EXAMINE

Cardiovascular Outcomes With Alogliptin in Patients With Type 2 Diabetes Mellitus and Recent Acute Coronary Syndromes

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DECLARATION OF INTEREST

- Consulting/Royalties/Owner/ Stockholder of a healthcare company

Background

- The risk of CV disease is 2-4 times higher in people with type 2 diabetes; recent studies have not shown a favorable impact of intensive glycemic therapy on macrovascular events (e.g. ACCORD, ADVANCE, VADT)
- Concerns regarding adverse CV outcomes with some anti-diabetic agents prompted the U.S. FDA to release guidance (2008) outlining specific requirements for CV safety for new anti-diabetic therapies
- Alogliptin is a new selective dipeptidyl peptidase-4 (DPP-4) inhibitor approved for the treatment of type 2 diabetes. No imbalance in CV events was seen during phase 2/3 development but the background CV risk of that population was low. This led to the development of the EXAMINE trial.

Objectives and End Points of EXAMINE

- **Primary objective**: To demonstrate that major CV event rates are not higher with alogliptin than with placebo in type 2 diabetes patients with recent ACS who are receiving standard of care for diabetes and secondary CV prevention
  - **Primary end point**: composite of first occurrence of CV death, nonfatal MI, and nonfatal stroke

  Secondary Objectives:

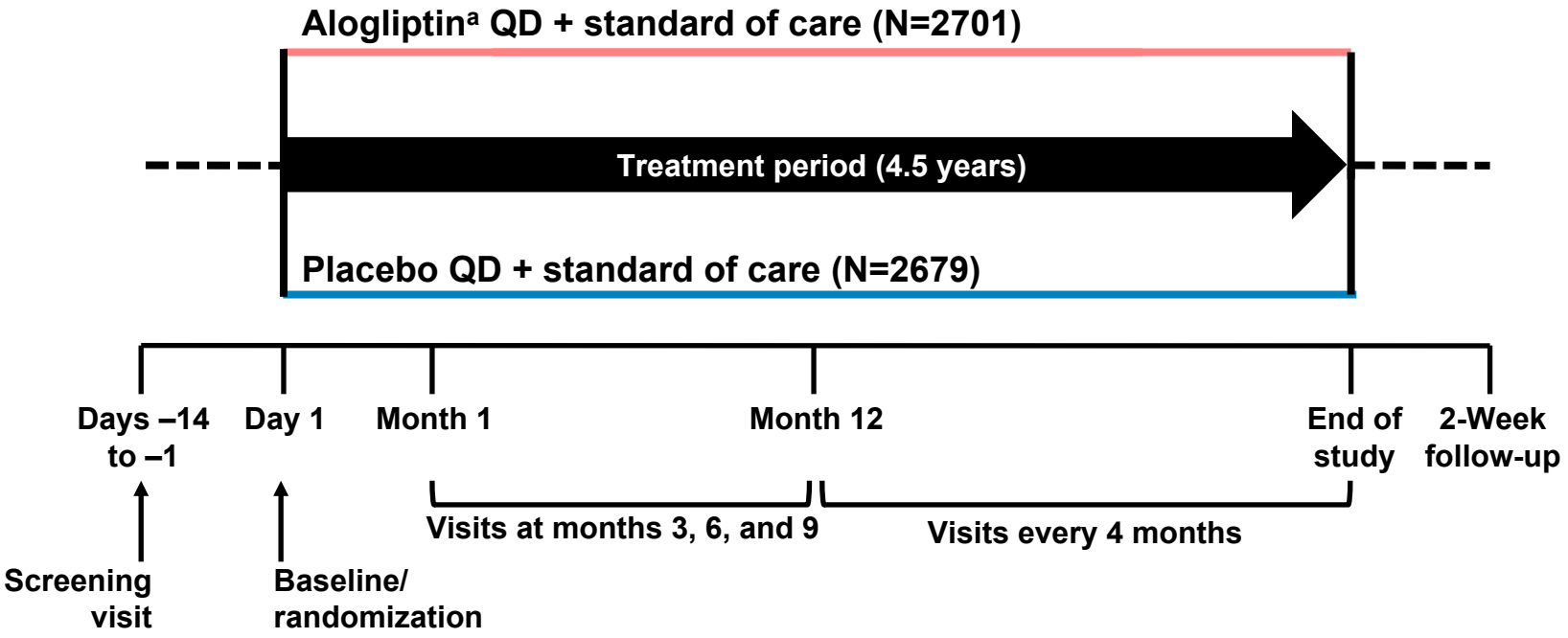
  Superiority assessment: If non-inferiority proven, to demonstrate that major CV event rates were lower on alogliptin than with placebo

  Secondary end point: Evaluate the time from randomization to the first occurrence of the expanded MACE:
  - Composite of CV death, nonfatal MI, nonfatal stroke, and urgent revascularization due to UA
- **Major exploratory end points**: all CV deaths, all-cause mortality

Abbreviations: ACS, acute coronary syndrome; CV, cardiovascular; MI, myocardial infarction; UA, unstable angina.

Study Design

- Randomized, double-blind, placebo-controlled study of alogliptin with diabetes standard of care versus placebo with diabetes and cardiovascular standard of care



Abbreviation: QD, once daily.

[a] At randomization, patients were assigned to receive 25, 12.5, or 6.25 mg QD based on renal function. After randomization, dose adjustments were allowed on the basis of changes in renal function.

White WB, et al. *Am Heart J*. 2011;162(4):620-626.

Study Patients

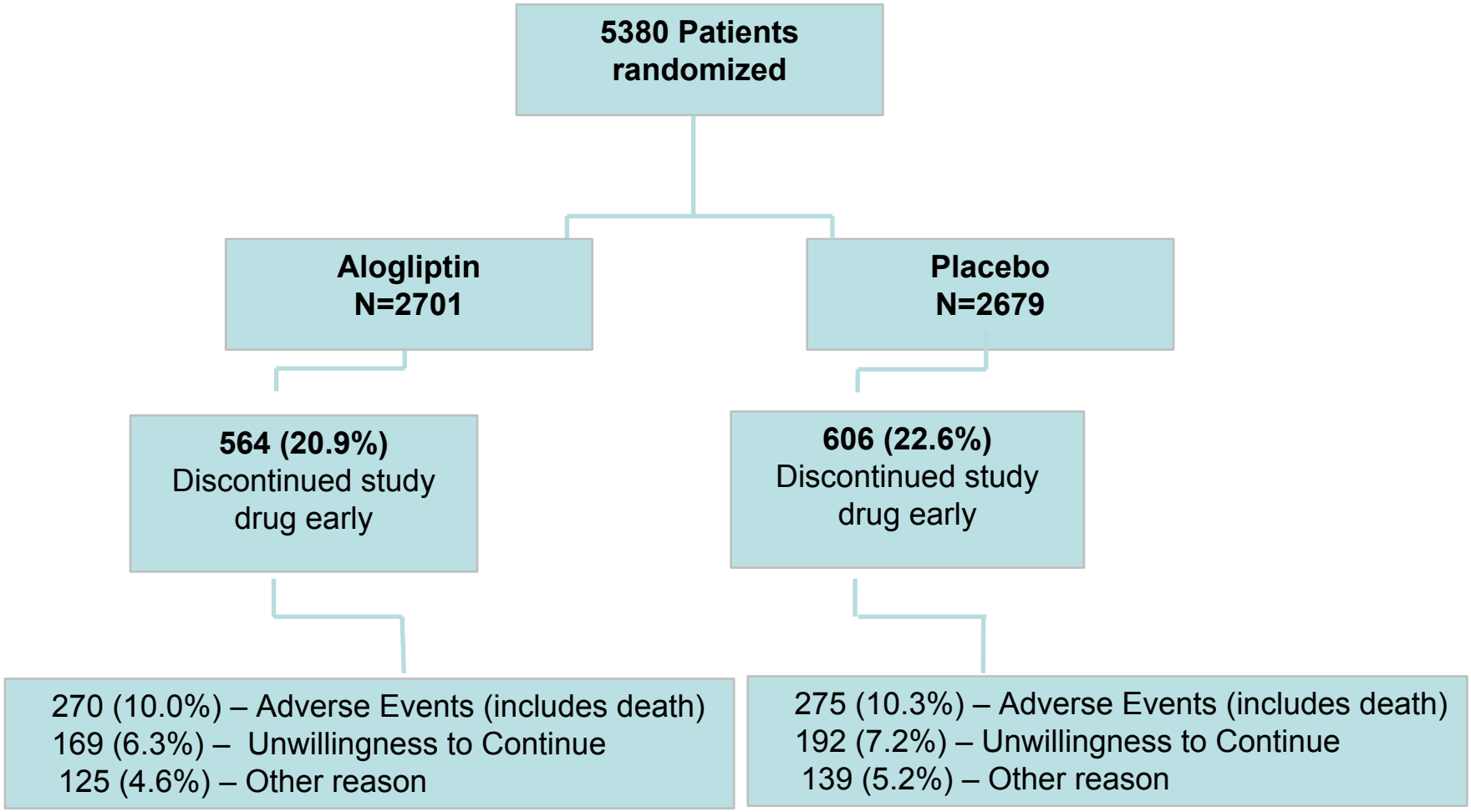
- Diagnosis of type 2 diabetes and receiving antihyperglycemic therapy (single or combination therapies)
- Acute coronary syndrome* within 15 to 90 days before randomization
- Receiving local standard of care for type 2 diabetes care and secondary CV prevention (excluded were DPP-4 inhibitors and GLP-1 agonists)
- Patients with unstable cardiovascular conditions or those on dialysis within 14 days of planned randomization were excluded

* Myocardial infarction or hospitalized unstable angina

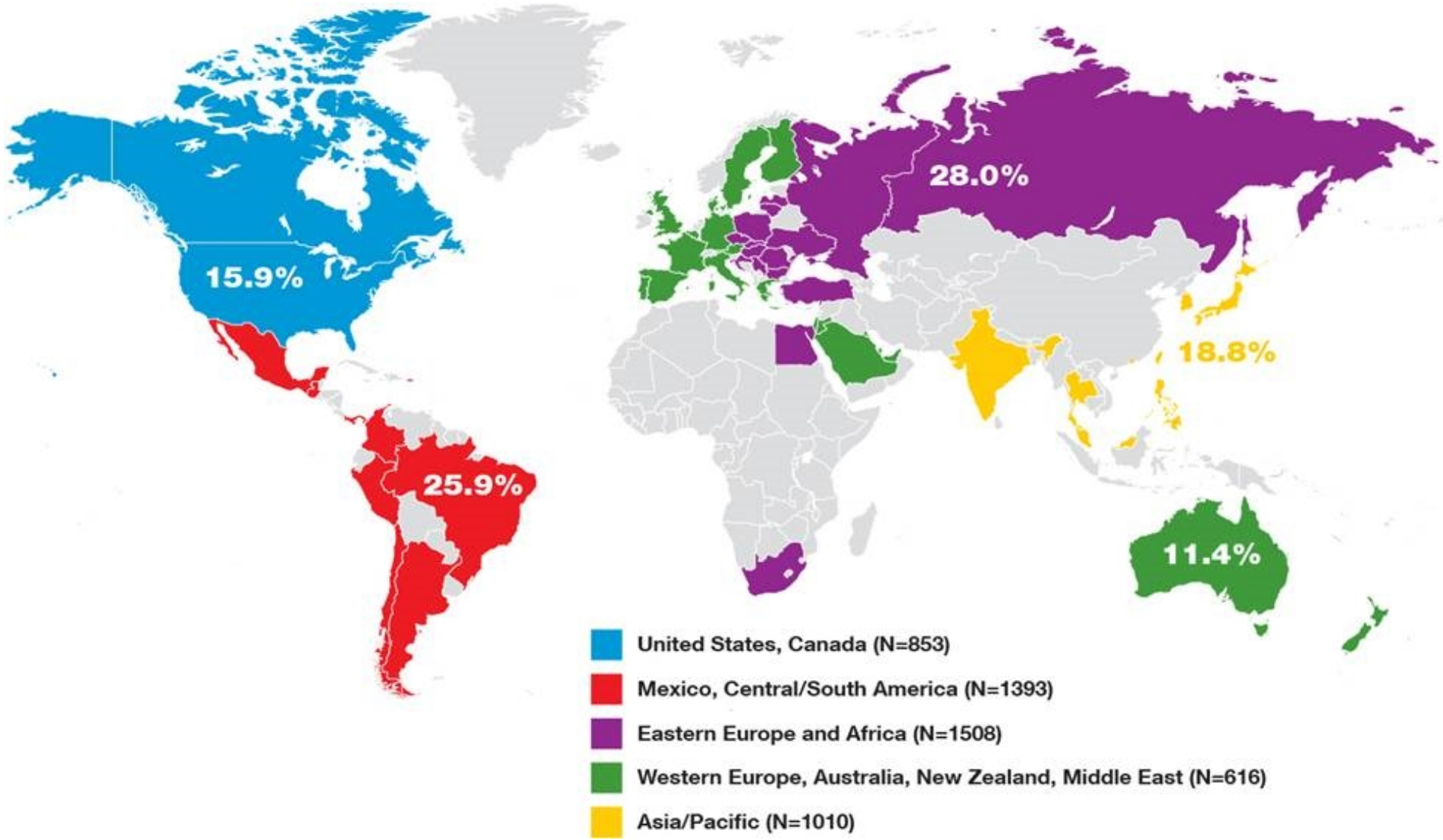
Statistical Analyses

- **Primary end point**
  - Cox proportional hazards (PH) model of time to primary endpoint stratified by geographic region and baseline renal function
    - One-sided repeated confidence interval (CI) for hazard ratio (HR) formed using critical value from pre-specified alpha-spending function
- **Secondary and major exploratory end points**
  - Cox PH model of time to endpoint stratified by geographic region and baseline renal function
    - Two-sided 95% CI calculated for HR of exploratory end points
    - One-sided repeated CI performed for secondary endpoint (expanded MACE)
- **Interim analyses for primary end point**
    - Initially performed to rule out upper bound of 1.8 (alpha = 0.002 [O'Brien-Fleming-type spending function]) at 83 events
    - Subsequently performed to rule out upper bound of 1.3 (alpha = 0.01) at 550 events

Disposition of Patients



Enrollment by Region (N=5380)



Baseline Patient Characteristics

EXAMINE

	Alogliptin (N=2701)	Placebo (N=2679)
Age		
Median, years	61.0	61.0
Patients ≥ 65 y, No. (%)	973 (36)	934 (35)
Sex		
Male, No (%)	1828 (68)	1823 (68)
Race, No. (%)		
White	1966 (73)	1943 (73)
Black	101 (4)	115 (4)
Asian	547 (20)	542 (20)
Other	87 (3)	79 (3)

Baseline Patient Characteristics (2)

	Alogliptin (N=2701)	Placebo (N=2679)
Duration of diabetes		
Median, years	7.1	7.3
BMI		
Median, kg/m^2	28.7	28.7
HbA_{1C} level		
Mean ± SD, %	8.0 ± 1.1	8.0 ± 1.1
Qualifying index ACS event for trial entry, No. (%)		
Myocardial infarction (MI)	2084 (77)	2068 (77)
Procedure-related MI	180 (7)	188 (7)
Unstable angina requiring hospitalization	609 (23)	605 (23)
Time from index ACS to randomization		
Median, days	44	46

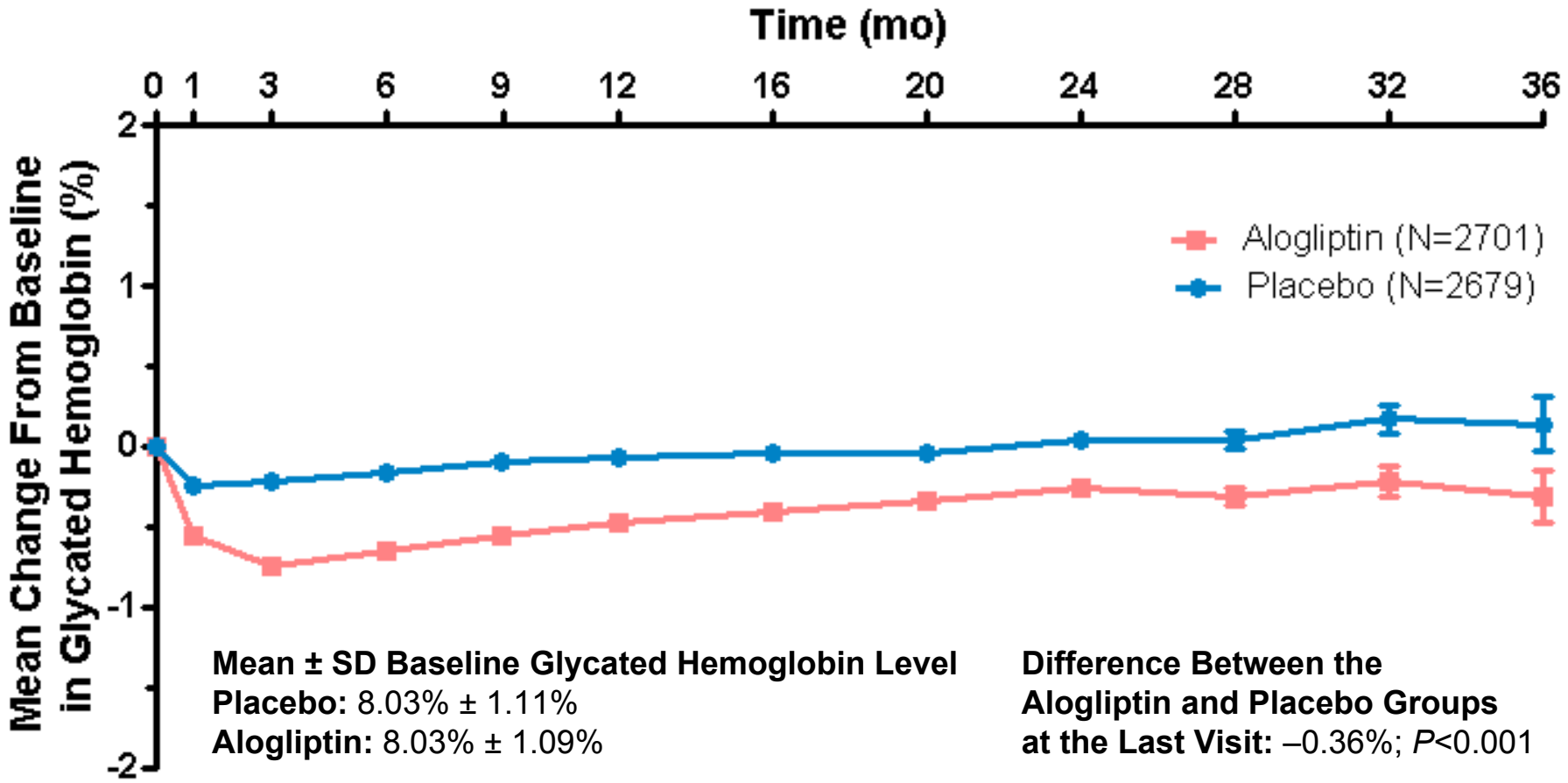
Baseline Cardiovascular Therapies

	Alogliptin (N=2701)	Placebo (N=2679)
Medications administered at baseline, No. (%)		
Antiplatelet agents	2630 (97)	2602 (97)
Aspirin	2448 (91)	2433 (91)
Thienopyridine	2155 (80)	2165 (81)
Statins	2446 (91)	2420 (90)
β-Blockers	2208 (82)	2203 (82)
Renin-angiotensin system blockers	2201 (82)	2210 (83)

Baseline Anti-hyperglycemic Therapies

	Alogliptin (N=2701)	Placebo (N=2679)
Medications administered at baseline, No. (%)		
All agents	**2676 (99)**	**2649 (99)**
Metformin	1757 (65)	1805 (67)
Sulfonylureas	1266 (47)	1237 (46)
Thiazolidinediones	67 (3)	64 (2)
Insulin	793 (29)	812 (30)

Change From Baseline in Glycated Hemoglobin

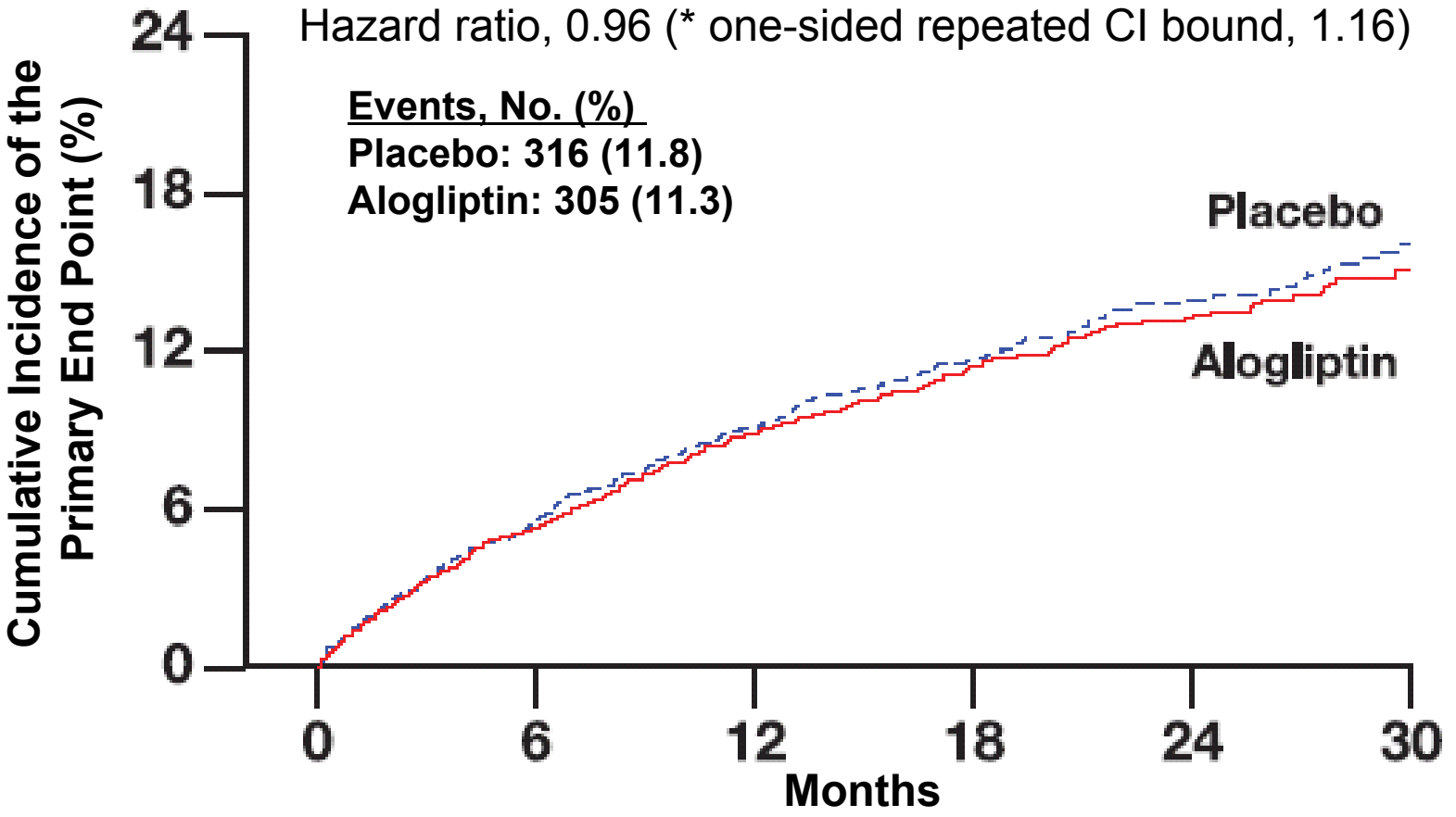


Mean ± SD Baseline Glycated Hemoglobin Level
Placebo: 8.03% ± 1.11%
Alogliptin: 8.03% ± 1.09%

Difference Between the Alogliptin and Placebo Groups at the Last Visit: –0.36%; *P*<0.001

Placebo (n):	2679	2583	2470	2299	2135	1932	1647	1320	986	593	283	82
Alogliptin (n):	2700	2613	2495	2332	2157	1952	1693	1349	984	611	271	81

Time to Primary End Point (CV Death, Nonfatal MI, Nonfatal Stroke)



Placebo (n):	2679	2299	1891	1375	805	286
Alogliptin (n):	2701	2316	1899	1394	821	296

* Using alpha=0.01.

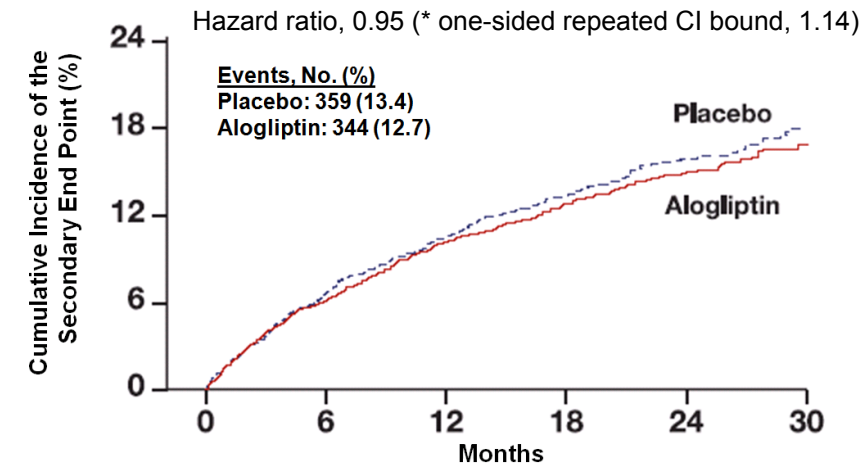
Primary End Point by Components

	Alogliptin (N=2701)	Placebo (N=2679)	Hazard Ratio for Alogliptin Group (95% CI)
Primary end point: CV death, nonfatal MI, or nonfatal stroke, No. (%)	**305 (11.3)**	**316 (11.8)**	**0.96 (≤1.16)***
CV death	89 (3.3)	111 (4.1)	0.79 (0.60, 1.04)
Nonfatal MI	187 (6.9)	173 (6.5)	1.08 (0.88, 1.33)
Nonfatal stroke	29 (1.1)	32 (1.2)	0.91 (0.55, 1.50)

*** 99% one-sided confidence interval, p < 0.001 for non-inferiority; p = 0.32 for superiority**

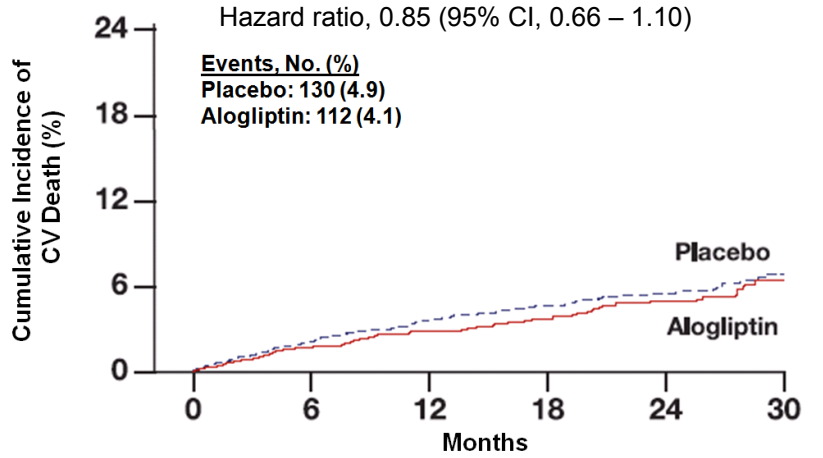
Other End Points

Secondary End Point



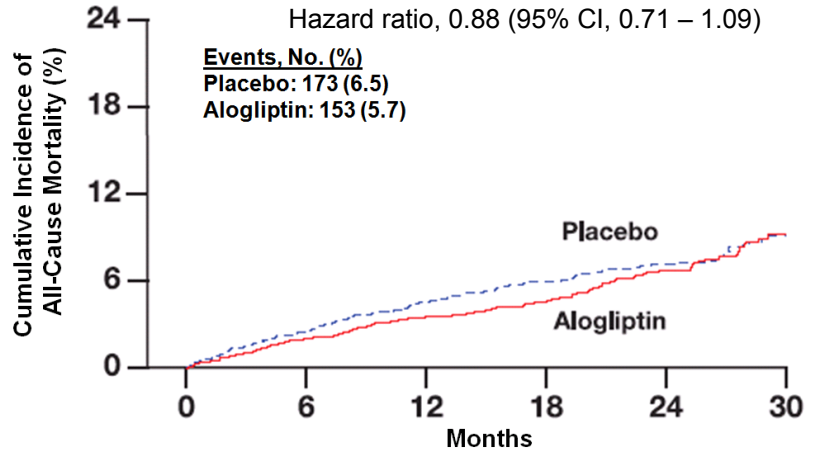
Placebo (n):	2679	2275	1861	1345	784	278
Alogliptin (n):	2701	2297	1873	1373	806	287

Any CV Death



Placebo (n):	2679	2384	1996	1477	889	324
Alogliptin (n):	2701	2402	2023	1504	894	320

All-Cause Mortality



Placebo (n):	2679	2384	1996	1477	889	324
Alogliptin (n):	2701	2401	2023	1504	894	320

* Using alpha=0.01.

Adverse Events of Special Interest

	Alogliptin (N=2701)	Placebo (N=2679)	*P* Value*
Patients, No. (%)			
Pancreatitis, acute	12 (0.4)	8 (0.3)	0.50
Pancreatitis, chronic	5 (0.2)	4 (0.1)	1.00
Angioedema	17 (0.6)	13 (0.5)	0.58
Malignancy Pancreatic cancer	55 (2.0) 0	51 (1.9) 0	0.77 -
Renal dialysis	24 (0.9)	22 (0.8)	0.88
Hypoglycemia†	181 (6.7)	173 (6.5)	0.74

* *P* values were calculated by Fisher exact test with no adjustment for multiple comparisons.
† Hypoglycemia was reported by site investigators.

Summary

- Rates of major adverse cardiovascular events were similar with alogliptin compared with placebo in patients with type 2 diabetes and recent acute coronary syndromes
- This observation occurred in the following context:
  - Significantly lower HbA_{1C} level (–0.36%) with alogliptin
  - High overall CV event rate (11% over the median follow-up of 18 months)
  - High levels of standard of care for both diabetes and cardiovascular prevention
- Outcomes were similar for the secondary end point (composite of CV death, nonfatal MI, nonfatal stroke, urgent revascularization due to UA)

Summary (2)

- Rates of cardiovascular and all-cause mortality were similar in the alogliptin and placebo groups
- Similar rates of withdrawal due to adverse events in the alogliptin and placebo groups
- Other adverse events of interest
  - No differences between alogliptin and placebo groups in
    - Incidence of Hypoglycemia
    - Reported malignancies (including pancreatic cancer)
    - Renal function
  - Low and similar frequencies of acute and chronic pancreatitis were observed

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ORIGINAL ARTICLE

Alogliptin after Acute Coronary Syndrome in Patients with Type 2 Diabetes

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Conclusion:

In patients with type 2 diabetes and recent acute coronary syndrome, major adverse cardiovascular event rates for the DPP-4 inhibitor alogliptin were not increased compared with placebo