VIII Convegno Nazionale Fondazione AMD
Palermo 18 novembre 2016

Il valore della DPP4 e di Sitagliptin inibizione nella pratica clinica

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2016 Classi di farmaci per il diabete

1. *Metformina*
2. *Sulfoniluree*
3. *Glinidi*
4. *Glitazoni*
5. *Acarbose*
6. *Insulina*
7. *Inibitori della DPP-4*
8. *Agonisti del GLP-1*
9. *Inibitori del trasporto renale del glucosio*

Più di 1200 possibili combinazioni..

2018 Classi di farmaci per il diabete

1. *Metformina*
2. *Sulfoniluree*
3. *Glinidi*
4. *Glitazoni*
5. *Acarbose*
6. *Insulina*
7. *Inibitori della DPP-4*
8. *Agonisti del GLP-1 + GLP1 RA coformulati con insulina*
9. *SGLT-2 inibitori di I e II generazione*
10. *Inibitori sintesi cortisolo*
11. *Bromocriptina*

Più di 2000 possibili combinazioni..

Le evidenze degli studi di outcome CV (CVOT): pro e contro

FDA Guidance for Industry to Evaluate CV Risk in New Antihyperglycemic Medications[1]

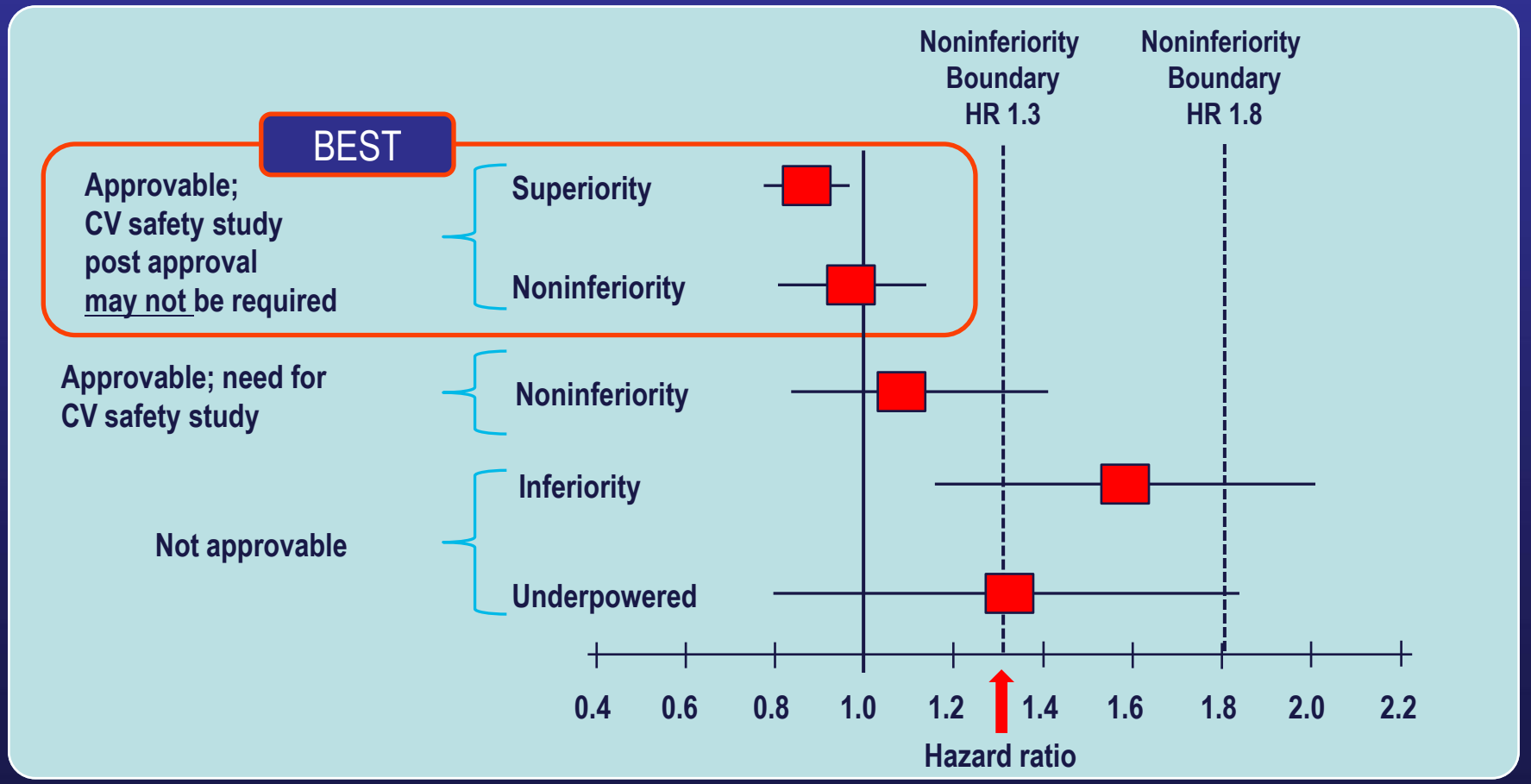
- July 2008: In order to establish the safety of a new antihyperglycemic medication to treat T2DM, FDA's Endocrinologic and Metabolic Drugs Advisory Committee provided guidance on risk assessment
  - Effects on CV risk to be more thoroughly addressed during antihyperglycemic medication development
  - Recommendation to demonstrate that therapy will not result in unacceptable increase in CV risk
  - Key areas to be addressed by study sponsors (inclusion of patients with a higher risk of CV events [eg, patients with advanced CV disease, elderly patients, and patients with impaired renal function], study duration ≥2 years)

FDA = Food and Drug Administration; T2DM = type 2 diabetes mellitus; CV = cardiovascular.

1. Center for Drug Evaluation and Research. Guidance for Industry: Diabetes Mellitus—Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes. December 2008. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071627.pdf. Accessed September 12, 2014.

FDA Statistical Criteria for Approval[1]

Five hypothetical examples of possible HRs, and regulatory consequences



FDA = Food and Drug Administration; HR = hazard ratio; CV = cardiovascular.

1. Reproduced with permission from Hirshberg B et al. *Diabetes Care.* 2011:34 (Suppl 2);S101–S106.

Traditional CV Outcome Trials vs Diabetes CV Safety Trials

Traditional (eg, LDL-C) CV Outcome Trials
Designed to Demonstrate CV Benefit[1,2]

Lower CV risk vs placebo or active comparator

Initiation of blinded treatment or placebo or active comparator

No adjustment to maintain LDL-C levels the same in both groups

Difference in LDL-C between treatment and placebo or active comparator

CV benefit of treatment demonstrated by significant reduction in CV outcomes

Diabetes CV Safety Trials
Primarily Designed to Demonstrate CV Safety[3–5]

No increased CV risk vs placebo as part of standard care

Initiation of blinded treatment or placebo

Adjustment to maintain HbA_{1c} levels the same in both groups

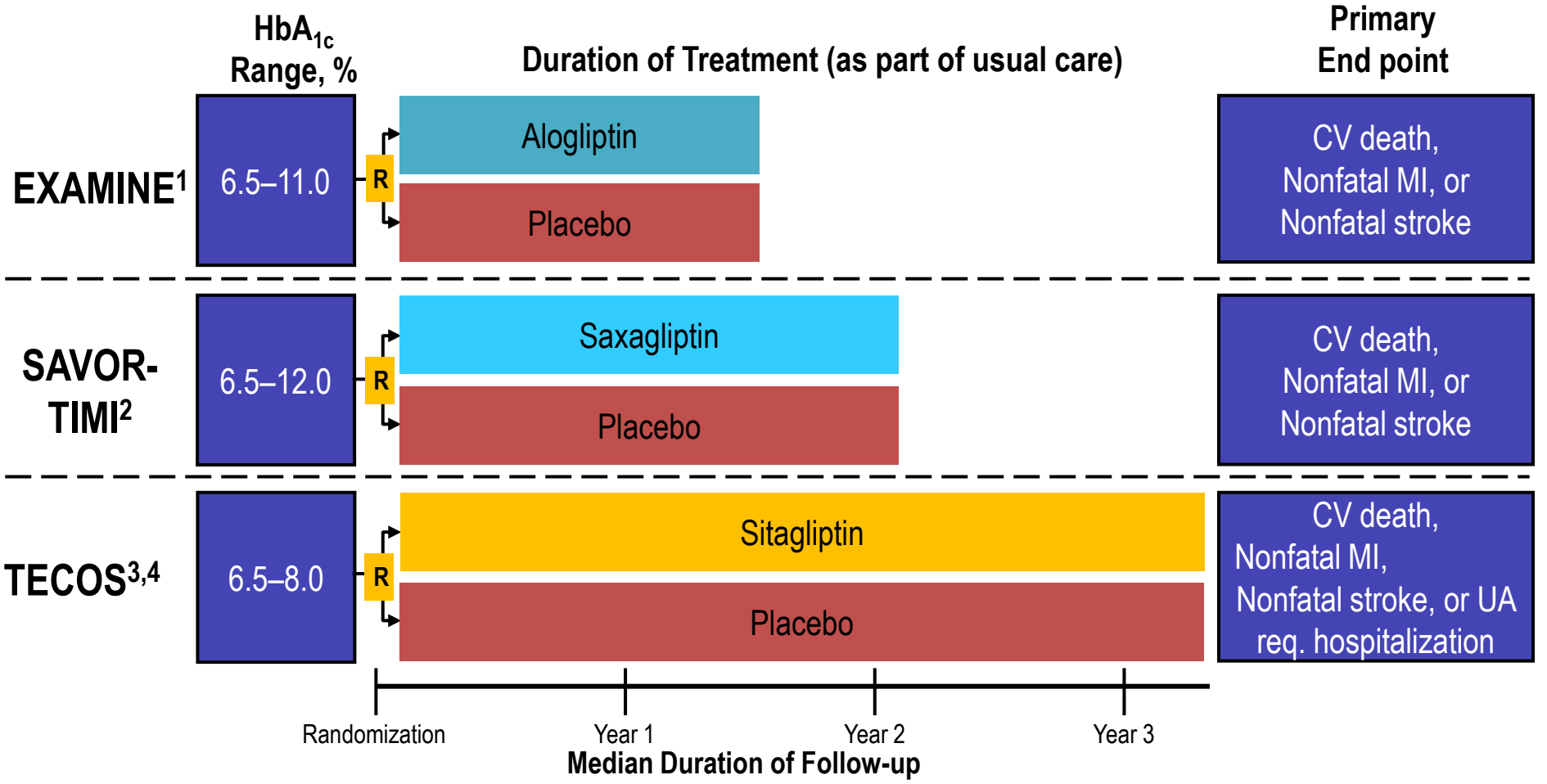
Small or no difference in HbA_{1c} between treatment and placebo

No increased CV risk (CV safety) of treatment demonstrated by noninferiority

CV = cardiovascular; DPP-4 = dipeptidyl peptidase-4; LDL-C = low density lipoprotein cholesterol.

1. Heart Protection Study Collaborative Group. *Lancet*. 2002;360:7–22. **2.** Heart Protection Study Collaborative Group. *Lancet*. 2003;361:2005–2016. **3.** White WB et al. *N Engl J Med*. 2013;369:1327–1335. **4.** Scirica BM et al. *N Engl J Med*. 2013;369:1317–1326. **5.** Green JB et al. *Am Heart J*. 2013;166:983–989.e7.

DPP i CVOT TRIALS: EXAMINE, SAVOR-TIMI, and TECOS



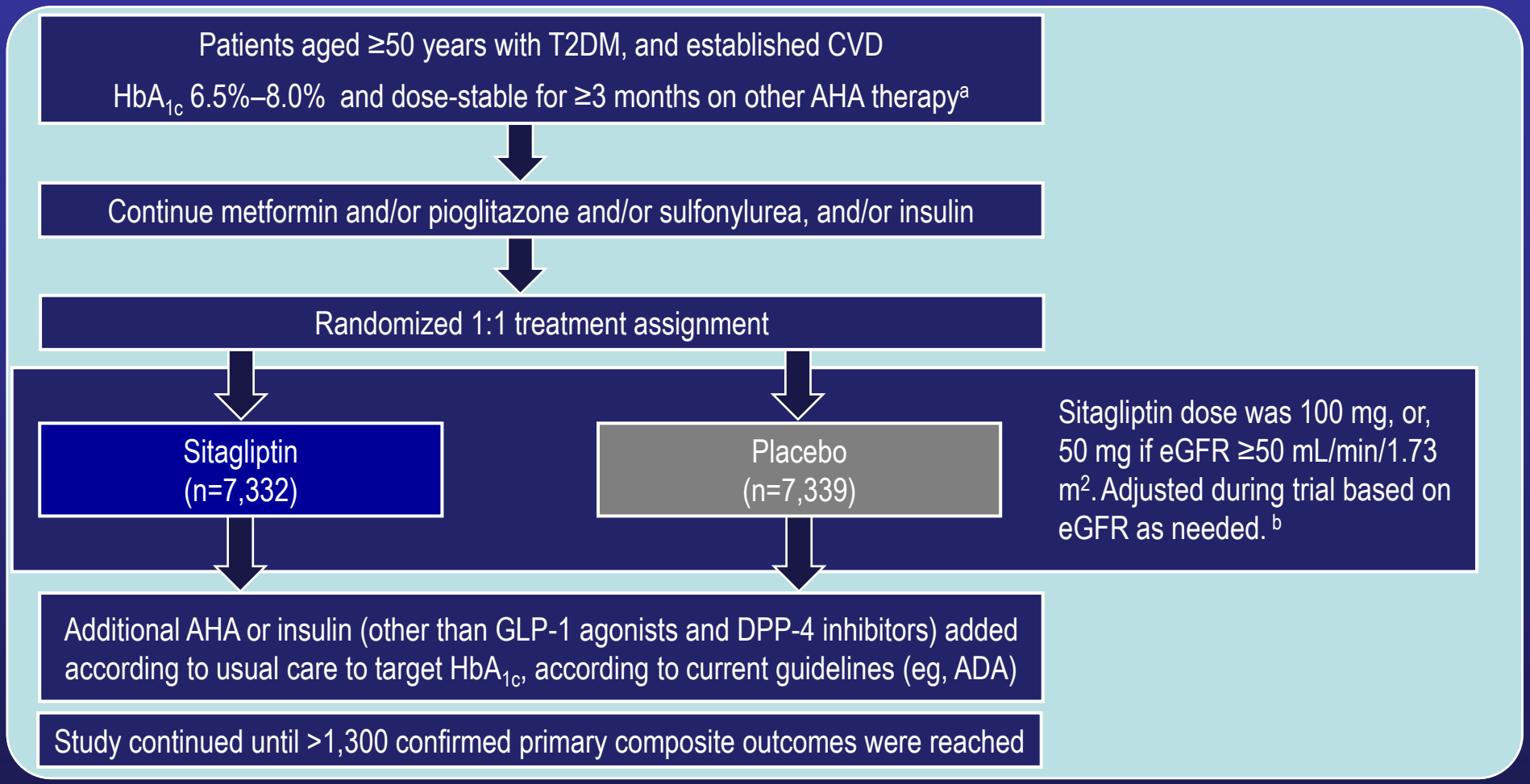
EXAMINE = Examination of Cardiovascular Outcomes: Alogliptin vs Standard of Care in Patients With Type 2 Diabetes Mellitus and Acute Coronary Syndrome;SAVOR-TIMI = Saxagliptin Assessment of Vascular Outcomes Recorded in Patients With Diabetes Mellitus Trial-Thrombolysis in Myocardial Infarction; TECOS = Trial Evaluating Cardiovascular Outcomes With Sitagliptin. CV = cardiovascular; MI = myocardial infarction; UA = unstable angina.

White WB et al. *N Engl J Med.* 2013;369:1327–1335. Scirica BM et al. *N Engl J Med* 2013;369:1317–1326. Green JB et al. *Am Heart J.* 2013;166:983–989.e7. 4. Bethel MA et al. *Diabetes Obes Metab*. 2015; 10.1111/dom.12441.

LO STUDIO TECOS
il trial della sicurezza a 360°

Trial Evaluating Cardiovascular Outcomes With Sitagliptin (TECOS) Cardiovascular Safety Trial

TECOS CV Safety Trial: Study Design[1,2]



[a]Mono- or dual therapy with metformin, sulfonylurea, or pioglitazone, or insulin alone or in combination with metformin.

[b]If eGFR is ≥50 mL/min/1.73 m^2, dose of sitagliptin or placebo will be 100 mg/day; if eGFR is 30 to <50 mL/min/1.73 m^2 at screening, dose of sitagliptin or placebo will be 50 mg/day; if eGFR is <30 mL/min/1.73 m^2 during the study, dose will be reduced to 25 mg/day.

TECOS = Trial Evaluating Cardiovascular Outcomes With Sitagliptin; CV = cardiovascular; T2DM = type 2 diabetes mellitus; CVD = cardiovascular disease; AHA = antihyperglycemic agent;DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; ADA = American Diabetes Association; eGFR = estimated glomerular filtration rate.

1. Green JB et al. *Am Heart J.* 2013;166:983–989.e7. **2.** Green JB et al. [published online ahead of print June 8, 2015] *N Engl J Med*. doi: 10.1056/NEJMoa1501352.

TECOS CV Safety Trial: Primary and Secondary Outcomes[1]

Primary Outcome

Primary outcome[a] was time from randomization to the first confirmed[b]:

CV-related death, nonfatal MI, nonfatal stroke, or unstable angina requiring hospitalization

Secondary Outcomes

- Composite end point of: time to first adjudicated, confirmed CV-related death, nonfatal MI, or nonfatal stroke
- Time to the occurrence of the individual components of the primary end point
- Time to all-cause mortality
- Time to hospital admission for adjudicated congestive heart failure

Other Prespecified Outcomes

- Changes from baseline in urinary albumin:creatinine ratio, eGFR, HbA_{1c}, body weight
- Time to initiation of additional antihyperglycemic therapy and/or initiation of chronic insulin
- Time to non-CV death; time to first CV or peripheral revascularization procedure; frequency of severe hypoglycemia
- Counts of outpatient visits and hospitalizations

[a]If both MACE+ and MACE analyses met noninferiority and HR <1.0, superiority was to be tested.
[b]CV events were adjudicated by an independent committee, blinded to study therapy.
TECOS = Trial Evaluating Cardiovascular Outcomes With Sitagliptin; CV = cardiovascular; MI = myocardial infarction; eGFR = estimated glomerular filtration rate.

1. Green JB et al. *Am Heart J.* 2013;166:983–989.e7.

TECOS CV Safety Trial: Baseline Disease Characteristics[1]

Baseline Characteristics[a]	Sitagliptin N=7,332	Placebo N=7,339
Duration of diabetes, y[b]	11.6±8.1	11.6±8.1
HbA_{1c}, %	7.2±0.5	7.2±0.5
Body mass index, kg/m^2	30.2±5.6	30.2±5.6
Systolic BP, mmHg	135±16.9	135±17.1
Diastolic BP, mmHg	77.1±10.3	77.2±10.6
eGFR[c], $mL/min/1.73m^2$	74.9±21.3	74.9±20.9
eGFR[c] <50 $mL/min/1.73m^2$, n (%)	686 (9.4)	683 (9.3)
Median urine albumin:creatinine ratio, mg/g (Q1, Q3)[d]	10.3 (3.5, 34.6)	11.4 (3.6, 36.2)
Total cholesterol, mg/dL	166.1±44.8	165.4±45.9
LDL cholesterol, mg/dL	91.2±63.8	90.7±51.2
HDL cholesterol, mg/dL	43.5±12.0	43.4±13.0
Triglycerides, mg/dL	166.0±101.0	164.8±98.8

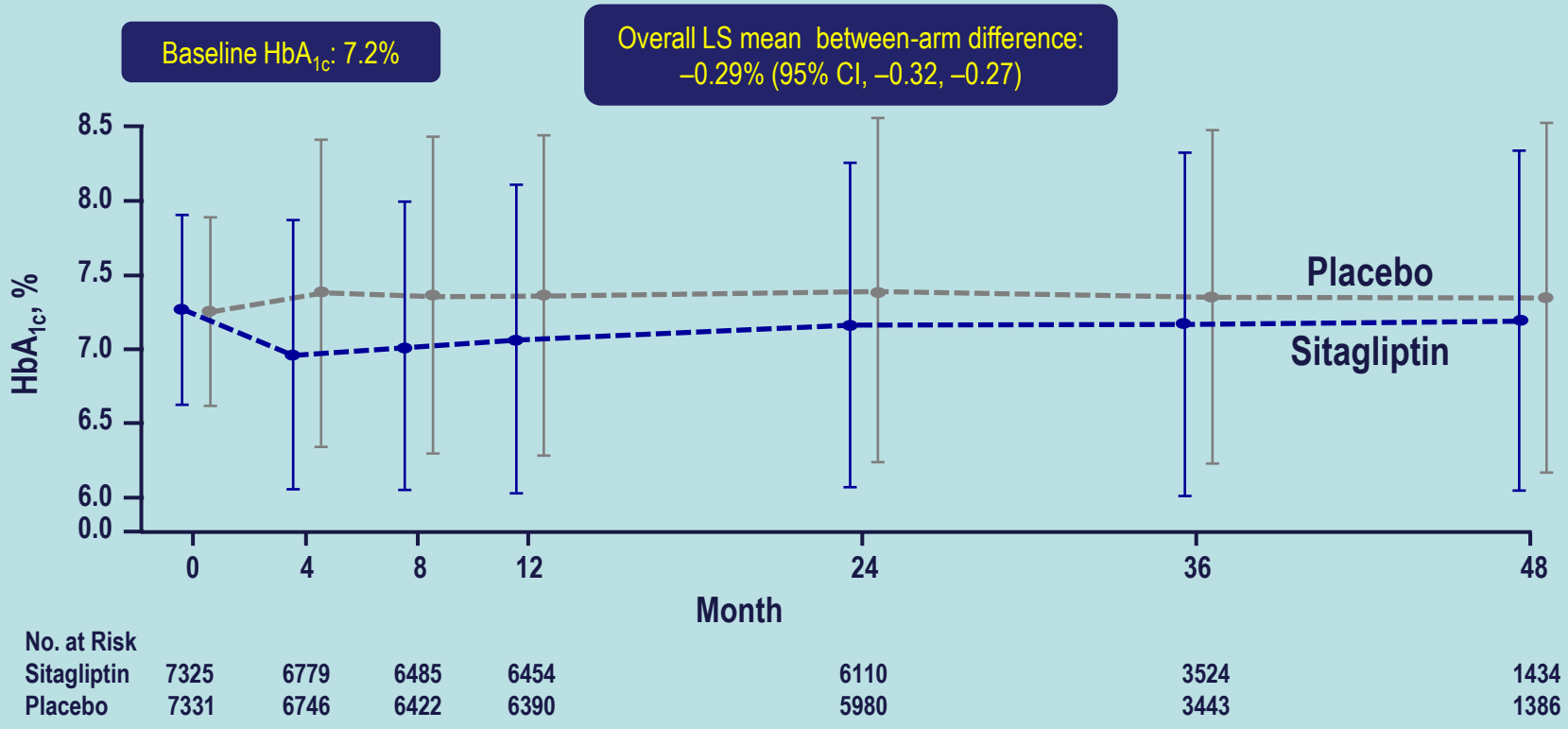
[a]All values are mean ± SD unless otherwise specified.
[b]Duration = (year of randomization – year of diagnosis) + 1.
[c]MDRD formula used to calculate eGFR. Site-reported values are presented.
[d]Urinary albumin:creatinine ratio data available for only 5148 patients (n= 2606 for sitagliptin, n=2542 for placebo).
TECOS = Trial Evaluating Cardiovascular Outcomes With Sitagliptin; CV = cardiovascular; BP = blood pressure; eGFR = estimated glomerular filtration rate; HDL = high-density lipoprotein; LDL = low-density lipoprotein.

1. Green JB et al. [published online ahead of print June 8, 2015] *N Engl J Med*. doi: 10.1056/NEJMoa1501352.

TECOS

TECOS CV Safety Trial: Glycemic Control

- **First 4 months:** AHA dose stability recommended[1]
- **Subsequently:** Physicians counseled to implement individualized standard of care consistent with local/regional guidelines, with a resulting narrowing of HbA_{1c} between arms[2]



TECOS = Trial Evaluating Cardiovascular Outcomes With Sitagliptin; CV = cardiovascular; AHA = antihyperglycemic; LS = least-squares.

1. Green JB et al. *Am Heart J.* 2013;166:983–989.e7. **2.** Green JB et al. [published online ahead of print June 8, 2015] *N Engl J Med*. doi: 10.1056/NEJMoa1501352.

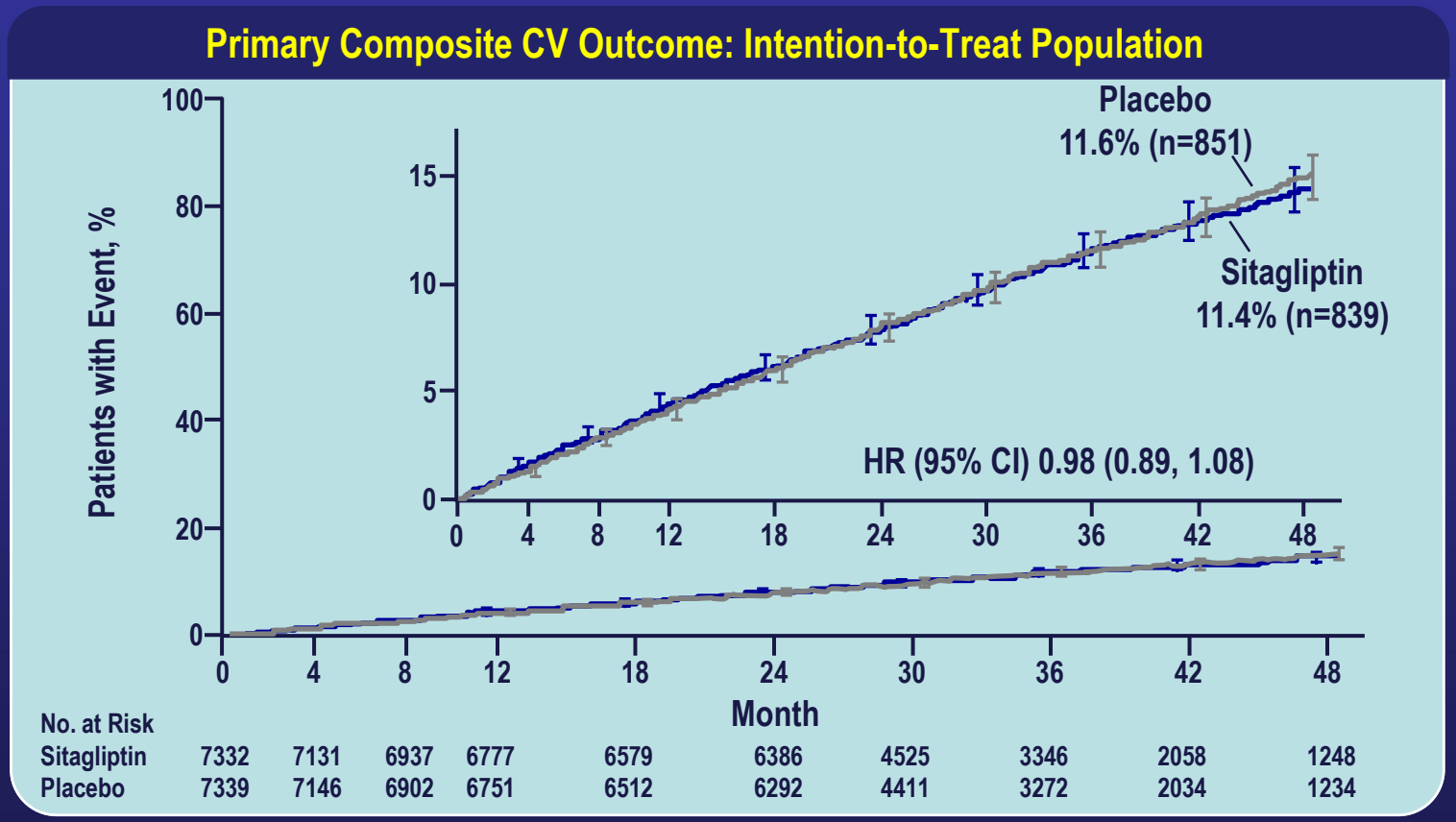
TECOS CV Safety Trial: Primary Composite CV Outcome[1]

The TECOS CV Safety Trial achieved its primary CV end point of noninferiority of sitagliptin added to usual care vs placebo added to usual care

Primary Composite CV Outcome[a] , n/N (%)	Sitagliptin	Placebo	HR (95% CI)
Per-protocol (PP) population	695/7,257 (9.6)	695/7,266 (9.6)	0.98 (0.88, 1.09)
PP was primary analysis for primary composite CV outcome	*P* value for noninferiority: *P*<0.001[b]		

[a]Primary composite CV outcome was a composite endpoint of time to CV death, nonfatal stroke, nonfatal MI, and hospitalization for unstable angina.
[b]Noninferiority *P*-value for a margin of 1.30 in hazard ratio.
TECOS = Trial Evaluating Cardiovascular Outcomes With Sitagliptin; CV = cardiovascular; HR = hazard ratio; CI = confidence interval.
1. Green JB et al. [published online ahead of print June 8, 2015] *N Engl J Med*. doi: 10.1056/NEJMoa1501352.

TECOS CV Safety Trial: Primary Composite CV Outcome (ITT)[1]



Between group difference was not statistically significant for superiority: *P*=0.65

[a]Noninferiority *P*-value for a margin of 1.30 in hazard ratio.

TECOS = Trial Evaluating Cardiovascular Outcomes With Sitagliptin; CV = cardiovascular; ITT = intention-to-treat; PP = per protocol; HR = hazard ratio; CI = confidence interval.

1. Green JB et al. [published online ahead of print June 8, 2015] *N Engl J Med*. doi: 10.1056/NEJMoa1501352.

TECOS CV Safety Trial: Components of Primary Composite CV Outcome (ITT)[1]

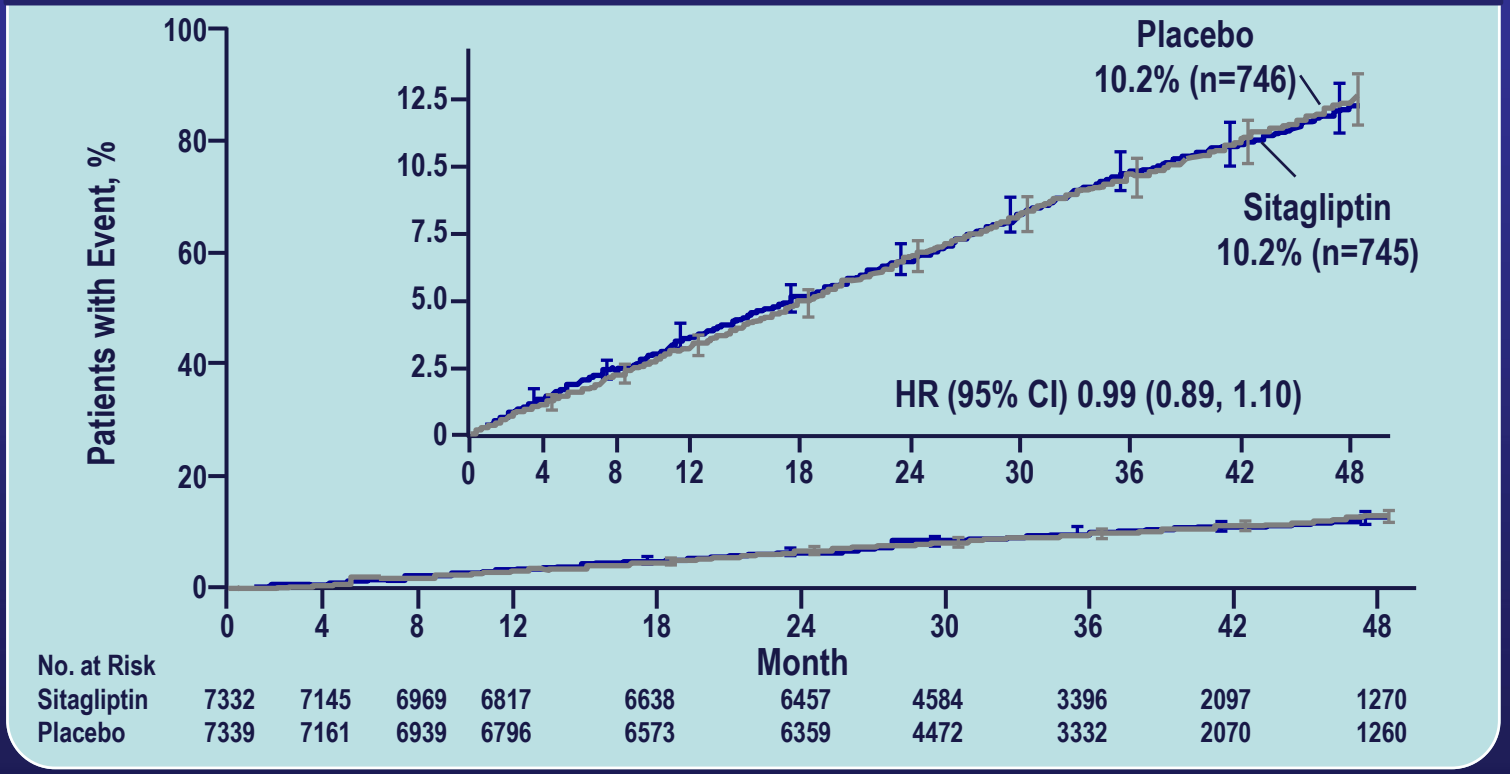
Cardiovascular Outcomes: Intention-to-Treat Population	Sitagliptin N=7,332	Placebo N=7,339
Primary composite CV outcome, n (%); rate per 100 patient-years	839 (11.4); 4.06	851 (11.6); 4.17
HR (95% CI)	0.98 (0.89, 1.08)	
Components of composite primary CV outcome, n (%)		
CV death	311 (4.2)	291 (4.0)
Nonfatal MI	275 (3.8)	286 (3.9)
Nonfatal stroke	145 (2.0)	157 (2.1)
Hospitalization for unstable angina	108 (1.5)	117 (1.6)

TECOS = Trial Evaluating Cardiovascular Outcomes With Sitagliptin; CV = cardiovascular; ITT = intention-to-treat; HR = hazard ratio; CI = confidence interval; MI = myocardial infarction.

1. Green JB et al. [published online ahead of print June 8, 2015] *N Engl J Med*. doi: 10.1056/NEJMoa1501352.

TECOS CV Safety Trial: Secondary Composite CV Outcome (ITT)[1]

Secondary Composite CV Outcome: Intention-to-Treat Population



Between group difference was not statistically significant for superiority: *P*=0.84

[a]Noninferiority *P*-value for a margin of 1.30 in hazard ratio.

TECOS = Trial Evaluating Cardiovascular Outcomes With Sitagliptin; CV = cardiovascular; HR = hazard ratio; CI = confidence interval; ITT = intention-to-treat; PP = per protocol.

1. Green JB et al. [published online ahead of print June 8, 2015] *N Engl J Med*. doi: 10.1056/NEJMoa1501352.

TECOS CV Safety Trial: Components of Secondary Composite CV Outcome (ITT)[1]

Cardiovascular outcomes: Intention-to-Treat Population	Sitagliptin N=7,332	Placebo N=7,339
Secondary composite CV outcome, n (%); rate per 100 patient-years	745 (10.2); 3.58	746 (10.2); 3.62
HR (95% CI); *P*-value[a]	0.99 (0.89–1.10); *P*=0.84	
Components of secondary composite CV outcome, n (%)		
CV death	313 (4.3)	293 (4.0)
Nonfatal MI	285 (3.9)	294 (4.0)
Nonfatal stroke	147 (2.0)	159 (2.2)

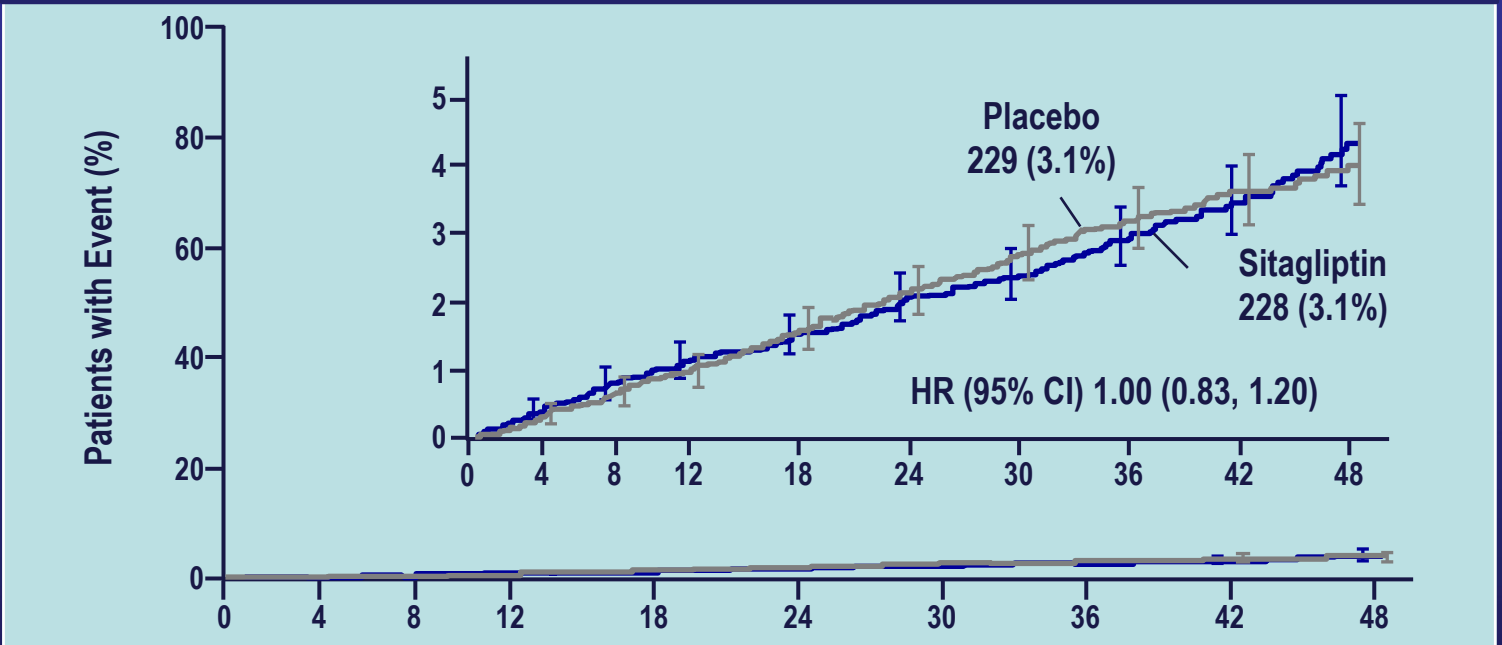
[a]*P*-value is for superiority analysis of intention-to-treat population.

TECOS = Trial Evaluating Cardiovascular Outcomes With Sitagliptin; CV = cardiovascular; ITT = intention-to-treat; HR = hazard ratio; CI = confidence interval; MI = myocardial infarction.

1. Green JB et al. [published online ahead of print June 8, 2015] *N Engl J Med*. doi: 10.1056/NEJMoa1501352.

TECOS CV Safety Trial: Hospitalizations for Heart Failure (ITT)[1]

Hospitalizations for Heart Failure: Intention-to-Treat Population



No. at Risk										
Sitagliptin	7332	7189	7036	6917	6780	6619	4728	3515	2175	1324
Placebo	7339	7204	7025	6903	6712	6549	4599	3443	2131	1315

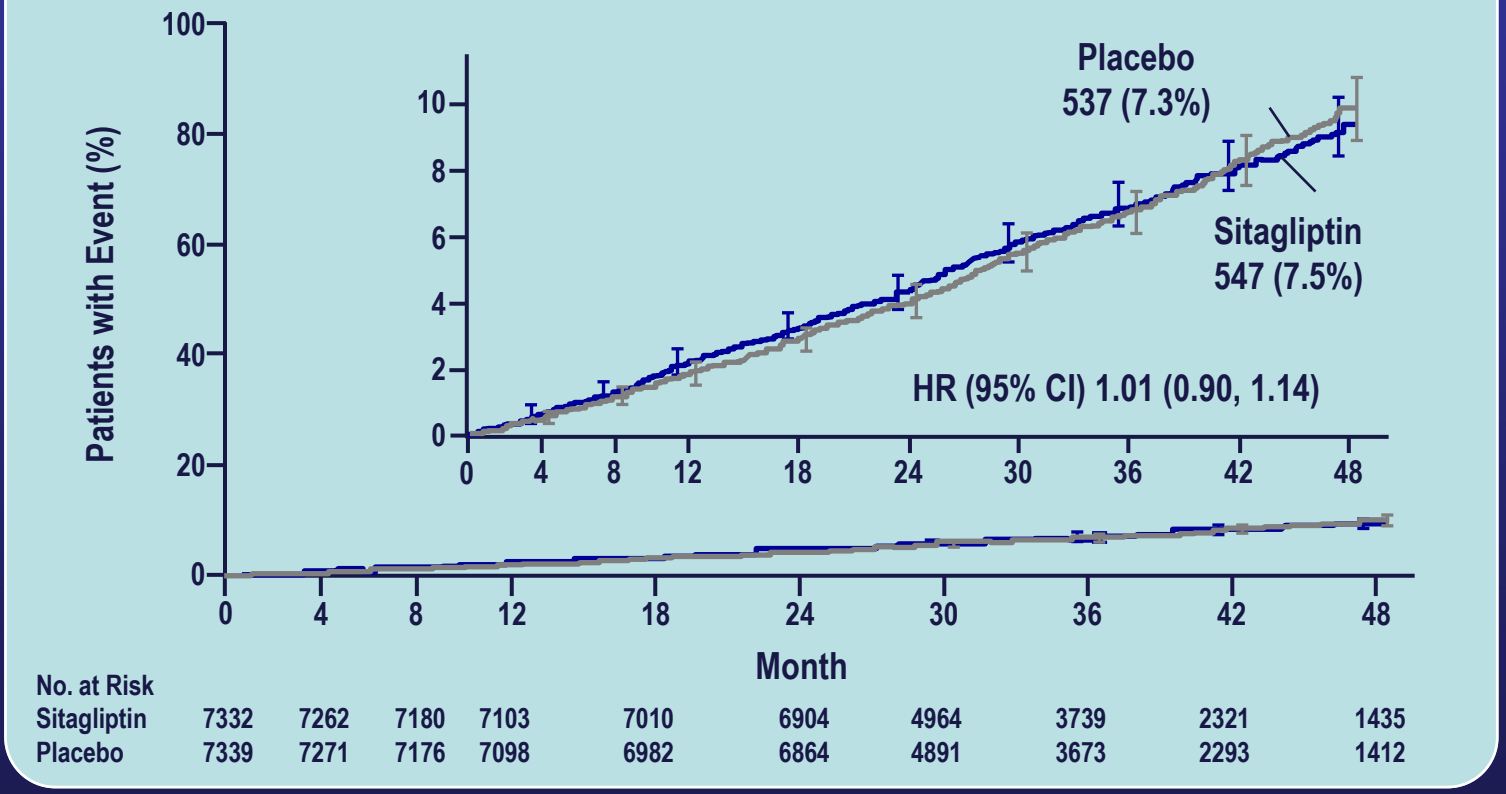
Between group difference was not statistically significant (*P*=0.98)

TECOS = Trial Evaluating Cardiovascular Outcomes With Sitagliptin; CV = cardiovascular; HR = hazard ratio; CI = confidence interval; ITT = intention-to-treat.

1. Green JB et al. [published online ahead of print June 8, 2015] *N Engl J Med*. doi: 10.1056/NEJMoa1501352.

TECOS CV Safety Trial: Total Mortality (ITT)[1]

Total Mortality: Intention-to-Treat Population



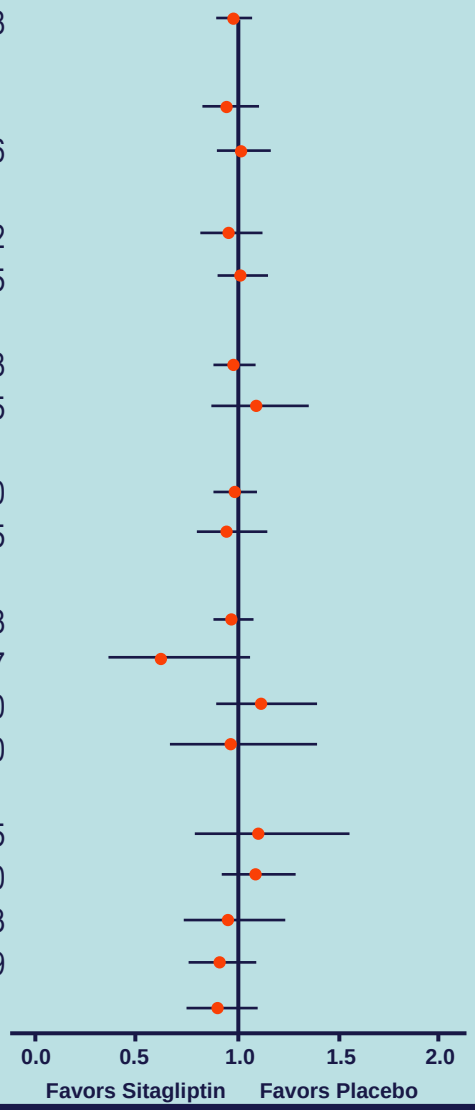
Between group difference was not statistically significant (*P*=0.88)

TECOS = Trial Evaluating Cardiovascular Outcomes With Sitagliptin; CV = cardiovascular; HR = hazard ratio; CI = confidence interval; ITT = intention-to-treat.

1. Green JB et al. [published online ahead of print June 8, 2015] *N Engl J Med*. doi: 10.1056/NEJMoa1501352.

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

Subject Group	Interaction *P* Value	n/N	Hazard Ratio	95% CI
Overall		1,690/14,671	0.98	0.89, 1.08
Age subgroups				
≤median	0.473	669/7,316	0.95	0.82, 1.11
>median		950/7,035	1.02	0.90, 1.16
<65 years	0.557	593/6,616	0.95	0.81, 1.12
≥65 years		1,026/7,735	1.01	0.90, 1.15
<75 years	0.346	1,281/12,347	0.97	0.87, 1.08
≥75 years		338/2,004	1.09	0.88, 1.35
Sex				
Male	0.706	1,272/10,374	0.99	0.88, 1.10
Female		418/4,297	0.95	0.78, 1.15
Race				
White	0.262	1,214/9,957	0.97	0.87, 1.08
Black		58/447	0.62	0.36, 1.07
Asian		302/3,265	1.11	0.89, 1.40
Other		116/1,002	0.97	0.67, 1.40
Region				
Latin America	0.534	132/1,471	1.10	0.78, 1.55
Asia Pacific and Other		500/4,565	1.09	0.91, 1.30
Western Europe		226/2,076	0.95	0.73, 1.23
Eastern Europe		465/3,965	0.91	0.76, 1.09
North America		367/2,594	0.90	0.74, 1.11

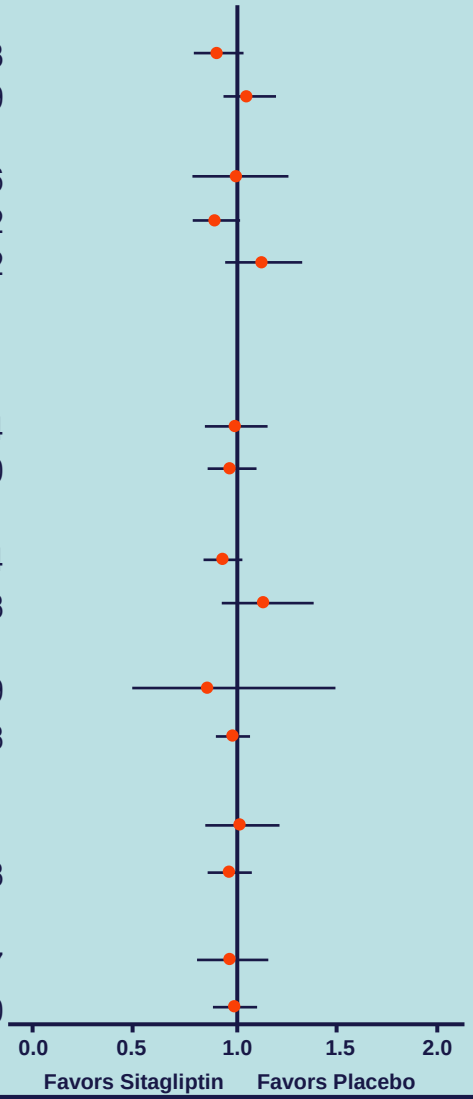


TECOS = Trial Evaluating Cardiovascular Outcomes With Sitagliptin; CV = cardiovascular; CI = confidence interval.

1. Green JB et al. [published online ahead of print June 8, 2015] *N Engl J Med*. doi: 10.1056/NEJMoa1501352.

TECOS CV Safety Trial: Subgroup Analyses For the Primary Composite CV Outcome *(continued)*[1]

Subject Group	Interaction *P* Value	n/N	Hazard Ratio	95% CI
Diabetes duration subgroups				
≤median	0.116	796/7,708	0.90	0.78, 1.03
>median		891/6,951	1.05	0.92, 1.19
< 5 years	0.107	264/2,858	0.99	0.78, 1.26
≥5–<15 years		855/7,511	0.89	0.78, 1.02
≥15 years		568/4,290	1.12	0.95, 1.32
Diabetes therapy at baseline (alone or in combination)				
Sulfonylurea				
Yes	0.841	776/6,645	0.99	0.86, 1.14
No		914/8,026	0.97	0.85, 1.10
Metformin				
Yes	0.086	1,289/11,966	0.93	0.83, 1.04
No		401/2,705	1.13	0.93, 1.38
Thiazolidinedione (includes Pioglitazone)				
Yes	0.636	50/396	0.86	0.49, 1.49
No		1,640/14,275	0.98	0.89, 1.08
Insulin				
Yes	0.629	469/3,408	1.01	0.85, 1.21
No		1,221/11,263	0.96	0.86, 1.08
Prior congestive heart failure				
Yes	0.866	444/2,643	0.97	0.80, 1.17
No		1,246/12,028	0.99	0.88, 1.10

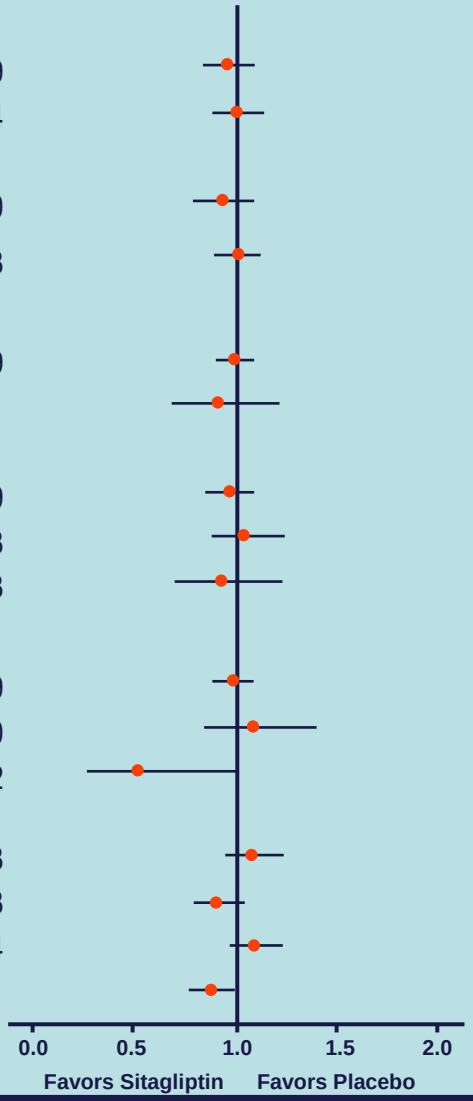


TECOS = Trial Evaluating Cardiovascular Outcomes With Sitagliptin; CV = cardiovascular; CI = confidence interval.

1. Green JB et al. [published online ahead of print June 8, 2015] *N Engl J Med*. doi: 10.1056/NEJMoa1501352.

TECOS CV Safety Trial: Subgroup Analyses For the Primary Composite CV Outcome *(continued)*[1]

Subject Group	Interaction *P* Value	n/N	Hazard Ratio	95% CI
HbA_{1c} subgroups				
≤median	0.592	828/7,606	0.95	0.83, 1.09
>median		861/7,050	1.00	0.88, 1.14
Renal function subgroups				
eGFR <60 mL/min/1.73 m^2	0.443	538/3,324	0.92	0.78, 1.10
eGFR ≥60 mL/min/1.73 m^2		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
Body mass index subgroups				
≤median	0.070	827/7,265	1.07	0.94, 1.23
>median		836/7,269	0.90	0.78, 1.03
<30 kg/m^2	0.030	887/7,735	1.08	0.95, 1.24
≥30 kg/m^2		776/6,799	0.88	0.76, 1.01

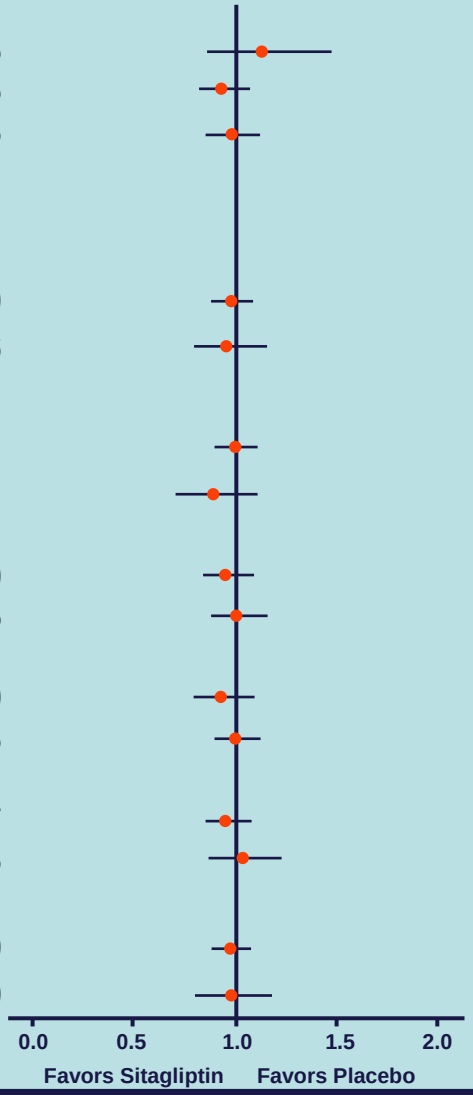


TECOS = Trial Evaluating Cardiovascular Outcomes With Sitagliptin; CV = cardiovascular; CI = confidence interval; eGFR = estimated glomerular filtration rate.

1. Green JB et al. [published online ahead of print June 8, 2015] *N Engl J Med*. doi: 10.1056/NEJMoa1501352.

TECOS CV Safety Trial: Subgroup Analyses For the Primary Composite CV Outcome *(continued)*[1]

Subject Group	Interaction *P* Value	n/N	Hazard Ratio	95% CI
Cigarette smoking status				
Current	0.484	213/1,678	1.13	0.86, 1.48
Former		720/5,844	0.93	0.81, 1.08
Never		757/7,149	0.98	0.85, 1.13
Medications taken at time of randomization				
Statins				
Yes	0.827	1,280/11,719	0.98	0.88, 1.10
No		410/2,952	0.96	0.79, 1.16
ACE inhibitors or ARB				
Yes	0.364	1,381/11,555	1.00	0.90, 1.11
No		309/3,116	0.89	0.71, 1.11
Diuretics				
Yes	0.600	860/6,020	0.96	0.84, 1.09
No		830/8,651	1.01	0.88, 1.15
Calcium channel blockers				
Yes	0.458	604/4,961	0.93	0.79, 1.09
No		1,086/9,710	1.01	0.89, 1.13
Beta blockers				
Yes	0.446	1,172/9,322	0.96	0.85, 1.07
No		518/5,349	1.04	0.87, 1.23
Aspirin				
Yes	0.986	1,285/11,518	0.98	0.88, 1.09
No		405/3,153	0.98	0.81, 1.19



TECOS = Trial Evaluating Cardiovascular Outcomes With Sitagliptin; CV = cardiovascular; CI = confidence interval; ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker.

1. Green JB et al. [published online ahead of print June 8, 2015] *N Engl J Med*. doi: 10.1056/NEJMoa1501352.

TECOS CV Safety Trial: Non-CV Mortality[1]

- Non-CV death rate was the same in both treatment groups
  - 2.3% for both sitagliptin and placebo
- Death due to infection did not differ between treatment groups
  - 0.6% for sitagliptin vs 0.7% for placebo

TECOS = Trial Evaluating Cardiovascular Outcomes With Sitagliptin; CV = cardiovascular.

1. Green JB et al. [published online ahead of print June 8, 2015] *N Engl J Med*. doi: 10.1056/NEJMoa1501352.

TECOS CV Safety Trial: Key Non-CV Outcomes (ITT)[1]

Non-CV outcomes[a] n (%); rate per 100 patient-years	Sitagliptin N=7,332	Placebo N=7,339	HR (95% CI)	*P*-value
Acute pancreatitis	23 (0.3); 0.11	12 (0.2); 0.06	1.93 (0.96, 3.88)	0.07
Charter-defined cancer	268 (3.7); 1.25	290 (4.0); 1.37	0.91 (0.77, 1.08)	0.27
Pancreatic cancer	9 (0.1); 0.04	14 (0.2); 0.07	0.66 (0.28, 1.51)	0.32
Severe hypoglycemia	160 (2.2); 0.78	143 (1.9); 0.70	1.12 (0.89, 1.40)	0.33

[a]ITT population.

TECOS = Trial Evaluating Cardiovascular Outcomes With Sitagliptin; CV = cardiovascular; ITT = intention-to-treat; HR = hazard ratio; CI = confidence interval.

1. Green JB et al. [published online ahead of print June 8, 2015] *N Engl J Med*. doi: 10.1056/NEJMoa1501352.

Durability

TECOS CV Safety Trial: Time-to-Initiation of Additional AHA Therapy[1]

Intention-to-Treat Population	Sitagliptin N=7,332	Placebo N=7,339	HR (95% CI)	*P*-value
Initiation of next antihyperglycemic medication, n (%); rate per 100 patient-years	1,591 (21.7); 8.53	2,046 (27.9); 11.59	0.72 (0.68, 0.77)	<0.001

Intention-to-Treat Population Cumulative incidence of events, % (95% CI)	Sitagliptin N=7,332	Placebo N=7,339
1 year	6.7 (6.10, 7.27)	9.3 (8.64, 10.00)
2 years	14.9 (14.05, 15.74)	20.3 (19.38, 21.30)
3 years	23.4 (22.23, 24.52)	31.3 (30.05, 32.60)
4 years	33.1 (31.37, 34.91)	41.5 (39.62, 43.34)

TECOS = Trial Evaluating Cardiovascular Outcomes With Sitagliptin; CV = cardiovascular; AHA = antihyperglycemic agent; HR = hazard ratio; CI = confidence interval

1. Green JB et al. [published online ahead of print June 8, 2015] *N Engl J Med*. doi: 10.1056/NEJMoa1501352.

TECOS CV Safety Trial: Time-to-Initiation of Insulin Therapy[1]

Intention-to-Treat Population[a]	Sitagliptin N=5,608	Placebo N=5,655	HR (95% CI)	*P*-value
Initiation of insulin , n (%); rate per 100 patient-years	542 (9.7) 3.44	744 (13.2); 4.85	0.70 (0.63, 0.79)	<0.001

Intention-to-Treat Population[a] Cumulative incidence of events, % (95% CI)	Sitagliptin N=5,608	Placebo N=5,655
1 year	3.2 (2.77, 3.72)	4.8 (4.29, 5.43)
2 years	6.4 (5.75, 7.07)	9.7 (8.93, 10.53)
3 years	9.8 (8.96, 10.71)	14.1 (13.09, 15.12)
4 years	13.2 (12.09, 14.50)	17.5 (16.27, 18.89)

[a]In patients not receiving insulin at baseline

TECOS = Trial Evaluating Cardiovascular Outcomes With Sitagliptin; CV = cardiovascular; HR = hazard ratio; CI = confidence interval.

1. Green JB et al. [published online ahead of print June 8, 2015] *N Engl J Med*. doi: 10.1056/NEJMoa1501352.

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Diabetes & Metabolism xxx (2015) xxx–xxx

Diabetes & Metabolism

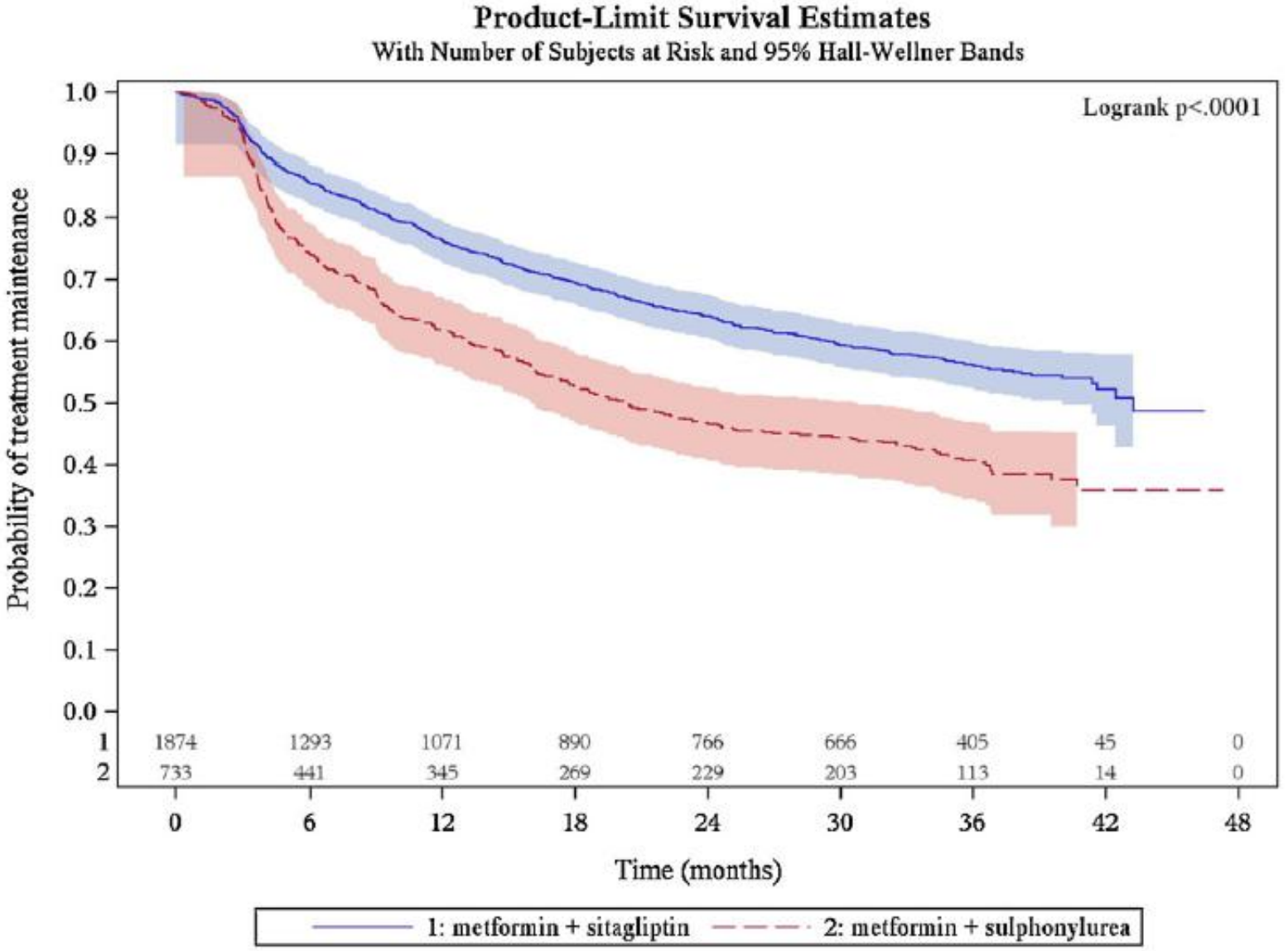
Original article

Treatment maintenance duration of dual therapy with metformin and sitagliptin in type 2 diabetes: The ODYSSEE observational study

P. Valensi [a], G. de Pouvourville [b], N. Benard [c], C. Chanut-Vogel [c], C. Kempf [d], E. Eymard [c,*], C. Moisan [c], J. Dallongeville [e]

Under everyday conditions of primary diabetes care, dual therapy with M-Sita can be maintained for longer than M-SU. In addition, while efficacy, as measured by changes in HbA1c, was similar between treatments, the incidence of hypoglycaemia was lower in patients taking M-Sita

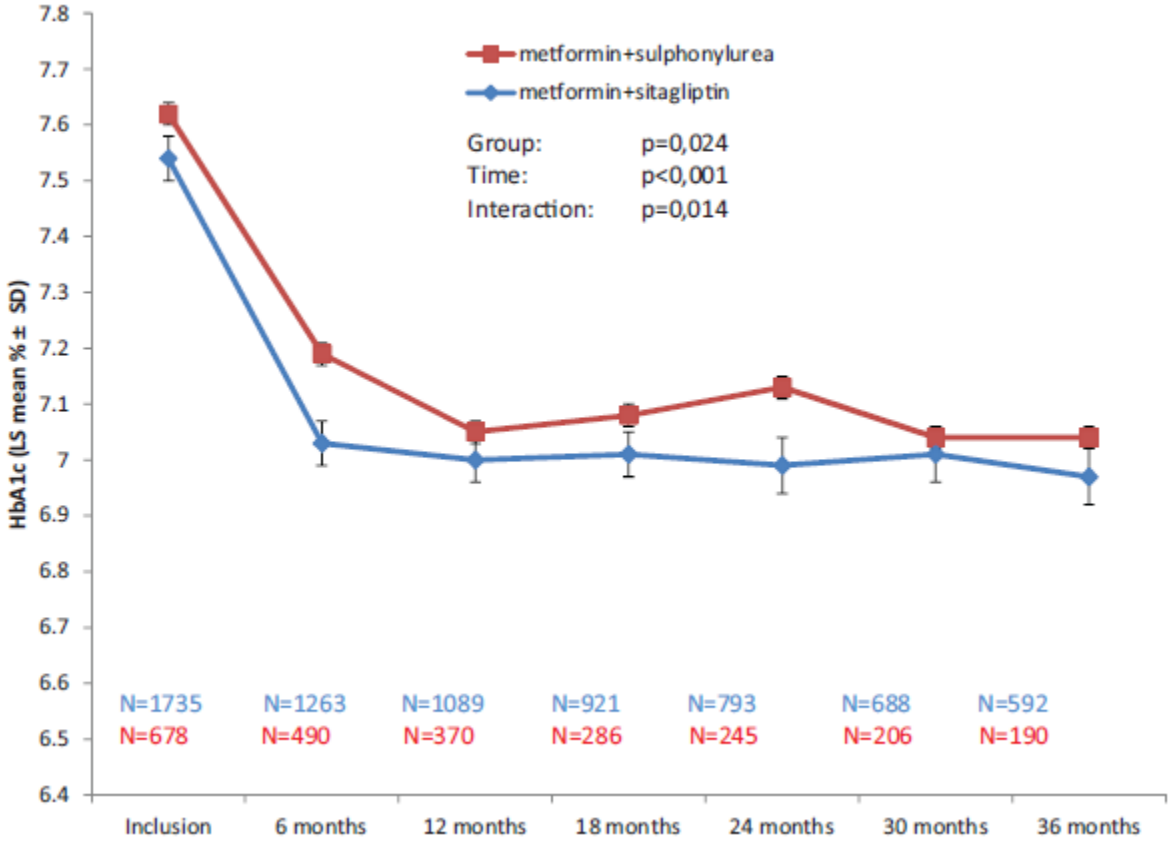
Valensi P et al. *Diabetes Metab*. 2015;41:231-238 (48w/3543pts) .



Valensi P et al. *Diabetes Metab*. 2015;41:231-238 (48w/3543pts) .

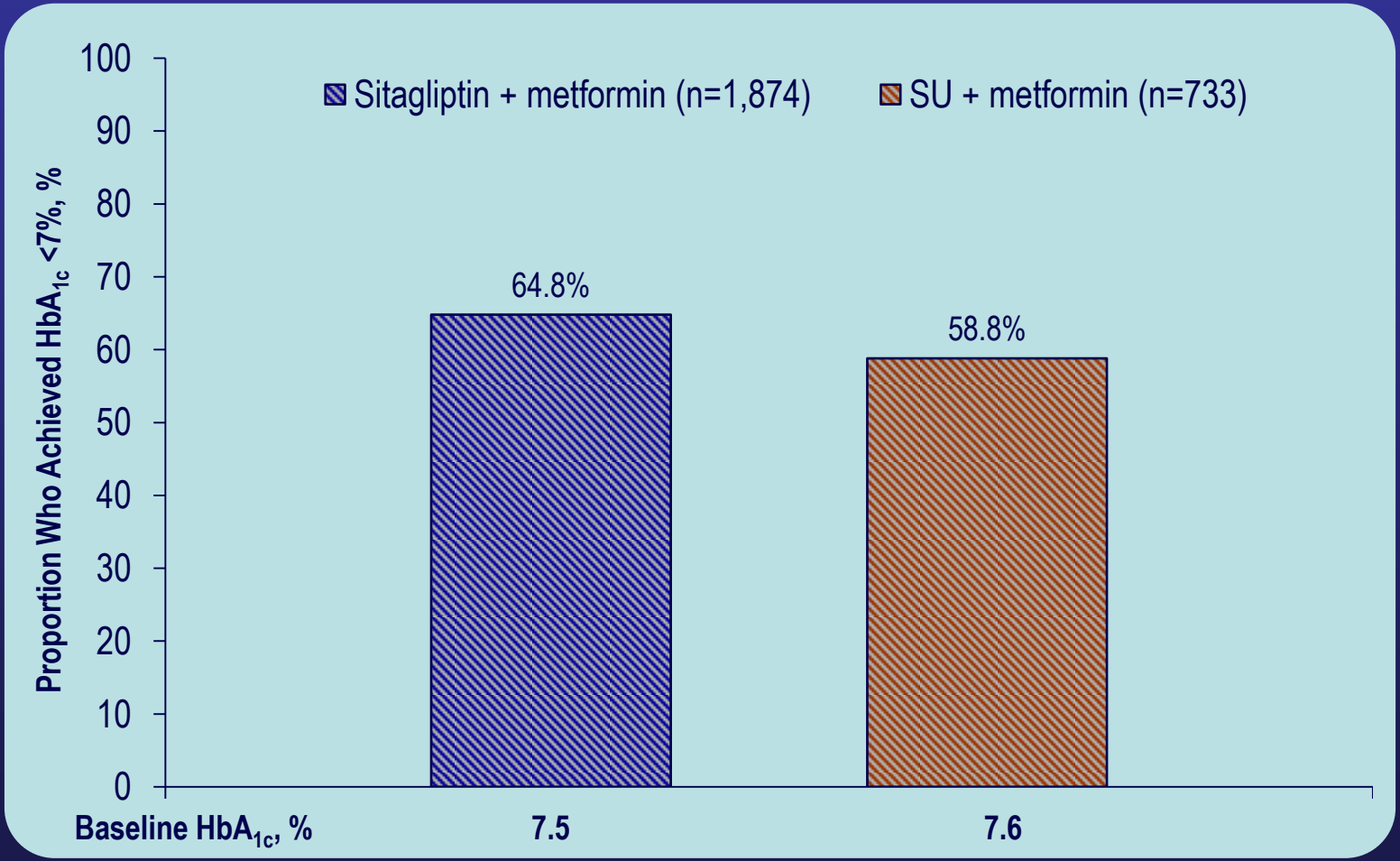
Treatment maintenance duration of dual therapy with metformin and sitagliptin in type 2 diabetes: The ODYSSEE observational study

P. Valensi [a], G. de Pouvourville [b], N. Benard [c], C. Chanut-Vogel [c], C. Kempf [d], E. Eymard [c,*], C. Moisan [c], J. Dallongeville [e]



Valensi P .et al. Diabetes & Metabolism xxx (2015) xxx–xxx in press

ODYSSÉE: Proportion of Patients Achieving HbA_{1c} <7% at Least Once During the Study[1]

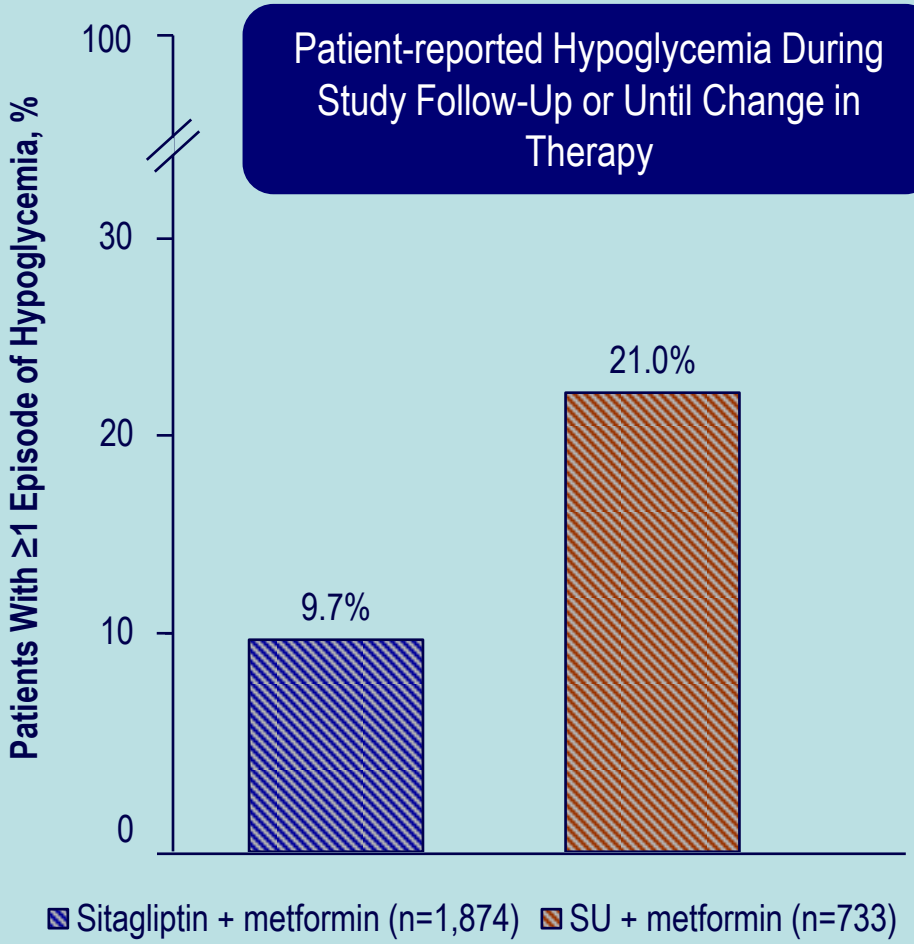


SU = sulfonylurea.

1. Valensi P et al. *Diabetes Metab*. 2015;41:231–238.

ODYSSÉE: Patient-reported Hypoglycemia and Change in Weight[1,2]

Patient-reported Hypoglycemia During Study Follow-Up or Until Change in Therapy



Change in Body Weight at 36 Months[a]

- Change in weight was similar between groups
- Mean change from baseline at 36 months:
  - Sitagliptin + metformin (n=405): –2.5 kg
  - SU + metformin (n=124): –1.6 kg

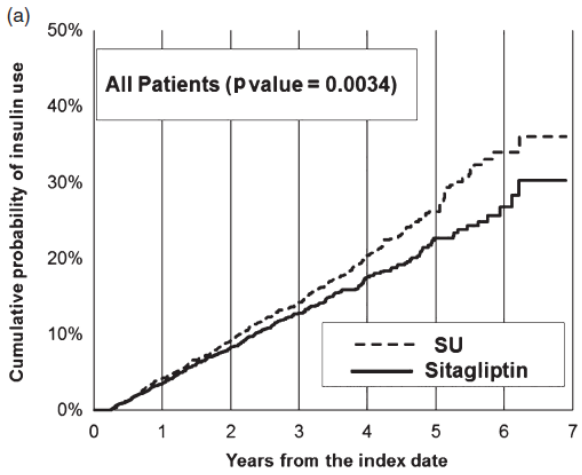
(*P*=0.985)

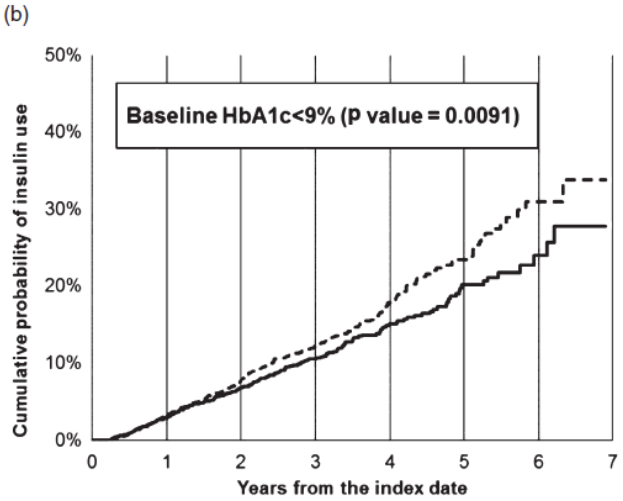
[a]Difference between baseline weight was statistically significant: sitagliptin + metformin, 85.0 kg; SU + metformin, 83.4 kg (*P*=0.002)
SU = sulfonylurea.

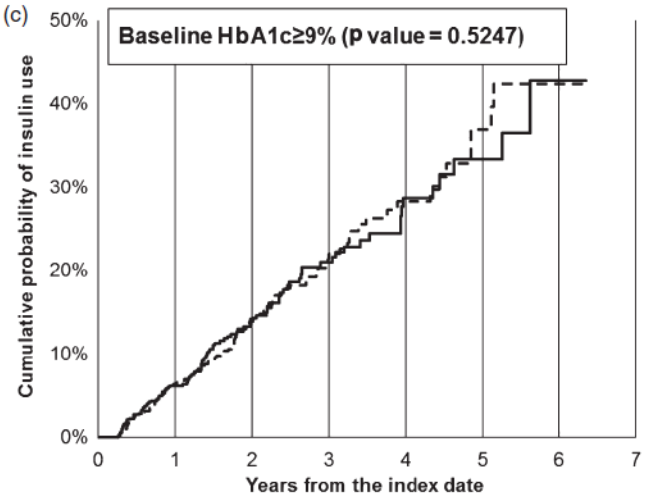
1. Valensi P et al. *Diabetes Metab*. 2015;41:231–238. **2.** Data on File.

Diabetes, Obesity and Metabolism 17: 956–964, 2015.

Progression to insulin therapy among patients with type 2 diabetes treated with sitagliptin or sulphonylurea plus metformin dual therapy







In conclusion, in this real-world study, patients in the USA with T2DM treated with a combination of sitagliptin and metformin had a significantly lower risk of initiating insulin therapy compared with patients treated with a combination of sulphonylurea and metformin, driven mainly by the subgroup of patients with lower HbA1c levels

Inzucchi et al:. Diabetes, Obesity and Metabolism 17: 956–964, 2015 (7 y/7728 pts)

Altri dati di sicurezza
Anziani, IRC e rischio fratture

Assessing the Safety of Sitagliptin in Elderly Participants in the Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS)

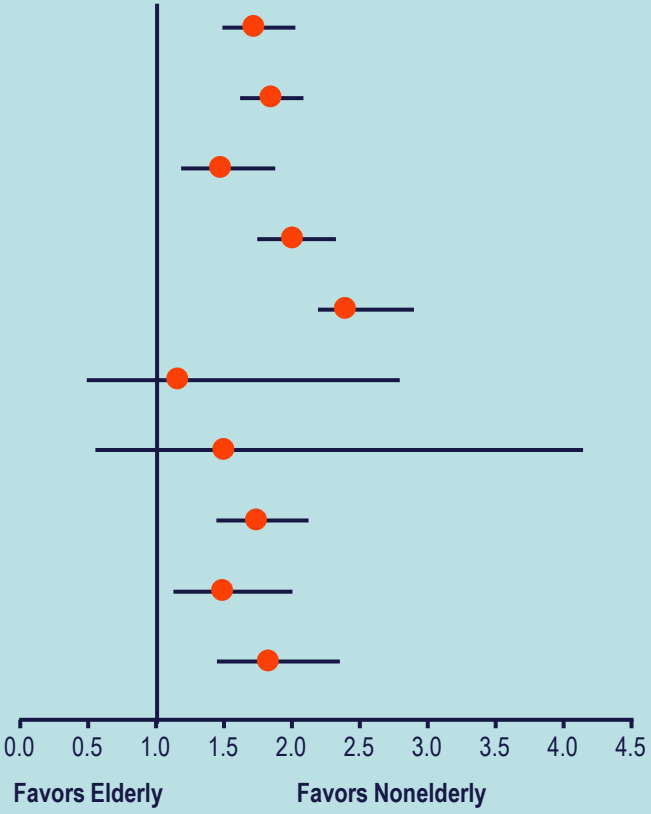
M. Angelyn Bethel, M.D., Samuel S. Engel, M.D., Jennifer B. Green, M.D., Zhen Huang, M.S., Keith D. Kaufman, M.D., Eberhard Standl, M.D., Ph.D., Shailaja Suryawanshi, Ph.D., Frans Van de Werf, M.D., Ph.D., Eric D. Peterson, M.D., M.P.H. and Rury R. Holman, M.B., Ch.B. for the TECOS Study Group

TECOS
TRIAL EVALUATING CARDIOVASCULAR OUTCOMES WITH SITAGLIPTIN

TECOS CV Safety Trial: Primary and Key Secondary Outcomes in the Elderly vs Nonelderly Cohorts[1]

All participants (N=14,351)
Elderly (≥75 years) vs Nonelderly (<75 years)

Outcome	HR (95% CI)	*P* value
4-point MACE	1.72 (1.52, 1.94)	<0.001
3-point MACE	1.86 (1.63, 2.11)	<0.001
Hospitalization for heart failure	1.48 (1.18, 1.87)	<0.001
Hospitalization for heart failure or death	2.02 (1.75, 2.34)	<0.001
All-cause mortality	2.52 (2.20, 2.89)	<0.001
Pancreatitis	1.17 (0.48, 2.83)	0.73
Pancreatic malignancy	1.52 (0.56, 4.14)	0.41
Overall malignancy	1.76 (1.43, 2.15)	<0.001
Severe hypoglycemia	1.53 (1.15, 2.03)	0.004
Bone fracture	1.84 (1.44, 2.35)	<0.001



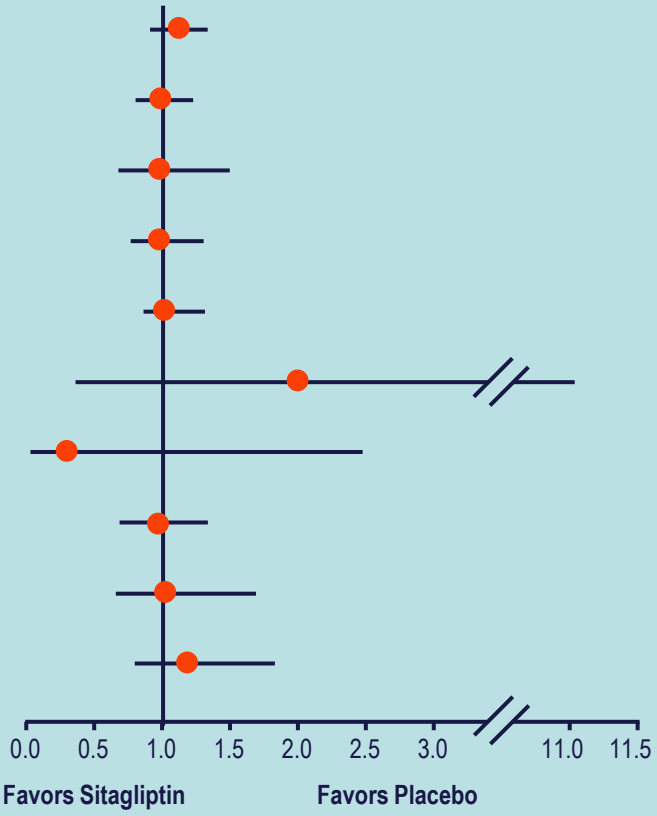
TECOS = Trial Evaluating Cardiovascular Outcomes With Sitagliptin; CV = cardiovascular; CI = confidence interval; MACE = major adverse cardiovascular events.
eGFR = estimated glomerular filtration rate.

1. Bethel MA et al. Assessing the Safety of Sitagliptin in Elderly Participants in the Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS).

TECOS CV Safety Trial: Primary and Key Secondary Outcomes in the Elderly Cohort by Treatment Group[1]

Elderly (≥75 years) participants (N=2,004)
Sitagliptin vs Placebo

Outcome	HR (95% CI)	*P* value
4-point MACE	1.10 (0.89, 1.36)	0.39
3-point MACE	1.01 (0.81, 1.26)	0.94
Hospitalization for heart failure	0.99 (0.65, 1.49)	0.94
Hospitalization for heart failure or death	1.00 (0.77, 1.29)	0.99
All-cause mortality	1.05 (0.83, 1.32)	0.71
Pancreatitis	2.01 (0.36, 11.04)	0.42
Pancreatic malignancy	0.28 (0.03, 2.50)	0.25
Overall malignancy	0.95 (0.67, 1.36)	0.78
Severe hypoglycemia	1.03 (0.62, 1.71)	0.92
Bone fracture	1.21 (0.78, 1.85)	0.39



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

1. Bethel MA et al. Assessing the Safety of Sitagliptin in Elderly Participants in the Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS).

Summary[1]

- Elderly participants in TECOS had age-related differences in their baseline characteristics, including longer duration of T2DM and an approximately 2-fold higher frequency of participants with eGFR <60 mL/min/1.73 m^2
- The primary and secondary composite outcomes occurred more often in elderly participants, as did key secondary outcomes of heart failure, all-cause mortality, severe hypoglycemia, and overall malignancy
- In the elderly cohort:
  - There were no differences between the treatment groups for the primary or key secondary outcomes
  - Serious adverse event rates were low
  - Sitagliptin was associated with a lower incidence of basal cell and squamous cell carcinomas, hyponatremia, and dehydration, and a higher incidence for gastroesophageal reflux, osteoarthritis, and eye disorders

Among elderly patients with T2DM and established CV disease, adding sitagliptin to usual care did not increase the risk of major adverse CV events, hospitalization for heart failure, or other adverse events

TECOS = Trial Evaluating Cardiovascular Outcomes With Sitagliptin; T2DM = type 2 diabetes mellitus; eGFR = estimated glomerular filtration rate;.

1. Bethel MA et al. Assessing the Safety of Sitagliptin in Elderly Participants in the Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS).

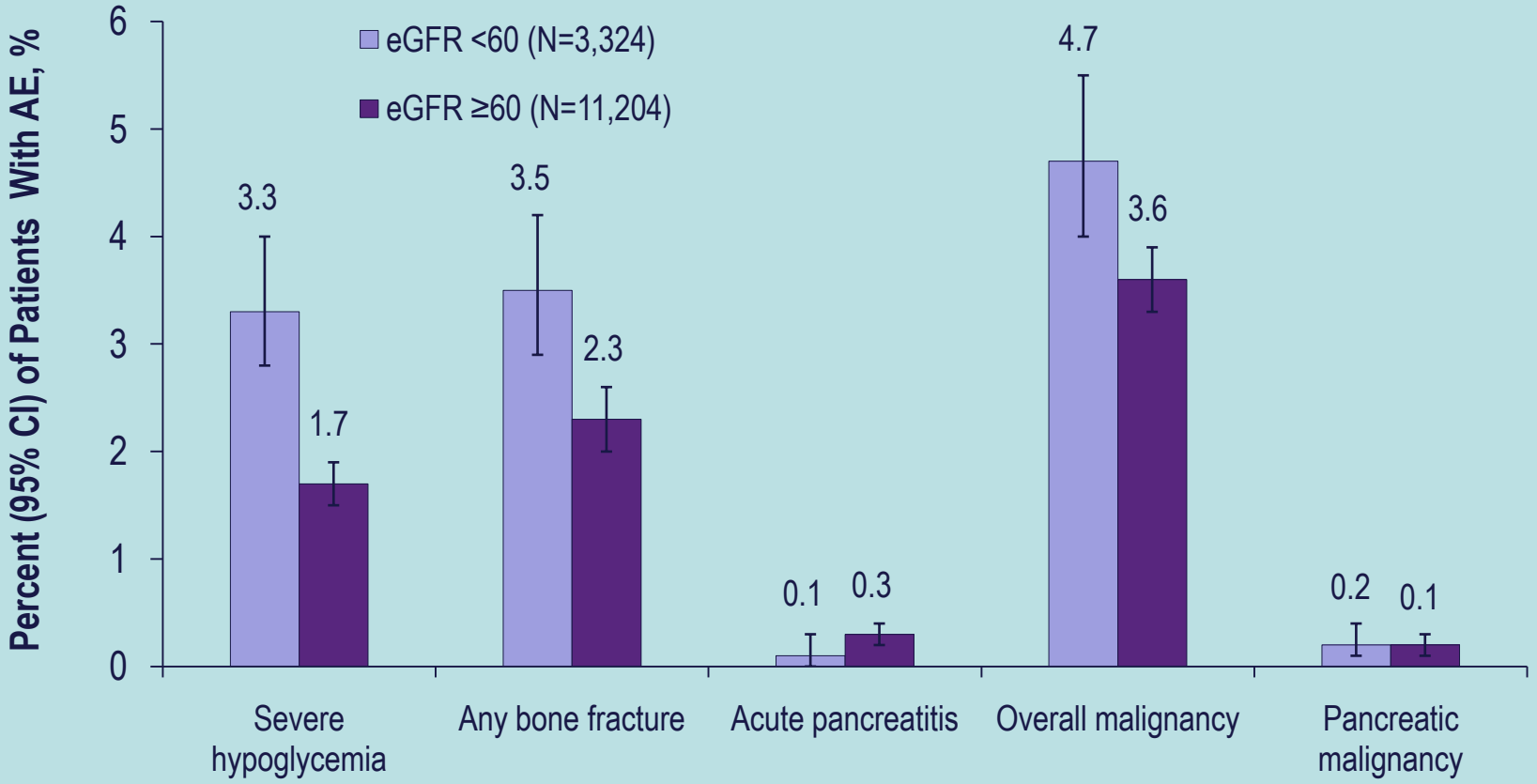
Assessing the Safety of Sitagliptin in Patients With Type 2 Diabetes and Chronic Kidney Disease in the TECOS Trial

Samuel S. Engel, MD, Shailaja Suryawanshi, PhD, Robert G. Josse, MBBS, FRCP, Eric D. Peterson, MD, MPH, Rury R. Holman, MB ChB, FRCP, FMedSci,
on behalf of the TECOS Study Group

TECOS
TRIAL EVALUATING CARDIOVASCULAR OUTCOMES WITH SITAGLIPTIN

Safety of Sitagliptin in Patients With T2DM and CKD in the TECOS Trial: Adverse Events of Interest by CKD Status[1]

Summary of incidence of adverse events of interest in participants with or without CKD



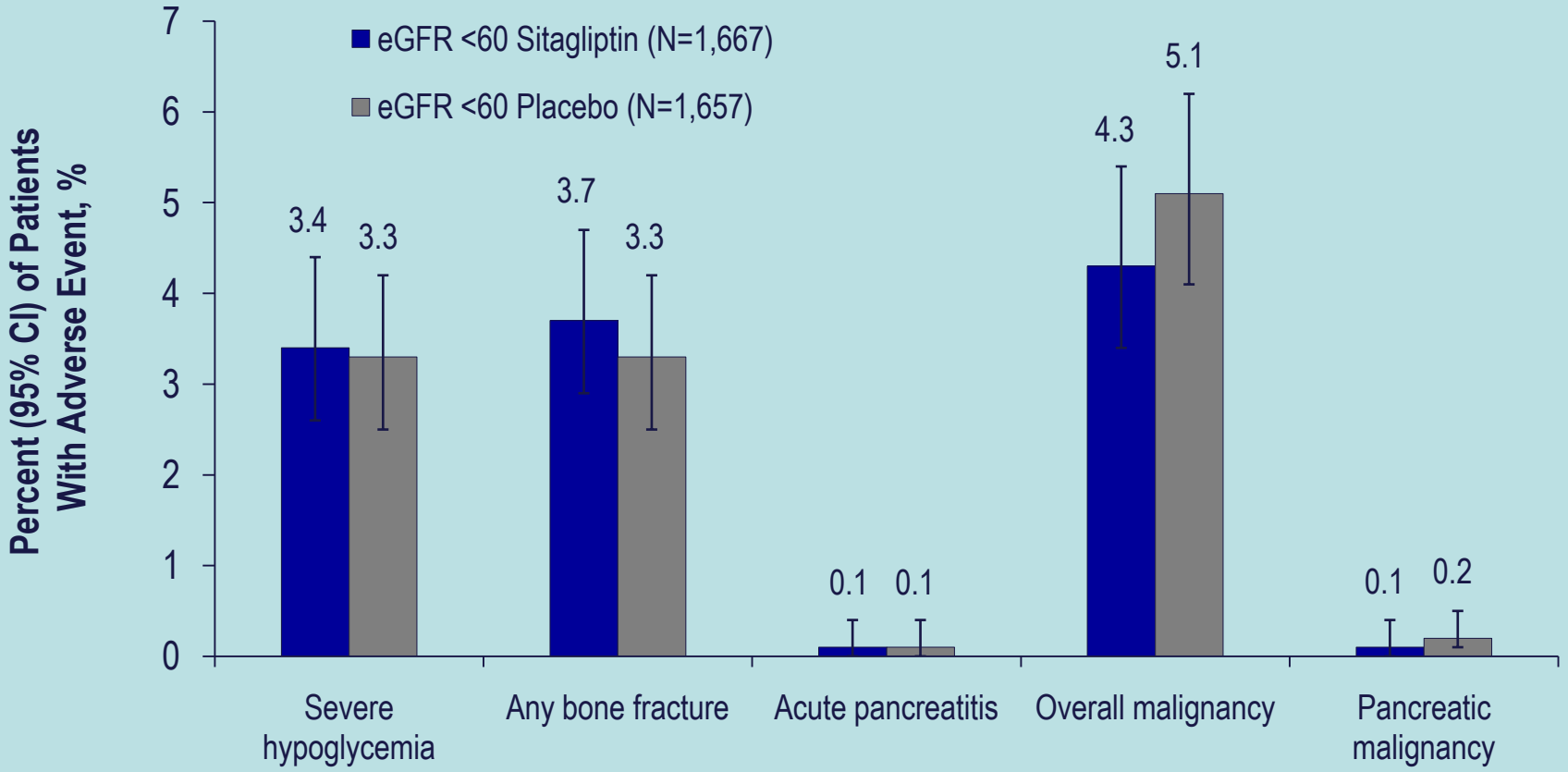
T2DM = type 2 diabetes mellitus; CKD = chronic kidney disease; TECOS = Trial Evaluating Cardiovascular Outcomes With Sitagliptin; eGFR = estimated glomerular filtration rate; CI = confidence interval.

1. Engel SS et al. Assessing the Safety of Sitagliptin in Patients with Type 2 Diabetes and Chronic Kidney Disease in the TECOS Trial. Presented at the 2016 American Diabetes Association Scientific Sessions. June 10–14, 2016. New Orleans, Louisiana.

TECOS

Safety of Sitagliptin in Patients With T2DM and CKD in the TECOS Trial: Adverse Events of Interest of CKD Patients by Treatment[1]

Summary of incidence of adverse events of interest for treatment groups in CKD participants



T2DM = type 2 diabetes mellitus; CKD = chronic kidney disease; TECOS = Trial Evaluating Cardiovascular Outcomes With Sitagliptin; eGFR = estimated glomerular filtration rate; CI = confidence interval.

1. Engel SS et al. Assessing the Safety of Sitagliptin in Patients with Type 2 Diabetes and Chronic Kidney Disease in the TECOS Trial. Presented at the 2016 American Diabetes Association Scientific Sessions. June 10–14, 2016. New Orleans, Louisiana.

TECOS

Summary[1]

- Baseline characteristics of participants with CKD were generally similar to those without CKD (except eGFR, duration of diabetes, and sex), and were similar for participants with CKD assigned sitagliptin vs placebo
- Incidences of diabetes complications in TECOS CKD participants were, in general, greater compared with non-CKD participants
- There were no meaningful differences in the incidences of diabetes complications in TECOS CKD participants assigned sitagliptin vs placebo
- The incidences of severe hypoglycemia, bone fracture, and malignancy in TECOS CKD participants were greater compared with non-CKD participants.
- There were no notable eGFR changes from baseline in participants with or without CKD

In TECOS, no specific safety concerns were identified with the use of sitagliptin in T2DM patients with CKD

CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; TECOS = Trial Evaluating Cardiovascular Outcomes With Sitagliptin.

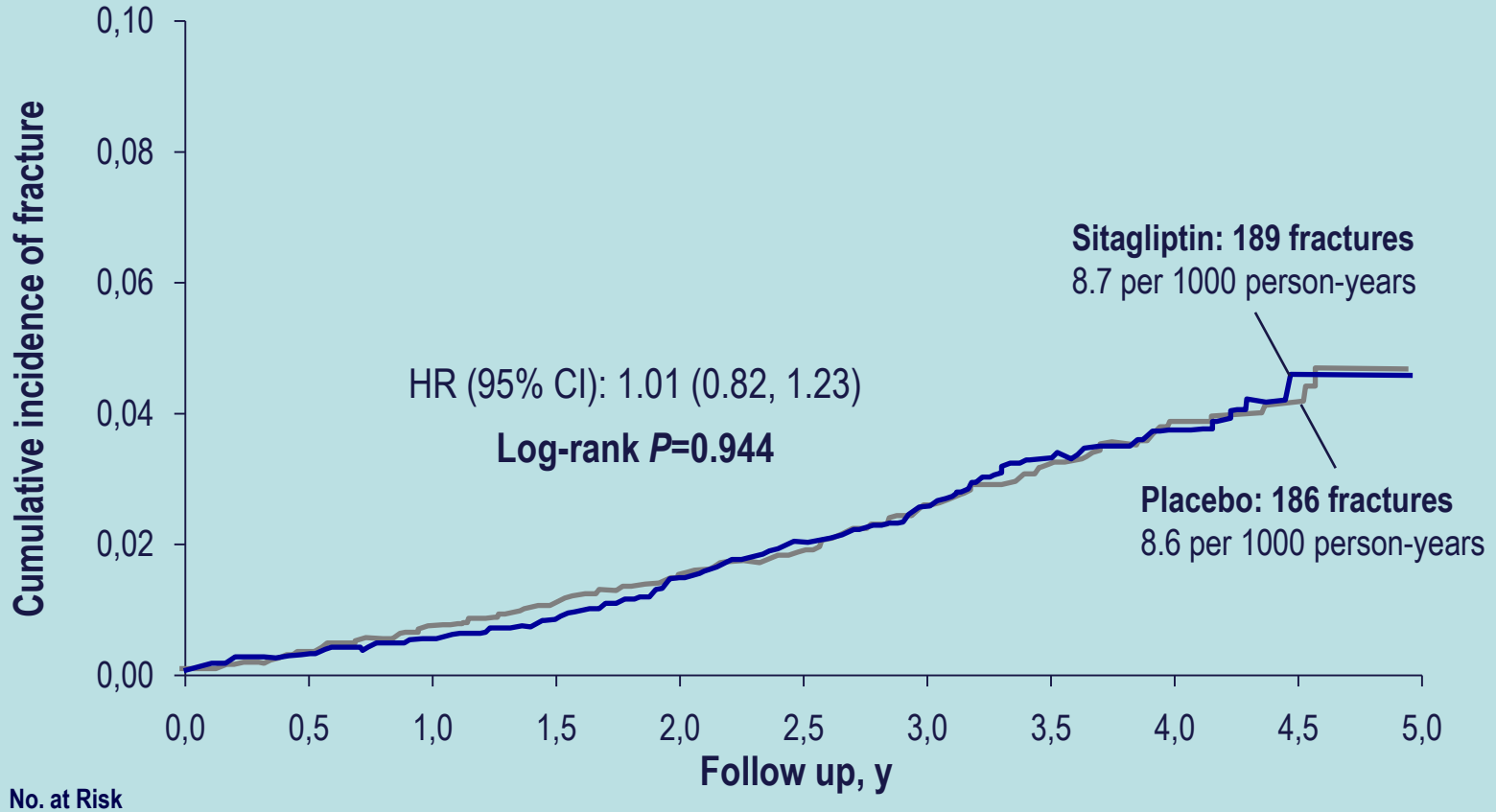
1. Engel SS et al. Assessing the Safety of Sitagliptin in Patients with Type 2 Diabetes and Chronic Kidney Disease in the TECOS Trial. Presented at the 2016 American Diabetes Association Scientific Sessions. June 10–14, 2016. New Orleans, Louisiana.

Sitagliptin and Risk of Fractures in Type 2 Diabetes: Results from the TECOS Trial

Robert G. Josse, MBBS, FRCP, FRCPC, Sumit R. Majumdar, MD, MPH, Yinggan Zheng, MA, MEd, John B. Buse, MD, PhD, Jennifer B. Green, MD, Keith D. Kaufman, MD, Cynthia M. Westerhout, PhD, Eric D. Peterson, MD, MPH, Rury R. Holman, MB ChB, FRCP, FMedSci, Paul W. Armstrong, MD,
on behalf of the TECOS Study Group

Sitagliptin and Risk of Fractures in the TECOS Trial: Cumulative Incidence of Fracture[1]

Kaplan-Meier estimated cumulative incidence of any fracture according to treatment assignment



No. at Risk											
Sitagliptin	7,332	7,167	7,029	6,894	6,713	4,740	3,511	2,161	1,294	479	49
Placebo	7,339	7,173	7,012	6,853	6,669	4,674	3,452	2,129	1,245	441	43

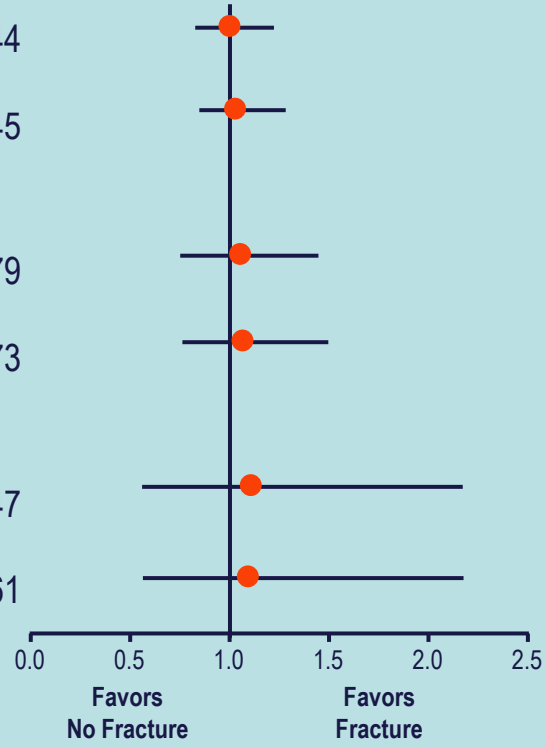
T2DM = type 2 diabetes mellitus; CKD = chronic kidney disease; TECOS = Trial Evaluating Cardiovascular Outcomes With Sitagliptin.

1. Josse RG et al. Sitagliptin and Risk of Fractures in Type 2 Diabetes: Results from the TECOS Trial. Presented at the 2016 American Diabetes Association Scientific Sessions. June 10–14, 2016. New Orleans, Louisiana.

TECOS

Sitagliptin and Risk of Fractures in the TECOS Trial: Sensitivity Analysis for Risk of Fracture by Treatment[1]

Variable	Observed fracture rate, n (%) per 1,000 person-years: Sitagliptin (N=7,332)	Placebo (N=7,339)	HR (95% CI)	*P* value
Overall fracture	189 (2.6)	186 (2.5)	Unadjusted: 1.01 (0.82, 1.23)	0.944
	8.7	8.6	Adjusted[a]: 1.04 (0.84, 1.27)	0.745
Major osteoporotic fracture	75 (1.0)	71 (1.0)	Unadjusted: 1.05 (0.76, 1.45)	0.779
	3.5	3.3	Adjusted[a]: 1.07 (0.77, 1.49)	0.673
Hip fracture	18 (0.3)	16 (0.2)	Unadjusted: 1.12 (0.57, 2.19)	0.747
	0.8	0.7	Adjusted[a]: 1.11 (0.57, 2.18)	0.761



[a]Adjusted for age, sex, white race, diastolic blood pressure, current smoker, diabetes duration, diabetic neuropathy, and use of metformin, sulfonylurea, thiazolidinedione, and insulin.
T2DM = type 2 diabetes mellitus; TECOS = Trial Evaluating Cardiovascular Outcomes With Sitagliptin; HR = hazard ratio; CI = confidence interval.

1. Josse RG et al. Sitagliptin and Risk of Fractures in Type 2 Diabetes: Results from the TECOS Trial. Presented at the 2016 American Diabetes Association Scientific Sessions. June 10–14, 2016. New Orleans, Louisiana.

TECOS

Summary[1]

- In TECOS, a large, prospective, randomized, placebo-controlled trial of sitagliptin in patients with T2DM, we demonstrated that:
  - Fractures were common in this population
  - Sitagliptin use was not associated with an increased risk of fracture compared to placebo
  - Insulin use was associated with a significantly increased risk of fracture, while metformin use was associated with a significantly decreased risk

In TECOS, no increase in risk of fractures with sitagliptin compared with placebo was demonstrated

TECOS = Trial Evaluating Cardiovascular Outcomes With Sitagliptin; T2DM = type 2 diabetes mellitus.

1. Josse RG et al. Sitagliptin and Risk of Fractures in Type 2 Diabetes: Results from the TECOS Trial. Presented at the 2016 American Diabetes Association Scientific Sessions. June 10–14, 2016. New Orleans, Louisiana.

Conclusioni

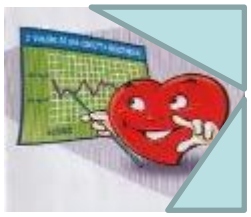
DPP4i:
stato dell'arte
ATTUALE

Abbiamo bisogno di terapie di primo utilizzo da sostituire alle sulfaniluree e per personalizzare la terapia: i DPP4i si offrono per questo ruolo

Il Sitagliptin in particolare appare molto sicuro e maneggevole. Ha dati ed evidenze uniche a favore dell'uso negli anziani e IRC

L'associazione tra DPP-4i e SGLT-2i avrebbe una sua logica ma per ora si scontra con problemi di rimborsbilità AIFA

Grazie per l'attenzione



Implicazioni

- Cambio filosofico: con le vecchie terapie studi di strategia di intervento (intensiva vs standard)
- Con le nuove terapie obbligo dati di safety
- No SU, fanno male
- No meglitinidi, assenza dati
- No acarbose, assenza dati
- Insulina, da monitorare
- Pioglitazone, dato positivo su MACE ma negativo su HF
- Metformina, nessun effetto negativo, da approfondire sui positivi
- Incretine, DPP4i con molti più dati vs GLP1-RA (solo lixisenatide)
- DPP4i, vilda e lina no dati, saxa alo e sita nessun effetto negativo su MACE.
- DPP4i, solo sitagliptin neutro su HF, effetti positivi da approfondire
- SGLT2, empaglifozin migliora eventi CV, da approfondire la ricerca delle motivazioni

TECOS: Initiation of Chronic Insulin Therapy

	Sitagliptin* n=5608	Placebo* n=5655
Initiation of insulin		
# Patients	542 (9.7%)	744 (13.2%)
Event rate per 100 pyrs	3.44	4.85
Cumulative incidence (%) of event		
1 year, % (95% CI)	3.2 (2.8, 3.7)	4.8 (4.3, 5.4)
2 years, % (95% CI)	6.4 (5.8, 7.1)	9.7 (8.9, 10.5)
3 years, % (95% CI)	9.8 (9.0, 10.7)	14.1 (13.1, 15.1)
4 years, % (95% CI)	13.2 (12.1, 14.5)	17.5 (16.3, 18.9)

**Patients not on insulin at baseline*

Green JB et al. NEJM 2015; DOI: 10.1056/NEJMoa1501352

TECOS: Initiation of Additional Antihyperglycemic Agents

	Sitagliptin n=7332	**Placebo** n=7339
Initiation of next antidiabetic medication ITT HR 0.72 (95% CI 0.68, 0.77), p<0.001		
# Patients	1591 (21.7%)	2046 (27.9%)
Event rate per 100 pyrs	8.5	11.6
Cumulative incidence (%) of event		
1 year, % (95% CI)	6.7 (6.1, 7.3)	9.3 (8.6, 10.0)
2 years, % (95% CI)	14.9 (14.1, 15.7)	20.3 (19.4, 21.3)
3 years, % (95% CI)	23.4 (22.2, 24.5)	31.3 (30.1, 32.6)
4 years, % (95% CI)	33.1 (31.4, 34.9)	41.5 (39.6, 43.3)

Green JB et al. NEJM 2015; DOI: 10.1056/NEJMoa1501352

EXAMINE and SAVOR-TIMI: Hospitalization for Heart Failure

EXAMINE

	Alogliptin n=2,701	Placebo n=2,679	HR (95% CI)
HHF[a]	3.9%	3.3%	1.19 (0.89–1.58)

SAVOR-TIMI

	Saxagliptin n=8,280	Placebo n=8,212	HR (95% CI)
HHF	3.5%	2.8%	1.27 (1.07–1.51)

EXAMINE: In a post-hoc analysis, there was a trend (*P*=NS) for increased hospitalization for HF with alogliptin compared with placebo

SAVOR-TIMI: Hospitalization for HF was significantly increased with saxagliptin compared with placebo

Mortality due to HF was not significantly different between saxagliptin and placebo (0.5% for both)[3]

EXAMINE = Examination of Cardiovascular Outcomes: Alogliptin vs Standard of Care in Patients With Type 2 Diabetes Mellitus and Acute Coronary Syndrome; SAVOR-TIMI = Saxagliptin Assessment of Vascular Outcomes Recorded in Patients With Diabetes Mellitus Trial-Thrombolysis in Myocardial Infarction; HHF = hospitalization for heart failure; HR = hazard ratio; CI = confidence interval; HF = heart failure.

Reproduced with permission from White WB et al. *N Engl J Med* 2013;369:1327–1335. Sanon VP et al. *Clin Diabetes.* 2014;32:121–126. **3.** Reproduced with permission from Scirica BM et al. *N Engl J Med* 2013;369:1317–1326.

Sitagliptin vs SU:
Riduzione degli eventi di ipoglicemia sintomatica

Figure 1A. Incidence of AEs of symptomatic hypoglycemia

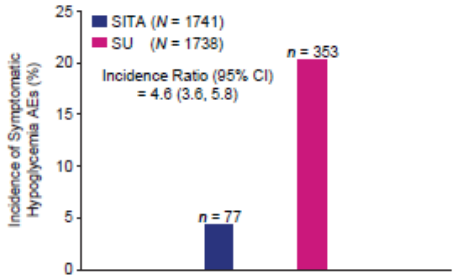


Figure 1B. Kaplan-Meier estimates of probability of patients having at least one AE of symptomatic hypoglycemia

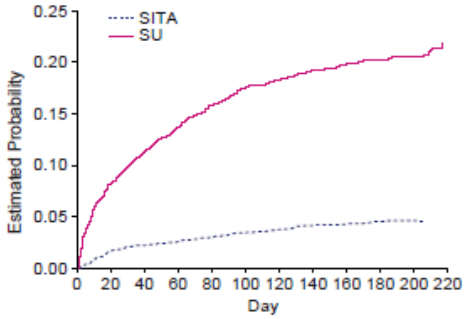


Figure 2A. Event rate of AEs of symptomatic hypoglycemia

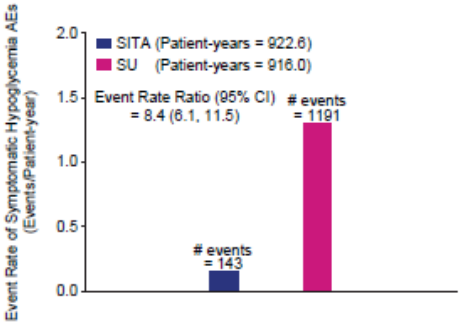


Figure 2B. Cumulative number of AEs of symptomatic hypoglycemia

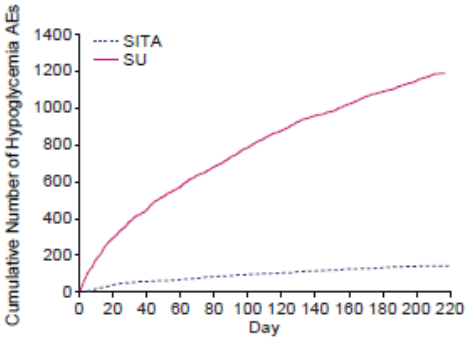


Figure 2C. Event rates of AEs of symptomatic hypoglycemia across time

L'incidenza ed il tasso di episodi di ipoglicemia sintomatica sono risultati rispettivamente 4,6 e 8,4 volte più elevati con SU rispetto a sitagliptin anche nell'ambito di tutti i sottogruppi di pazienti definiti in base all'età e la funzionalità renale

Jie Liu et al., ADA 2016 P1112

Esiste un conflitto tra DPP-4i (Sita) e SGLT2?

2 farmaci e 2 classi diverse

Sitagliptin (DPP-4i)	SGLT-2 i
Sicuro, ma non prove di efficacia s	Efficaci sulla mortalità in DM e CVD
Provata durability	*mancano dati*
Effetto sulle complicanze micro	*mancano dati*
Non effetti indesiderati	Effetti indesiderati minori (Infezioni genitali)
Positivo sulla betacellula	Efficaci su glucotossicità iniziale
Utilizzabile con IRC	Utilizzabili con IRC moderata
Caratteristiche favorevoli a DM anziano fragile con comorbilità	*Caratteristiche favorevoli al paz complicato soprattutto HF*

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Il futuro prossimo degli SGLT-2 inibitori

EXPERT OPINION

An evaluation of US patent 2015065565 (A1) for a new class of SGLT2 inhibitors for treatment 1 of type II diabetes mellitus

Meiyan Jiang & Peter S Steyger†
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Introduction: Type 2 diabetes mellitus (T2DM) is a growing and serious global health problem. Pharmacological inhibition of the sodium–glucose cotransporter-2 (SGLT2; SLC5A2) increases urinary glucose excretion, decreasing plasma glucose levels in an insulin-independent manner. Agents that inhibit SGLT2 have recently become available for clinical therapy of T2DM.

Areas covered: The patent claims a new class of SGLT2 inhibitors: derivatives of dioxa-bicyclo[3.2.1]octane-2,3,4-triol (including ertugliflozin; PF-04971729). The invention describes the design, synthesis and pharmacological tests related to ertugliflozin, which could ultimately lead to efficacious therapy for T2DM alone or in combination with other anti-diabetic agents.

Expert opinion: Ertugliflozin is likely to be of great clinical significance in the near future. Continued analysis of ertugliflozin derivatives to now validate safe and efficacious treatment of T2DM in a larger number of clinical subjects over an extended period is needed to further support clinical utility. Identification, and discussion, of likely contra-indications is also needed.

Keywords: clinical therapy, diabetes, dioxa-bicyclo[3.2.1]octane-2,3,4-triol derivatives, ertugliflozin, inhibitors, PF-04971729, sodium–glucose linked co-transporter, type 2 diabetes mellitus