# EXAMINE: Cardiovascular Outcome Trial of Alogliptin

Takeda Development Center Americas, Inc.

Endocrinologic and Metabolic Drugs
Advisory Committee Meeting

April 14, 2015

# Introduction

**Stuart Kupfer, MD**

Vice President
Clinical Science, Cardiovascular/Metabolic (CVM)

Takeda Development Center Americas, Inc.

# Agenda for Takeda Presentation

| | |
|---|---|
| **Introduction** | **Stuart Kupfer, MD**<br>Vice President, Clinical Science CVM<br>Takeda Development Center Americas, Inc. |
| **EXAMINE Study Results** | **William B. White, MD**<br>Chair, EXAMINE Steering Committee<br>Professor of Medicine<br>Calhoun Cardiology Center<br>University of Connecticut School of Medicine |
| **Clinical Perspective** | **Marc Pfeffer, MD, PhD**<br>Dzau Professor of Medicine, Harvard Medical School<br>Cardiovascular Division, Brigham & Women's Hospital |
| **Overall Safety and Conclusions** | **Stuart Kupfer, MD**<br>Vice President, Clinical Science CVM<br>Takeda Development Center Americas, Inc. |

# Additional EXAMINE Experts

| | |
|---|---|
| **George Bakris, MD** | Member, EXAMINE Steering Committee<br>Professor of Medicine<br>Director, ASH Comprehensive Hypertension Center<br>University of Chicago |
| **Kevin Carroll, PhD** | Independent Statistical Consultant<br>Honorary Senior Lecturer Sheffield University<br>Owner KJC Statistics Ltd. |
| **Venu Menon, MD** | Chair, Clinical Events Committee<br>Director CCU<br>Cleveland Clinic |
| **Richard Pratley, MD** | Director , Florida Hospital Diabetes Institute<br>Senior Scientist Florida Hospital Translational Research Institute<br>Samuel Crockett, Chair in Diabetes Research<br>Adjunct Professor, Sanford-Burnham Medical Research Institute |
| **Paul Watkins, MD** | Chair, Liver Safety Evaluation Committee<br>Director, Hamner–UNC Institute for Drug Safety Sciences<br>Verne S. Caviness Distinguished Professor of Medicine |

# Alogliptin Overview

- Alogliptin is a potent and highly selective DPP-4 inhibitor
- Over 17,000 type 2 diabetes (T2D) patients enrolled in Phase 2/3 clinical trials as monotherapy, as well as on a background of a broad range of commonly used anti-diabetic therapies
- Significant and clinically meaningful reductions of HbA1c compared to placebo (0.6 – 1.0%)
- Well tolerated with good benefit-risk profile
  - Common adverse reactions include nasopharyngitis, headache, and upper respiratory tract infection

# Regulatory History

- Alogliptin approved in over 40 countries worldwide including Japan (April 2010), US (January 2013) and EU (September 2013)
  - Adjunct to diet and exercise to improve glycemic control in adults with T2D
- EXAMINE pre-specified interim analysis provided support for US approval
- Also approved as fixed-dose combinations with pioglitazone and metformin

# Post-Marketing Requirements (PMR)

- Evaluate the effect of alogliptin on the incidence of major adverse cardiovascular events (MACE) in patients with T2D
  - Establish the upper bound of the 2-sided 95% confidence interval (CI) for the estimated MACE risk ratio comparing alogliptin to control group <1.3
- Study the long-term effects of alogliptin on hepatotoxicity, hypersensitivity reactions, serious hypoglycemia, pancreatitis, and renal safety

# EXAMINE Objectives

## Primary Objective

- To evaluate for non-inferiority of alogliptin versus placebo for the primary MACE composite, in patients with T2D and recent Acute Coronary Syndrome (ACS)

## Secondary Objectives

- To evaluate superiority of alogliptin versus placebo for the primary MACE composite
- To evaluate superiority of alogliptin versus placebo for the secondary MACE composite

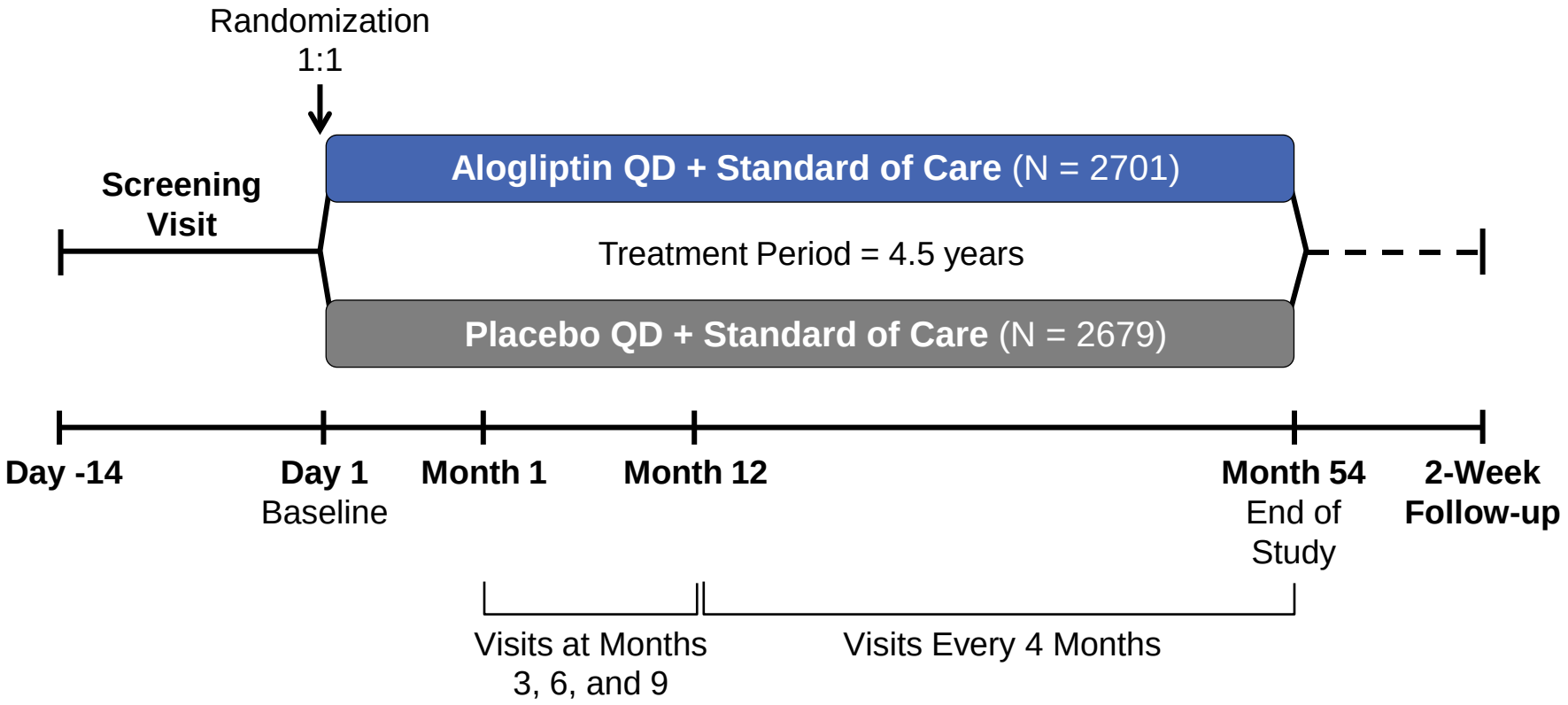
# Pre-Specified Composite Endpoints

| Time to first event of: | Primary MACE | Secondary MACE | Exploratory |
|---|---|---|---|
| CV death | ✓ | ✓ | |
| Nonfatal myocardial infarction (MI) | ✓ | ✓ | ✓ |
| Nonfatal stroke | ✓ | ✓ | ✓ |
| Urgent revascularization due to unstable angina | | ✓ | ✓ |
| All-cause mortality | | | ✓ |
| Hospitalization for heart failure (HHF) | | | ✓ |

# Study Patients

- T2D patients receiving antidiabetic mono or combination therapy (with the exception of any DPP-4 inhibitor or GLP-1 agonist)
- HbA1c between 6.5% and 11.0%
- High CV risk – diagnosed with ACS (acute myocardial infarction or unstable angina requiring hospitalization) within 15 to 90 days before randomization
- Included patients with mild, moderate, and severe renal impairment

# EXAMINE Study Design



# Statistical Analyses and Sample Size

**Primary Endpoint Analysis**

- Cox proportional hazards model of time to first event in the primary composite endpoint
  - Stratified by geographic region and baseline renal function
  - Estimated that a maximum 650 events required to rule out excess CV risk based on a non-inferiority margin of 1.3 with an interim analysis at 550 events

**Key Sample Size Assumptions**

- 5400 patients based on:
  - Estimated annual placebo event rate of 3.5%
  - 1% annual lost-to-follow-up rate
  - Estimated 3.3 year enrollment with 4.5 year trial duration
  - 91% power to detect non-inferiority

# Study Governance

## EXAMINE Steering Committee

**William B. White**, ***Chair*****,** Professor of Medicine, University of Connecticut

**Steven Nissen**, Professor of Medicine, Case Western Reserve University, Chairman, Department of Cardiovascular Medicine, Cleveland Clinic

**Faiez Zannad**, Professor of Cardiology and Therapeutics, Henri Poincaré University

**Richard Bergenstal**, Clinical Professor, University of Minnesota, Executive Director, Park Nicollet International Diabetes Center

**George Bakris**, Professor of Medicine, University of Chicago

**Simon Heller**, Professor of Clinical Diabetes, University of Sheffield

**William Cushman**, Professor of Preventive Medicine, University of Tennessee College of Medicine, Chief, Preventive Medicine Section, VA Memphis Medical Center

**Christopher Cannon**, Professor of Medicine, Harvard Medical School, Senior Physician, Brigham and Women's Hospital, Executive Director, HCRI, Harvard University

**Cyrus R. Mehta**, Adjunct Professor of Biostatistics, Harvard University

**Alfonso Perez**, Vice President, Takeda Clinical Science (non-voting member)

**Stuart Kupfer**, Vice President, Takeda Clinical Science (non-voting member)

# Study Governance

## Data Monitoring Committee (DMC)

**Vivian Fonseca**, ***Chair***, Professor of Medicine Chief, Section of Endocrinology, Tulane University

**Peter A. McCullough**, Vice Chief of Medicine, Cardiology, Baylor University Medical Center

**Cyrus Desouza**, Professor and Chief, Diabetes, Endocrinology & Metabolism University of Nebraska Medical Center

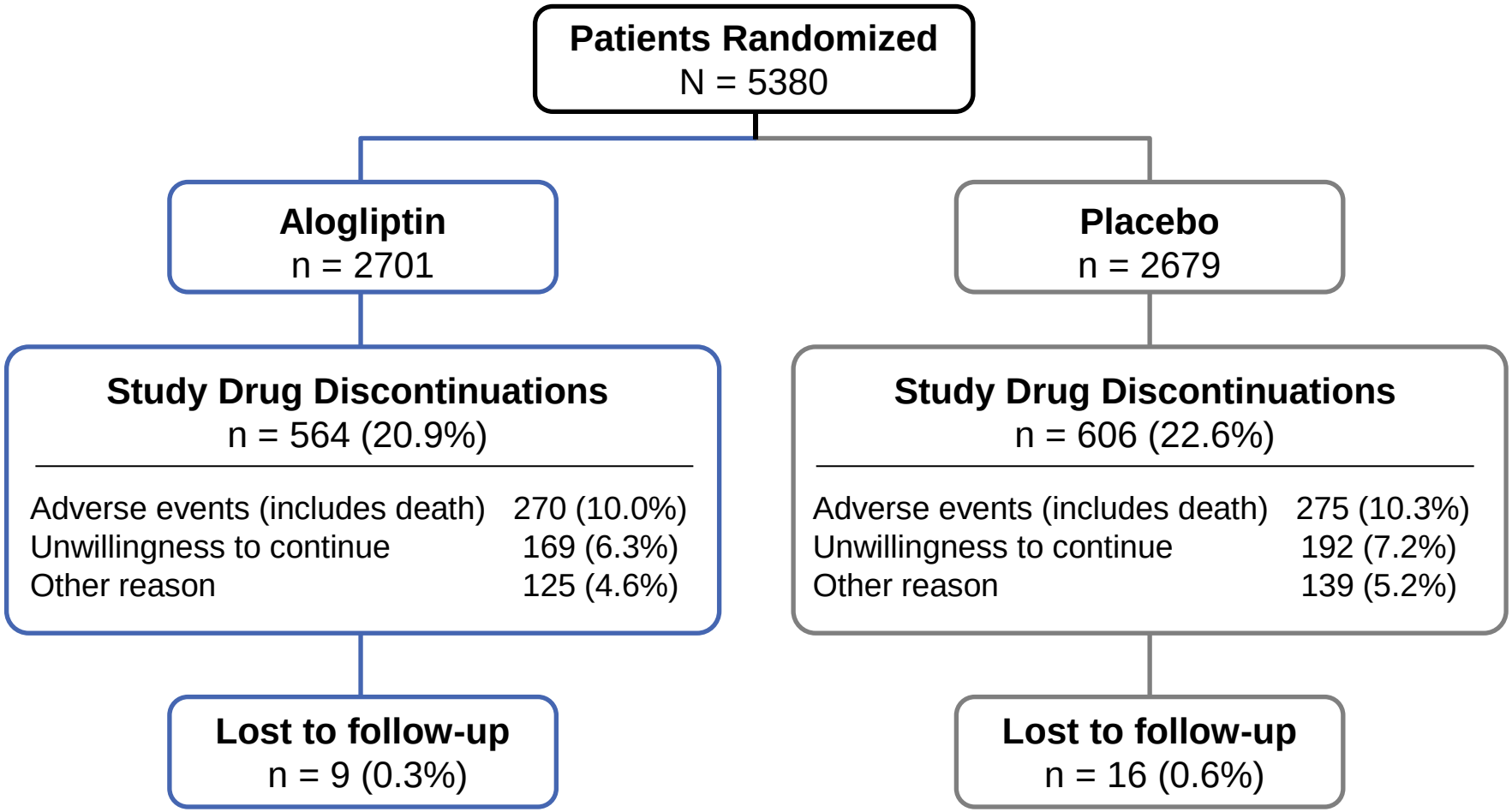
**David C Goff**, Professor of Public Health Sciences and Internal Medicine, Wake Forest University Health Sciences

**Frank Harrell**, Professor of Biostatistics & Chair, Department of Biostatistics, Vanderbilt University Department of Biostatistics

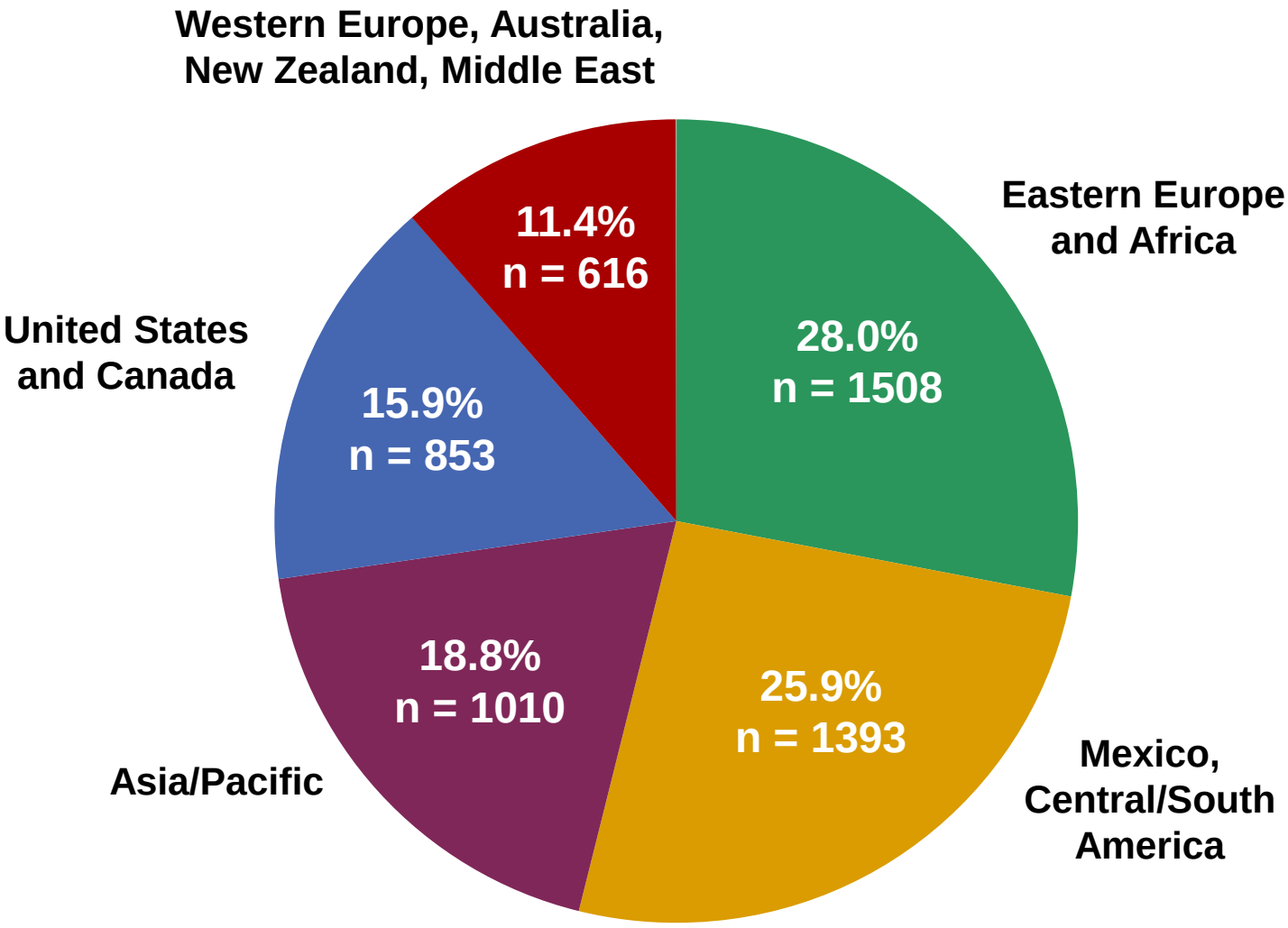
## Clinical Events Committee (CEC)

**Venu Menon**, ***Chair***, CEC Medical Director, Director of CCU Cleveland Clinic (C5 Research Group)

# Patient Disposition



# Enrollment by Region
# N = 5380



# Baseline Patient Characteristics

| | | Alogliptin N = 2701 | Placebo N = 2679 |
|---|---|---|---|
| Age | Median, years | 61.0 | 61.0 |
| | Patients ≥65 y, n (%) | 973 (36) | 934 (35) |
| Sex, n (%) | Male | 1828 (68) | 1823 (68) |
| Race, n (%) | White | 1966 (73) | 1943 (73) |
| | Black | 101 (4) | 115 (4) |
| | Asian | 547 (20) | 542 (20) |
| | Other | 87 (3) | 79 (3) |

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# Baseline Patient Characteristics

| | Alogliptin N = 2701 | Placebo N = 2679 |
|---|---|---|
| Median duration of diabetes, years | 7.1 | 7.3 |
| Median BMI, kg/m$^2$ | 28.7 | 28.7 |
| Mean HbA1c level (%) ±SD | 8.0 ± 1.1 | 8.0 ± 1.1 |
| Qualifying index ACS event for trial entry, n (%) | | |
| Myocardial infarction (MI) | 2084 (77) | 2068 (77) |
| Unstable angina requiring hospitalization | 609 (23) | 605 (23) |
| Median time from index ACS to randomization, days | 43 | 45 |
| Median eGFR*, mL/min/1.73 m$^2$ | 71 | 71 |
| ≥60 mL/min/1.73 m$^2$, n (%) | 1929 (71) | 1886 (70) |
| <60 mL/min/1.73 m$^2$, n (%) | 772 (29) | 793 (30) |

*Calculated using Modification of Diet in Renal Disease [MDRD] formula

# Cardiovascular History – High Risk Population



| | Alogliptin N = 2701 n (%) | Placebo N = 2679 n (%) |
|---|---|---|
| Myocardial infarction (MI)* | 2389 (88.4) | 2345 (87.5) |
| MI prior to index event | 801 (29.7) | 748 (27.9) |
| CABG | 347 (12.8) | 341 (12.7) |
| PCI | 1689 (62.5) | 1683 (62.8) |
| Hospitalization for unstable angina* | 815 (30.2) | 859 (32.1) |
| Cardiac arrhythmia | 383 (14.2) | 410 (15.3) |
| Peripheral artery disease | 262 (9.7) | 252 (9.4) |
| Congestive heart failure | 757 (28.0) | 744 (27.8) |
| Cerebrovascular accident | 195 (7.2) | 193 (7.2) |

*Includes index event

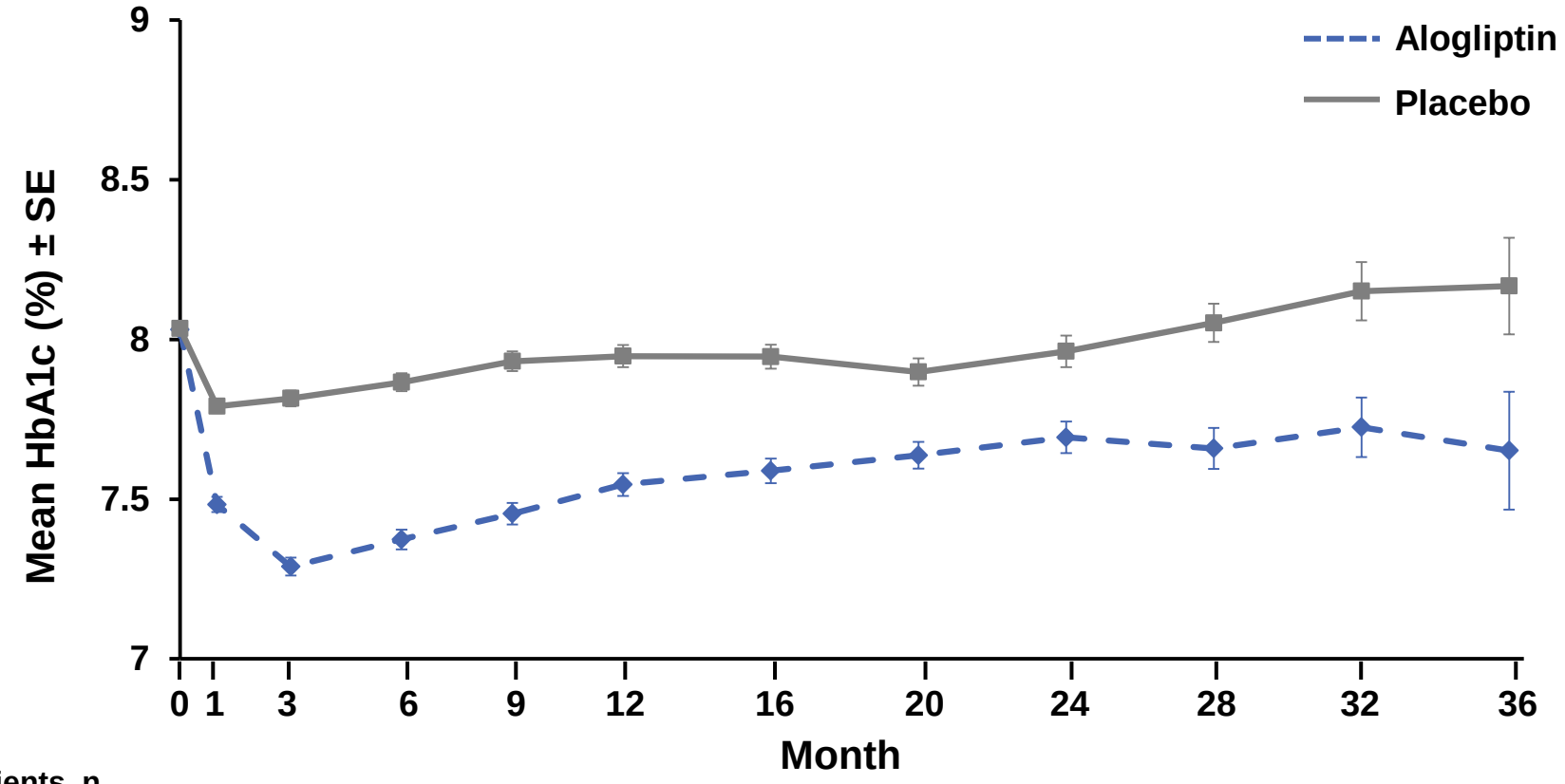
# Baseline Cardiovascular Therapies

| Medications Administered at Baseline, n (%) | Alogliptin N = 2701 | Placebo N = 2679 |
|---|---|---|
| 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) |
| Diuretics | 1005 (37) | 1009 (38) |
| Loop | 482 (18) | 458 (17) |
| Thiazide | 387 (14) | 415 (16) |

# Baseline Anti-Diabetic Therapies

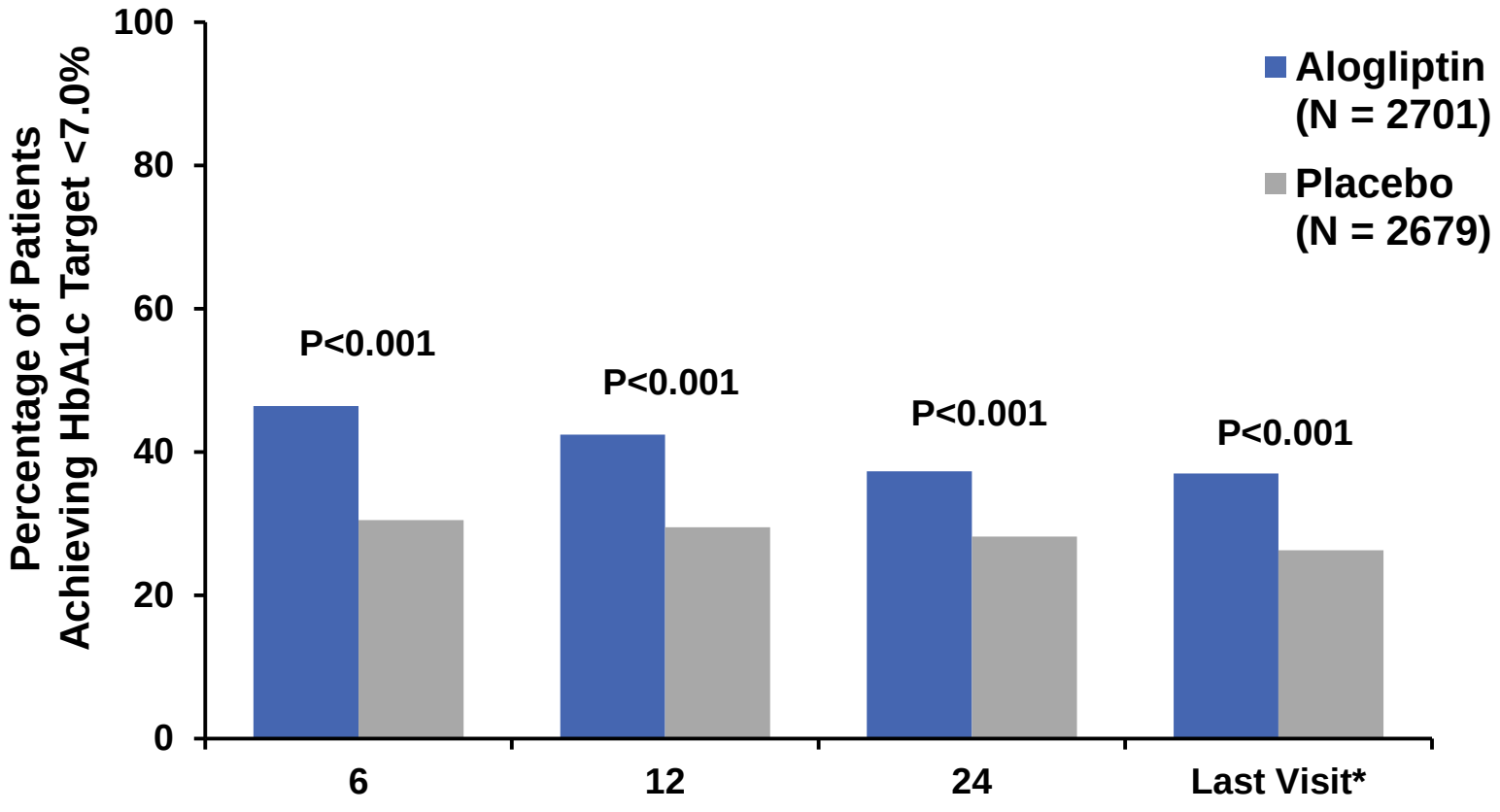
| Medications Administered at Baseline, n (%) | Alogliptin N = 2701 | Placebo N = 2679 |
|---|---|---|
| **All agents** | **2676 (99)** | **2649 (99)** |
| Metformin | 1757 (65) | 1805 (67) |
| Sulfonylureas | 1266 (47) | 1237 (46) |
| Insulin | 793 (29) | 812 (30) |
| Thiazolidinediones | 67 (3) | 64 (2) |
| **Receiving 2 or more agents** | **1192 (44)** | **1244 (46)** |

# HbA1c Levels Over Time




| Patients, n | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Alogliptin | 2700 | 2496 | 2332 | 2157 | 1952 | 1693 | 1349 | 984 | 611 | 271 | 81 |
| Placebo | 2679 | 2470 | 2299 | 2135 | 1932 | 1647 | 1320 | 986 | 593 | 283 | 82 |

# Achievement of HbA1c Target <7.0%




| Total Patients, N | | | | |
|---|---|---|---|---|
| Alogliptin | 2332 | 1952 | 984 | 2648 |
| Placebo | 2299 | 1932 | 986 | 2621 |

* The last visit includes all patients who had a final HbA1c level.

# Agenda for Takeda Presentation

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| **Clinical Perspective** | **Marc Pfeffer, MD, PhD**<br>Dzau Professor of Medicine, Harvard Medical School<br>Cardiovascular Division, Brigham & Women's Hospital |
| **Overall Safety and Conclusions** | **Stuart Kupfer, MD**<br>Vice President, Clinical Science CVM<br>Takeda Development Center Americas, Inc. |

# Cardiovascular Outcomes with Alogliptin in Patients with Type 2 Diabetes Mellitus and Acute Coronary Syndromes

**William B. White, MD**

Chair, EXAMINE Steering Committee and

Professor, Calhoun Cardiology Center,

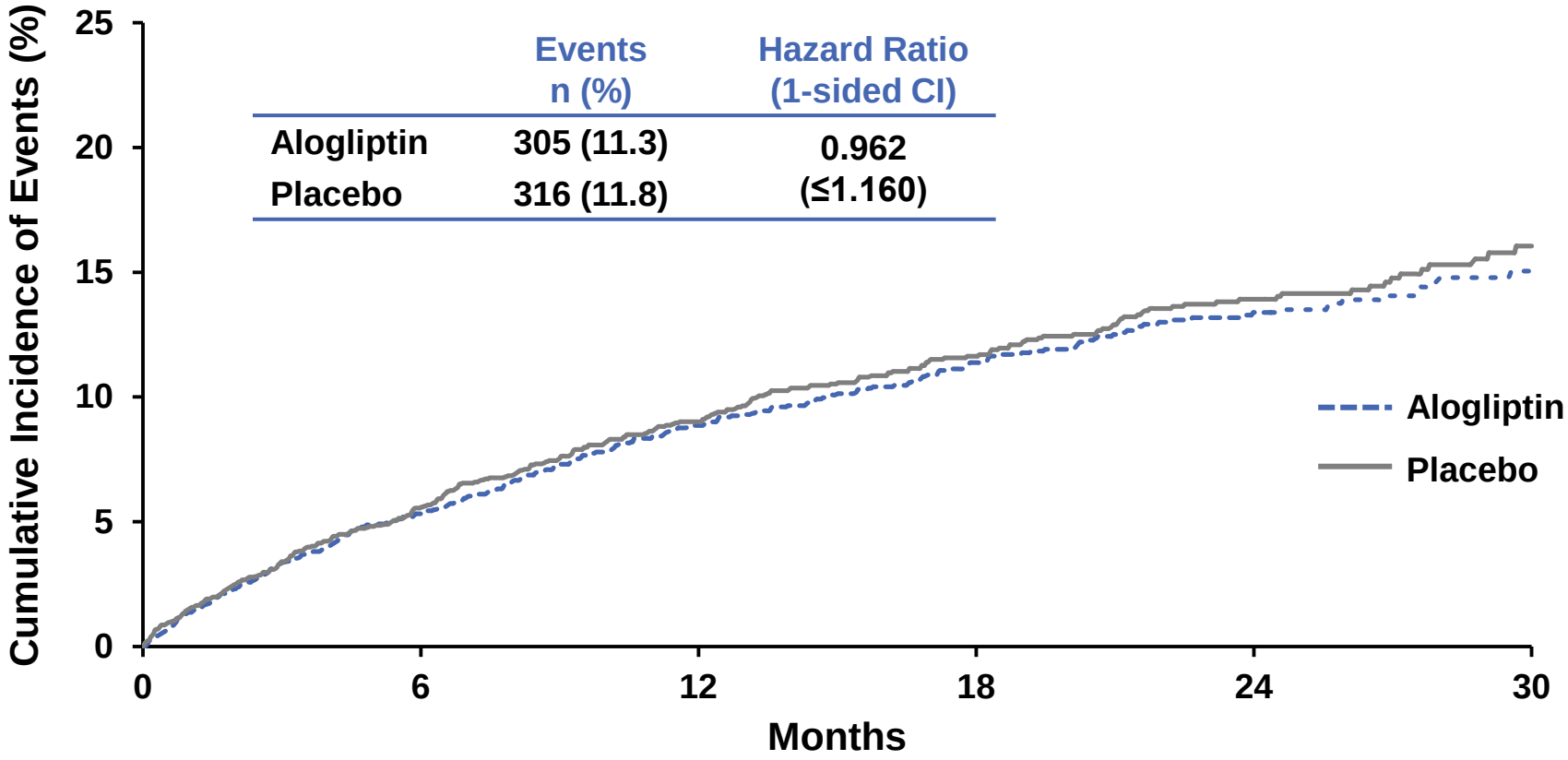
University of Connecticut School of Medicine, Farmington, CT

# Agenda for Cardiovascular Results

- Primary and Secondary Composite Endpoints
- Subgroup Analysis of Primary MACE
- Evaluation of Mortality
- Heart Failure Findings
  - Pre-specified analysis
  - Post-hoc analyses
- Summary

# Time to First Event in Primary MACE Composite Endpoint






| | Events n (%) | Hazard Ratio (1-sided CI) |
|---|---|---|
| Alogliptin | 305 (11.3) | 0.962 (≤1.160) |
| Placebo | 316 (11.8) | |

**No. at risk**

| | | | | | | |
|---|---|---|---|---|---|---|
| Alogliptin | 2701 | 2316 | 1899 | 1394 | 817 | 290 |
| Placebo | 2679 | 2299 | 1890 | 1375 | 803 | 282 |

*N Engl J Med*. 2013;369:1327-1335.

# Comparison Between Alogliptin and Placebo on Primary MACE and Components

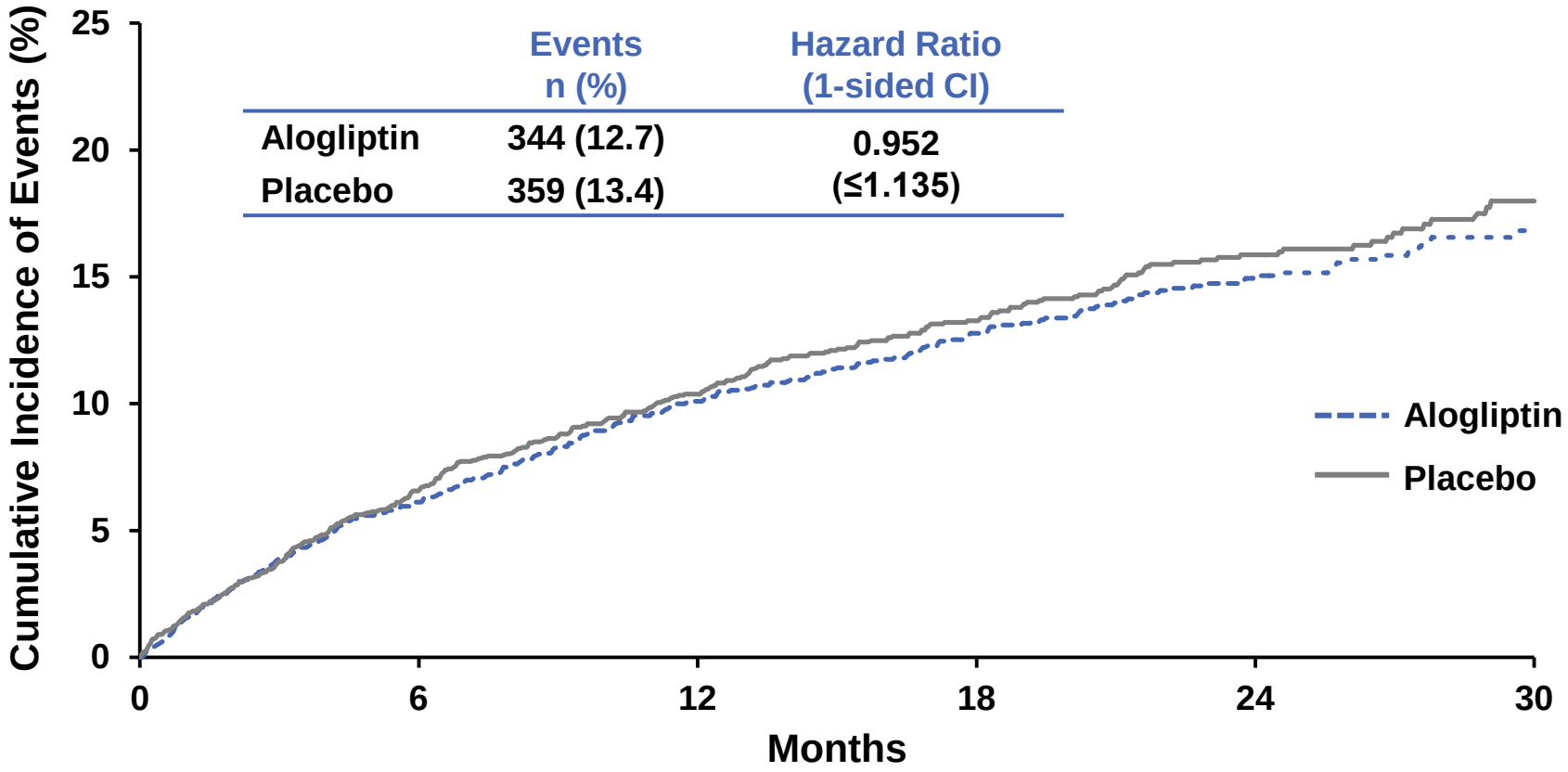
| | Alogliptin N = 2701 n (%) | Placebo N = 2679 n (%) | Hazard Ratio for Alogliptin Group (95% CI) |
|---|---|---|---|
| Primary end point: CV death, nonfatal MI, or nonfatal stroke | 305 (11.3) | 316 (11.8) | 0.962 (≤1.160)[a] |
| CV death | 89 (3.3) | 111 (4.1) | 0.790 (0.598, 1.044) |
| Nonfatal MI | 187 (6.9) | 173 (6.5) | 1.080 (0.878, 1.329) |
| Nonfatal stroke | 29 (1.1) | 32 (1.2) | 0.908 (0.550, 1.449) |

[a]99% 1-sided CI, P<0.001 for non-inferiority.

*N Engl J Med*. 2013;369:1327-1335.

# Time to First Event in the Secondary MACE Composite Endpoint*






| | Events n (%) | Hazard Ratio (1-sided CI) |
|---|---|---|
| Alogliptin | 344 (12.7) | 0.952 (≤1.135) |
| Placebo | 359 (13.4) | |

**No. at risk**

| | | | | | | |
|---|---|---|---|---|---|---|
| Alogliptin | 2701 | 2297 | 1873 | 1373 | 802 | 281 |
| Placebo | 2679 | 2275 | 1860 | 1356 | 783 | 274 |

*Includes CV death, nonfatal MI, nonfatal stroke, and urgent revascularization due to unstable angina.

*N Engl J Med*. 2013;369:1327-1335.

# Agenda for Cardiovascular Results

- Primary and Secondary Composite Endpoints
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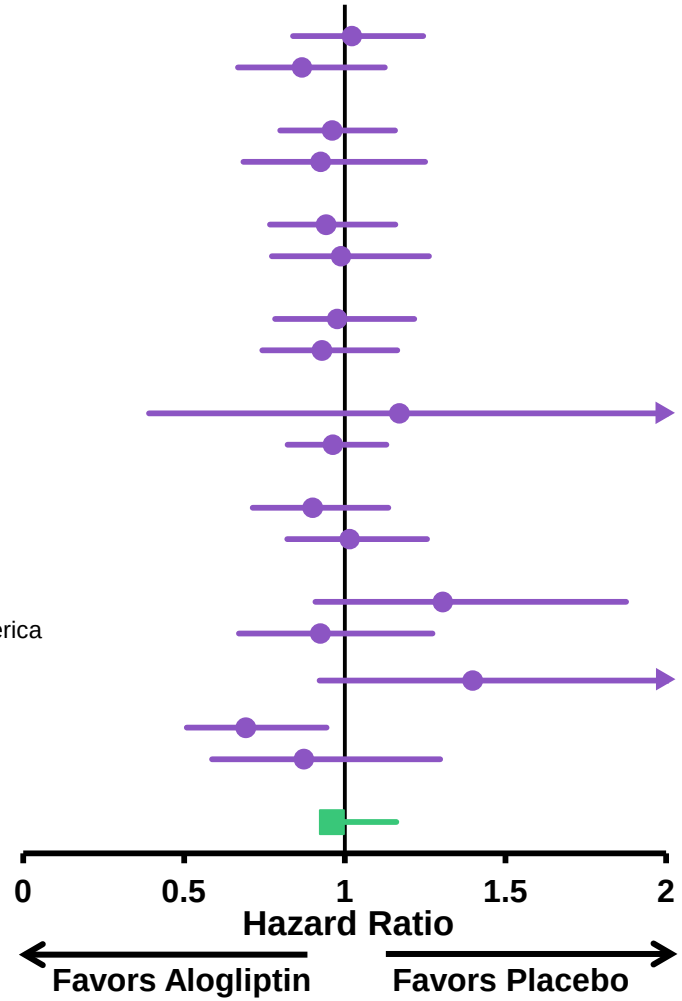
# Subgroup Analyses of Primary MACE (1)



| Subgroup | | Alogliptin n (%)[a] | Placebo n (%)[a] | P-value[b] |
|---|---|---|---|---|
| **Sex** | Male | 1828 (10.8) | 1823 (10.6) | 0.338 |
| | Female | 873 (12.3) | 856 (14.3) | |
| **Race** | White | 1966 (11.3) | 1943 (11.8) | 0.992 |
| | Non-white | 735 (11.3) | 736 (11.8) | |
| **Baseline BMI** | <30 kg/m$^2$ | 1565 (11.2) | 1606 (11.7) | 0.785 |
| | ≥30 kg/m$^2$ | 1136 (11.4) | 1072 (11.9) | |
| **Baseline $HbA_{1c}$** | <8% level | 1403 (11.0) | 1412 (11.5) | 0.805 |
| | ≥8% level | 1297 (11.6) | 1267 (12.1) | |
| **Thiazolidinedione use at Baseline** | Yes | 67 (10.4) | 64 (12.5) | 0.870 |
| | No | 2634 (11.3) | 2615 (11.8) | |
| **Sulfonylurea use at Baseline** | Yes | 1266 (10.7) | 1237 (12.0) | 0.472 |
| | No | 1435 (11.8) | 1442 (11.7) | |
| **Geographic region** | US, Canada | 427 (15.5) | 426 (12.4) | 0.034 |
| | Mexico, Central/South America | 700 (10.3) | 693 (11.1) | |
| | West. Europe, Australia, New Zealand, Middle East | 313 (16.6) | 303 (12.5) | |
| | Eastern Europe, Africa | 755 (9.1) | 753 (12.7) | |
| | Asia/Pacific | 506 (9.1) | 504 (10.3) | |
| **Overall MACE** | | | | |

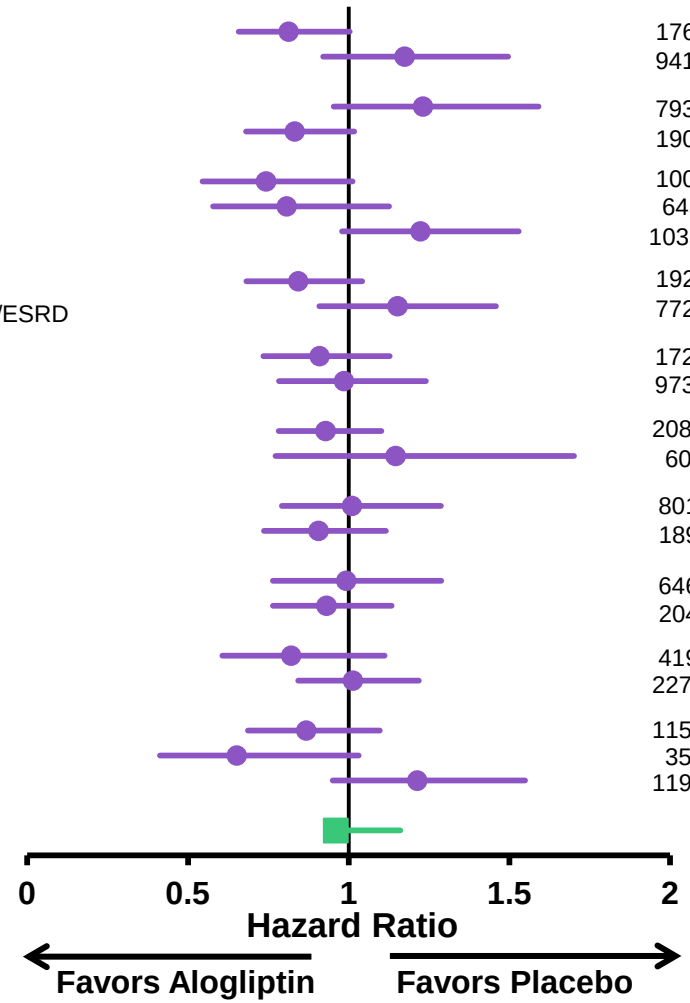



[a]N = total number of patients in subgroup, % = percent of patients with an event within the subgroup. [b]Treatment interaction p-value.

# Subgroup Analyses of Primary MACE (2)



| Subgroup | | Alogliptin n (%)[a] | Placebo n (%)[a] | P-value[b] |
|---|---|---|---|---|
| **Biguanide use at baseline** | Yes | 1760 (8.8) | 1808 (10.9) | 0.029 |
| | No | 941 (16.0) | 871 (13.7) | |
| **Insulin use at Baseline** | Yes | 793 (16.1) | 812 (13.3) | 0.018 |
| | No | 1908 (9.3) | 1867 (11.1) | |
| **Duration of diabetes** | <5 years | 1009 (7.0) | 973 (9.7) | 0.014 |
| | ≥5 to <10 years | 645 (9.6) | 665 (11.9) | |
| | ≥10 years | 1035 (16.5) | 1032 (13.8) | |
| **Baseline renal function (MDRD)** | Normal or mild impairment | 1929 (8.3) | 1886 (9.8) | 0.046 |
| | Mod to severe impairment/ESRD | 772 (18.8) | 793 (16.6) | |
| **Baseline age** | <65 years | 1728 (9.1) | 1745 (9.9) | 0.570 |
| | ≥65 years | 973 (15.1) | 934 (15.3) | |
| **Index event** | MI | 2084 (12.1) | 2068 (13.0) | 0.323 |
| | Unstable angina | 609 (8.7) | 605 (7.8) | |
| **History of MI before index event** | Yes | 801 (17.1) | 748 (17.0) | 0.478 |
| | No | 1892 (8.9) | 1925 (9.8) | |
| **History of PCI or CABG before index event** | Yes | 646 (17.6) | 628 (17.7) | 0.692 |
| | No | 2047 (9.3) | 2045 (10.0) | |
| **History of CHF before index event** | Yes | 419 (18.1) | 404 (22.3) | 0.251 |
| | No | 2274 (10.1) | 2269 (10.0) | |
| **Smoking status** | Never smoked | 1158 (11.5) | 1144 (13.5) | 0.029 |
| | Current smoker | 351 (8.0) | 383 (12.0) | |
| | Ex-smoker | 1192 (12.1) | 1152 (10.1) | |
| **Overall MACE** | | | | |



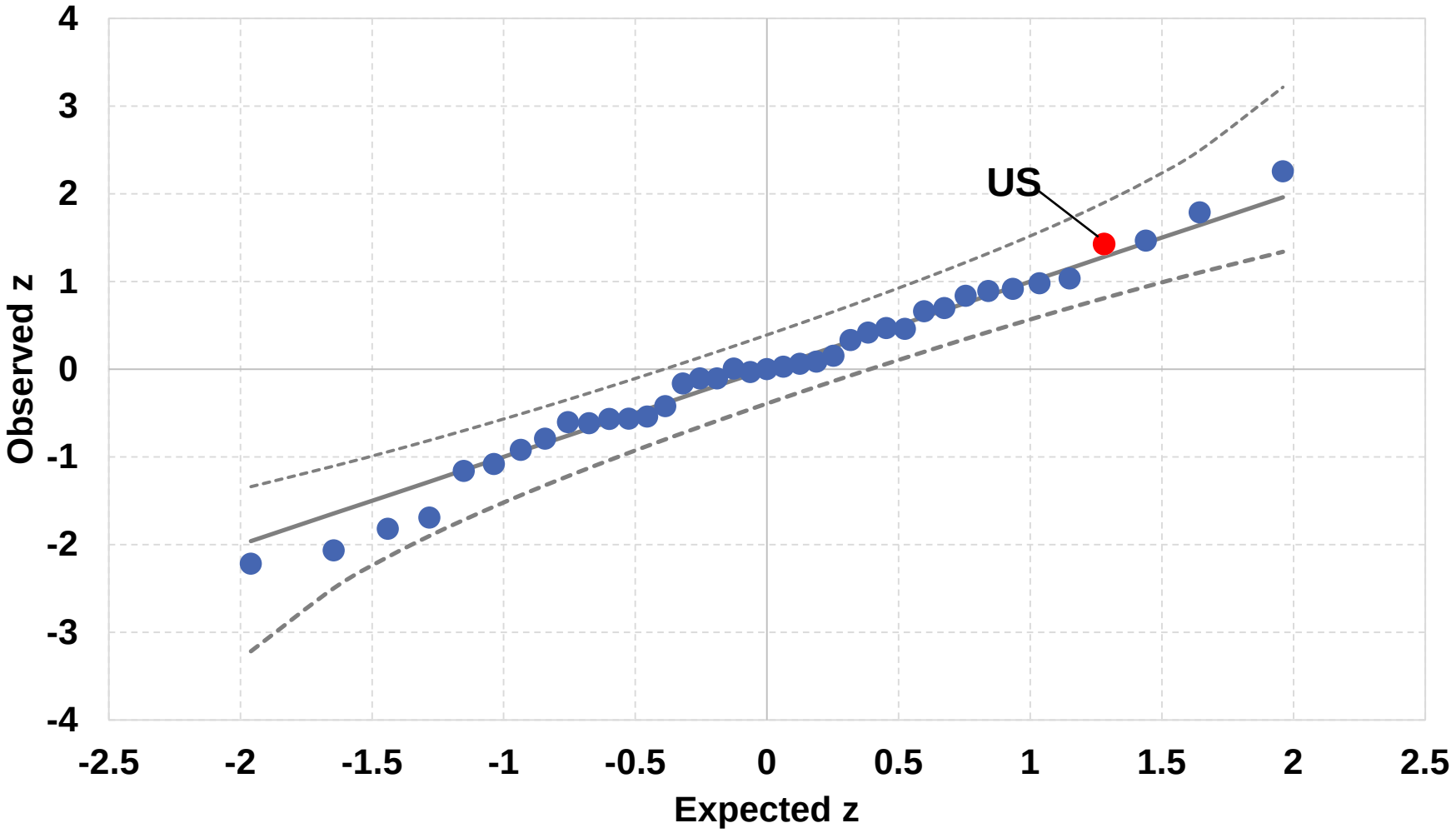

[a]N = total number of patients in subgroup, % = percent of patients with an event within the subgroup. [b]Treatment interaction p-value.

# Further Analysis of Geographic Region Interaction



- No baseline imbalances or treatment interactions with any of the CV risk factors explained the observation
- No differences in study conduct by region explained the observation
- Analysis by individual countries performed to determine if the interaction could be a result of random chance

# Normal Probability Plot by Country



# Summary of Subgroup Analyses

- EXAMINE was designed and powered to evaluate non-inferiority of the overall MACE composite; subgroup analyses performed to explore consistency of primary endpoint
- Heterogeneity was observed in some subgroups
  - When adjusted for multiplicity no subgroup interaction remained significant
  - No individual baseline factor was responsible for geographic region differences
- These additional analyses suggest findings are consistent with random variation

# Agenda for Cardiovascular Results

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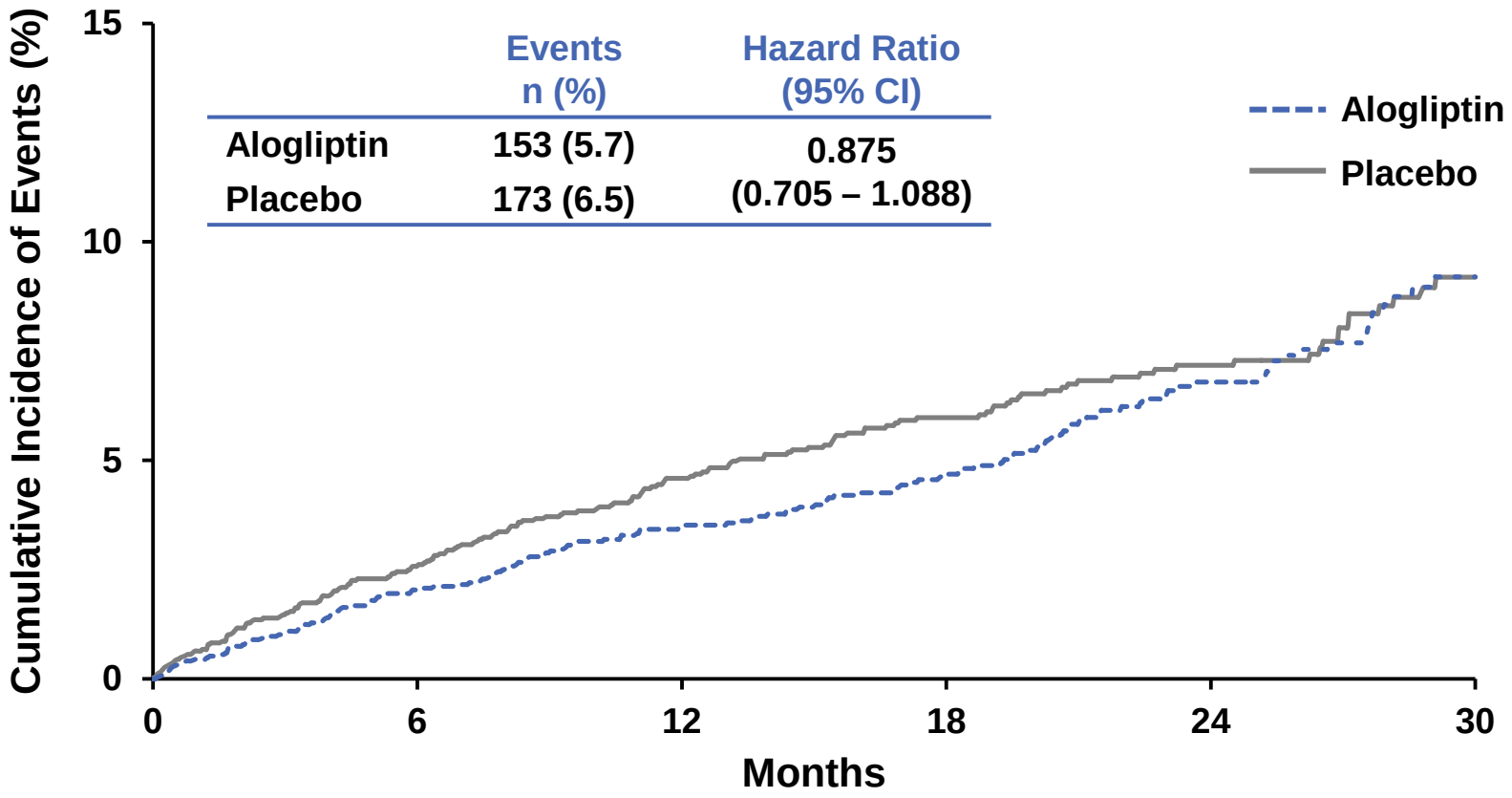
# Time to All-Cause Mortality



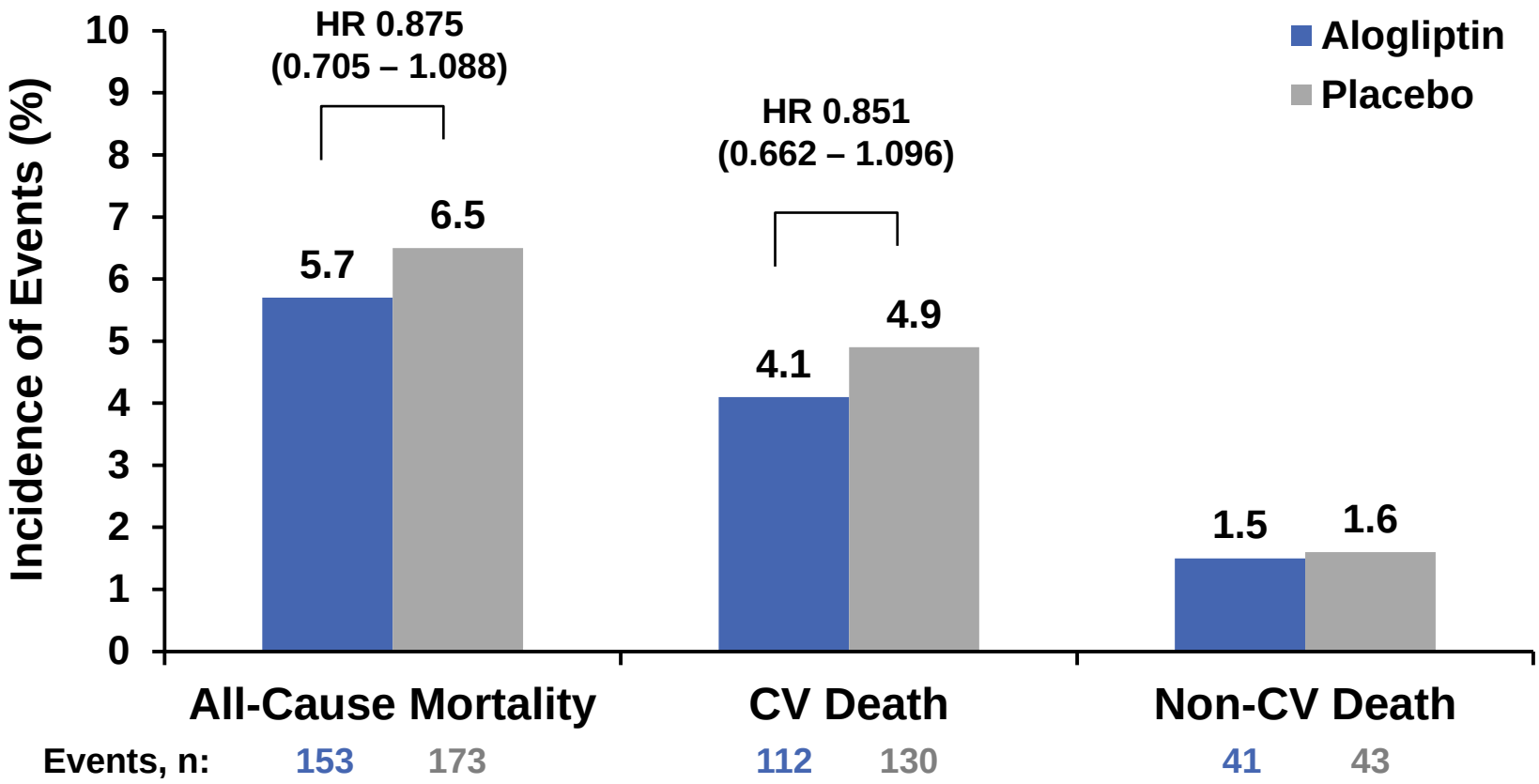

| | Events n (%) | Hazard Ratio (95% CI) |
|---|---|---|
| Alogliptin | 153 (5.7) | 0.875 (0.705 – 1.088) |
| Placebo | 173 (6.5) | |

**No. at risk**

| | | | | | | |
|---|---|---|---|---|---|---|
| Alogliptin | 2701 | 2401 | 2023 | 1504 | 891 | 314 |
| Placebo | 2679 | 2384 | 1995 | 1477 | 887 | 320 |

*N Engl J Med*. 2013;369:1327-1335.

# Overview of Mortality



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# Pre-Specified Composite Endpoint with Hospitalization for Heart Failure (HHF)

| Time to first event of: | Primary MACE | Secondary MACE | Exploratory |
|---|---|---|---|
| CV death | ✓ | ✓ | |
| Nonfatal myocardial infarction (MI) | ✓ | ✓ | ✓ |
| Nonfatal stroke | ✓ | ✓ | ✓ |
| Urgent revascularization due to unstable angina | | ✓ | ✓ |
| All-cause mortality | | | ✓ |
| HHF | | | ✓ |

# Results for the Pre-Specified Composite Endpoint that Included HHF



- Time to first event of all-cause mortality, nonfatal MI, nonfatal stroke, urgent revascularization due to UA, HHF

| | Alogliptin N = 2701 n (%) | Placebo N = 2679 n (%) | Hazard Ratio for Alogliptin Group (95% CI) | P-value |
|---|---|---|---|---|
| **Exploratory Endpoint: Composite** | **433 (16.0)** | **441 (16.5)** | **0.977 (0.856 – 1.115)** | **0.728** |
| All-cause mortality | 106 (3.9) | 131 (4.9) | 0.797 (0.617 – 1.029) | 0.081 |
| Nonfatal MI | 171(6.3) | 155 (5.8) | 1.100 (0.884 – 1.367) | 0.393 |
| Nonfatal stroke | 28 (1.0) | 29 (1.1) | 0.967 (0.575 – 1.624) | 0.898 |
| Urgent revascularization due to unstable angina | 43 (1.6) | 47 (1.8) | 0.904 (0.598 – 1.366) | 0.632 |
| HHF | 85 (3.1) | 79 (2.9) | 1.072 (0.789 – 1.456) | 0.657 |

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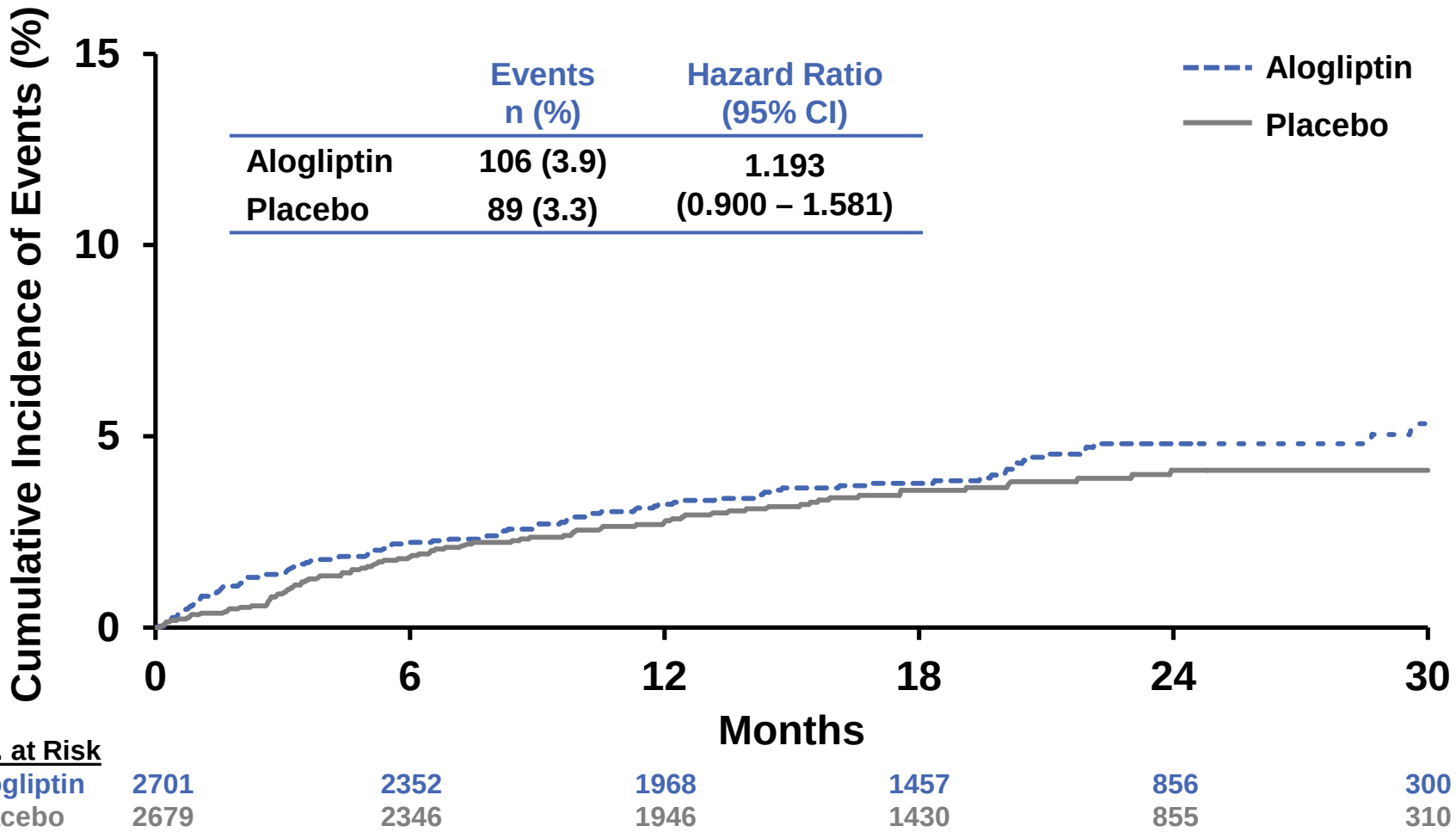
- Summary

# Time to First Event of HHF




| | Events n (%) | Hazard Ratio (95% CI) |
|---|---|---|
| Alogliptin | 106 (3.9) | 1.193 (0.900 – 1.581) |
| Placebo | 89 (3.3) | |

**No. at Risk**

| | | | | | | |
|---|---|---|---|---|---|---|
| Alogliptin | 2701 | 2352 | 1968 | 1457 | 856 | 300 |
| Placebo | 2679 | 2346 | 1946 | 1430 | 855 | 310 |

# Initial and Recurrent Events of HHF

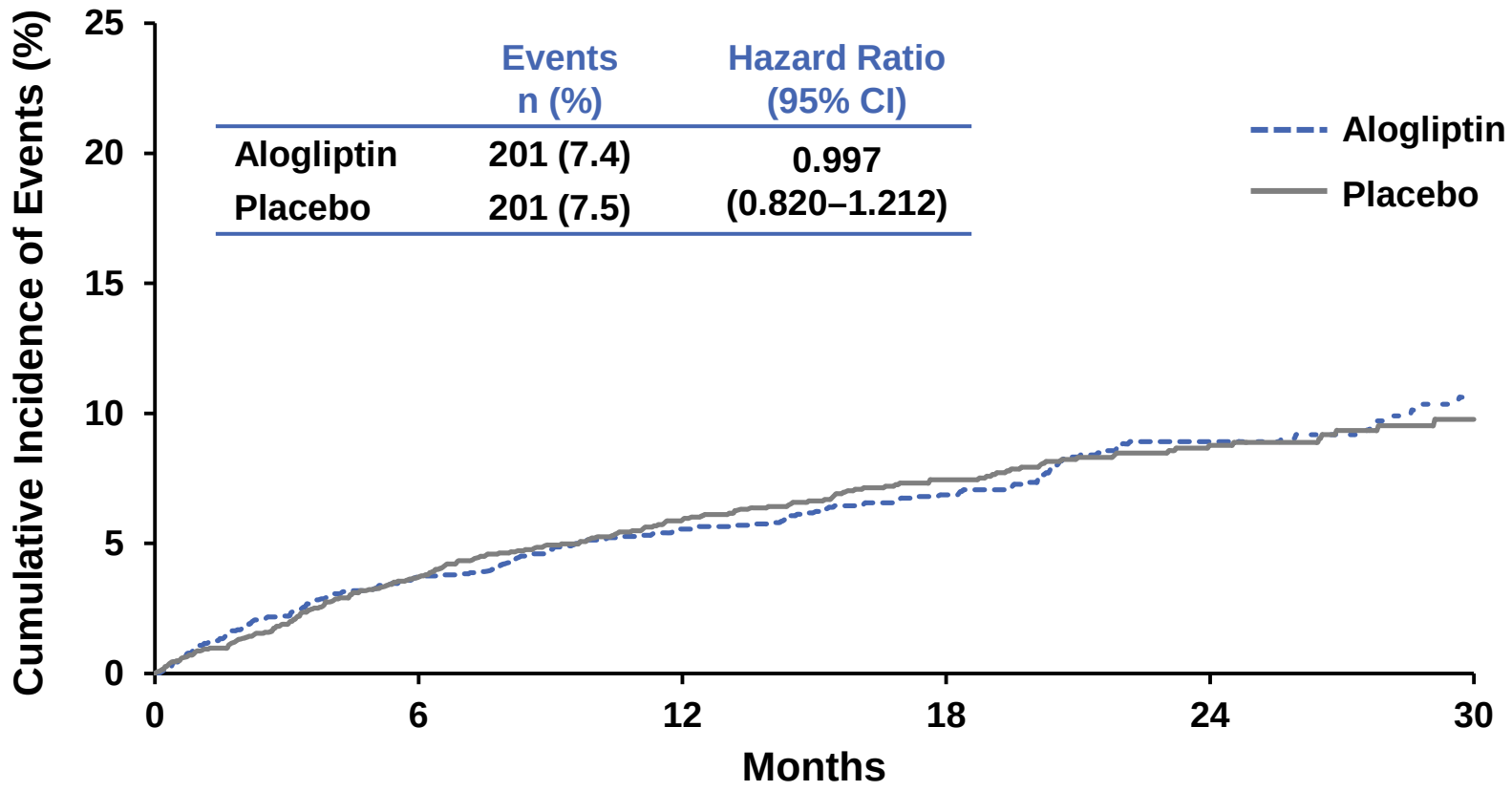
| | Alogliptin N = 2701 | Placebo N = 2679 |
|---|---|---|
| **Number of events that met the criteria for HHF** | **163[a]** | **136** |
| Number of patients HHF | 106 | 89 |
| Number of patients with 2 or more events of HHF (total events) | 32 (87 events) | 28 (75 events) |
| **Andersen-Gill Model[b]** | **HR: 1.185 (0.939, 1.495) P=0.153** | |

[a]Two events of HHF occurred prior to randomization and were not included in the analysis.

[b]Recurrent events of HHF were fit using the Andersen-Gill model with treatment as the single factor, stratified by screening renal function and geographic region.

# Time to First Event in Composite Endpoint of CV Death and HHF






| | Events n (%) | Hazard Ratio (95% CI) |
|---|---|---|
| Alogliptin | 201 (7.4) | 0.997 (0.820–1.212) |
| Placebo | 201 (7.5) | |

| No. at risk | | | | | | |
|---|---|---|---|---|---|---|
| Alogliptin | 2701 | 2352 | 1968 | 1457 | 866 | 300 |
| Placebo | 2679 | 2346 | 1946 | 1430 | 855 | 310 |

# Baseline Characteristics by History of Heart Failure (HF)



| | With History of HF | | No History of HF | |
|---|---|---|---|---|
| | Alogliptin N = 771 | Placebo N = 762 | Alogliptin N = 1930 | Placebo N = 1917 |
| Median age, years | 63 | 62 | 60 | 60 |
| Age ≥65 years, % | 43.7 | 40.0 | 33.0 | 32.8 |
| Male, % | 60.6 | 60.9 | 70.5 | 70.9 |
| Race, % | | | | |
| White | 82.2 | 79.3 | 69.0 | 69.8 |
| Black | 5.1 | 5.2 | 3.2 | 3.9 |
| Asian | 10.8 | 14.0 | 24.0 | 22.7 |
| Median duration of diabetes, years | 7.9 | 6.8 | 6.8 | 7.3 |
| Median NT-proBNP, pg/mL | 699 | 630 | 376 | 340 |
| Mean HbA1c, % | 8.1 | 8.2 | 8.0 | 8.0 |
| Median eGFR, mL/min/1.73 $m^2$ [a] | 66.4 | 65.0 | 72.7 | 73.2 |
| ≥60 mL/min/1.73 $m^2$, % | 62.5 | 59.6 | 75.0 | 74.7 |
| <60 mL/min/1.73 $m^2$, % | 37.5 | 40.4 | 25.0 | 25.3 |

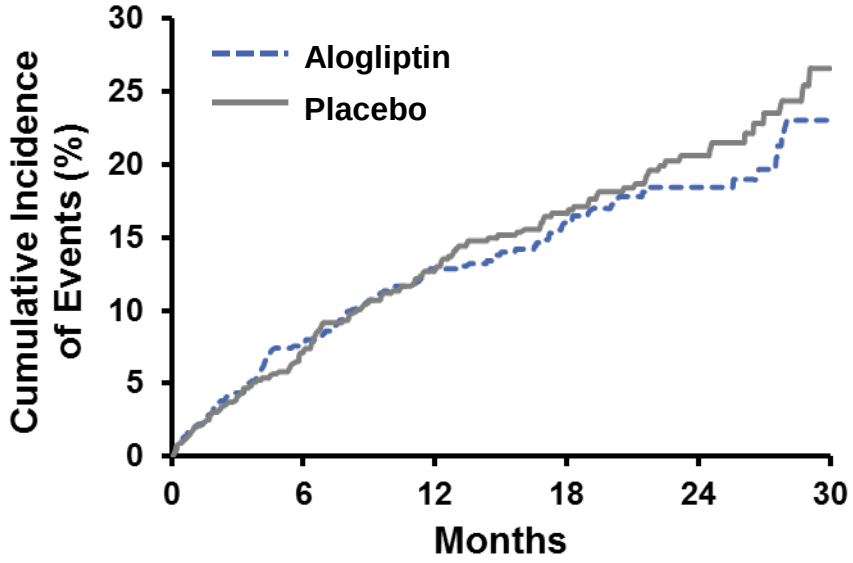
[a]Calculated by the MDRD formula.

# Primary MACE by History of Heart Failure



## Patients With History of HF

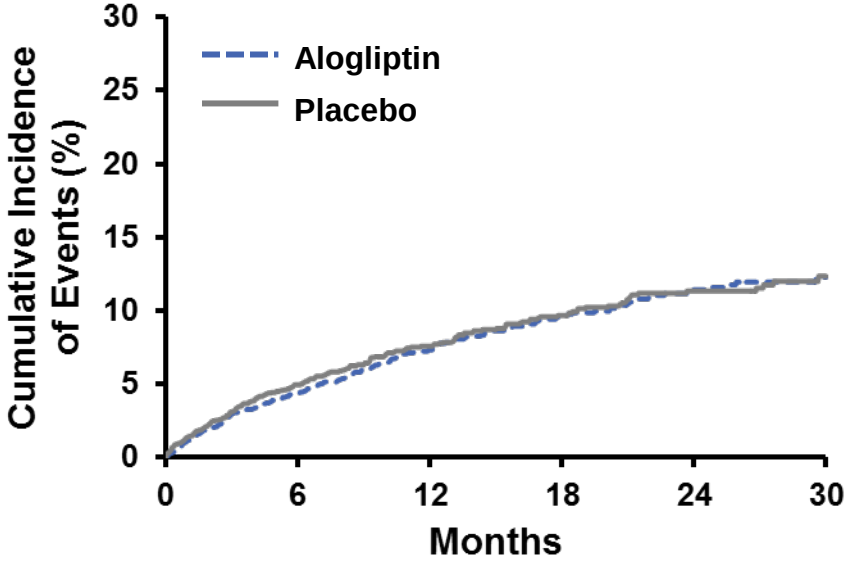
| | Events n (%) | Hazard Ratio (95% CI) |
|---|---|---|
| Alogliptin | 123 (16.0) | 0.940 (0.736 - 1.201) |
| Placebo | 131 (17.2) | |




| No. at risk | | | | | | |
|---|---|---|---|---|---|---|
| Alogliptin | 771 | 637 | 505 | 358 | 194 | 52 |
| Placebo | 762 | 639 | 509 | 360 | 190 | 53 |

## Patients With No History of HF

| | Events n (%) | Hazard Ratio (95% CI) |
|---|---|---|
| Alogliptin | 182 (9.4) | 0.970 (0.791 - 1.190) |
| Placebo | 185 (9.7) | |



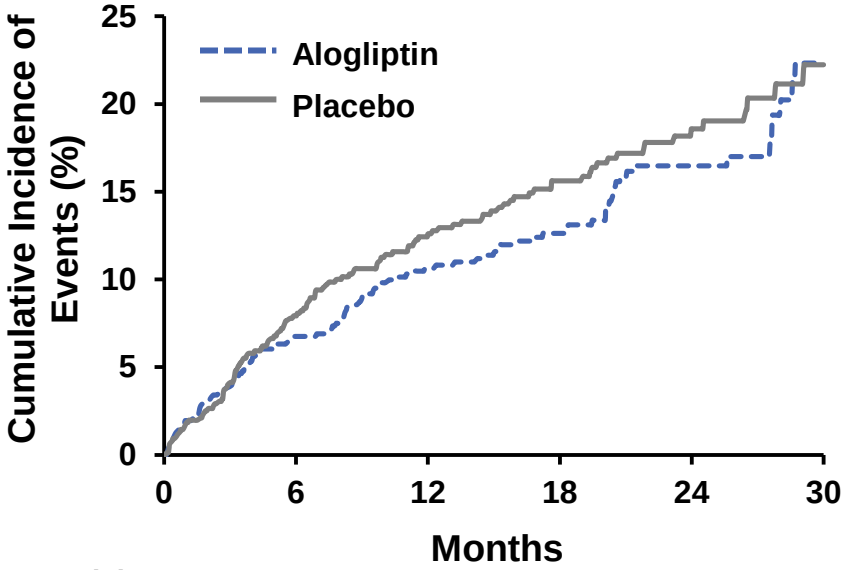

| No. at risk | | | | | | |
|---|---|---|---|---|---|---|
| Alogliptin | 1930 | 1679 | 1394 | 1036 | 623 | 238 |
| Placebo | 1917 | 1660 | 1381 | 1015 | 613 | 229 |

# CV Death and HHF Composite by History of Heart Failure



## Patients With History of HF

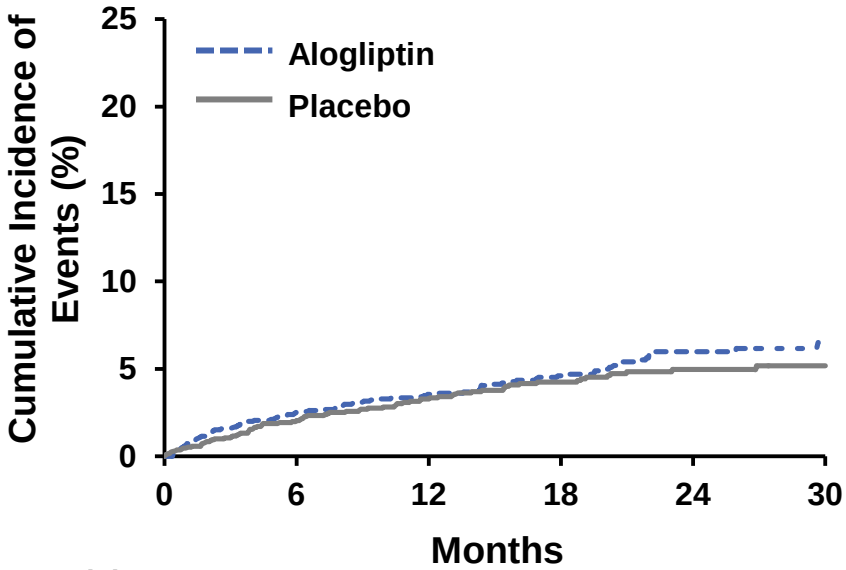
| | Events n (%) | Hazard Ratio (95% CI) |
|---|---|---|
| Alogliptin | 107 (13.9) | 0.904 (0.697–1.172) |
| Placebo | 120 (15.7) | |




| No. at risk | | | | | | |
|---|---|---|---|---|---|---|
| Alogliptin | 771 | 643 | 522 | 374 | 200 | 50 |
| Placebo | 762 | 635 | 504 | 356 | 193 | 60 |

## Patients With No History of HF

| | Events n (%) | Hazard Ratio (95% CI) |
|---|---|---|
| Alogliptin | 94 (4.9) | 1.144 (0.849–1.540) |
| Placebo | 81 (4.2) | |

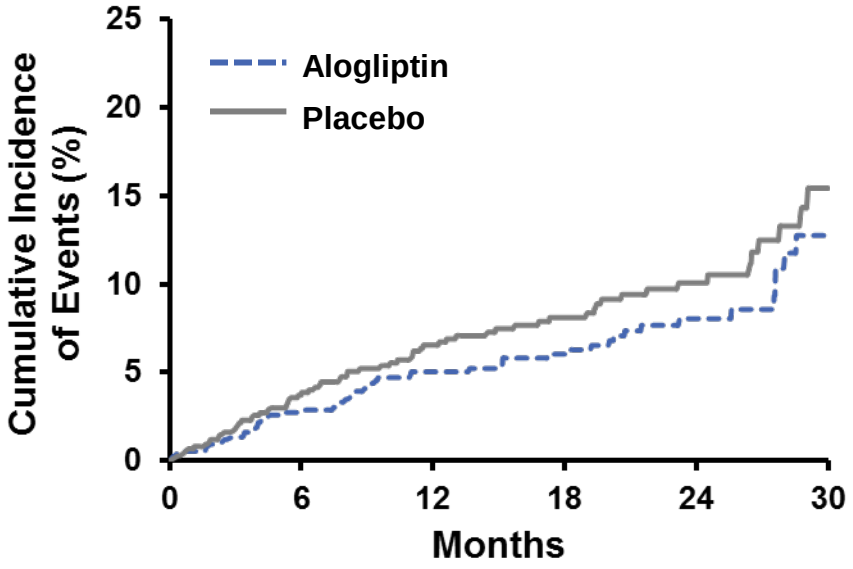



| No. at risk | | | | | | |
|---|---|---|---|---|---|---|
| Alogliptin | 1930 | 1709 | 1446 | 1083 | 656 | 250 |
| Placebo | 1917 | 1711 | 1442 | 1074 | 662 | 250 |

# CV Death by History of Heart Failure

## Patients With History of HF

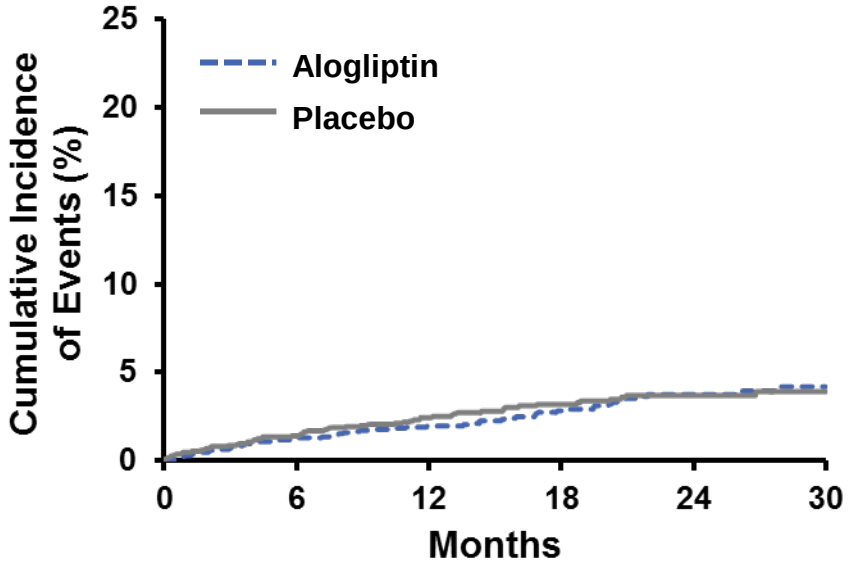
| | Events n (%) | Hazard Ratio (95% CI) |
|---|---|---|
| Alogliptin | 55 (7.1) | 0.769 (0.542 - 1.091) |
| Placebo | 69 (9.1) | |




| No. at risk | | | | | | |
|---|---|---|---|---|---|---|
| Alogliptin | 771 | 672 | 555 | 403 | 224 | 59 |
| Placebo | 762 | 662 | 539 | 391 | 217 | 65 |

## Patients With No History of HF

| | Events n (%) | Hazard Ratio (95% CI) |
|---|---|---|
| Alogliptin | 57 (3.0) | 0.918 (0.639 - 1.318) |
| Placebo | 61 (3.2) | |

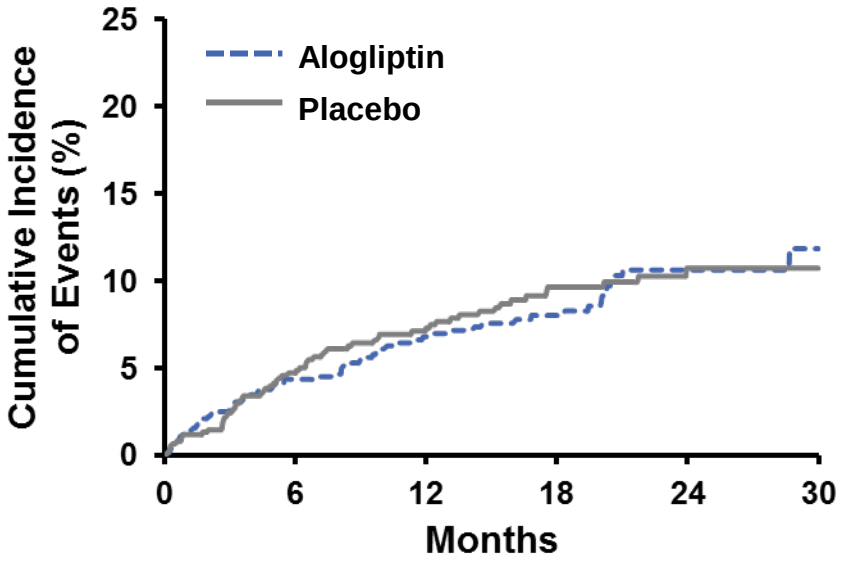



| No. at risk | | | | | | |
|---|---|---|---|---|---|---|
| Alogliptin | 1930 | 1730 | 1468 | 1101 | 667 | 255 |
| Placebo | 1917 | 1722 | 1456 | 1068 | 670 | 255 |

# HHF by History of Heart Failure

## Patients With History of HF

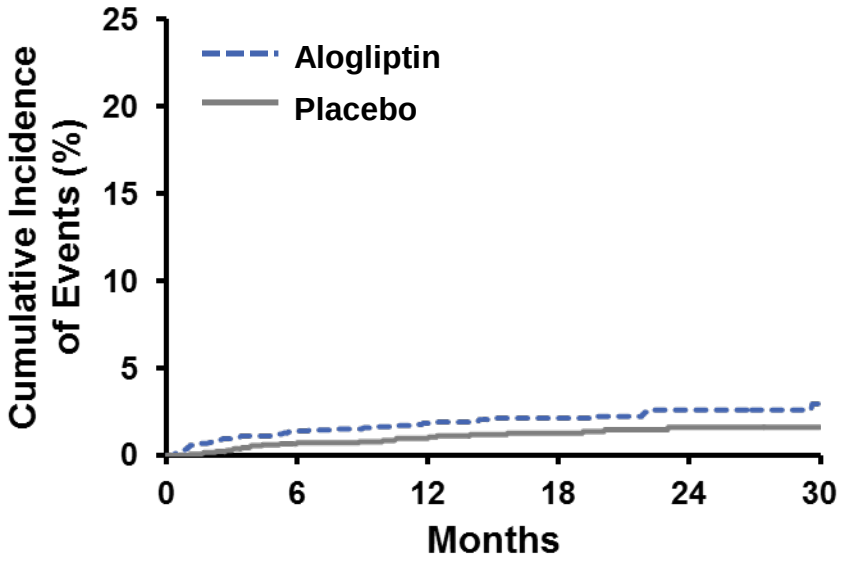
| | Events n (%) | Hazard Ratio (95% CI) |
|---|---|---|
| Alogliptin | 63 (8.2) | 1.001 (0.708 - 1.415) |
| Placebo | 65 (8.5) | |




| No. at risk | | | | | | |
|---|---|---|---|---|---|---|
| Alogliptin | 771 | 643 | 522 | 374 | 200 | 50 |
| Placebo | 762 | 635 | 504 | 356 | 193 | 60 |

## Patients With No History of HF

| | Events n (%) | Hazard Ratio (95% CI) |
|---|---|---|
| Alogliptin | 43 (2.2) | 1.761 (1.070 - 2.900) |
| Placebo | 24 (1.3) | |




| No. at risk | | | | | | |
|---|---|---|---|---|---|---|
| Alogliptin | 1930 | 1709 | 1446 | 1083 | 656 | 250 |
| Placebo | 1917 | 1711 | 1442 | 1074 | 662 | 250 |

# Baseline Characteristics for Patients Who Developed HHF During the Study by History of HF Prior to Randomization

| | Patients With History of HF and Developed HHF | | Patients Without History of HF and Developed HHF | |
|---|---|---|---|---|
| | Alogliptin N = 63 | Placebo N = 65 | Alogliptin N = 43 | Placebo N = 24 |
| Median age, y | 65 | 65 | 63 | 62 |
| Age ≥65, % | 50.8 | 50.8 | 41.9 | 37.5 |
| Male, % | 60.3 | 53.8 | 65.1 | 66.7 |
| Race, % White | 68.3 | 69.2 | 60.5 | 62.5 |
| Asian | 22.2 | 18.5 | 32.6 | 29.2 |
| Median diabetes duration, y | 15.6 | 9.9 | 11.0 | 5.9 |
| Insulin use, % | 60.3 | 49.2 | 37.2 | 29.2 |
| Index ACS, % MI | 68.6 | 71.6 | 79.8 | 78.7 |
| Unstable angina | 31.2 | 28.0 | 19.8 | 21.2 |
| Mean baseline HbA1c, % | 8.1 | 8.0 | 8.3 | 8.3 |
| Median eGFR (MDRD) (mL/min/1.73 $m^2$) | 53.8 | 52.1 | 61.0 | 68.8 |
| Median NT-proBNP, pg/mL | 2026 | 2096 | 1375 | 1110 |

# Hospitalization for Heart Failure Adjusted for Baseline Risk Factors



| Baseline Factors Adjusted | Hazard Ratio (95% CI) | P-Value |
|---|---|---|
| **Treatment** (Alogliptin vs Placebo) | 1.097 (0.818, 1.471) | 0.538 |
| **History of HF** (with vs without) | 3.236 (2.312, 4.528) | <0.001 |
| **Baseline NT-proBNP** (2nd quartile vs 1st quartile) | 3.618 (1.207, 10.84) | 0.022 |
| **Baseline NT-proBNP** (3rd quartile vs 1st quartile) | 7.524 (2.630, 21.53) | <0.001 |
| **Baseline NT-proBNP** (4th quartile vs 1st quartile) | 24.70 (8.874, 68.77) | <0.001 |
| **Baseline insulin use** (Yes vs No) | 1.428 (1.057, 1.929) | 0.020 |
| **History of MI** (Yes vs No) | 1.780 (1.287, 2.462) | <0.001 |
| **Mild renal impairment at baseline** (vs Normal) | 1.589 (0.715, 3.533) | 0.256 |
| **Moderate renal impairment at baseline** (vs Normal) | 1.922 (0.851, 4.343) | 0.116 |
| **Severe renal impairment/ESRD at Baseline** (vs Normal) | 2.727 (1.074, 6.924) | 0.035 |
| **Age** (<65y vs ≥65y ) | 1.143 (0.828, 1.576) | 0.417 |
| **Sex** (Male vs Female) | 0.786 (0.570, 1.084) | 0.143 |
| **Duration of diabetes** (1 year increase) | 1.017(0.999, 1.036) | 0.064 |
| **Time from index ACS to randomization** (1 day increase) | 0.995 (0.988, 1.002) | 0.143 |

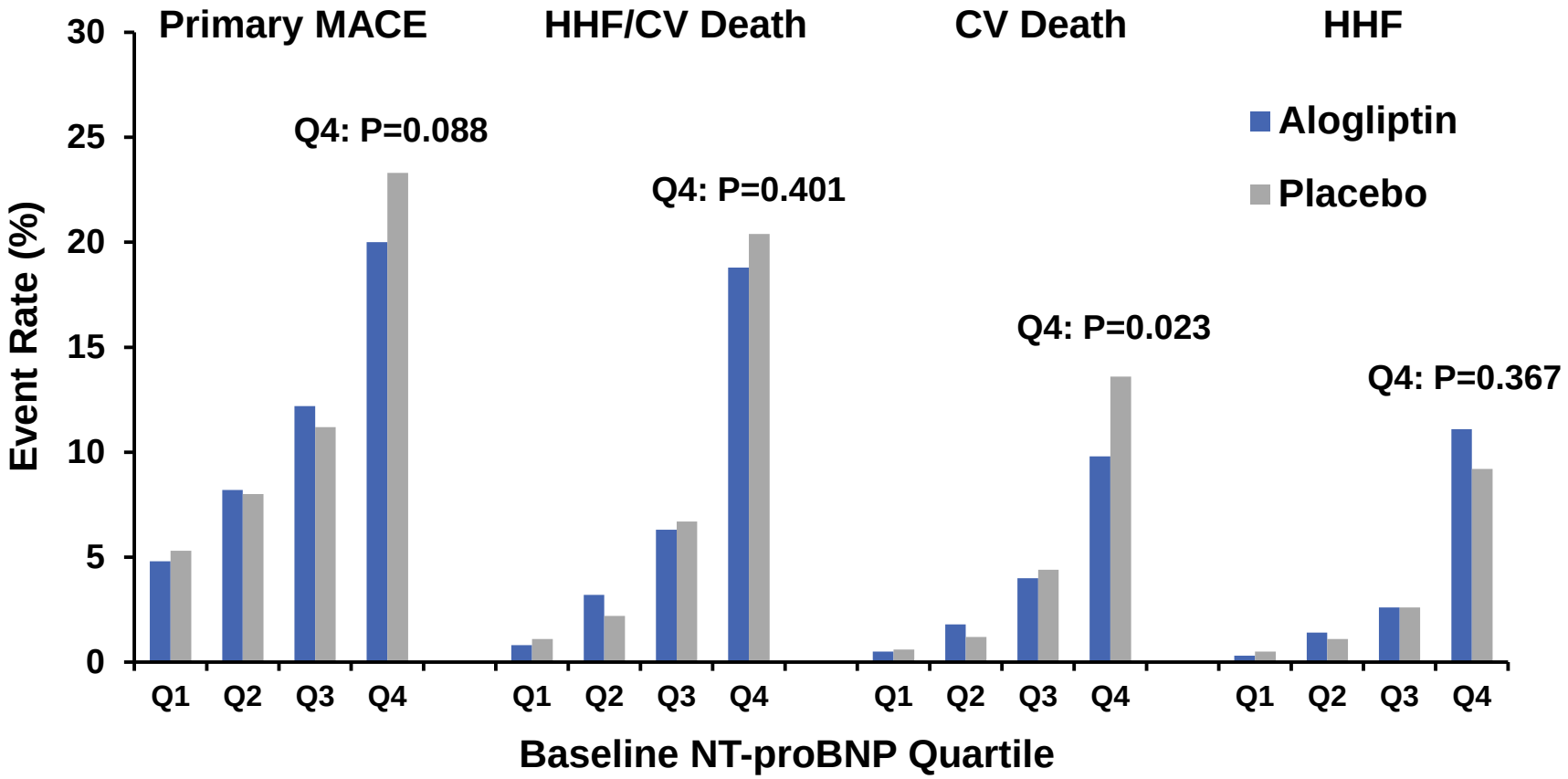
# Biomarkers for CV Death and Heart Failure



- Biomarkers of BNP and NT-proBNP were evaluated as they were shown to be indicators of risk for CV death and heart failure in EXAMINE
- Assessment of post-Baseline changes of NT-proBNP is preferred over changes in BNP as it is not a substrate for DPP-4
- Quartiles of Baseline NT-proBNP were defined to assess its relations with the primary endpoint, the composite of CV death/HHF and its components
  - Q1 = <154.0 pg/mL
  - Q2 = ≥154.0 to <420.2 pg/mL
  - Q3 = ≥420.2 to <1083 pg/mL
  - Q4 = ≥1083 pg/mL

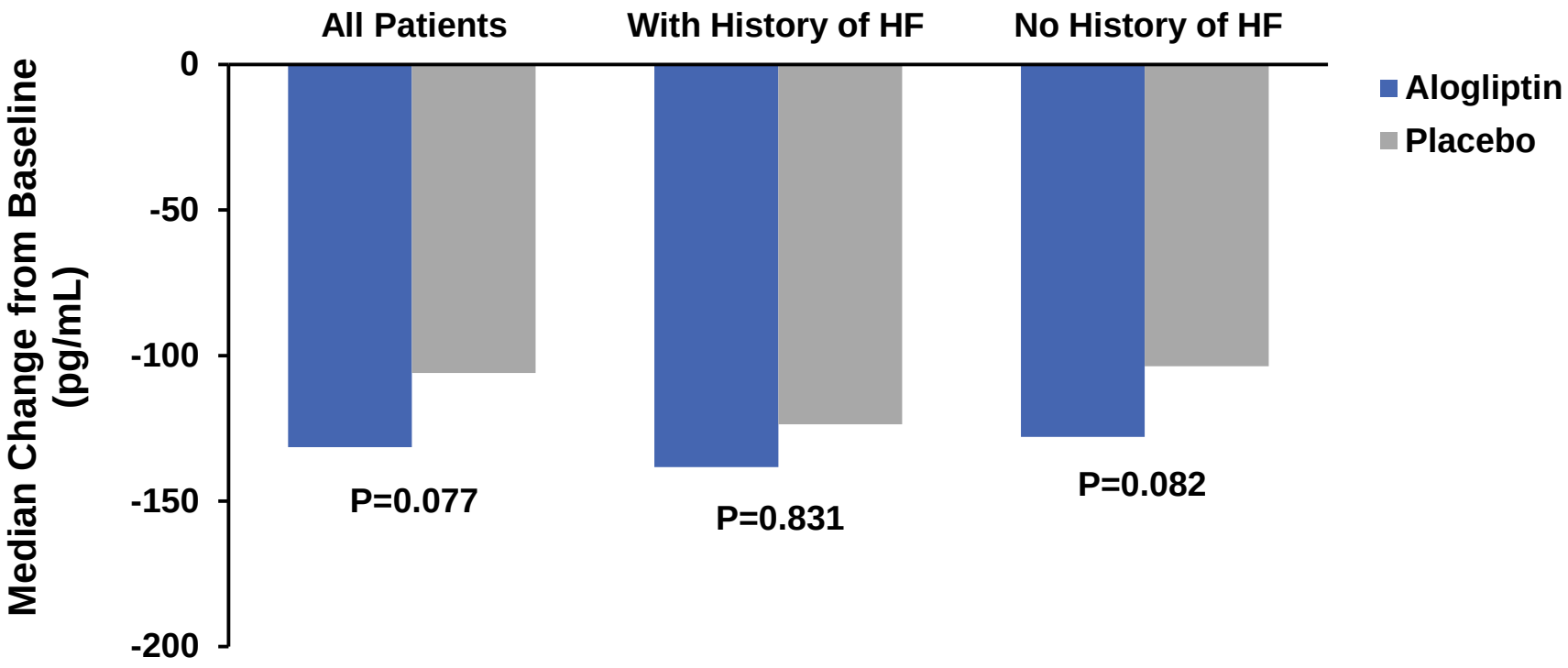
# CV Events by Quartile of Baseline NT-proBNP Level





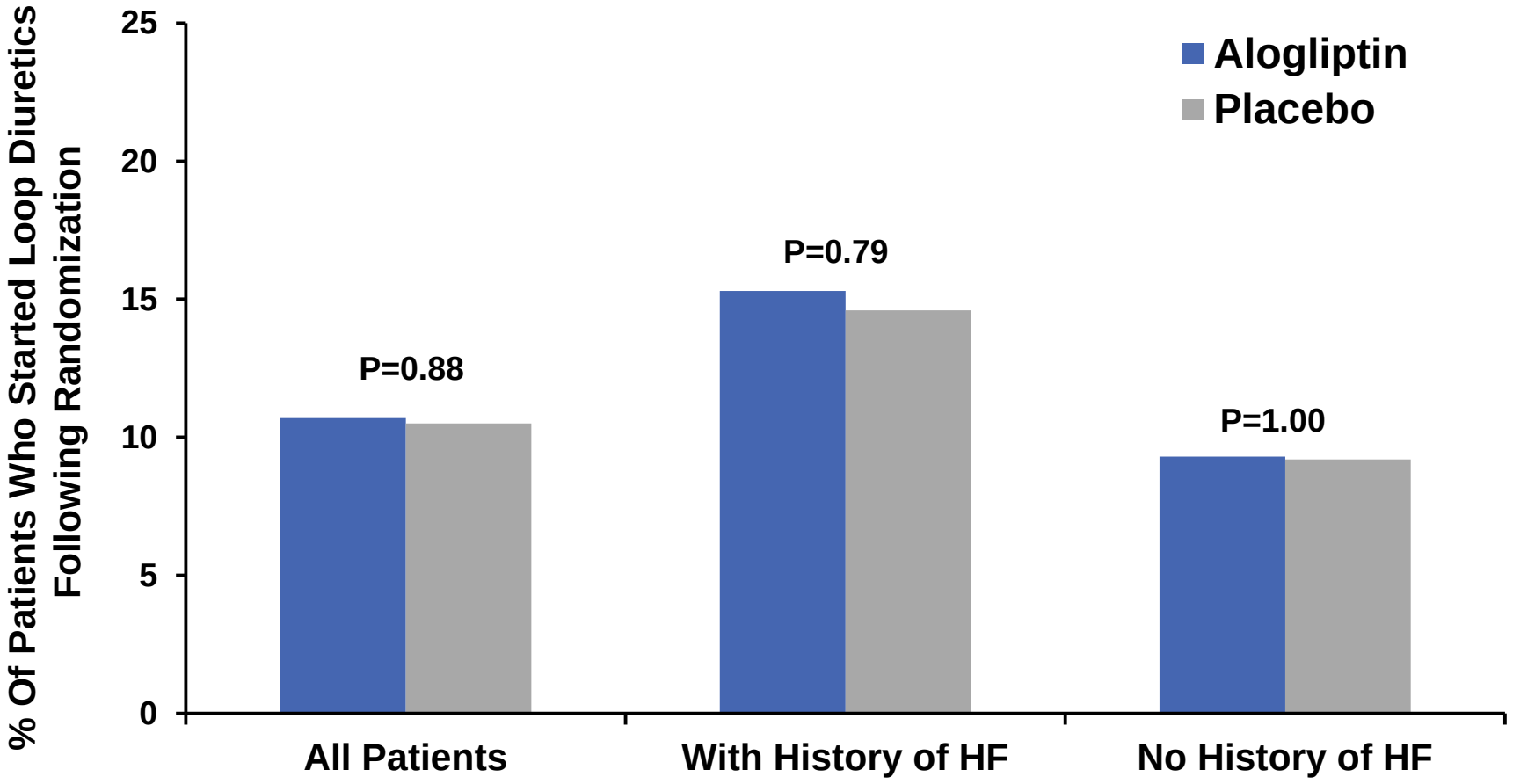
# Changes from Baseline in NT-proBNP at 6 Months by Treatment Assignment






| | All Patients | With History of HF | No History of HF |
|---|---|---|---|
| **Patients, N** | | | |
| Alogliptin | 2154 | 596 | 1558 |
| Placebo | 2130 | 597 | 1533 |
| **NT-proBNP at baseline (pg/mL)** | | | |
| Alogliptin | 423 | 699 | 376 |
| Placebo | 400 | 630 | 340 |

# Initiation of Loop Diuretics Following Randomization by Heart Failure History at Baseline




| Patients, N | | | |
|---|---|---|---|
| Alogliptin | 2219 | 517 | 1702 |
| Placebo | 2221 | 512 | 1709 |

# Summary

- In EXAMINE, rates of MACE were similar for alogliptin and placebo and met non-inferiority to rule out excess CV risk in a high-risk population
- Some heterogeneity was observed in subgroup analyses for the primary endpoint; this finding was consistent with random variation
- These observations occurred in the context of a high overall CV event rate (>11% over 19 months) and high levels of standard of care
- Rates of CV and all-cause mortality as well as exploratory composites that included heart failure were similar in the alogliptin and placebo groups
- Patients with heart failure at baseline and elevated NT-proBNP levels at baseline had similar results to the overall EXAMINE cohort

# Agenda for Takeda Presentation

| | |
|---|---|
| **Introduction** | **Stuart Kupfer, MD**<br>Therapeutic Area Head (CVM)<br>Takeda Development Center Americas, Inc. |
| **EXAMINE Study Results** | **William B. White, MD**<br>Chair, EXAMINE Steering Committee<br>Professor of Medicine<br>Calhoun Cardiology Center<br>University of Connecticut School of Medicine |
| **Clinical Perspective** | **Marc Pfeffer, MD, PhD**<br>Dzau Professor of Medicine, Harvard Medical School<br>Cardiovascular Division, Brigham & Women's Hospital |
| **Overall Safety and Conclusions** | **Stuart Kupfer, MD**<br>Therapeutic Area Head (CVM)<br>Takeda Development Center Americas, Inc. |

# CARDIOVASCULAR BURDEN in Type 2 Diabetes

## EXAMINEing HEART FAILURE Events

Marc A. Pfeffer, MD, PhD

Dzau Professor of Medicine, Harvard Medical School
Cardiovascular Division, Brigham & Women's Hospital
Boston, Massachusetts

Consults to Abbott Vascular, Amgen, AstraZeneca, Bayer, Concert, Daiichi Sankyo, Fibrogen, Genzyme, Medicines Company, MedImmune, Medtronic, Merck, Novartis, Novo Nordisk, Relypsa, Roche, Sanderling, Servier, Teva, and Vericel; and receives grant support from Amgen, Celladon, Novartis, and Sanofi-Aventis. Co-inventor: patent to BWH use of renin-angiotensin inhibitors in survivors of MI with Novartis- licensing agreement irrevocably and unconditionally assigned to charity.

**Note: New Consulting to Takeda Development Center Americas, Inc**

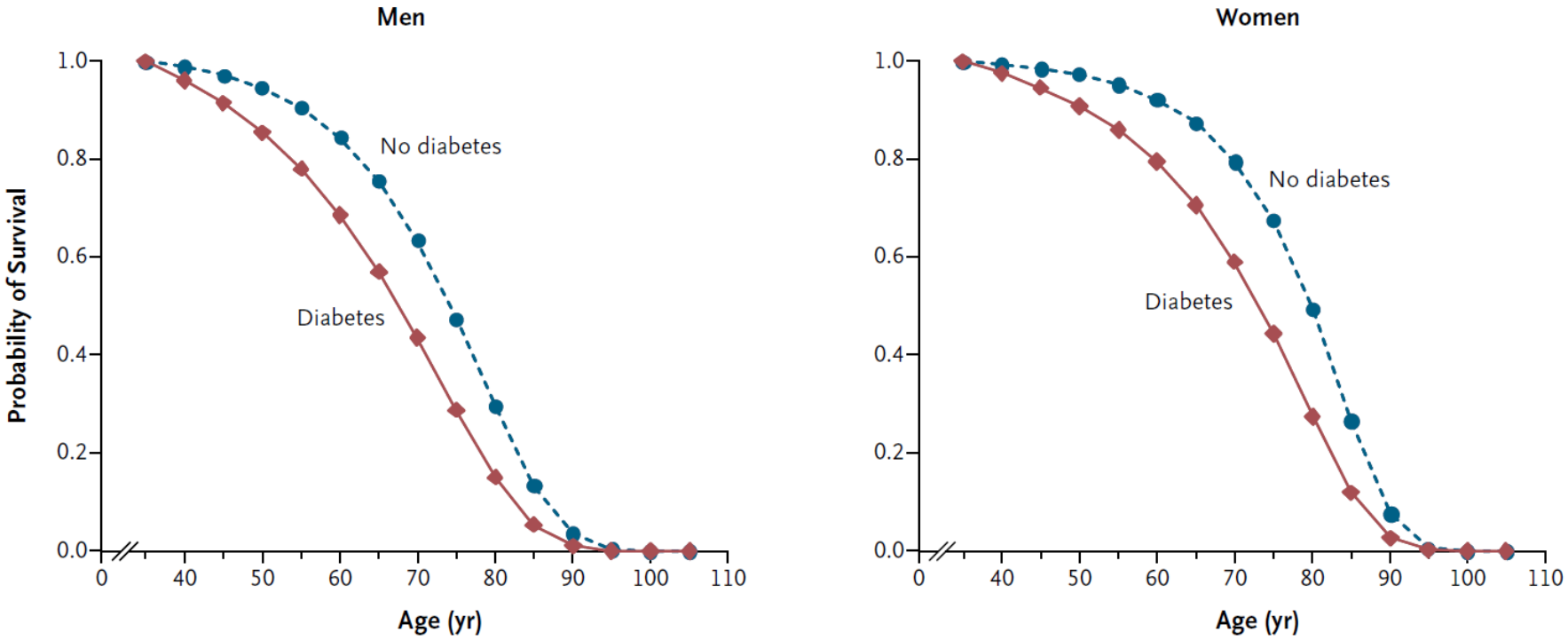
The NEW ENGLAND JOURNAL of MEDICINE

# Diabetes Mellitus, Fasting Glucose, and Risk of Cause-Specific Death

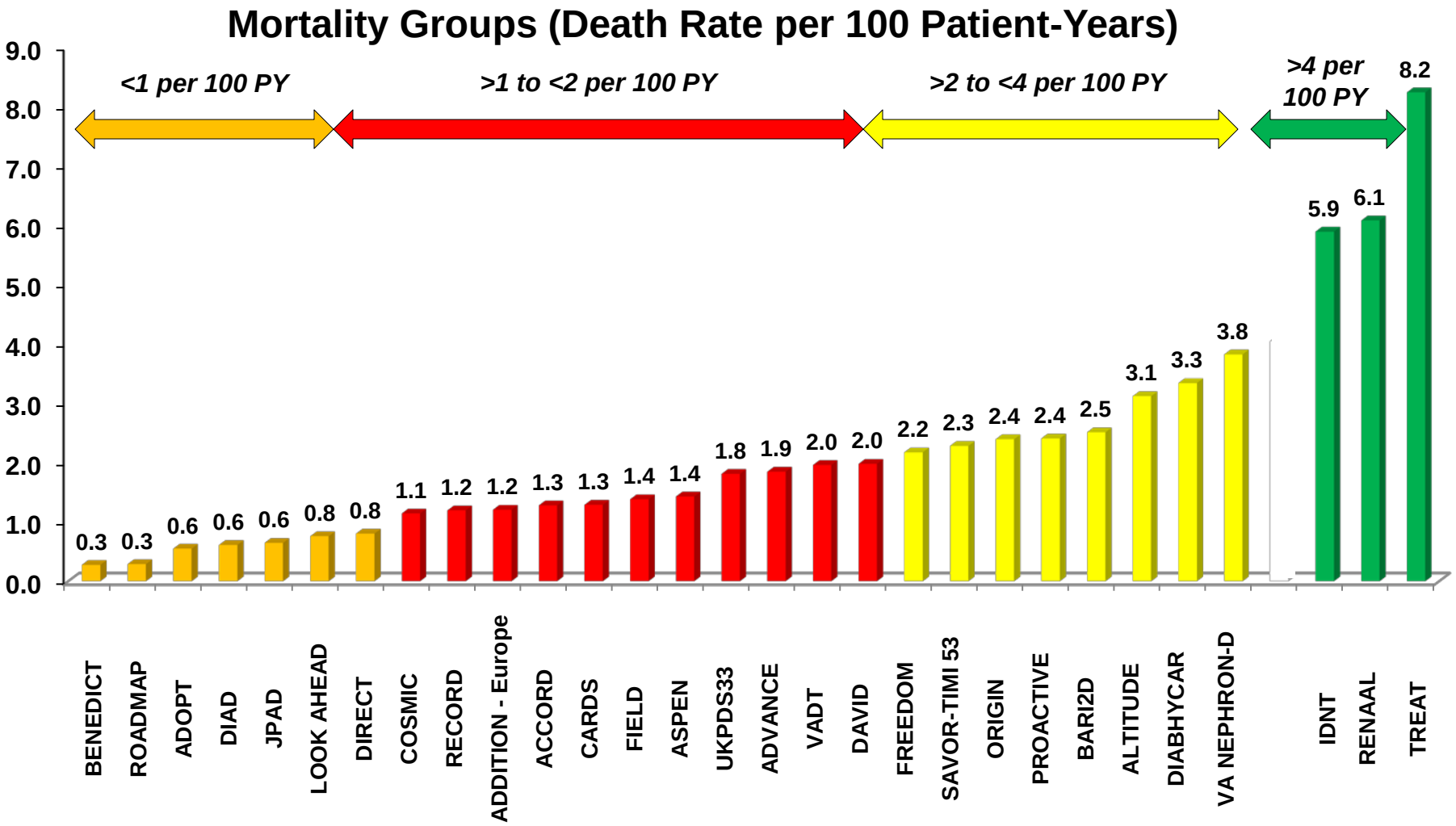
The Emerging Risk Factors Collaboration

N Engl J Med 2011;364:829-41.

123,205 deaths among 820,900 people in 97 prospective studies

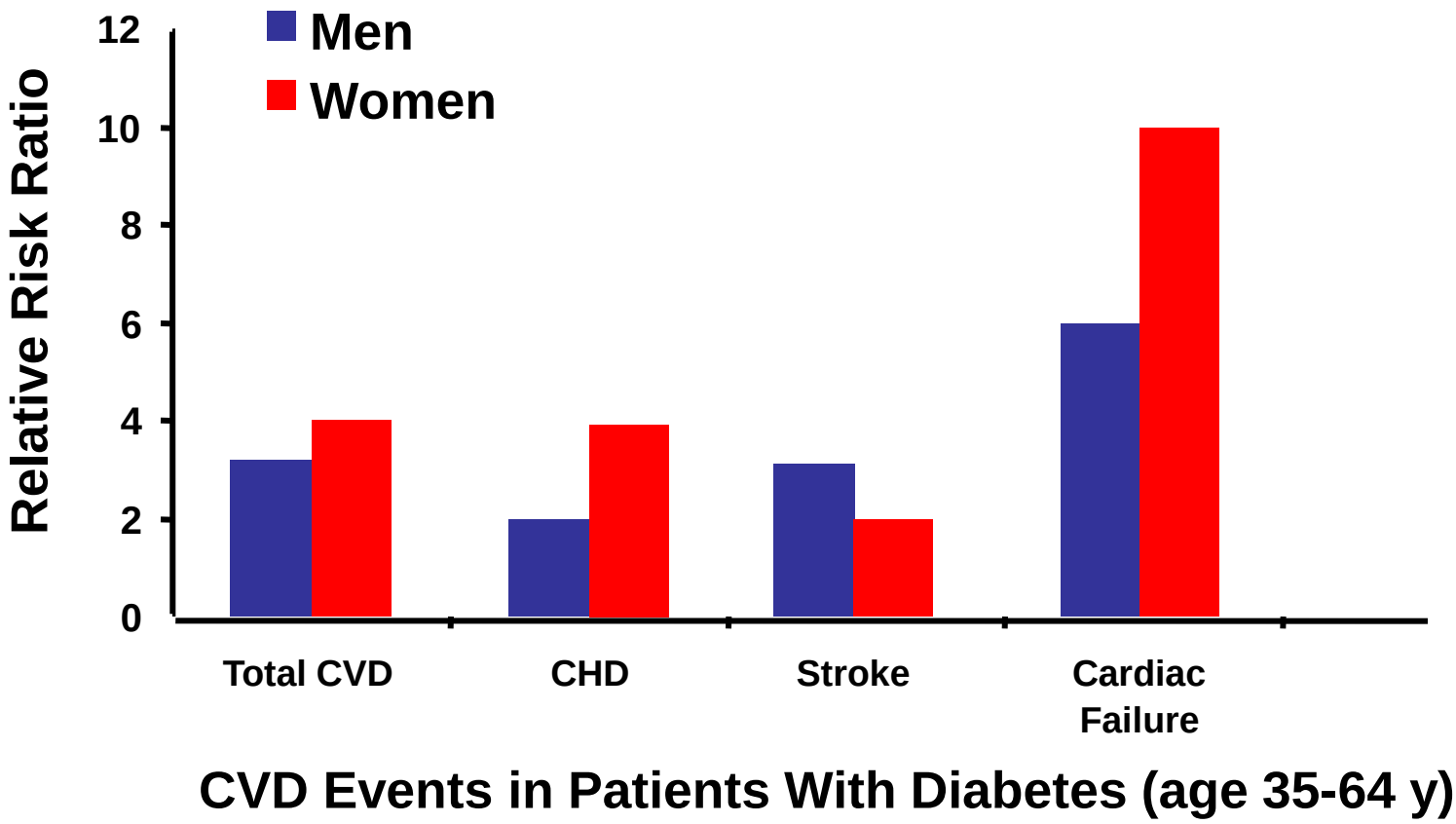


# Mortality Rates in Trials of Subjects With Type 2 Diabetes




Updated from *J Am Heart Assoc. 2012; 1: 8-15*

# Relative Risk of CVD in Patients With Diabetes: Framingham Heart Study 30-Year Follow-up




Wilson P, Kannel W. In: Ruderman N et al, eds. *Hyperglycemia, Diabetes and Vascular Disease*. Oxford University Press; 1992.
Wilson P, Cupples L, Kannel W. Am Heart J. 1991 Feb;121(2 Pt 1):586-90.

The NEW ENGLAND JOURNAL of MEDICINE

# Effect of Rosiglitazone on the Risk of Myocardial Infarction and Death from Cardiovascular Causes

Steven E. Nissen, M.D., and Kathy Wolski, M.P.H.

N Engl J Med 2007;356:2457-71.

**Table 4. Rates of Myocardial Infarction and Death from Cardiovascular Causes.**

| Study | Rosiglitazone Group | Control Group | Odds Ratio (95% CI) | P Value |
|---|---|---|---|---|
| | *no. of events/total no. (%)* | | | |
| **Myocardial infarction** | | | | |
| Small trials combined | 44/10,285 (0.43) | 22/6106 (0.36) | 1.45 (0.88–2.39) | 0.15 |
| DREAM | 15/2,635 (0.57) | 9/2634 (0.34) | 1.65 (0.74–3.68) | 0.22 |
| ADOPT | 27/1,456 (1.85) | 41/2895 (1.42) | 1.33 (0.80–2.21) | 0.27 |
| Overall | | | 1.43 (1.03–1.98) | 0.03 |
| **Death from cardiovascular causes** | | | | |
| Small trials combined | 25/6,845 (0.36) | 7/3980 (0.18) | 2.40 (1.17–4.91) | 0.02 |
| DREAM | 12/2,635 (0.46) | 10/2634 (0.38) | 1.20 (0.52–2.78) | 0.67 |
| ADOPT | 2/1,456 (0.14) | 5/2895 (0.17) | 0.80 (0.17–3.86) | 0.78 |
| Overall | | | 1.64 (0.98–2.74) | 0.06 |

# Guidance for Industry

## Diabetes Mellitus — Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes

2008

### III. RECOMMENDATIONS

- Sponsors should establish an independent cardiovascular endpoints committee to prospectively adjudicate, in a blinded fashion, cardiovascular events during all phase 2 and phase 3 trials. These events should include cardiovascular mortality, myocardial infarction, and stroke, and can include hospitalization for acute coronary syndrome, urgent revascularization procedures, and possibly other endpoints.

Available at:http://www.fda.gov/downloads/Drugs/Guidances/ucm071624.pdf

THE LANCET Diabetes & Endocrinology 2014

# Heart failure: a cardiovascular outcome in diabetes that can no longer be ignored

*John J V McMurray, Hertzel C Gerstein, Rury R Holman, Marc A Pfeffer*

In patients with type 1 or type 2 diabetes, glycaemic exposure assessed as $HbA_{1c}$ correlates strongly with risk of future microvascular and macrovascular complications. Improved glucose control substantially reduces the risk of microvascular complications and, with extended follow-up, modestly reduces the risk of atherosclerotic events. The lowering of $HbA_{1c}$ concentrations by newly developed glucose-lowering drugs (alone or when added to other glucose-

This omission is important because hospital admission for heart failure is a common and prognostically important cardiovascular complication of diabetes. Moreover, it is the one cardiovascular outcome for which the risk has been shown unequivocally to be increased by some glucose-lowering therapies. As such, we believe that heart failure should be systematically evaluated in cardiovascular outcome trials of all new glucose-lowering drugs.

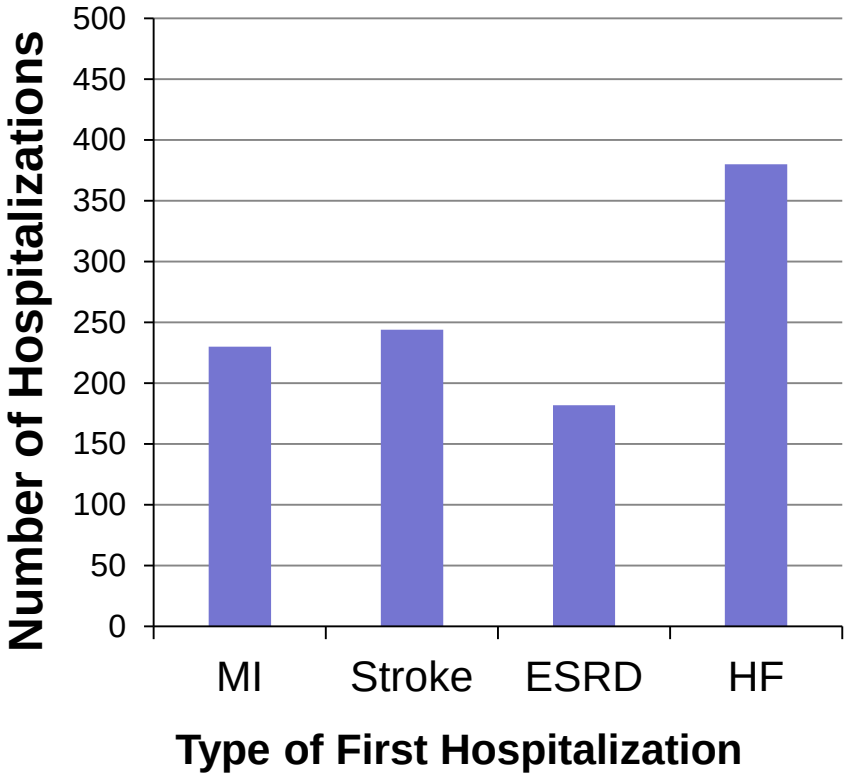
prognostically important cardiovascular complication of diabetes. Moreover, it is the one cardiovascular outcome for which the risk has been shown unequivocally to be increased by some glucose-lowering therapies. As such, we believe that heart failure should be systematically evaluated in cardiovascular outcome trials of all new glucose-lowering drugs.

The NEW ENGLAND JOURNAL of MEDICINE

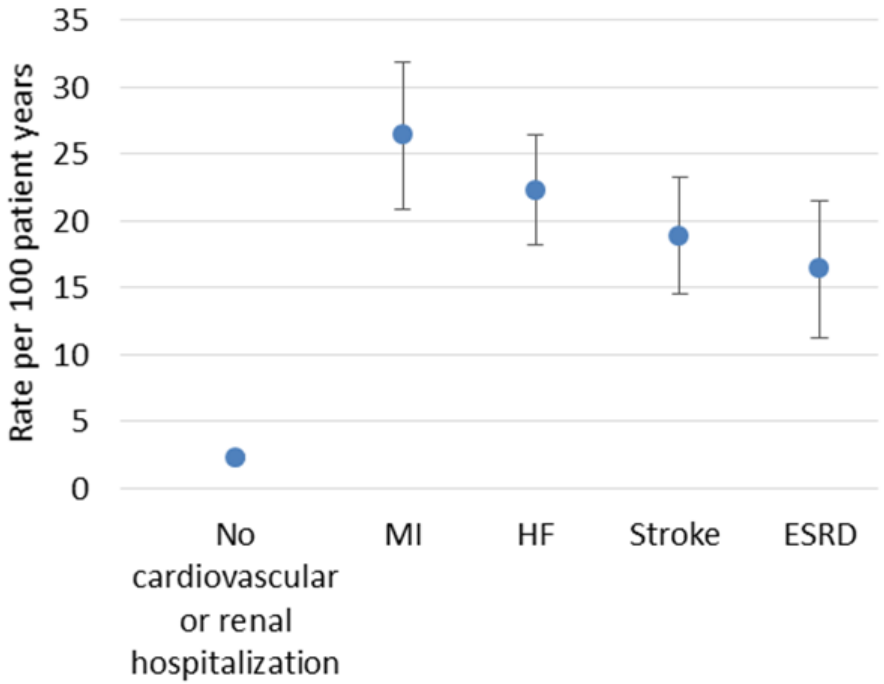
# Cardiorenal End Points in a Trial of Aliskiren for Type 2 Diabetes

Hans-Henrik Parving, M.D., D.M.Sc., Barry M. Brenner, M.D., Ph.D., John J.V. McMurray, M.D., Dick de Zeeuw, M.D., Ph.D., Steven M. Haffner, M.D., Scott D. Solomon, M.D., Nish Chaturvedi, M.D., Frederik Persson, M.D., Akshay S. Desai, M.D., M.P.H., Maria Nicolaides, M.D., Alexia Richard, M.Sc., Zhihua Xiang, Ph.D., Patrick Brunel, M.D., and Marc A. Pfeffer, M.D., Ph.D., for the ALTITUDE Investigators*

## Hospitalizations (N = 8561)

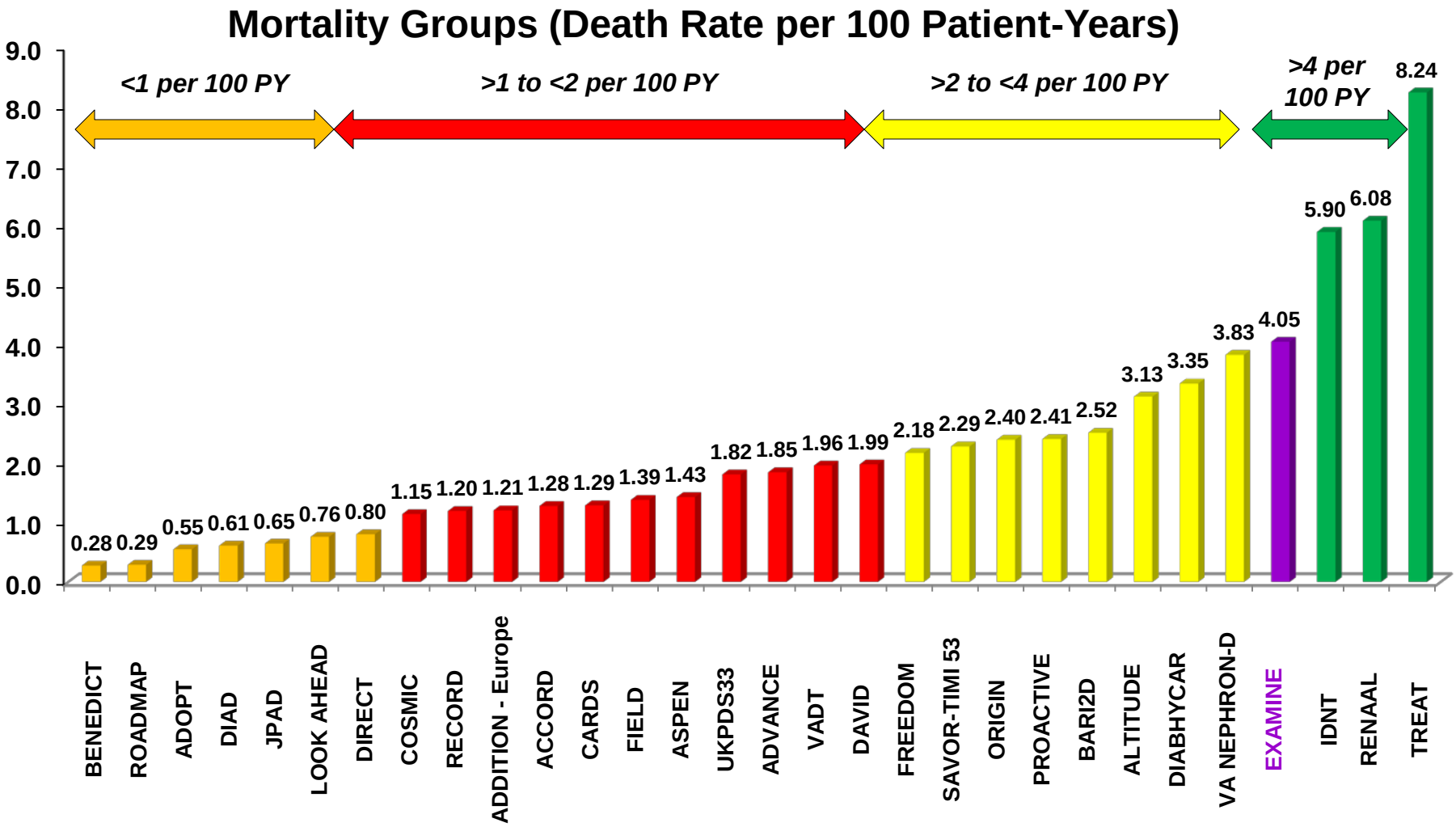



## Death (per 100 pt-yrs)




NEJM. 2012;367:23

# Mortality Rates in Trials of Subjects With Type 2 Diabetes




Updated from *J Am Heart Assoc.* 2012; 1: 8-15.

# Alogliptin vs. Placebo on Primary MACE Composite, MACE Components & All-Cause Mortality

| | Alogliptin N = 2701 n (%) | Placebo N = 2679 n (%) | Hazard Ratio (95% CI) |
|---|---|---|---|
| **Primary end point: CV death, nonfatal MI, or nonfatal stroke** | **305 (11.3)** | **316 (11.8)** | **0.962 (≤1.160)[a]** |
| **First Event** | | | |
| 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) |
| **Any Patient** | | | |
| CV death | 112 (4.1) | 130 (4.9) | 0.85 (0.66, 1.10) |
| Nonfatal MI | 188 (7.0) | 176 (6.6) | 1.07 (0.87, 1.31) |
| Nonfatal stroke | 30 (1.1) | 39 (1.4) | 0.81 (0.50, 1.31) |
| **All Deaths** | 153 (5.7) | 173 (6.5) | 0.88 (0.71, 1.09) |

[a]99% one-sided confidence interval, P<0.001 for non-inferiority.

# Alogliptin vs. Placebo on Primary MACE and HHF Composite, and Individual Components

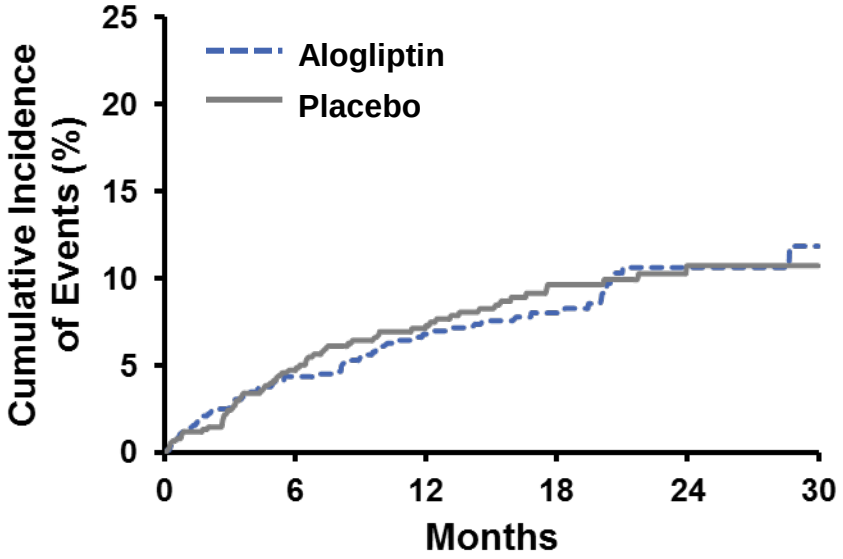
- Time to first event of CV death, nonfatal MI, nonfatal stroke, hospitalization for heart failure (HHF)

| | Alogliptin N = 2701 n (%) | Placebo N = 2679 n (%) | Hazard Ratio (95% CI) | P-value |
|---|---|---|---|---|
| **Composite Endpoint:** | **365 (13.5)** | **365 (13.6)** | **0.998 (0.863, 1.154)** | **0.98** |
| **First Event** | | | | |
| CV death | 79 (2.9) | 97 (3.6) | 0.80 (0.60, 1.08) | 0.15 |
| Nonfatal MI | 173 (6.4) | 159 (5.9) | 1.09 (0.88, 1.35) | 0.45 |
| Nonfatal stroke | 28 (1.0) | 29 (1.1) | 0.97 (0.58, 1.63) | 0.91 |
| HHF | 85 (3.1) | 80 (3.0) | 1.07 (0.79, 1.45) | 0.68 |
| **Any Patients** | | | | |
| CV death | 112 (4.1) | 130 (4.9) | 0.85 (0.66, 1.10) | 0.21 |
| Nonfatal MI | 188 (7.0) | 176 (6.6) | 1.07 (0.87, 1.31) | 0.53 |
| Nonfatal stroke | 30 (1.1) | 39 (1.4) | 0.81 (0.50, 1.31) | 0.81 |
| HHF | 106 (3.9) | 89 (3.3) | 1.19 (0.90, 1.58) | 0.22 |

# HHF by History of Heart Failure

## Patients With History of HF

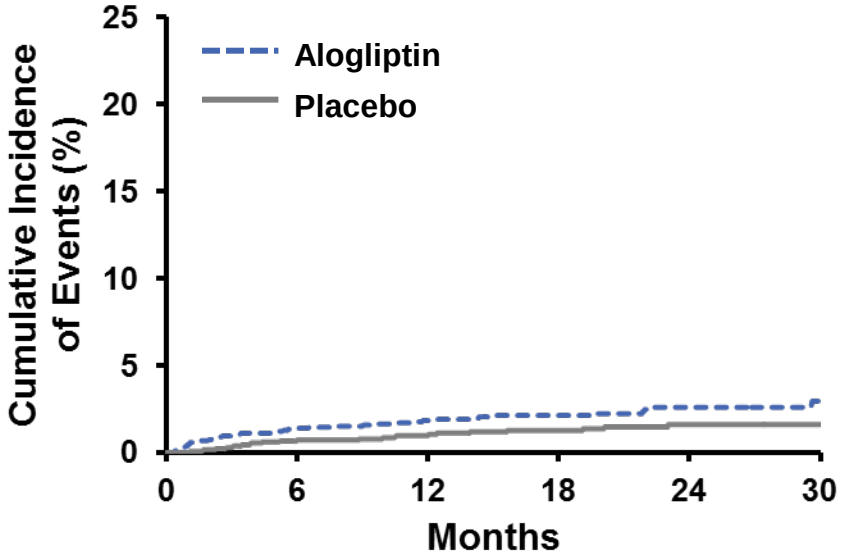
| | Events n (%) | Hazard Ratio (95% CI) |
|---|---|---|
| Alogliptin | 63 (8.2) | 1.001 (0.708 - 1.415) |
| Placebo | 65 (8.5) | |




| No. at risk | | | | | | |
|---|---|---|---|---|---|---|
| Alogliptin | 771 | 643 | 522 | 374 | 200 | 50 |
| Placebo | 762 | 635 | 504 | 356 | 193 | 60 |

## Patients With No History of HF

| | Events n (%) | Hazard Ratio (95% CI) |
|---|---|---|
| Alogliptin | 43 (2.2) | 1.761 (1.070 - 2.900) |
| Placebo | 24 (1.3) | |




| No. at risk | | | | | | |
|---|---|---|---|---|---|---|
| Alogliptin | 1930 | 1709 | 1446 | 1083 | 656 | 250 |
| Placebo | 1917 | 1711 | 1442 | 1074 | 662 | 250 |

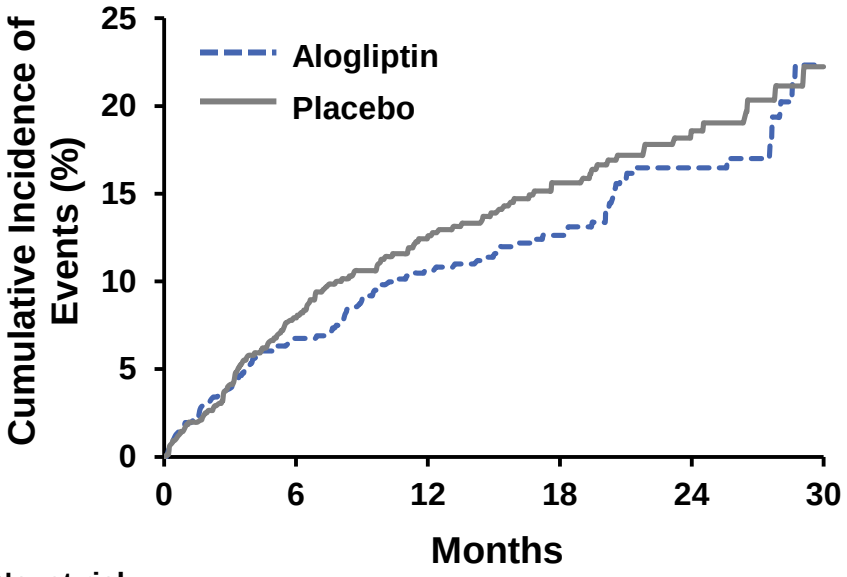
**Total Alo: 106; Total Pbo: 89  Overall HR 1.193  95% CI (0.900, 1.581)**

# CV Death and HHF Composite by History of Heart Failure



## Patients With History of HF

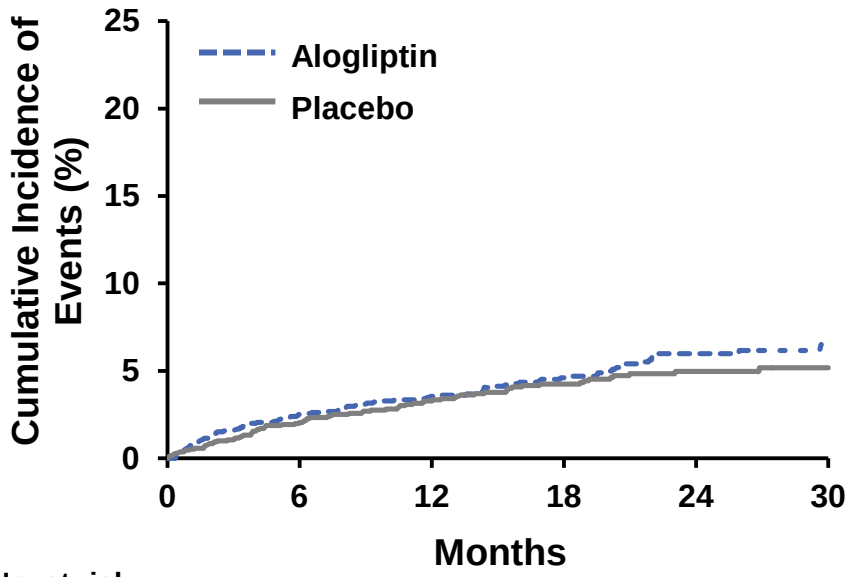
| | Events n (%) | Hazard Ratio (95% CI) |
|---|---|---|
| Alogliptin | 107 (13.9) | 0.904 (0.697–1.172) |
| Placebo | 120 (15.7) | |




| No. at risk | | | | | | |
|---|---|---|---|---|---|---|
| Alogliptin | 771 | 643 | 522 | 374 | 200 | 51 |
| Placebo | 762 | 635 | 505 | 356 | 198 | 60 |

## Patients With No History of HF

| | Events n (%) | Hazard Ratio (95% CI) |
|---|---|---|
| Alogliptin | 94 (4.9) | 1.144 (0.849–1.540) |
| Placebo | 81 (4.2) | |



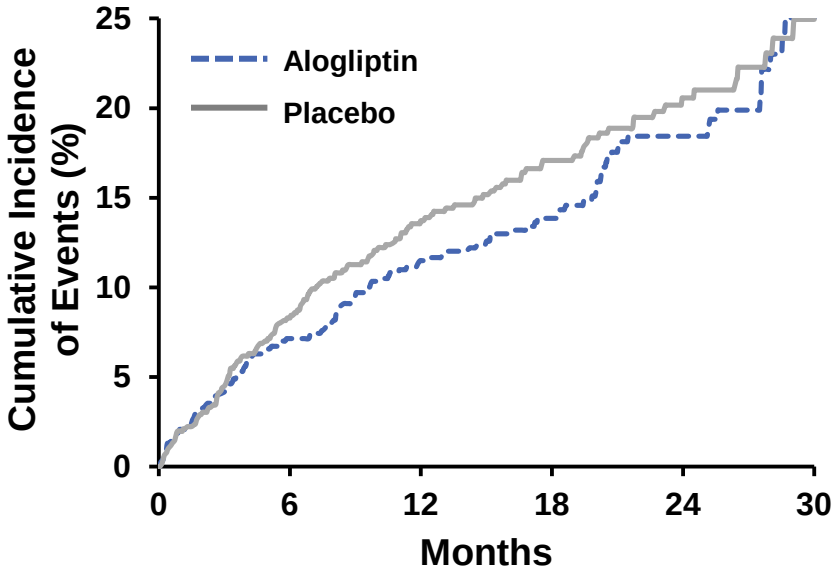

| No. at risk | | | | | | |
|---|---|---|---|---|---|---|
| Alogliptin | 1930 | 1709 | 1446 | 1085 | 663 | 257 |
| Placebo | 1917 | 1712 | 1443 | 1076 | 665 | 254 |

**Total Alo: 201; Total Pbo: 201  Overall HR 0.997  95% CI (0.820, 1.212)**

# All-Cause Mortality and HHF Composite by Baseline History of Heart Failure

## Patients With History of HF

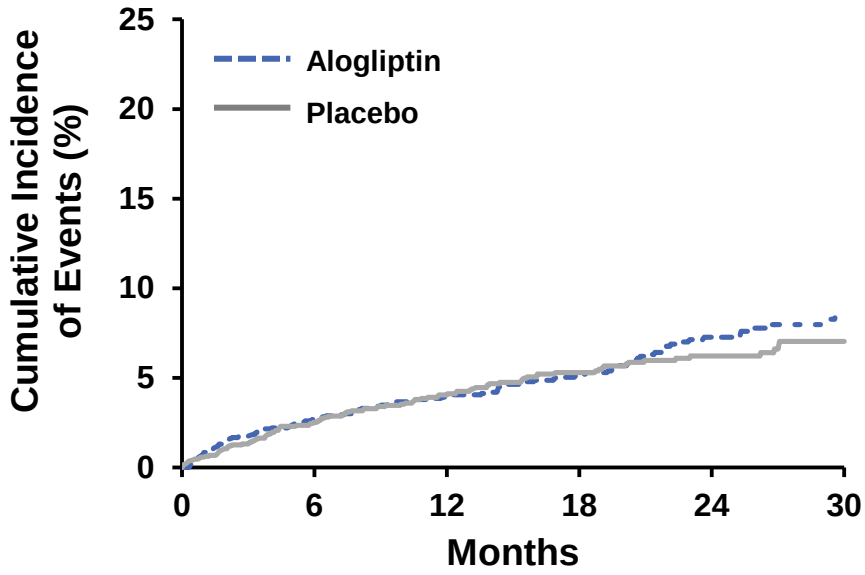
| | Events n (%) | Hazard Ratio (95% CI) |
|---|---|---|
| Alogliptin | 120 (15.6) | 0.909 (0.711–1.162) |
| Placebo | 133 (17.5) | |




| No. at risk | | | | | | |
|---|---|---|---|---|---|---|
| Alogliptin | 771 | 643 | 522 | 374 | 200 | 50 |
| Placebo | 762 | 635 | 504 | 356 | 193 | 60 |

## Patients With No History of HF

| | Events n (%) | Hazard Ratio (95% CI) |
|---|---|---|
| Alogliptin | 114 (5.9) | 1.065 (0.817–1.387) |
| Placebo | 106 (5.5) | |

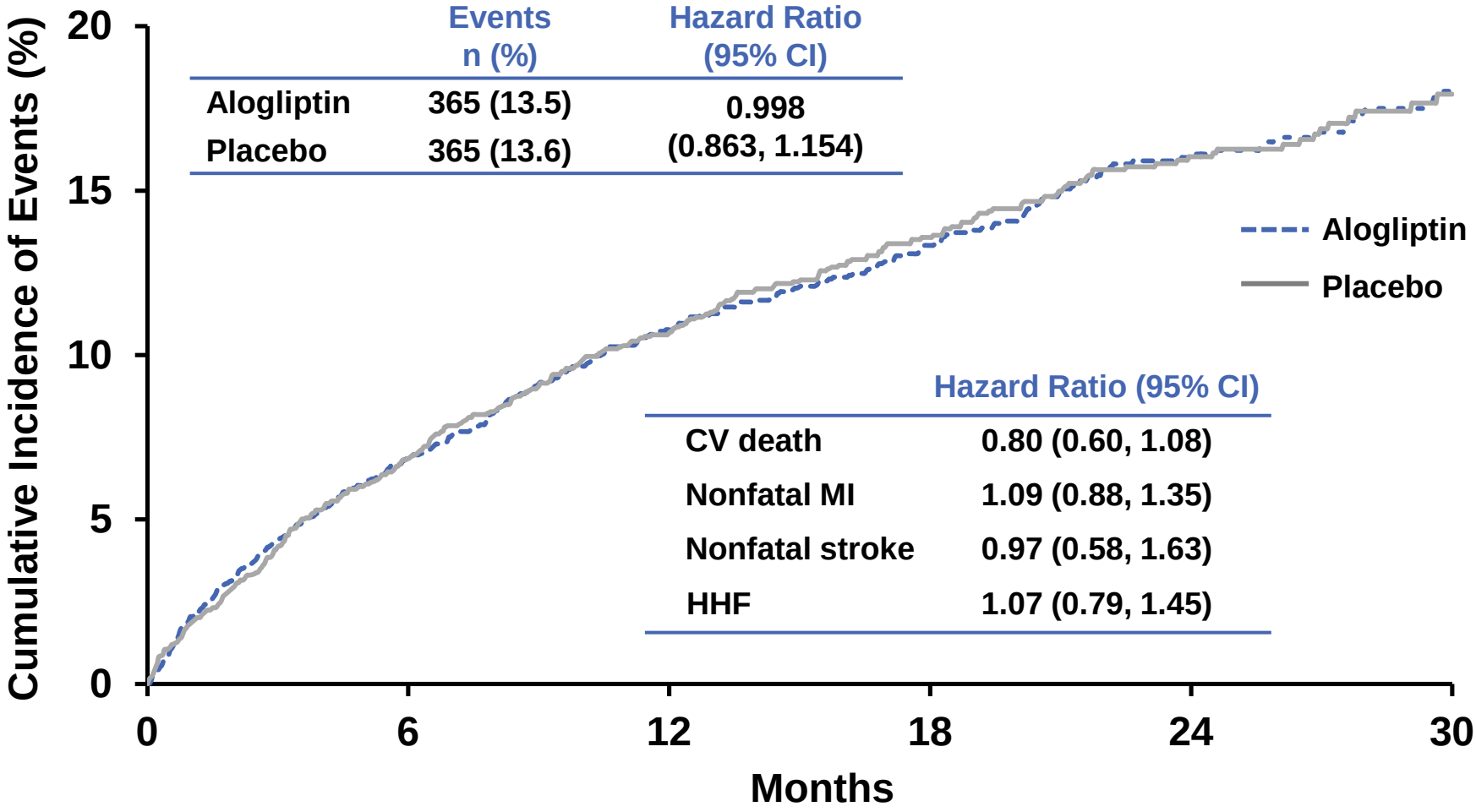



| No. at risk | | | | | | |
|---|---|---|---|---|---|---|
| Alogliptin | 1930 | 1708 | 1446 | 1083 | 656 | 250 |
| Placebo | 1917 | 1711 | 1442 | 1074 | 662 | 250 |

**Total Alo: 234; Total Pbo: 239  Overall HR 0.976  95% CI (0.816, 1.169)**

# Alogliptin vs. Placebo on Primary MACE and HHF Composite, and Individual Components

- Time to first event of CV death, nonfatal MI, nonfatal stroke, hospitalization for heart failure (HHF)



# Agenda for Takeda Presentation

| | |
|---|---|
| **Introduction** | **Stuart Kupfer, MD**<br>Therapeutic Area Head (CVM)<br>Takeda Development Center Americas, Inc. |
| **EXAMINE Study Results** | **William B. White, MD**<br>Chair, EXAMINE Steering Committee<br>Professor of Medicine<br>Calhoun Cardiology Center<br>University of Connecticut School of Medicine |
| **Clinical Perspective** | **Marc Pfeffer, MD, PhD**<br>Dzau Professor of Medicine, Harvard Medical School<br>Cardiovascular Division, Brigham & Women's Hospital |
| **Overall Safety and Conclusions** | **Stuart Kupfer, MD**<br>Therapeutic Area Head (CVM)<br>Takeda Development Center Americas, Inc. |

# Overall Safety and Conclusions

**Stuart Kupfer, MD**

Vice President

Clinical Science Cardiovascular/Metabolic (CVM)

Takeda Development Center Americas, Inc.

# Adverse Events of Special Interest

| Adverse Event, n (%) | Alogliptin N = 2701 | Placebo N = 2679 |
|---|---|---|
| Pancreatitis, acute | 12 (0.4) | 8 (0.3) |
| Pancreatitis, chronic | 5 (0.2) | 4 (0.1) |
| Hypersensitivity | 17 (0.6) | 13 (0.5) |
| Malignancy | 55 (2.0) | 51 (1.9) |
| Pancreatic cancer | 0 | 0 |
| Renal dialysis | 24 (0.9) | 22 (0.8) |
| Hypoglycemia | 181 (6.7) | 173 (6.5) |
| Hypoglycemia SAEs | 18 (0.7) | 16 (0.6) |

# Changes from Baseline in Liver Enzymes for Alogliptin and Placebo

| Markedly Abnormal Hepatic Criteria, n (%) | Alogliptin N = 2701 | Placebo N = 2679 |
|---|---|---|
| ALT >3x ULN | 64 (2.4) | 46 (1.8) |
| ALT >5x ULN | 24 (0.9) | 19 (0.7) |
| ALT >8x ULN | 9 (0.3) | 5 (0.2) |
| ALT 3x ULN and total bilirubin 2x ULN | 2 (<0.1) | 3 (0.1) |
| AST 3x ULN and total bilirubin 2x ULN | 2 (<0.1) | 4 (0.2) |

ULN – upper limits of normal.
Note: Liver function tests were monitored at every study visit following randomization, visits occurred every 3 to 4 months.

# Shifts in Renal Function from Baseline to Last Visit

CC-4

| Last Visit Renal Function | Baseline Renal Function, n (%) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Alogliptin N = 2701 | | | | Placebo N = 2679 | | | |
| | Normal N = 394 | Mild N = 1507 | Moderate N = 677 | Severe N = 72 | Normal N = 436 | Mild N = 1422 | Moderate N = 691 | Severe N = 75 |
| Normal | 266 (67.5) | 173 (11.5) | 3 (0.4) | 0 | 304 (69.7) | 195 (13.7) | 4 (0.6) | 0 |
| Mild | 126 (32.0) | 1123 (74.5) | 148 (21.9) | 0 | 129 (29.6) | 1054 (74.1) | 169 (24.5) | 3 (4.0) |
| Moderate | 2 (0.5) | 209 (13.9) | 475 (70.2) | 14 (19.4) | 3 (0.7) | 172 (12.1) | 474 (68.6) | 13 (17.3) |
| Severe | 0 | 2 (0.1) | 51 (7.5) | 58 (80.6) | 0 | 1 (0.1) | 44 (6.4) | 59 (78.7) |

- Shifts in renal function from mild to moderate and moderate to severe, were similar between alogliptin and placebo

# Renal Function Parameters for Alogliptin and Placebo



| Markedly Abnormal Renal Criteria, n (%) | Alogliptin N = 2650[a] | Placebo N = 2624[a] |
|---|---|---|
| BUN >3x ULN | 68 (2.6) | 73 (2.8) |
| Serum creatinine increase >1.5x baseline | 185 (7.0) | 157 (6.0) |
| Serum creatinine increase ≥2x from baseline | 54 (2.0) | 49 (1.9) |
| Serum creatinine increase >0.3 mg/dL from baseline | 411 (15.5) | 339 (12.9) |
| Serum creatinine >2.0 mg/dL | 183 (6.9) | 161 (6.1) |
| MDRD formula | | |
| eGFR decrease >25% from baseline | 560 (21.1) | 491 (18.7) |
| eGFR decrease >50% from baseline | 74 (2.8) | 64 (2.4) |

[a]Patients with a post-baseline value. Total patients randomized in study: Alogliptin = 2701; Placebo = 2679.

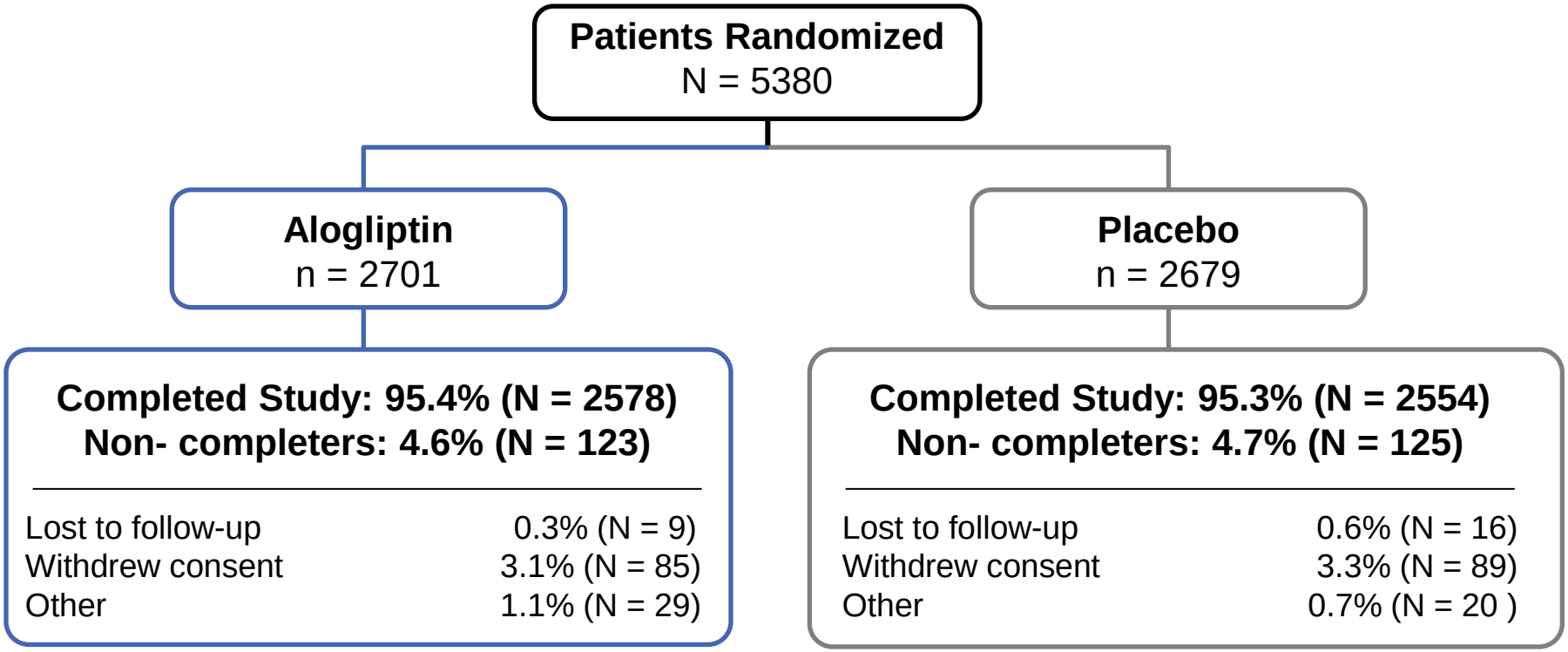
# EXAMINE Conclusions

EXAMINE results rule out excess CV risk, strengthen the favorable benefit-risk profile of alogliptin, and further support its use for the treatment of patients with T2D:

- Well conducted CV outcomes trial in a high-risk, T2D population
- CV risk was not increased with alogliptin treatment compared with placebo based on the conventional MACE composite endpoint of CV death, MI, and stroke
- Pattern of subgroup heterogeneity suggests random variation and supports the generalizability of results observed in the overall population
- Evaluation of heart failure burden, including mortality, did not indicate a clinically meaningful increased risk of heart failure
- Assessment of renal safety and other adverse events of special interest did not identify any new safety signals

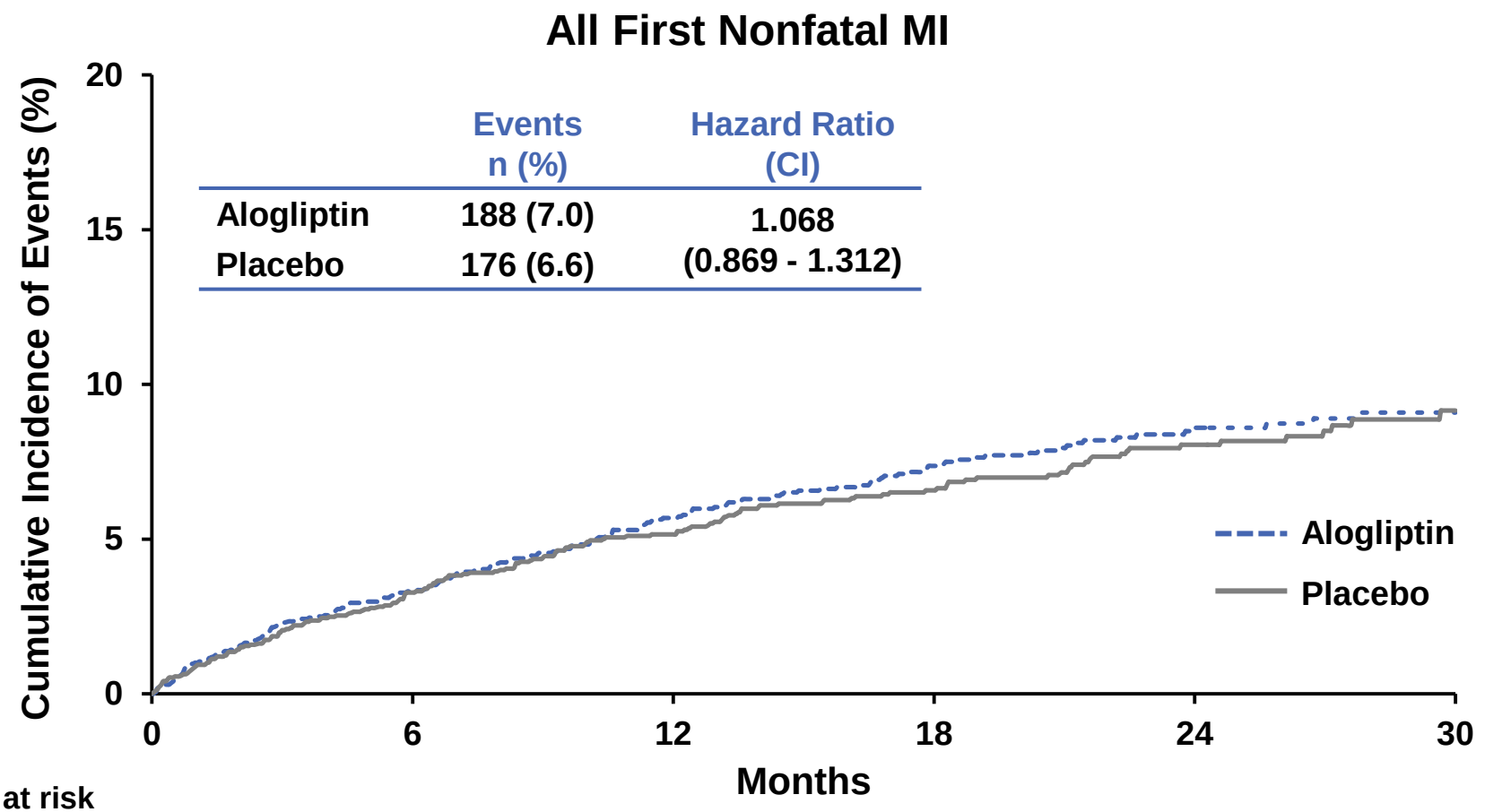
# BACKUP SLIDES SHOWN

# EXAMINE: Percentage of Study Completers*




* At end of study visit/ end of study telephone contact confirming whether any AE/SAEs were reported since last visit. All AEs/SAEs that met the predefined SMQ for CV events/ all deaths were submitted for adjudication

# Time to First Nonfatal MI



# Primary Adjudicated MACE Composite, Excluding MACE that Occur >30 Days Post-Treatment (FAS)

| | Alogliptin N = 2701 | Placebo N = 2679 |
|---|---|---|
| Number of Patients with, n (%) | | |
| Primary MACE composite | 272 (10.1) | 284 (10.6) |
| CV death | 72 (2.7) | 92 (3.4) |
| Nonfatal MI | 174 (6.4) | 163 (6.1) |
| Nonfatal stroke | 26 (1.0) | 29 (1.1) |
| Results from the Cox Proportional Hazards Model[a] | | |
| Hazard ratio (Alogliptin to Placebo) | 0.948 | |
| 1-sided P-value[b] | 0.262 | |
| Repeated 1-sided CI[c] | (0, 1.154) | |

Note: Primary MACE composite consists of CV death, nonfatal MI, and nonfatal stroke.
[a]Time from randomization to the first occurrence of any event in primary MACE composite was fit using the Cox proportional hazards model with treatment as the single factor, stratified by screening renal function and geographic region.
[b]P-value corresponds to the superiority test.
[c]Repeated 1-sided confidence interval (CI) corresponds to the non-inferiority tests.

# Sensitivity (On Treatment) Analysis of Composite of CV Death And HHF

| | Number of Patients, n (%) | | |
|---|---|---|---|
| | Alogliptin N = 2701 | Placebo N = 2679 | HR (95% CI) |
| Primary analysis (ITT) | 201 (7.5) | 201 (7.4) | 0.997 (0.820, 1.212) |
| Excluding events that occur >30 Days Post-Treatment | 172 (6.4) | 173 (6.5) | 0.981 (0.795, 1.211) |
| Excluding events that occur >7 Days Post-Treatment | 149 (5.5) | 151 (5.6) | 0.972 (0.776, 1.218) |

# On Treatment Analysis of CV Death and All-Cause Mortality

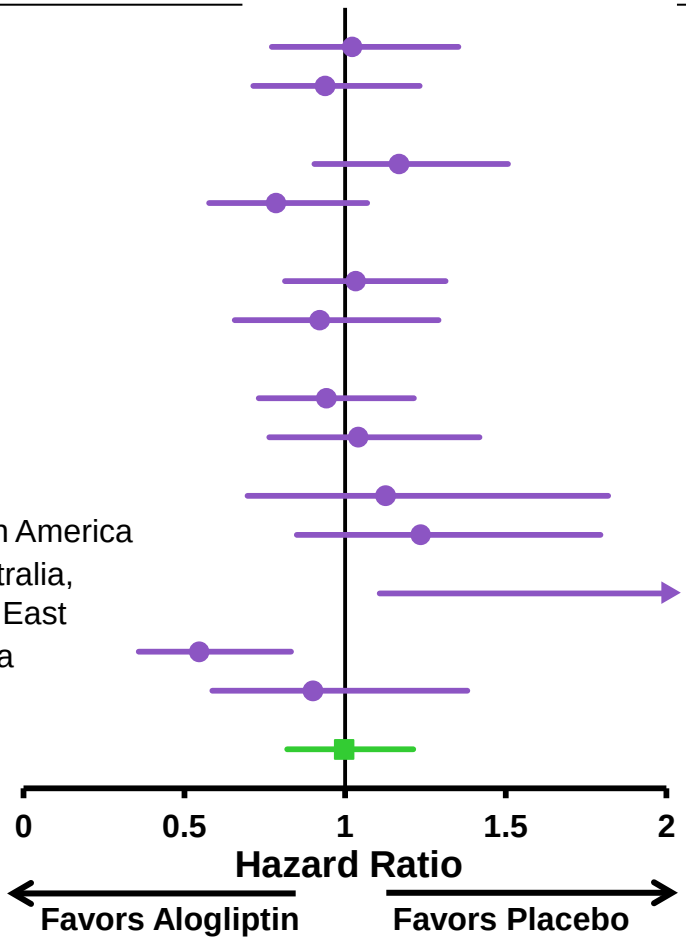


| | CV Death | | All-Cause Mortality | |
|---|---|---|---|---|
| | Alogliptin N = 2701 | Placebo N = 2679 | Alogliptin N = 2701 | Placebo N = 2679 |
| Intent to Treat analysis (ITT) N (%), HR (95% CI) | 112 (4.1) | 130 (4.9) | 153 (5.7) | 173 (6.5) |
| | 0.85 (0.66, 1.10) | | 0.88 (0.71, 1.09) | |
| Excluding Events >30 days post treatment N (%), HR (95% CI) | 86 (3.2) | 104 (3.9) | 108 (4.0) | 133 (5.0) |
| | 0.81 (0.61, 1.08) | | 0.80 (0.62, 1.03) | |
| Excluding Events > 7 days post treatment N (%), HR (95% CI) | 69 (2.6) | 84 (3.1) | 87 (3.2) | 104 (3.9) |
| | 0.81 (0.59, 1.11) | | 0.82 (0.62, 1.09) | |

# Composite of CV Death and HHF – Subgroup Analyses by Demographics (1)

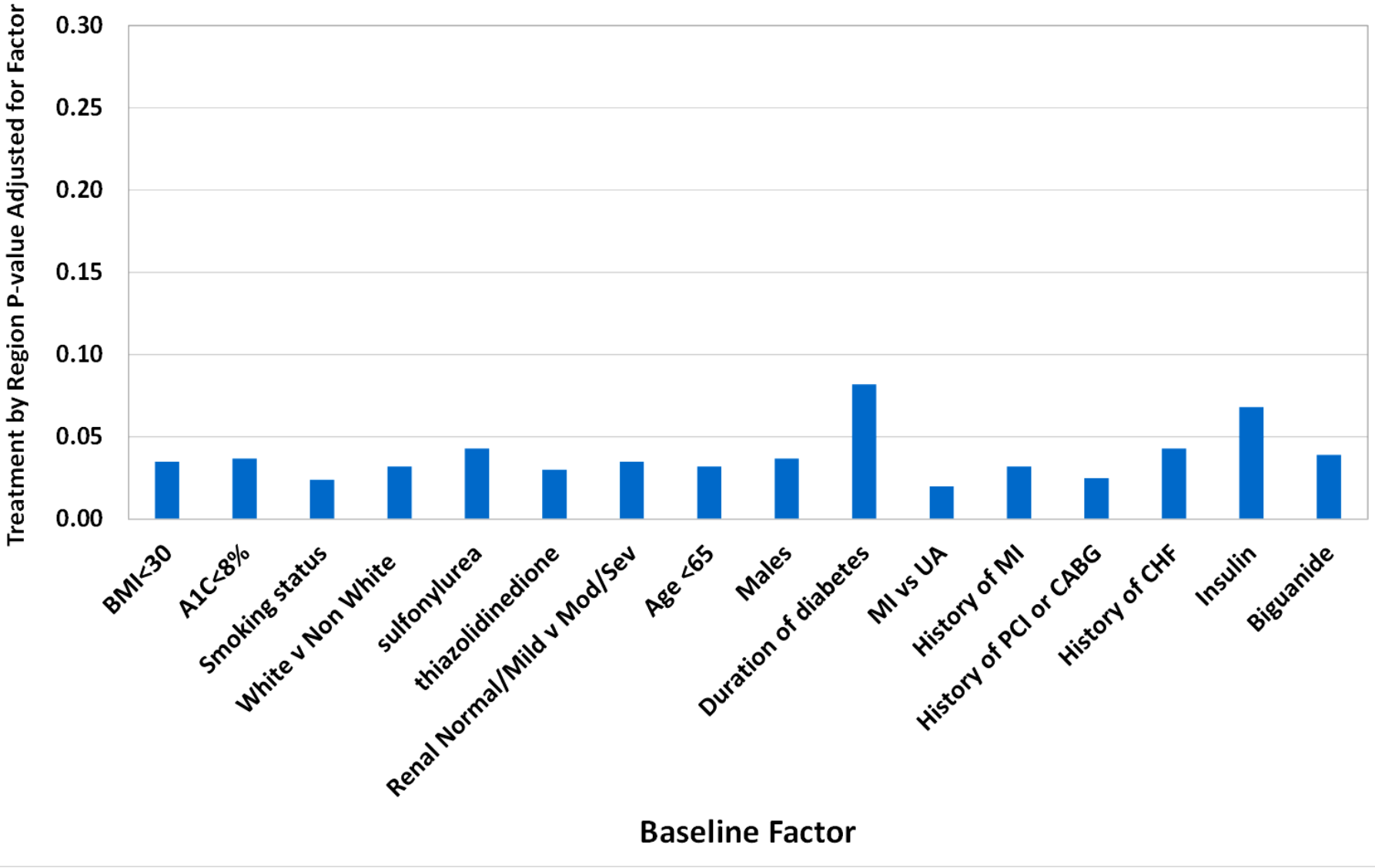


| Subgroup | | Alogliptin n (%)[a] | Placebo n (%)[a] | p-value[b] |
|---|---|---|---|---|
| **Baseline age** | <65 years | 98 (5.7) | 97 (5.6) | 0.686 |
| | ≥65 years | 103 (10.6) | 104 (11.1) | |
| **Sex** | Male | 128 (7.0) | 110 (6.0) | 0.059 |
| | Female | 73 (8.4) | 91 (10.6) | |
| **Race** | White | 137 (7.0) | 131 (6.7) | 0.609 |
| | Non-white | 64 (8.7) | 70 (9.5) | |
| **Baseline BMI** | <30 kg/m$^2$ | 116 (7.4) | 124 (7.7) | 0.611 |
| | ≥30 kg/m$^2$ | 85 (7.5) | 77 (7.2) | |
| **Geographic region** | US, Canada | 35 (8.2) | 32 (7.5) | |
| | Mexico, Central/South America | 61 (8.7) | 50 (7.2) | |
| | Western Europe, Australia, New Zealand, Middle East | 31 (9.9) | 15 (5.0) | 0.004 |
| | Eastern Europe, Africa | 34 (4.5) | 60 (8.0) | |
| | Asia/Pacific | 40 (7.9) | 44 (8.7) | |
| **Overall** | | | | |

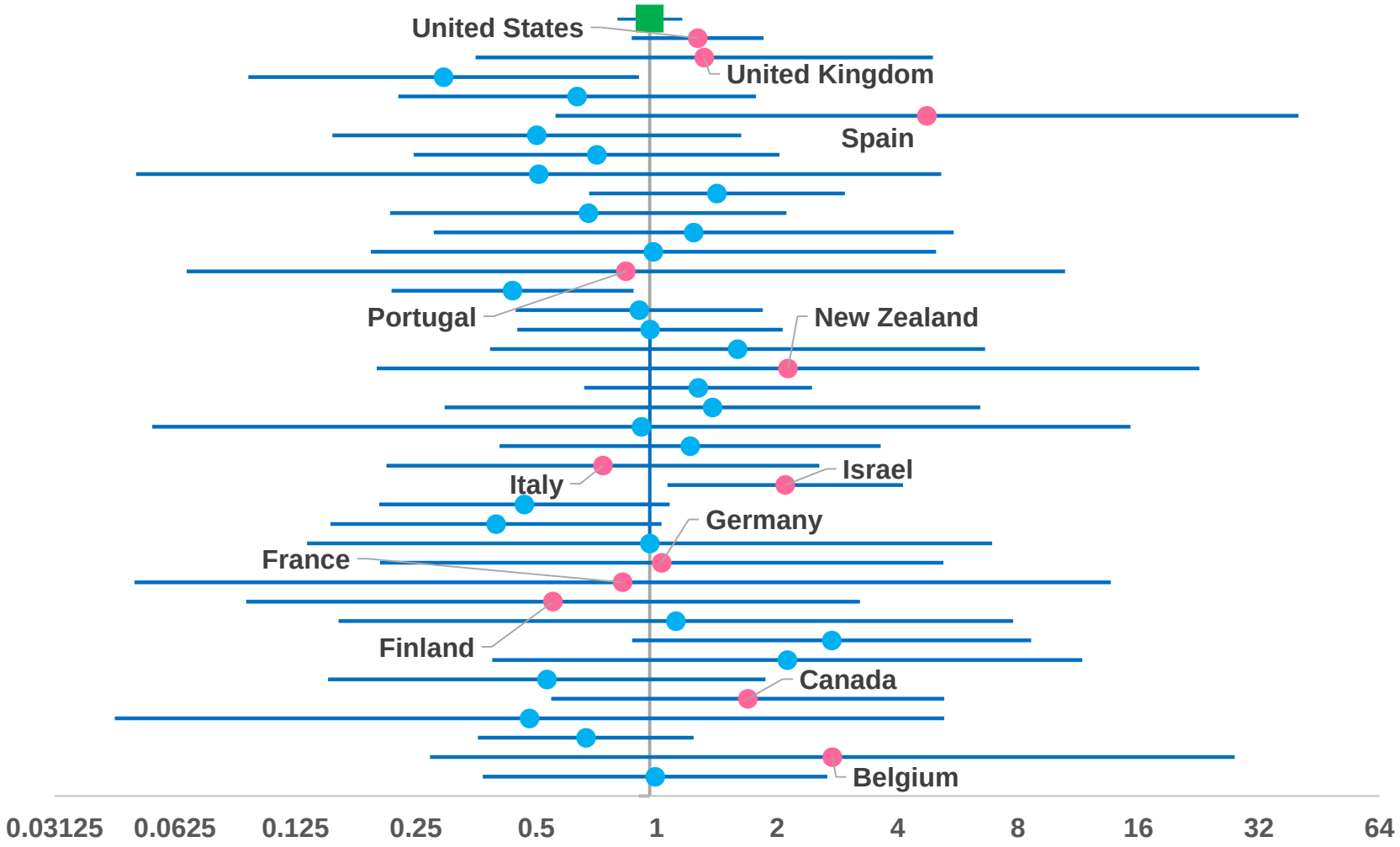



[a]N = total number of patients in subgroup, % = percent of patients with an event within the subgroup.
[b]Treatment interaction p-value.

# No Baseline Factors Confounded Geographic Region by Treatment Interaction



# Examine Primary Endpoint by Country: NA and West EU/Aus/NZ/M East



# Revascularization by Region:

| Type of Revascularization | Index ACS Event Type | Within 7 Days Post Index Event: US/Canada N = 853 | Mexico, Cen/ S. America N= 1393 | W. EU, AUS, NZ, ME N=616 | E.EU/Africa N=1508 | Asia Pacific N=1010 |
|---|---|---|---|---|---|---|
| Coronary Artery Bypass Graft Procedure, n (%) | Myocardial Infarction | 52 (6.1) | 15 (1.1) | 8 (1.3) | 15(0.9) | 7 (1.4) |
| | Unstable Angina | 21 (2.5) | 8 (0.6) | 5(0.8) | 5(0.3) | 5 (1.0) |
| Percutaneous Coronary Intervention (PCI), n (%) | Myocardial Infarction | 414 (48.5) | 453 (32.5) | 348 (56.4) | 473 (33.5) | 422 (41.7) |
| | Unstable Angina | 102 (12.0) | 86 (6.2) | 60 (9.7) | 98 (6.5) | 105 (10.4) |
| **Total, n (%)** | | **589 (69.1)** | **562 (40.3)** | **421 (68.3)** | **591 (39.1)** | **539 (53.3)** |

# Addition of Anti-Diabetic Medication During Study /Insulin Discontinuation