The Role of DPP-4 inhibitors in patients with CV risk

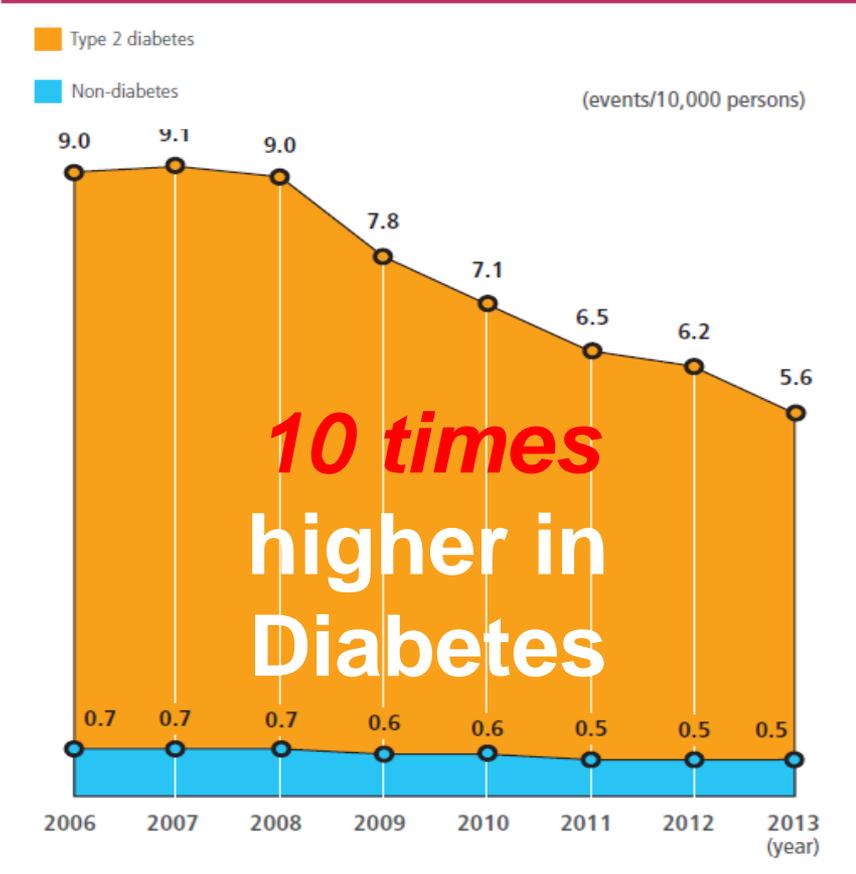**Soo LIM, MD, PHD**
Internal Medicine
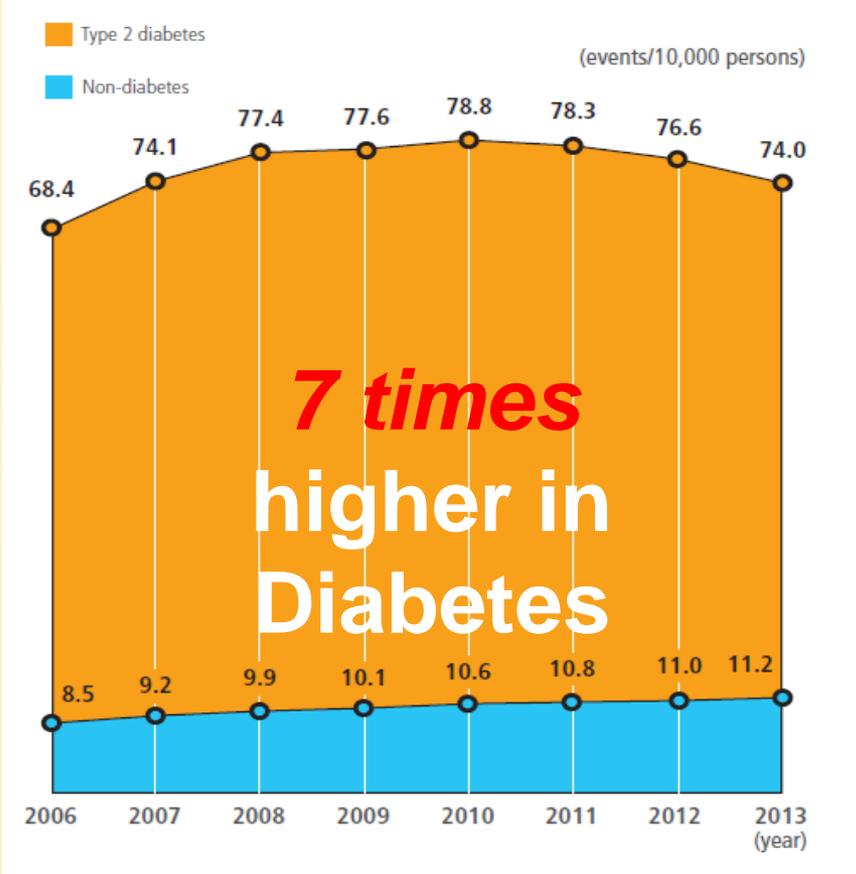**Seoul National University Bundang Hospital**

Agenda

- Association between Cardiovascular Disease and Type 2 Diabetes

- Importance of HbA1c Management esp. High risk patients incl. Renal impaired patients

- Consideration for Diabetes treatment with Renal impaired patients
    1) Evidence
    2) Safety
    3) Convenience

The Risk of CVD in Diabetes is Much Higher than Non−Diabetes Patients.

Coronary artery bypass graft (CABG)

Type 2 diabetes
Non-diabetes

(events/10,000 persons)

9.0 9.1 9.0 7.8 7.1 6.5 6.2 5.6

10 times
higher in Diabetes

0.7 0.7 0.7 0.6 0.6 0.5 0.5 0.5

2006 2007 2008 2009 2010 2011 2012 2013 (year)

Percutaneous coronary intervention(PCI)

Type 2 diabetes
Non-diabetes

(events/10,000 persons)

68.4 74.1 77.4 77.6 78.8 78.3 76.6 74.0

7 times
higher in Diabetes

8.5 9.2 9.9 10.1 10.6 10.8 11.0 11.2

2006 2007 2008 2009 2010 2011 2012 2013 (year)

CVD: Cardio Vascular Disease

Cardiovascular Events is much Higher in Type 2 Diabetes Patients

(events/10,000 persons)

Ischemic Stroke

295 / **62**

4.8Times

Type 2 diabetes   Non-diabetes

Ischemic heart disease

248 / **59**

4.2Times
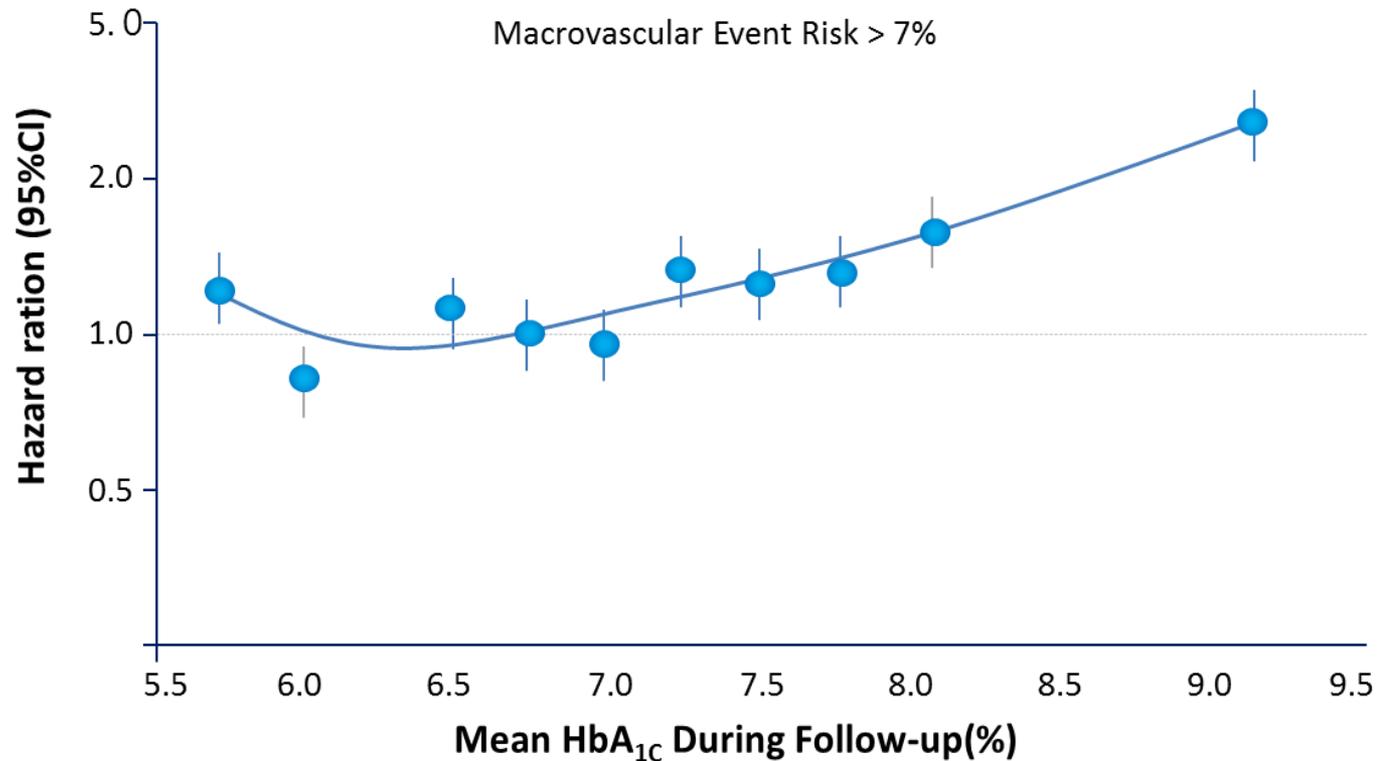
Type 2 diabetes   Non-diabetes

Cerebral hemorrhage

41 / **17**

2.4Times

Type 2 diabetes   Non-diabetes

Adapted from KDA Fact sheet 2015

1. KDA Fact Sheet 2015. Available at < http://www.diabetes.or.kr/pro/news/admin.php?mode=list > Accessed April 4, 2016.

CV Event Risk is associated with HbA$_{1c}$ Level.[1]

Macrovascular Event Risk > 7%

Hazard ration (95%CI) vs Mean HbA$_{1c}$ During Follow-up(%)

ADVANCE=action in diabetes and vascular disease: preterax and diamicron mr controlled evaluation

1. Zoungas S et al. Diabetologia 2012;55:636-643.
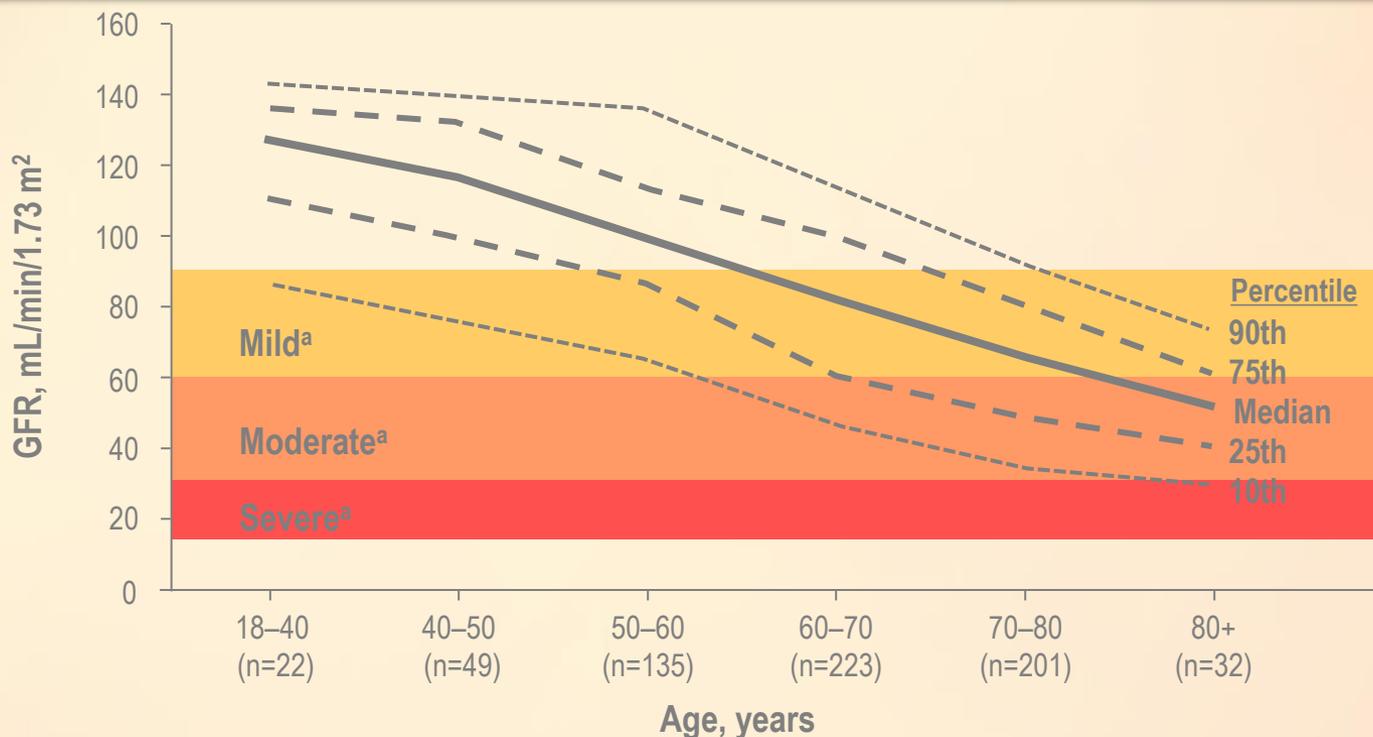
HbA$_{1c}$ management is the most Important
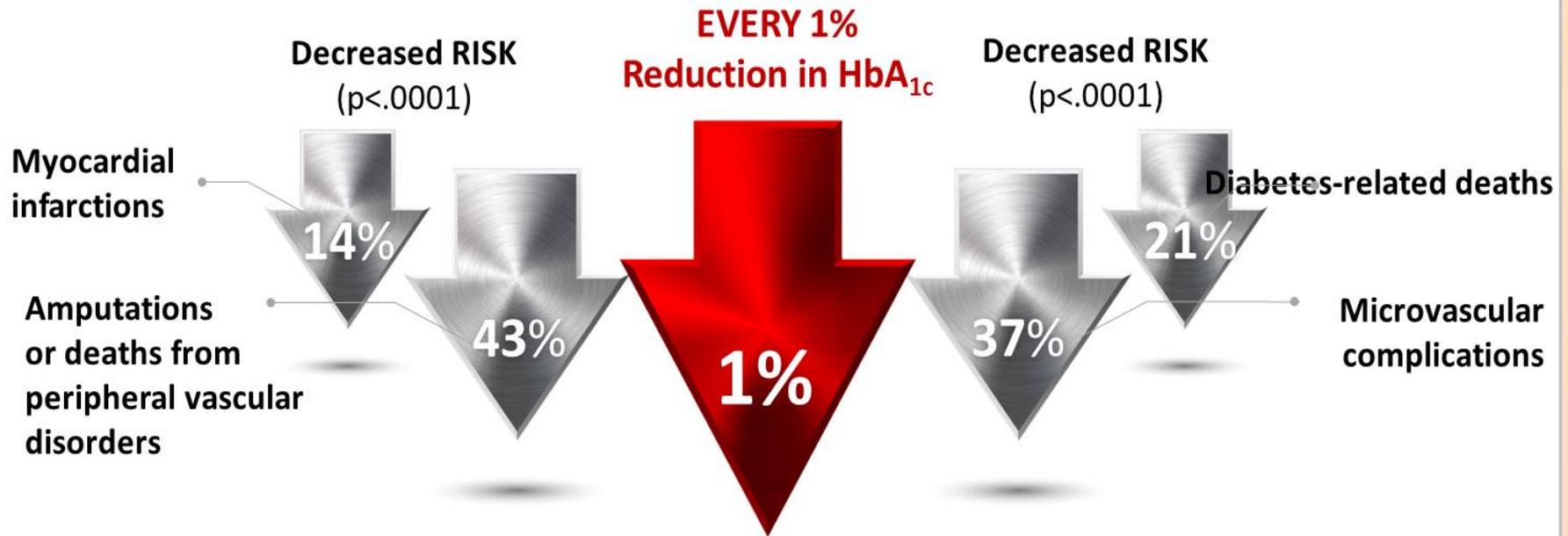
Relative risk (n=3642): Diabetes-related deaths, Microvascular complications, Myocardial infarctions, Amputations or deaths from peripheral vascular disorders

Increased Age Is Associated With a Lower eGFR Among Patients With T2DM

Age-Related Decline in Renal Function Among Patients With T2DM[1]

Additional observational studies have demonstrated an age-related decline in eGFR in the range of 1.5–5.2 mL/min/1.73 m² in patients with T2DM[2–4]

Adapted with permission from Premaratne E et al.[1]
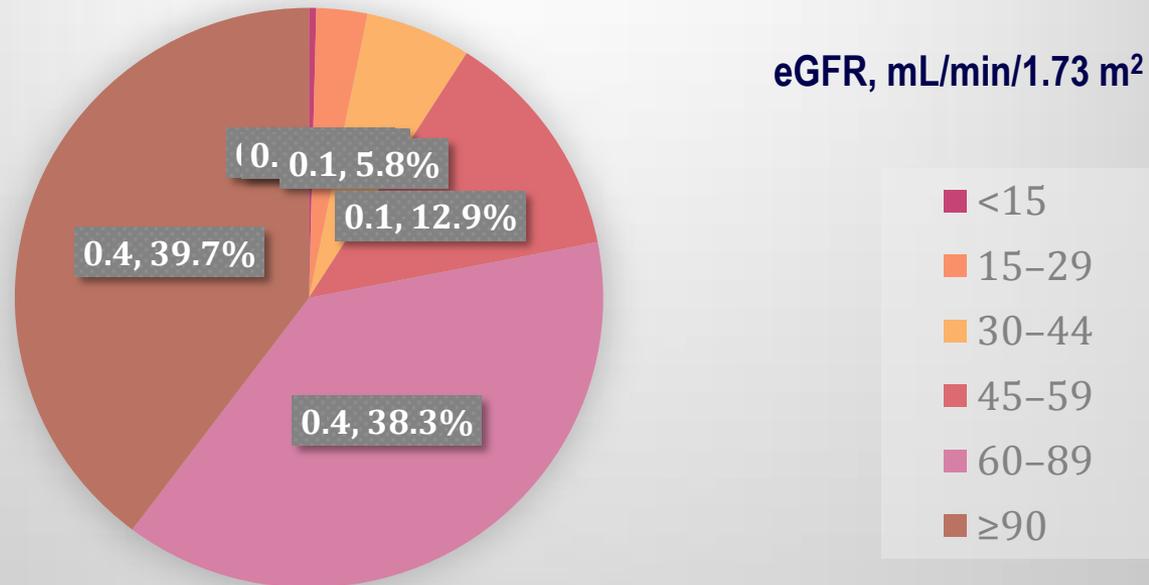[a]National Kidney Foundation severity scale of renal impairment.
 GFR = glomerular filtration rate; T2DM = type 2 diabetes mellitus; eGFR = estimated GFR.

1. Premaratne E et al. *Diabetologia*. 2005;48:2486–2493. **2**. Altemtam N et al. *Nephrol Dial Transplant*. 2012;27:1847–1854. **3**. Ali O et al. *BMJ Open*. 2013;3:e001855. **4**. Rossing K et al. *Kidney Int*. 2004;66:1596–1605.

About 22% T2DM Patients have Renal Insufficiency

Based on US NHANES Database 1999–2012 Data (N=2,915), Patients With Renal Insufficiency[a] Comprise an Estimated Proportion of Patients With T2DM[b]

Proportion of T2DM Population

eGFR, mL/min/1.73 m^2

- 0.1, 5.8%
- 0.1, 12.9%
- 0.4, 39.7%
- 0.4, 38.3%

Legend:
- ■ <15
- ■ 15–29
- ■ 30–44
- ■ 45–59
- ■ 60–89
- ■ ≥90

[a]Based on eGFR, which was calculated using the CKD-EPI equation.
[b]Age adjusted to 2012 NHIS diabetes population.
[c]Proportion of patients did not meet CKD criteria based on eGFR or albuminuria.
T2DM = type 2 diabetes mellitus; NHANES = National Health and Nutrition Examination Survey; eGFR = estimated glomerular filtration rate; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; NHIS = National Health Interview Survey.

1. Bailey RA et al. *BMC Research Notes*. 2014;7:415.

DPP-4 Inhibitors Appropriate Choice for Patients With T2DM and Renal Impairment

- Across all stages of renal function, DPP-4 inhibitors are

  – Efficacious

  – Well-tolerated

  – Weight neutral

  – Associated with a low risk of hypoglycemia when used as monotherapy

1. Nauck MA et al. *Diabetes Obes Metab.* 2007;9:194–205. **2.** Arjona Ferreira JC et al. *Diabetes Care.* 2013;36:1067–1073. **3.** Arjona Ferreira JC et al. *Am J Kidney Dis.* 2013;61:579–587. **4.** Deacon C et al. *Diabetes Obes Metab.* 2016;18:333–347.

Evidence?

Safety?

Convenience?

What is the optimal treatment choice
for renal impaired patients among DPP4Is?

Sitagliptin Shows Constant HbA$_{1c}$ Reduction Regardless Renal Function

HbA$_{1c}$ Reductions In 3 Active-Controlled Clinical Trials

Normal to Mild
Renal Impairment [a]

Sitagliptin 100 mg once daily

LS Mean Change in HbA$_{1c}$ From Baseline, %

0.1	
−0.1	
−0.3	
−0.5	
−0.7	**−0.7**
−0.9	
−1.1	
−1.3	
−1.5	

52 weeks

Mean Baseline HbA$_{1c}$: 7.5%

SU (glipizide) HbA$_{1c}$ reduction: −0.7%

Moderate-to-Severe
Renal Impairment [b]

Sitagliptin 50 mg or 25 mg once daily[2]

LS Mean Change in HbA$_{1c}$ From Baseline, %

0.1	
−0.1	
−0.3	
−0.5	
−0.7	**−0.8**
−0.9	
−1.1	
−1.3	
−1.5	

54 weeks

Mean Baseline HbA$_{1c}$: 7.8%

SU (glipizide) HbA$_{1c}$ reduction: −0.6%

ESRD
on Dialysis

Sitagliptin 25 mg once daily[3]

LS Mean Change in HbA$_{1c}$ From Baseline, %

0.1	
−0.1	
−0.3	
−0.5	
−0.7	**−0.7**
−0.9	
−1.1	
−1.3	
−1.5	

54 weeks

Mean Baseline HbA$_{1c}$: 7.9%

SU (glipizide) HbA$_{1c}$ reduction: −0.9%

[a]No renal function impairment inconsistent with the use of metformin.
[b]GFR <50 mL/min
ESRD = end-stage renal disease; SU = sulfonylurea; LS = least squares; GFR = glomerular filtration rate.

1. Nauck MA et al. *Diabetes Obes Metab.* 2007;9:194–205. **2.** Arjona Ferreira JC et al. *Diabetes Care.* 2013;36:1067–1073. **3.** Arjona Ferreira JC et al. *Am J Kidney Dis.* 2013;61:579–587.

Clinical Trial Exposure of DPP-4 Inhibitors in Patients With Renal Impairment

Clinical Trial Exposure in Patients With Renal Impairment					
	Sitagliptin	**Linagliptin**	**Vildagliptin**	**Saxagliptin**	**Alogliptin**
Moderate renal impairment	✓		✓	✓	✓
Severe renal impairment	✓	✓	✓	✓	✓
End-stage renal disease	✓			✓	✓
Completed CV safety trial	✓			✓	✓
Completed renal subanalysis	✓			✓	

[a]CAROLINA: Cardiovascular Outcome Study of Linagliptin Versus Glimepiride in Patients with Type 2 Diabetes has an estimated study completion date of March 2019.

DPP-4 = dipeptidyl peptidase-4; CV = cardiovascular.

1. JANUVIA™ (sitagliptin) [Summary of product characteristics]. Merck. 2016. **2.** *Galvus*™ (vildagliptin) [Summary of product characteristics]. Novartis. 2016. **3.** *Onglyza*™ (saxagliptin) [Summary of product characteristics]. Bristol-Myers Squibb/Astra Zeneca. 2016. **4.** *Tradjenta*™ (linagliptin) [Summary of product characteristics]. Boehringer Ingelheim /Lilly. 2015.

5. *Vipidia*™ (alogliptin) [Summary of product characteristics]. Takeda. 2015. **6.** Cornel JH et al. *Diabetes Care.* 2016;39:2304–2310. **7.** Mosenzon O et al. *Diabetes Care.* 2016 Oct 17. pii: dc160621. [Epub ahead of print].

TECOS CV Safety Trial: Primary Composite CV Outcome and Hospitalizations for Heart Failure

Primary Composite CV Outcome: Intention-to-Treat Population

Placebo 11.6% (n=851)

Sitagliptin 11.4% (n=839)

HR (95% CI) 0.98 (0.89, 1.08)

Patients with Event, % — Month
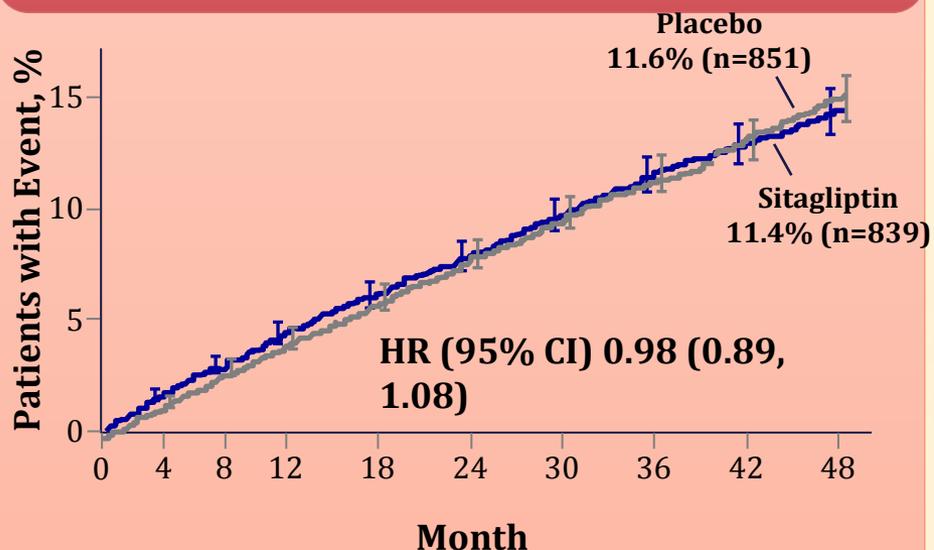
Between-group difference (ITT) was not statistically significant for superiority: *P*=0.65
Between-group difference (PP) was statistically significant for noninferiority: *P*<0.001[a]

Hospitalizations for Heart Failure: Intention-to-Treat Population

Placebo 229 (3.1%)

Sitagliptin 228 (3.1%)

HR (95% CI) 1.00 (0.83, 1.20)

Patients with Event, % — Month
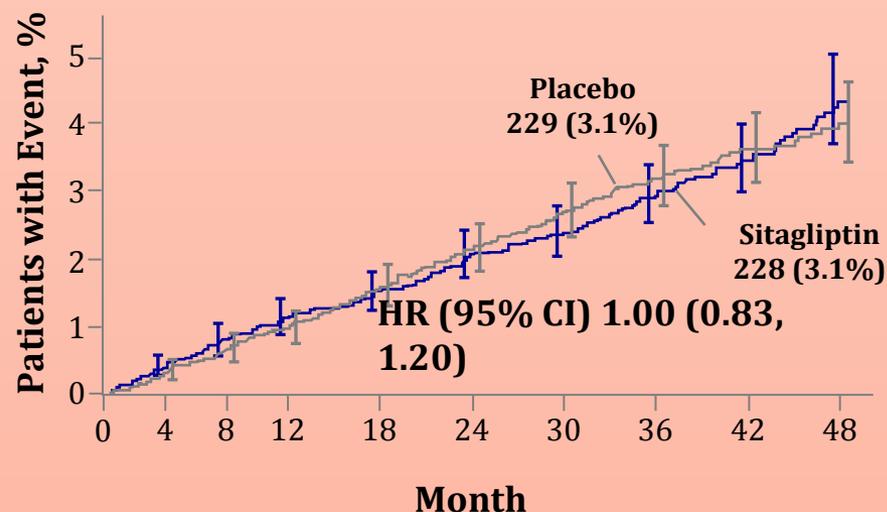
Between group difference was not statistically significant: *P*=0.98

TEC🜚S

TECOS CV Safety Trial: Subgroup Analyses for the Primary Composite CV Outcome[1]

Subject Group	Interaction *P* Value	n/N	Hazard Ratio	95% CI	
Renal function subgroups					
eGFR <60 mL/min/1.73 m²	0.443	538/3,324	0.92	0.78, 1.10	
eGFR ≥60 mL/min/1.73 m²		1,129/11,204	1.00	0.89, 1.13	
History of hypertension					
Yes	0.590	1,509/12,648	0.99	0.89, 1.09	
No		181/2,023	0.91	0.68, 1.21	
Systolic blood pressure subgroups					
<140 mmHg	0.735	968/8,815	0.96	0.85, 1.09	
≥140–<160 mmHg		526/4,511	1.03	0.87, 1.23	
≥160 mmHg		191/1,303	0.92	0.70, 1.23	
Diastolic blood pressure subgroups					
<90 mmHg	0.133	1,415/12,503	0.98	0.88, 1.09	
≥90–<100 mmHg		234/1,834	1.08	0.84, 1.40	
≥100 mmHg		36/292	0.51	0.25, 1.02	

Favors Sitagliptin Favors Placebo

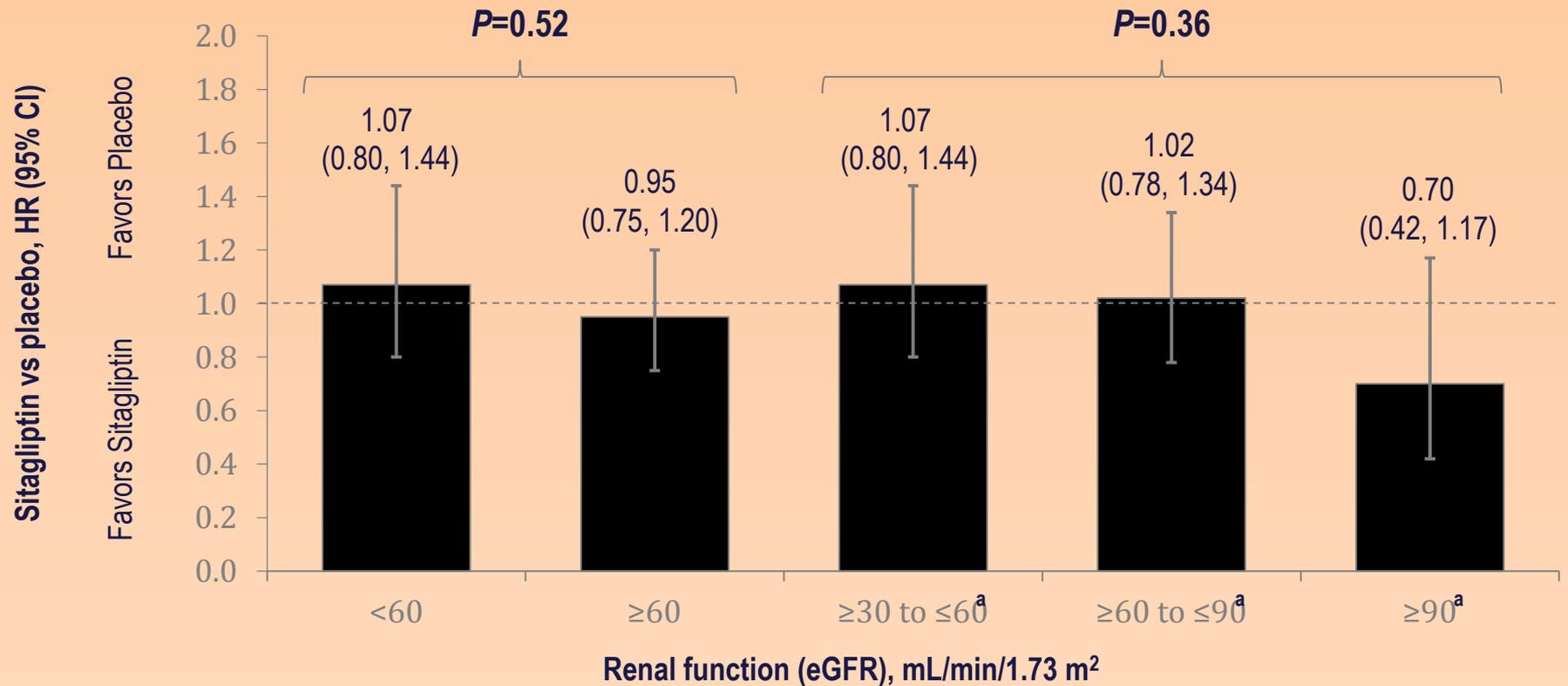Adapted with permission from Green JB et al.[1]

TECOS = Trial Evaluating Cardiovascular Outcomes With Sitagliptin; CV = cardiovascular; CI = confidence interval; eGFR = estimated glomerular filtration rate.

1. Green JB et al. *N Engl J Med.* 2015;373:232–242.

Secondary Analysis of TECOS CV Safety Trial: Hospitalization for HF by eGFR Subgroups

Stratified Analyses for Sitagliptin vs Placebo on First hHF for eGFR Subgroups

Y-axis: Sitagliptin vs placebo, HR (95% CI); Favors Placebo / Favors Sitagliptin

X-axis: Renal function (eGFR), mL/min/1.73 m²

P=0.52

P=0.36

<60: 1.07 (0.80, 1.44)
≥60: 0.95 (0.75, 1.20)
≥30 to ≤60[a]: 1.07 (0.80, 1.44)
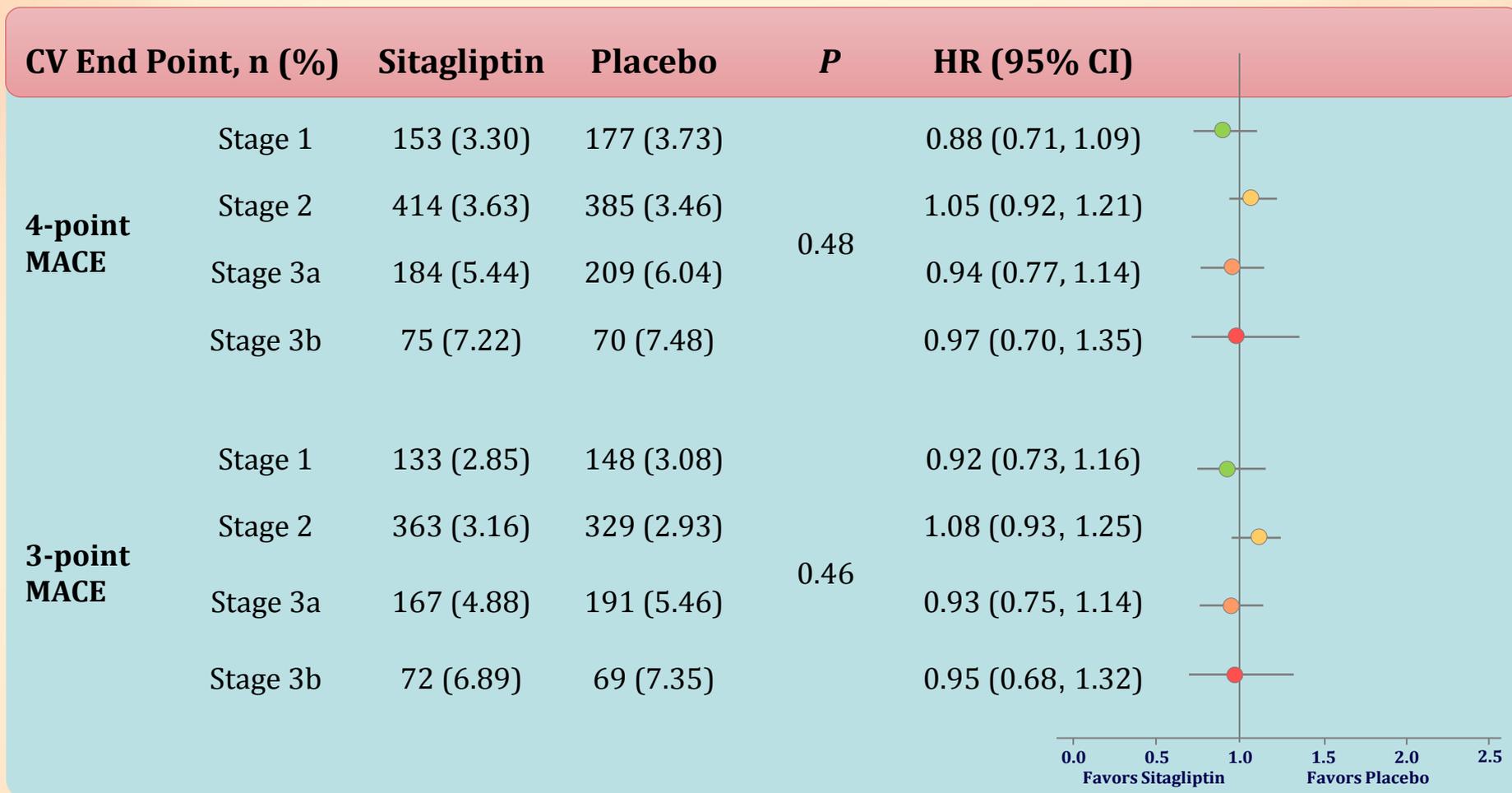≥60 to ≤90[a]: 1.02 (0.78, 1.34)
≥90[a]: 0.70 (0.42, 1.17)

[a]Post-hoc subgroups.
TECOS = Trial Evaluating Cardiovascular Outcomes With Sitagliptin; CV = cardiovascular; hHF = hospitalization for heart failure; HR = hazard ratio; CI = confidence interval; HF = heart failure; eGFR = estimated glomerular filtration rate.
1. McGuire DK et al. *JAMA Cardiol*. 2016;1:126–135.

Effect of Sitagliptin on Kidney Function and Respective CV Outcomes in T2DM in TECOS by eGFR at Baseline

CV End Point, n (%)		Sitagliptin	Placebo	*P*	HR (95% CI)	
4-point MACE	Stage 1	153 (3.30)	177 (3.73)		0.88 (0.71, 1.09)	
	Stage 2	414 (3.63)	385 (3.46)		1.05 (0.92, 1.21)	
	Stage 3a	184 (5.44)	209 (6.04)	0.48	0.94 (0.77, 1.14)	
	Stage 3b	75 (7.22)	70 (7.48)		0.97 (0.70, 1.35)	
3-point MACE	Stage 1	133 (2.85)	148 (3.08)		0.92 (0.73, 1.16)	
	Stage 2	363 (3.16)	329 (2.93)		1.08 (0.93, 1.25)	
	Stage 3a	167 (4.88)	191 (5.46)	0.46	0.93 (0.75, 1.14)	
	Stage 3b	72 (6.89)	69 (7.35)		0.95 (0.68, 1.32)	

0.0 0.5 1.0 1.5 2.0 2.5
Favors Sitagliptin   Favors Placebo
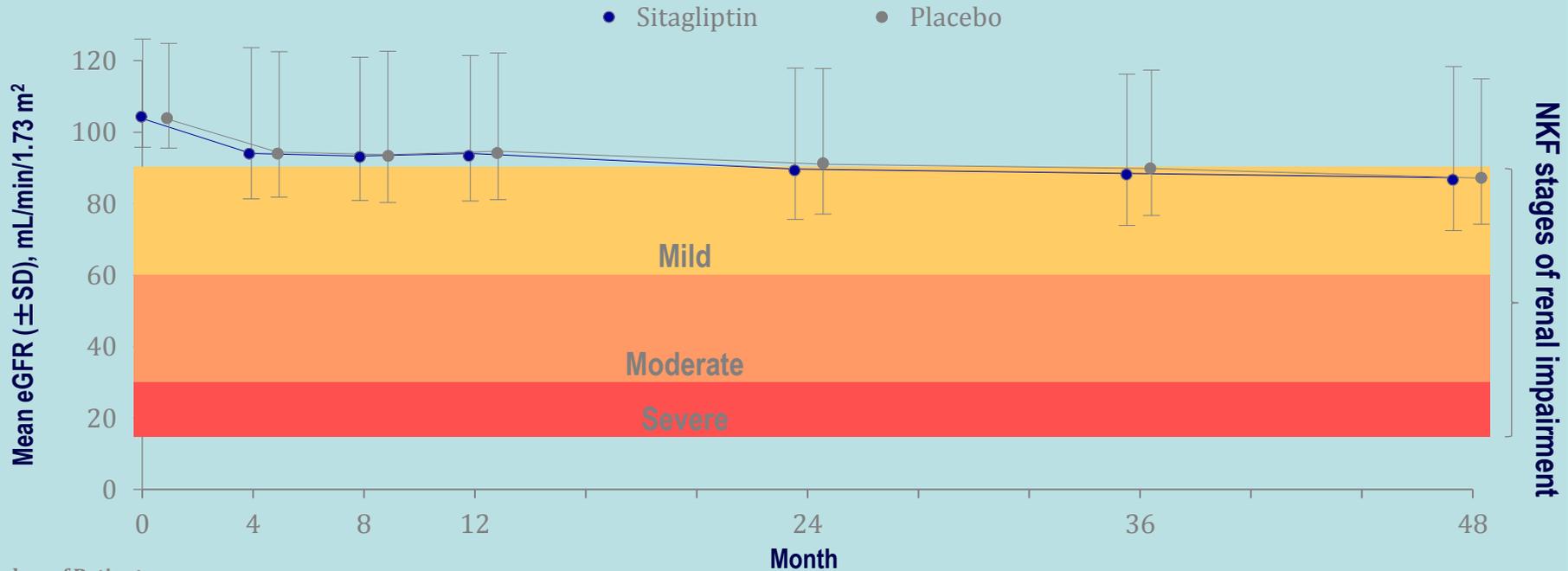
Adapted with permission from Cornel JH et al.[1]

CV = cardiovascular; T2DM = type 2 diabetes mellitus; TECOS = Trial Evaluating Cardiovascular Outcomes With Sitagliptin; eGFR = estimated glomerular filtration rate; MACE = major adverse cardiovascular event; HR = hazard ratio; CI = confidence interval.

1. Cornel JH et al. *Diabetes Care.* 2016;39:2304–2310.

Effect of Sitagliptin on Kidney Function and Respective CV Outcomes in T2DM in TECOS: Change in eGFR[1]

Change from baseline in eGFR for patients with eGFR ≥90 at baseline (Stage 1)

Number of Patients:							
Sitagliptin	1,157	734	653	875	956	533	245
Placebo	1,183	746	674	913	966	513	220

- Other observational studies have shown a similar age-related decline in eGFR[2–5]
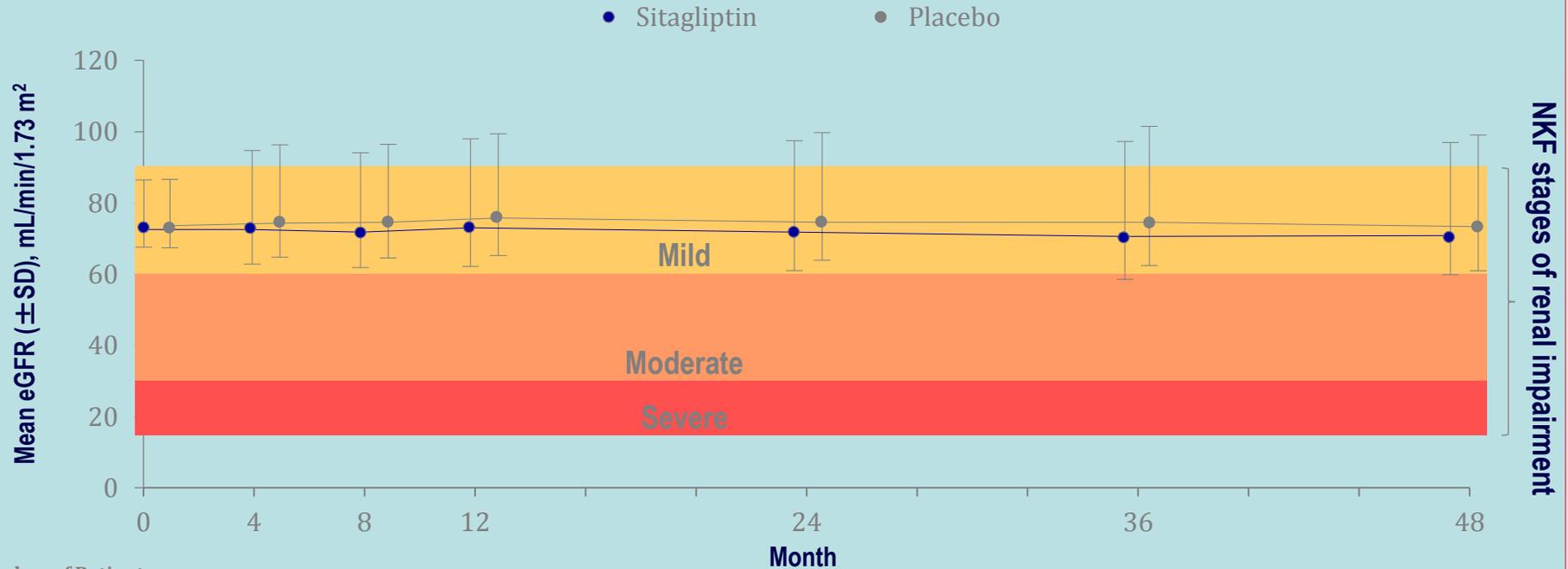- These decreases in eGFR were within NICE guidelines of acceptable annual reduction[6]

1. Cornel JH et al. *Diabetes Care.* 2016;39:2304–2310. 2. Altemtam et al. *Nephrol Dial Transplant.* 2012;27:1847-1854. 3. Ali O et al. *BMJ Open.* 2013;3:e001855. 4. Premaratne E et al. *Diabetologia.* 2005;48:2486–2493. 5. Rossing K et al. *Kidney Int.* 2004;66:1596–1605. 6. National Institute for Health and Care Excellence. Chronic Kidney Disease Guidelines. http://www.nice.org.uk/guidance/cg182/evidence/update-full-guideline-191905165. Accessed December 4, 2016.

TEC⬡S

Effect of Sitagliptin on Kidney Function and Respective CV Outcomes in T2DM in TECOS: Change in eGFR[1]

Change from baseline in eGFR for patients with eGFR 60–89 at baseline (Stage 2)

- Sitagliptin
- Placebo

Mean eGFR (±SD), mL/min/1.73 m² (y-axis)

Month (x-axis)

NKF stages of renal impairment (right axis)

Mild / Moderate / Severe

Number of Patients:							
Month	0	4	8	12	24	36	48
Sitagliptin	1,157	734	653	875	956	533	245
Placebo	1,183	746	674	913	966	513	220

- Other observational studies have shown a similar age-related decline in eGFR[2–5]
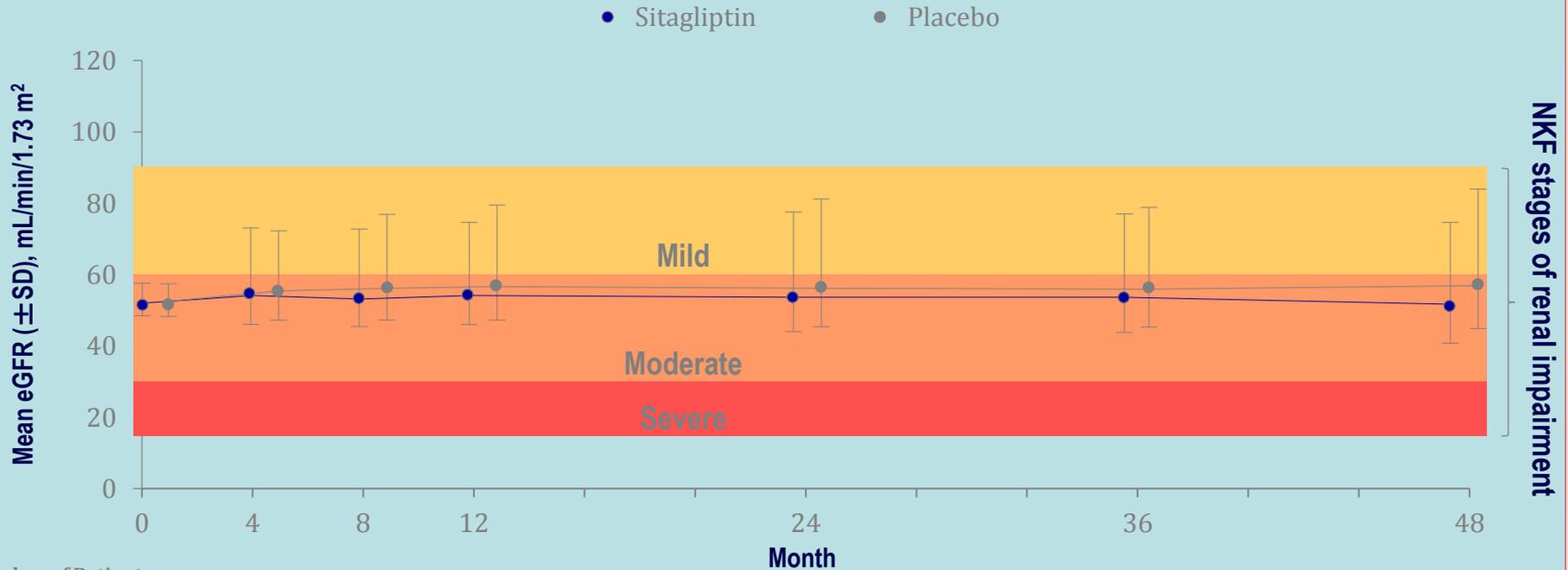- These decreases in eGFR were within NICE guidelines of acceptable annual reduction[6]

1. Cornel JH et al. *Diabetes Care*. 2016;39:2304–2310. 2. Altemtam et al. *Nephrol Dial Transplant*. 2012;27:1847-1854. 3. Ali O et al. *BMJ Open*. 2013;3:e001855. 4. Premaratne E et al. *Diabetologia*. 2005;48:2486–2493. 5. Rossing K et al. *Kidney Int*. 2004;66:1596–1605. 6. National Institute for Health and Care Excellence. Chronic Kidney Disease Guidelines. http://www.nice.org.uk/guidance/cg182/evidence/update-full-guideline-191905165. Accessed December 4, 2016.

Effect of Sitagliptin on Kidney Function and Respective CV Outcomes in T2DM in TECOS: Change in eGFR[1]

Change from baseline in eGFR for patients with eGFR 45–59 at baseline (Stage 3A)

Number of Patients:

	0	4	8	12	24	36	48
Sitagliptin	1,157	734	653	875	956	533	245
Placebo	1,183	746	674	913	966	513	220

- Other observational studies have shown a similar age-related decline in eGFR[2–5]
- These decreases in eGFR were within NICE guidelines of acceptable annual reduction[6]

1. Cornel JH et al. *Diabetes Care*. 2016;39:2304–2310. 2. Altemtam et al. *Nephrol Dial Transplant*. 2012;27:1847-1854. 3. Ali O et al. *BMJ Open*. 2013;3:e001855. 4. Premaratne E et al. *Diabetologia*. 2005;48:2486–2493. 5. Rossing K et al. *Kidney Int*. 2004;66:1596–1605. 6. National Institute for Health and Care Excellence. Chronic Kidney Disease Guidelines. http://www.nice.org.uk/guidance/cg182/evidence/update-full-guideline-191905165. Accessed December 4, 2016.

Effect of Sitagliptin on Kidney Function and Respective CV Outcomes in T2DM in TECOS: Change in eGFR[1]

Change from baseline in eGFR for patients with eGFR 30–44 at baseline (Stage 3B)

- Sitagliptin
- Placebo

Mean eGFR (±SD), mL/min/1.73 m^2

NKF stages of renal impairment

Mild

Moderate

Severe

Month

Number of Patients:

	0	4	8	12	24	36	48
Sitagliptin	1,157	734	653	875	956	533	245
Placebo	1,183	746	674	913	966	513	220

- Other observational studies have shown a similar age-related decline in eGFR[2–5]
- These decreases in eGFR were within NICE guidelines of acceptable annual reduction[6]

Adapted with permission from Cornel JH et al.[1]

CV = cardiovascular; T2DM = type 2 diabetes mellitus; TECOS = Trial Evaluating Cardiovascular Outcomes With Sitagliptin; eGFR = estimated glomerular filtration rate; SD = standard deviation; NKF = National Kidney Foundation; NICE = National Institute for Health Care Excellence.
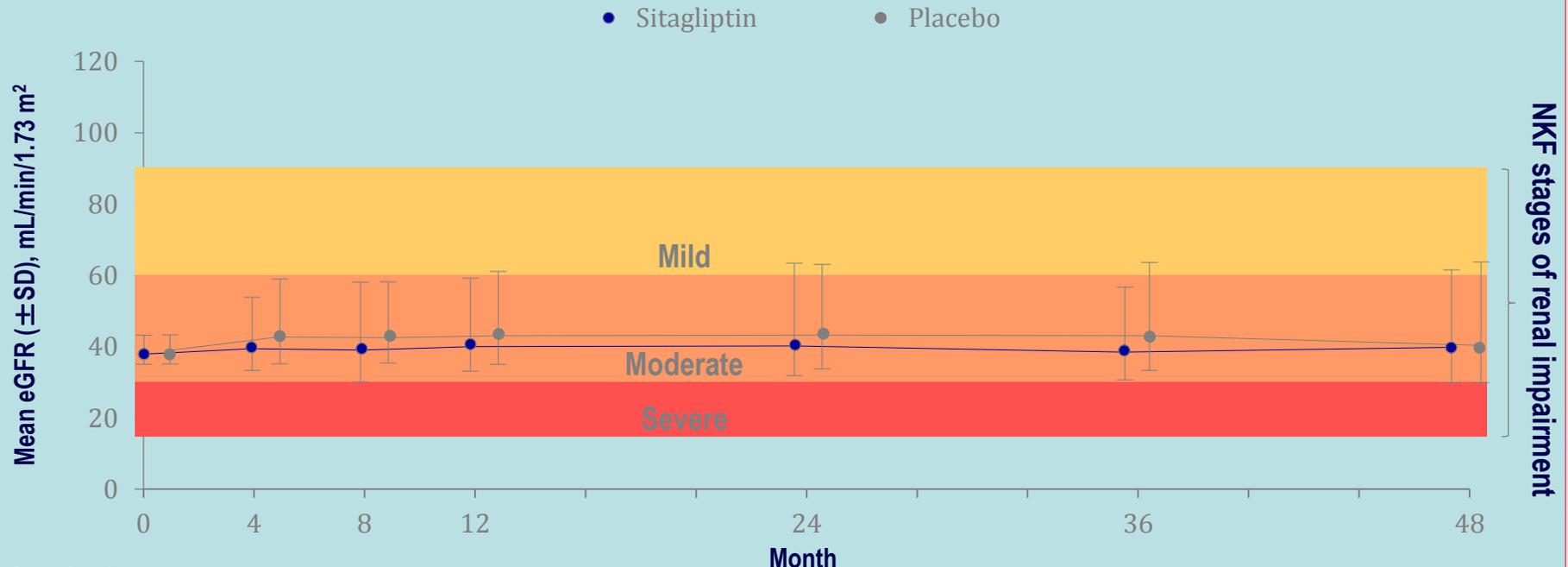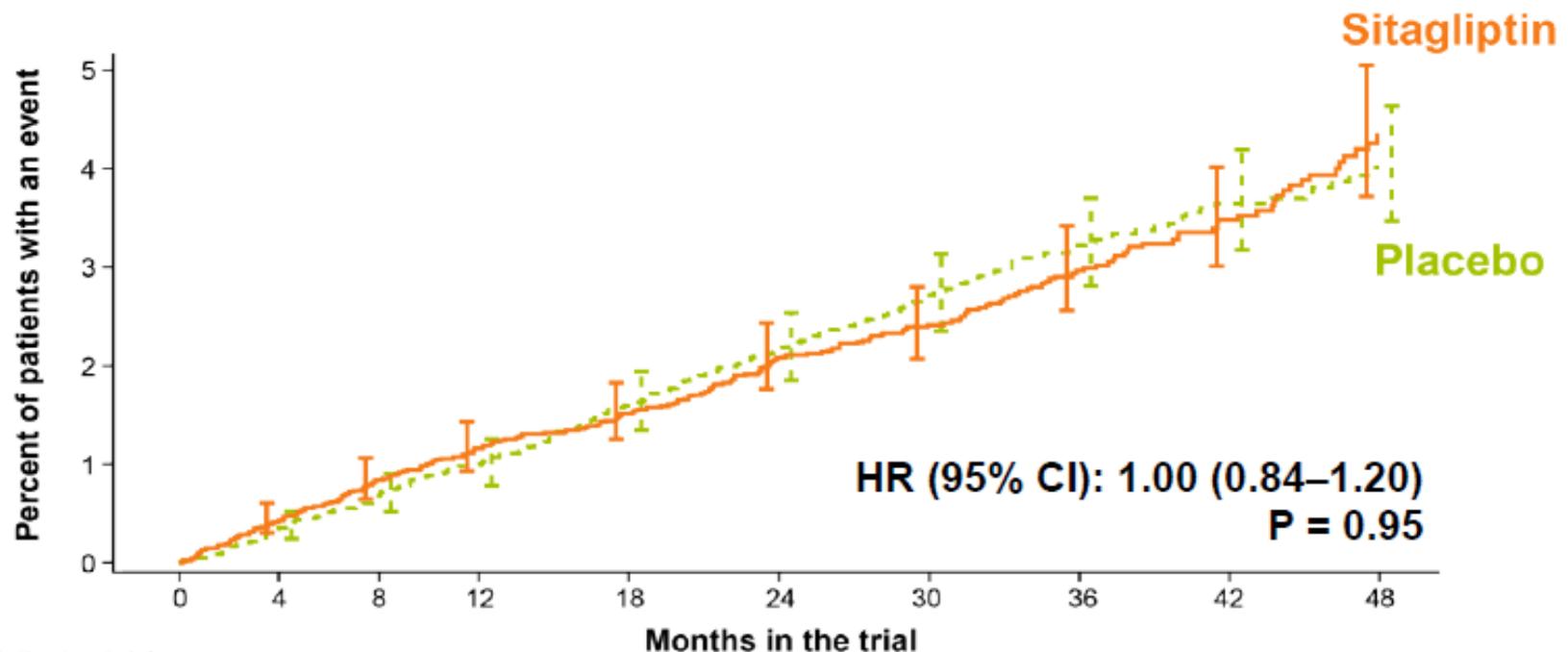
1. Cornel JH et al. *Diabetes Care.* 2016;39:2304–2310. **2.** Altemtam et al. *Nephrol Dial Transplant.* 2012;27:1847-1854. **3.** Ali O et al. *BMJ Open.* 2013;3:e001855. **4.** Premaratne E et al. *Diabetologia.* 2005;48:2486–2493. **5.** Rossing K et al. *Kidney Int.* 2004;66:1596–1605. **6.** National Institute for Health and Care Excellence. Chronic Kidney Disease Guidelines. http://www.nice.org.uk/guidance/cg182/evidence/update-full-guideline-191905165. Accessed December 4, 2016.

TEC♥S

TECOS: Time to First Hospitalization for Heart Failure*

* ITT population

SAVOR-TIMI 53, EXAMINE, TECOS*: Hospitalization for Heart Failure

Trial	HR (95% CI)		P-Value
SAVOR-TIMI 53	1.27 (1.07–1.51)		0.007
EXAMINE	1.19 (0.89–1.59)		0.235
TECOS	1.00 (0.84–1.20)		1.000
SAVOR-TIMI 53 + EXAMINE + TECOS	1.14 (0.97–1.34)		0.102

0   1   2

Favors Treatment   Favors Placebo
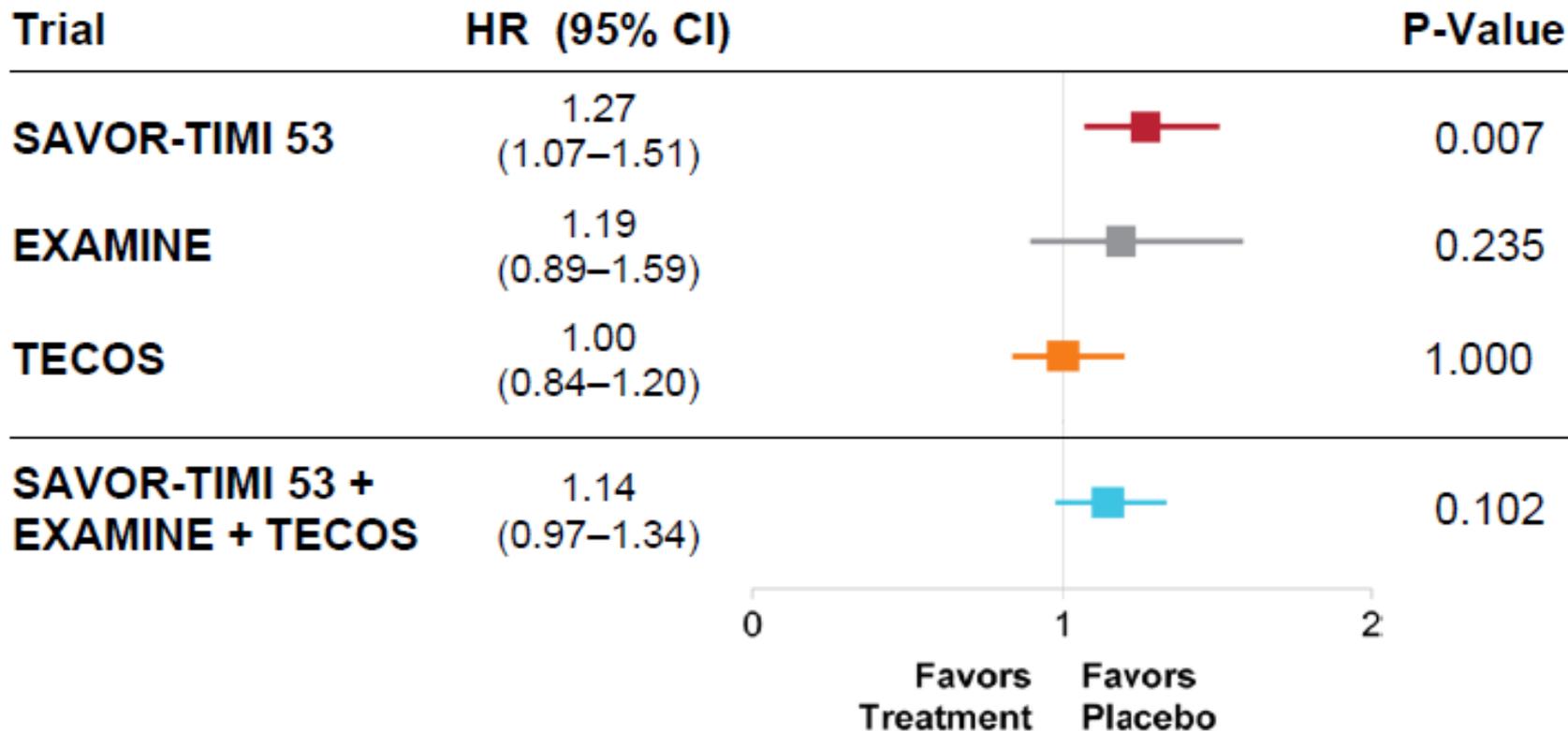
Test for heterogeneity for 3 trials:
p=0.16, I^2=44.9

1. EASD 2015 updated, JAMA Cardiol. doi:10.1001/jamacardio.2016.0103 (Published online April 13, 2016.)

Dose adjustment is recommended to achieve plasma concentrations in Patients With Renal Impairment

Sitagliptin Clearance Decreases with Worsening Renal Function, Increasing Exposure

Left chart — Sitagliptin Clearance, mL/min vs CrCl, mL/min

CrCl, mL/min	Sitagliptin Clearance, mL/min
>80	339
50–50	242
30–50	126
<30	60.2
ESRD*	N/A

Right chart — Sitagliptin Exposure: AUC, μM · h vs CrCl, mL/min

CrCl, mL/min	Sitagliptin Exposure: AUC, μM · h
>80	4.40
50–80	7.09
30–50	9.96
<30	16.6
ESRD*	19.8

*Hemodialysis at 48 h postdose in subjects with ESRD

Single-dose (50 mg), open-label pharmacokinetic study in participants without diabetes with varying degrees of renal function compared

CrCl = creatinine clearance; AUC = area under the curve; ESRD = end-stage renal disease.

1. Bergman AJ et al. *Diabetes Care.* 2007;30:1862–1864. **2.** Evans M et al. *Diabetes Ther.* 2015;6:1–5.

Dose adjustment give price benefit to patients

eGFR	Dosage	price
CrCl ≥50 mL/min[1]	100 mg once daily	910 KRW
CrCl ≥30 to <50 mL/min	50 mg once daily	604 KRW
CrCl <30 mL/min	25 mg once daily	402 KRW

- Sitagliptin may be administered without regard to the timing of dialysis

- Assessment of renal function is recommended prior to initiation of sitagliptin and periodically thereafter

ESRD = end-stage renal disease; CrCI = creatinine clearance.

1. JANUVIA™ (sitagliptin) [Summary of product characteristics]. Merck. 2016. 2. 보건복지부고시 제 2017-7호 .

Summary

- DPP-4 inhibitors may be an appropriate choice for patients with T2DM and renal impairment
- Sitagliptin has clinical evidence supporting use in patients with renal impairment
- Among patients with T2DM and established CVD, sitagliptin did not increase the risk of major adverse CV events, hospitalization for heart failure, or other adverse events

Thank you!