Outcome Reduction with an Initial Glargine INtervention

The Big Picture - ORIGIN

- A large international RCT in people with new or recently diagnosed diabetes, IFG or IGT & additional CV risk factors lasting > 6 years
- Assessed the effect of 2 independent therapies on serious CV outcomes in > 12,500 people:
  a) titrated basal insulin using insulin glargine
  b) 1 g of omega 3 FA

ORIGIN Research Questions

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

a) does insulin replacement therapy targeting fasting normoglycemia (≤ 5.3 mM or 95 mg/dl) with insulin glargine, reduce CV outcomes more than standard approaches to dysglycemia?

b) does adding omega 3 FA reduce CV death?

Participants (Key Inclusion Criteria)

- **Age ≥ 50 yrs** *AND*
- **Dysglycemia** *AND*
  - *EITHER* IFG or IGT or new type 2 DM by OGTT

    [i.e. FPG ≥ 110 (6.1); or 2 Hr PG ≥ 140 (7.8)]
  - *OR* prior type 2 DM @ stable dose ≥ 10 wks & …
    - on no OADs … + HbA1c < 9.0%
    - < half-max 1 OAD + HbA1c < 8.5%
    - ≥ half-max 1 OAD + HbA1c < 8.0%
- **High CV Risk**
  - *EITHER* Prior MI, stroke, revasc, angina + doc. ischemia
  - *OR* MA, proteinuria, LVH, 50% art. stenosis, ABI < 0.9

ORIGIN Factorial Design

N=12,537; 573 sites; 40 countries; 2 Comparisons

Glargine	Standard Care

Glargine (Lantus): open vs. standard care

Omega 3 FA (Omacor): double-blind; 1 cap/day*

Recruitment: Sept '03 – Dec'05 Final Visit: Q4 2011

Median (IQR) Follow-up: 6.2 y (5.8-6.6)

**Omacor contains EPA 465 mg & DHA 375 mg*

Major Outcomes: Glargine Trial

Primary

- CV death OR MI OR stroke
- CV death OR MI OR stroke OR revasc OR CHF hosp'n

Secondary

- Microvascular composite

  (i.e. doubling of serum Cr, progression of albuminuria category, dialysis/renal transplant, laser Rx/vitrectomy for retinopathy)
- New type 2 diabetes (in those without baseline diabetes)
- All cause death

Other Outcomes & Measures

- Cancers
- Angina, amputation for ischemia,
- CV & other hospitalizations
- Hypoglycemia, weight
- Cognition
- Erectile dysfunction

Randomized By Region

N=12537 from 573 sites in 40 countries

N. America	1314 (11%)	Europe/Africa	6060 (48%)	Australia	202 (2%)
S. America	3853 (31%)	Asia	1108 (9%)		

Baseline Characteristics

Mean Age = 63.5 yrs; Females = 35%

Characteristic	%	Drug Use	%
Smoking	12	Statin	54
Hypertension	80	ACE-I/ARB	69
Any Albuminuria	15	Thiazide	19
Previous CVD	59	Beta Blocker	53
		Other BP Drug	41
		Antiplatelet	69

Baseline Characteristics (Mean Level)

	Conventional Units	SI Units
BMI (kg/m^2)	29.8	29.8
Blood Pressure (mm)	146/84	146/84
Cholesterol (mg/dl or mM)	190	4.9
LDL (mg/dl or mM)	112	2.90
HDL (mg/dl or mM)	46	1.19
TG (Median mg/dl or mM)	140	1.58

Baseline Glycemia (N=12,537)

	N	%
Prior Diabetes (for ~ 5.4 y)	10321	82
New Diabetes	760	6
IFG &/or IGT	1452	12
No G Drug	5052	40
Metformin	3435	27
Sulfonylurea	3711	30
Other G Drug	351	3

Median FPG	125 mg/dl	6.9 mM
Median A1C	6.4%	

CV Prevention with Insulin-Mediated Normoglycemia?

- *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 & antithombotic*
- *Improves endothelial repair & dysfunction*
- *Clues from UKPDS, DCCT & other trials*

90 yrs uncertainty re insulin's role in type 2 diabetes

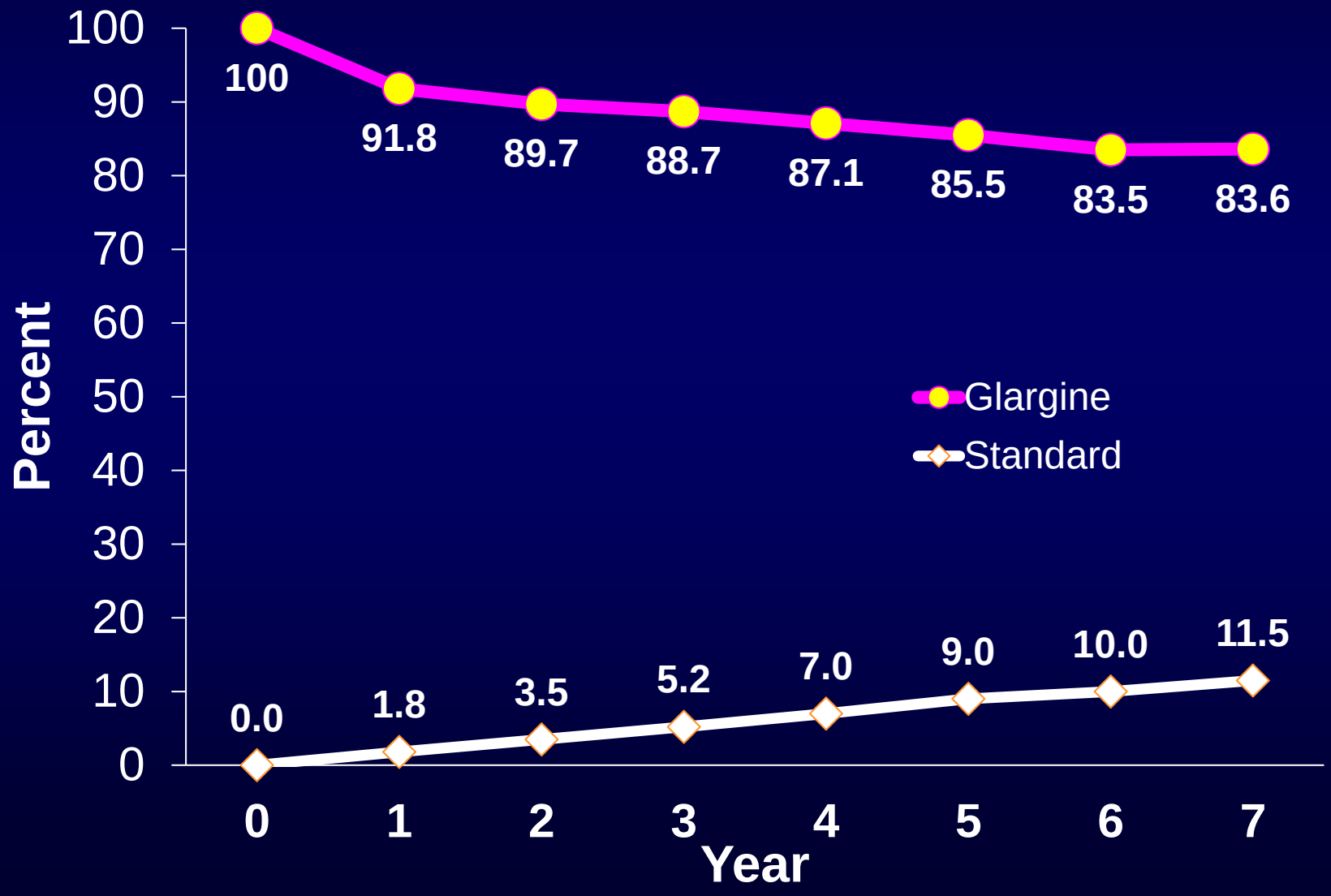
Interventions (Added to Lifestyle)

- ***Insulin Glargine Group***
  - Same approach for people with/without DM
  - Add evening glargine to 0 or 1 oral agent
  - Self-titrate @ 1-2 units, 2/wk; target capillary FPG $\leq$ 95 mg/dl (5.3 mM)
  - Metformin could be added to mitigate hypoglycemia

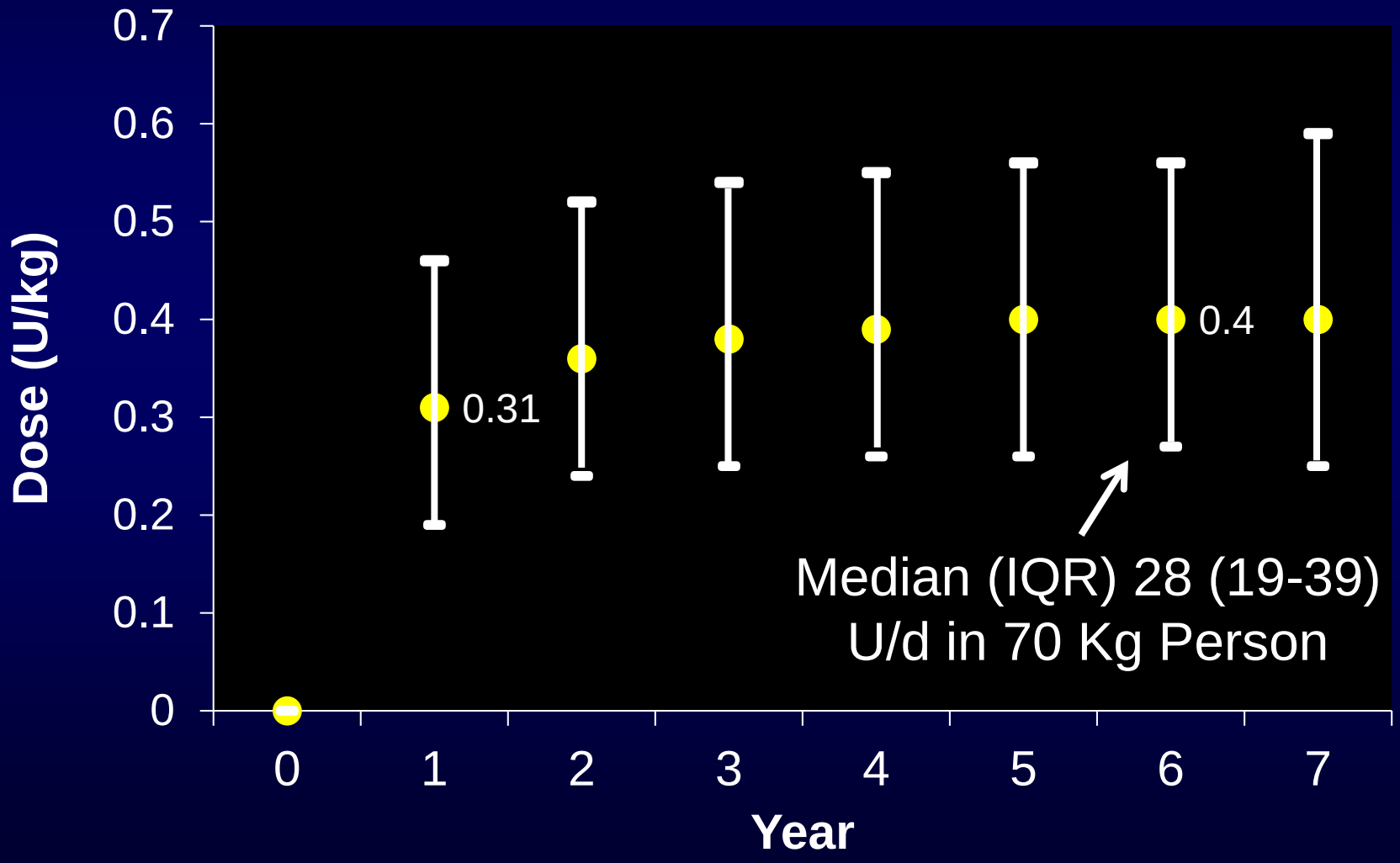
- ***Standard Care Group***
  - Non-DM $\longrightarrow$ Screen for DM yearly
  - DM $\longrightarrow$ Guideline-based + MD's judgment
    No insulin until $\geq$ 2 OADs & no glargine

Insulin Use by Allocated Group

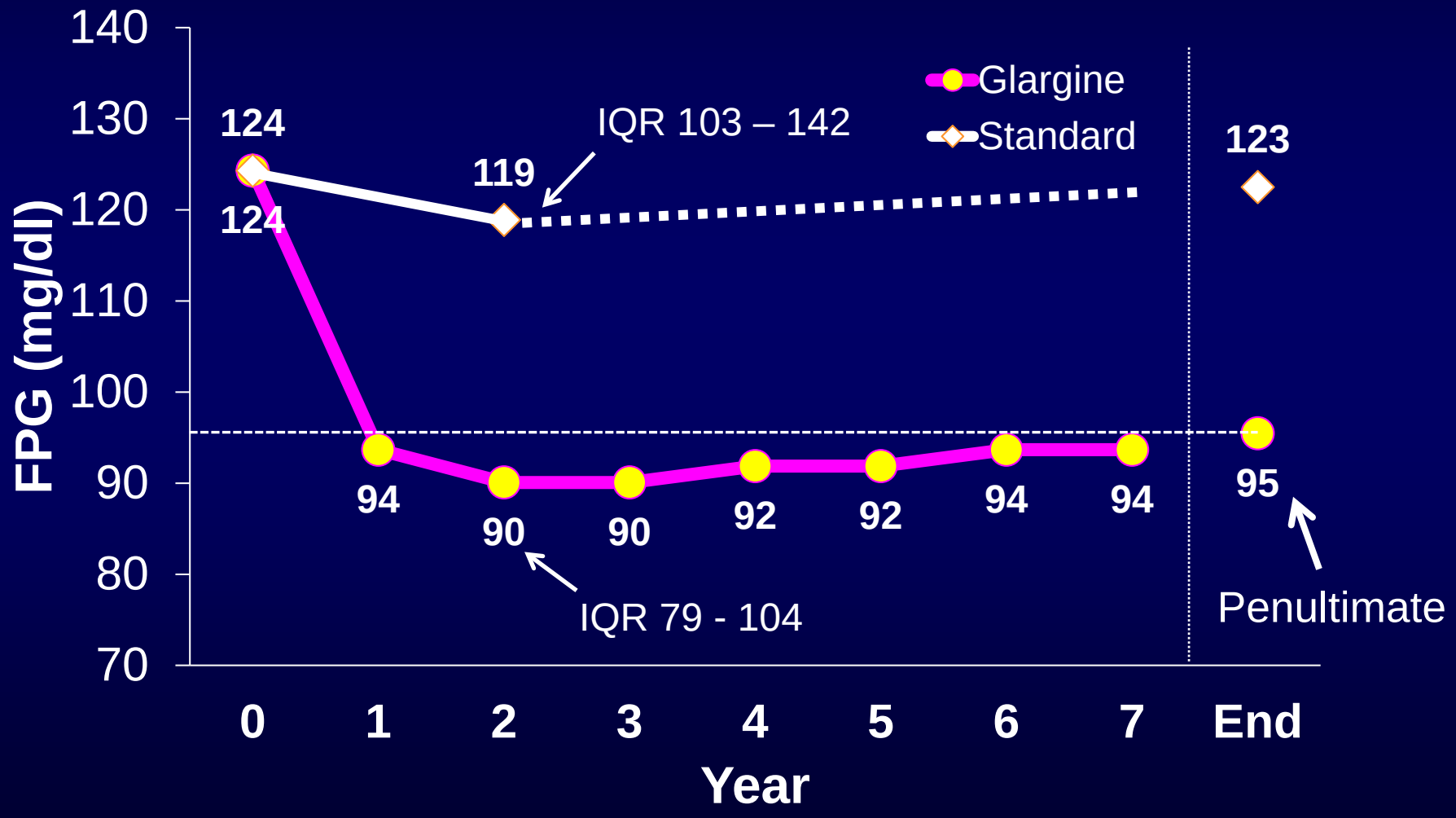
Glargine vs. Other insulins in Standard Care



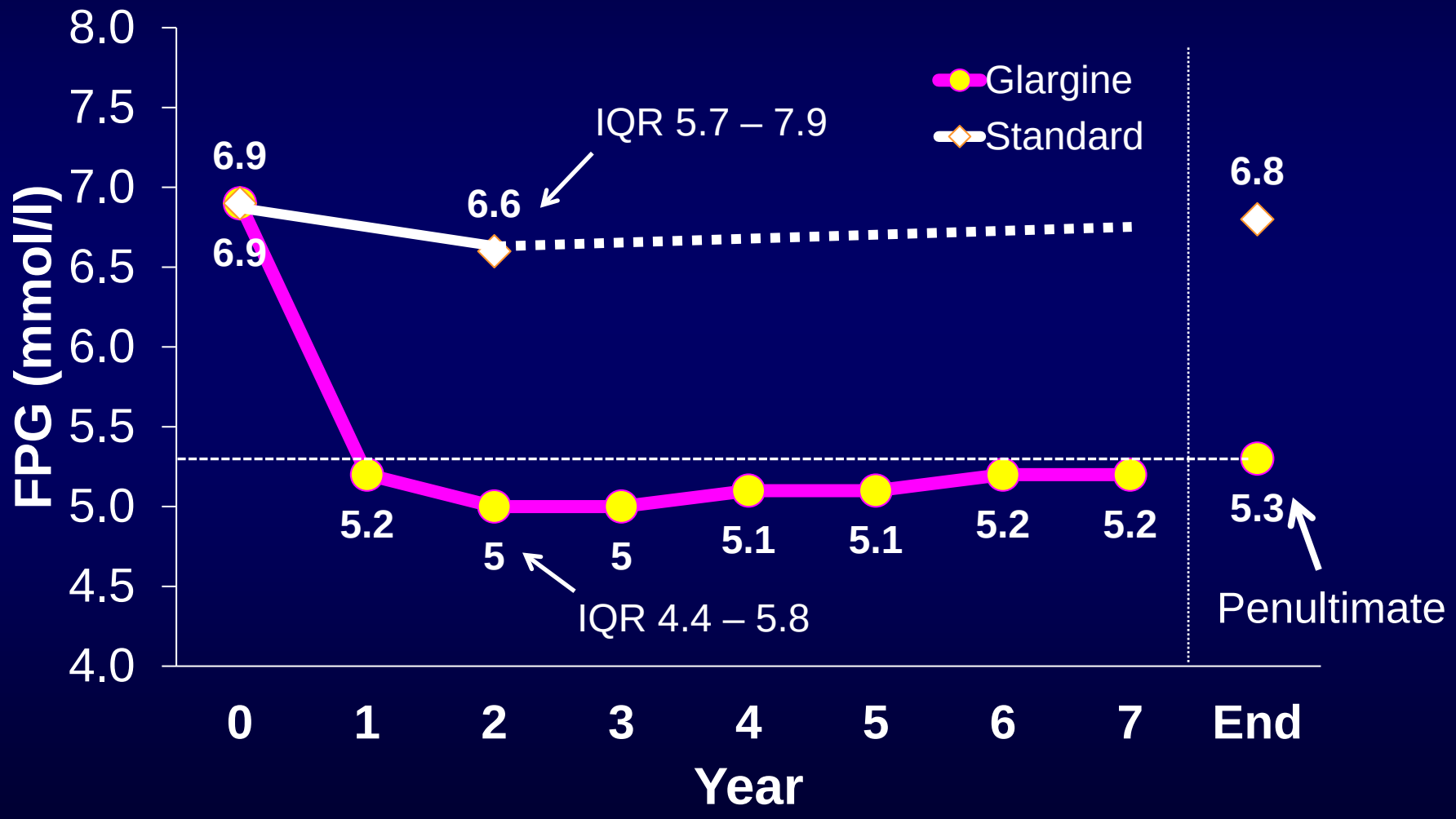
Median Glargine Dose & IQR (U/kg)



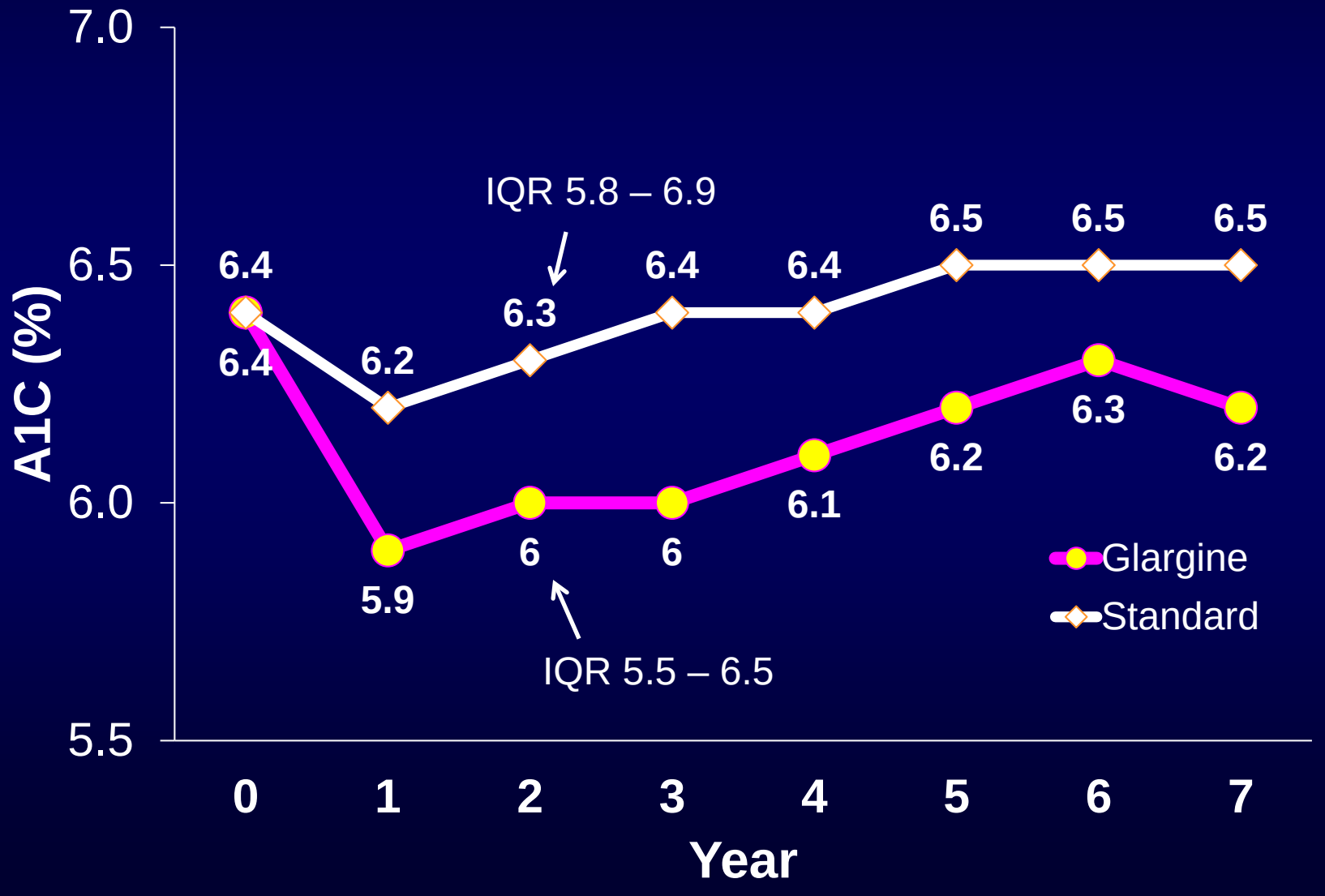
Median FPG (Conventional Units)



Median FPG (SI Units)



Median A1C Levels



Adherence to Insulin Glargine

in 6264 Allocated to Insulin

	Permanently Stopped During the Trial (%)
N stopped drug	19
Reason for Stopping	
Refusal	90
Hypoglycemia	4
Weight Gain	0.3
Hyperglycemia	0.3
Other	5

Drug Use at Study End

Before Stopping Insulin in People without Diabetes

	Insulin Glargine	Standard Care	P
No Oral Agents (%)	35	19	<0.001
1 Oral Agents (%)	51	39	<0.001
2 Oral Agents (%)	12	28	<0.001
≥ 3 Oral Agents (%)	3	14	<0.001
Rapid insulin (%)	2	5	<0.001
Any Insulin (%)	80	11	<0.001
Metformin (%)	47	60	<0.001
Sulfonylurea (%)	25	47	<0.001

Drug Use at Study End

	Insulin Glargine	Standard Care	P
Statin (%)	62	60	0.06
ACE-I/ARB (%)	77	76	0.71
Beta Blocker (%)	56	56	0.98
Antiplatelet (%)	71	71	0.57

Definitions of Hypoglycemia

- **Any Non-severe**
  - *a) Signs &/or symptoms of hypoglycemia*
- **Confirmed Non-severe**
  - *a) Signs &/or symptoms of hypoglycemia*
  - *b) Capillary glucose ≤ 54 mg/dl (3 mmol/l)*
- **Severe – need all 3 of…….**
  - *a) Signs &/or symptoms of hypoglycemia*
  - *b) Required assistance (unable to help self)*
  - *c) Spontaneous recovery with carbohydrate/glucagon OR any measured glucose ≤ 36 mg/dl (2 mmol/l)*

Hypoglycemia & Weight (6 -7 years)

	Glargine (N=6264)		Standard (N=6273)		P
	%	/100py	%	/100py	
Any Non-severe					
1 or more episodes	57	17	25	5	<0.001
Severe					
1 or more episodes	6	1.0	2	0.3	<0.001

	Glargine	Standard	P
Weight Change Since Randomized	1.6 kg (3.5 lbs)	-0.5 kg (1 lb)	<0.001

Final CV Risk Factors

Conventional Units

	Insulin Glargine	Standard Care	P
Cholesterol (mg/dl)	175	177	0.09
LDL (mg/dl)	102	102	0.51
HDL (mg/dl)	45	46	<0.001
Triglyceride (mg/dl)	124	128	<0.001
HR	69.2	69.7	0.08
SBP/DBP	141/79	141/79	0.4

Final CV Risk Factors

SI Units

	Insulin Glargine	Standard Care	P
Cholesterol (mM)	4.53	4.58	0.09
LDL (mM)	2.64	2.63	0.51
HDL (mM)	1.17	1.20	<0.001
Triglyceride (Median mM)	1.40	1.44	<0.001
HR	69.2	69.7	0.08
SBP/DBP	141/79	141/79	0.4

1st Co-primary: MI, Stroke, or CV Death

Outcome Status Known for 99% of Participants

1st Co-primary: MI, Stroke, or CV Death

Adj. HR 1.02 (0.94, 1.11)

Log Rank P = 0.63

2nd Co-Primary: MI, Stroke, CV Death, Revascularization, Heart Failure

Adj. HR 1.04 (0.97, 1.11)

Log Rank P = 0.27

All-cause Death

Adj. HR 0.98 (0.90, 1.08)

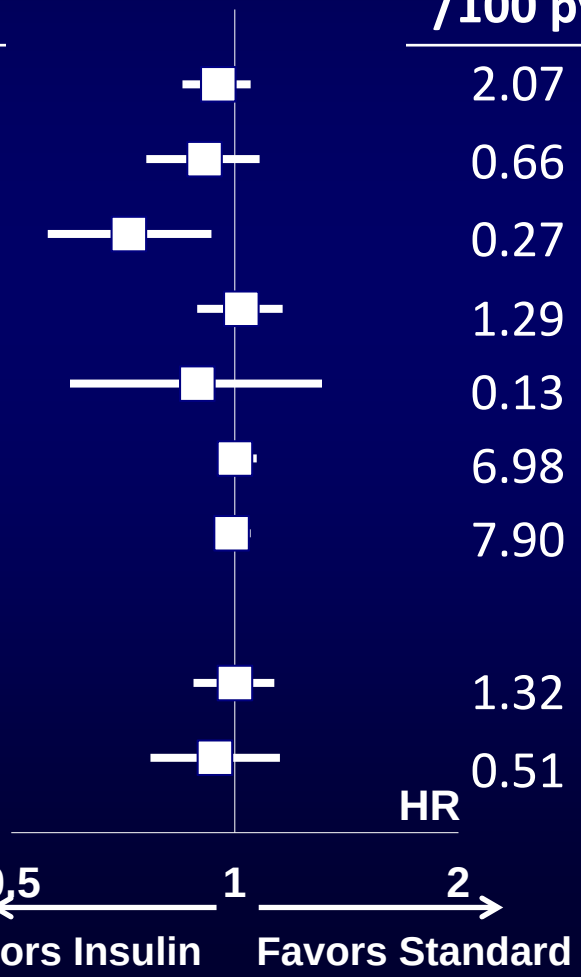
Log Rank P = 0.70

Primary & Secondary Outcomes & their Components

	HR (95% CI)	P	Insulin /100 py	Standard /100 py
1st Coprimary	1.02 (0.94, 1.11)	0.63	2.94	2.85
2nd Coprimary	1.04 (0.97, 1.11)	0.27	5.52	5.28
Microvascular	0.97 (0.90, 1.05)	0.43	3.87	3.99
Death	0.98 (0.90, 1.08)	0.70	2.57	2.60
MI	1.02 (0.88, 1.19)	0.75	0.93	0.90
Stroke	1.03 (0.89, 1.21)	0.69	0.91	0.88
CV Death	1.00 (0.89, 1.13)	0.98	1.57	1.55
CHF Hospital	0.90 (0.77, 1.05)	0.16	0.85	0.95
Revascularized	1.06 (0.96, 1.16)	0.24	2.69	2.52

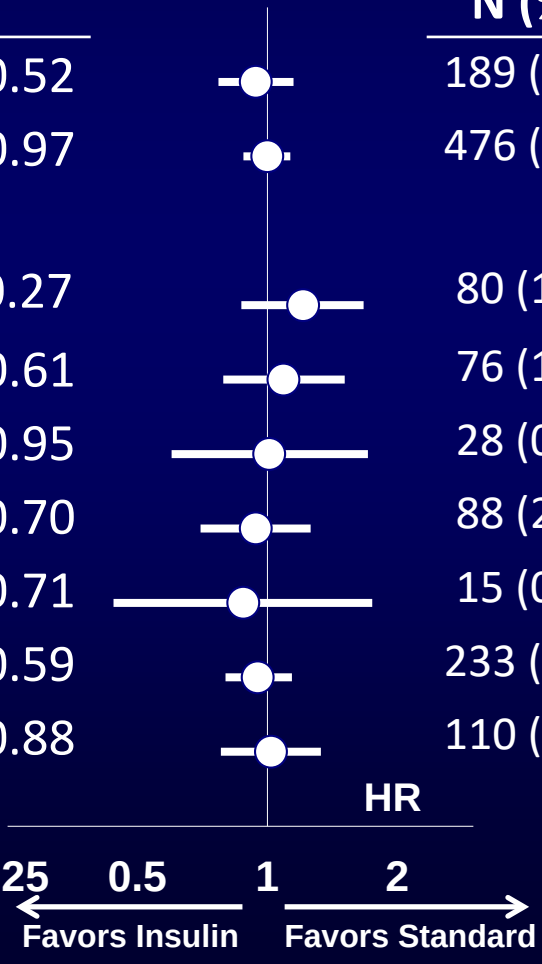
Additional Outcomes

	HR (95% CI)	P	Insulin /100 py	Standard /100 py
Angina	0.95 (0.85, 1.05)	0.29	2.07	2.17
Unstable	0.91 (0.76, 1.08)	0.28	0.66	0.72
New angina	0.72 (0.56, 0.93)	0.01	0.27	0.38
Worsening	1.02 (0.89, 1.16)	0.80	1.29	1.26
Amputation	0.89 (0.60, 1.31)	0.55	0.13	0.14
CV Hosp	1.00 (0.95, 1.07)	0.90	6.98	6.91
Non-CV Hosp	0.99 (0.94, 1.05)	0.85	7.90	7.93
Any Cancer	1.00 (0.88, 1.13)	0.97	1.32	1.32
Cancer Death	0.94 (0.77, 1.15)	0.52	0.51	0.54



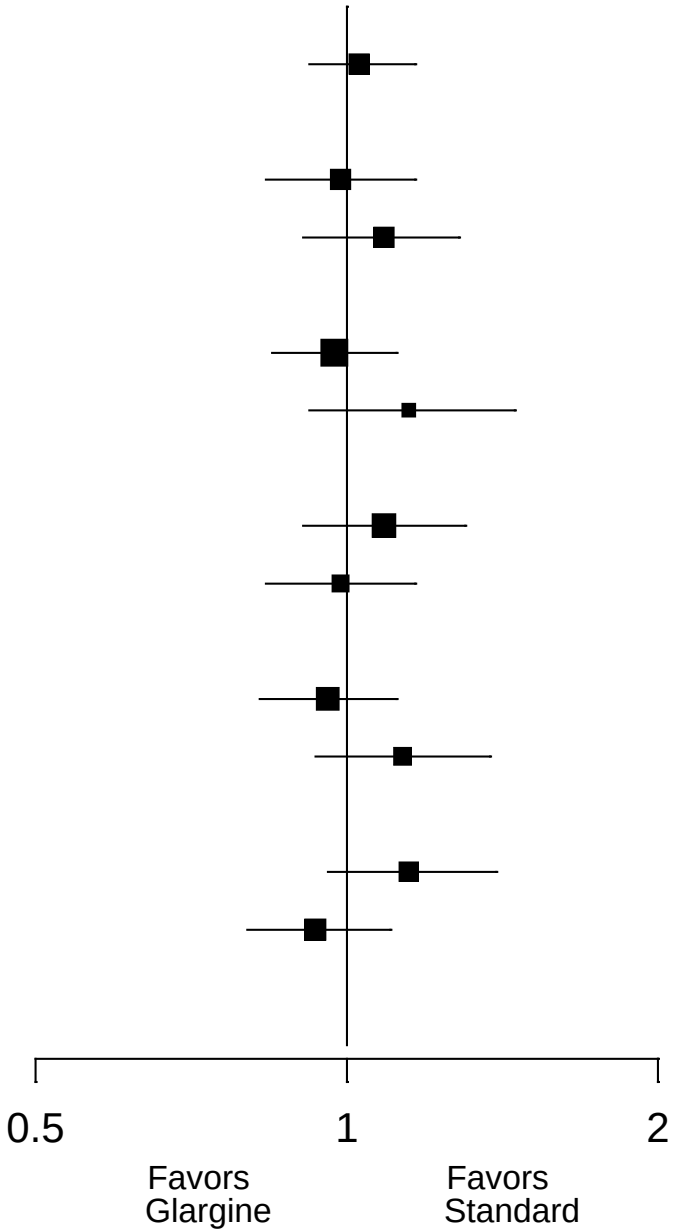
Cancers Overall & by Type (N=953)

	HR (95%CI)	P	Glargine N (%)	Glargine Rate	Standard N (%)	Standard Rate
Cancer Death	0.94 (0.77, 1.15)	0.52	189 (3.0)	0.51	201 (3.2)	0.54
Any Cancer	1.00 (0.88, 1.13)	0.97	476 (7.6)	1.32	477 (7.6)	1.32
Lung	1.21 (0.87, 1.67)	0.27	80 (1.3)	0.22	66 (1.1)	0.18
Colon	1.09 (0.79, 1.51)	0.61	76 (1.2)	0.21	70 (1.1)	0.19
Breast	1.01 (0.60, 1.71)	0.95	28 (0.4)	0.08	28 (0.4)	0.08
Prostate	0.94 (0.70, 1.26)	0.70	88 (2.1)	0.36	89 (2.2)	0.38
Melanoma	0.88 (0.44, 1.75)	0.71	15 (0.2)	0.04	17 (0.3)	0.05
Other	0.95 (0.80, 1.14)	0.59	233 (3.7)	0.64	245 (3.9)	0.67
Any Skin	1.02 (0.78, 1.33)	0.88	110 (1.8)	0.30	108 (1.7)	0.29



1st Co-Primary - Subgroups

	HR (95% CI)	P Interaction
Overall	1.02 (0.94 -1.11)	
Placebo Allocation	0.99 (0.88 -1.12)	
Omega 3 Allocation	1.06 (0.94 -1.19)	0.47
Male	0.98 (0.89 -1.09)	
Female	1.11 (0.94 -1.31)	0.22
Age < 65 yrs	1.06 (0.93 -1.21)	
Age >= 65 yrs	0.99 (0.88 -1.11)	0.43
BMI <= 30	0.97 (0.87 -1.09)	
BMI > 30	1.09 (0.95 -1.26)	0.18
A1C<6.4% (Median)	1.11 (0.97 -1.27)	
A1C>=6.4% (Median)	0.95 (0.85 -1.07)	0.09



MI, Stroke, CV Death

Interaction

MI, Stroke, CV Death, Revascularization, CHF Hospitalization

Interaction

MI, Stroke, CV Death

Interaction

MI, Stroke, CV Death, Revascularization, CHF Hospitalization

Summary: CV / Other Outcomes

- A high risk population was recruited (MACE~ 2.9%/y)
- Adherence & follow-up (99%) were high
- A large contrast in appropriately titrated insulin was maintained for up to 7 yrs; few controls used insulin
- *Basal insulin glargine titrated to a normal FPG…*
  - *Has a neutral effect on CV outcomes*
  - *Has a neutral effect on cancer*

…compared to standard care

Effect on Incidence of Diabetes

Could Insulin Prevent Diabetes?

- In type 2 diabetes, IFG & IGT, there is insufficient insulin to maintain normal glucose levels

- In recent type 2 diabetes,
  - *Reducing beta cell work with metformin/TZDs reduces need for other drugs (ADOPT trial)*
  - *Intensive insulin (IV, pump, or sc) → some drug-free remissions & preserves secretion (small RCTs/series)*

- In IFG & IGT,
  - *Reducing beta cell work (by lifestyle, TZDs, metformin, acarbose) reduces diabetes*

Secondary Research Question

Does insulin replacement therapy with insulin glargine reduce the incidence of new diabetes in people with IFG/IGT & other risk factors for CV disease?

N = 1456 at risk for diabetes

Diabetes Definition in ORIGIN

During the Trial

- 2 consecutive FPGs ≥ 126 mg/dl (7 mM) within 4 mo
- All 3 of : a) a diagnosis of diabetes
  b) ≥ 1 prescribed glucose lowering drug
  c) ≥ 1 FPG ≥ 126 mg/dl / any glucose ≥ 200 mg/dl

During Glargine Taper Before Last Visit (by 10 U/day)

- ≥ 1 cap glucose ≥ 200 mg/dl + lab FPG ≥ 126 mg/dl OR any lab value ≥ 200 mg/dl (11.1 mM)

Diabetes Definition in ORIGIN

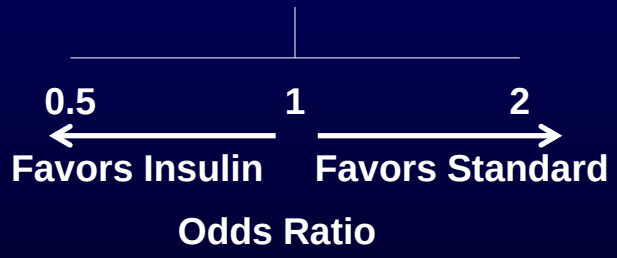
After stopping insulin (in people with no diabetes)

- A FPG ≥ 126 mg/dl OR a 2 hr PG ≥ 200 mg/dl during
  - The 1st OGTT (a median of 24 days after last visit)
  - The 2nd OGTT (a median of 100 days after the last visit)

Predefined Diabetes Outcome: New Diabetes From the Time of Randomization to 1st OGTT

New Diabetes

	OR (95%CI)	P	Glargine (N=737)	Standard (N=719)
New Diabetes*	0.72 (0.58, 0.91)	0.006	182 (24.7)	225 (31.2)



**Predefined New Diabetes Outcome – results up to & including first OGTT*

Summary of Findings

Compared to standard glycemic care of people with early diabetes, IGT &/or IFG … using once daily basal insulin glargine to target a FPG ≤ 95 mg/dl (5.3 mmol/l) for a median of 6.2 years ...

- Maintains near-normal glycemic control
- Has a neutral effect on CV outcomes & on cancers
- Slows progression of dysglycemia
- Modestly increases hypoglycemia
- Modestly increases weight

Summary of Findings

ORIGIN clearly assessed the effect of basal insulin glargine on important health outcomes:

- 1st CV Composite: HR = 1.02 (0.94, 1.11)
- 2nd CV Composite: HR = 1.04 (0.97, 1.11)
- Microvascular Composite: HR = 0.97 (0.90, 1.05)
- Death: HR = 0.98 (0.90, 1.08)
- Cancer: HR = 1.00 (0.88, 1.13)
- Conversion IFG/IGT to DM: HR = 0.72 (0.58, 0.91) P=0.006

Conclusions

- Insulin glargine is now the best-studied glucose drug
- No new side effects of basal insulin over 6-7 years
- Low risk of hypoglycemia & minimal weight gain
- *Clear answers to patient's questions*
  - Basal insulin glargine has a neutral effect on CV events
  - Basal insulin glargine reduces progression of diabetes
  - Basal insulin glargine has a neutral effect on cancers

After 90 yrs of uncertainty regarding the safety of insulin in type 2 diabetes…… we now know its long-term (6-7 year) effect on important health outcomes