
TECOS
TRIAL EVALUATING CARDIOVASCULAR
OUTCOMES WITH SITAGLIPTIN

Presenter Disclosure Information

M. Angelyn Bethel

Divisional Research Funding:

Astra Zeneca, Merck & Co. Inc., GlaxoSmithKline

Honoraria:

Astra Zeneca, Boehringer Ingelheim, NovoNordisk, GlaxoSmithKline, Merck & Co. Inc.

TECOS
TRIAL EVALUATING CARDIOVASCULAR OUTCOMES WITH SITAGLIPTIN

Glycemic Control: Benefits and Challenges

Good glycemic control

- Reduces the risk of microvascular complications
- Modestly reduces the risk of macrovascular complications
- Usually requires multiple therapies over time due to progression of disease

Effects of Antihyperglycemic Therapies

- Many drug classes available but concerns raised about possible off-target effects:
  - Increased cardiovascular event rates, heart failure events
  - Pancreatitis and malignancy
- International regulatory agencies require that all new antihyperglycemic agents demonstrate glucose lowering AND exclude clinically meaningful increases in major adverse cardiovascular events

1. Holman RR et al. NEJM 2008; 359: 15
2. Hemmingsen et al. BMJ 2012; 344: d8277

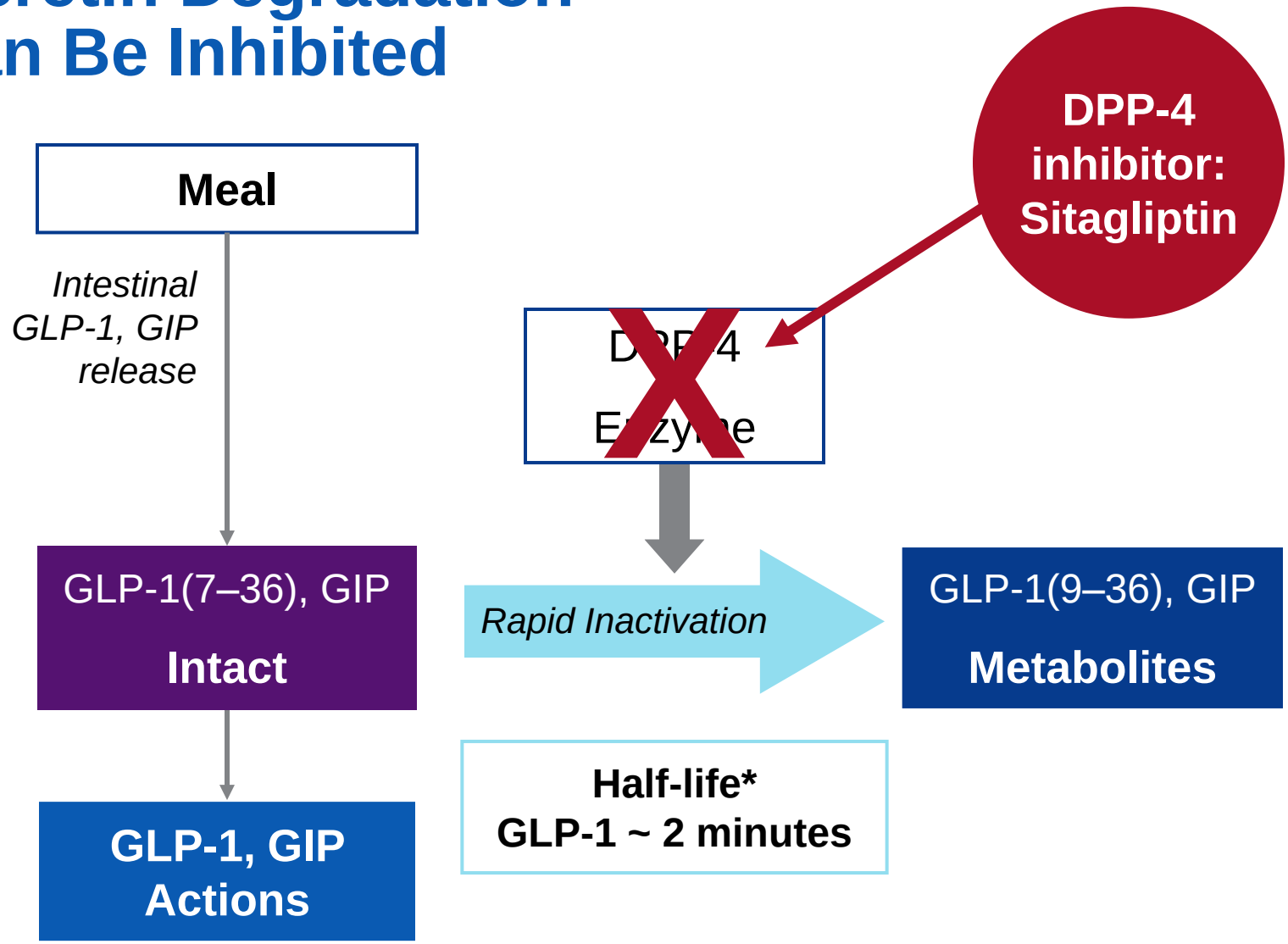
Glucagon-Like Peptide-1 (GLP-1) and Glucose-dependent Insulinotropic Peptide (GIP) are Incretin Hormones

GLP-1	GIP
Is released from L cells in ileum and colon[1,2]	Is released from K cells in duodenum[1,2]
Stimulates insulin response from beta cells in a glucose-dependent manner[1]	Stimulates insulin response from beta cells in a glucose-dependent manner[1]
Inhibits gastric emptying[1,2]	Has minimal effects on gastric emptying[2]
Reduces food intake and body weight[2]	Has no significant effects on satiety or body weight[2]
Inhibits glucagon secretion from alpha cells in a glucose-dependent manner[1]	Does not appear to inhibit glucagon secretion from alpha cells[1,2]

1. Meier JJ et al. Best Pract Res Clin Endocrinol Metab 2004; 18: 587–606.
2. Drucker DJ. Diabetes Care 2003; 26: 2929–2940.

TECOS TRIAL EVALUATING CARDIOVASCULAR OUTCOMES WITH SITAGLIPTIN

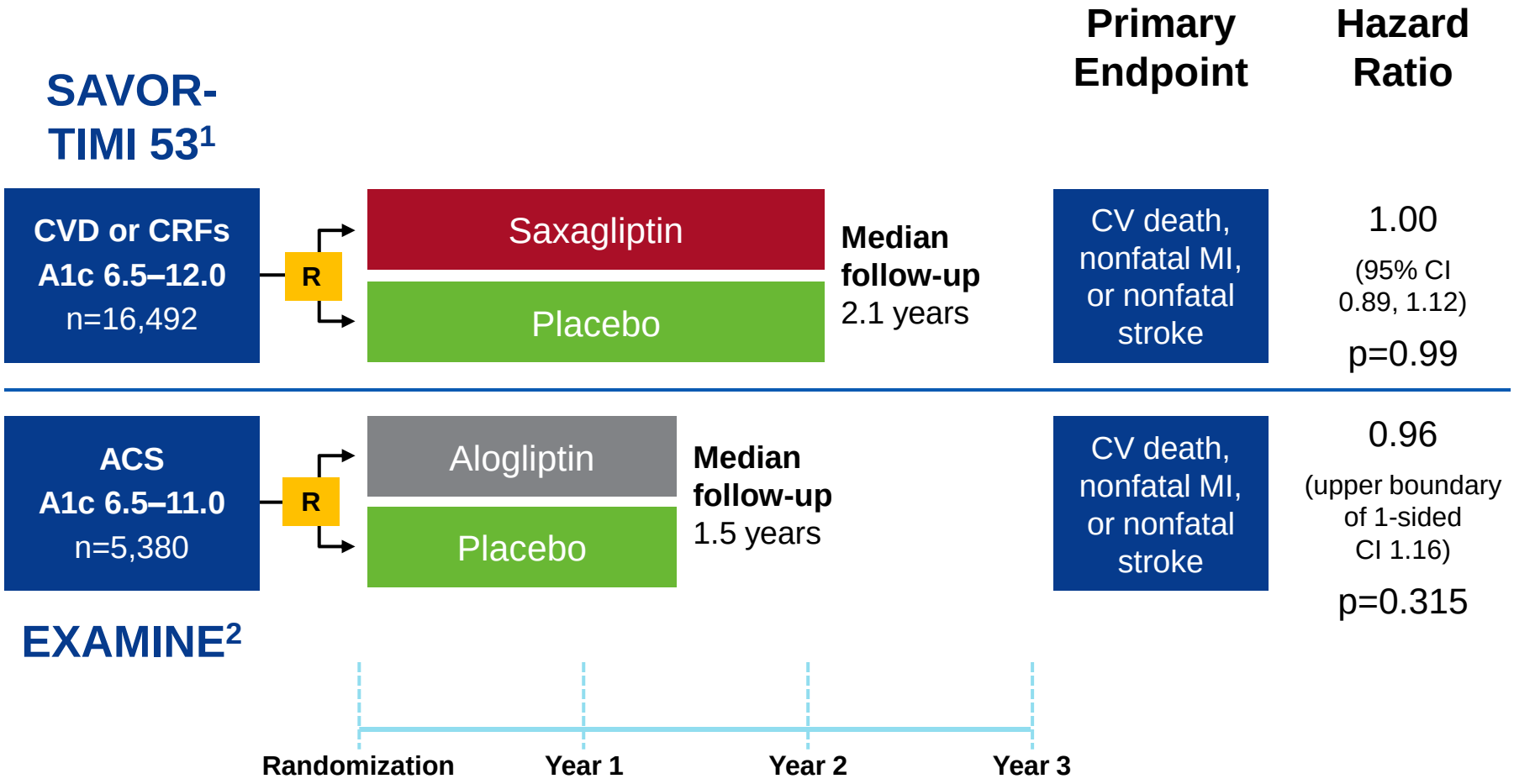
Incretin Degradation Can Be Inhibited



1. Deacon CF et al. Diabetes 1995; 44: 1126–1131.
2. *Meier JJ et al. Diabetes 2004; 53: 654–662.

TECOS
TRIAL EVALUATING CARDIOVASCULAR OUTCOMES WITH SITAGLIPTIN

Completed Cardiovascular Outcomes Studies for DPP-4 Inhibitors



EXAMINE = Examination of Cardiovascular Outcomes: Alogliptin vs Standard of Care in Patients With Type 2 Diabetes Mellitus and Acute Coronary Syndrome; SAVOR-TIMI 53 = Saxagliptin Assessment of Vascular Outcomes Recorded in Patients With Diabetes Mellitus Trial-Thrombolysis in Myocardial Infarction

1. Scirica BM et al. N Engl J Med 2013; 369: 1317–1326.
2. White WB et al. N Engl J Med. 2013; 369: 1327–1335.

TECOS
TRIAL EVALUATING CARDIOVASCULAR OUTCOMES WITH SITAGLIPTIN

TECOS

- Initiated in advance of FDA requirements, but consistent with that guidance
- Large, international trial designed to assess the impact of sitagliptin (100mg) versus placebo on cardiovascular event rates
  - When added to usual diabetes care
  - Minimize difference in glycemia between groups
  - Dose adjusted for eGFR
- Randomized, double-blind, placebo-controlled
- Academically led in collaboration with industry sponsorship

TECOS
TRIAL EVALUATING CARDIOVASCULAR OUTCOMES WITH SITAGLIPTIN

Other Key Design Features

- Population: Type 2 DM & Secondary CV prevention
- Event driven, 1300 confirmed primary events
- Primary outcome (MACE+)
  - CV death
  - Nonfatal myocardial infarcion
  - Nonfatal stroke
  - Hospitalization for unstable angina
- Pre-specified CHF secondary outcome
- Independent blinded event adjudication

TECOS
TRIAL EVALUATING CARDIOVASCULAR OUTCOMES WITH SITAGLIPTIN

Major Inclusion Criteria

- **Type 2 diabetes** (A1c ≥6.5% and ≤8.0%)
  - Stable monotherapy OR dual combination therapy with metformin, pioglitazone, or sulfonylurea or *stable dose of insulin with or without metformin
- **≥50 years old**
- **Preexisting vascular disease** defined as having:
  - History of myocardial infarction
  - Prior coronary revascularization
  - Coronary angiography with at least one ≥50% stenosis
  - History of ischemic stroke
  - Carotid arterial disease with ≥50% carotid stenosis
  - Peripheral arterial disease with objective evidence
- **Able to see usual care provider at least twice yearly**

**Amended 13Sept2010*

TECOS
TRIAL EVALUATING CARDIOVASCULAR OUTCOMES WITH SITAGLIPTIN

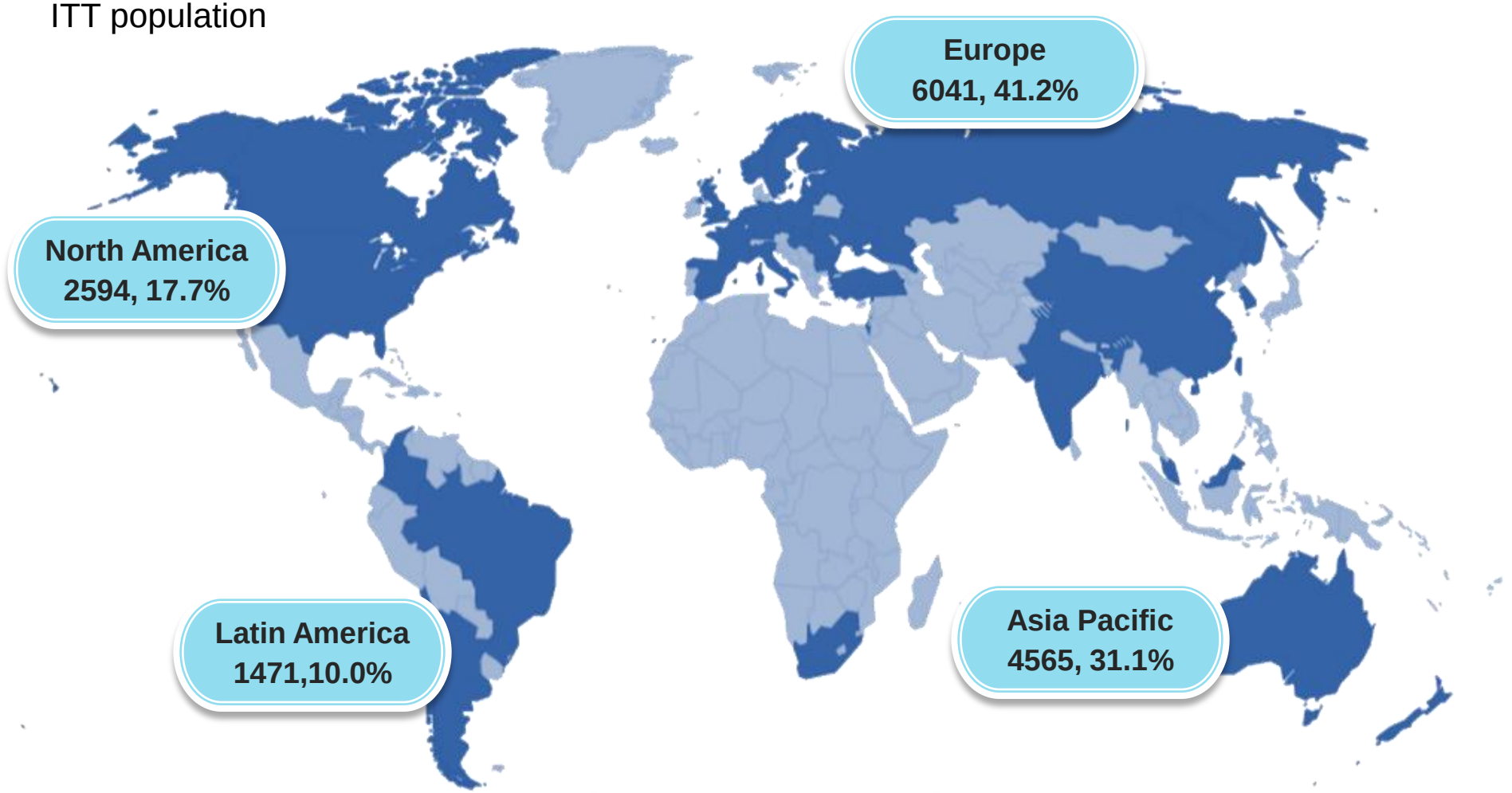
Major Exclusion Criteria

- Type 1 diabetes or history of ketoacidosis
- History of ≥2 episodes of severe hypoglycemia during the 12 months prior to enrollment
- Estimated glomerular filtration rate (eGFR) <30mL/min/1.73 m^2
- Use of another DPP-4 inhibitor, GLP-1 analogue, or thiazolidinedione other than pioglitazone in previous three months
- Cirrhosis of the liver
- Planned revascularization procedure
- Pregnancy or planned pregnancy

Recruitment:
December 2008 – July 2012

ITT population

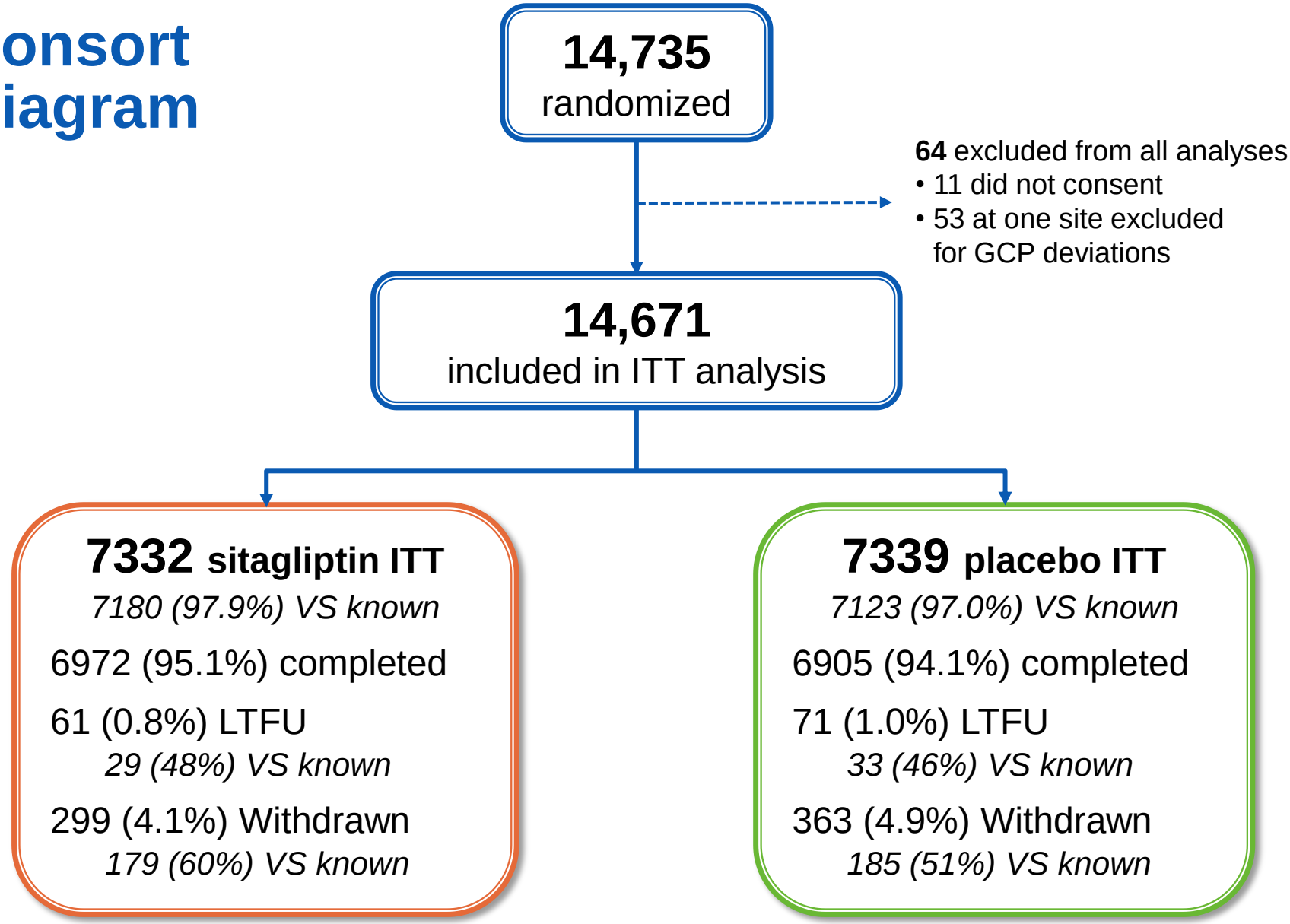
= country involved in TECOS



Total 14,671

TECOS
TRIAL EVALUATING CARDIOVASCULAR OUTCOMES WITH SITAGLIPTIN

Consort Diagram



ITT = intention-to-treat; LTFU = lost to follow-up; VS = vital status, GCP = Good Clinical Practice

TECOS
TRIAL EVALUATING CARDIOVASCULAR OUTCOMES WITH SITAGLIPTIN

Baseline Characteristics

Characteristic	Sitagliptin n=7332	Placebo n=7339
Age (years)	65.4 ± 7.9	65.5 ± 8.0
Women	2134 (29.1%)	2163 (29.5%)
Race		
White	4955 (67.6%)	5002 (68.2%)
Black	206 (2.8%)	241 (3.3%)
Asian	1654 (22.6%)	1611 (22.0%)
Other	517 (7.1%)	485 (6.6%)
Hispanic or Latino	886 (12.1%)	912 (12.4%)
BMI (kg/m^2)	30.2 ± 5.6	30.2 ± 5.7
eGFR ($mL/min/1.73\ m^2$)*	74.9 ± 21.3	74.9 ± 20.9

Values are mean ±SD for continuous variables or n,% for categorical variables.
**MDRD formula used to calculate eGFR. Site-reported values are presented.*

TECOS
TRIAL EVALUATING CARDIOVASCULAR OUTCOMES WITH SITAGLIPTIN

Baseline Characteristics—CV Risk Management

Characteristic	Sitagliptin n=7332	Placebo n=7339
Systolic blood pressure (mmHg)	135 ± 16.9	135 ± 17.1
Diastolic blood pressure (mmHg)	77.1 ± 10.3	77.2 ± 10.6
Total cholesterol (mmol/L)	4.3 ± 1.2	4.3 ± 1.2
LDL-C (mmol/L)	2.4 ± 1.7	2.3 ± 1.3
HDL-C (mmol/L)	1.1 ± 0.3	1.1 ± 0.3
Triglycerides (mmol/L)	1.9 ± 1.1	1.9 ± 1.1
Medication		
Aspirin use	5764 (78.6%)	5754 (78.4%)
Statin use	5851 (79.8%)	5868 (80.0%)

Values are mean ±SD for continuous variables or n,% for categorical variables.

TECOS TRIAL EVALUATING CARDIOVASCULAR OUTCOMES WITH SITAGLIPTIN

Baseline Characteristics—Diabetes

Characteristic	Sitagliptin n=7332	Placebo n=7339
Duration of diabetes (years)	11.6 ± 8.1	11.6 ± 8.1
HbA1c (%)	7.2 ± 0.5	7.2 ± 0.5
Medication taken alone or in combination		
Metformin	5936 (81.0%)	6030 (82.2%)
Sulfonylurea	3346 (45.6%)	3299 (45.0%)
Thiazolidinedione	196 (2.7%)	200 (2.7%)
Insulin	1724 (23.5%)	1684 (22.9%)
Median daily dose (units)	50 (33, 80)	50 (32, 80)
Monotherapy	3496 (47.7%)	3498 (47.7%)
Dual combination therapy	3766 (51.4%)	3768 (51.3%)

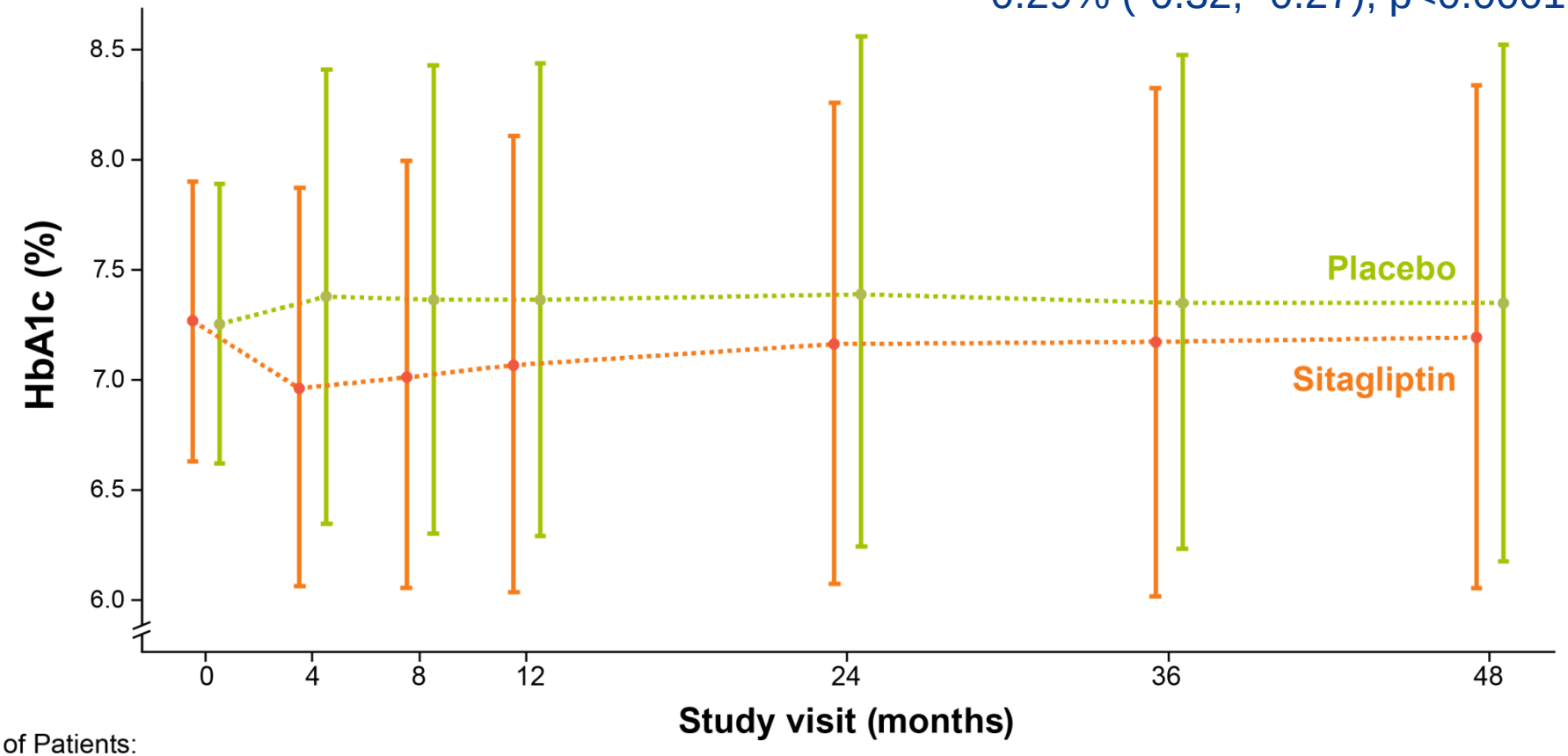
Values are mean ±SD or median (IQR) for continuous variables or n,% for categorical variables.

TECOS
TRIAL EVALUATING CARDIOVASCULAR OUTCOMES WITH SITAGLIPTIN

Glycemic Control

Least Squares Mean HbA1c ± 1SD

Overall LS Mean difference
-0.29% (-0.32, -0.27), p<0.0001



# of Patients:							
Sitagliptin	7,325	6,779	6,485	6,454	6,110	3,524	1,434
Placebo	7,331	6,746	6,422	6,390	5,980	3,443	1,386

TECOS
TRIAL EVALUATING CARDIOVASCULAR OUTCOMES WITH SITAGLIPTIN

Severe Hypoglycemia*

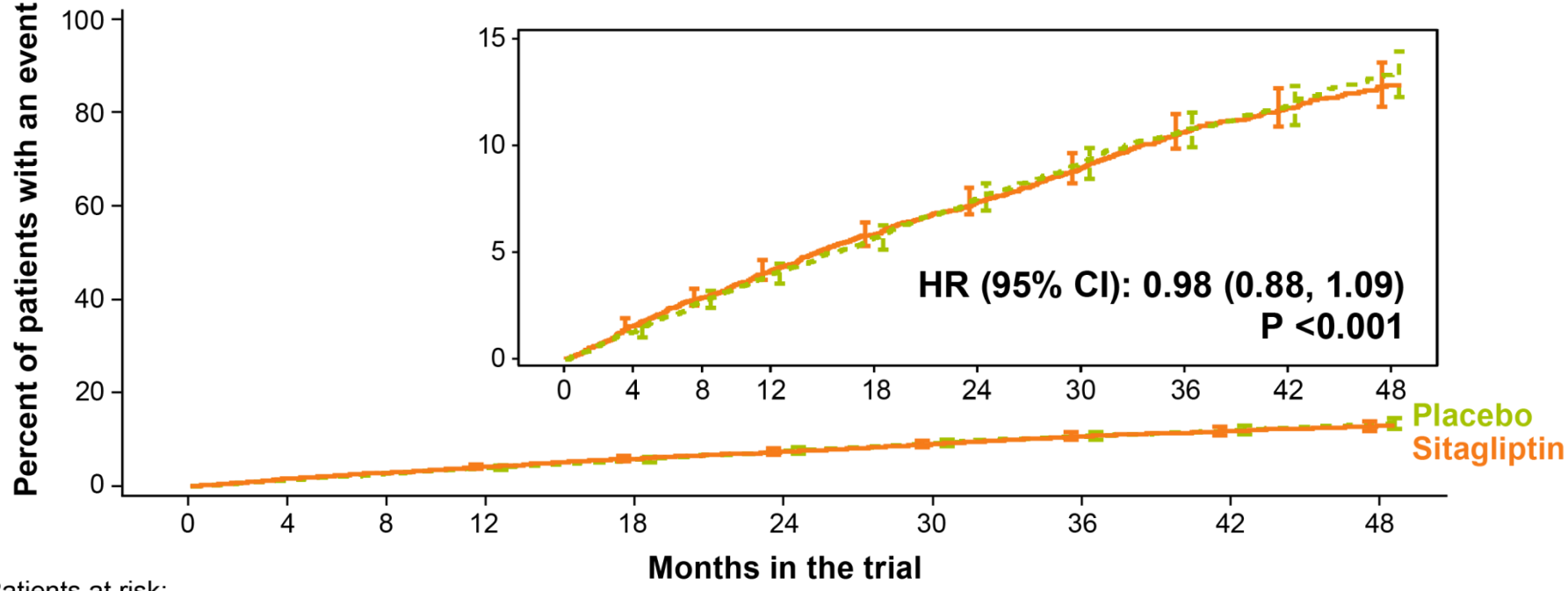
ITT HR (95% CI): 1.12 (0.89–1.40), p=0.33

	Sitagliptin	Placebo
	Participants with event n (%)	Participants with event n (%)
	160 (2.2%)	143 (1.9%)
Events per 100 patient-years	0.78	0.70

**Hypoglycemia requiring assistance*

TECOS TRIAL EVALUATING CARDIOVASCULAR OUTCOMES WITH SITAGLIPTIN

Primary Composite Cardiovascular Outcome*
PP Analysis for Non-inferiority

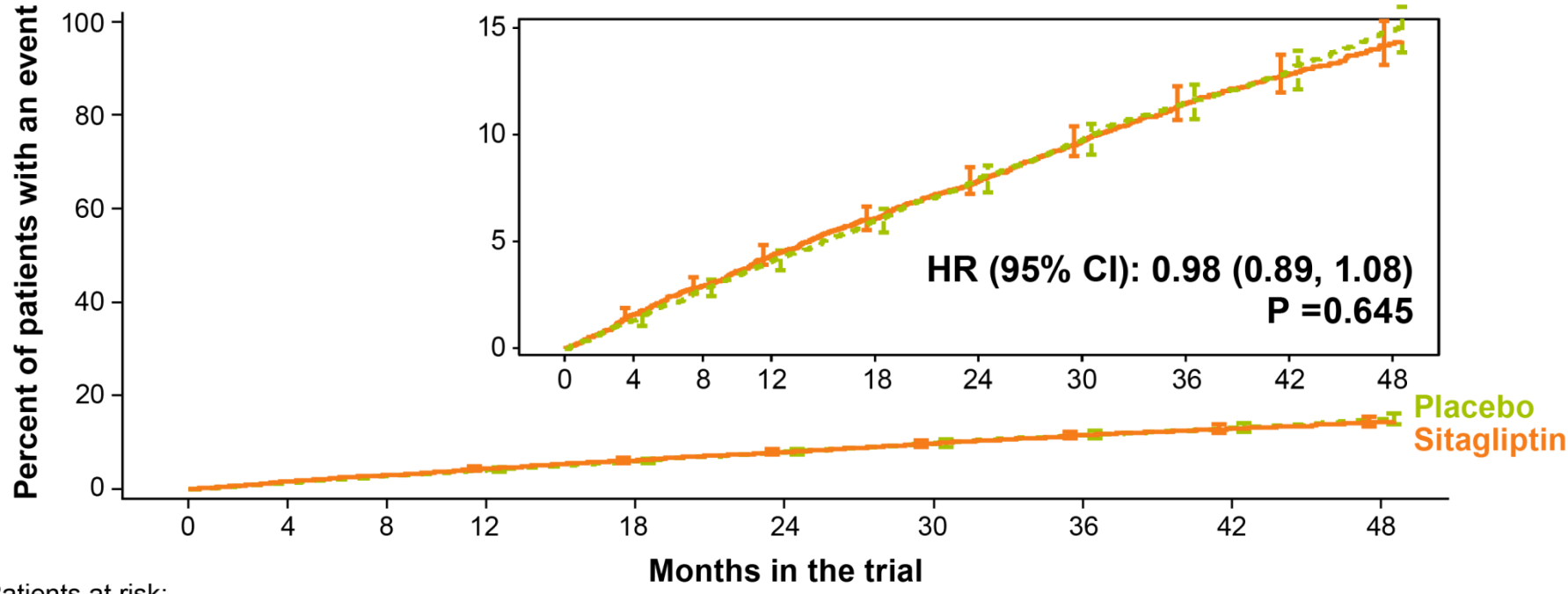


Patients at risk:										
Sitagliptin	7,257	6,857	6,519	6,275	5,931	5,616	3,919	2,896	1,748	1,028
Placebo	7,266	6,846	6,449	6,165	5,803	5,421	3,780	2,743	1,690	1,005

** CV death, nonfatal MI, nonfatal stroke, hospitalization for unstable angina*

TECOS
TRIAL EVALUATING CARDIOVASCULAR OUTCOMES WITH SITAGLIPTIN

Primary Composite Cardiovascular Outcome*
ITT Analysis for Superiority

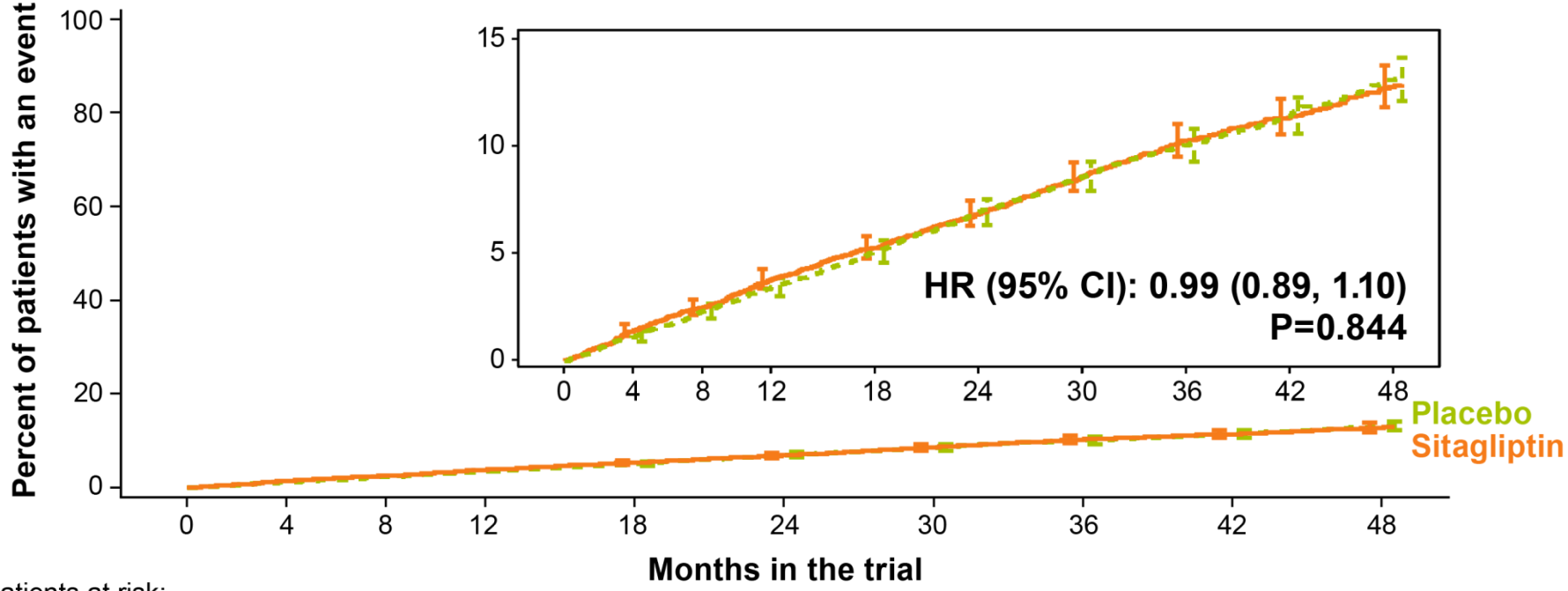


Patients at risk:										
Sitagliptin	7,332	7,131	6,937	6,777	6,579	6,386	4,525	3,346	2,058	1,248
Placebo	7,339	7,146	6,902	6,751	6,512	6,292	4,411	3,272	2,034	1,234

** CV death, nonfatal MI, nonfatal stroke, hospitalization for unstable angina*

TECOS
TRIAL EVALUATING CARDIOVASCULAR OUTCOMES WITH SITAGLIPTIN

Secondary Composite Cardiovascular Outcome*
ITT Analysis for Superiority



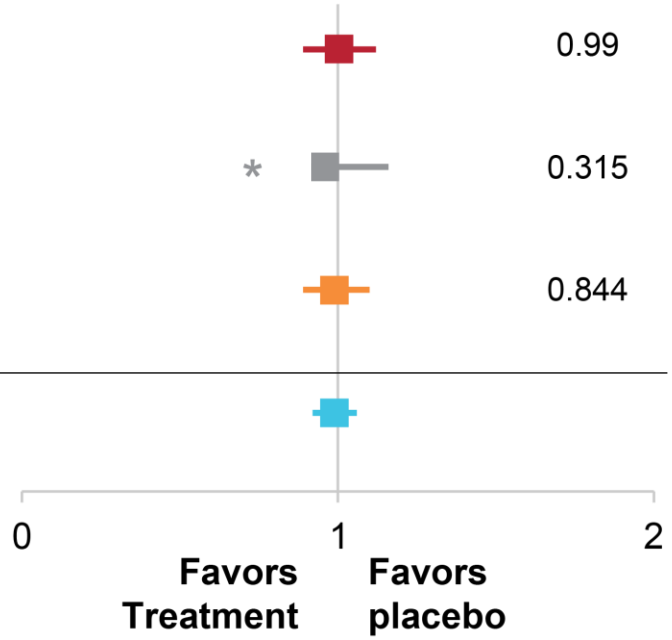
Patients at risk:										
Sitagliptin	7,332	7,145	6,969	6,817	6,638	6,457	4,584	3,396	2,097	1,270
Placebo	7,339	7,161	6,939	6,796	6,573	6,359	4,472	3,332	2,070	1,260

** CV death, nonfatal MI, nonfatal stroke*

TECOS
TRIAL EVALUATING CARDIOVASCULAR OUTCOMES WITH SITAGLIPTIN

SAVOR-TIMI 53, EXAMINE, and TECOS: MACE Events

	Study Drug n/N (%)	Placebo n/N (%)	Hazard Ratio	95% CI	P Value
SAVOR-TIMI (saxagliptin vs. placebo)	613/8280 (7.4%)	609/8212 (7.4%)	1.00	0.89, 1.12	0.99
EXAMINE (alogliptin vs. placebo)	305/2701 (11.3%)	316/2679 (11.8%)	0.96	NA, 1.16	0.315
TECOS (sitagliptin vs. placebo)	745/7332 (10.2%)	746/7339 (10.2%)	0.99	0.89, 1.10	0.844
SAVOR + EXAMINE + TECOS	1663/18313 (9.1%)	1671/18230 (9.2%)	0.99	0.92, 1.06	



Test for heterogeneity for 3 trials: p=0.877, I^2=0%

1. Scirica BM et al. N Engl J Med 2013; 369: 1317–1326
2. White WB et al. N Engl J Med 2013; 369: 1327–1335
3. Green JB et al. NEJM 2015; DOI: 10.1056/NEJMoa1501352

**Lower Confidence Limit not given for EXAMINE trial*

TECOS
TRIAL EVALUATING CARDIOVASCULAR OUTCOMES WITH SITAGLIPTIN

Summary of TECOS Results (1)

- TECOS was a *cardiovascular safety study* initiated ahead of the 2008 FDA guidance
- The study aimed for glycemic equipoise to minimize possible glycemic confounding effects on the outcomes of interest, with the result that there was only *a small difference in the HbA_{1c} levels* between the sitagliptin and placebo groups
- The utility of sitagliptin as a glucose-lowering agent was confirmed by the more frequent *initiation of insulin therapy* and the greater need for *additional antihyperglycemic agents* in the placebo group compared with the sitagliptin group

TECOS
TRIAL EVALUATING CARDIOVASCULAR OUTCOMES WITH SITAGLIPTIN

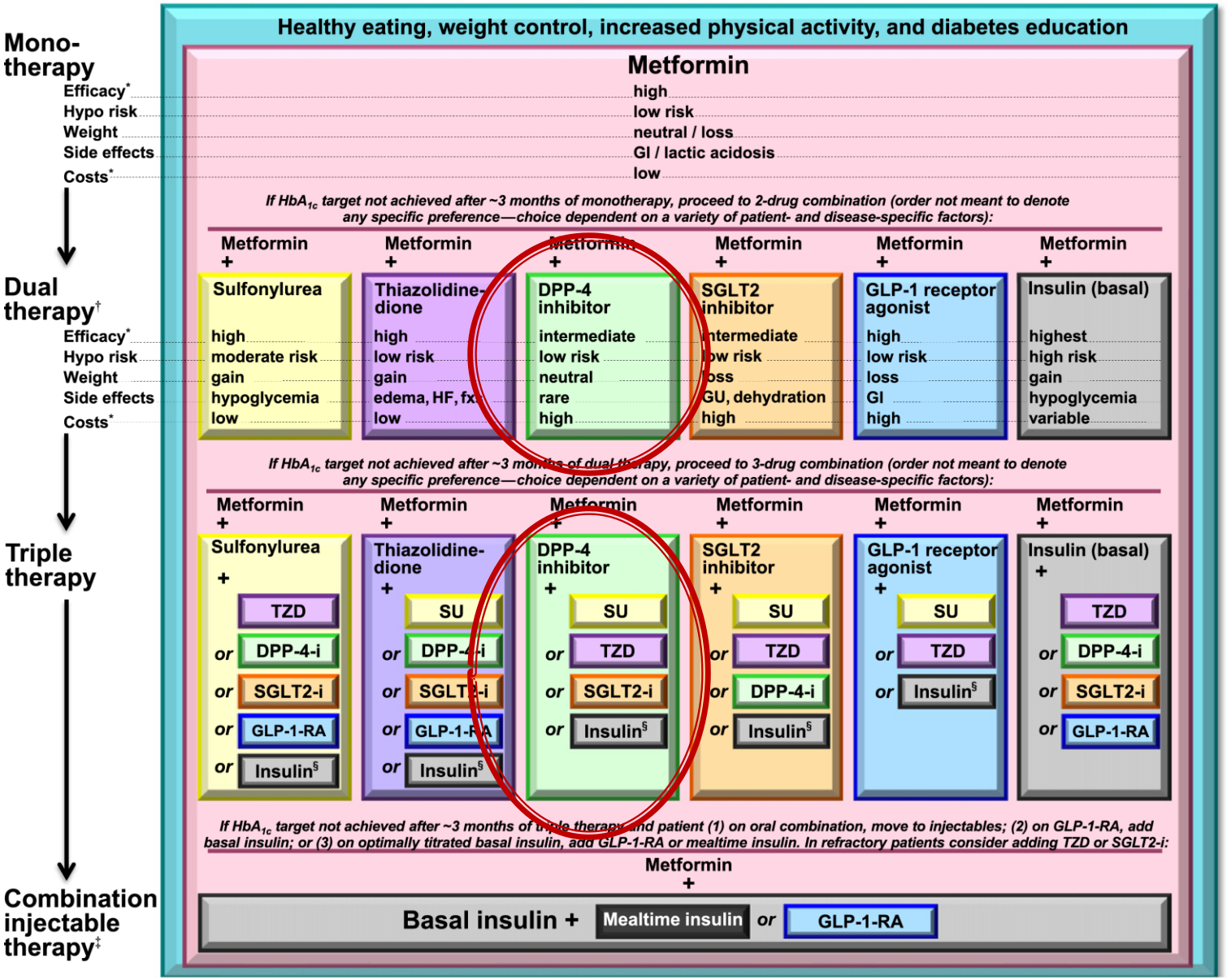
Summary of TECOS Results (2)

- Sitagliptin, compared with placebo, was *noninferior, and not superior* for the primary and secondary (MACE) composite cardiovascular outcomes
- The rate of *hospitalization for heart failure* did not differ between sitagliptin and placebo treatment groups
- Overall, confirmed events of *acute pancreatitis* were uncommon, but numerically more frequent in the sitagliptin group
- Overall, confirmed events of *pancreatic cancer* were uncommon, but numerically more frequent in the placebo group

TECOS
TRIAL EVALUATING CARDIOVASCULAR OUTCOMES WITH SITAGLIPTIN

Where does that leave us with DPP-4 inhibitors

ADA/EASD Position Statement



Diabetes Care 2015; 38: 140-149

TECOS
TRIAL EVALUATING CARDIOVASCULAR OUTCOMES WITH SITAGLIPTIN

What Do Providers and Patients Want from an Antihyperglycemic Medication? (1)

#1—Efficacy

- DPP-4 inhibitors are effective in the setting of optimal intended use, in combination with metformin early in the disease course.

#2—Tolerability

- DPP-4 inhibitors have long-standing reputation as arguably the best tolerated class of antihyperglycemic medication

What Do Providers and Patients Want from an Antihyperglycemic Medication? (2)

#3—Safety above all

- All DPP-4 inhibitors have demonstrated CV safety (MACE endpoints)
- Heart failure findings are inconsistent between completed trials
- Pancreatitis is uncommon overall, but more events occur with DPP-4 inhibitors.
  - Rate ~1 per 1000 patient years
  - Meta-analyses show a marginally statistically significant increase in pancreatitis, but should be interpreted with caution
  - Current recommendations to avoid DPP-4 inhibitors in those with a history of pancreatitis seem prudent
- Pancreatic cancer is uncommon, and rates do not increase with DPP-4 inhibitors

TECOS
TRIAL EVALUATING CARDIOVASCULAR OUTCOMES WITH SITAGLIPTIN

Acknowledgements

TECOS Executive Committee*

Rury Holman, *Joint Chair*
Eric Peterson, *Joint Chair*
Paul Armstrong
John Buse
Robert Josse
Keith Kaufman
Joerg Koglin
Scott Korn
John Lachin
Darren McGuire
Eberhard Standl
Peter Stein
Shailaja Suryawanshi
Frans Van de Werf

TECOS was conducted jointly by

UNIVERSITY OF OXFORD
DIABETES TRIALS UNIT
The Oxford Centre for Diabetes, Endocrinology and Metabolism

Duke Clinical Research Institute

…in an academic collaboration with

MERCK

** Robert M. Califf served as Joint Chair until taking up the post of deputy FDA commissioner on March 1, 2015*

TECOS
TRIAL EVALUATING CARDIOVASCULAR OUTCOMES WITH SITAGLIPTIN

Patients and Sites

- We thank the patients, without whom this study and these analyses would not have been possible
- We also thank the many investigators and their staff from 673 sites in 38 countries who worked diligently to help ensure TECOS was run to the highest possible standards

TECOS
TRIAL EVALUATING CARDIOVASCULAR OUTCOMES WITH SITAGLIPTIN


TECOS
TRIAL EVALUATING CARDIOVASCULAR
OUTCOMES WITH SITAGLIPTIN

Thank you