Beta Cell Function and T2DM: Human Studies

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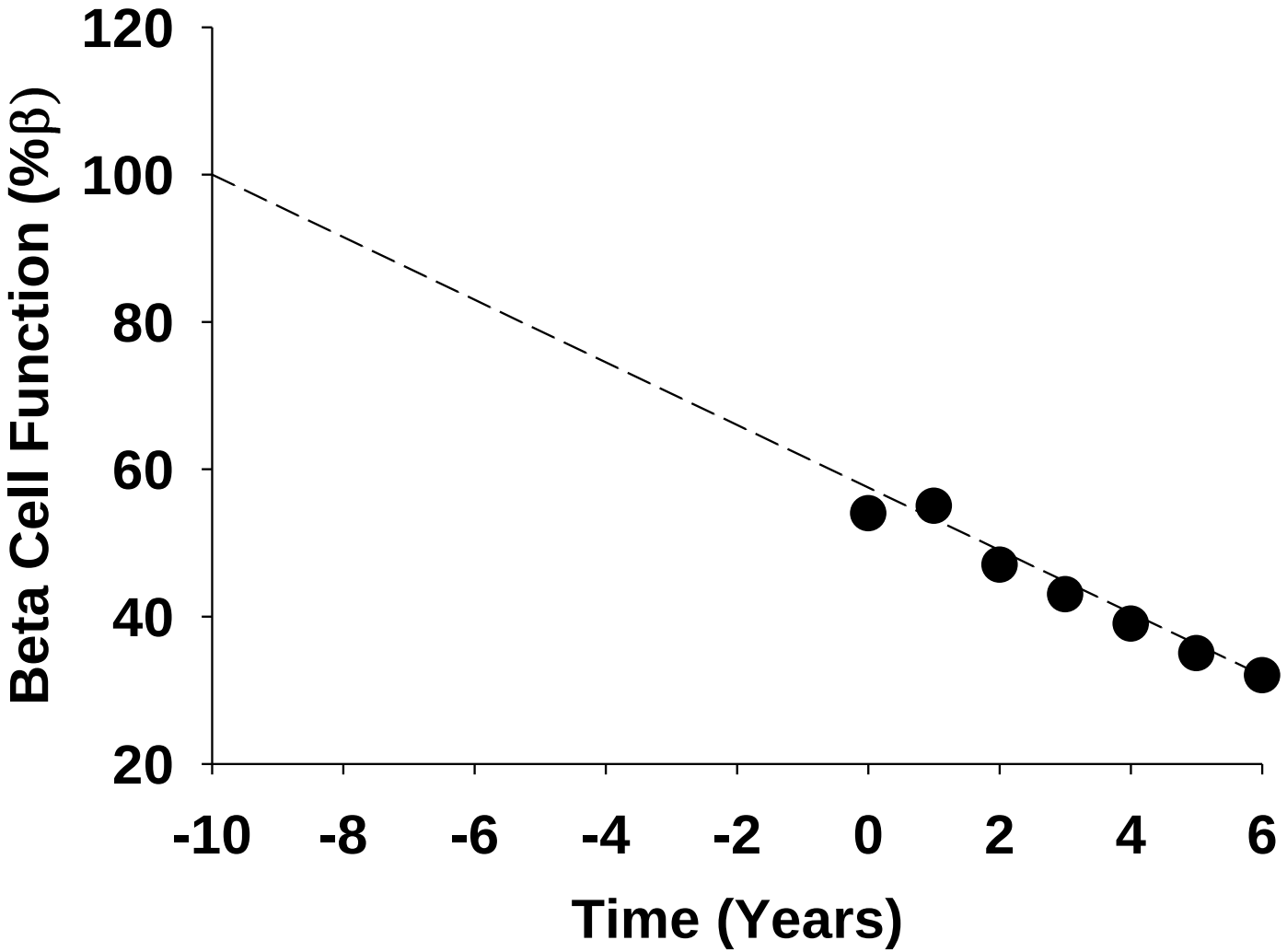
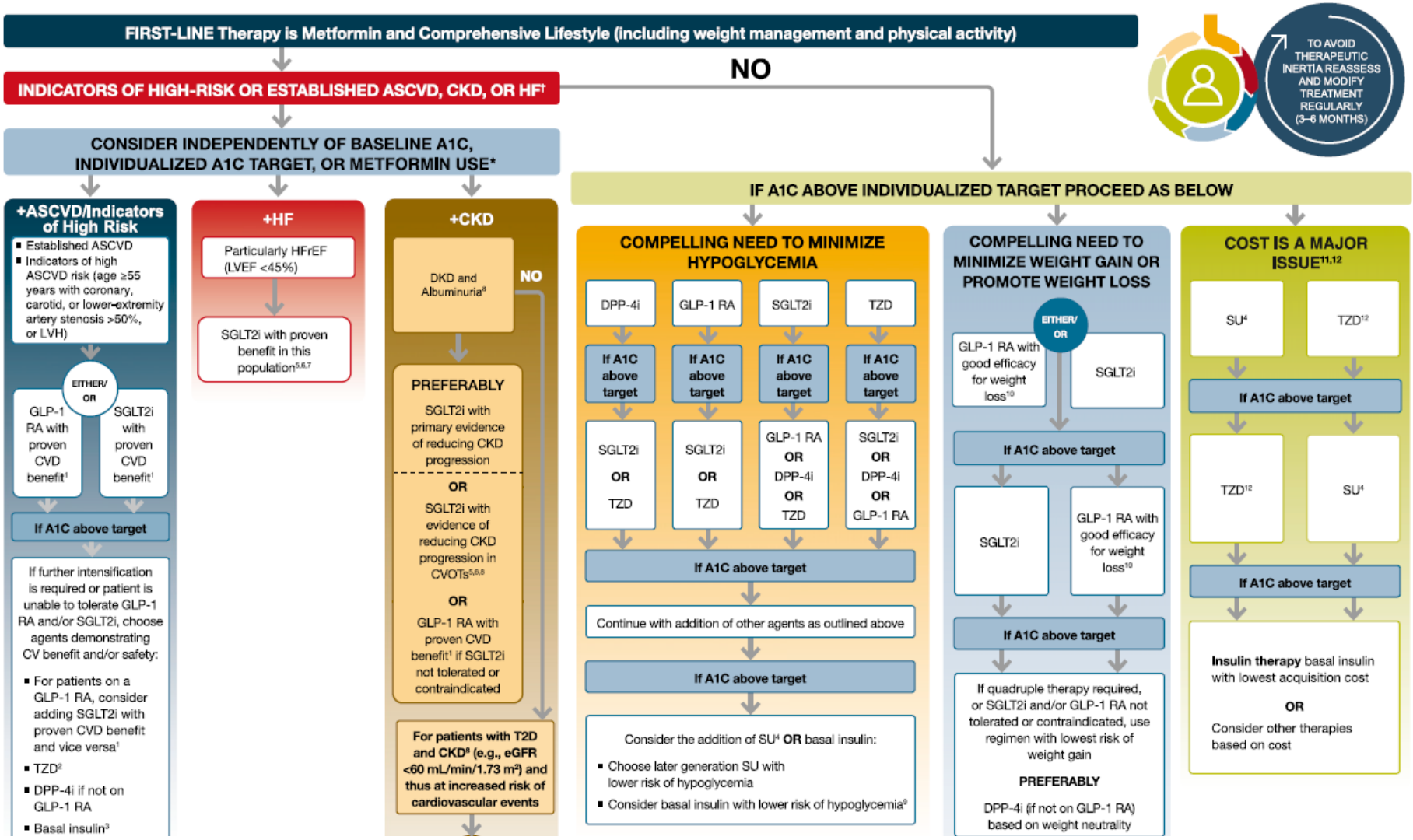
UKPDS: β-Cell Function for the Patients Remaining on Diet for 6 Years

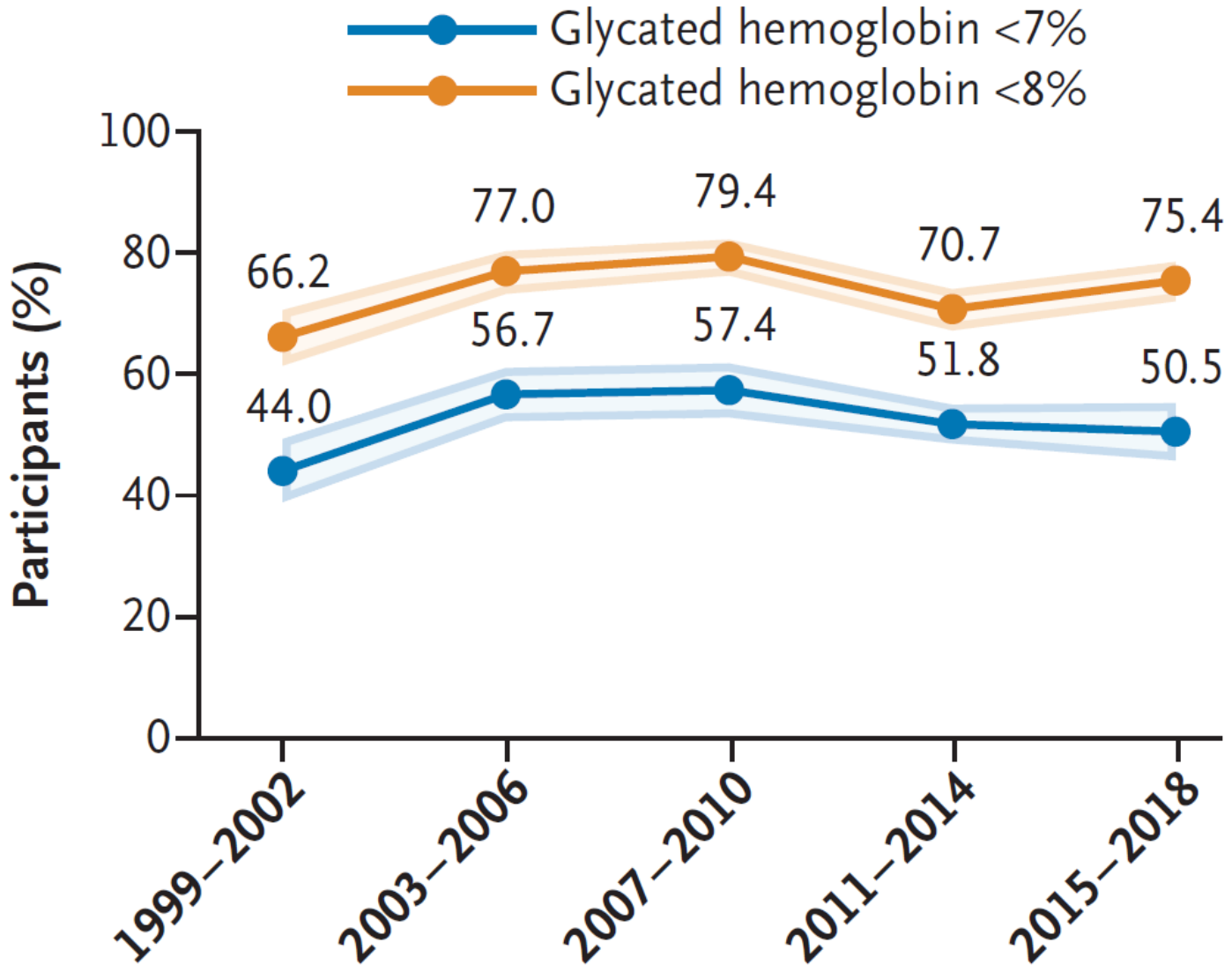
UKPDS Group. *Diabetes.* 1995; 44:1249.



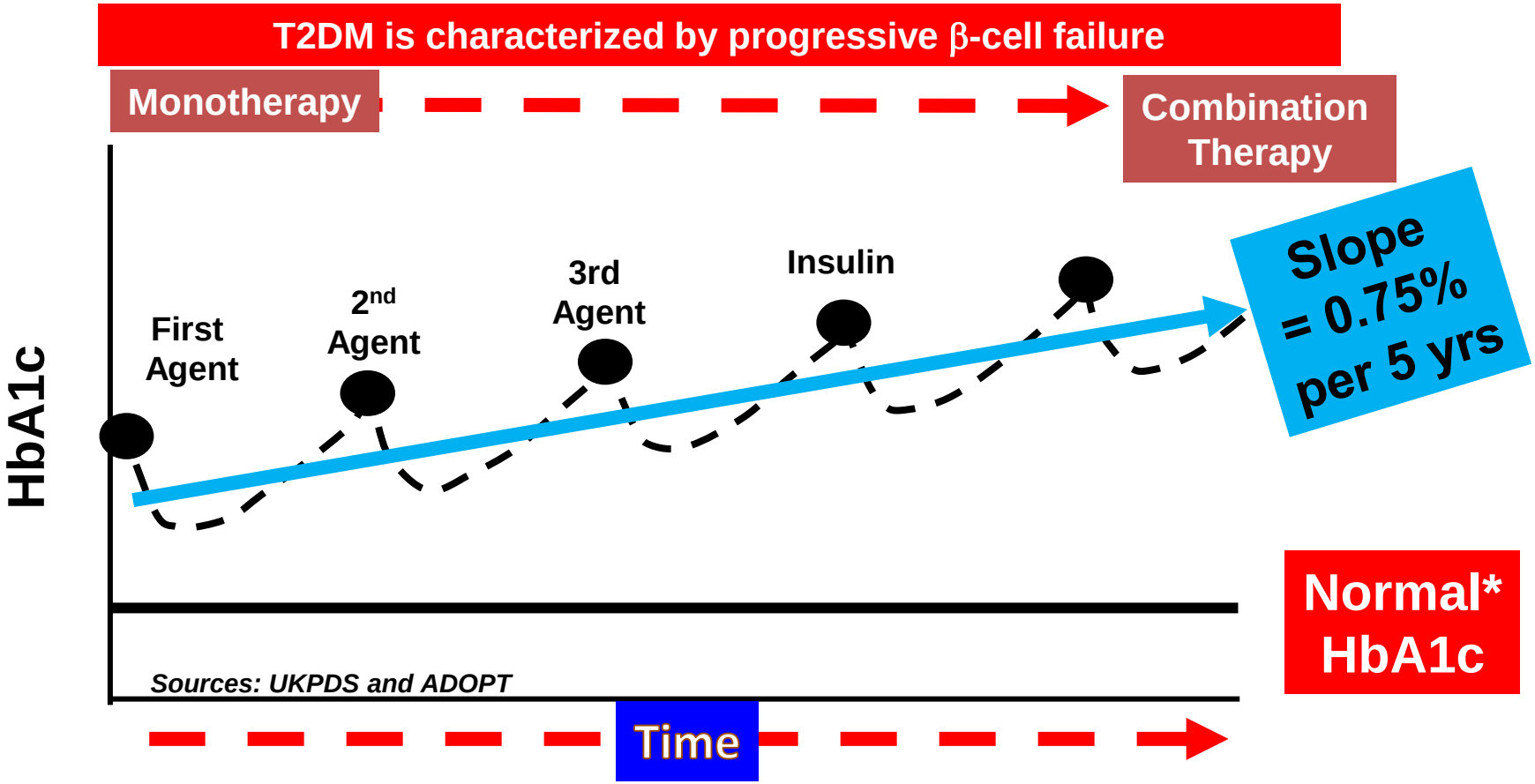
2021 ADA Guidelines for Glycemic Management of T2DM



T2DM Patients (%) with HbA1c <7%



Clinical Inertia in T2DM Management



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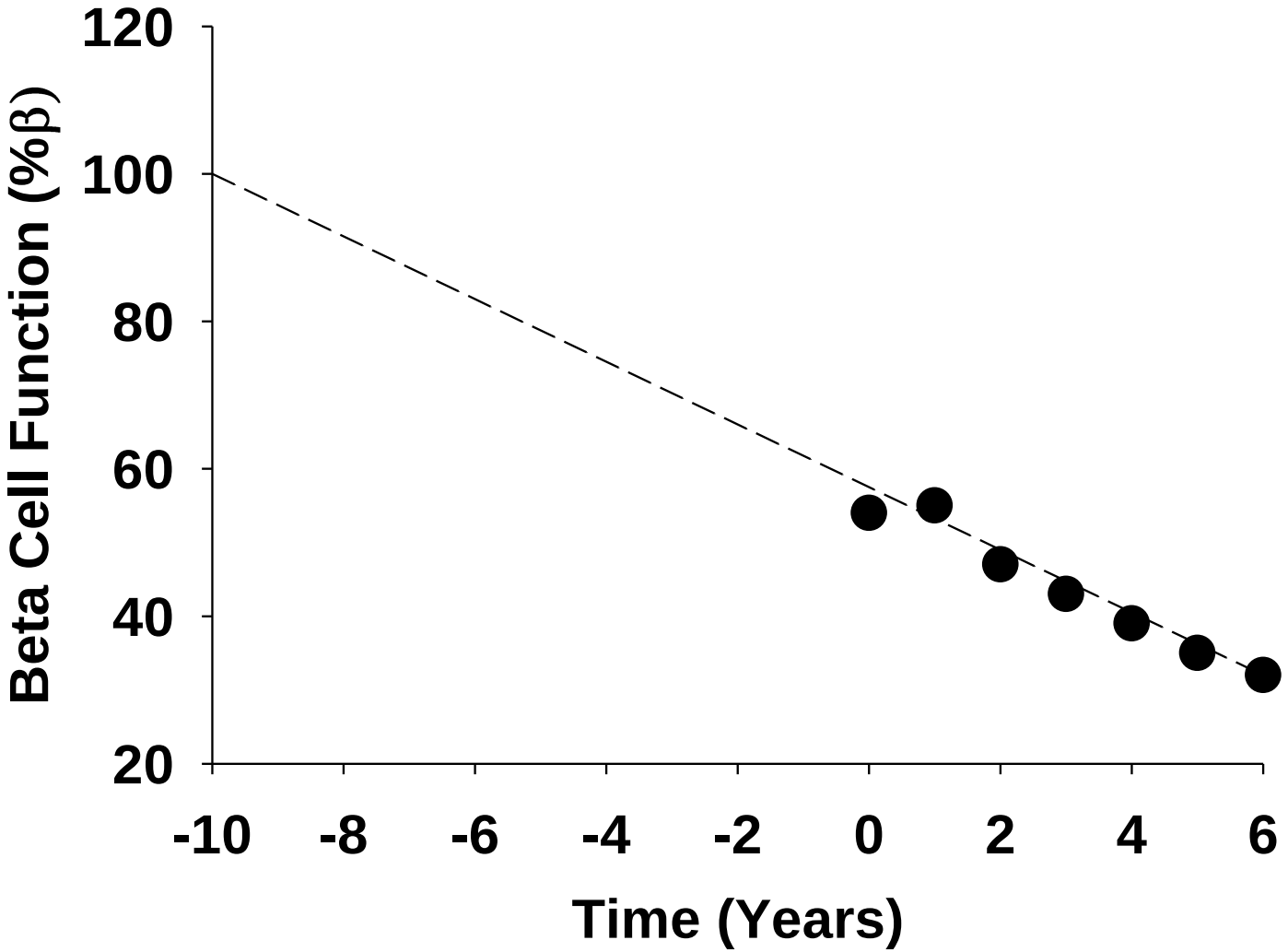
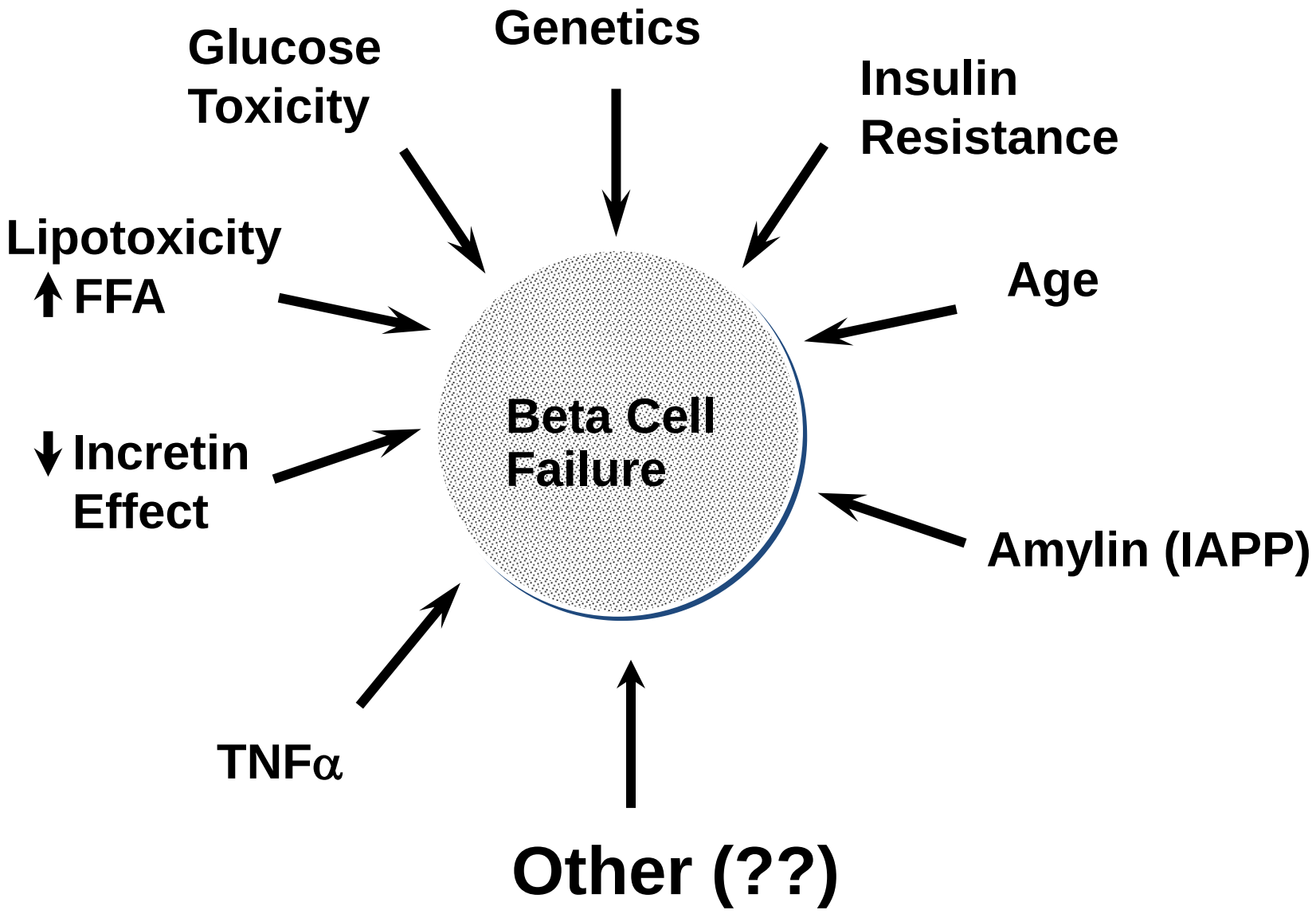


Factors That Influence Beta Cell Function



Impact of Glucose Lowering Medications on Beta Cell Function

Improve Beta Cell Function

- GLP-1 RA
- Thiazolidinediones
- SGLT2 Inhibitors
- DPP-4 Inhibitors ?

- **No Effect On beta Cell**
- Metformin
- Sulfonylurea
- Glycoside Hydrolase Inhibitors
- Insulin

The Decrease in HbA1c Is Strongly Related to the Improvement in Beta Cell Function

Effect of Liraglutide with and Without Canagliflozin on Beta Cell Function and HbA1c

- 45 Patients with T2DM

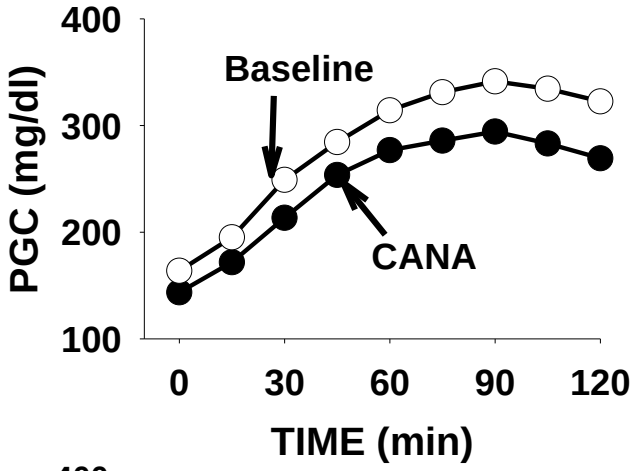
  (Age=53±2; BMI=34.8±1.3; Diabetes Duration=7.4±1.5 y; HbA1c=8.2±0.3%)

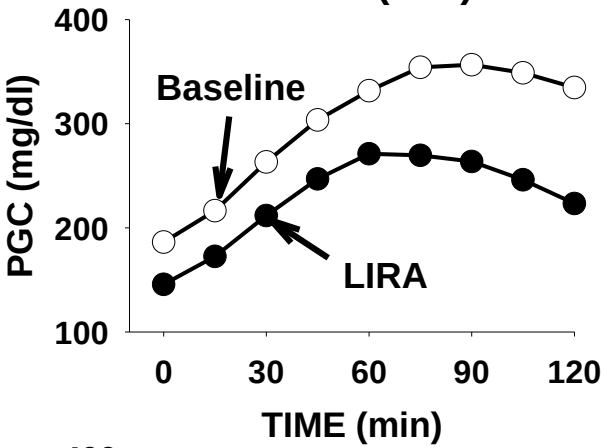
- Randomized to Receive for 4 Months:
  - Liraglutide (1.8 mg/d)
  - Canagliflozin (300 mg/d)
  - Liraglutide (1.8 mg/d) plus Canagliflozin (300 mg/d)

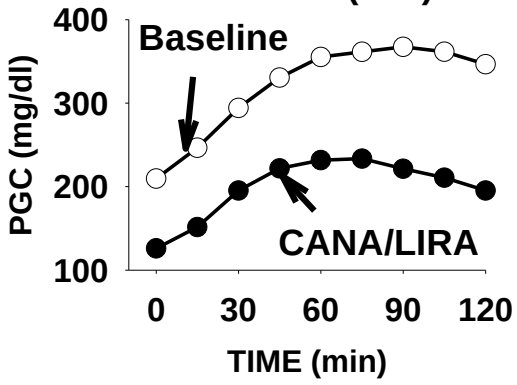
- HbA1c and Beta Cell Glucose Sensitivity were Measured at Baseline and at 4 Months

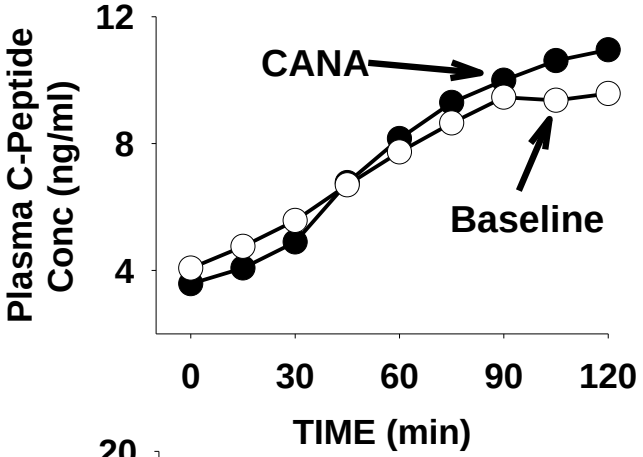
Ali AM. et. al. J Clin Endocrinol Metab 105: 3226–3233, 2020

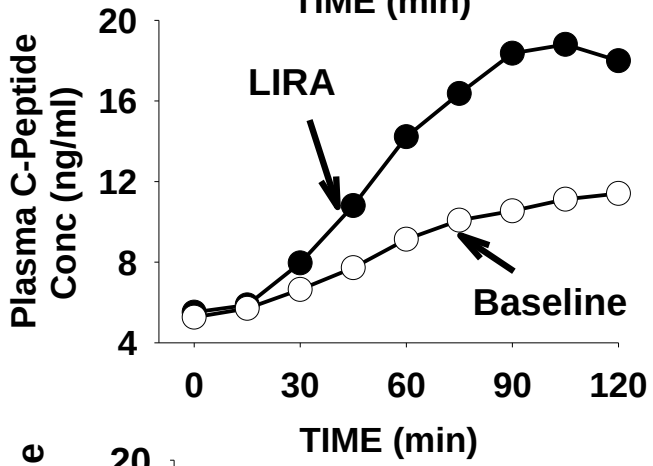
Effect of Liraglutide with and Without Canagliflozin on Plasma Glucose & C-Peptide

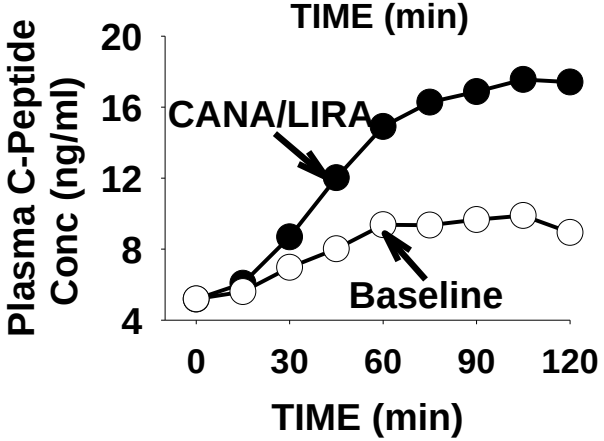




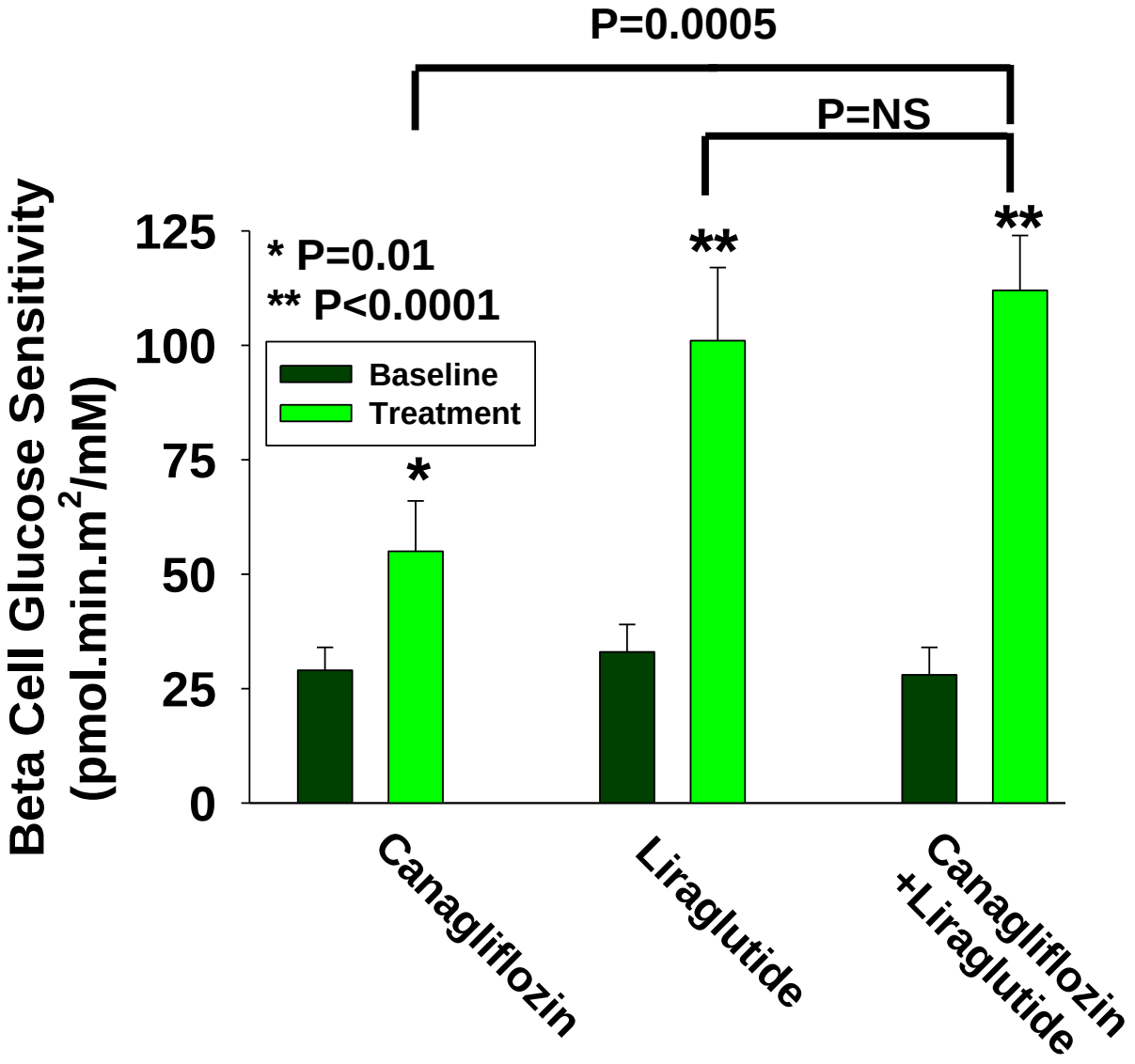




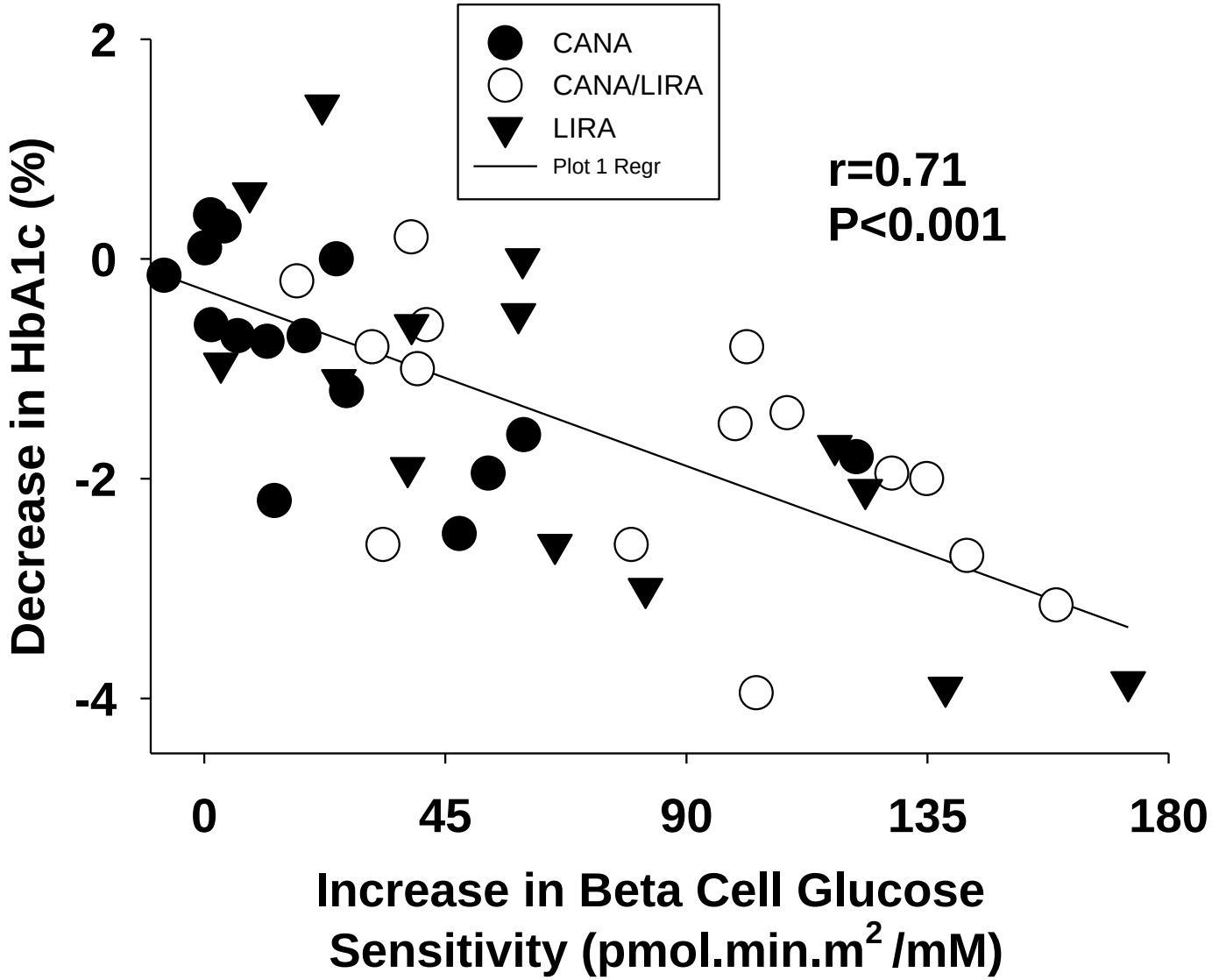




Effect of Liraglutide with and Without Canagliflozin on Beta Glucose Sensitivity

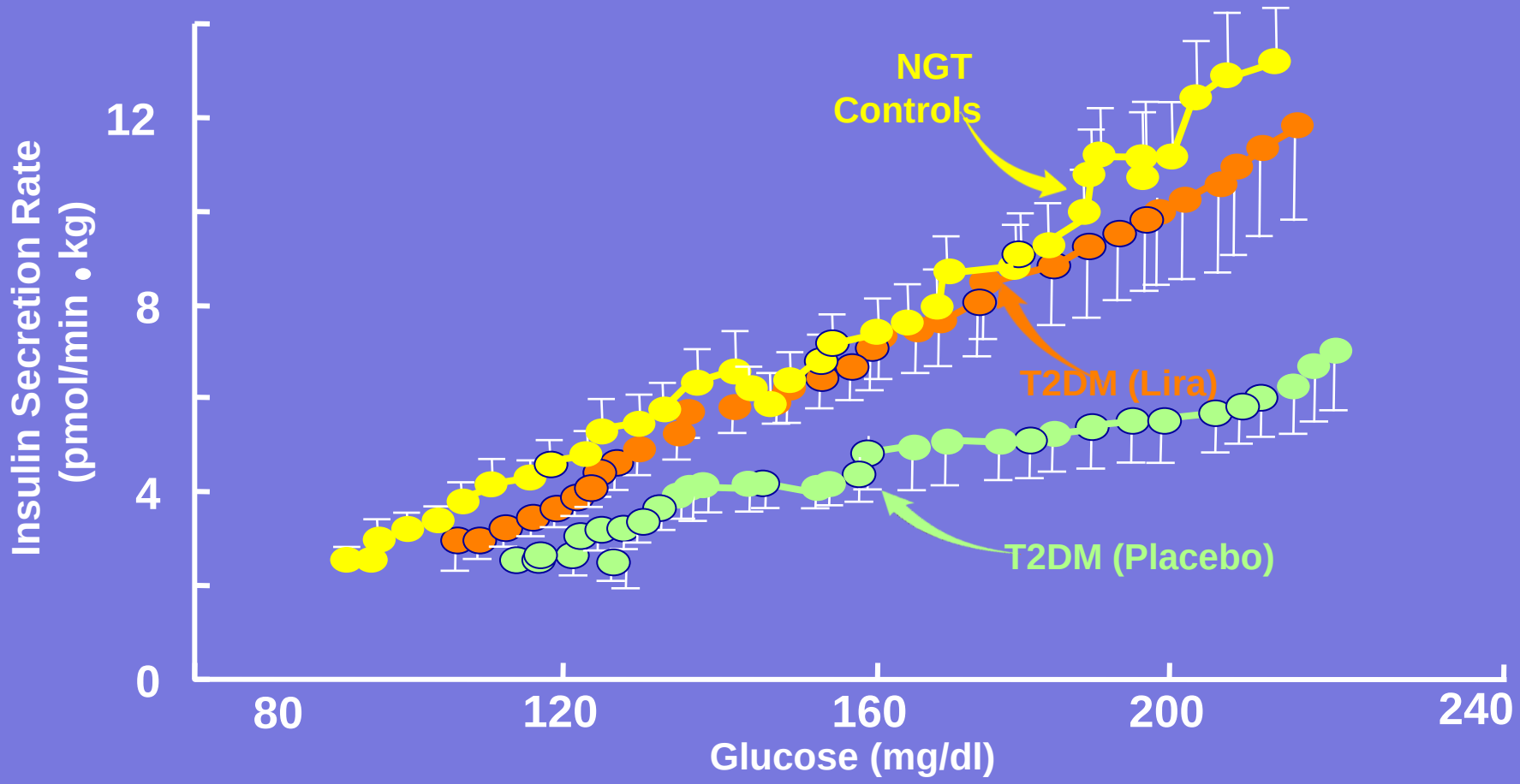


Relationship Between Beta Cell Glucose Sensitivity and Decrease in HbA1c



A SINGLE DOSE OF LIRAGLUTIDE (7.5 ug/kg) RESTORES BETA CELL INSULIN RESPONSE TO HYPERGLYCEMIA IN T2DM PATIENTS

Chang et al, Diabetes 52:1786-91, 2003



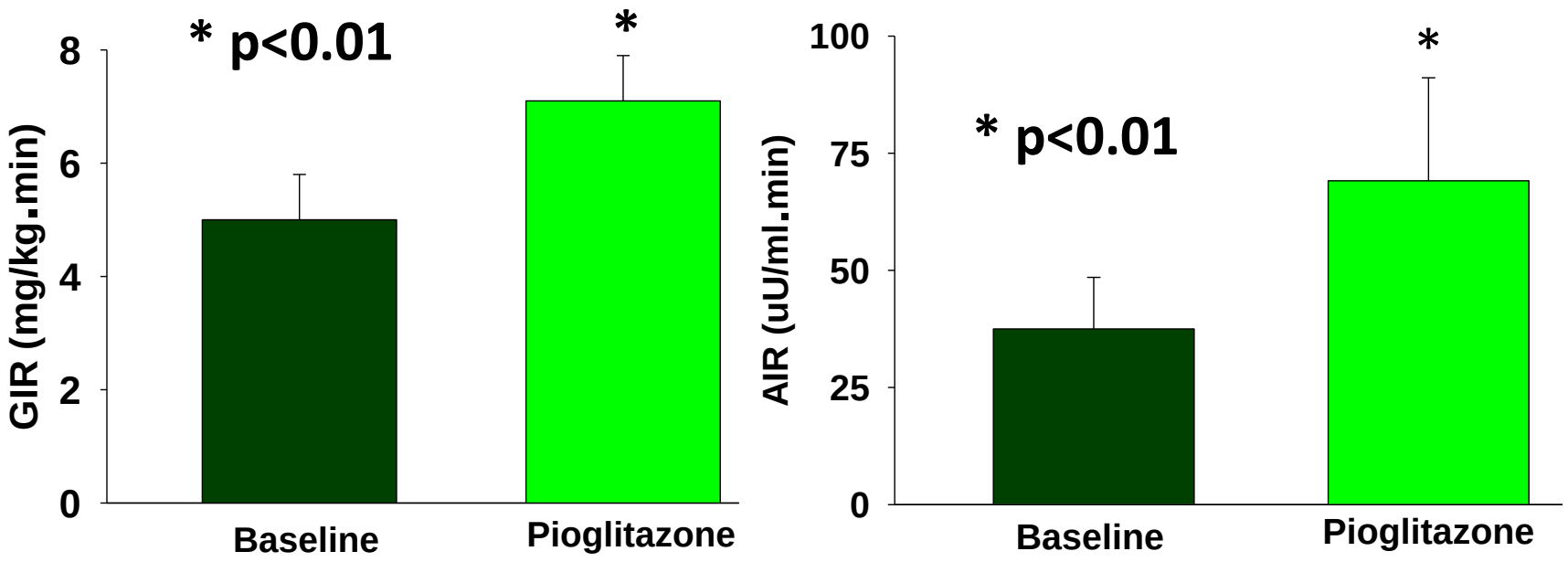
Thiazolidinediones and Beta Cell Function

Study Design

- 68 Drug-naïve T2DM patients (age= 46±1.8; BMI=26.6±1.5; HbA1c=7.6%±1.2).
- Insulin sensitivity measured with the insulin clamp and insulin secretion measured with IVGTT (AIR).
- Patients received 16-week treatment with pioglitazone (45 mg/d). Insulin sensitivity and insulin secretion were measured at baseline and at 16 weeks

Diabetes Ther (2018) 9:815–826

Effect of Pioglitazone on Insulin Sensitivity and Insulin Secretion in T2DM Patients



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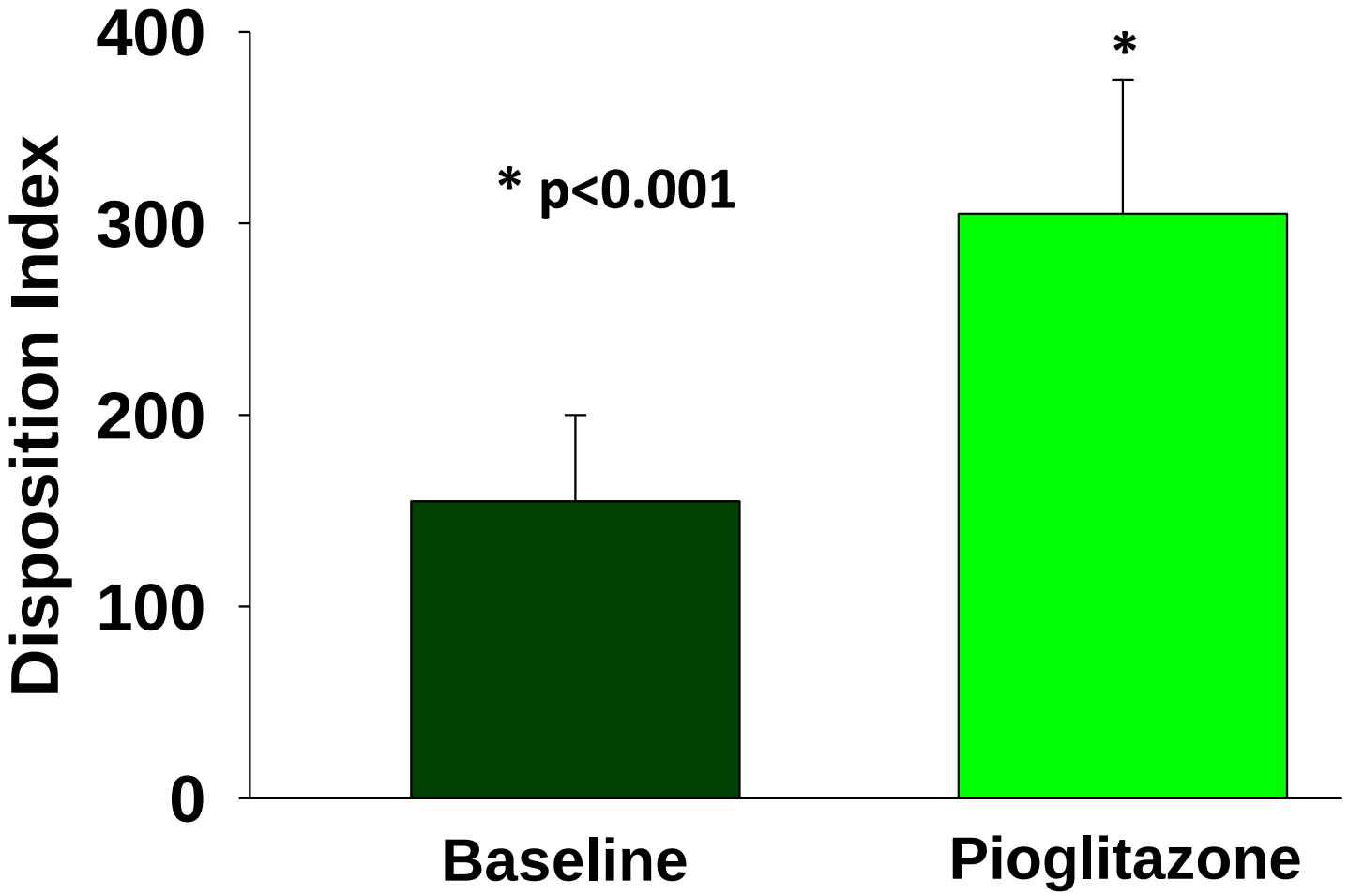
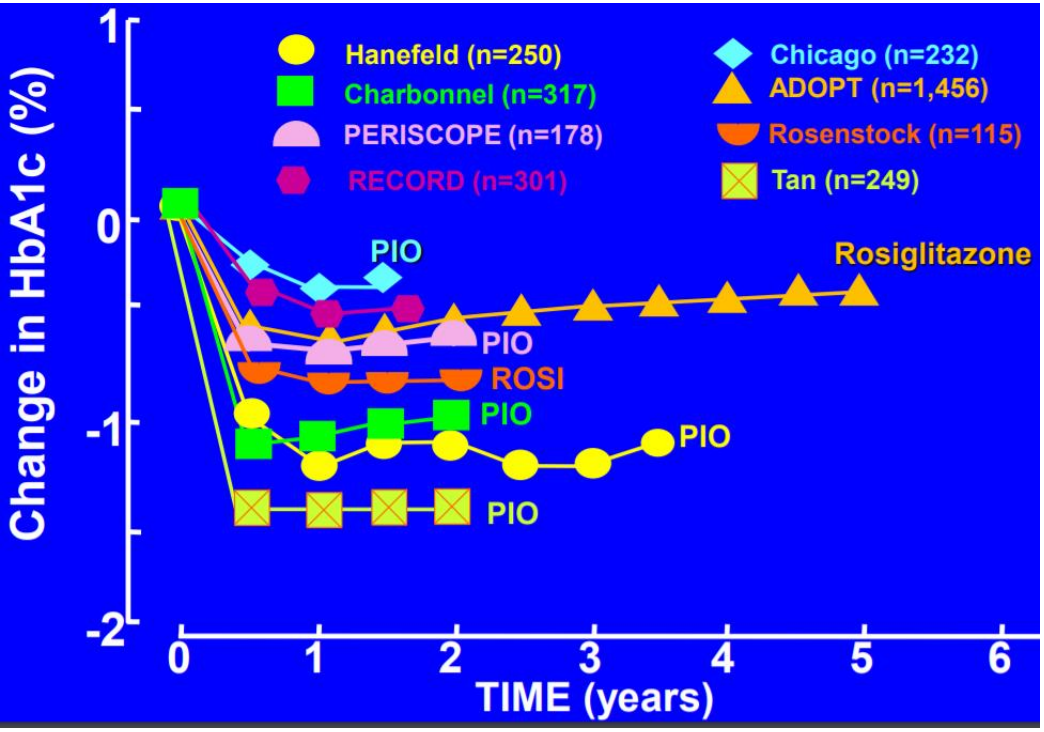
Effect of Pioglitazone on Beta Cell Function in T2DM Patients

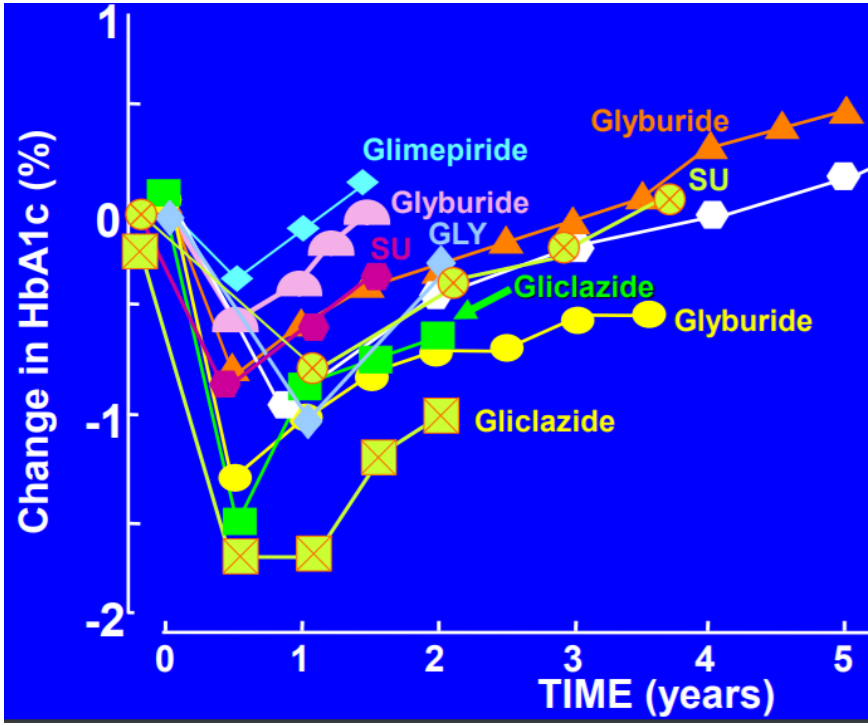


Durability of Glycemic Control With Sulfonylurea and Thiazolidendiones

Thiazolidinediones



Sulfonylureas



DeFronzo RA. Diabetes, 58:773-795, 2009

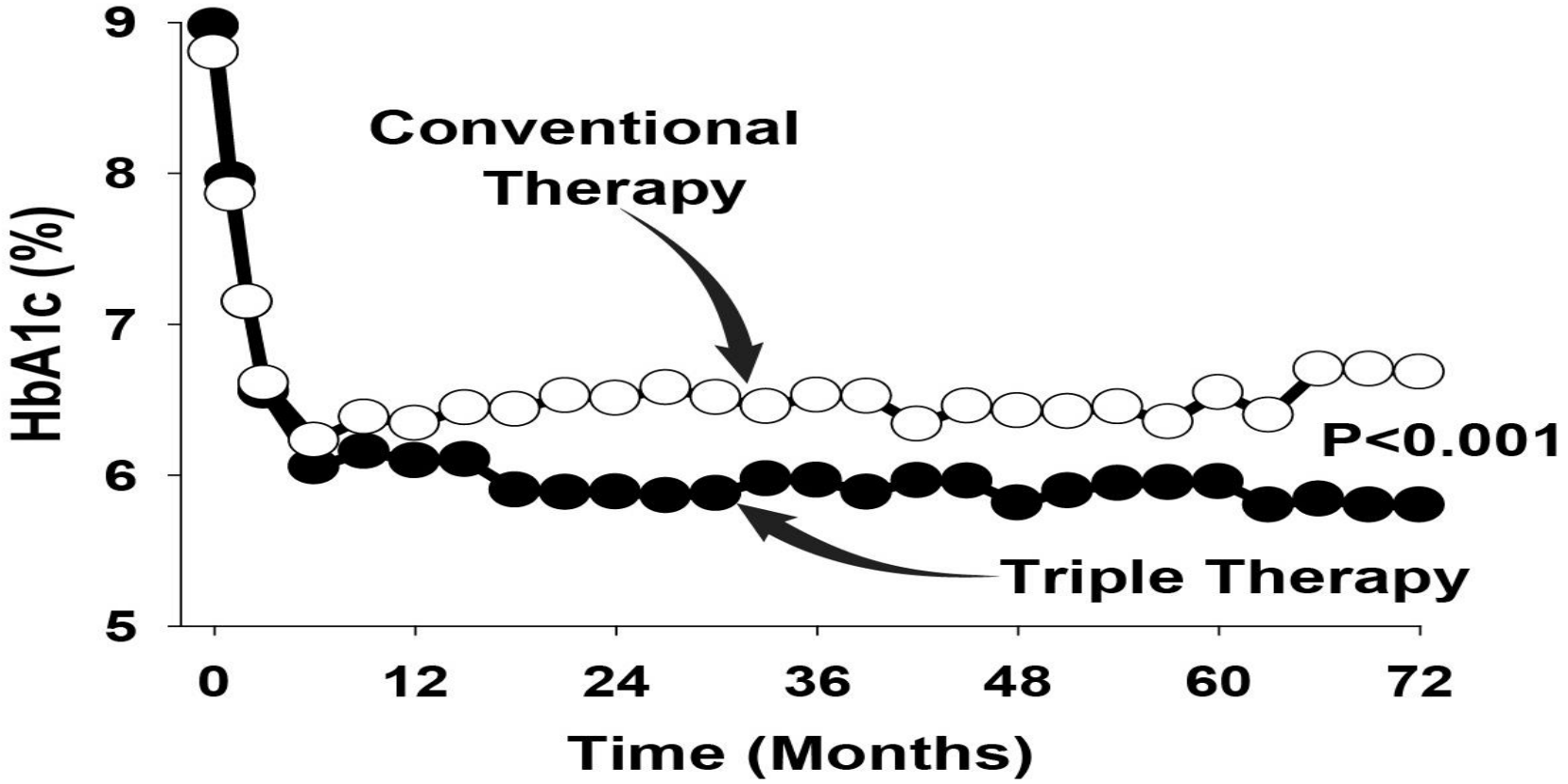
Glucose Lowering Agents That Improve Beta Cell Function Produce **Durable Reduction in the HbA1c**

Effect of Initial Combination Therapy With Agents That Improve Beta Cell Function Versus "Focusing on Glucose Lowering Approach" on Durability of Glycemic Control in Newly Diagnosed T2DM Patients

EDICT- Study Design

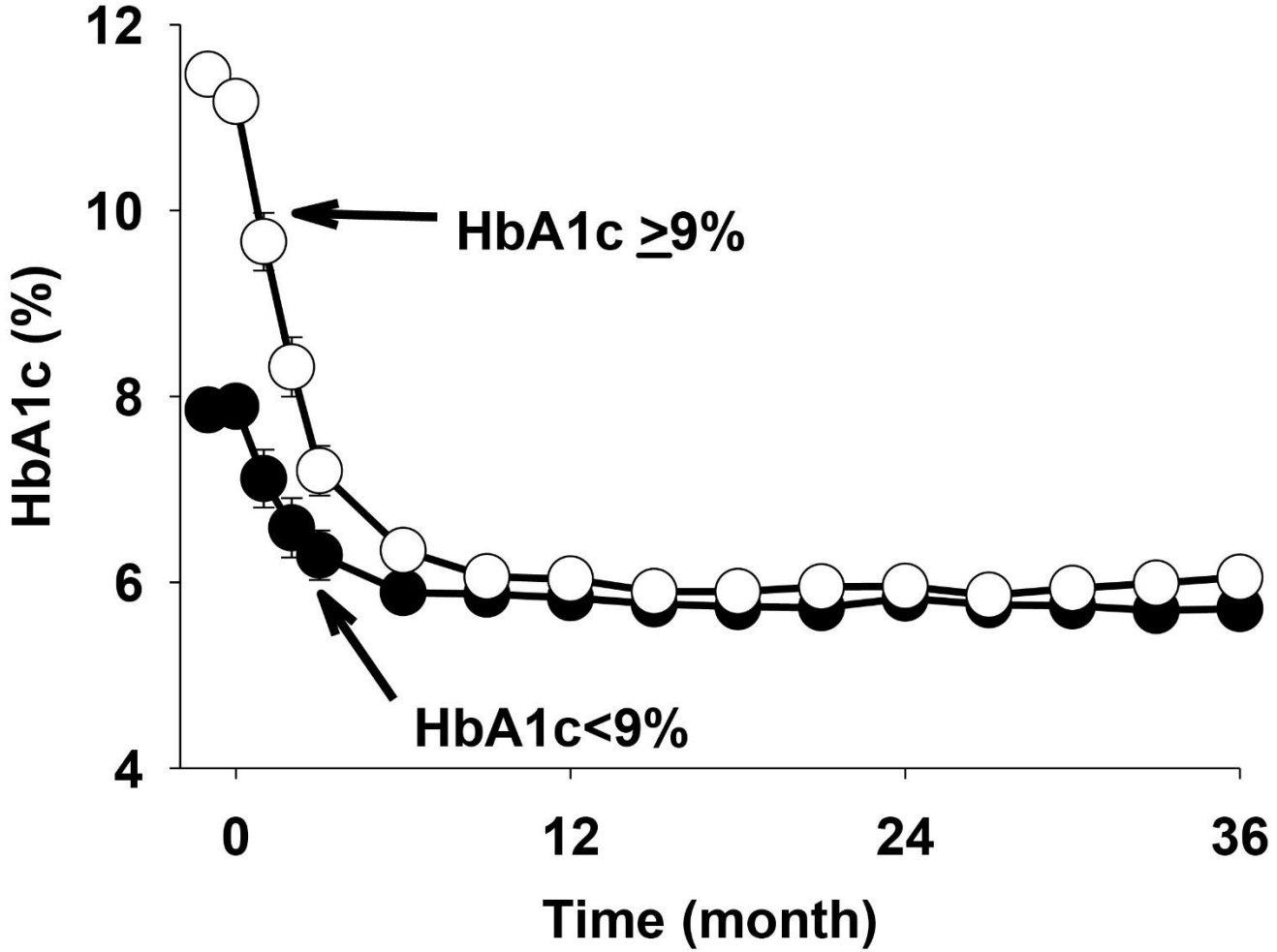
- 323 Newly diagnosed drug naïve T2DM (Age=46, BMI=36, Baseline A1c=8.8%).
- Patients received 75-grams OGTT for the measurement of insulin sensitivity and beta cell function.
- Patients were randomize to receive: (i) initial triple therapy with metformin, pioglitazone & exenatide; or (ii) sequential add on of metformin followed by glipizide and glargine to maintain HbA1c <6.5%.
- HbA1c was measured every 3 months for 3 years.

TIME-RELATED CHANGE IN HbA1c IN TRIPLE AND CONVENTIONAL THERAPY GROUPS AFTER 72 MONTHS

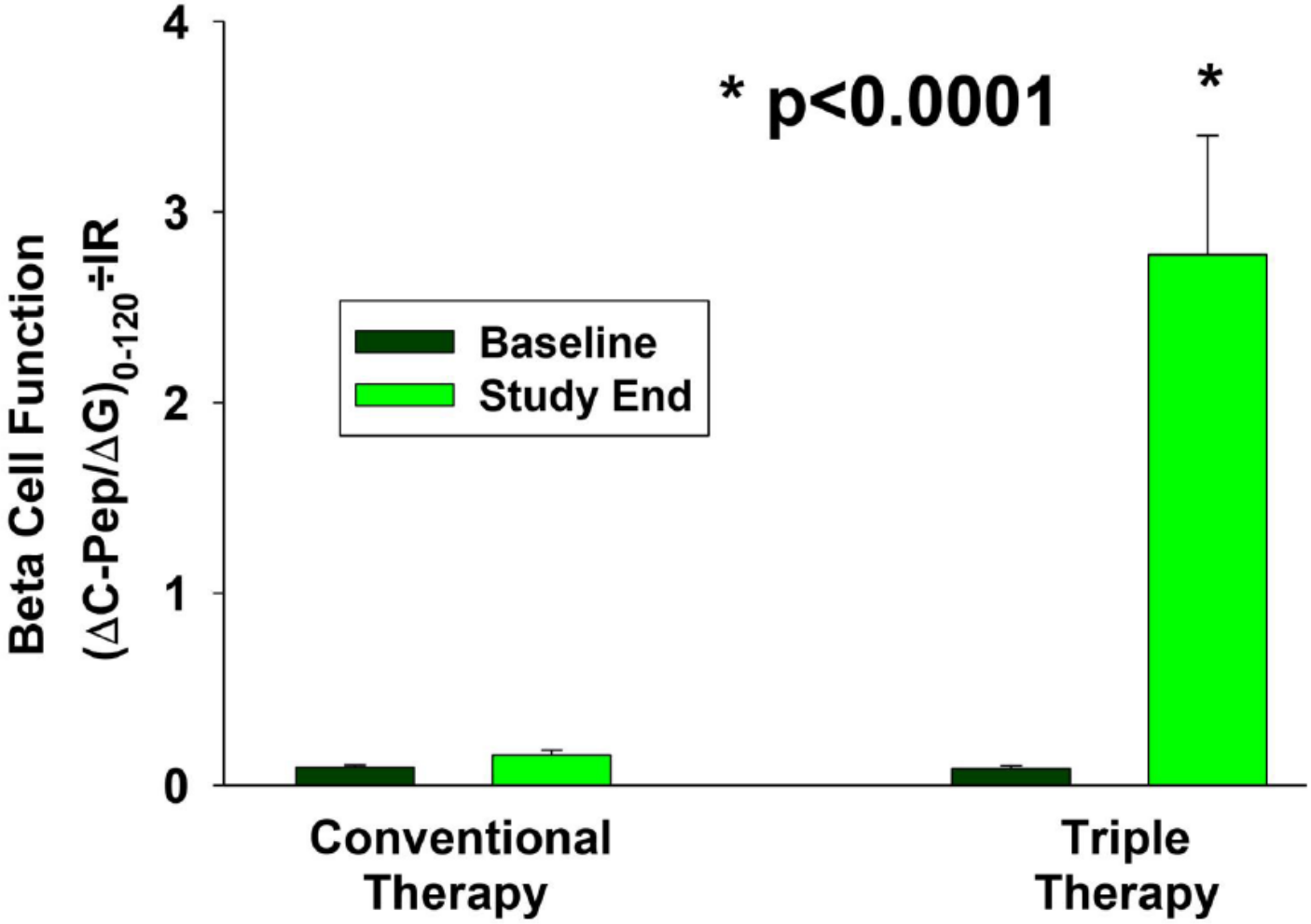


Effect of Baseline HbA1c on Triple Therapy Efficacy

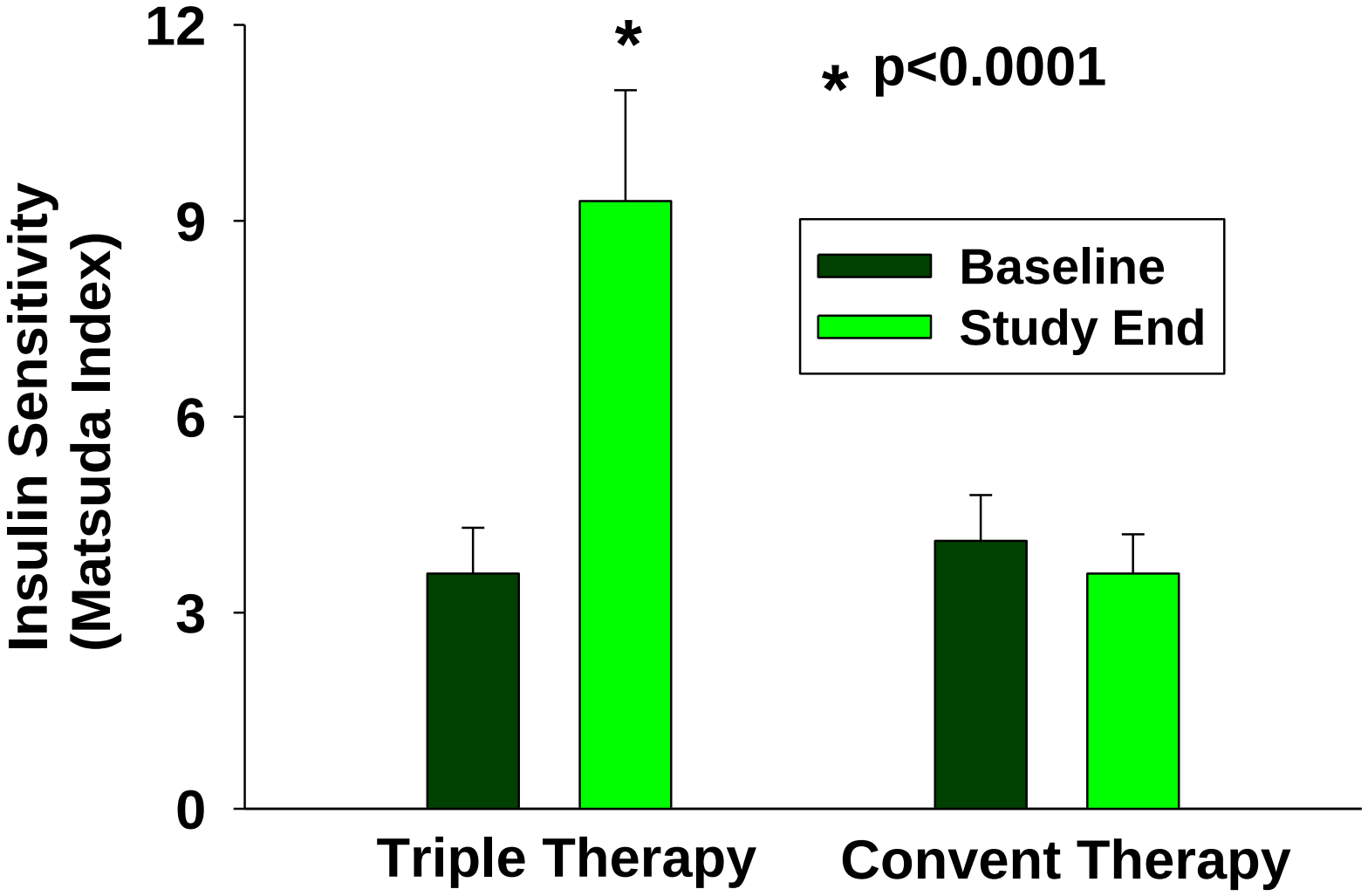
Abdul-Ghani et.a. Diabetes Care. 44:433-439, 2021



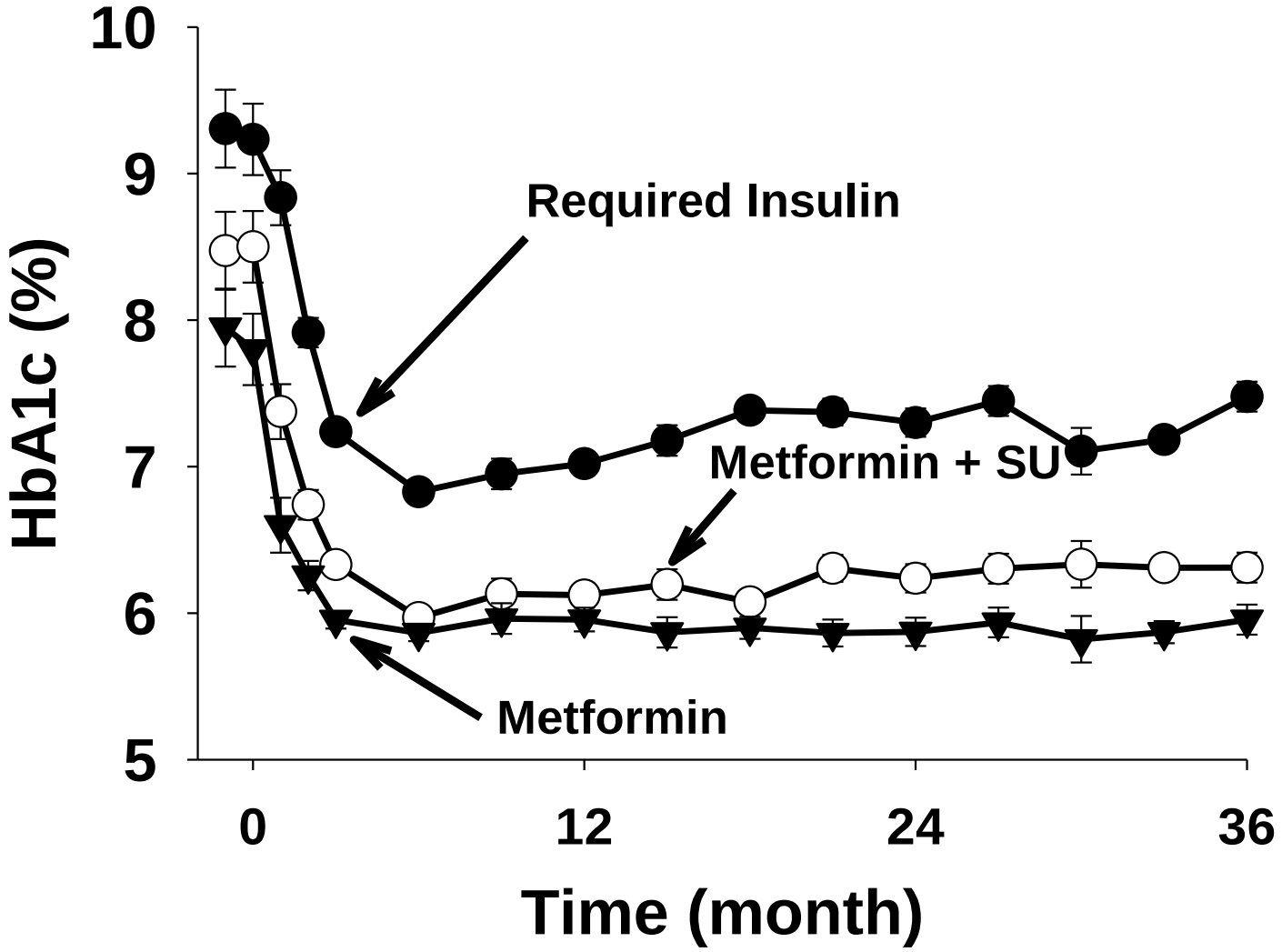
Effect of Therapy on Insulin Secretion



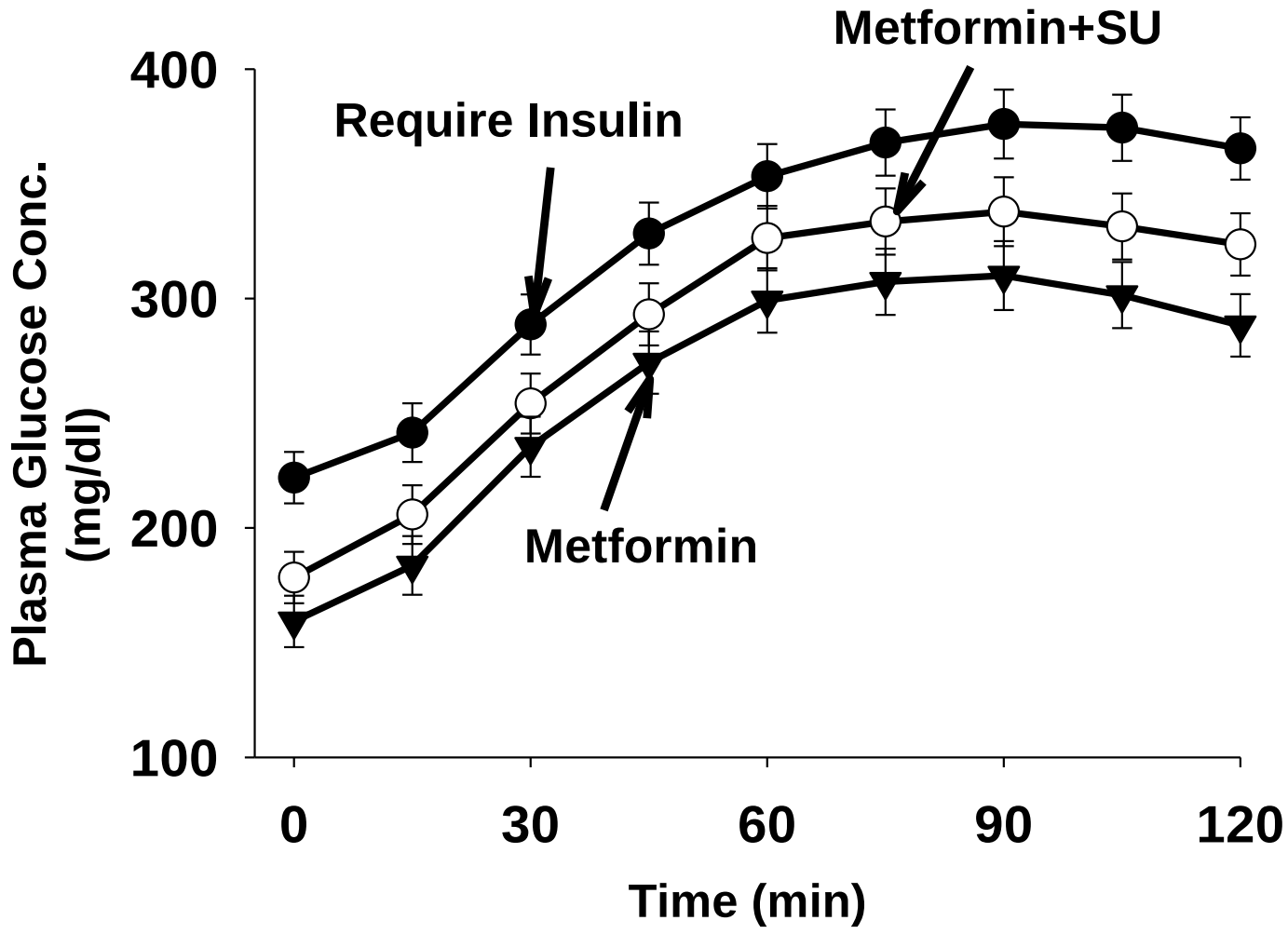
Effect of Therapy on Insulin Resistance



Time-Dependent Change in HbA1c in Subjects Achieving the Goal With Metformin Alone or Require Other Agents



Plasma Glucose Concentration in Subjects Achieving the Goal With Metformin Alone or Require Other Agents



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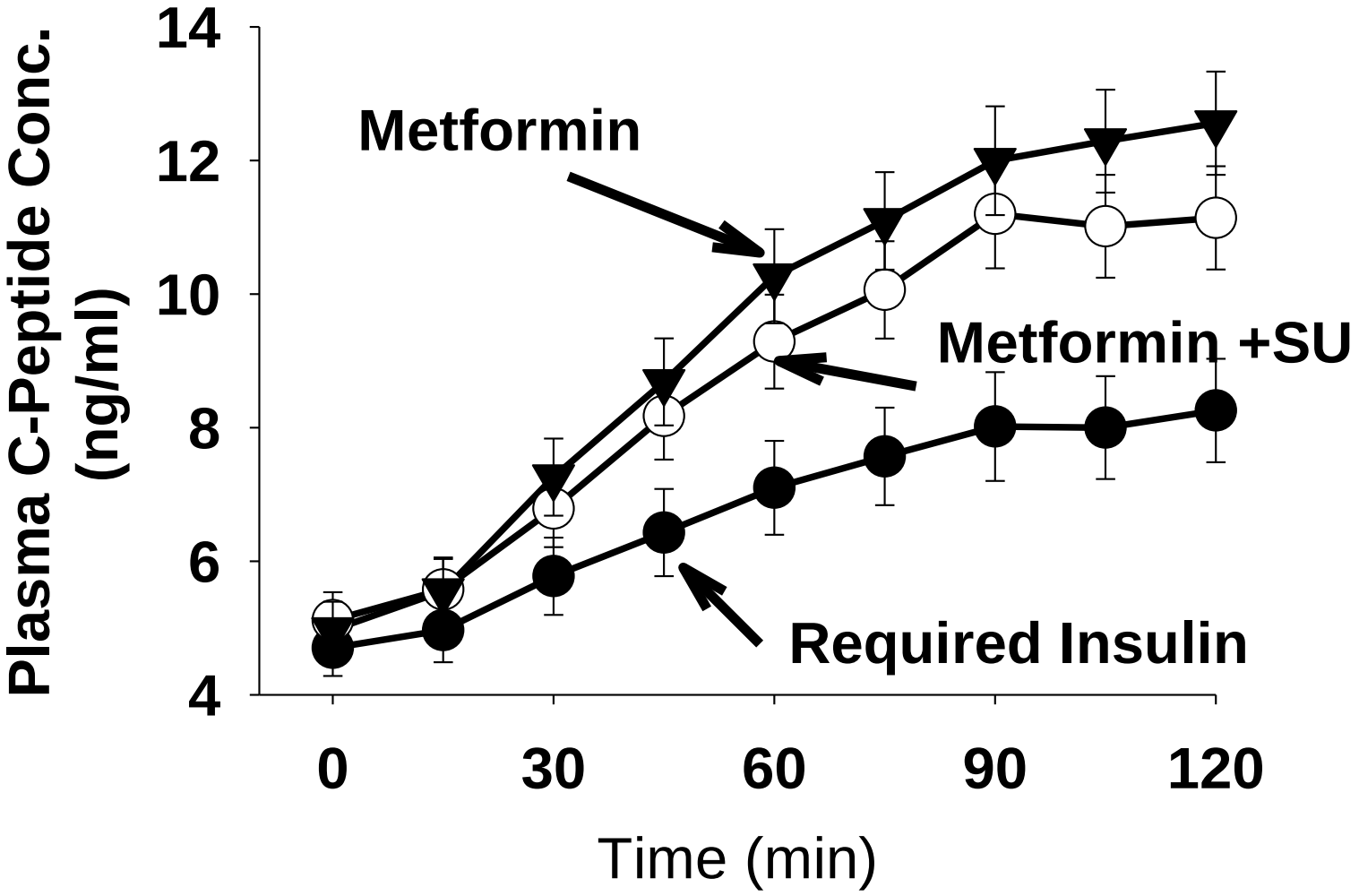
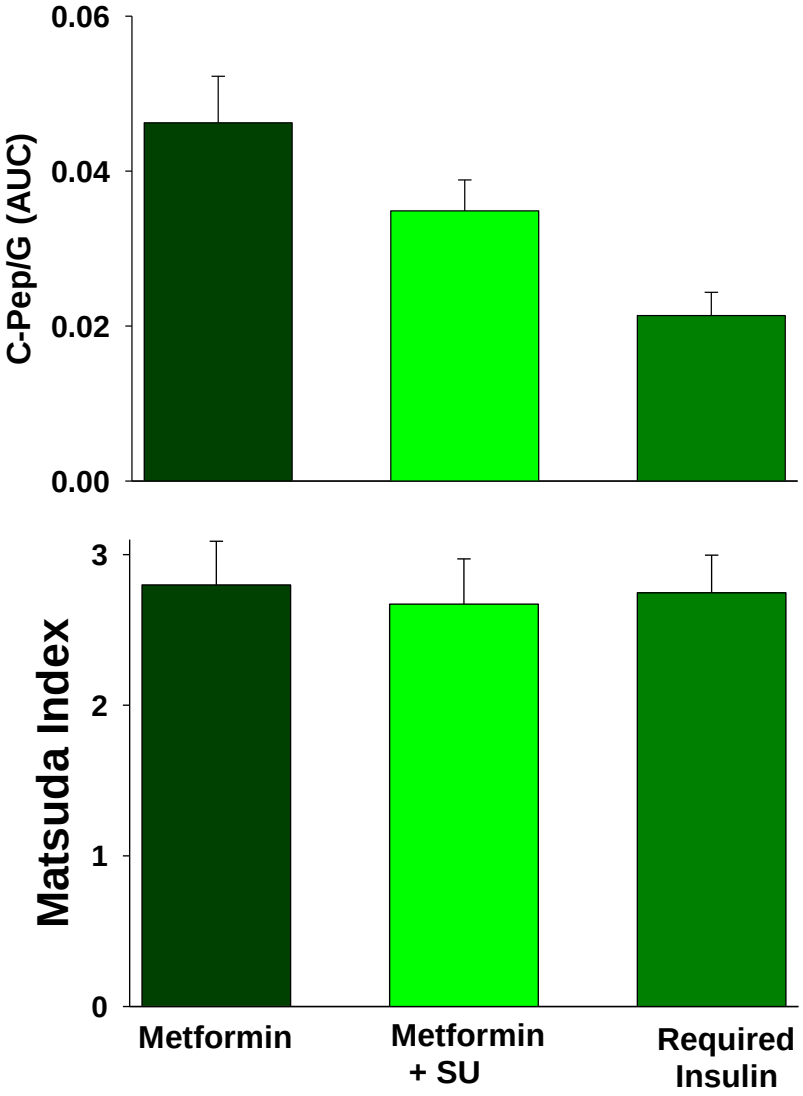


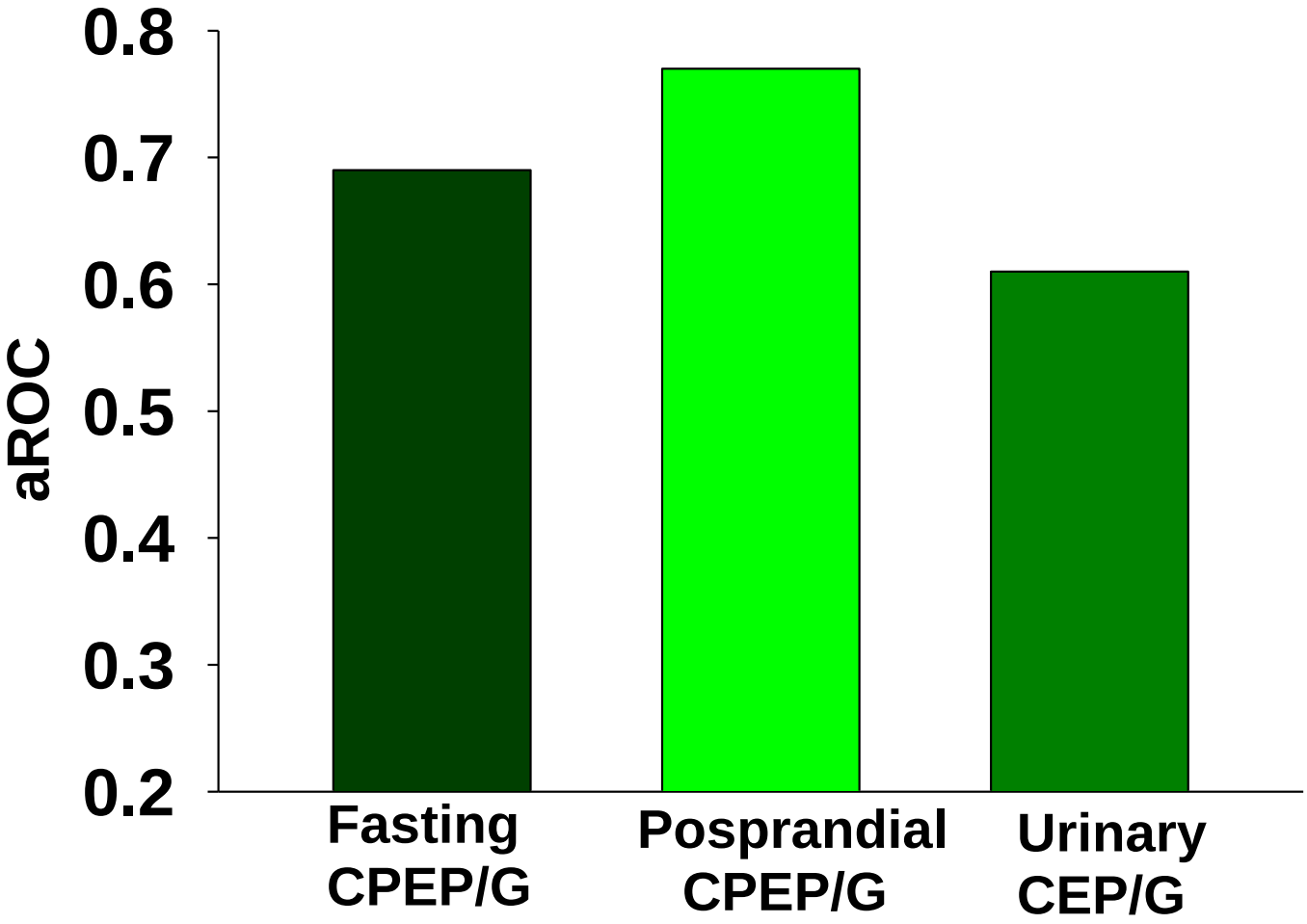
Insulin Secretion and Resistance in Subjects Achieving the Goal With Metformin Alone or Require Other Agents



Predictors of Subjects Achieved the Treatment Goal on Metformin Alone or Needed Insulin

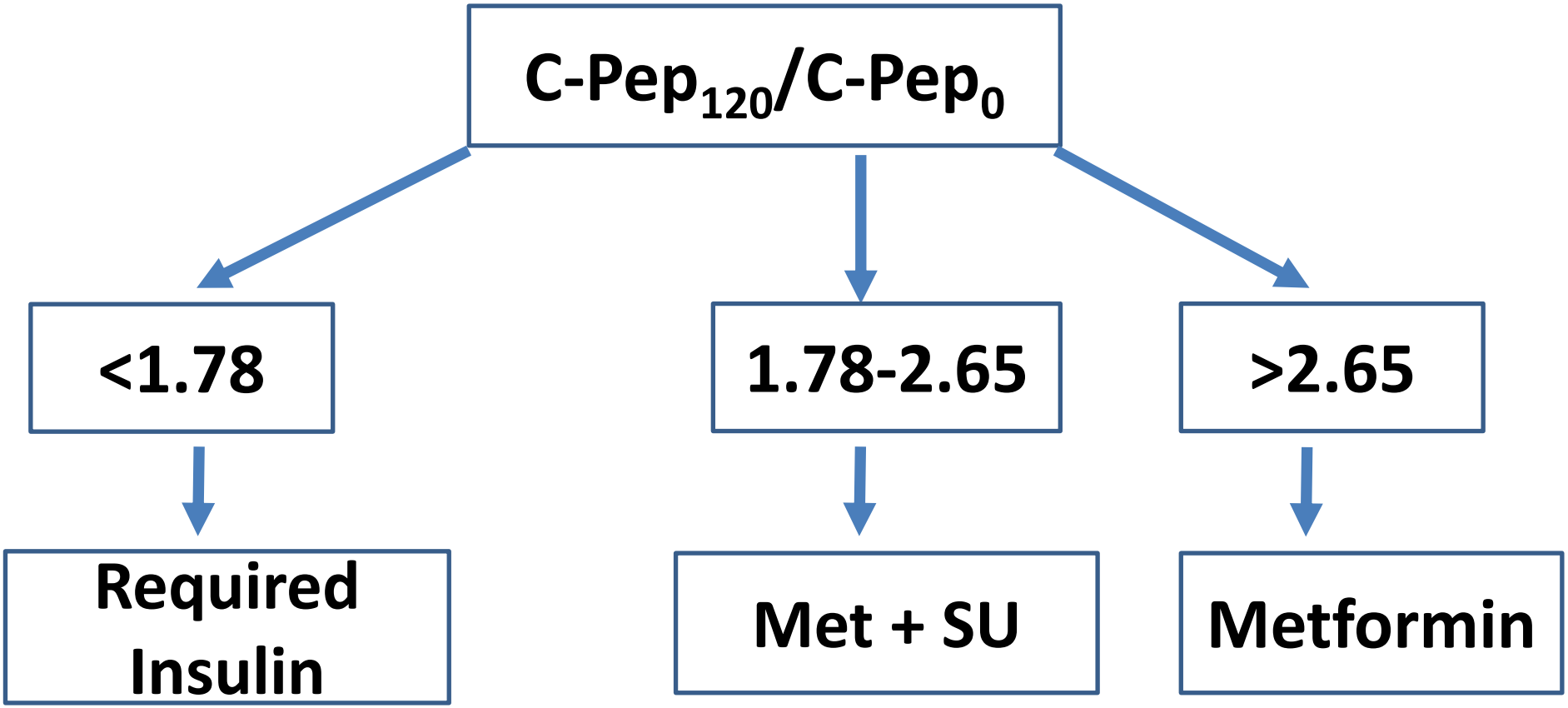
	Metformin Alone	Requiring Insulin
ΔC-pep$_{0\text{-}120}$	0.696	0.737
ΔC-pep$_{0\text{-}120}$/ΔG$_{0\text{-}120}$	0.689	0.715
Insulinogenic Index	0.584	0.649
Matsuda Index	0.523	0.509
ΔC-pep$_{0\text{-}120}$/ΔG$_{0\text{-}120}$ ÷ IR	0.672	0.725
C-pep$_{120}$ minus C-Pep$_{0}$	0.705	0.729
C-Pep$_{120}$/C-Pep$_{0}$	0.724	0.776
HbA1c	0.661	0.677

aROC of C-Peptide to Glucose Ratio in Predicting Requirement for Insulin



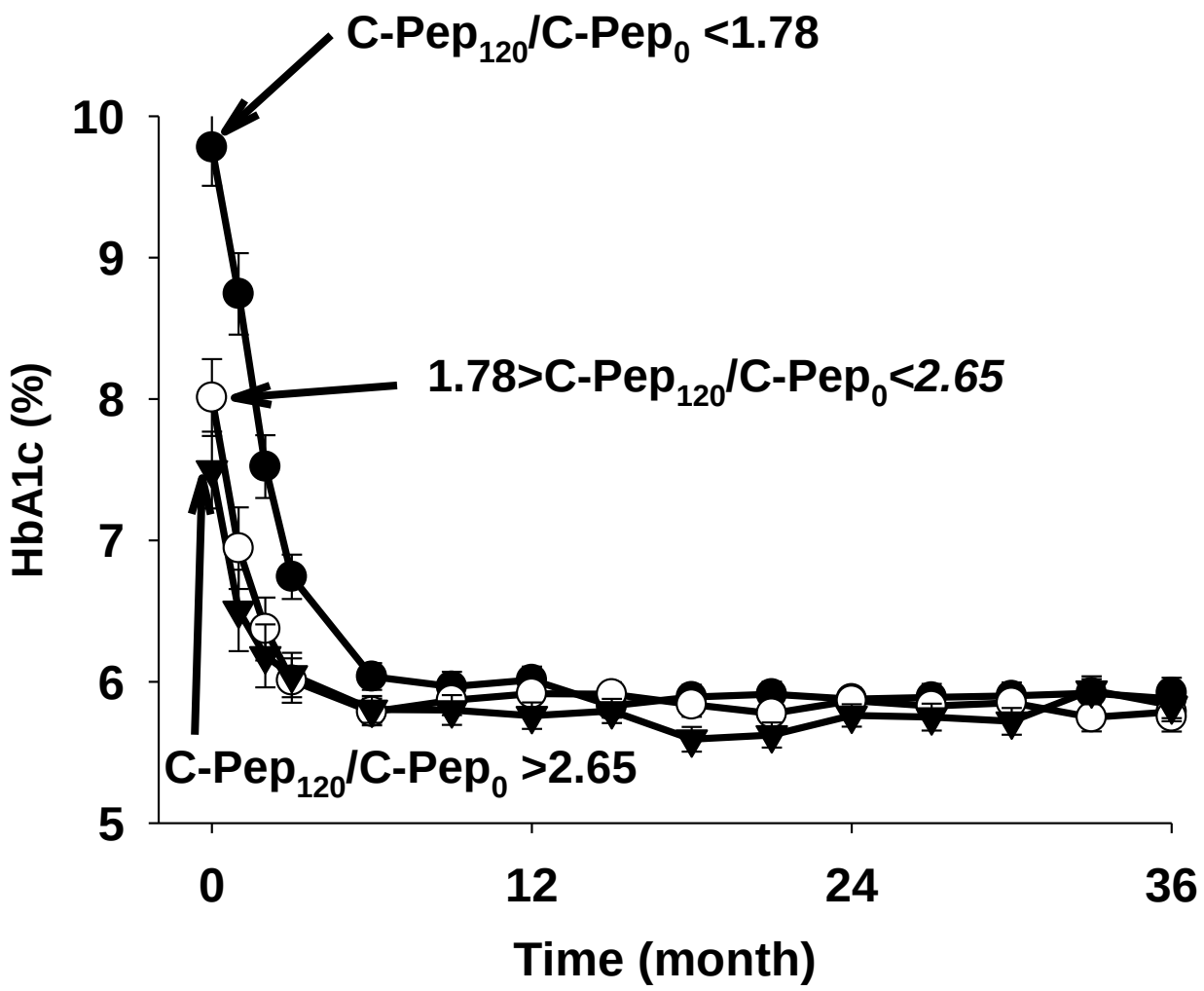
Endocrine Journal 2011, 58 (4), 315-322

Baseline C-Peptide Secretion Markedly Influenced Glucose Lowering Ability Conventional Therapy



Abdelgani et. al. JCEM 106:3497-3504, 2021

Baseline C-Peptide Secretion Did Not Influence Glucose Lowering Ability of Triple Therapy



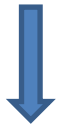
The QATAR Study-Aim

To compare the efficacy of combination therapy with agents that correct known pathophysiologic defects (i.e. pioglitazone plus GLP-1 RA) on glycemic control versus basal/bolus insulin in poorly controlled T2DM patients on metformin plus SU.

Abdul-Ghani et. Al. Diabetes Care. 40:325-331, 2017.

The QATAR Study- Research Design

Poorly Controlled T2DM (>7.5%)
SU + Metformin



GLP-1 RA Plus TZD

Basal-Bolus Insulin

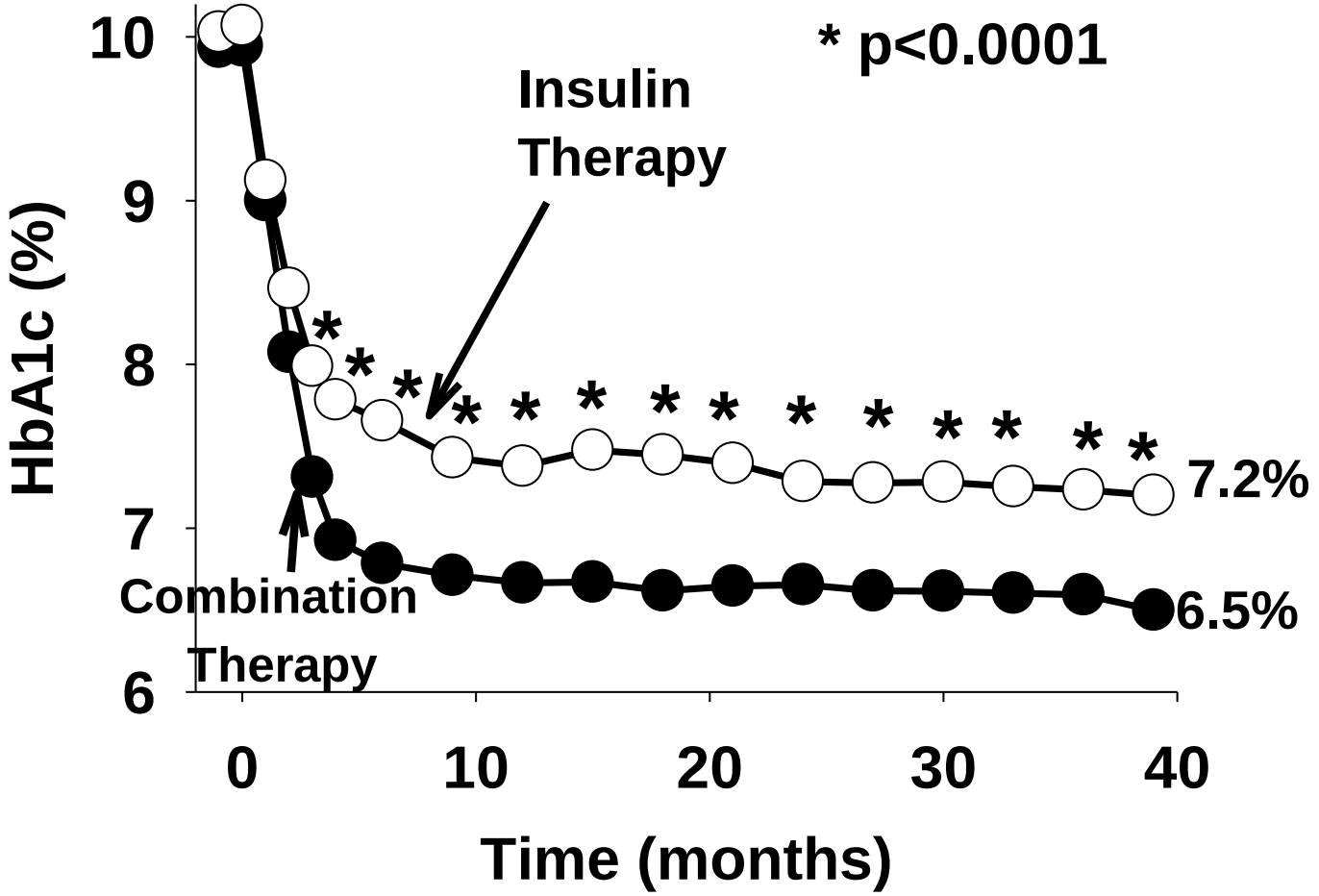
Aim
Maintain HbA1c <7.0%

Baseline Characteristics

	Combination Therapy	Insulin Therapy
Number	161	152
Age (yrs)	52±1	52±1
Sex (male %)	40	37
BMI (kg/m^2)	31.1±0.5	30.5±0.5
Diabetes Duration (y)	10.5±0.5	10.9±0.5
HbA1c (%)	9.9±0.2	10.0±0.2
FPG (mg/dl)	231±8	237±7
Background Therapy		
Metformin mg(%)	1908 (100)	1953 (100)
SU		
Gliclazide mg (%)	101 (58)	106 (42)
Glimepiride mg(%)	7.4 (55)	7.2 (45)

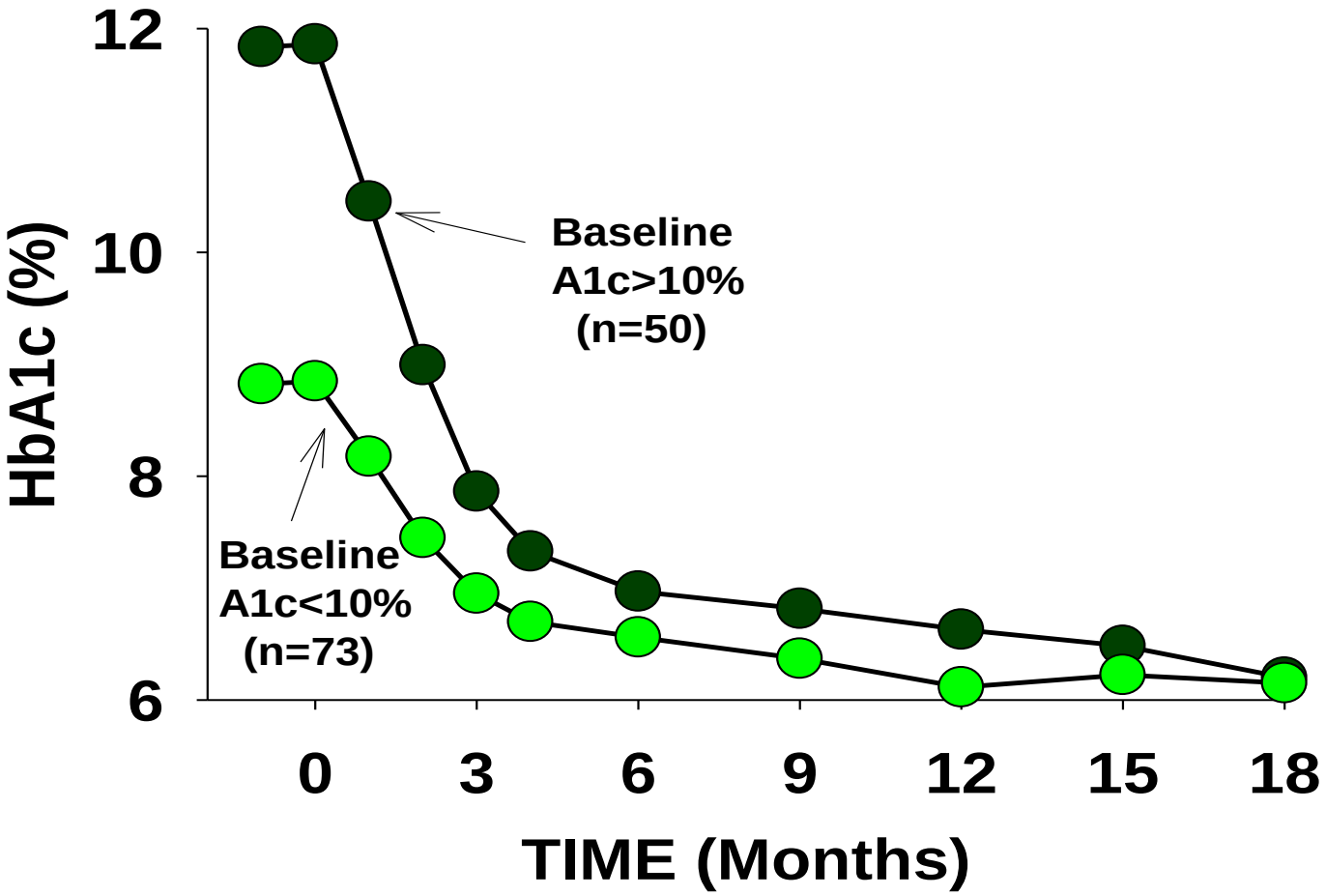
Effect of Therapy (36 months) on HbA1c in QATAR Study

Abdul-Ghani et. Al. Diabetes Obes Metab. 22:2287-2294, 2020.

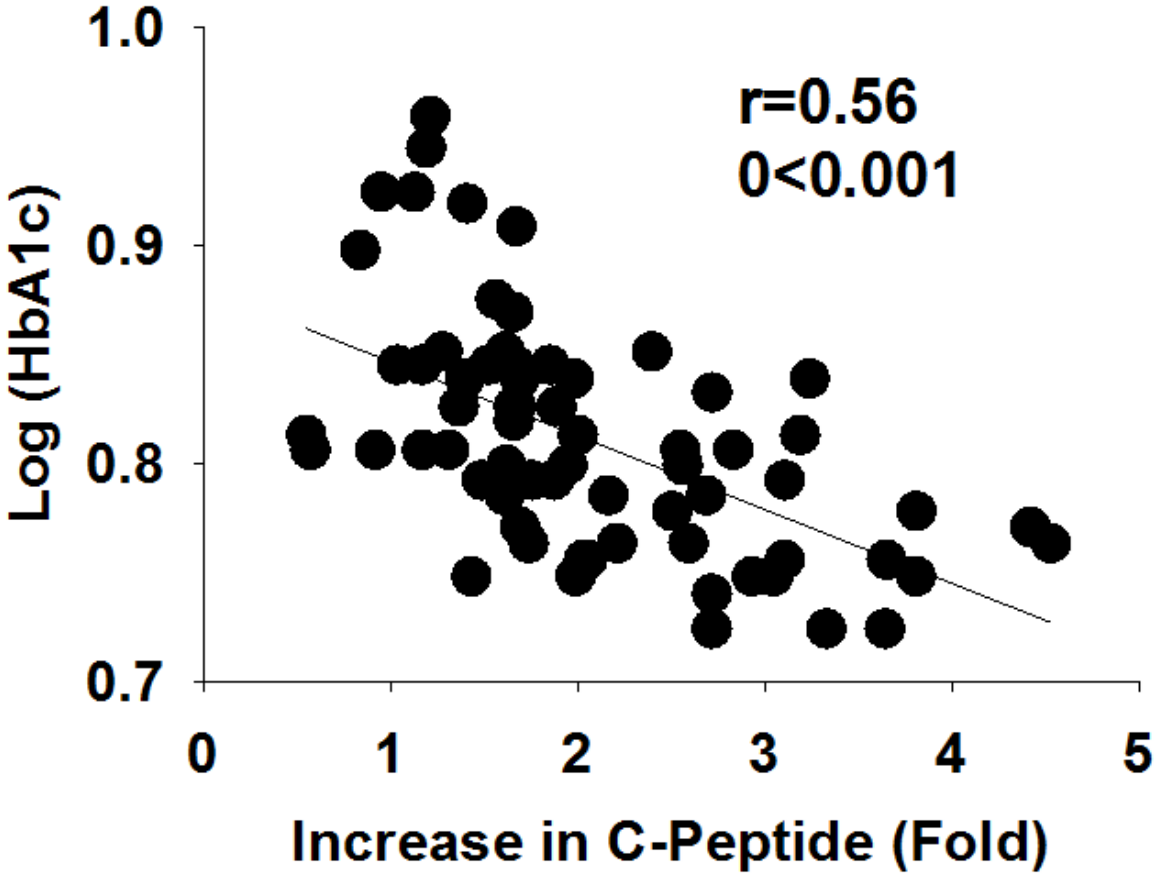


Effect of Combination Therapy on HbA1c Based Upon Baseline HbA1c

Abdul-Ghani et. Al. Diabetes Care. 40:325-331, 2017.



Relationship Between Insulin Secretion and HbA1c at Follow-up



Conclusion

- Because progressive beta cell failure is the principal factor responsible for the development and progression of hyperglycemia, it should be assessed in all T2DM patients
- Because TZD and GLP-1 RA preserve beta cell function, the combination of the two produces durable reduction in the HbA1c independent of **diabetes duration** or the **level of HbA1c**
- The level of beta cell function influences the response to glucose lowering therapies, and $CPEP_{120}/CPEP_0$ can be used as an index to individualize therapy in T2DM patients