4-fold

Heart failure ↑2- to 5-fold

Bell DSH. Diabetes Care 2003;26:2433-41.
Centers for Disease Control (CDC). www.cdc.gov.

High FPG correlates with High Risk of CHD even in non-DM Pts

- Meta-analysis of 102 prospective studies
- ~700,000 participants without prior cardiovascular disease

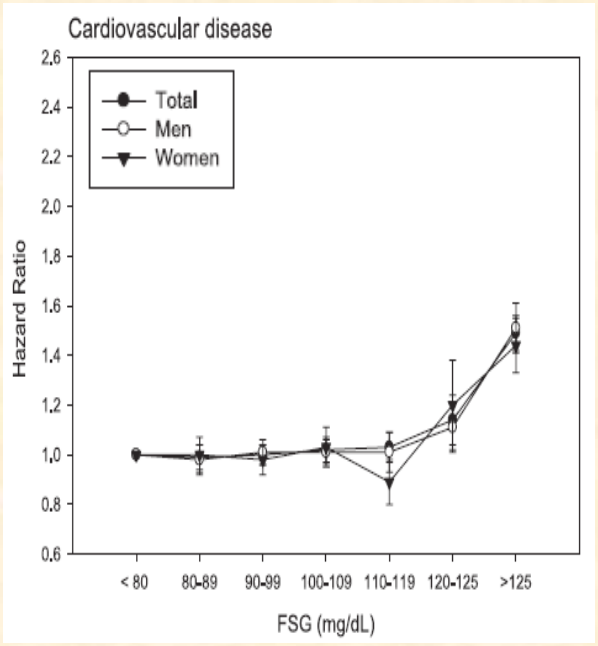


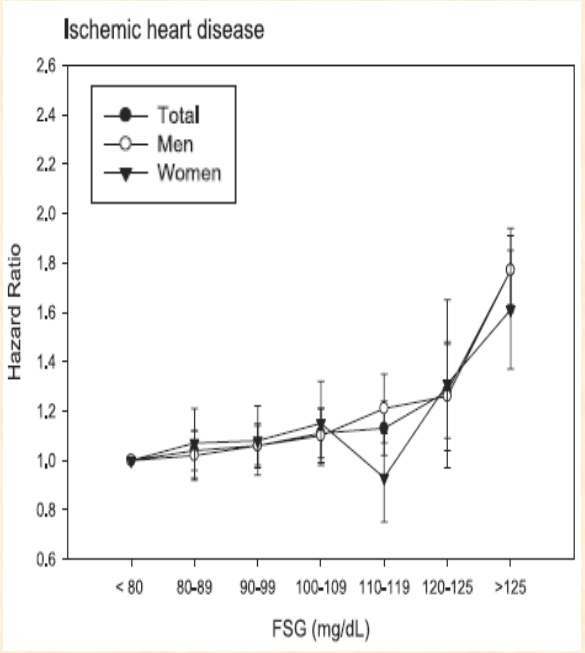
HR in figure adj. for age, smoking, BMI, SBP

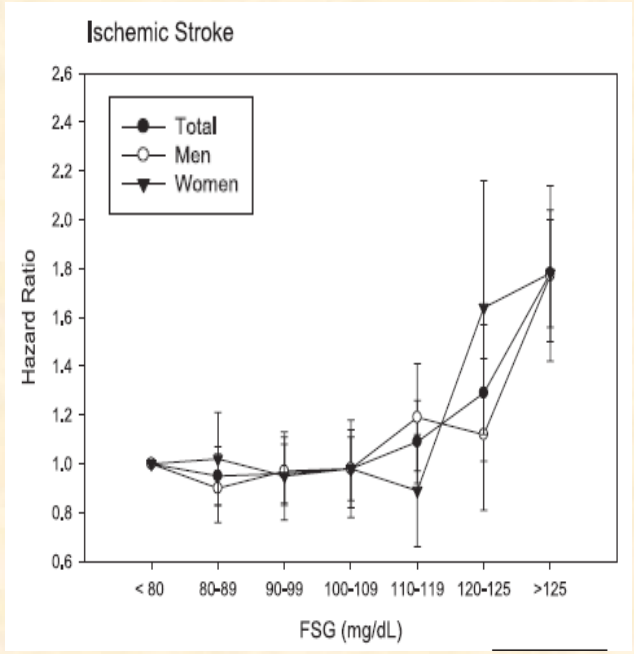
The Emerging Risk Factors Collaboration. Lancet 2010;375:2215–22.

IFG and Risk of CVD in Korean Men and Women

- The relationship between IFG and CVD or IHD among Korean men and women.
- 408,022 individuals who underwent voluntary private health examinations
- 17 centers, Followed for 10 years







- HRs (95% CIs) for the risk of CVD (top), IHD (middle), and ischemic strokes (bottom) associated with FPG in Korean men and women adjusted for age, systolic blood pressure, antihypertensive medication, LDL cholesterol, HDL cholesterol, current smoking, BMI, and family history of CVD.
- FSG; Fasting Serum Glucose

Diabetes Care 2013; 36: 328-335.

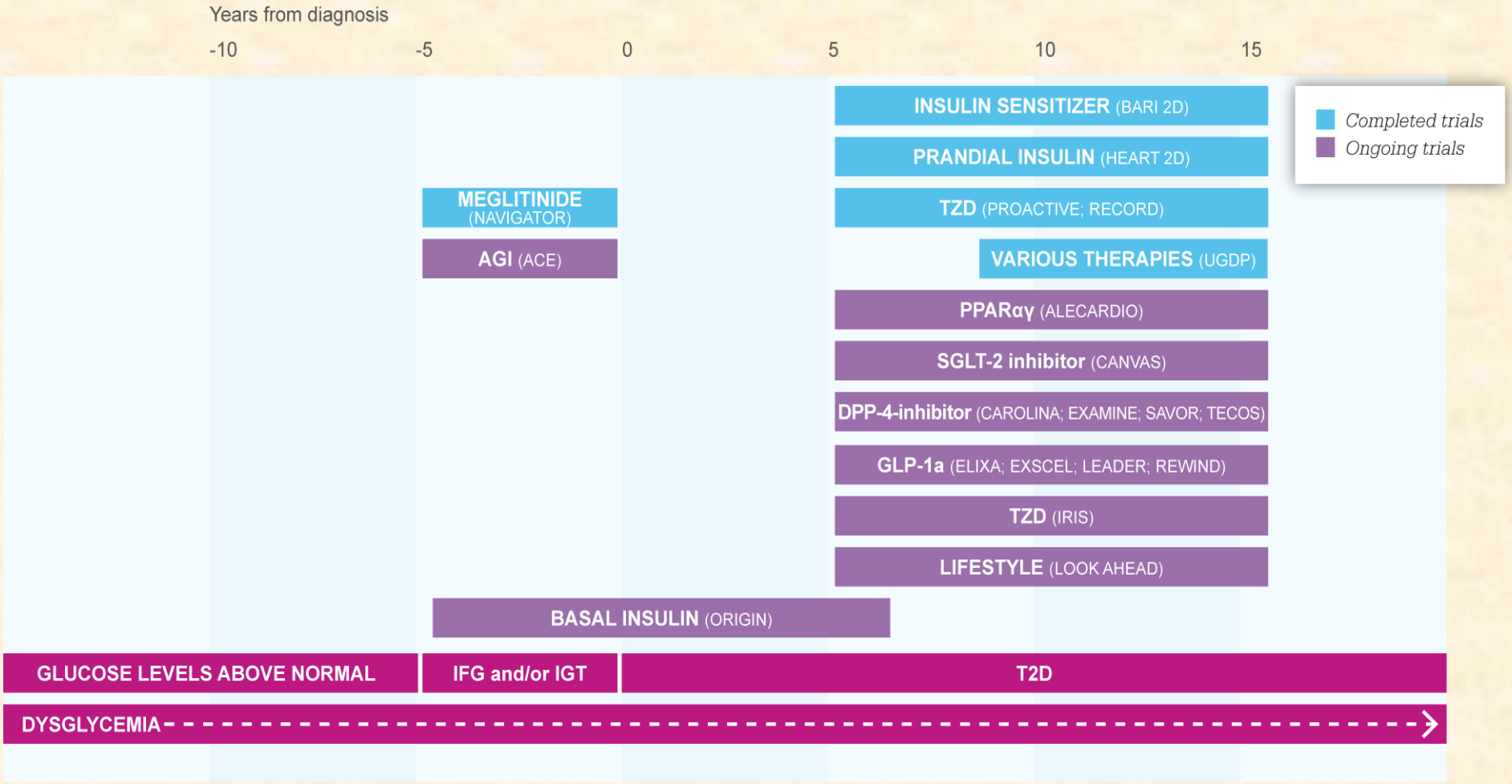
CV prevention with Insulin-Mediated Normoglycemia?

90 years uncertainty regarding insulin's role in type 2 diabetes

- Restores insulin deficit in dysglycemia
- Reduces need for pancreatic insulin so it can better buffer glucose changes
- Reduces toxic pro-oxidant effects of glucose
- Anti-inflammatory, vasodilatory & antithrombotic
- Improves endothelial repair & dysfunction
- Clues from UKPDS, DCCT & other trials

Gerstein HC, et al. Am Heart J 2008;155:26-32.

CV Outcomes Trials Evaluating Individual Treatment For Patients With Dysglycemia



The trials are shown in relation to the eligibility criteria, with respect to diabetes duration at randomization.

Adapted from Gerstein, HC Nat Rev Endocrinol 2009;5:270-275.

	Trial	Treatment(s) evaluated	Patients
Completed	BARI 2D	2x2 factorial: early vs. delayed revascularization; insulin sensitizing vs. insulin providing drug	T2D indicated for coronary revascularization
	HEART 2D	Prandial vs. basal glucose control	T2D + recent MI
	NAVIGATOR	2x2 factorial: nateglinide and/or valsartan vs. placebo (diabetes prevention)	IGT + elevated but non-diabetic FPG
	PROACTIVE	Pioglitazone vs. placebo	T2D at high CV risk
	RECORD	Rosiglitazone + SU or metformin vs. SU + metformin	T2D
	UGDP	Diet, tolbutamide, phenformin, insulin (constant dose), insulin (titrated)	T2D
Ongoing	ACE	Acarbose vs. placebo	T2D at high CV risk
	ALECARDIO	Aleglitazar vs. placebo	T2D + recent ACS
	CANVAS	Canagliflozin vs. placebo	T2D at high CV risk
	CAROLINA	Linagliptin vs. glimep	
	ELIXA	Lixisenatide vs. pla	
	EXAMINE	Alogliptin vs. placeb	
	EXSCEL	Exenatide vs. usua	
	IRIS	Pioglitazon	or TIA
	LEADER	Li ide ± standard care (CV safety)	
	LOOK AHEAD	Intensive lifestyle intervention vs. diabetes support and education	T2D
	ORIGIN	2x2 factorial: insulin glargine vs. standard care and ω-3 polyunsaturated fatty acids vs. placebo	IGT, IFG or recent diabetes
	REWIND	Dulagutide vs. placebo	T2D at high CV risk
	SAVOR-TIMI 53	Saxagliptin vs. placebo	T2D at high CV risk
	TECOS	Sitagliptin vs. placebo	T2D at high CV risk

Insulin glargine is the only insulin with CV outcome results & well-established safety profile

ORIGIN study

Outcome Reduction with an Initial Glargine Intervention (ORIGIN) Trial

ORIGIN Research Questions

In high CV risk people with IFG, IGT or early diabetes,

Does insulin glargine therapy targeting fasting normoglycemia (< 95 mg/dl) reduce CV outcomes more than standard approaches?

Gerstein HC, et al. Am Heart J 2008;155:26-32.

ORIGIN

- 40 countries, 573 sites, 12,537 patients, 6.2 years of follow-up
- 8 sites, 131 enrolled in Korea

Gerstein HC, et al. Am Heart J 2008;155:26-32.

Major Outcomes

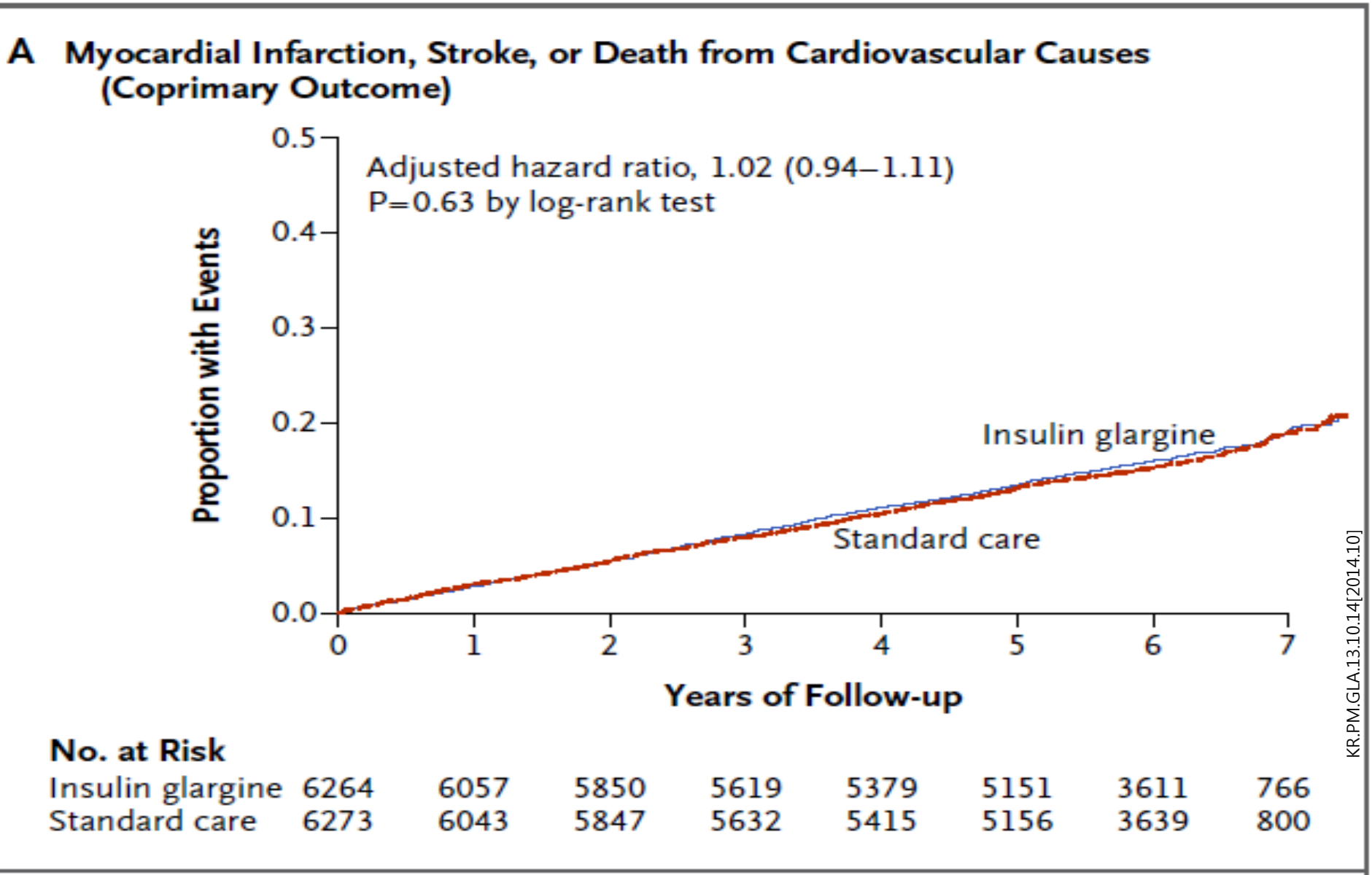
- **Co-primary outcomes**
  1. Composite of **CV Death, non-fatal MI, or non-fatal stroke**
  2. A revascularization procedure or hospitalization for heart failure.

- **Main secondary outcomes**
  1. Composite **Microvascular Outcome** (kidney or eye disease)
  2. **Development of T2DM** in people with IGT or IFG
  3. All-cause mortality

- **Other Outcomes**
  1. **Cancers**
  2. Hypoglycemia, Weight
  3. Cognition, Angina, amputation for ischemia, Erectile dysfunction, CV & other hospitalizations

Gerstein HC, et al. Am Heart J 2008;155:26-32.

Primary Outcome



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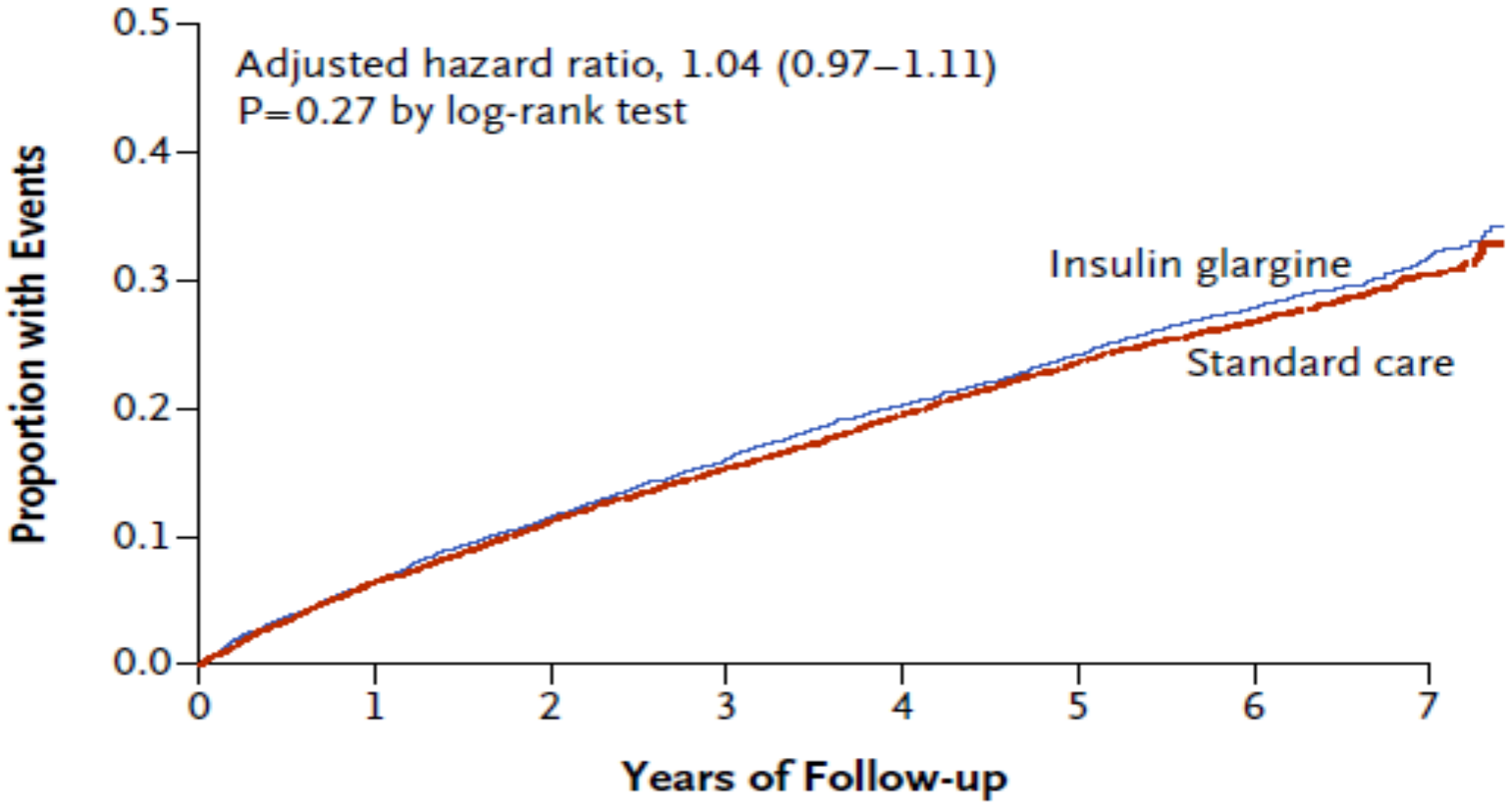
Primary Outcomes & Mortality

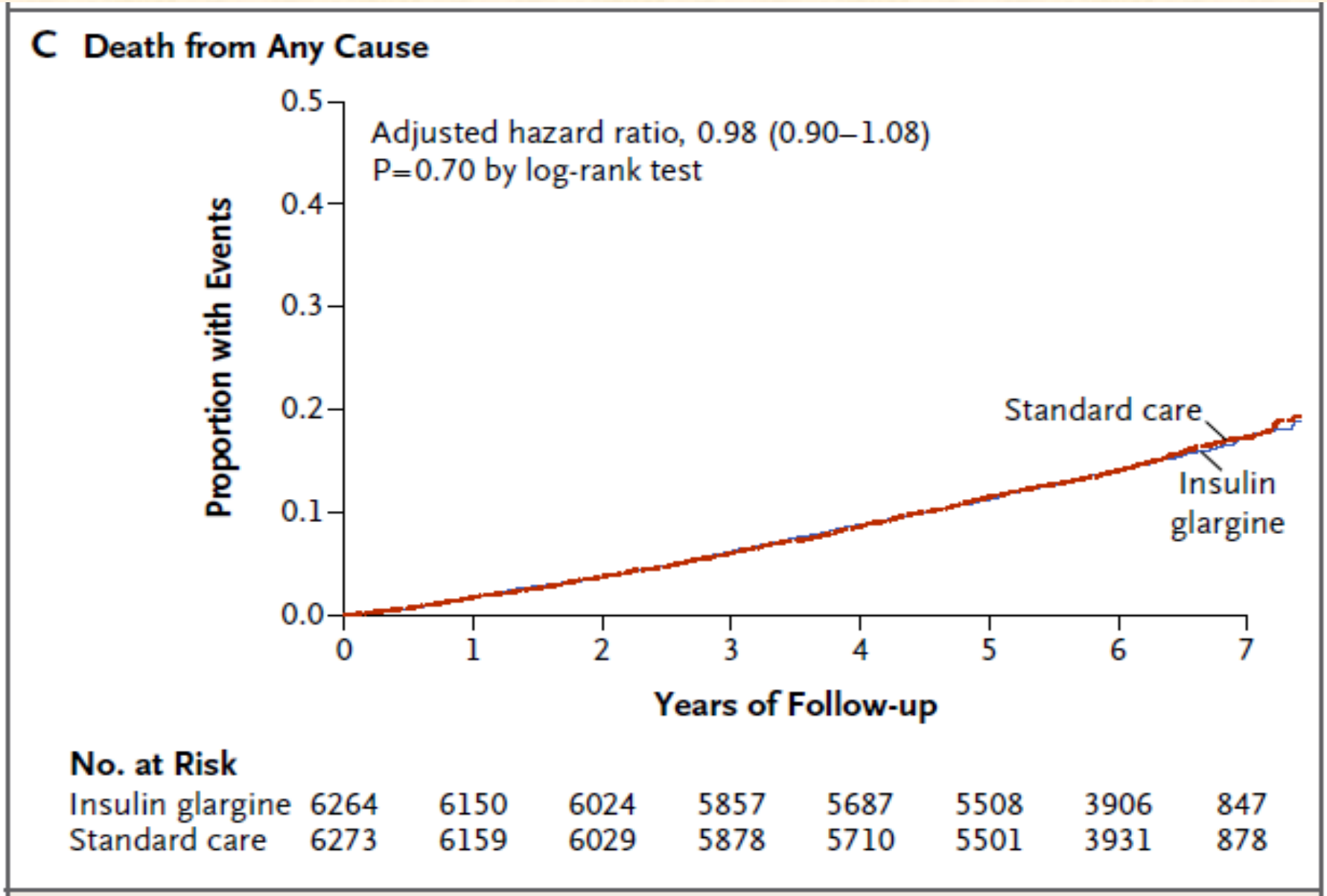
B Coprimary Outcome plus Revascularization or Hospitalization for Congestive Heart Failure



No. at Risk

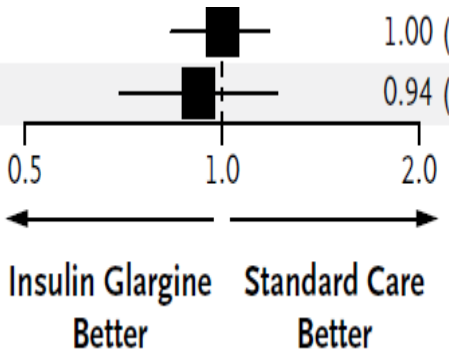
Insulin glargine	6264	5827	5474	5153	4835	4523	3076	631
Standard care	6273	5833	5493	5186	4880	4555	3142	663

Mortality


C Death from Any Cause
Adjusted hazard ratio, 0.98 (0.90–1.08)
P=0.70 by log-rank test
Proportion with Events
0.5
0.4
0.3
0.2
0.1
0.0
Standard care
Insulin glargine
0
1
2
3
4
5
6
7
Years of Follow-up
No. at Risk
Insulin glargine 6264 6150 6024 5857 5687 5508 3906 847
Standard care 6273 6159 6029 5878 5710 5501 3931 878

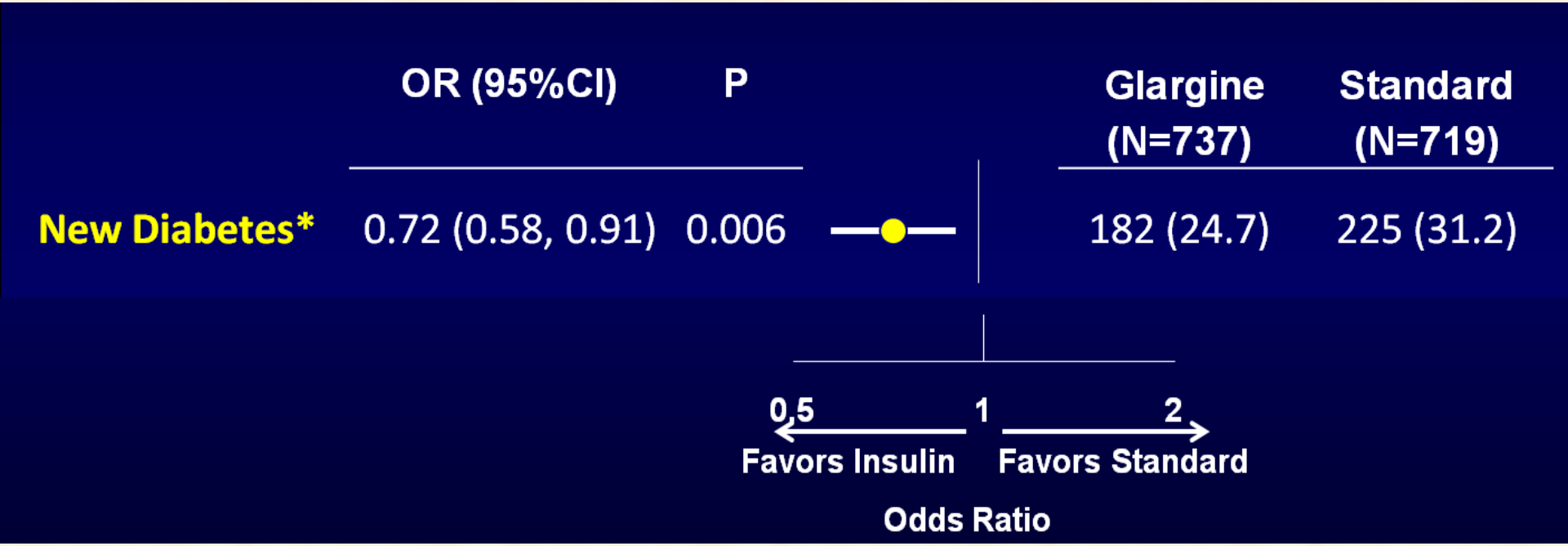
Cancer

Outcome	Insulin Glargine (N=6264)		Standard Care (N=6273)		Hazard Ratio (95% CI)	P Value
	no. (%)	*no./100 patient-yr*	*no. (%)*	*no./100 patient-yr*		
Any cancer	476 (7.6)	1.32	477 (7.6)	1.32	1.00 (0.88–1.13)	0.97
Death from cancer	189 (3.0)	0.51	201 (3.2)	0.54	0.94 (0.77–1.15)	0.52



There was no significant difference in cancers (HR 1.00; 95% CI, 0.88 to 1.13; P = 0.97).

New DM Development



Characteristic	Insulin Glargine (N = 6264)	Standard Care (N = 6273)
New diabetes — no. (%)	365 (5.8)	395 (6.3)

The development of new DM in people without DM at baseline was reduced by 28%.

Summary

Compared to standard care of Patients with early DM, IGT or IFG, using once daily glargine insulin to target a FPG≤95 mg/dl for a median of 6.2 years showed that

Insulin glargine has a neutral effect on CV events.
Insulin glargine reduces progression of diabetes.
Insulin glargine has a neutral effect on cancers.

GRACE study

Glucose **R**eduction and **A**therosclerosis
Continuing **E**valuation Study (ORIGIN-GRACE)

GRACE: SubStudy of ORIGIN

GRACE study was to evaluate the effects of insulin glargine on carotid intima-media thickness (CIMT).

This study was conducted at 32 ORIGIN centers in 7 countries.

GRACE=Glucose Reduction and Atherosclerosis Continuing Evaluation; ORIGIN=Outcome Reduction with Initial Glargine Intervention; CUS=carotid ultrasound;

ORIGIN Trial Investigators. New Engl J Med 2012;367:309–18

Key Inclusion Criteria

Age > 50 years **AND**

Dysglycemia (IFG, IGT, T2DM) **AND**

High CV Risk **AND**

Adequate baseline CIMT

– ≥ 4 measurable segments

GRACE and ORIGIN Trial Investigators. Diabetes Care 2013; 36:2466-74.

Outcomes

- **Primary Outcome**
  - The annualized change in Maximum CIMT form 12 sites
- **Secondary Outcomes**
  - The annualized change in Maximum CIMT for the Common Carotid (4 segments)
  - The annualized change in Maximum CIMT for the Common Carotid and Bifurcation (8 segments)

GRACE and ORIGIN Trial Investigators. Diabetes Care 2013; 36:2466-74.

Baseline Characteristics (N=1,184)

Mean Age (years)	63±7.9
Females	429 (36.2%)
C. Smoking	122 (10.3%)
Hypertension	981 (80.3%)
Hyperlipidemia	707 (59.7%)
Previous CVD	583 (49.2%)
Diabetes	1071 (90.5%)
IFG/IGT	113 (9.5%)
N. America	166 (14.0%)
S. America	824 (69.6%)
Europe	14 (1.1%)
Australia	7 (0.6%)
BMI	29.8±5.7
BP	146/84±22/12
Cholesterol	4.90±1.1

LDL-C	2.95±1.0
HDL-C	1.15±0.3
TG	1.9±1.2
Waist/Hip	M 0.98; F 0.91
eGFR	77.9±20.8
FPG	7.3±2.1
A1c	6.8±1.0
ASA	749 (63.3%)
Statins	485 (41.0%)
ACE-I or ARB	805 (68.0%)
Beta-Blocker	593 (50.1%)
CCB	271 (22.9%)
Thiazide	155 (13.1%)
Metformin	302 (25.5%)
Sulfonylurea	477 (40.3%)

GRACE and ORIGIN Trial Investigators. Diabetes Care 2013; 36:2466-74.

Baseline IMT

- **All 1,184 participants were followed for a median of 6.2 years**
- **The median time from baseline to study end US was 4.9 years**

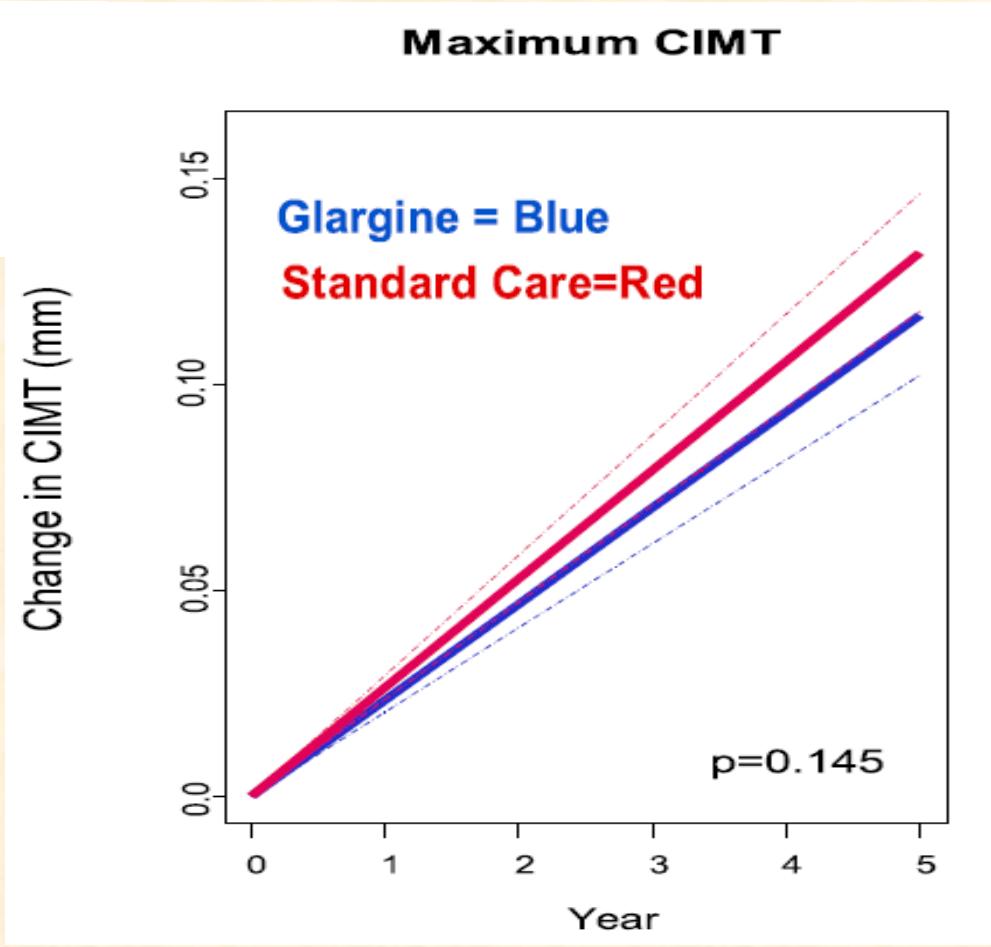
- **Baseline CIMT did not differ significantly between treatment arms**

Carotid ultrasound	Insulin glargine (n=580)	Standard care (n=604)
Average maximum CIMT(mm)	1.08 ± 0.34	1.09 ± 0.34
Average of Maximum Common Carotid IMT(mm)	**0.88 ± 0.25**	**0.89 ± 0.25**
Average maximum common and bifurcation CIMT(mm)	1.10 ± 0.33	1.11 ± 0.33
Average maximum far wall CIMT(mm)	1.08 ± 0.38	1.09 ± 0.34

CUS=carotid ultrasound; IQR=interquartile range; ORIGIN=Outcome Reduction with Initial Glargine Intervention; CIMT=Carotid Intima-Media Thickness

GRACE and ORIGIN Trial Investigators. Diabetes Care 2013; 36:2466-74.

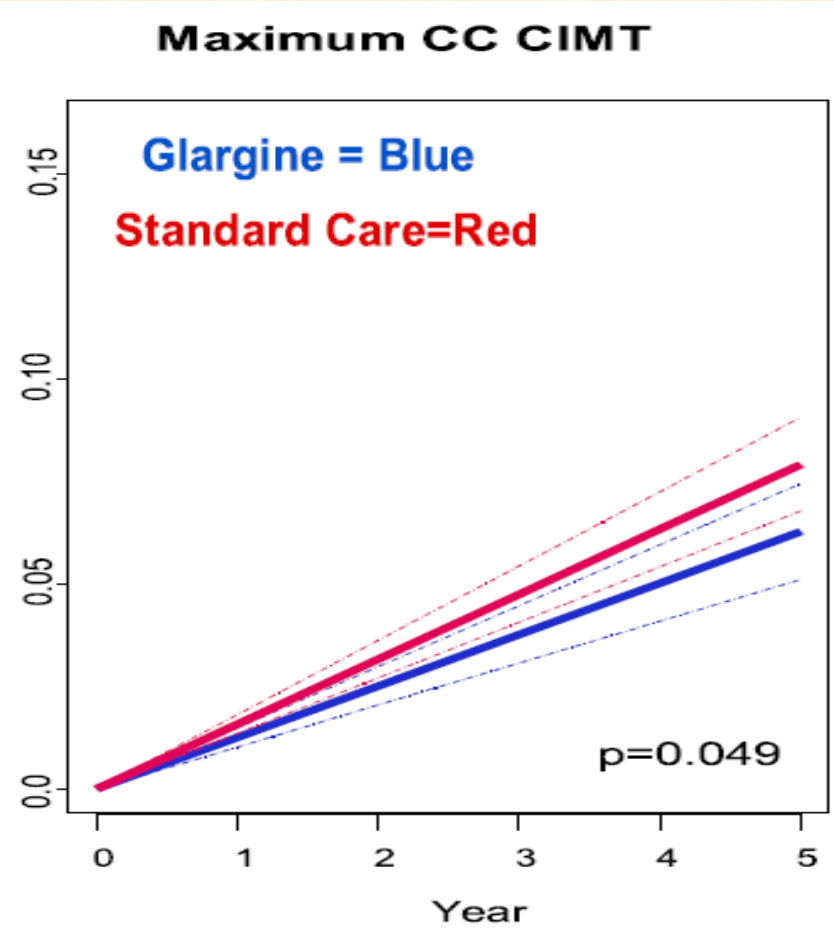
Results: Average of Maximum Common Carotid IMT (Primary Outcome)

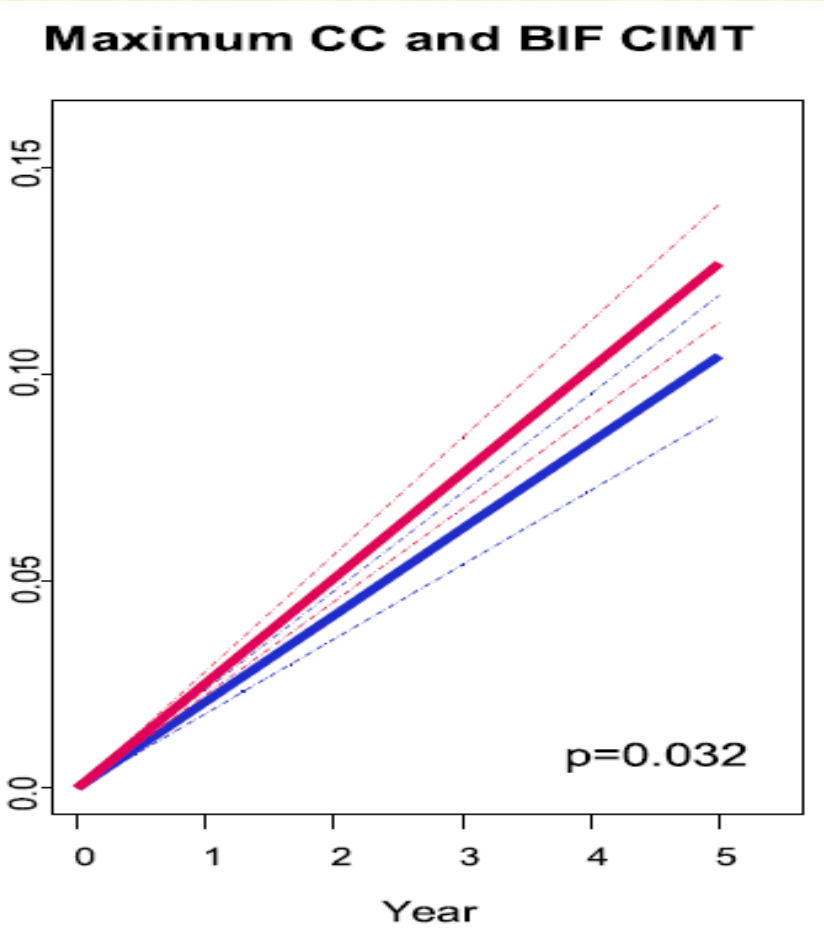


(N=1,091)

GRACE and ORIGIN Trial Investigators. Diabetes Care 2013; 36:2466-74.

Results – Secondary Efficacy Outcomes





Common Carotid Maximum IMT

Common Carotid and Bifurcation IMT

GRACE and ORIGIN Trial Investigators. Diabetes Care 2013; 36:2466-74.

Summary

ORIGIN-GRACE study was the largest reported clinical trial to evaluate the effects of insulin on atherosclerosis progression.

There was a statistically non-significant 11% reduction in the slope of CIMT progression for the primary outcome

And significant 20% and 18% reduction for secondary outcomes for people receiving insulin glargine compared with standard care.

This study showed that Glargine Insulin, at least, did not Promote Carotid Atherosclerosis.

ORIGINALE study

ORIGINALE: ORIGIN And Legacy Effects

As shown in DCCT-EDIC and UKPDS follow up, CV Event in Post-trial follow-up period is interesting.

To evaluate the long term Legacy Effects Of Glargine Insulin, ORIGINALE study is ongoing until March 2014.

About 8,000 participants will be included in this study.

GALAPAGOS study

The Insulins Glargine And gluLisine strAtegy vs. Premixed insulin strAteGy: a cOmparative Study (GALAPAGOS) study

Glargine ± Glulisine *vs.* Premix QD/BID

GALAPAGOS study (include Korean sites)

Glargine ± Glulisine *vs.* Premix QD/BID

A 24-week, open-label, multinational trial

To prove the superiority glargine ± glulisine to premixed insulin in insulin-naive T2DM patients uncontrolled on Oral Anti-diabetic medications.

Primary Outcome

The percentage of patients who achieved A1c < 7% at study end with no symptomatic hypoglycemia (PG ≤ 56 mg/dL)

PRE : premixed insulin

Pablo Aschner et al., 2013 ADA

Baseline Characteristics

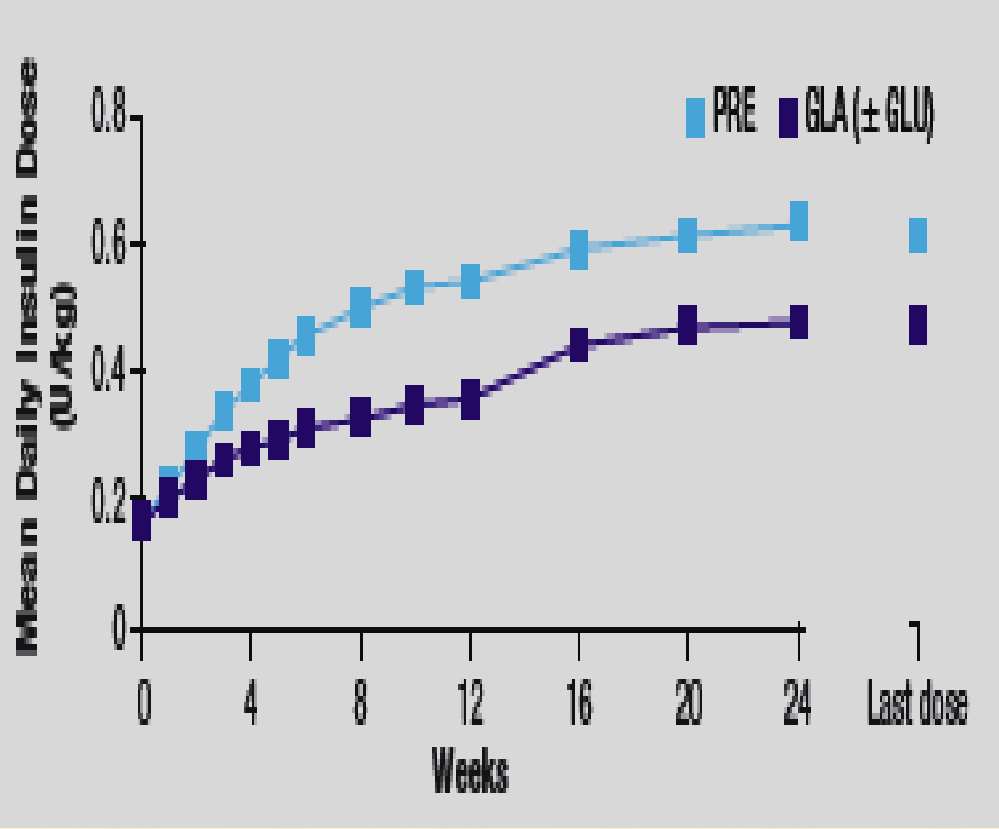
	GLA N=462	PRE N=461
Age, yrs	**56.7(9.0)**	**55.8(9.5)**
Female, n(%)	231(50.0)	221(47.9)
Weight, kg	75.7(13.5)	76.0(13.9)
BMI, kg/m^2	28.4(4.7)	28.3(4.4)
Duration of DM, yrs	**9.1(6.0)**	**8.8(5.8)**
Duration of OAD treatment, yrs	7.9(5.8)	7.6(5.5)
Patients with ≥1 late diabetes complication, n(%)	125(27.1)	122(26.5)
No. of meals and snacks	4.1(1.0)	4.0(1.0)
Any prior medication (except antidiabetics), n(%)	339(73.2)	339(73.7)
Prior antidiabetic drugs, n(%)		
Anyprior antidiabetic	461(99.8(	461(100)
Biguanides	460(99.6)	461(100)
Sulfonylureas	333(72.1)	324(70.3)
Glinides	35(7.6)	33(7.2)
GLP-1 agonists	1(0.2)	0(0.0)

	GLA N=462	PRE N=461
DPP-4 agonists	66(14.3)	57(12.4)
a-Glucosidase inhibitors	38(8.2)	39(8.5)
Thiazolidinediones	37(8.0)	43(9.3)
Blood pressure, mmHg		
Systolic	129(14)	131(14)
Diastolic	78(8)	79(8)
Cholesterol, mg/dL		
Total	181(40)	181(43)
LDL	110(35)	110(35)
HDL	49(12)	47(12)
Triglycerides, mgl/dL	171(103)	176(128)
A1c, % units	**8.7(0.9)**	**8.7(0.9)**
mmol/mol	72(10)	72(10)
FPG, mg/dL	**160(37)**	**162(42)**
Mean daily PG, mg/dL	186(41)	189(43)

Pablo Aschner et al., 2013 ADA

Results: Insulin Dose

- Starting dose of glargine was 0.2 U/kg or 12U given in the evening
- For PRE, starting dose was 12U at dinner (QD) or 6 U at breakfast and at dinner (BID)

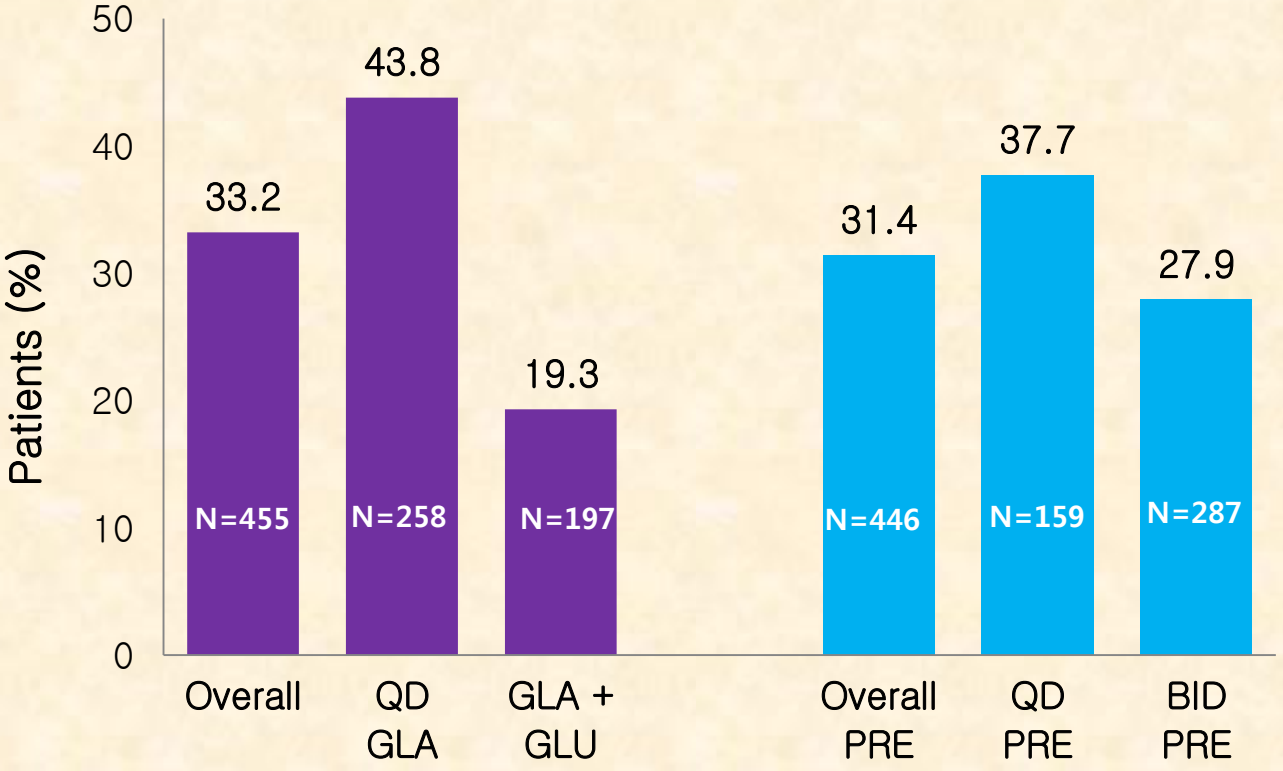


Glargine < Premix

Pablo Aschner et al., 2013 ADA

Results: % of Pts achieved A1c<7%

- Similar % of Patients reached the primary endpoint in both groups.
- More glargine than premix patients stayed on 1 injection/day.

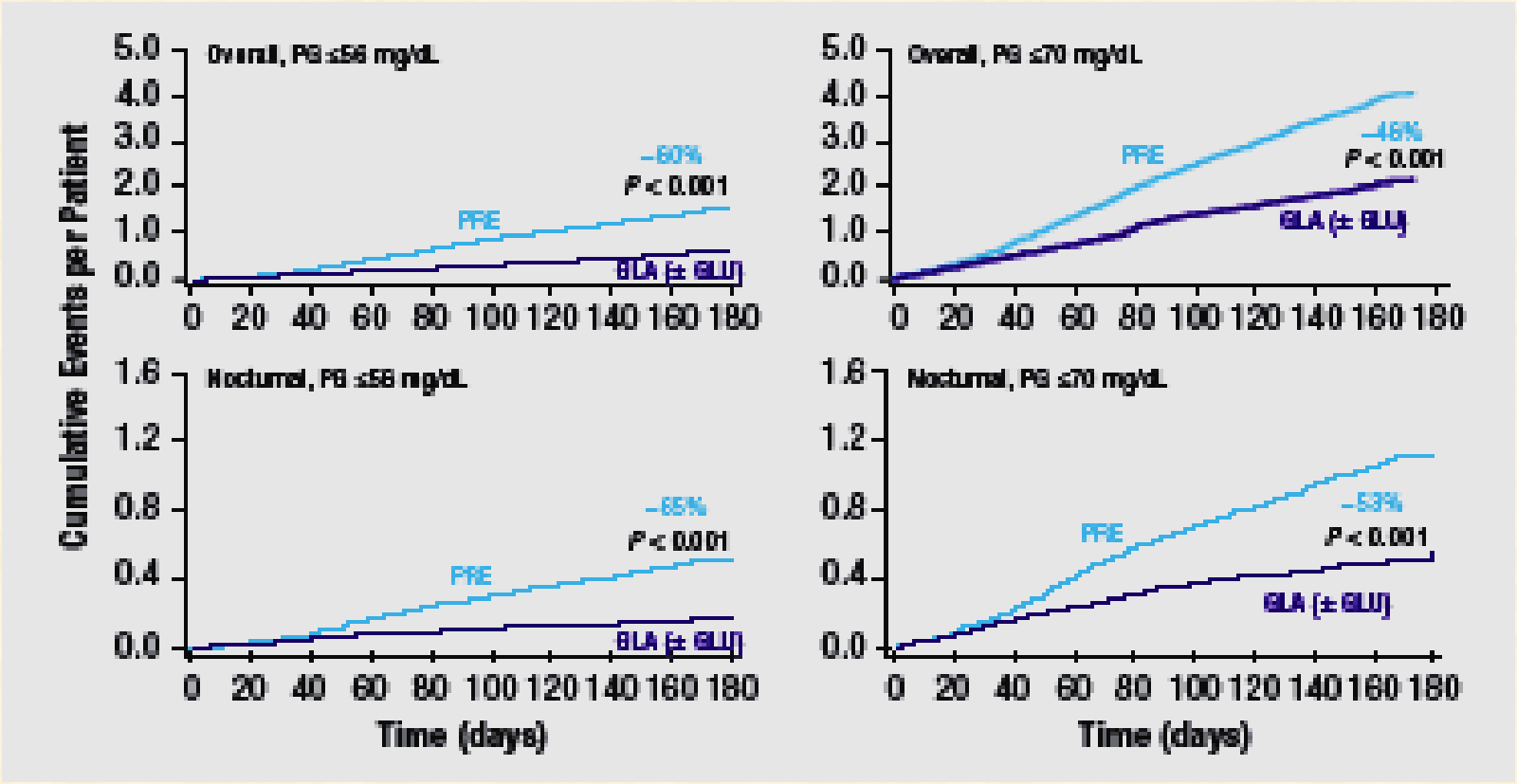


the percentage of patients who achieved A1c < 7%

Pablo Aschner et al., 2013 ADA

Results: Hypoglycemia

- **Overall Hypoglycemia was greater with premix insulin than glargine group.**



Pablo Aschner et al., 2013 ADA

Label Change

Label update of Insulin Glargine with ORIGIN in EU (Jun.2013)

ORIGIN Results on Insulin Glargine Cardiovascular Safety Integrated into European Union Product Label

JUN
6

Sanofi Updates Lantus Label in EU, ORIGIN Results on Lantus® Cardiovascular Safety Integrated Into European Union Product Label

Lantus® (insulin glargine)

Sanofi announced today that the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) has issued a positive opinion for inclusion in the Lantus® (insulin glargine) product label of safety and efficacy data from the insulin glargine cardiovascular (CV) outcomes trial ORIGIN (Outcome Reduction with Initial Glargine INtervention). The revised label is evidence of Sanofi's ongoing commitment to further assert the well-known safety and efficacy profile of insulin glargine, the most-studied basal insulin. The indication for the use of Lantus® remains unchanged.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Label update of Insulin Glargine with ORIGIN in US (Oct. 2013)

6. ADVERSE REACTIONS / 6.1. Clinical Trial Experience

- *Severe hypoglycemia (ORIGIN: only severe symptomatic hypoglycemia)*
- ***Cardiovascular safety***
  - **The ORIGIN study design and detailed baseline characteristics**
  - **Cardiovascular (CV) : "Overall, the incidence of major adverse cardivascular outcomes was similar between groups. All-cause mortality was also similar between groups. "**
  - HbA1c
  - Dose
  - Body weight
  - Adherence
- *Cancer data*

Label of Insulin Glargine is not updated in Korea yet.

U.S Food and Drug Administration

SUMMARY

* ORIGIN study showed that there were no new side effects of glargine insulin over 6-7 years.

- Glargine Insulin has a Neutral Effect On CV Events
- Glargine Insulin Reduces Progression Of Diabetes
- Glargine Insulin has a Neutral Effect On Cancers

* GRACE study showed that Glargine Insulin, at least, did not Promote Carotid Atherosclerosis.

* Compared with Premix Insulin, Glargine insulin has lower insulin dose needed and less hypoglycemia.

Thank you for your Attention.