# Effective and Safe Management of Patients With Type 2 Diabetes and Chronic Kidney Disease Using Sitagliptin

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# Contents

- CKD Prevalence In Type 2 Diabetes Mellitus
- Complications In Type 2 Diabetes Mellitus With CKD
- KDOQI Guideline Update In 2012
- Sitagliptin Clinical Trials In CKD

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# Chronic Kidney Disease and Diabetes

- CKD is defined as progressive, irreversible loss in kidney function
- Stages of chronic kidney disease

| Stages | Description | eGFR(ml/min/1.73m²) |
|---|---|---|
| I | Normal or increased eGFR* | >90 |
| II | Mildly decreases eGFR* | 60-89 |
| III | Moderately reduced eGFR | 30-59 |
| IV | Severely reduced eGFR | 15-29 |
| V | Kidney failure | <15 or dialysis |

* With evidence of structural kidney damage such as albuminuria, abnormal urinary sediment (i.e. casts, tubular epithelial cells), abnormal imaging studies, renal transplant recipients

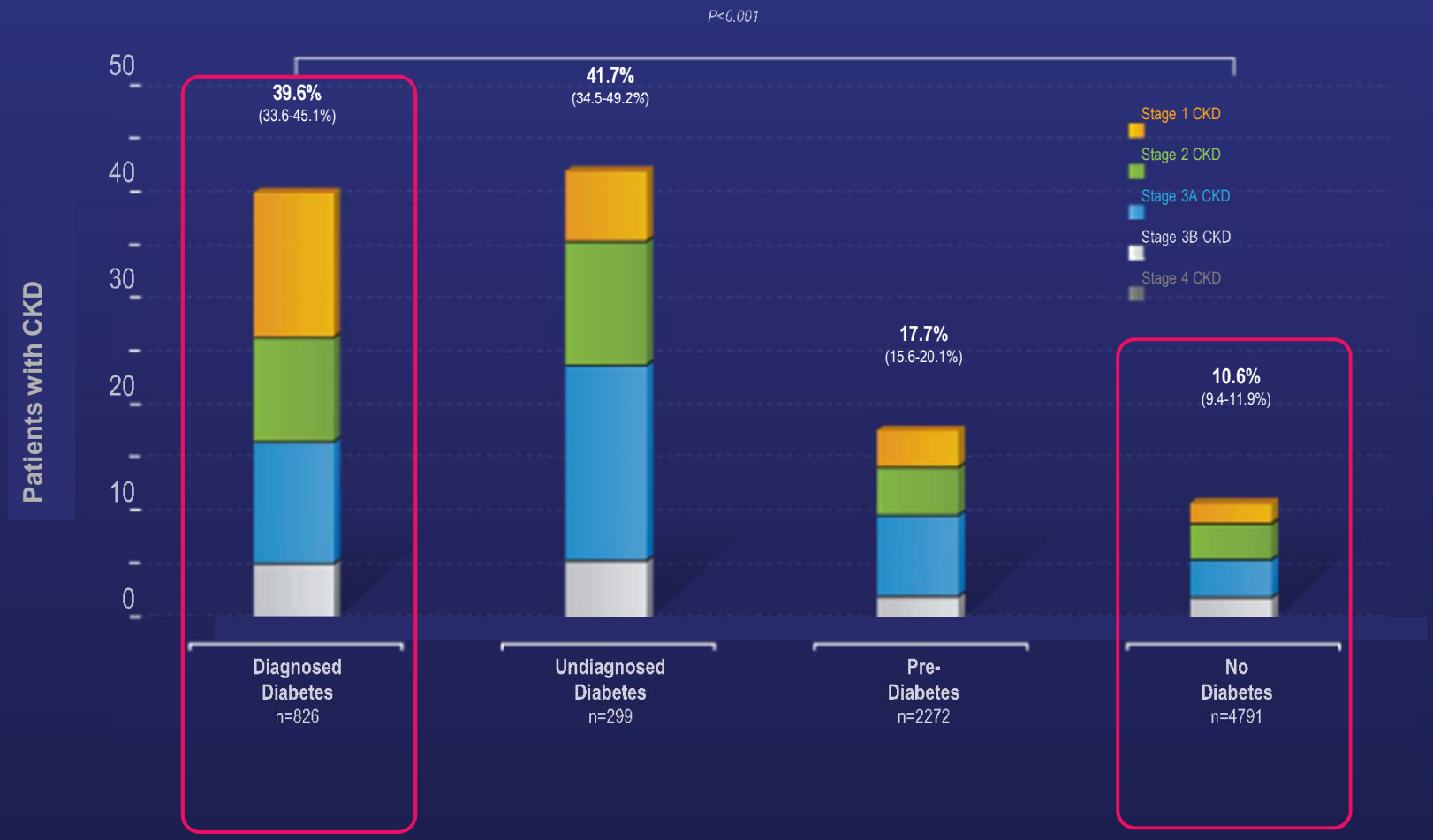
Risk factors of Diabetic nephropathy

Elevated blood pressure, Diabetes, Cholesterol, Microalbuminuria, Smoking, Genetic factors, Age and BMI

CKD – Chronic Kidney Disease
eGFR – estimated Glomerular Filtration Rate

1. Pyram R, et al. *Maturitas. 2012;71:94-103.*

# CKD prevalence among DM patients or people without DM

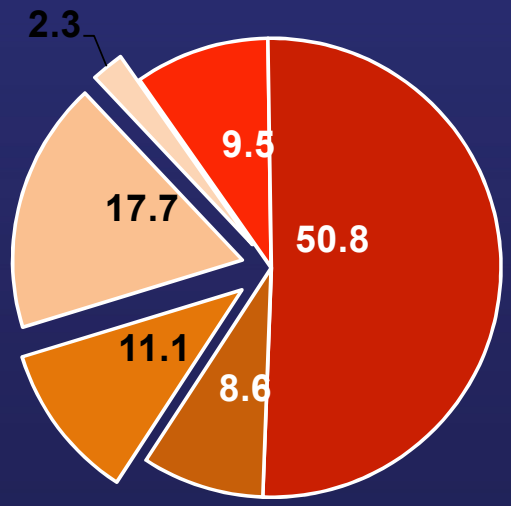



a Diagnosed diabetes was defined by the answer "yes" to the question, "Have you ever been told by a doctor or other health professional that you have diabetes or sugar diabetes?" Those who answered "no" or "borderline" (n=43) to the same question were classified according to their measured FPG only: Undiagnosed diabetes, FPG ≥ 126 mg/dl; prediabetes, FPG ≥100 but <126 mg/dl; and no diabetes, FPG <100 mg/dl.
b Definitions of stages : Stage 1, eGFR>90 ml/min/1.73m$^2$ and presence of albuminuria at a single measurement; stage 2, eGFR 60 to 89 ml/min/1.73m$^2$ and presence of albuminuria at a single measurement; and stages 3 and 4, eGFR 15 to 59 ml/min/1.73 m$^2$.

1. Plantinga LC, et al. *Clin J Am Soc Nephrol.* 2010;5:673-682.

# 40% of Patients with T2DM show signs of CKD

Chronic kidney disease (CKD) prevalence was greater among people with diabetes than among those without diabetes (40.2% versus 15.4%)




| *CKD Stage* | *eGFR (mL/min)* |
|---|---|
| **No CKD** | ≥ 90* |
| **1** | ≥ 90** |
| **2** | 60–89 |
| **3** | 30–59 |
| **4** | 15–29 |
| **5** | < 15 or dialysis |

* Normal kidney function, no sign of kidney damage
** Albuminuria – kidney damage

†Based on data from 1,462 patients aged ≥ 20 years with T2DM who participated in the Fourth National Health and Nutrition Examination Survey (NHANES IV) from 1999 to 2004.

Koro CE, et al. *Clin Ther*. 2009;31:2608–2617; Saydah S, et al. *JAMA*. 2007;297(16):1767.

# Higher $HbA_{1c}$ level was associated with the increased incidence of CKD[1]

| Variable | Total Incidence | $HbA_{1C}$ Concentration Category % <6 | 6-7 | 7-8 | >8 | $P_{trend}$ |
|---|---|---|---|---|---|---|
| **$HbA_{1C}$ concentration, mean** (SD) | 7.07 (2.16) | 5.28 (0.43) | 6.46 (0.31) | 7.53 (0.28) | 10.15 (1.50) | |
| **CKD defined by visit 4 eGFR** <60 mL/in/1.73 $m^2$ or *ICD*-9 Code hospitalization | | | | | | |
| • No. of events | 361 of 1871 | 91 of 770 | 67 of 407 | 46 of 193 | 157 of 501 | |
| • Incidence per 1000 person-years | 17.00 | **9.87** | **14.15** | **21.87** | **30.29** | <.001 |
| • Unadjusted HR (95% CI) | 1.25 (1.20-1.30)[a] | 1 (Reference) | 1.44 (1.05-1.97) | 2.30 (1.61-3.28) | 3.39 (2.62-4.39) | <.001 |
| • Adjusted HR[b] (95% CI) | 1.31 (1.25-1.38)[a] | 1 (Reference) | 1.37 (0.97-1.91) | 2.49 (1.70-3.66) | 3.67 (2.76-4.90) | <.001 |
| **CKD defined by visit 4 eGFR** <60 mL/min/1.73$m^2$ | | | | | | |
| • No. of events | 120 of 1871 | 39 of 770 | 30 of 407 | 12 of 193 | 39 of 501 | |
| • Incidence per 1000 person-years | 14.92 | 11.20 | 16.35 | 14.83 | 20.37 | .01 |
| • Unadjusted HR (95% CI) | 1.10 (1.02-1.18)[a] | 1 (Reference) | 1.48 (0.92-2.39) | 1.41 (0.74-2.70) | 1.72 (1.10-2.70) | .02 |
| • Adjusted HR[b] (95% CI) | 1.13 (1.03-1.25)[a] | 1 (Reference) | 1.31 (0.78-2.20) | 1.27 (0.63-2.56) | 1.63 (0.95-2.79) | .08 |
| **CKD defined by *ICD*-9 code** Hospitalization only | | | | | | |
| • No. of events | 292 of 1871 | 62 of 770 | 49 of 407 | 41 of 193 | 140 of 501 | |
| • Incidence per 1000 person-years | 13.58 | 6.68 | 10.20 | 19.09 | 26.56 | .68 |
| • Unadjusted HR (95% CI) | 1.29 (1.23-1.35)[a] | 1 (Reference) | 1.54 (1.06-2.24) | 2.97 (2.00-4.40) | 4.36 (3.23-5.88) | <.001 |
| • Adjusted HR[b] (95% CI) | 1.33 (1.26-1.40)[a] | 1 (Reference) | 1.43 (0.96-2.12) | 3.12 (2.04-4.77) | 4.53 (3.26-6.30) | <.001 |

Abbreviations: CI, confidence interval; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; $HbA_{1c}$, glycated hemoglobin; HR, hazard ratio; ICD-9, International Classification of Diseases, Ninth Revision; DM, diabetes mellitus.

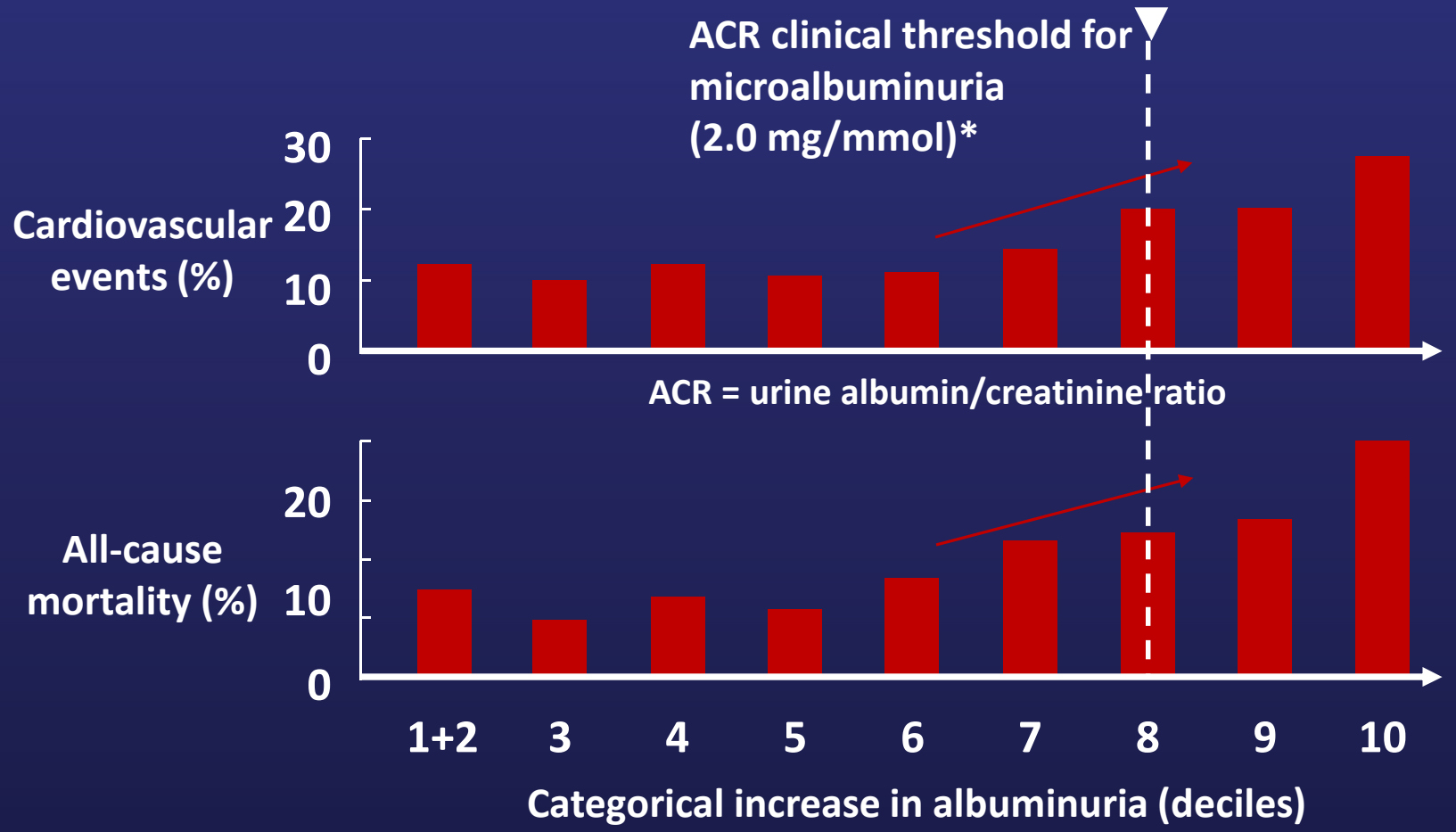
SI conversion factor: To convert $HbA_{1c}$ to proportion of total hemoglobin, multiply by 0.01.

[a] Per 1% increase in $HbA_{1c}$ concentration.

[b] Adjusted for age, sex, race, study center, baseline eGFR, body mass index, hypertension status, use of antihypertensive agents, prevalent coronary heart disease, smoking status, low- and high-density lipoprotein cholesterol concentrations, and triglyceride concentration.

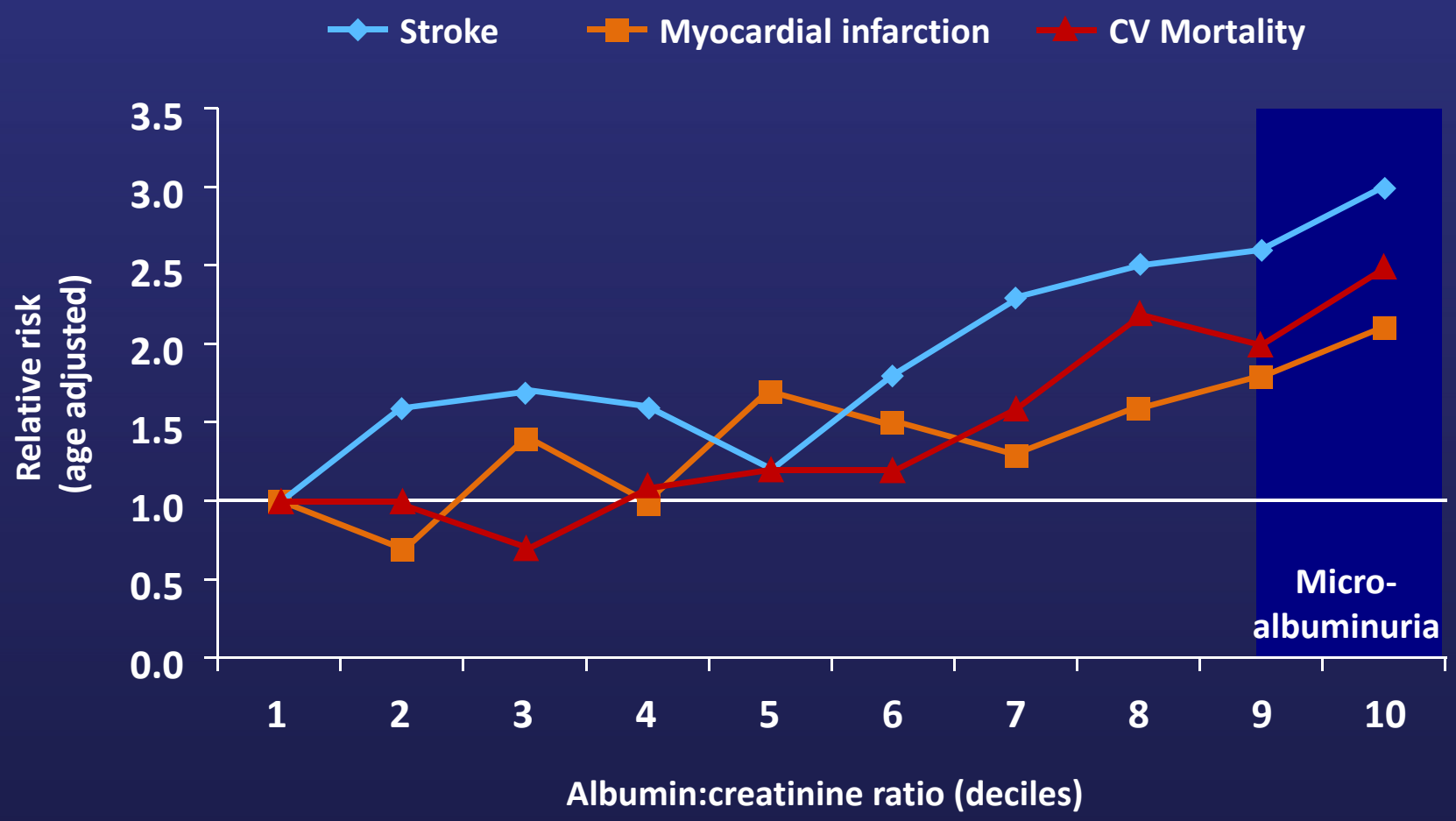
1. Bash LD, et al. *Arch intern Med.* 2008;168(22);2440-2447.

# Pts with microalbuminuria have an Increased CV Risk (HOPE study)




Gerstein HC et al for the HOPE Study Investigators. *JAMA.* 2001;286:421-426.

# Albuminuria is a risk factor for CV mortality (LIFE Study)




Wachtell et al. *Ann Intern Med* 2003;139:901–906

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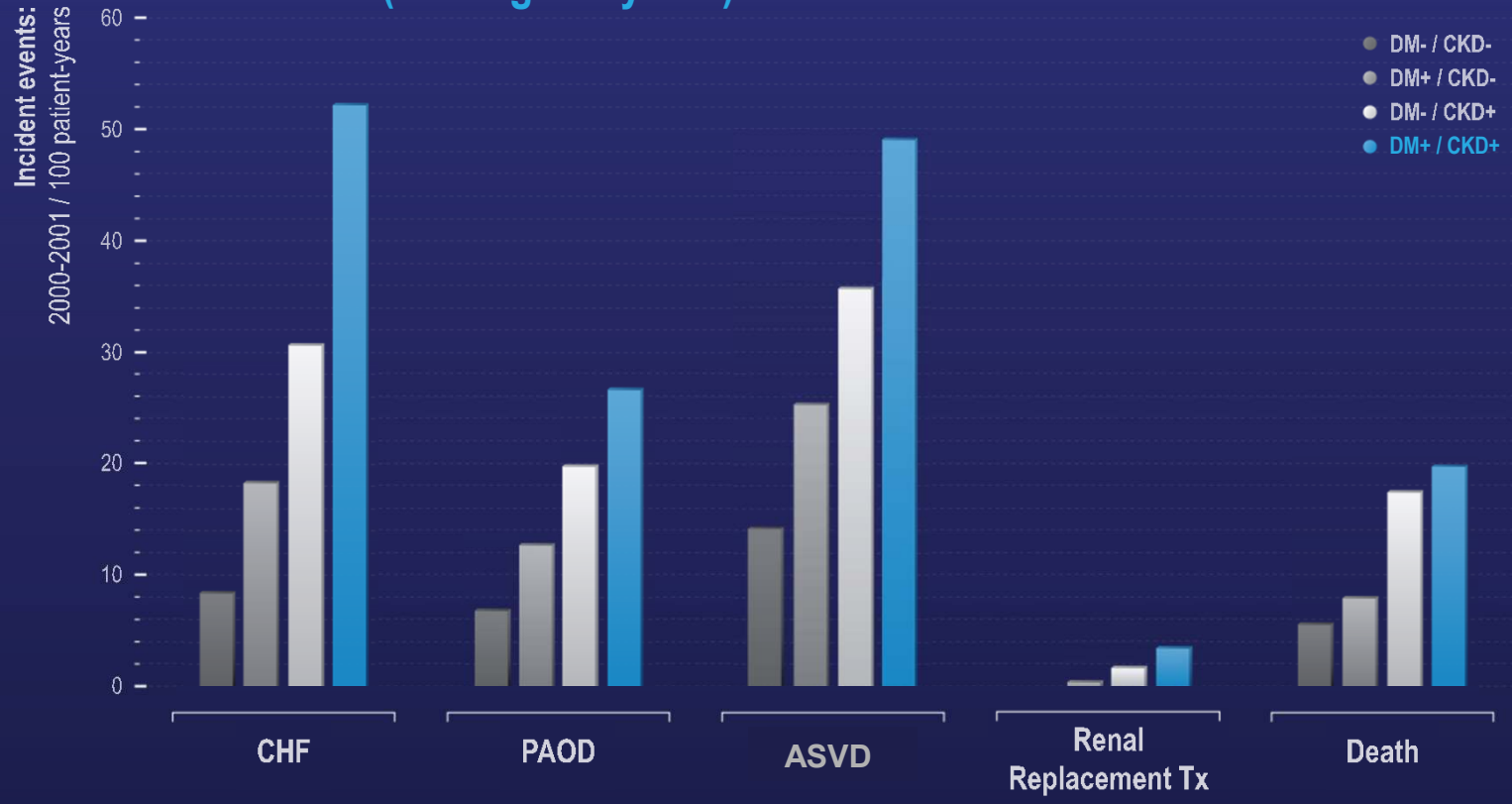
# Incidence of complications is greater with Pts with both DM and CKD



Study design: The rates of ASVD, CHF, RRT, and death were compared in a 5% sample of the United States Medicare population in 1998 and 1999(n=1,091,201). Patients were divided into the following groups: 1, no DM, no CKD; 2, DM, no CKD; 3, CKD, no DM; and 4, both CKD and DM. During the 2yr of follow-up, the rates in the 4 groups were analyzed.

## Incident event rates in 2000-2001 in over 1 million elderly US Medicare beneficiaries (over age 67 years)




**CHF** – Congestive Heart Failure / **PVD** – Peripheral vascular Disease / **ASCVI** ASVD-Atherosclerotic Vascular Disease
**RRT** – Renal Replacement Therapy / **DM** – Diabetes Mellitus / **CKD** – Chronic Kidney Disease

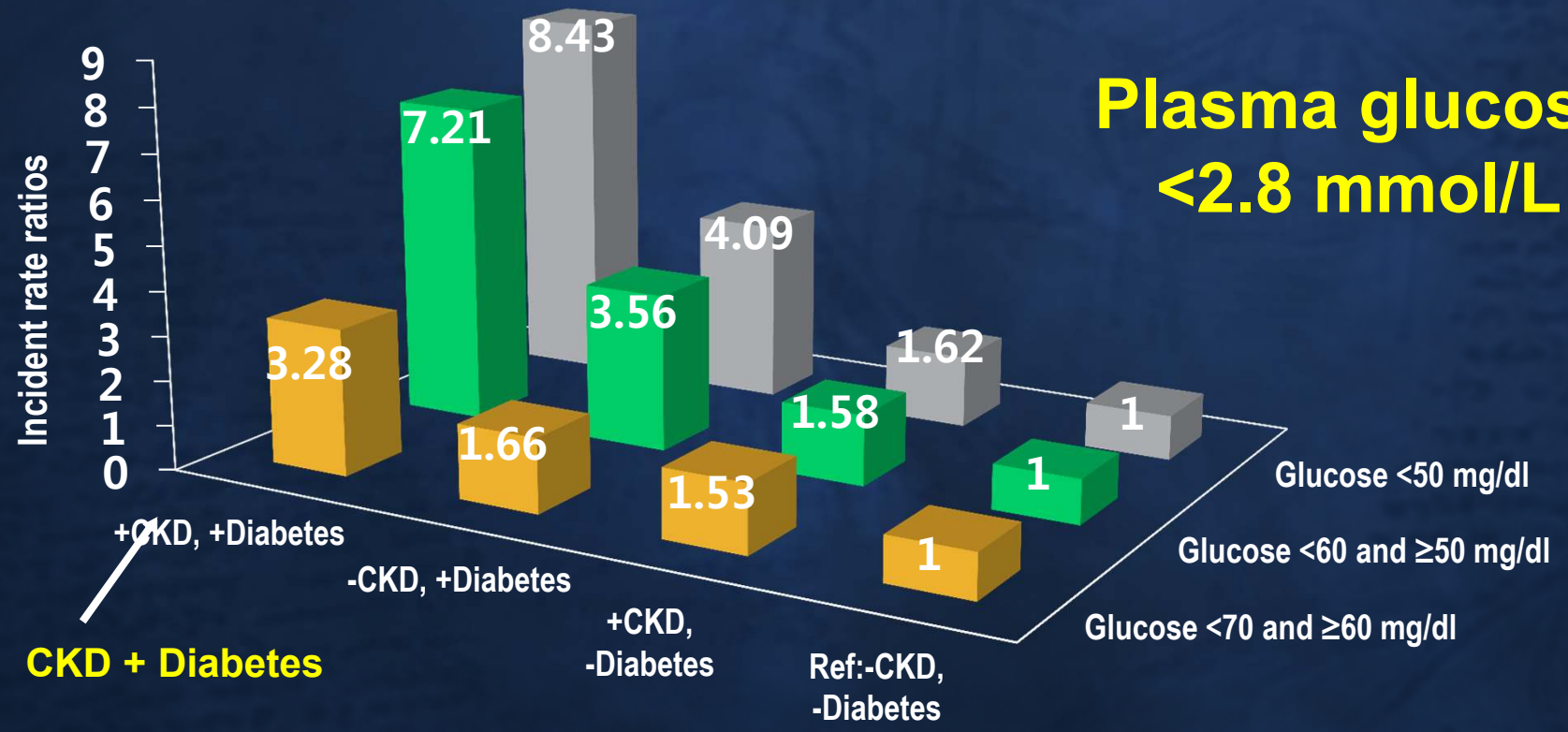
1. Foley R, Murray A, Li S, et al. Chronic kidney disease and the risk for cardiovascular disease, renal replacement, and death in the United States medicare population 1998 to 1999. J Am Soc Nephrol 2005;16:489-95, doi:10.1681/ASN.2004030203.

# Frequency of Hypoglycemia in Chronic Kidney Disease

- CKD defined as eGFR <60 ml/min/1.73 $m^2$
- Incidence in patients without Diabetes, with and without CKD: 3.46 vs. 2.23 episodes per 100 patient-months
- Incidence in patients With Diabetes with and without CKD: 10.72 vs. 5.33 episodes per 100 patient-months

*Moen et al (2009) Clin J Am Soc Nephrol;4:1121*

# Hypoglycemia and Chronic Kidney Disease ± Diabetes




**Plasma glucose <2.8 mmol/L**

All p-values <0.0001, (95% CI)

*Moen et al (2009) Clin J Am Soc Nephrol;4:1121*

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# Recommendations for Diabetes and CKD

| Management Topic | | Target / Action |
|---|---|---|
| Screening and diagnosis of Diabetic kidney disease | | Urinary albumin-creatinine ratio in a spot urine sample<br>Serum creatinine - eGFR |
| Management of Hyperglycemia and General Diabetes Care in CKD | | Target $HbA_{1c}$ for people with diabetes should be <7.0%, irrespective of the presence or absence of CKD. |
| | | In case of intensive treatment,<br>- monitor patients' glucose levels closely<br>- reduce doses of medicines (insulin and oral agents) as needed to avoid hypoglycemia |
| Comorbid diseases | Hypertension* | Should be treated with an ACE inhibitor or an ARB, usually in combination with a diuretic<br>Target blood pressure should be <130/80 mmHg |
| | Dyslipidemia* | Target LDL-C should be <100 mg/dL (<70 mg/dL is a therapeutic option)<br>LDL-C ≥100 mg/dL should be treated with a statin<br>Treatment with a statin should not be initiated in patients with type 2 diabetes on maintenance hemodialysis therapy who do not have a specific cardiovascular indication for treatment. |
| Nutrition* | | Target dietary protein intake should be the RDA of 0.8 g/kg body weight per day |

CKD – Chronic Kidney Disease
eGFR – estimated Glomerular Filtration Rate
ACE – Angiotensin Converting Enzyme
ARB – Angiotensin Receptor Blocker
LDL-C – low-density lipoprotein cholesterol
RDA – Recommended Daily Allowance

*** for people with diabetes and CKD stage 1-4**

1. KDOQI. *Am J Kidney Dis*. 2007;49(2,Supp12):S12-154.

# KDOQI Clinical practice guideline for Diabetes and CKD: 2012 UPDATE

- Recommend a target HbA1c of ~7.0% to prevent or delay progression of the microvascular complications of diabetes, including diabetic kidney disease (1A)
- Recommend not treating to an HbA1c target of <7.0% in patients at risk of hypoglycemia (1B)
- Suggest that target HbA1c be extended above 7.0% in individuals with co-morbidities or limited life expectancy and risk of hypoglycemia (2C)

National Kidney Foundation. KDOQI Clinical Practice Guideline for Diabetes and CKD: 2012 update. Am J Kidney Dis. 2012;60(5):850-886

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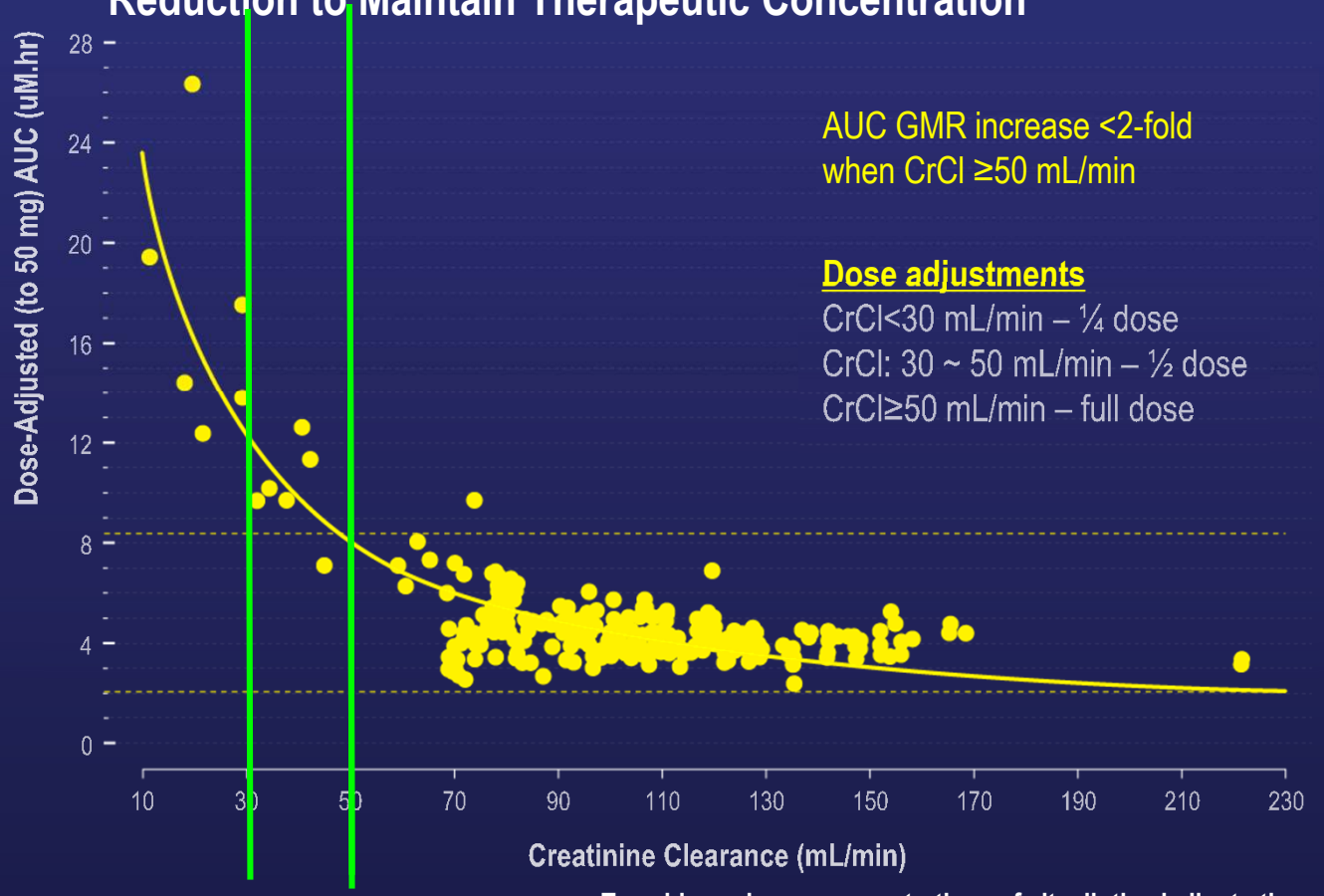
# Effect of Creatinine Clearance on Plasma Concentration AUC of a Single Dose of Sitagliptin

In a single-dose, open-label pharmacokinetic study,

## AUC Increases With Decreasing Creatinine Clearance Necessitating a Dose Reduction to Maintain Therapeutic Concentration




AUC GMR increase <2-fold when CrCl ≥50 mL/min

**Dose adjustments**

CrCl<30 mL/min – ¼ dose
CrCl: 30 ~ 50 mL/min – ½ dose
CrCl≥50 mL/min – full dose

### Abbreviations

*AUC (Area under the Curve)
*CrCl (Creatinine Clearance ml/min)
*GMR (Geometric Mean Ratio)
*ESRD (end-stage renal disease)

**To achieve plasma concentrations of sitagliptin similar to those in patients with normal renal function, lower dosages are recommended in patients with moderate and severe renal insufficiency, as well as in ESRD patients requiring hemodialysis.[3]**

1. Bergman AJ, et al. *Diabetes Care*. 2007;30:1862-1864.
2. Data on file, MSD Korea.
3. JANUVIA® prescribing information, MSD Korea.

STUDY #1

# Safety and Efficacy of Sitagliptin in Patients With Type 2 Diabetes and Chronic Renal Insufficiency

Chan JCN, Scott R, Arjona Ferreira JC, Sheng D, Gonzalez E, Davies MJ, Stein PP, Kaufman KD, Amatruda JM, Williams-Herman D.

*Diabetes Obes Metab*. 2008;10:545–555.

# Study Objective

- To assess the **Safety** of sitagliptin in patients with T2DM and
  - Moderate renal insufficiency (CrCl ≥30 mL/min to <50 mL/min and not on dialysis) → stratum 1, Sita 50mg/day
  - Severe renal insufficiency (CrCl <30 mL/min or ESRD with dialysis) → stratum 2, Sita 25mg/day
- **Efficacy** of sitagliptin in these patients was also assessed

CrCl=creatinine clearance.

**1.** Chan JCN et al. *Diabetes Obes Metab*. 2008;10:545–555.

# Study Design

**54-week, multinational, randomized, double-blind, parallel-group study**

**Patients with T2DM and CKD**
**Age ≥18 years**

- Not on OHA (≥8 weeks) with $HbA_{1c}$ ≥6.5% – ≤10%
- On a stable dose of insulin monotherapy (≥4 weeks) with $HbA_{1c}$ 7.5%–10% and FPG >7.2 mmol/L

Go directly to SB Placebo Phase

- On OHA with $HbA_{1c}$ 6%–10%

Run-in/ wash-off ≥6 weeks

SB placebo phase

R

**Sitagliptin**
- 50 mg/day (stratum 1)
- 25 mg/day (stratum 2)

**Placebo** → **Glipizide 5 mg/day (electively titrated to 20 mg/day)**

Screening Period → Run-in Period → DB Placebo-Controlled Phase → DB Continuation Phase

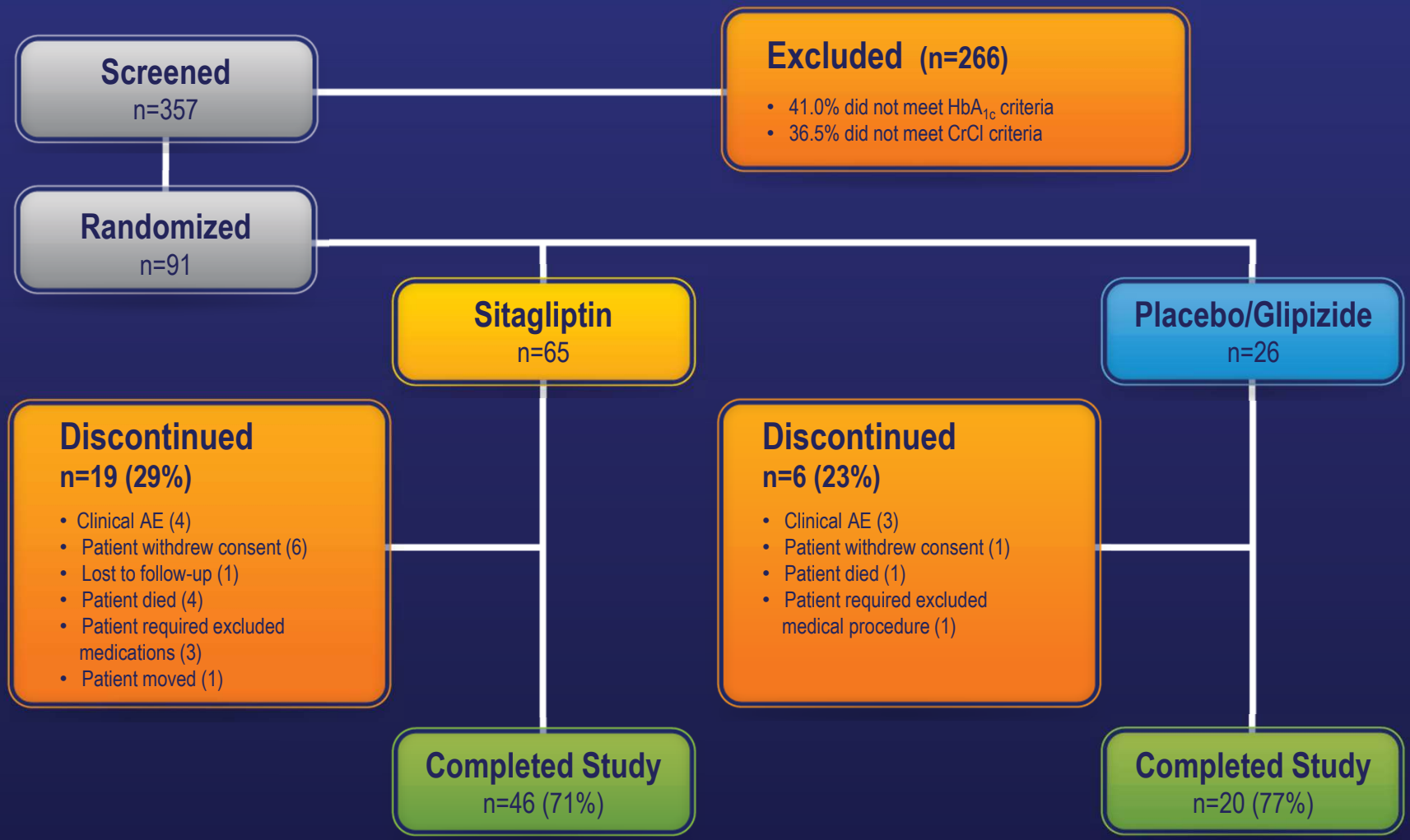
Screening | Run-in Start | Week –2 Start SB | Day1 | Week 12 | Week 54

To collect longer term data and maintain blinding for patients treated with sitagliptin, patients receiving placebo were transitioned to glipizide therapy after 12 weeks

**CKD**=chronic kindney disease; DB=double-blind; FPG=fasting plasma glucose; OHA=oral antihyperglycemic; SB=single-blind; T2DM=type 2 diabetes mellitus

1. Chan JCN et al. *Diabetes Obes Metab*. 2008;10:545-555.

# Patient Disposition




AE=adverse event; CrCl=creatinine clearance.

Adapted from Chan JCN et al. *Diabetes Obes Metab*. 2008;10:545-555 with permission from Blackwell Publishing Ltd., Boston, MA.

# Selected Baseline Characteristics

| | Sitagliptin (n=65) | Placebo/Glipizide (n=26) |
|---|---|---|
| **Age, y** | 68.9 | 65.3 |
| **Sex, n (%)** | | |
| • Males | **31** (48) | **16** (62) |
| • Females | **34** (52) | **10** (38) |
| **Renal disease history, n (%)** | | |
| • Stratum 1[a] | **37** (57) | **15** (58) |
| • Stratum 2[b] | **28** (43) | **11** (42) |
| **Dialysis patients, n (%)** | **12** (18.5) | **5** (19.2) |
| • Duration of dialysis, years | **2.4** | **1.8** |
| **Diabetes history** | | |
| • Duration reported, years | 13.6 | 13.2 |
| • Insulin therapy, n (%) | **7** (11) | **2** (8) |
| **$HbA_{1c}$, %** | 7.6 | 7.8 |
| **Fasting plasma glucose, mmol/L** | **8.9** | **8.6** |

[a]Patients with moderate renal insufficiency (CrCl ≥30 mL/min to <50 mL/min).
[b]Patients with severe renal insufficiency (CrCl <30 mL/min and not on dialysis) or ESRD with dialysis.

Adapted from Chan JCN et al. *Diabetes Obes Metab*. 2008;10:545-555

# Baseline Pre-Existing Cardiac-Related Disorders

| Cardiovascular Disease Category | Sitagliptin (n=65) n (%) | Placebo/Glipizide (n=26) n (%) |
|---|---|---|
| Prior cardiac-related disorder | **34** (52.3) | **10** (38.5) |
| History of prior HF | **9** (13.8) | **2** (7.7) |
| History consistent with CAD[a] | **26** (40.0) | **6** (23.1) |
| Prior history of HF and/or history consistent with CAD[a] | **27** (41.5) | **6** (23.1) |

[a]eg, diagnosis of CAD, prior stenting or bypass surgery, angina pectoris, ischemic cardiomyopathy, myocardial infarction, or myocardial ischemia.

**CAD**=coronary artery disease; HF=heart failure.

1. Chan JCN et al. *Diabetes Obes Metab*. 2008;10:545-555.

# Safety and Tolerability of Sitagliptin

| | Sitagliptin (n=65) | Placebo/Glipizide (n=26) |
|---|---|---|
| One or more clinical AEs, n (%) | 52 (80.0) | 22 (84.6) |
| Drug-related clinical AEs, n (%)[b] | 8 (12.3) | 5 (19.2) |
| Serious clinical AEs, n (%) | 20 (30.8) | 10 (38.5) |
| Drug-related serious clinical AEs, n (%)[b] | 1 (1.5) | 0 |
| Died, n (%) | 5 (7.7) | 1 (3.8) |
| Discontinued, n (%) | | |
| • Due to clinical AEs | 4 (6.2) | 2 (7.7) |
| • Due to drug-related clinical AEs | 1 (1.5) | 0 |
| • Due to serious clinical AEs | 4 (6.2) | 2 (7.7) |
| • Due to drug-related serious clinical AEs | 1 (1.5) | 0 |

AEs=Adverse experiences.
Patients may have experienced more than 1 AE but were only counted once within each category.
[a] To collect longer term data and maintain blinding for patients treated with sitagliptin, patients receiving placebo were switched to glipizide therapy after 12 weeks.
[b] Considered by the investigator as possibly, probably, or definitely related to treatment.
Adapted from Chan JCN et al. *Diabetes Obes Metab*. 2008;10:545-555

# Incidence of Adverse Experiences with Specific Cardiovascular Disease Categories and Death

| Cardiovascular Disease Category | Sitagliptin n/100 patient-years | Placebo/Glipizide[a] n/100 patient-years |
|---|---|---|
| ASVD | 10.8 | 12.4 |
| CAD | 5.3 | 8.3 |
| HF | 8.9 | 4.0 |
| CAD or HF | 10.8 | 12.4 |
| Death | 8.8 | 4.0 |

[a] To collect longer-term data and maintain blinding for patients treated with sitagliptin, patients receiving placebo were switched to glipizide therapy after 12 weeks.

## Rationale for adjustment of incidence of events for exposure[b]

- High prevalence of ASVD and HF in patients with T2DM and CKD
- Differences in exposure to therapy between groups

[b] Patient exposure (patient-years): time to event (years) for those patients who experienced an event or the time to the last day of study medication plus 14 days for those patients who did not experience an event.

**ASVD**=atherosclerotic vascular disease (including CAD); CAD=coronary artery disease; HF=heart failure; CKD=chronic kidney disease; T2DM=type 2 diabetes mellitus

Adapted from Chan JCN et al. *Diabetes Obes Metab*. 2008;10:545-555 with permission from Blackwell Publishing Ltd., Boston, MA.

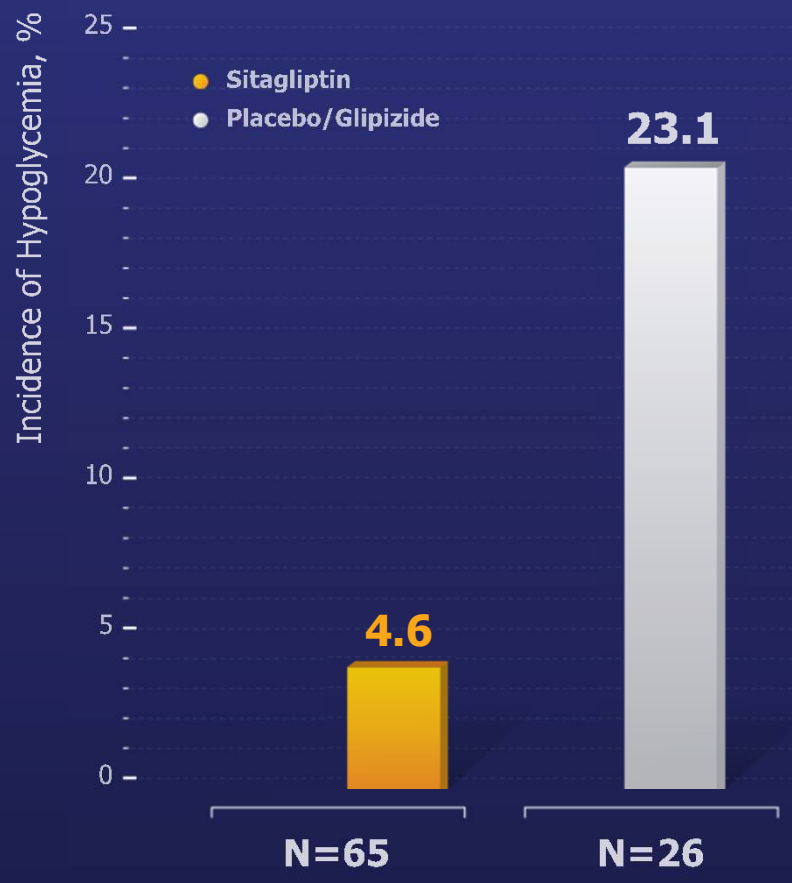
# Mortality

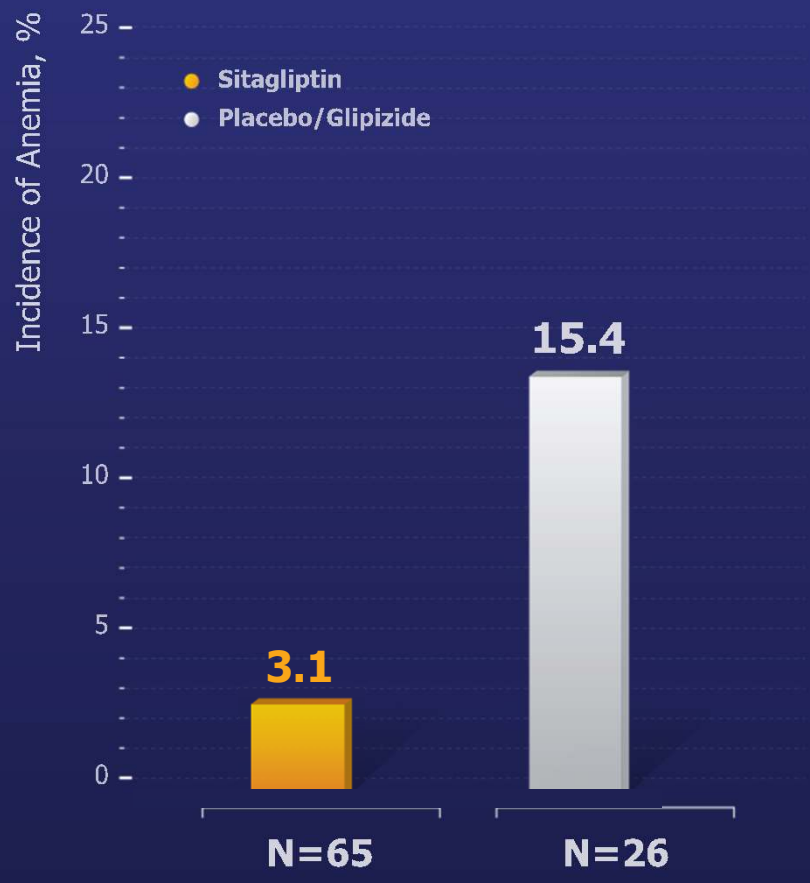
- 6 deaths among 91 randomized patients
  - 5 (7.7%) of 65 in the Sitagliptin group (8.8 deaths / 100 patient-years)
  - 1 (3.8%) of 26 in the placebo/glipizide group (4.0 deaths / 100 patient-years)
- Causes of death in sitagliptin group
  - 1 patient → pancreatic cancer
  - 4 patients → events consistent with underlying cardiovascular disease (myocardial infarction or sudden death)
- Cause of death in placebo/glipizide group
  - Septic shock in patient with ESRD and 28-year history of diabetes

ESRD=end-stage renal disease.

**1.** Chan JCN et al. *Diabetes Obes Metab*. 2008;10:545–555.

# Incidence of Hypoglycemia and Anemia Over 54 Weeks



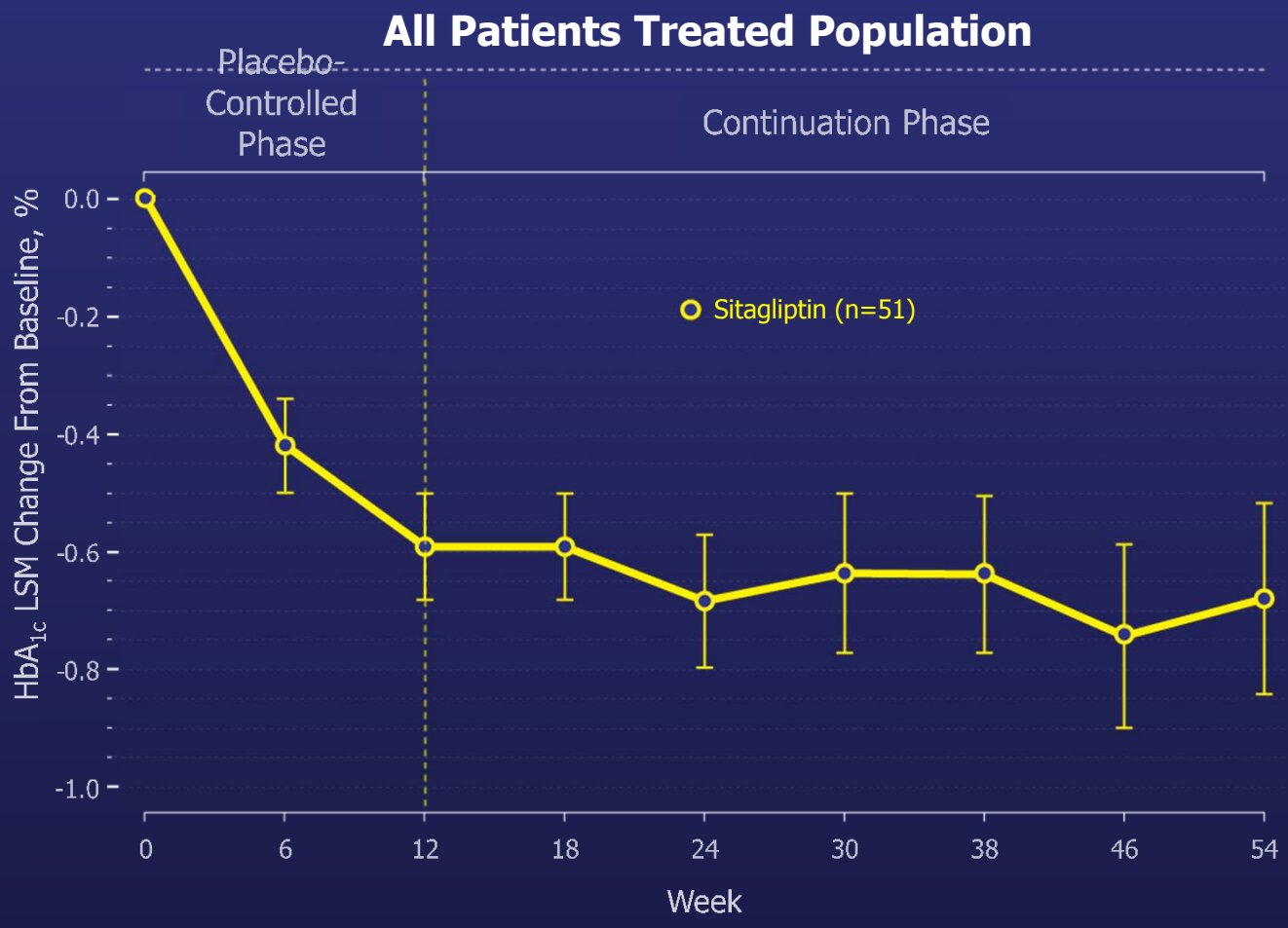

**1.** Chan JCN et al. *Diabetes Obes Metab*. 2008;10:545–555.

# Changes in Mean Serum Creatinine Level

| Mean Serum Creatinine Level | |
|---|---|
| **Baseline (moderate renal insufficiency, stratum 1)** | **138.8** µmol/L |
| **Change at week 12** | |
| • Sitagliptin | **+10.8** µmol/L |
| • Placebo/glipizide | **+6.2** µmol/L |
| **Change at week 54** | |
| • **Sitagliptin** | **-1.8 µmol/L** |
| • Placebo/glipizide | **+61.0** µmol/L |

**1.** Chan JCN et al. *Diabetes Obes Metab.* 2008;10:545–555.

# Change in $HbA_{1c}$ From Baseline in Patients Treated With Sitagliptin




**Placebo/Glipizide (n=25)**

*LSM change from baseline in $HbA_{1c}$ in the placebo/glipizide group was* ***–0.8%*** *at week 54.*

**LSM**=least squares mean.

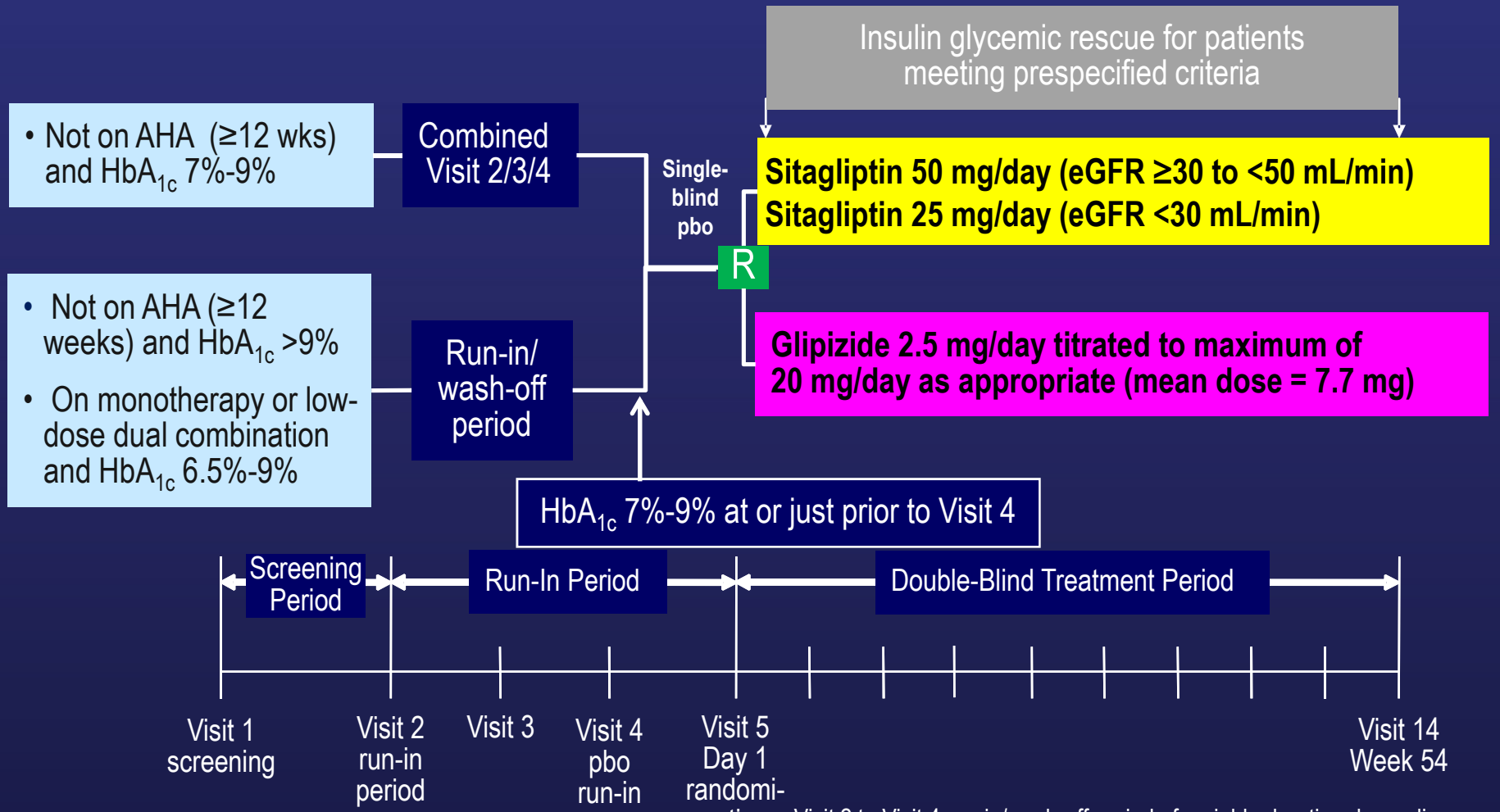
Adapted from Chan JCN et al. *Diabetes Obes Metab*. 2008;10:545-555 with permission from Blackwell Publishing Ltd., Boston, MA.

STUDY #2

# Efficacy and Safety of Sitagliptin vs. Glipizide in Patients With T2DM and Moderate-to-Severe Chronic Renal Insufficiency

# Study Design

Multinational, randomized, double-blind, parallel-group, active-controlled, 54-week study in patients with T2DM and eGFR <50mL/min aged ≥30 years

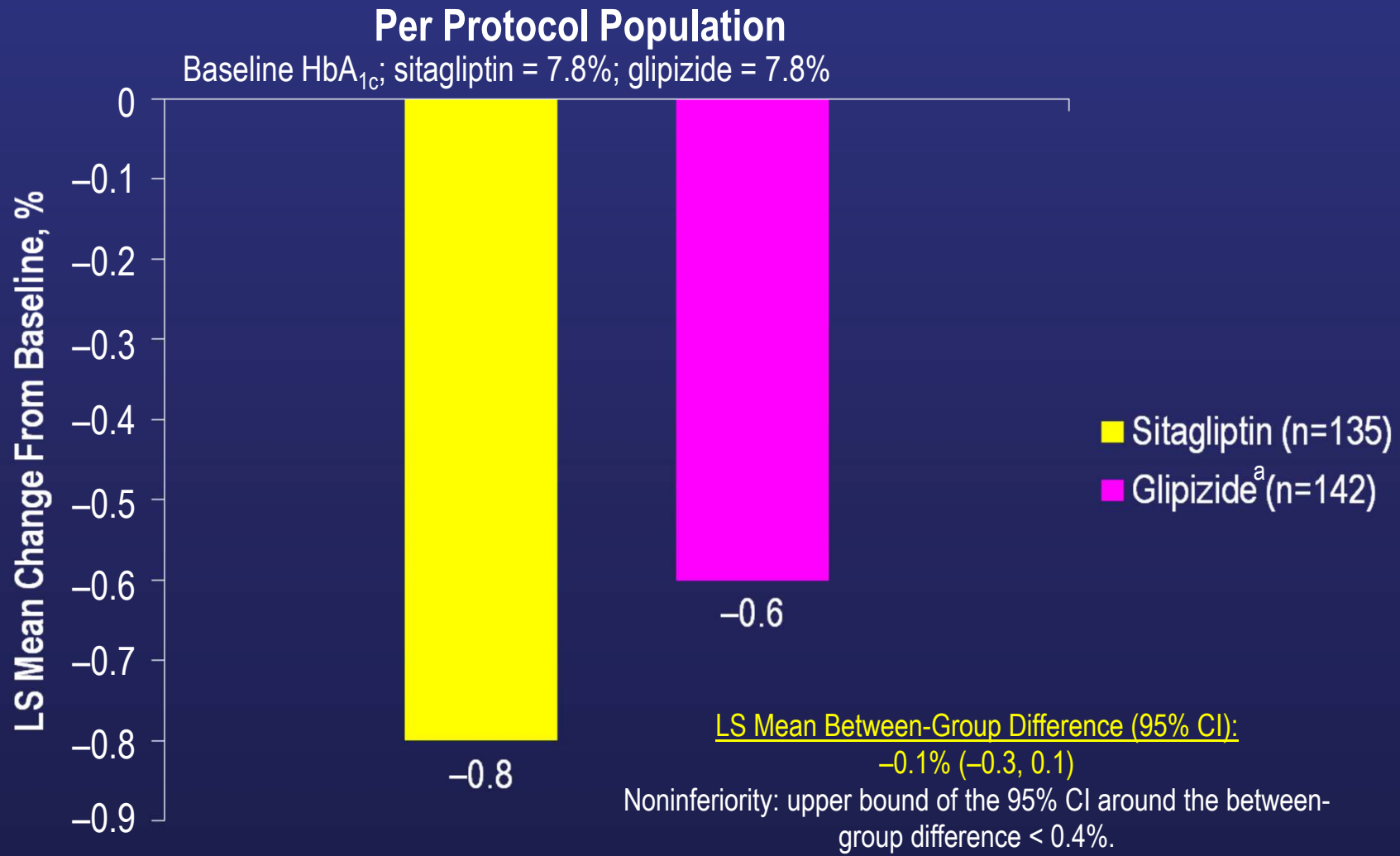



T2DM=type 2 diabetes mellitus; eGFR=estimated glomerular filtration rate; AHA=antihyperglycemic; pbo=placebo.

Visit 2 to Visit 4 run-in/wash-off period of variable duration depending on Visit 1 status, including diet and exercise, antihyperglycemic therapy, and baseline $HbA_{1c}$.

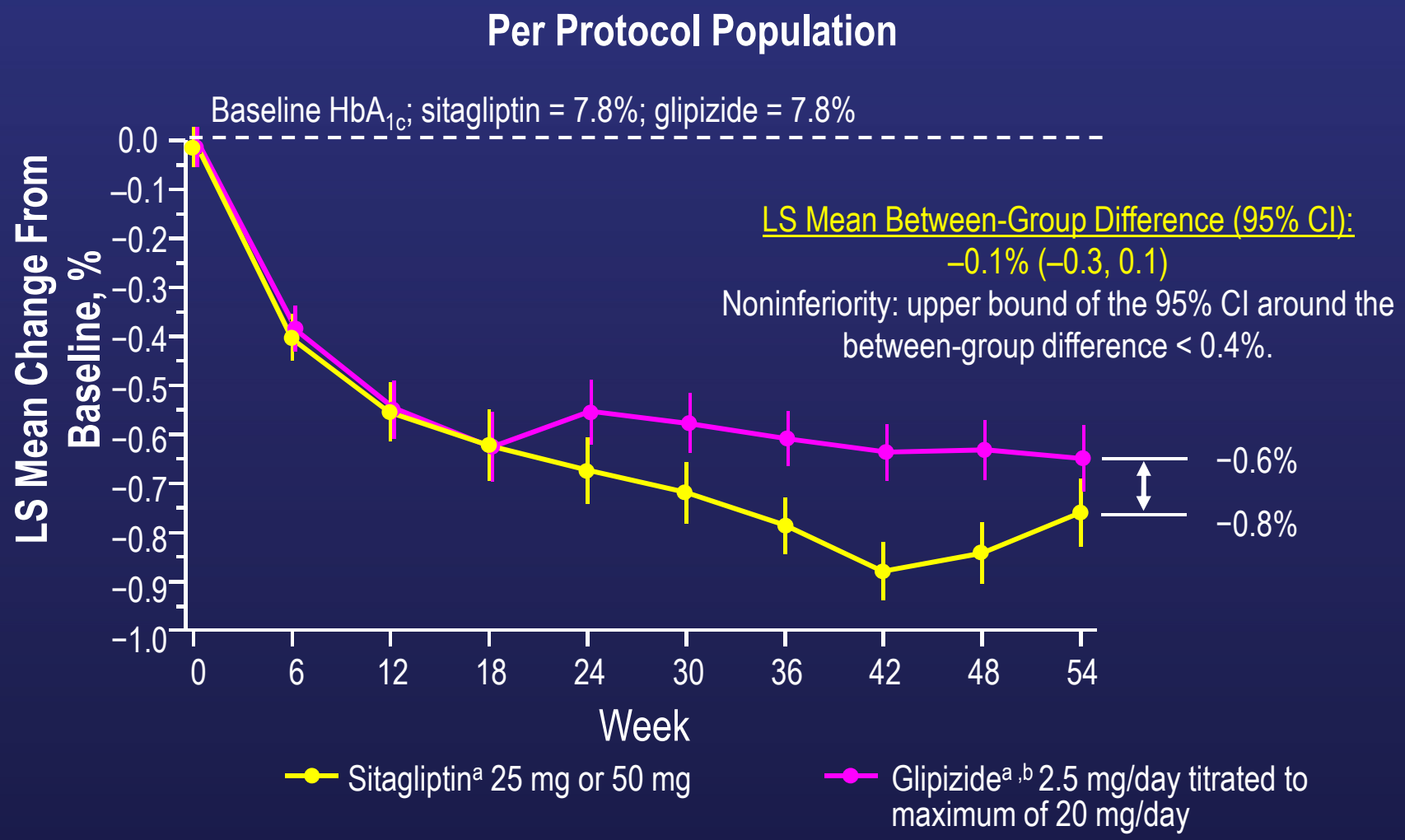
**1.** Arjona Ferreira JC et al. *Diabetes Care*. 2012 December 17. [Epub ahead of publication].

# $HbA_{1c}$ Results At Week 54




LS=least squares; CI=confidence interval. [a]Mean dose of glipizide was 7.7 mg per day. **1.** Arjona Ferreira JC et al. *Diabetes Care*. 2012 December 17.

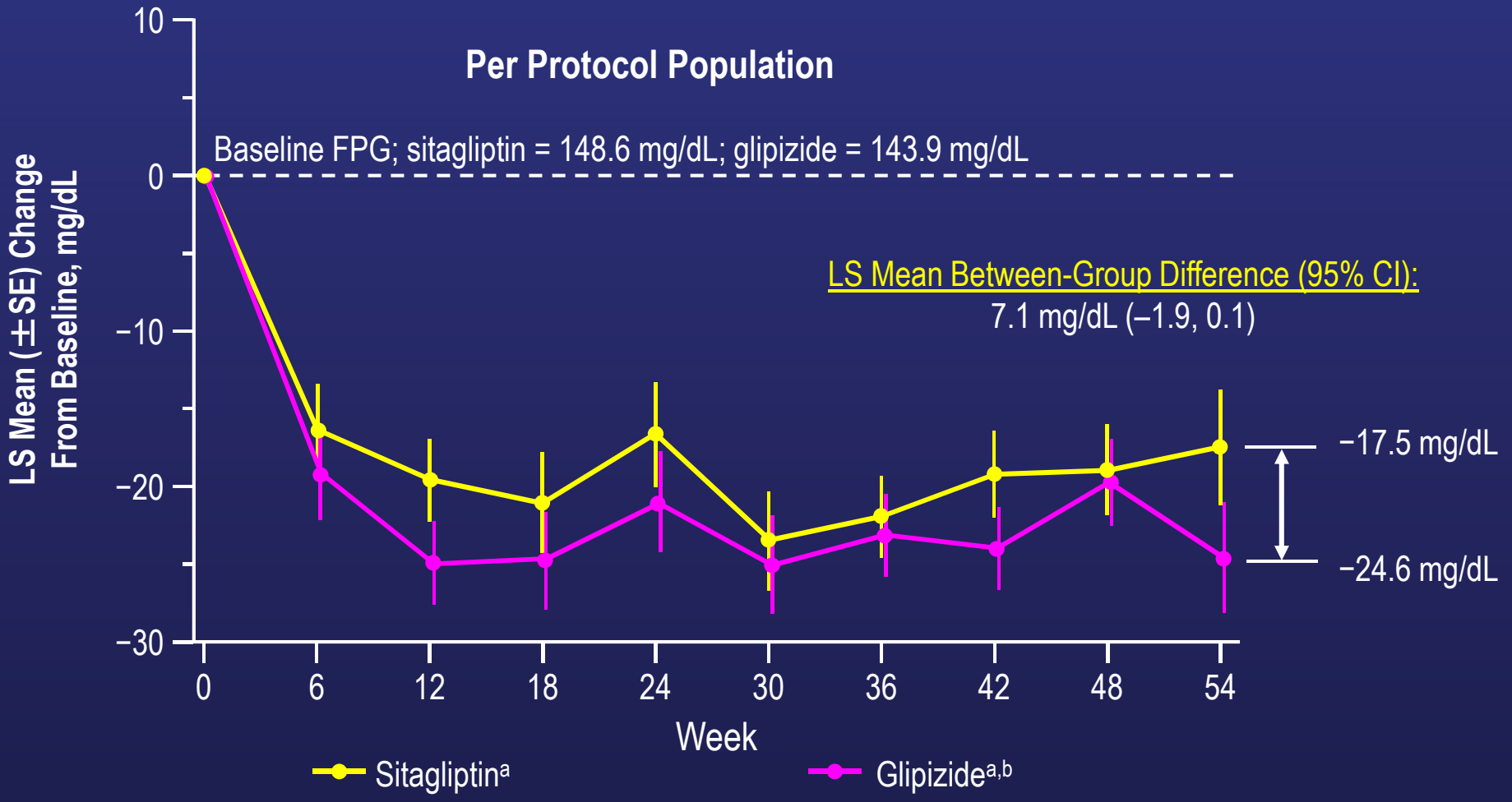
# Sitagliptin Reduced $HbA_{1c}$ Levels After 54 Weeks in Patients With Moderate-to-Severe Renal Insufficiency




LS=least squares; CI=confidence interval. [a]Sitagliptin (n=135), Glipizide (n=142) at week 54. [b]Mean dose of glipizide was 7.7 mg per day.

**1.** Arjona Ferreira JC et al. *Diabetes Care*. 2012 December 17. [Epub ahead of publication].

# FPG Results at 54 Weeks



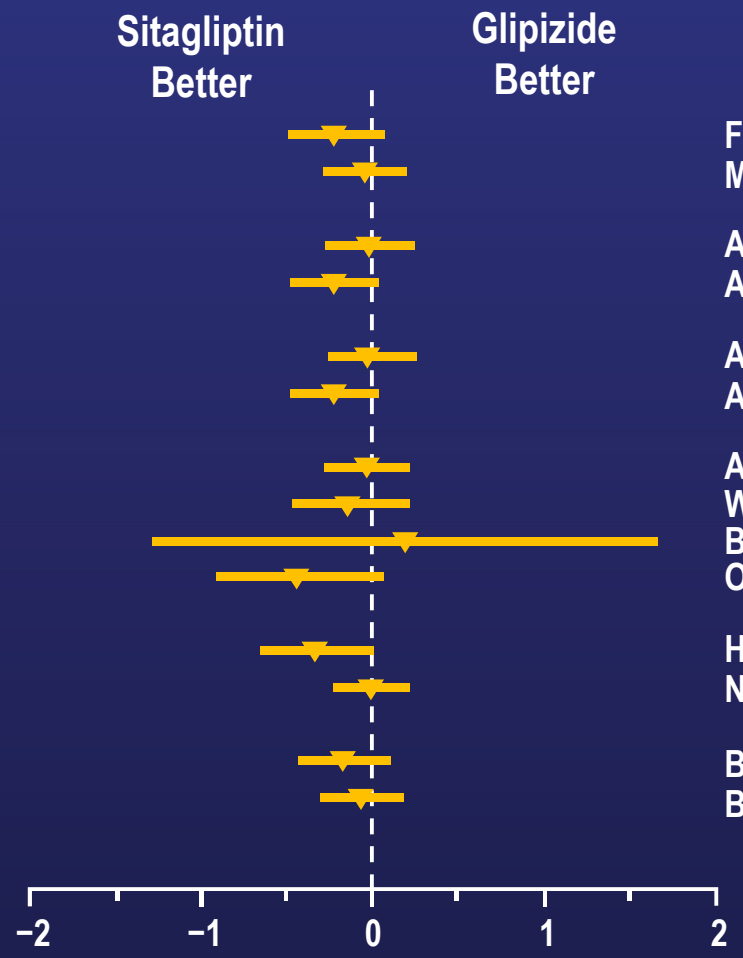

FPG=fasting plasma glucose; LS=least squares; SE=standard error; CI=confidence interval.

[a]Sitagliptin (n=136), Glipizide (n=142) at week 54.

[b]Mean dose of glipizide was 7.7 mg per day.

**1.** Adapted with permission from Arjona Ferreira JC et al. *Diabetes Care*. 2012 December 17. [Epub ahead of print].

# Subgroup Analyses at Week 54




Female (n=55, 64)
Male (n=80, 78)

Age ≤ median (64.0 years) (n=63, 79)
Age > median (64.0 years) (n=72, 63)

Age <65 years (n=63, 79)
Age ≥65 years (n=72, 63)

Asian (n=72, 83)
White (n=40, 40)
Black (n=2, 2)
Other (n=21, 17)

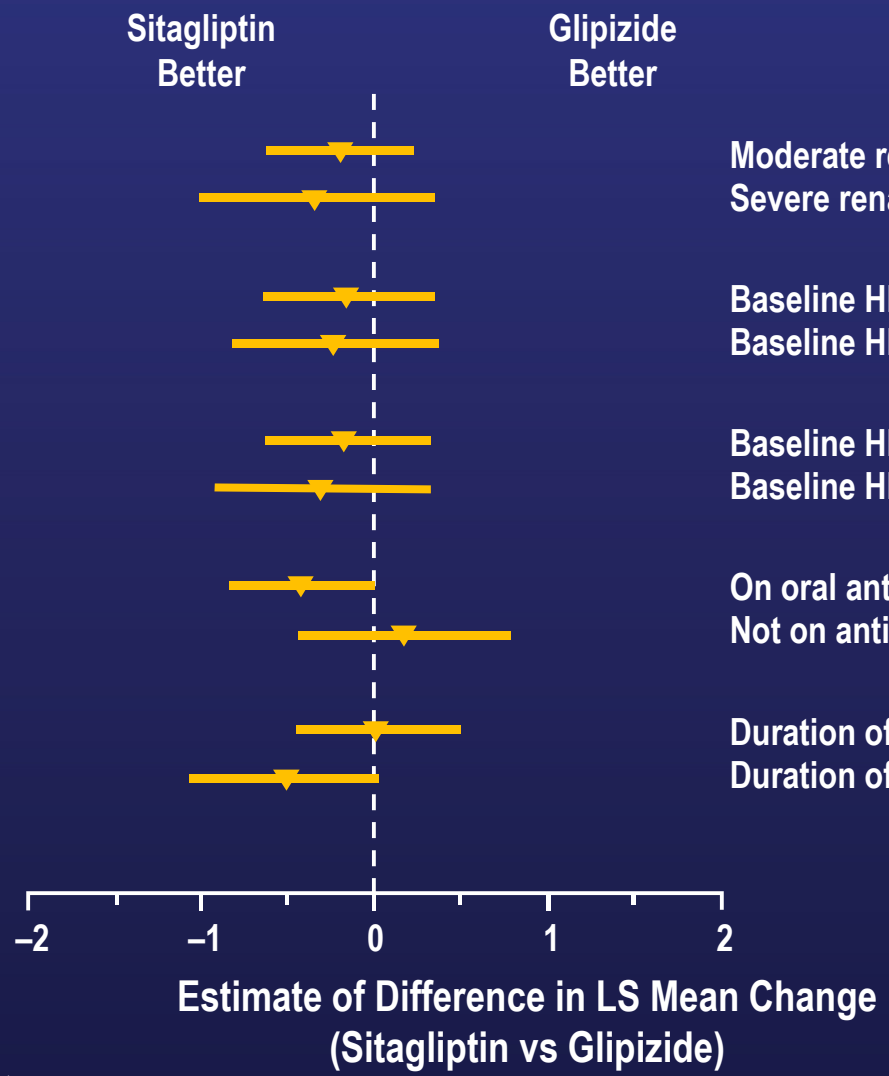
Hispanic or Latino (n=45, 41)
Not Hispanic or Latino (n=90, 101)

Baseline body mass index ≤ median (26.4 kg/m$^2$) (n=70, 72)
Baseline body mass index > median (26.4 kg/m$^2$) (n=65, 70)

LS=least squares.

**1.** Data on file, MSD.

# Subgroup Analyses at Week 54 (Per Protocol Population) (*continued*)[1]




Moderate renal insufficiency (n=98, 106)
Severe renal insufficiency (n=37, 36)

Baseline $HbA_{1c}$ ≤ median (7.80%) (n=80, 84)
Baseline $HbA_{1c}$ > median (7.80%) (n=55, 58)

Baseline $HbA_{1c}$ <8% (n=87, 88)
Baseline $HbA_{1c}$ ≥8% (n=48, 54)

On oral antihyperglycemic therapy (n=94, 93)
Not on antihyperglycemic therapy (n=41, 49)

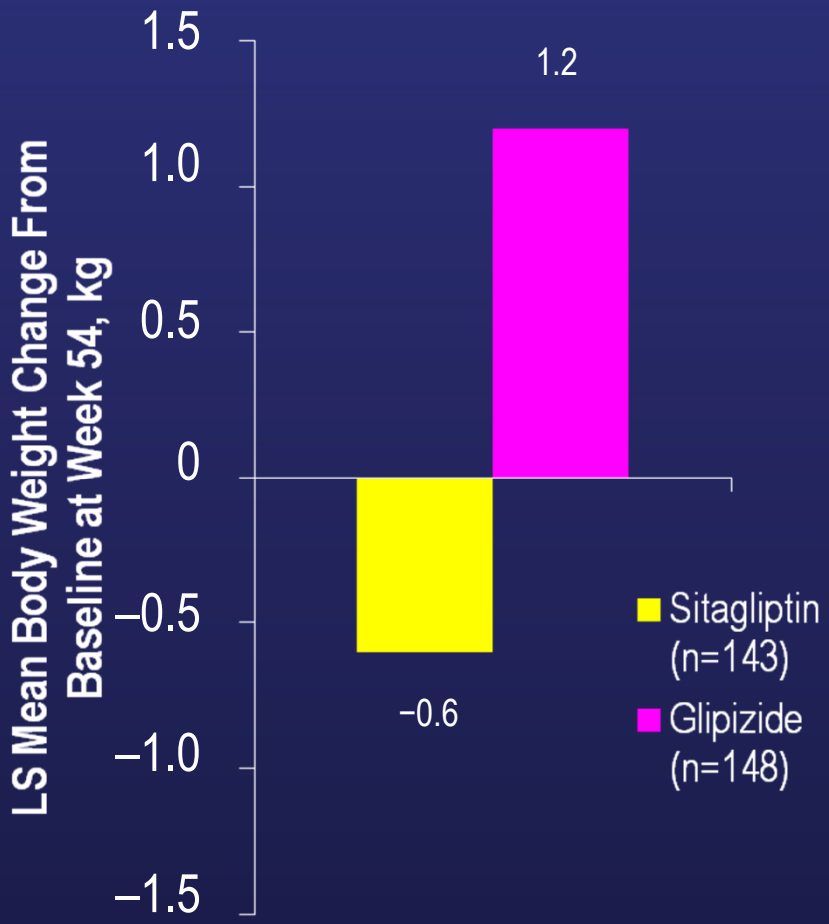
Duration of diabetes ≤ median (10.0 Years) (n=70, 89)
Duration of diabetes > median (10.0 Years) (n=65, 53)

LS=least squares.

**1.** Data on file, MSD.

# Sitagliptin Resulted in No Weight Gain Compared With Glipizide

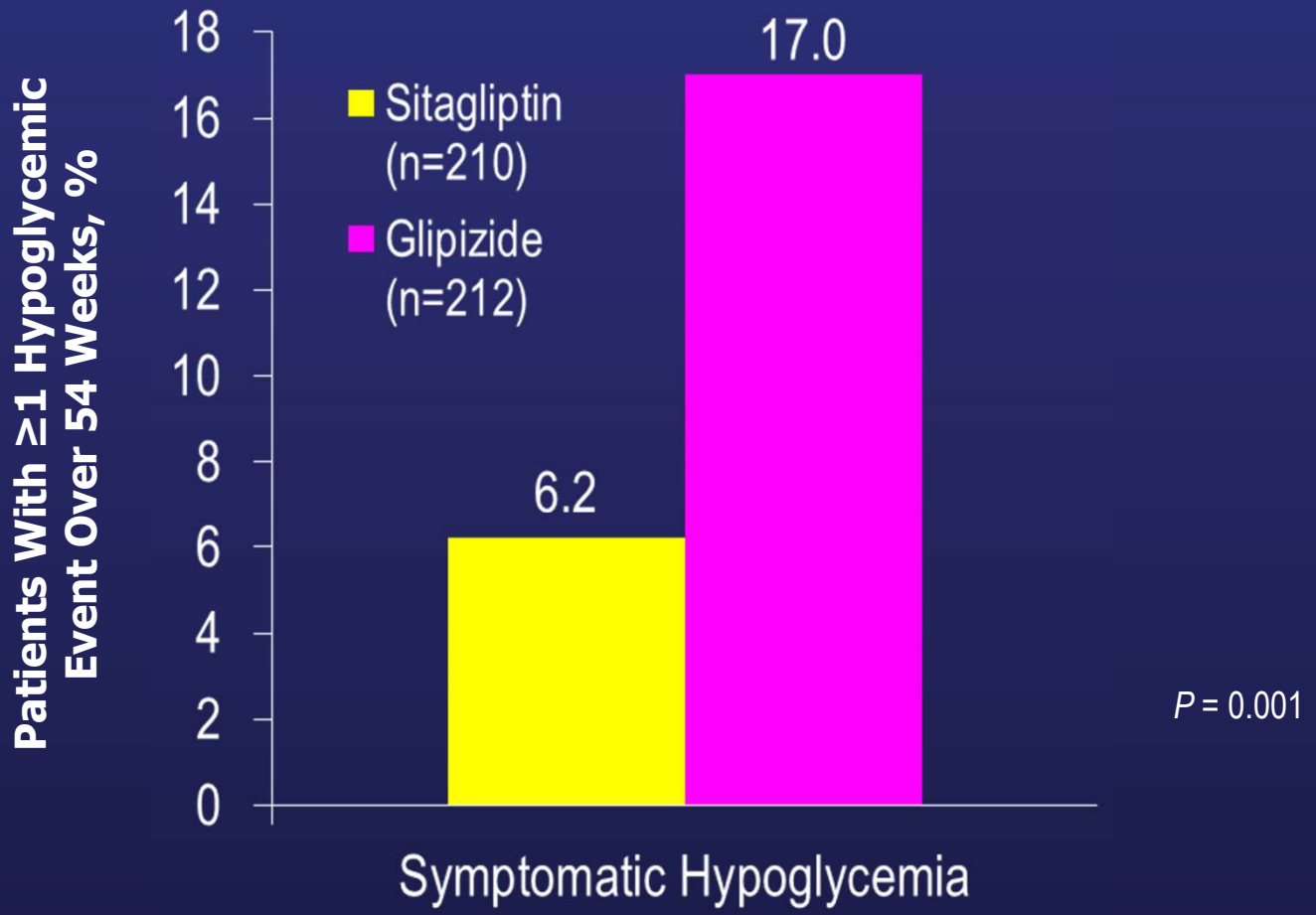
LS mean difference at week 54 −1.8; $P < 0.001$




**Baseline weight;**
**sitagliptin = 68.0 kg**
**glipizide = 70.2 kg**

APaT=All Patients as Treated; LS=least squares. [a]25 mg once daily or 50 mg once daily. [b]Mean dose of glipizide was 7.7 mg per day. Glipizide was initiated at 2.5 mg/day and titrated to a maximum of 20 mg/day. **1.** Arjona Ferreira JC et al. *Diabetes Care*. 2012 December 17. [Epub ahead of publication].

# Sitagliptin Resulted in a Lower Proportion of Patients Experiencing Symptomatic Hypoglycemia Compared With Glipizide




*P* = 0.001

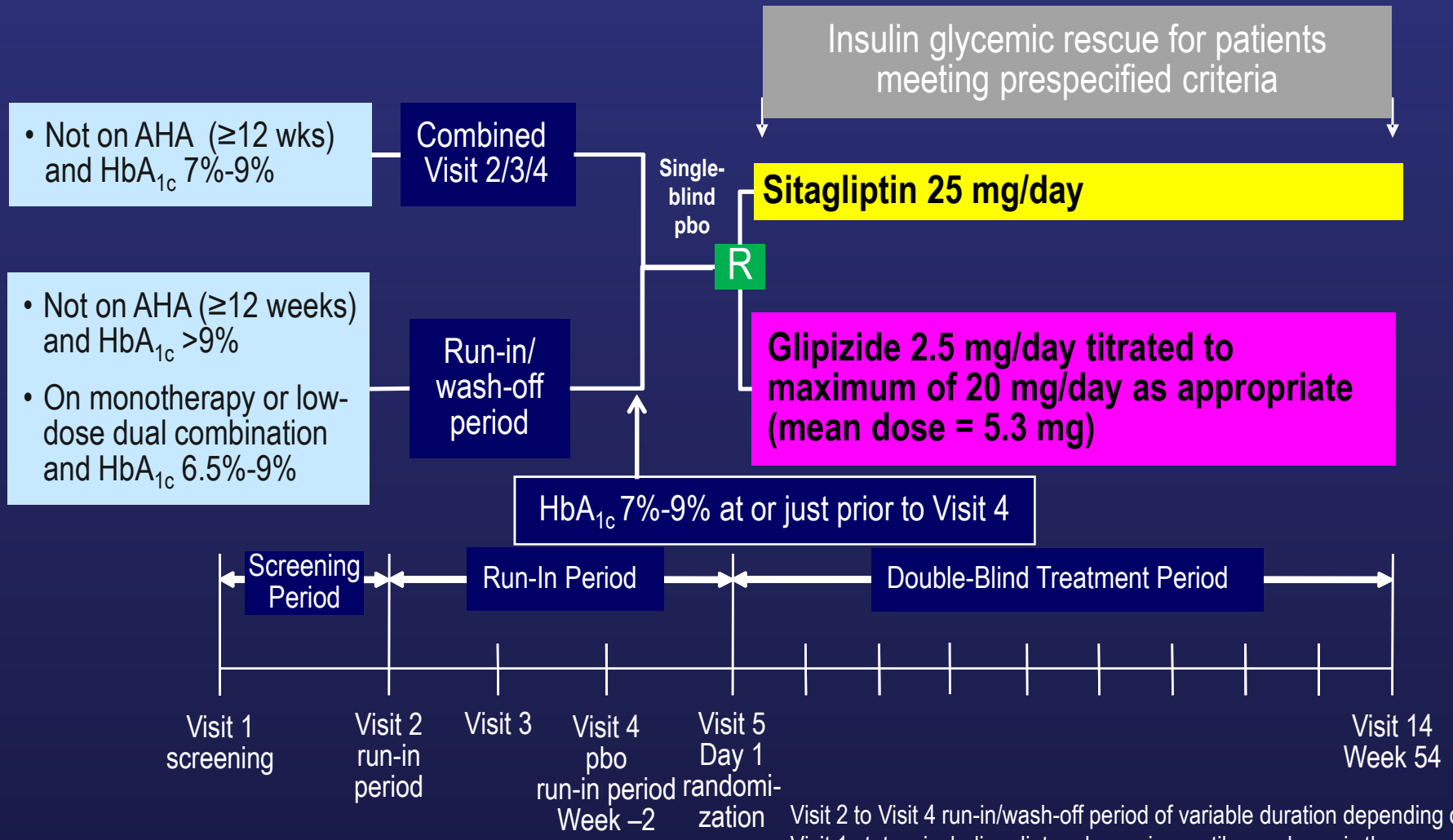
APaT=All Patients as Treated; LS=least squares. [a]25 mg once daily or 50 mg once daily. [b]Mean dose of glipizide was 7.7 mg per day. Glipizide was initiated at 2.5 mg/day and titrated to a maximum of 20 mg/day. **1.** Arjona Ferreira JC et al. *Diabetes Care*. 2012 December 17. [Epub ahead of publication].

STUDY #3

# Efficacy and Safety of Sitagliptin in Patients With Type 2 Diabetes and End-Stage Renal Disease on Dialysis — A 54-Week Randomized Trial

# Study Design

Multinational, randomized, double-blind, parallel-group, active-controlled study in patients with T2DM on dialysis aged ≥30 years

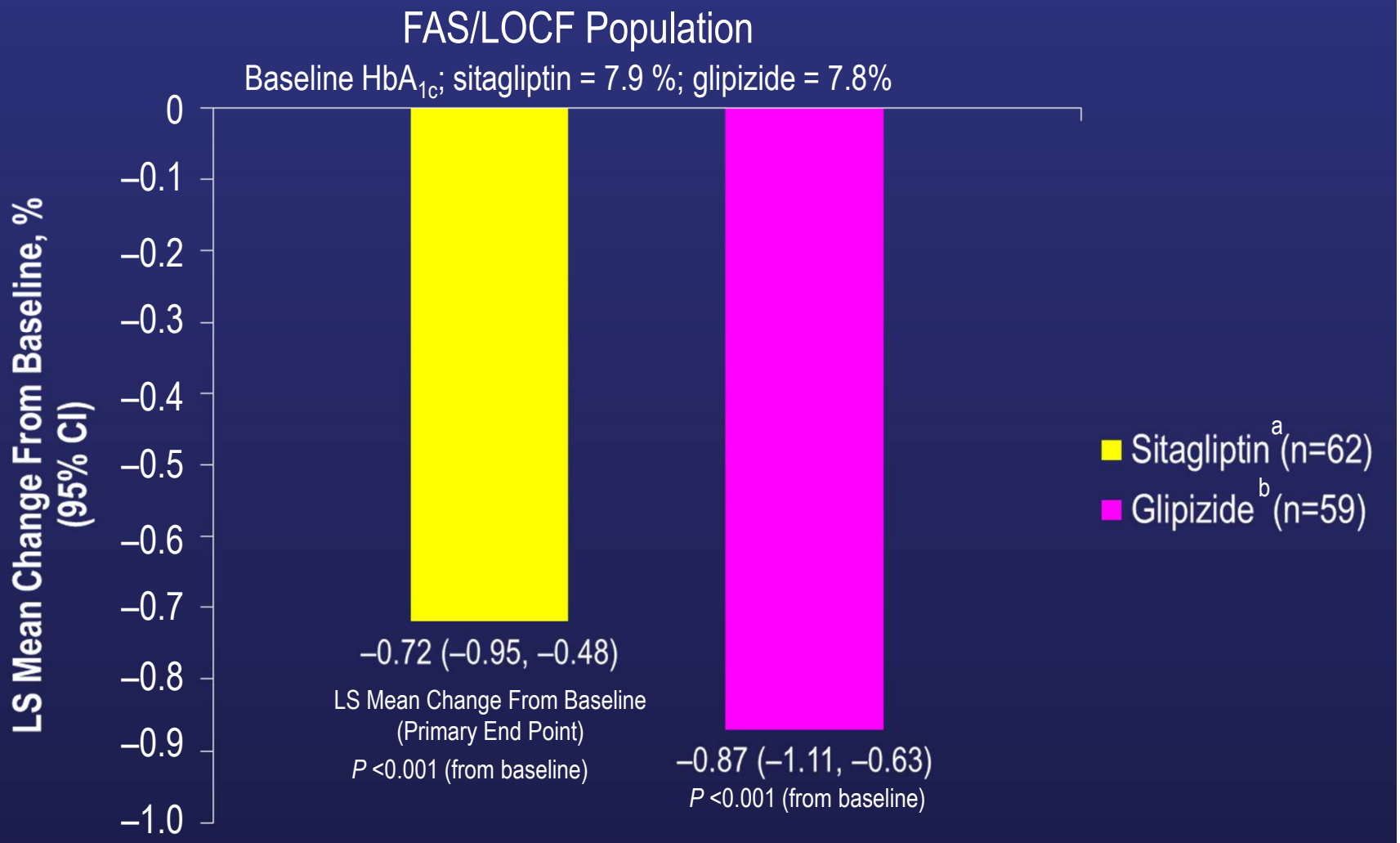



Visit 2 to Visit 4 run-in/wash-off period of variable duration depending on Visit 1 status, including diet and exercise, antihyperglycemic therapy, and baseline $HbA_{1c}$.

T2DM=type 2 diabetes mellitus; AHA=antihyperglycemic; pbo=placebo.

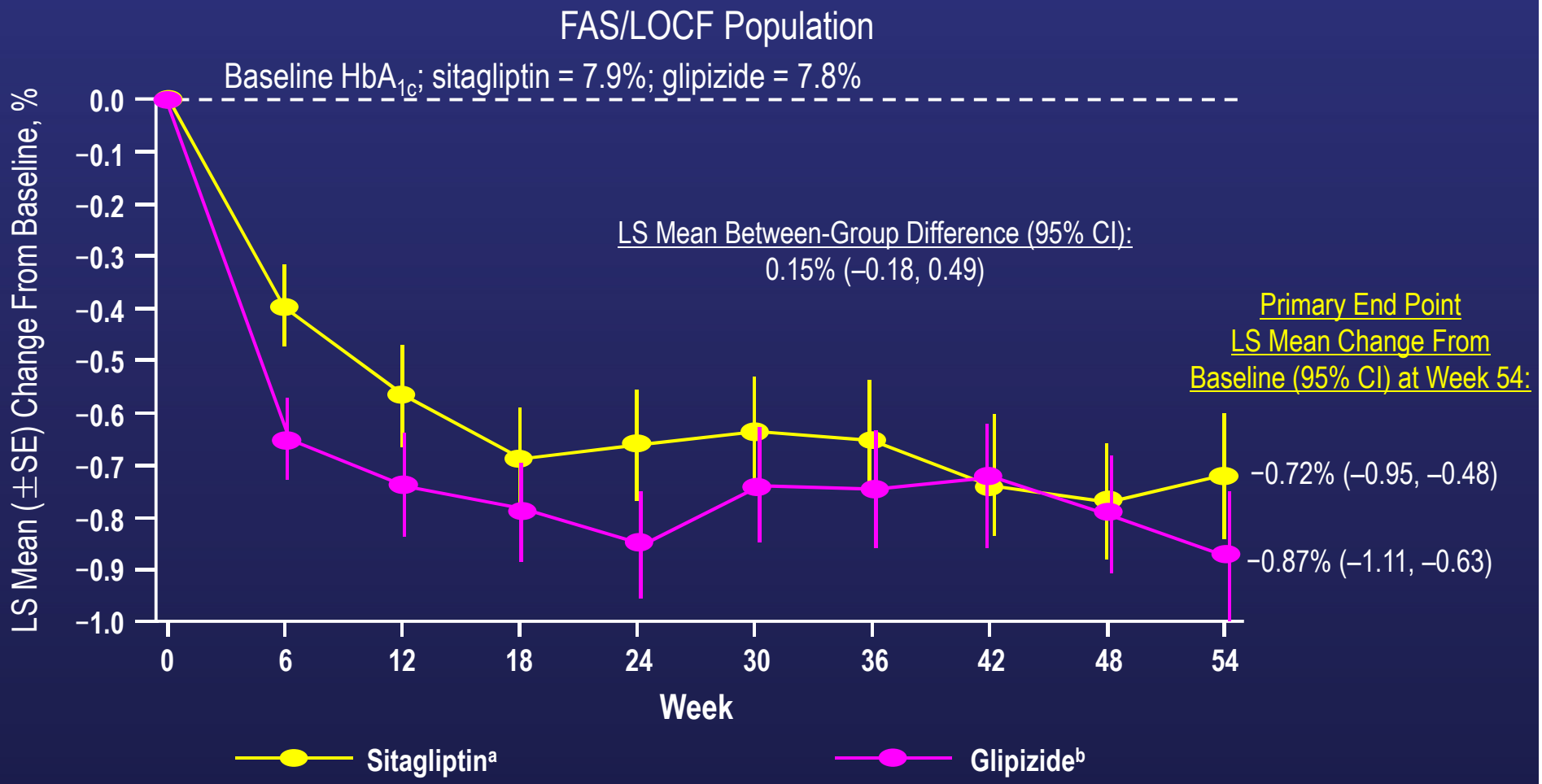
**1.** Arjona Ferreira JC et al. *Am J Kidney Dis.* DOI: 10.1053/j.ajkd.2012.11.043.

# Sitagliptin Significantly Reduced $HbA_{1c}$ at 54 Weeks From Baseline in Patients With ESRD on Dialysis



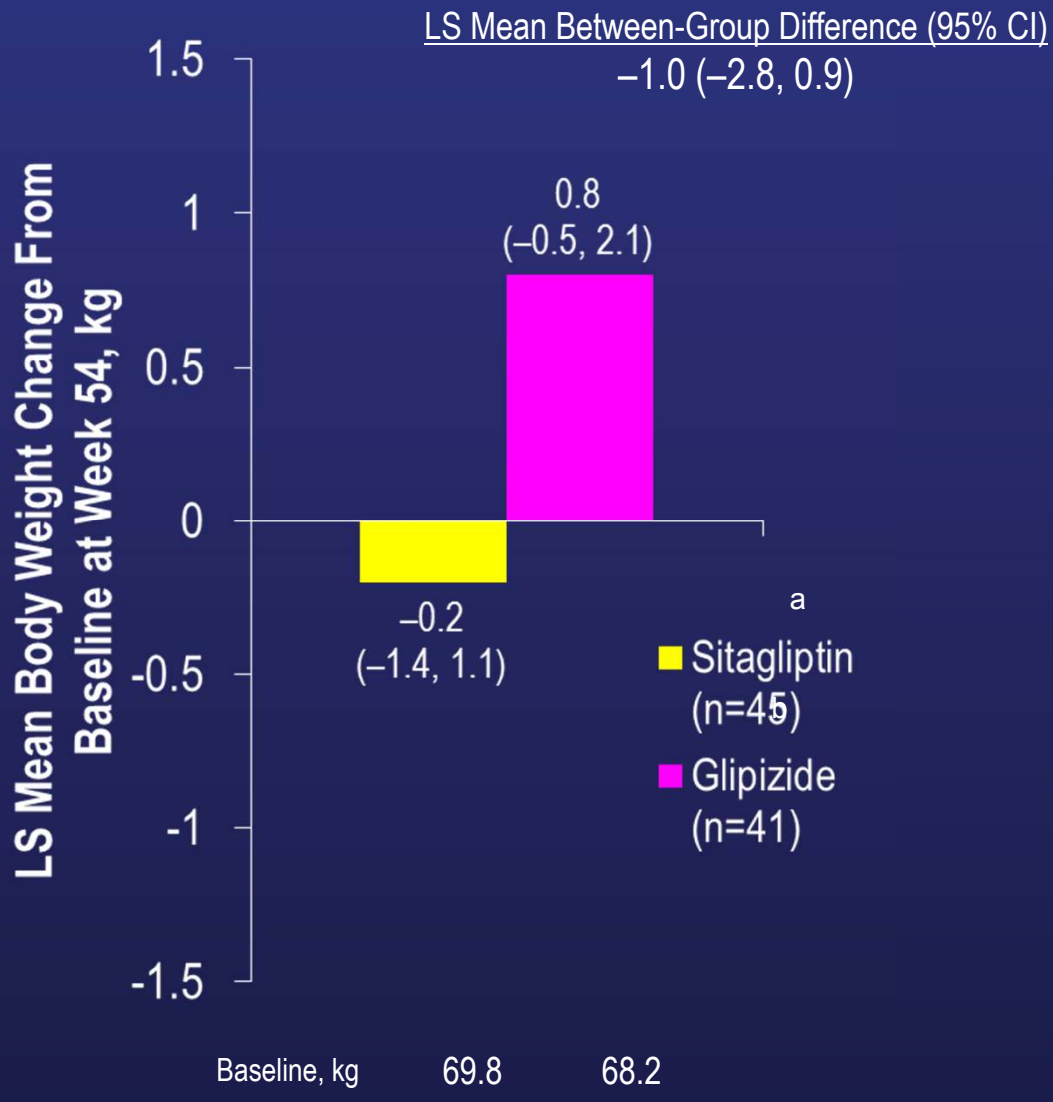

FAS=full analysis set; LOCF=last observation carried forward; LS=least squares; SE = standard error; CI=confidence interval. [a]25 mg once daily. [b]Mean dose of glipizide was 5.3 mg per day. Glipizide was initiated at 2.5 mg/day and titrated to a maximum of 20 mg/day. **1.** Arjona Ferreira JC et al. *Am J Kidney Dis.* DOI: 10.1053/j.ajkd.2012.11.043.

# Sitagliptin Significantly Reduced $HbA_{1c}$ at 54 Weeks From Baseline in Patients With ESRD on Dialysis




FAS=full analysis set; LOCF=last observation carried forward; LS=least squares; SE=standard error; CI=confidence interval. 25 mg once daily (n=62). [b]Mean dose of glipizide was 5.3 mg per day. Glipizide was initiated at 2.5 mg/day and titrated to a maximum of 20 mg/day (n=59). **1.** Arjona Ferreira JC et al. *Am J Kidney Dis*. DOI: 10.1053/j.ajkd.2012.11.043.

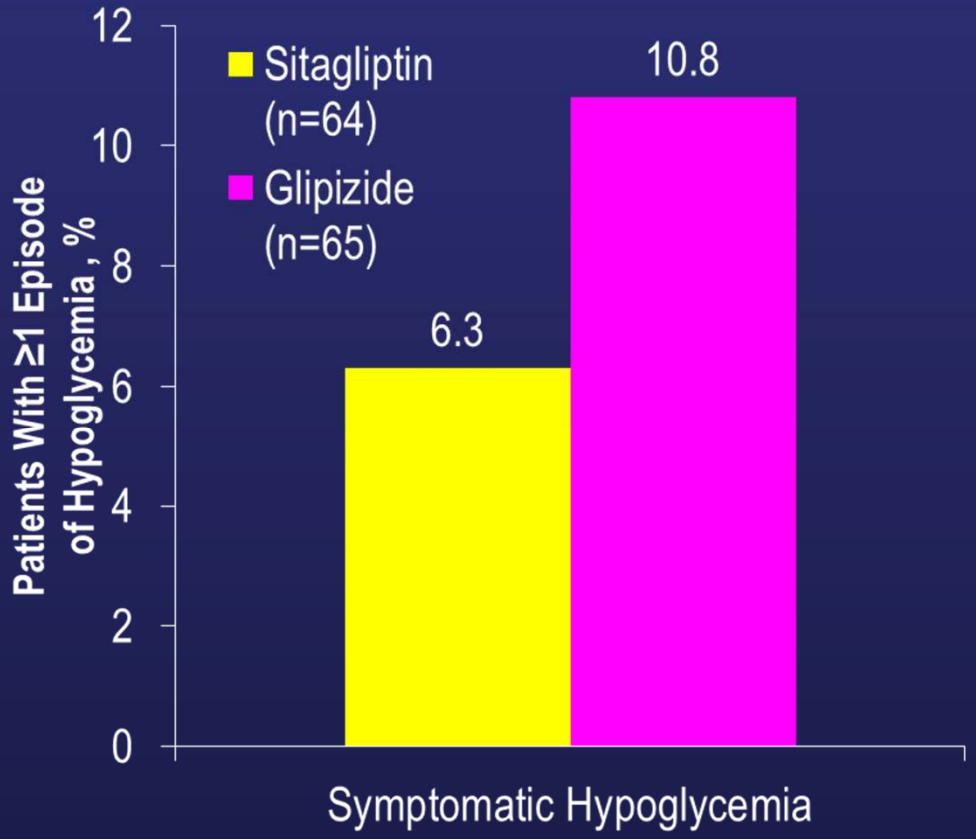
# Sitagliptin Did Not Result in Weight Gain




APaT=All Patients as Treated; LS=least squares; CI=confidence interval. [a]25 mg once daily. [b]Mean dose of glipizide was 5.3 mg per day. Glipizide was initiated at 2.5 mg/day and titrated to a maximum of 20 mg/day. **1.** Arjona Ferreira JC et al. *Am J Kidney Dis.* DOI: 10.1053/j.ajkd.2012.11.043.

# Sitagliptin Had a Generally Low Proportion of Patients With Symptomatic Hypoglycemia

LS Mean Between-Group Difference (95% CI):
–4.5% (–15.3, 5.6); *P*=0.3




APaT=All Patients as Treated; LS=least squares; CI=confidence interval. [a]25 mg once daily. [b]Mean dose of glipizide was 5.3 mg per day. Glipizide was initiated at 2.5 mg/day and titrated to a maximum of 20 mg/day. **1.** Arjona Ferreira JC et al. *Am J Kidney Dis.* DOI: 10.1053/j.ajkd.2012.11.043.

# Sitagliptin Dosing

| | |
|---|---|
| **Normal Renal Function** | Sitagliptin **100 mg** once daily |
| **Mild Renal Insufficiency** (CrCl ≥50 mL/min) | Sitagliptin **100 mg** once daily |
| **Moderate Renal Insufficiency** (CrCl ≥30 to <50 mL/min) | Sitagliptin **50 mg** once daily |
| **Severe Renal Insufficiency** (CrCl <30 mL/min) | Sitagliptin **25 mg** once daily |
| **ESRD requiring hemodialysis or peritoneal dialysis** | Sitagliptin **25 mg** once daily |

- Sitagliptin may be administered without regard to the timing of dialysis.
- Because there is a dosage adjustment based upon renal function, assessment of renal function is recommended prior to initiation of sitagliptin and periodically thereafter.
- When sitagliptin is used in combination with a sulfonylurea or with insulin, a lower dose of sulfonylurea or insulin may be considered to reduce the risk of sulfonylurea- or insulin-induced hypoglycemia.

# Conclusions

- **CKD prevalence** is **high in T2DM** and higher $HbA_{1c}$ level is associated with the increased incidence of CKD.
- Complications in patients with T2DM with CKD is higher than in patients with single underlying disease.
- **Sitagliptin is effective and safe** in T2DM with CKD.
  - 100 mg once daily for mild CKD to normal kidney function
  - 50 mg once daily for moderate CKD (eGFR <50)
  - 25 mg once daily for severe CKD (eGFR <30)

# 경청해주셔서 감사합니다.