



VI CONVEGNO NAZIONALE
CENTRO STUDI E RICERCHE - FONDAZIONE AMD
NAPOLI, 18-20 OTTOBRE 2012



CENTRO CONGRESSI
STAZIONE MARITTIMA



Lo Studio ORIGIN

Outcome Reduction with an Initial Glargine Intervention



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DISCLAIMER

**QUESTA PRESENTAZIONE NON E' SPONSORIZZATA DA ALCUNA AZIENDA
FARMACEUTICA**

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***RINGRAZIO LA ROCHE DIAGNOSTICS DELL'OPPORTUNITA' DATAMI A SOTEGNO DEL
MIGLIORAMENTO DELLE MIE COMPETENZE SCIENTIFICHE ED EDITORIALI
NELL'ULTIMO BIENNIO***



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ORIGINAL ARTICLE

Basal Insulin and Cardiovascular and Other Outcomes in Dysglycemia

The ORIGIN Trial Investigators*

N Engl J Med 2012;367:319-28.

DOI: 10.1056/NEJMoa1203858

**PARTE DEI DATI PRESENTATI NELLO STUDIO ORIGIN RIGUARDANO PAZIENTI PER I QUALI
LA PRESCRIZIONE DI INSULINA GLARGINE NON TROVA INDICAZIONE NEL NOSTRO PAESE**



Randomized By Region

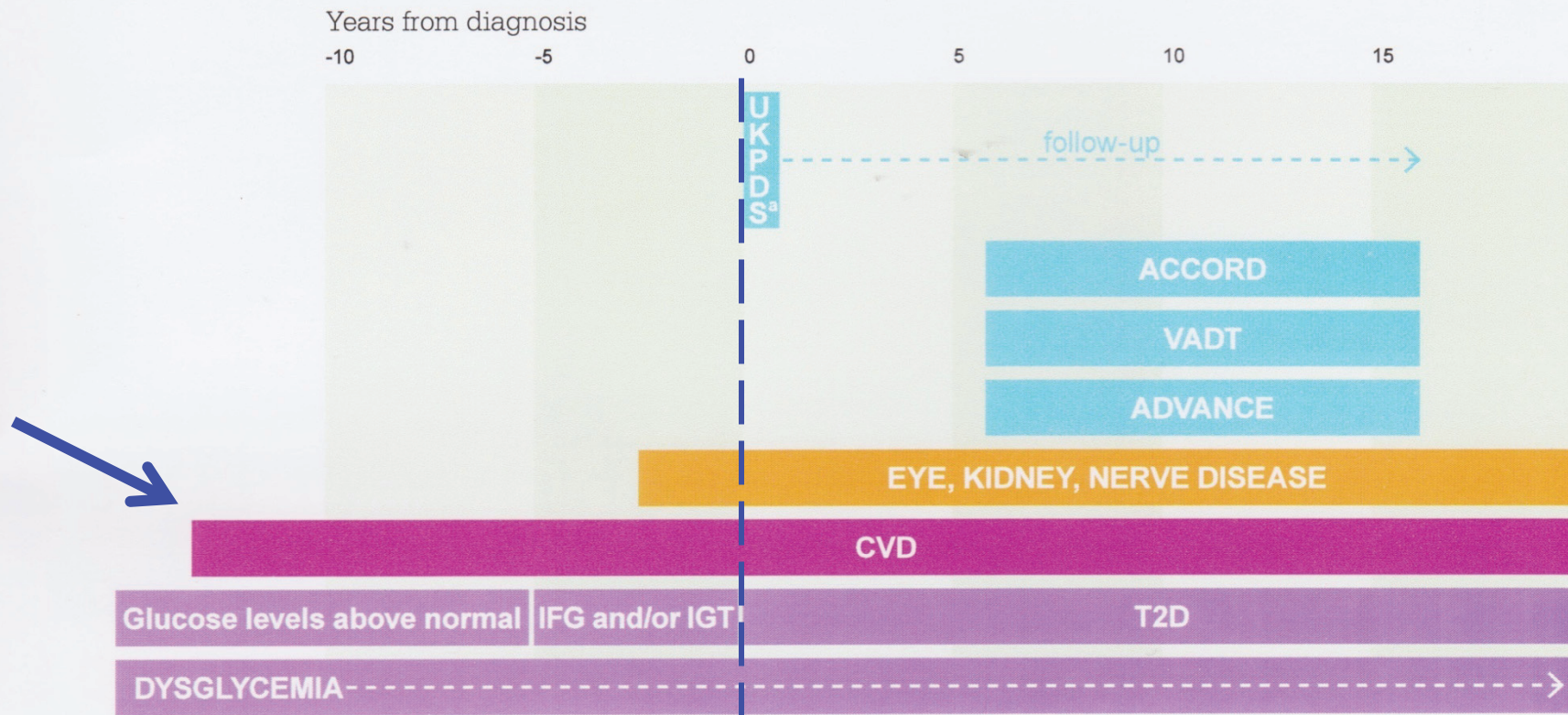
N=12.537 from 573 sites in 40 countries



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



More vs Less Intensive Glucose-Lowering on Cardiovascular Outcomes in T2DM



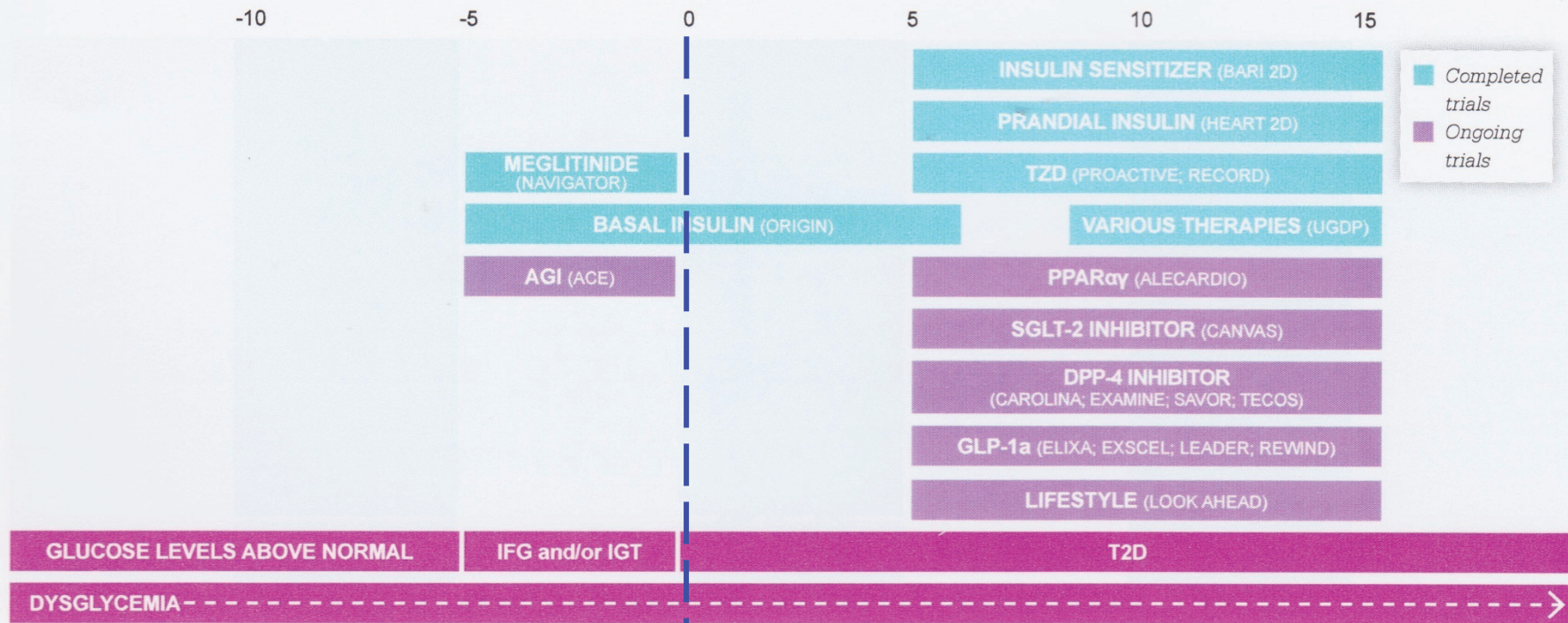
The trials are shown in relation to the eligibility criteria, with respect to diabetes duration at randomization.

352:837-53.); follow-up analysis (Holman RR et al. N Engl J Med 2008;359:1577-89.)



Outcomes Trials Evaluating Individual Treatments for Patients with Dysglycemia

Approximate number of years from diagnosis of diabetes



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



CV Outcomes in Individual Treatment Trials

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
	HEART2D	Prandial vs. basal glucose control	T2D + recent MI
	NAVIGATOR	2x2 factorial: nateglinide and/or valsartan vs. placebo	IGT + elevated but non-diabetic FPG
	ORIGIN	2x2 factorial: insulin glargine vs. standard care and n-3 polyunsaturated fatty acids vs. placebo	IGT, IFG or early T2D
	PROactive	Pioglitazone vs. placebo	T2D at high CV risk
	RECORD	Rosiglitazone + SU or metformin vs. SU + metformin	T2D
Ongoing	UGDP	Diet, tolbutamide, phenformin, insulin (constant dose), insulin (titrated)	T2D
	ACE	Acarbose vs. placebo	IGT at high CV risk
	ALECARDIO	Aleglitazar vs. placebo	T2D + recent ACS
	CANVAS	Canagliflozin vs. placebo	T2D at high CV risk
	CAROLINA	Linagliptin vs. glimepiride	T2D at high CV risk
	ELIXA	Lixisenatide vs. placebo	T2D + recent ACS
	EXAMINE	Alogliptin vs. placebo	T2D + recent ACS
	EXSCEL	Exenatide vs. placebo	T2D
	LEADER	Liraglutide vs. placebo	T2D at high CV risk
	Look AHEAD	Intensive lifestyle intervention vs. diabetes support and education	T2D
	REWIND	Dulaglutide 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



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

90 yrs uncertainty insulin's role in type 2 diabetes



Participants (Key Inclusion Criteria)

- Age \geq 50 yrs AND
- Dysglycemia AND
 - *EITHER* IFG or IGT or new type 2 DM by OGTT
 - *OR* prior type 2 DM
 - on no OADs ... + HbA1c < 9.0%
 - < half-max 1 OAD + HbA1c < 8.5%
 - \geq 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



Baseline Glycemia (N=12,537)

	N	%
Prior Diabetes (for ~ 5.4 y)	10321	82
New Diabetes	760	6
IFG &/or IGT	1452	12
<hr/>		
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%	



ORIGIN Factorial Design

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

Glargine	Standard Care
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Glargine: open vs standard care

Omega 3 FA: 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)



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/vitreectomy for retinopathy)
- New type 2 diabetes (*n. 1452 at risk for diabetes*)
- All cause death

Other

Cancers

Angina, amputation for ischemia,
CV & other hospitalizations

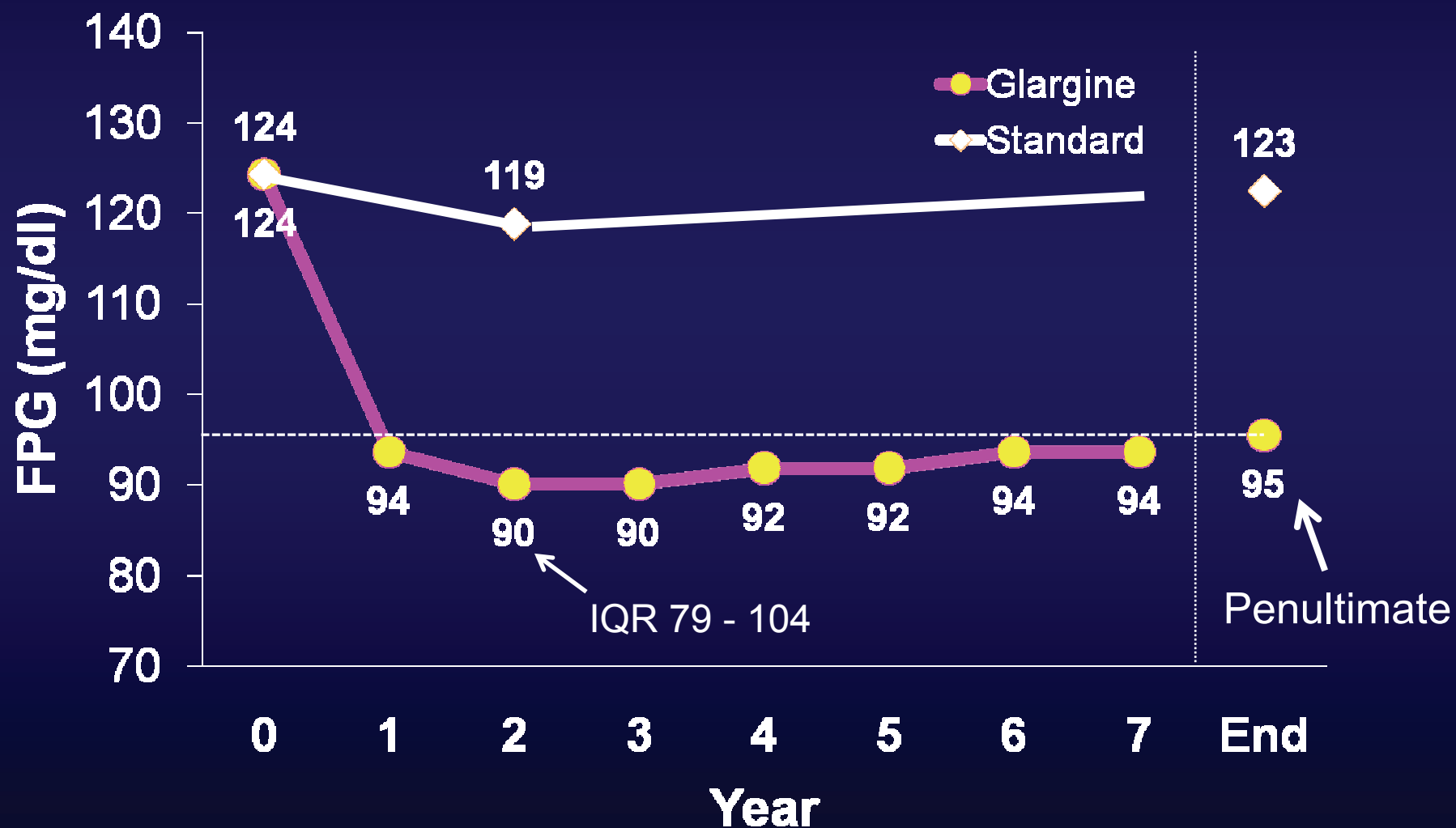
Hypoglycemia, weight

Cognition

Erectile dysfunction



Median FPG (Conventional Units)





Median A1C Levels





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



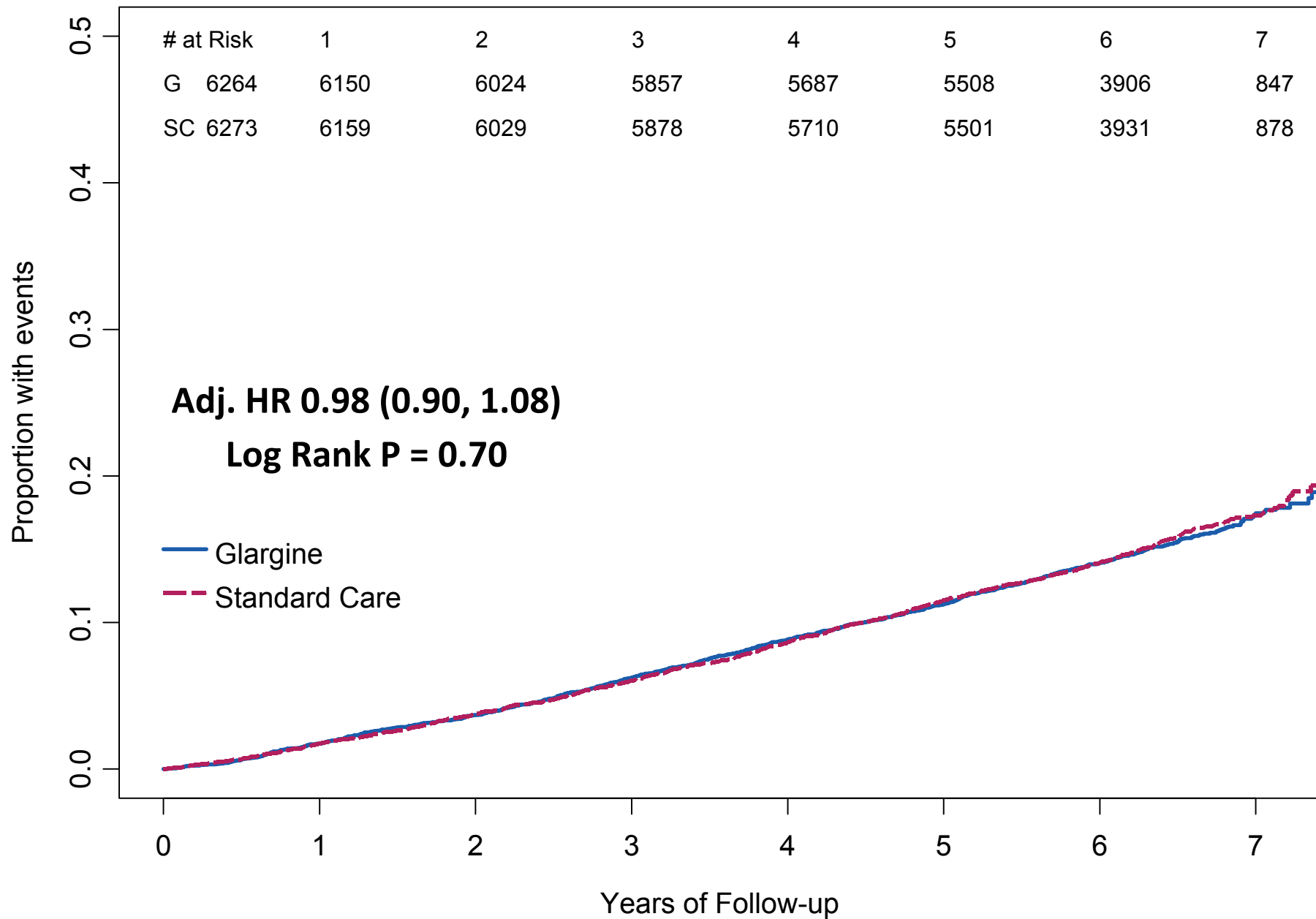
Hypoglycemia & Weight (6 -7 years)

	Glargine (N=6264)		Standard (N=6273)		P
	%	/100p/y	%	/100p/y	
<i>Any Non-severe</i>					
1 or more episodes	57	17	25	5	<0.001
<i>Severe</i>					
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

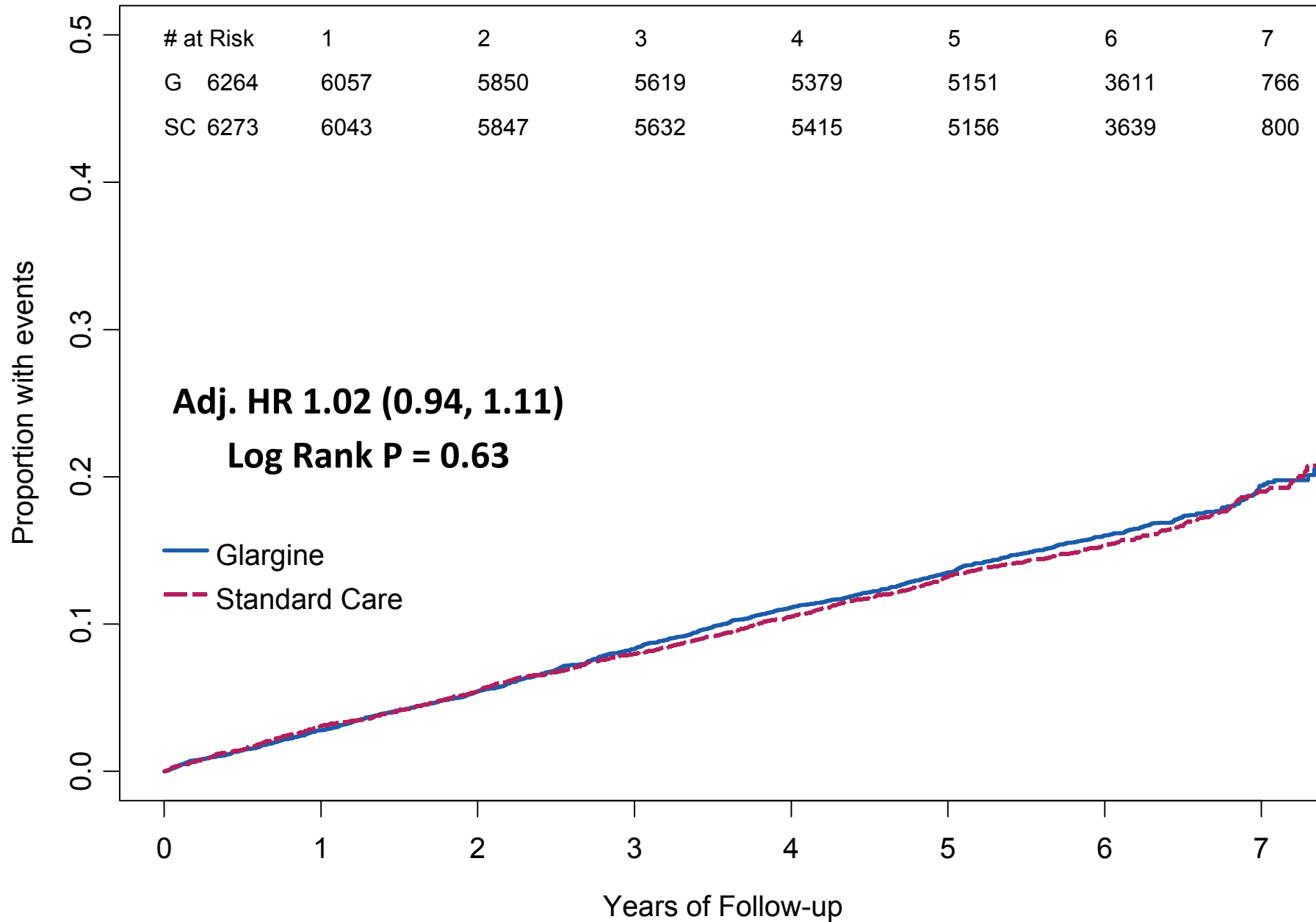


All-cause Death





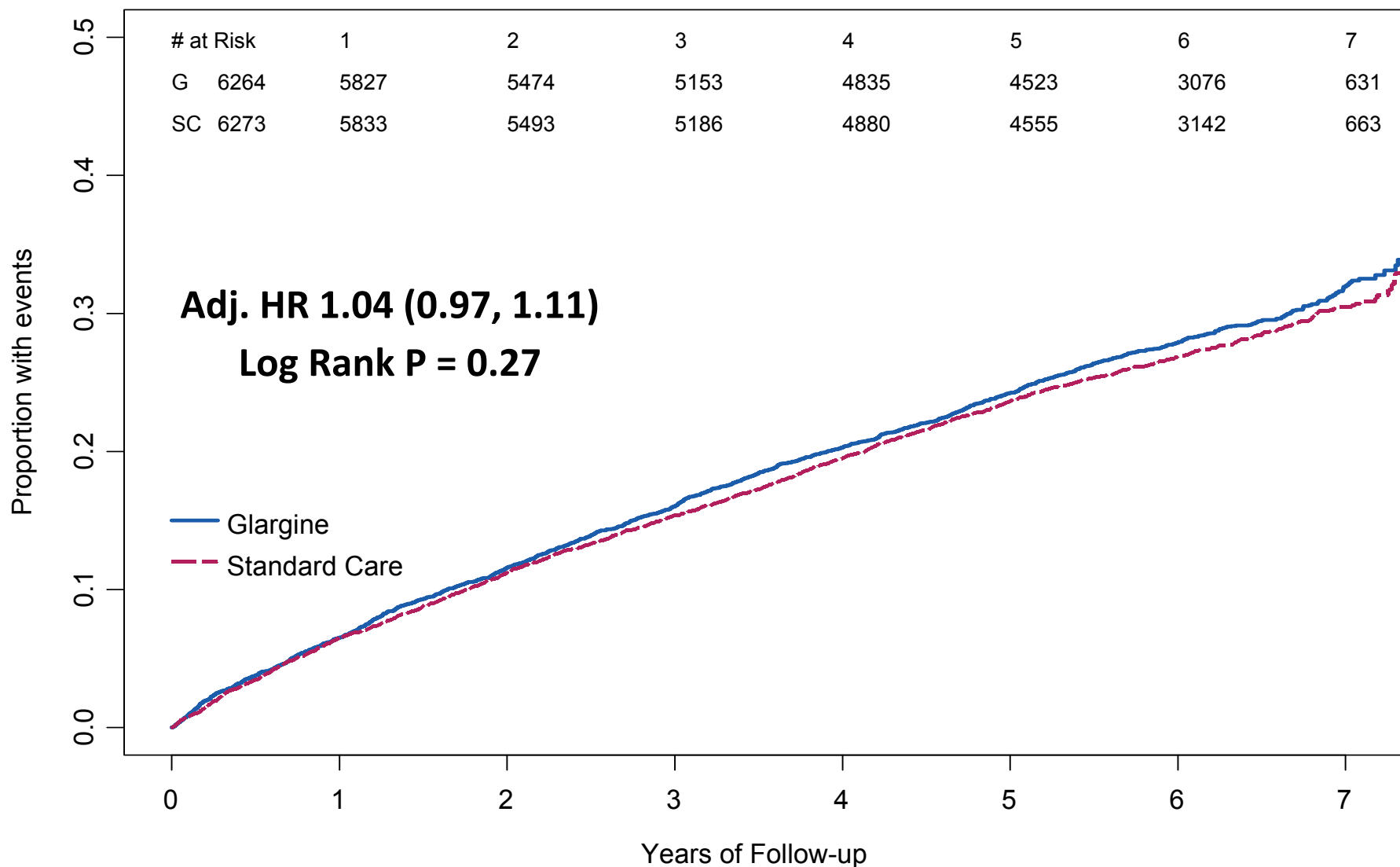
1st Co-primary: MI, Stroke, or CV Death





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

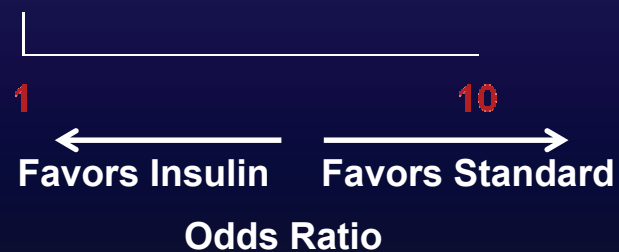
Time to Adjudicated Primary Outcome 2 - CV Death-MI-Stroke-HF Hosp-Revasc





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

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**

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



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 \leq 95 mg/dl 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



Conclusions

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