# Cardiovascular Outcome Trials vs. Cardiovascular Safety Trials Among DPP-4 Inhibitors

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# TECOS: Top Line results

On 27 April 2015, MSD announced that the Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) of MSD's DPP-4 inhibitor, JANUVIA® (sitagliptin), achieved its primary endpoint of non-inferiority for the composite cardiovascular (CV) endpoint.

Among secondary endpoints, there was no increase in hospitalization for heart failure in the sitagliptin group versus placebo.

The complete results of TECOS will be presented on June 8, 2015 at the 75th Scientific Sessions of the American Diabetes Association.

# Agenda

- CV outcome trials in diabetic patients
- FDA guidelines for CV safety of anti-diabetic drugs
- CV safety trials among the DPP-4 inhibitors
- TECOS

# Significance of Cardiovascular Outcomes in Patients With Diabetes

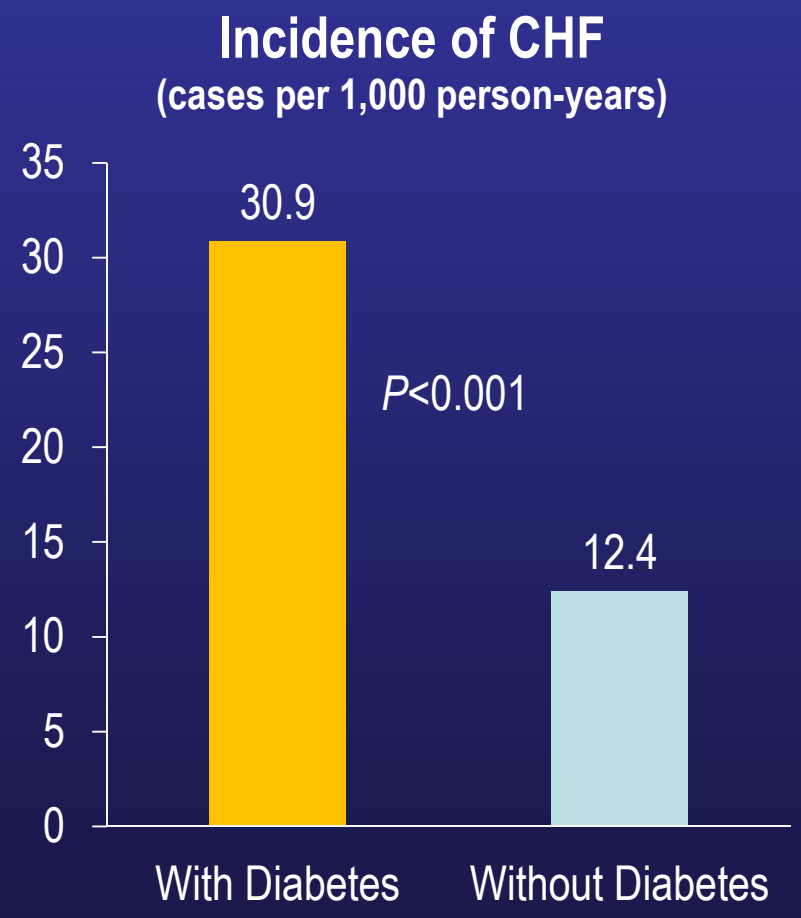
# Diabetes Is Associated With Increased Risk of CV Disease

- Diabetes confers an increased risk for MI, stroke, and PAD[1–3]
- It is not clear whether diabetes should be considered a cause or a comorbidity of heart failure[4]
  - Diabetes is associated with an increased risk of developing HF in patients with other causes (eg, acute MI) and is believed to promote diastolic dysfunction
- Diabetes is associated with a 2- to 3-fold increase in the risk of CV and all-cause mortality[5]

**1.** Emerging Risk Factors Collaboration. *Lancet.* 2010;375:2251–2222. **2.** American Diabetes Association. *Diabetes Care.* 2003;26:3333–3341. **3.** American Diabetes Association. *Diabetes Care.* 2014;37:S14–S80. **4.** McMurray JJV et al. *Lancet Diabetes Endocrinol.* 2014; DOI 10.1016/S2213-8587(14)70031-2. **5.** Gregg EW et al. *Ann Int Med.* 2007;147:149–156.

# Heart Failure in Patients With Type 2 Diabetes[1]

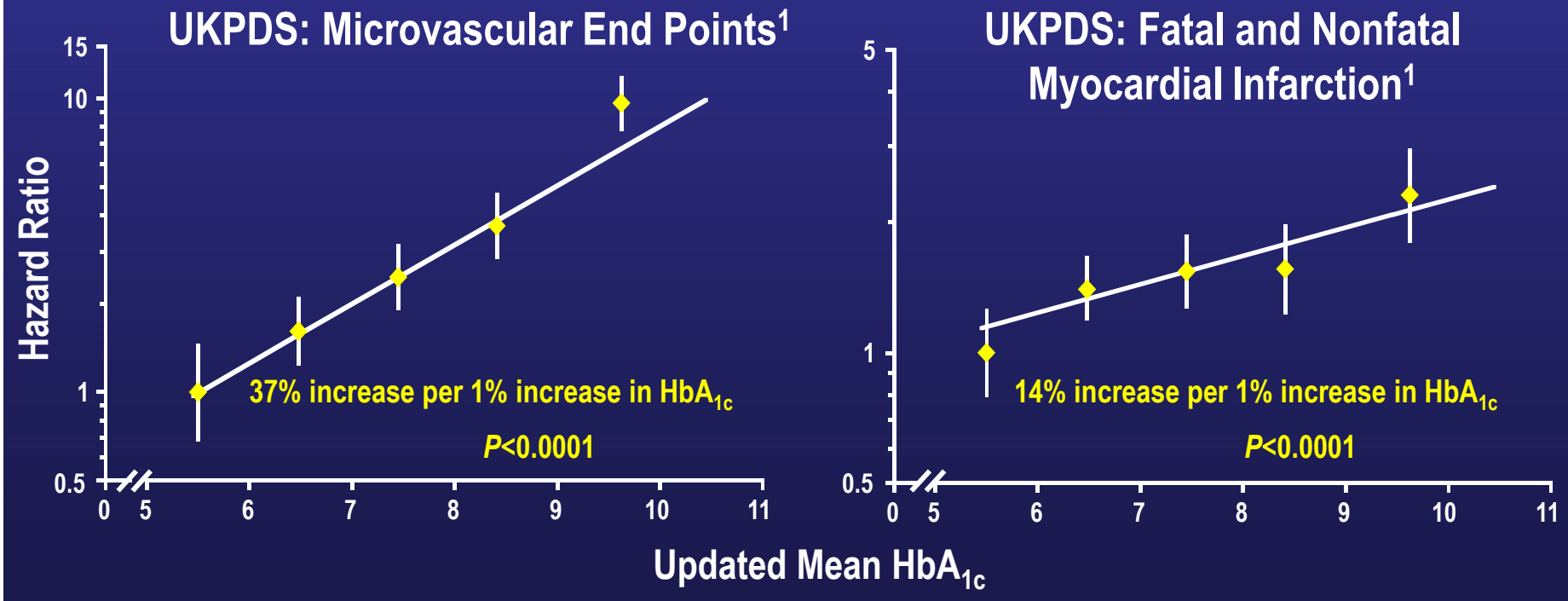
- Retrospective cohort study to update estimates of CHF rate in patients with T2DM
  - Follow-up of up to 72 months
- 1,167 of 8,231 patients with T2DM had incident CHF, vs 526 of 8,845 patients without T2DM
- Patients with T2DM experienced CHF at 2.5 times the rate of comparison subjects without T2DM
  - (rate ratio: 2.5 [95% CI 2.3–2.7])




**1.** Nichols G et al. *Diabetes Care*. 2004;27:1879–1884.

# $HbA_{1c}$ Is Associated With Outcomes

- Increases in $HbA_{1c}$ are correlated with both microvascular and macro-vascular disease complications[1,2]
- However, in clinical trials, interventions to lower $HbA_{1c}$ have only reduced microvascular complications[1,3,4]




**1.** Reproduced with permission from Stratton IM et al. *BMJ*. 2000;321:405–412. **2.** Gerstein HC et al. *Diabetologia*. 2010;53:2509–2517. **3.** ADVANCE Collaborative Group et al. *N Engl J Med*. 2008;358:2560–2572. **4.** Ismail-Beigi F et al. *Lancet*. 2010;376:419–430.

# Impact of Intensive vs Conventional Glycemic-Lowering Strategies on Risk of CV Outcomes Is Unclear

Lowering $HbA_{1c}$ may prevent macrovascular disease if started early, but the effects may not be apparent for a very long time

| Study | Diabetes Duration (mean) | Antihyperglycemic Medication[a] | Follow-up (median) | $HbA_{1c}$: Baseline, Between-arm Difference | Microvascular | CVD | Mortality |
|---|---|---|---|---|---|---|---|
| UKPDS[1] | Newly diagnosed | SU/insulin or metformin[a] vs dietary restriction | 10 years | 7.1% (all patients)[b], –0.9%[c] | ↓ | ↔ | ↔ |
| UKPDS Long-term follow-up[2] | | | 10 years post intervention | No difference in $HbA_{1c}$ between treatment arms[d] | ↓ | ↓ | ↓ |
| ADVANCE[3] | 8 years | Intensive glucose control including gliclazide vs standard treatment | 5 years | 7.5% (both arms)[b], –0.8%[d] | ↓ | ↔ | ↔ |
| ACCORD[4,5] | 10 years | Multiple drugs in both arms | 3.4 years | 8.1% (both arms)[e], –1.1%[c] | ↓ | ↔ | ↑ |
| VADT[6] | 11.5 years | Multiple drugs in both arms | 5.6 years | 9.4% (both arms)[b], –1.5%[d] | ↔ | ↔ | ↔ |

[a]Obese patients; [b]Mean baseline $HbA_{1c}$; [c]Median between-arm difference; [d]Mean between-arm difference; [e]Median baseline $HbA_{1c}$.
CV = cardiovascular; UKPDS = United Kingdom Prospective Diabetes Study (UKPDS); ADVANCE = Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation; ACCORD = Action to Control Cardiovascular Risk in Diabetes; VADT = Veterans Affairs Diabetes Trial.

**1.** UKPDS Group. *Lancet*. 1998;352:837–853. **2.** Holman RR et al. *N Engl J Med*. 2008;359:1577–1589. **3.** ADVANCE Collaborative Group et al. *N Engl J Med*. 2008;358:2560–2572. **4.** Gerstein HC et al. *N Engl J Med*. 2008;358:2545–2559. **5.** Ismail-Beigi F et al. *Lancet*. 2010;376:419–430. **6.** Duckworth W et al. *N Engl J Med*. 2009;360:129–139.

# Why CV Safety Is Important?


**FDA Issues Safety on Avandia,**

*"The U.S. Food and Drug Administration (FDA) is aware of a* ***potential safety issue*** *related to Avandia (rosiglitazone), a drug approved to treat type 2 diabetes. Safety data from controlled clinical trials have shown that there is a* ***potentially significant increase in the risk of heart attack and heart-related deaths*** *in patients taking Avandia…"*

Accessed 1st July: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2007/ucm108917.htm

# Impact of Antihyperglycemic Medications' Mechanisms of Action on Risk of CV Outcomes Is Unclear

| Study | Intervention (vs active/PBO) | Population | $HbA_{1c}$: Baseline, between-arm difference | Primary end point | Primary end point HR (95% CI) *P* value | Heart failure end point HR (95% CI) *P* value |
|---|---|---|---|---|---|---|
| RECORD[1] | Rosiglitazone + SU/Metformin vs SU/Metformin | No requirement for CV disease or risk factors[a] | 7.9%, –0.3%[b,c] | CV hospitalization, CV death | 0.99 (0.85–1.16) *P*=0.93 | 2.10 (1.35–3.27)[e] *P*=0.001 |
| ProACTIVE[2,3] | Pioglitazone vs Placebo | Extensive evidence or history of macrovascular disease | 7.8%–7.9%, –0.5%[b,d] | Death from any cause, nonfatal MI (including silent MI), stroke, ACS, leg amputation, revascularization of coronary or leg arteries | 0.90 (0.80–1.02) *P*=0.095 | 1.41 (1.10–1.80)[g] *P*=0.007 |
| SPREAD-DIMCAD[4] | Metformin vs Glipizide | History of CAD | 7.6%. –0.1%[c] | Death from any cause, CV death, nonfatal MI/stroke, PTCA, CABG | 0.54 (0.30–0.90) *P*=0.026 | 0.82 (0.31–2.13)[g] *P*=0.677 |

[a]Exclusions were hospitalization for a major CV event 3 months before the trial, planned CV intervention, and presence, history, or treatment for heart failure; [b]*P*<0.0001; [c]Mean between-arm difference; [d]Median between-arm difference; [e]Fatal and nonfatal HF; [f]Serious HF; [g]New or worsening HF.

**1.** Home PD et al. *Lancet.* 2009;373:2125–2135. **2.** Dormandy JA et al. *Lancet.* 2005;366:1279–1289. **3.** Erdmann E et al. *Diabetes Care.* 2007;30:2773–2278. **4.** Hong J et al. *Diabetes Care*. 2013;36:1304–1311.

# FDA Guidelines for Cardiovascular Safety Trials for Antihyperglycemic Medications

# 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**)

**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.

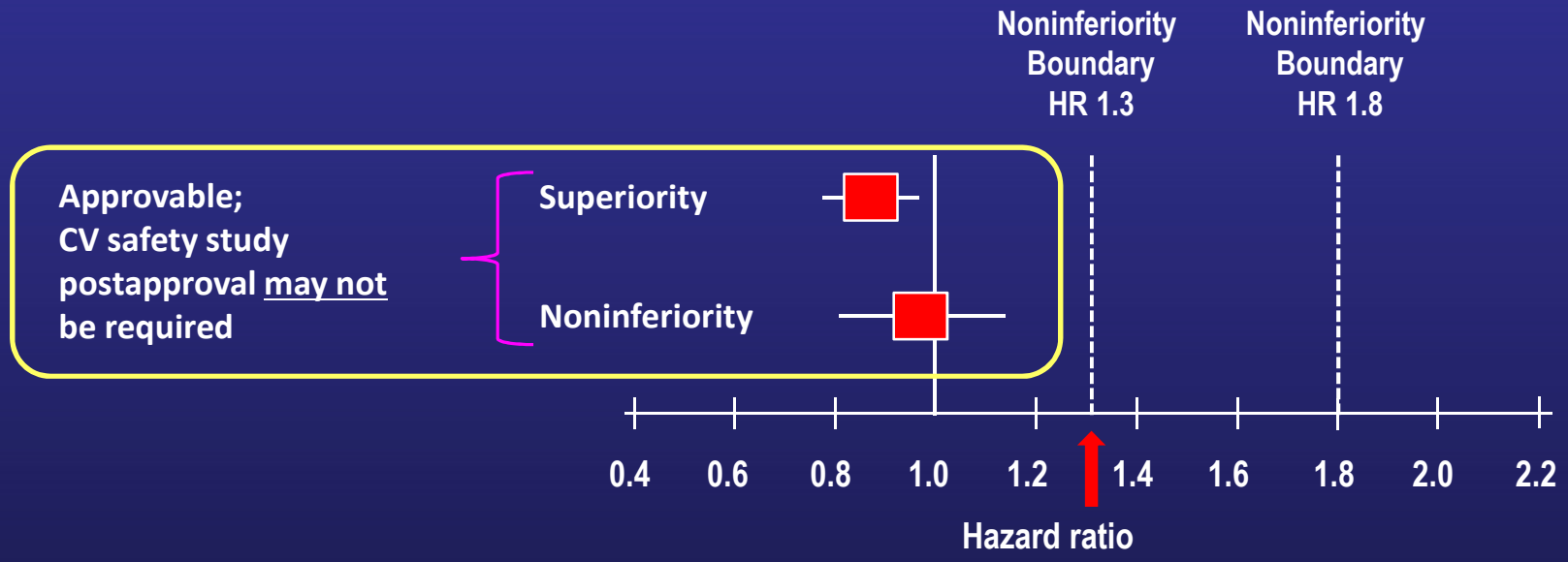
# FDA Statistical Hurdles for Approval[1]

- If the upper bound of the two-sided 95% CI for HR is <1.3 (after interim analysis) and the overall risk-benefit analysis **supports approval,** a postmarketing CV trial may not be needed
- If the upper bound of the two-sided 95% CI for HR is between 1.3 and 1.8, **a postmarketing trial** will be required to definitively assess whether upper bound is <1.3 before obtaining approval
- If the upper bound of the two-sided 95% CI for HR is >1.8, the drug is **not approvable**

**1.** Hirshberg B et al. *Diabetes Care.* 2011:34;S101–S106.

# FDA Statistical Hurdles for Approval[1]

Hypothetical examples of possible HRs, and regulatory consequences

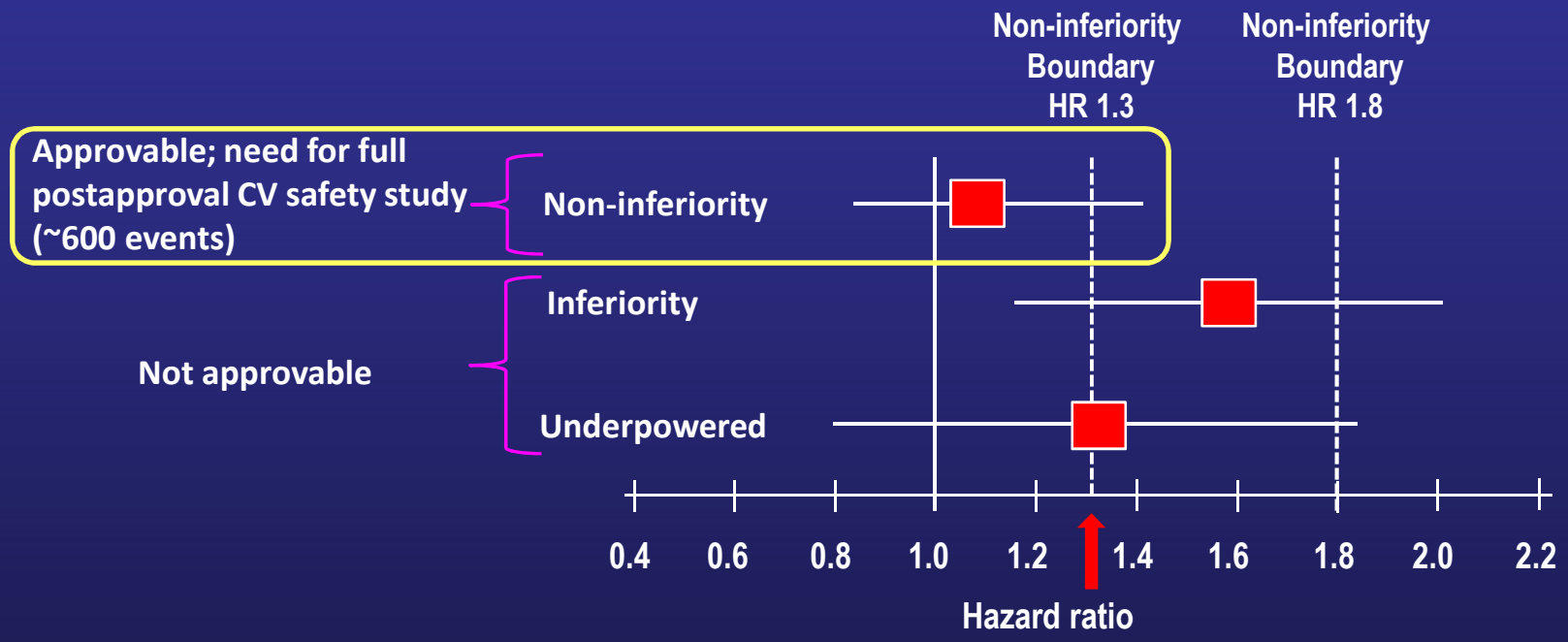



If the upper bound of two-sided 95% CI for HR is <1.3, a postmarketing CV trial may not be required under normal conditions.

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

# FDA Statistical Hurdles for Approval[1]

Hypothetical examples of possible HRs, and regulatory consequences

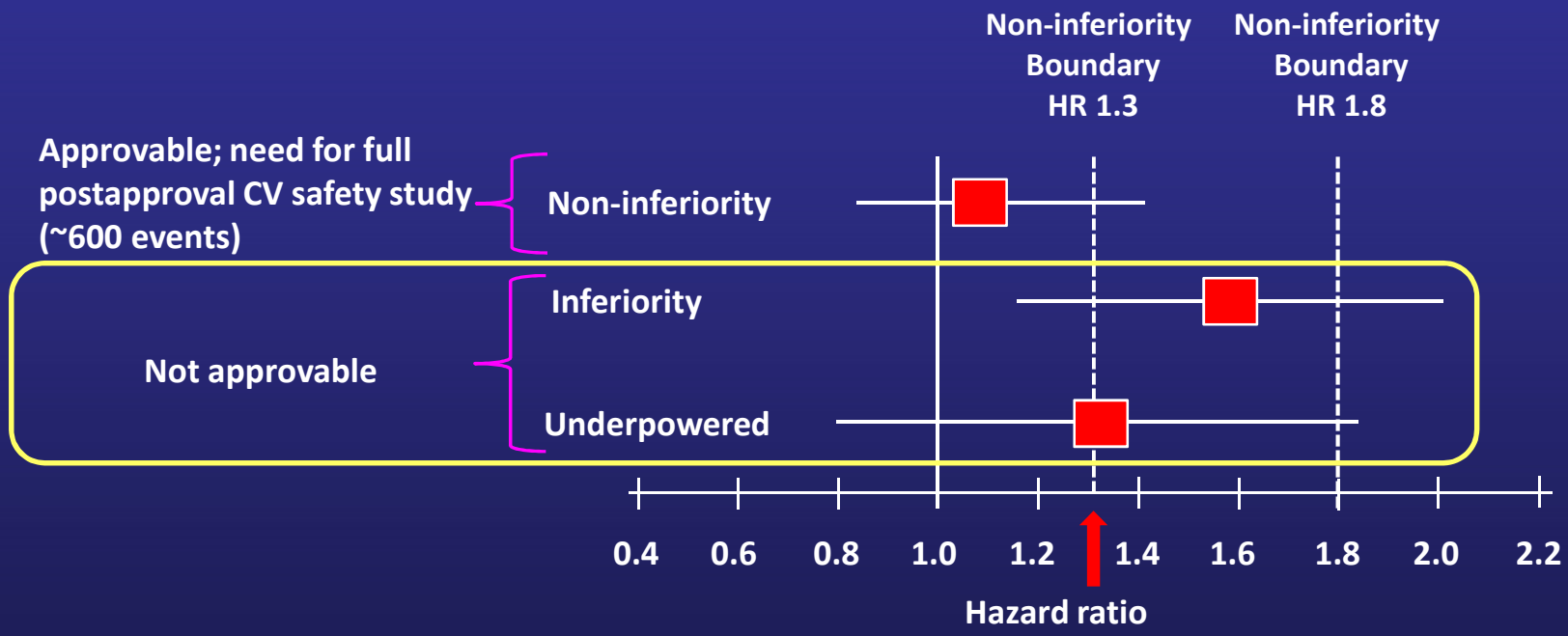



If upper bound of two-sided 95% CI for HR is between 1.3 and 1.8, a postmarketing full CV safety trial will be required to definitively assess whether upper bound is <1.3.

1. Reproduced with permission from Hirshberg B et al. Diabetes Care. 2011:34;S101–S106.

# FDA Statistical Hurdles for Approval[1]

Hypothetical examples of possible HRs, and regulatory consequences




If the upper bound of the two-sided 95% CI for HR is >1.8, the drug is not approvable and a full safety trial is required prior to approval.

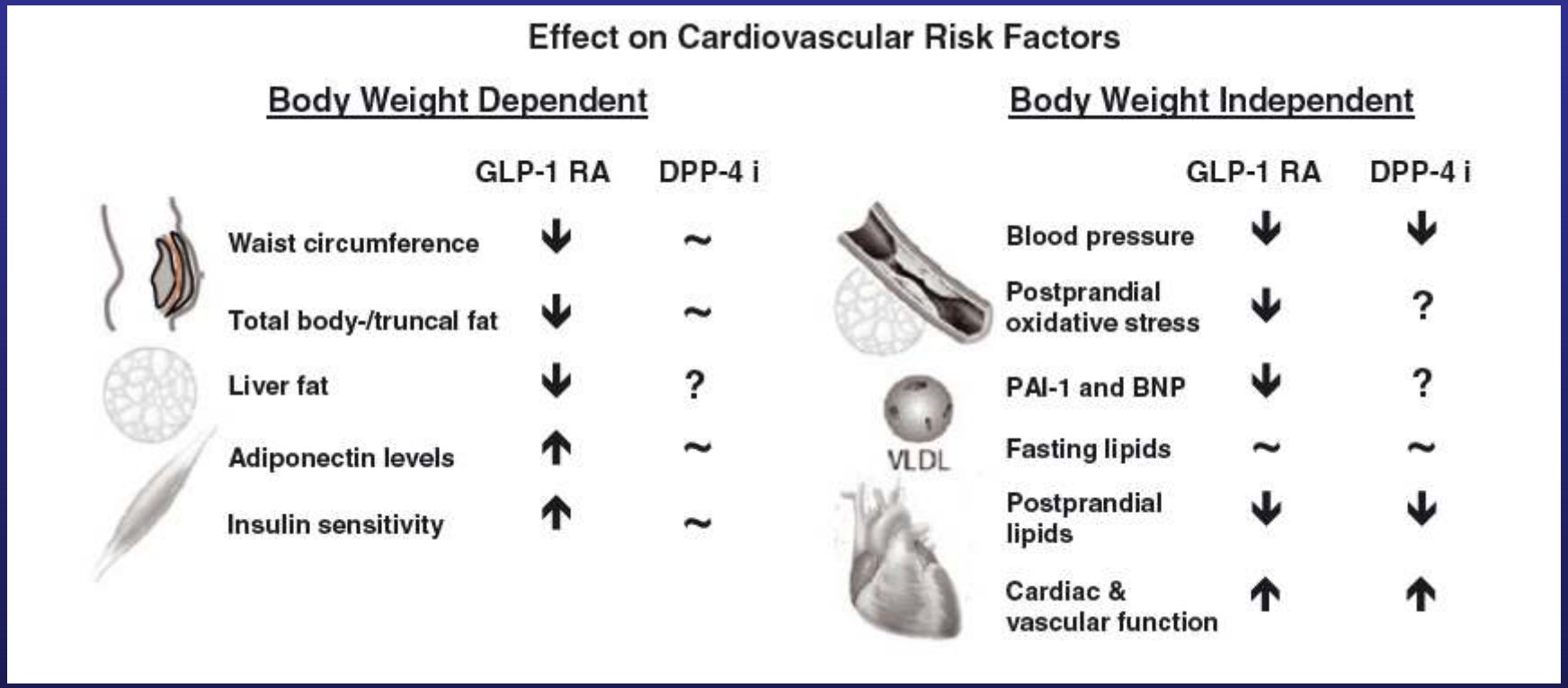
**1.** Reproduced with permission from Hirshberg B et al. *Diabetes Care.* 2011:34;S101–S106.

# Selected Cardiovascular Outcomes Trials Among DPP-4 Inhibitors

# Cardioprotective effect of GLP-1 in pre-clinical studies

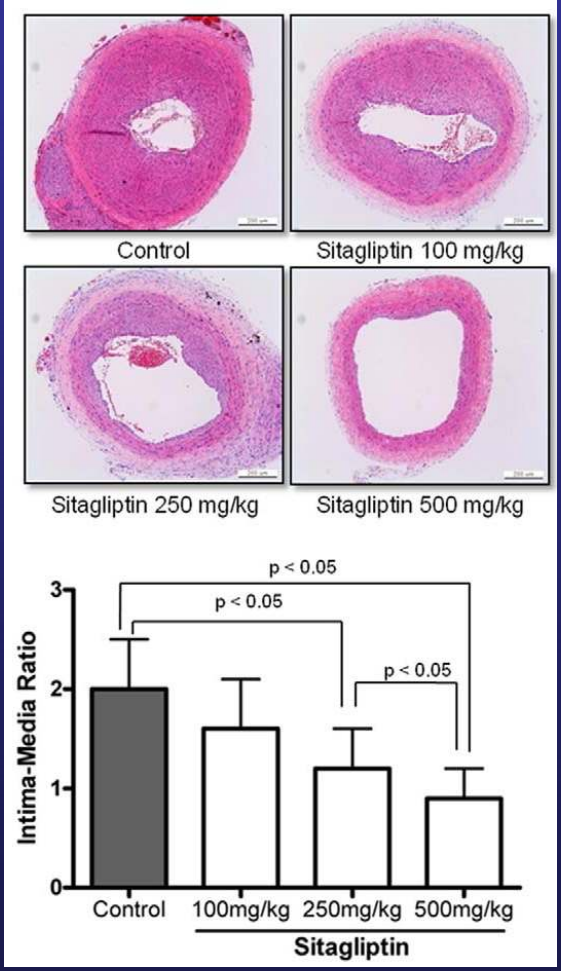
- Increase myocardial glucose uptake
- Enhance recovery of cardiac function after ischemia
- Limit myocardial infarction
- Reduction in infarct size
- Prevention of apoptosis of cardiomyocytes
- Decreased proliferation and migration of VSMCs
- Upregulate the production of vasodilatory NO
- Improve endothelial function

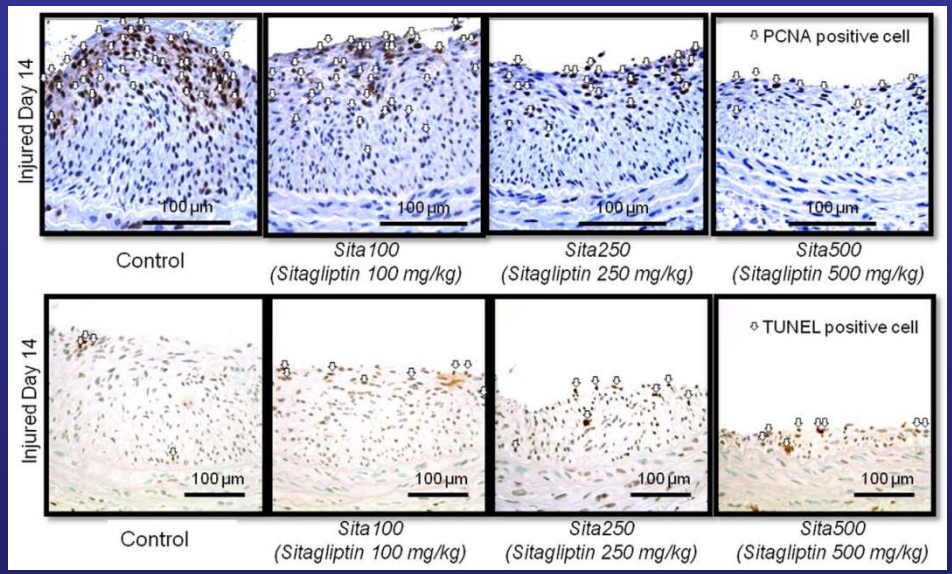
# The effect of incretin-based therapies on CV risk factors in patients with type 2 diabetes

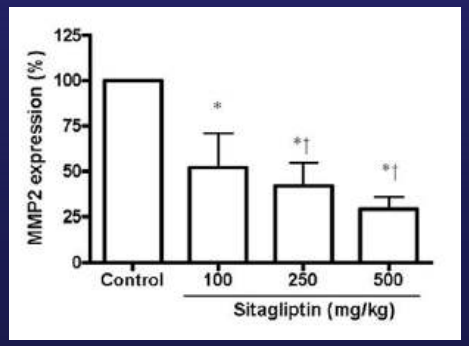


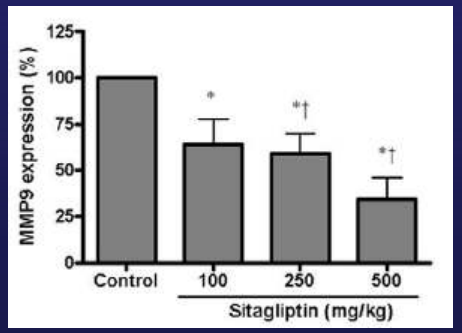

*Diabetes Obes Metab 2013:15;593-606*

# 3 wks of sitagliptin treatment on neointimal formation after balloon injury in rats




*PLoS One 2012:7;e35007*

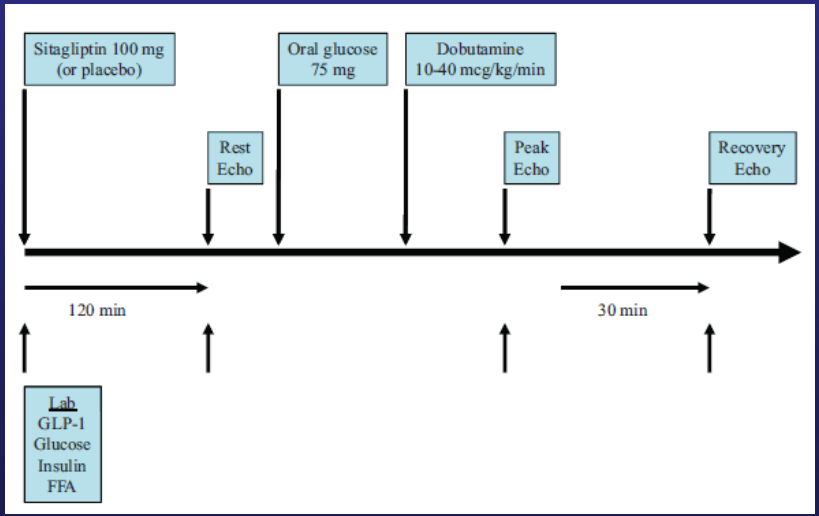
Circulation
Cardiovascular Imaging

American Heart Association

**DPP-4 Inhibition by Sitagliptin Improves the Myocardial Response to Dobutamine Stress and Mitigates Stunning in a Pilot Study of Patients With Coronary Artery Disease**

Philip A. Read, Fakhar Z. Khan, Patrick M. Heck, Stephen P. Hoole and David P. Dutka

A single dose of sitagliptin 100mg acutely prevented the decline in LV function induced by dobutamine infusion, in patients with coronary artery disease.



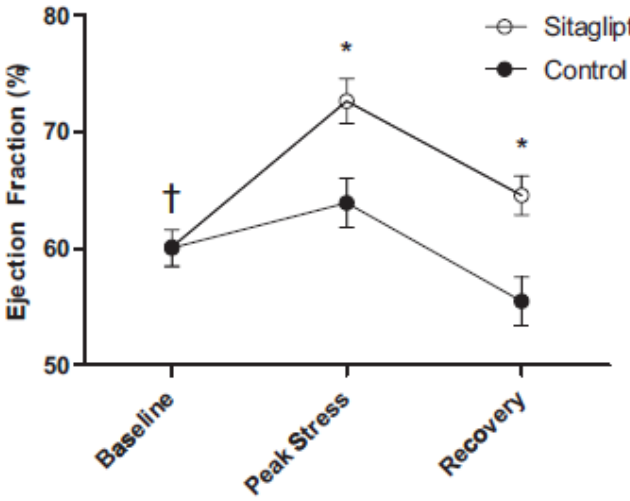
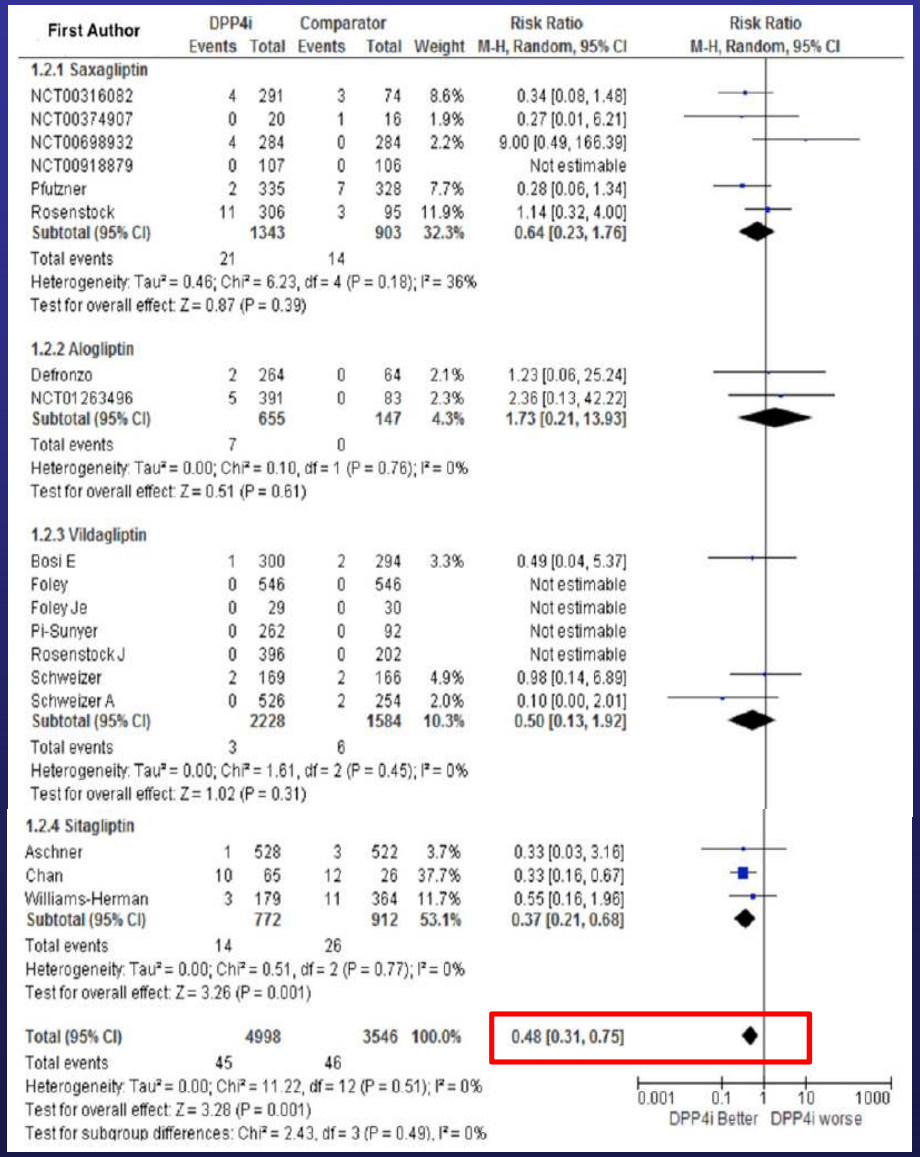




**Figure 4.** Global LV function assessed by LV ejection fraction (mean±SEM) at baseline, peak stress, and 30-minute recovery. *$P<0.001$. †No significant difference for comparisons between sitagliptin and control.

# Meta-analysis of effect of DPP-IV inhibitors on CV risk in type 2 diabetes




*Am J Cardiol 2012:110;826-833*

# Purpose of CV Outcomes Trials With DPP-4 Inhibitors

- CV outcomes trials for DPP-4 inhibitors are designed to demonstrate no increased CV risk vs placebo when used as part of usual care[1–3,a]
- CV outcomes trials for DPP-4 inhibitors are not designed to evaluate a CV benefit of $HbA_{1c}$ reduction[3–5]
  - $HbA_{1c}$ is intended to be similar between the two groups through adjustment of antihyperglycemic medications according to local treatment guidelines
  - CV safety and CV benefit can be evaluated independently of $HbA_{1c}$

[a]Patients enrolled in CV outcomes trials with DPP-4 inhibitors have a high risk of CV events (ie, have established CV disease or multiple CV risk factors).

**1.** White WB et al. *Am Heart J.* 2011;162:620–626.e7. **2.** Scirica BM *Am Heart J.* 2011;162:818–825.e6. **3.** Green JB et al. *Am Heart J.* 2013;166:983–989.e7. **4.** White WB et al. *N Engl J Med.* 2013;369:1327–1335. **5.** Scirica BM et al. *N Engl J Med*. 2013;369:1317–1326.

# Traditional CV Outcome Trials vs DPP-4 Inhibitor CV Outcome Trials

**Traditional CV outcome trials[1,2]:**
Demonstrate CV benefit *(lower CV risk vs placebo or active comparator)*

**DPP-4 inhibitor CV outcome trials[3–5]:**
Demonstrate CV safety *(no increased CV risk vs placebo as part of standard care)*

**Traditional (eg, LDL-C) CV Outcome Trials[1,2]**

Initiation of blinded treatment or placebo

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

↓

Difference in LDL-C between treatment and placebo

↓

CV benefit of treatment demonstrated by significant reduction in CV outcomes

**DPP-4 Inhibitor CV Outcome Trials[3–5]**

Initiation of blinded treatment or placebo

↓

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

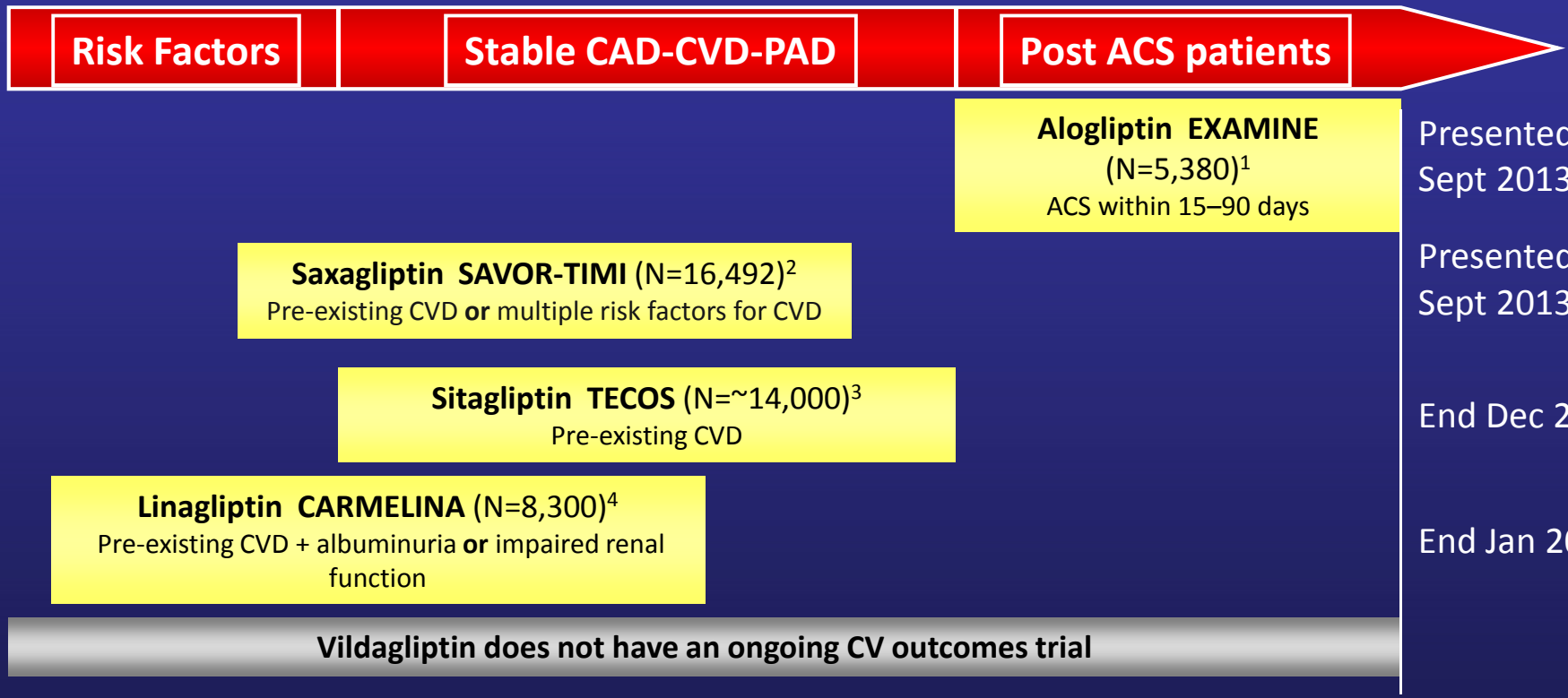
Small or no difference in $HbA_{1c}$ between treatment and placebo

↓

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

**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. .

# Baseline Risk of Patient Populations Enrolled in CV Safety Trials of DPP-4 Inhibitors



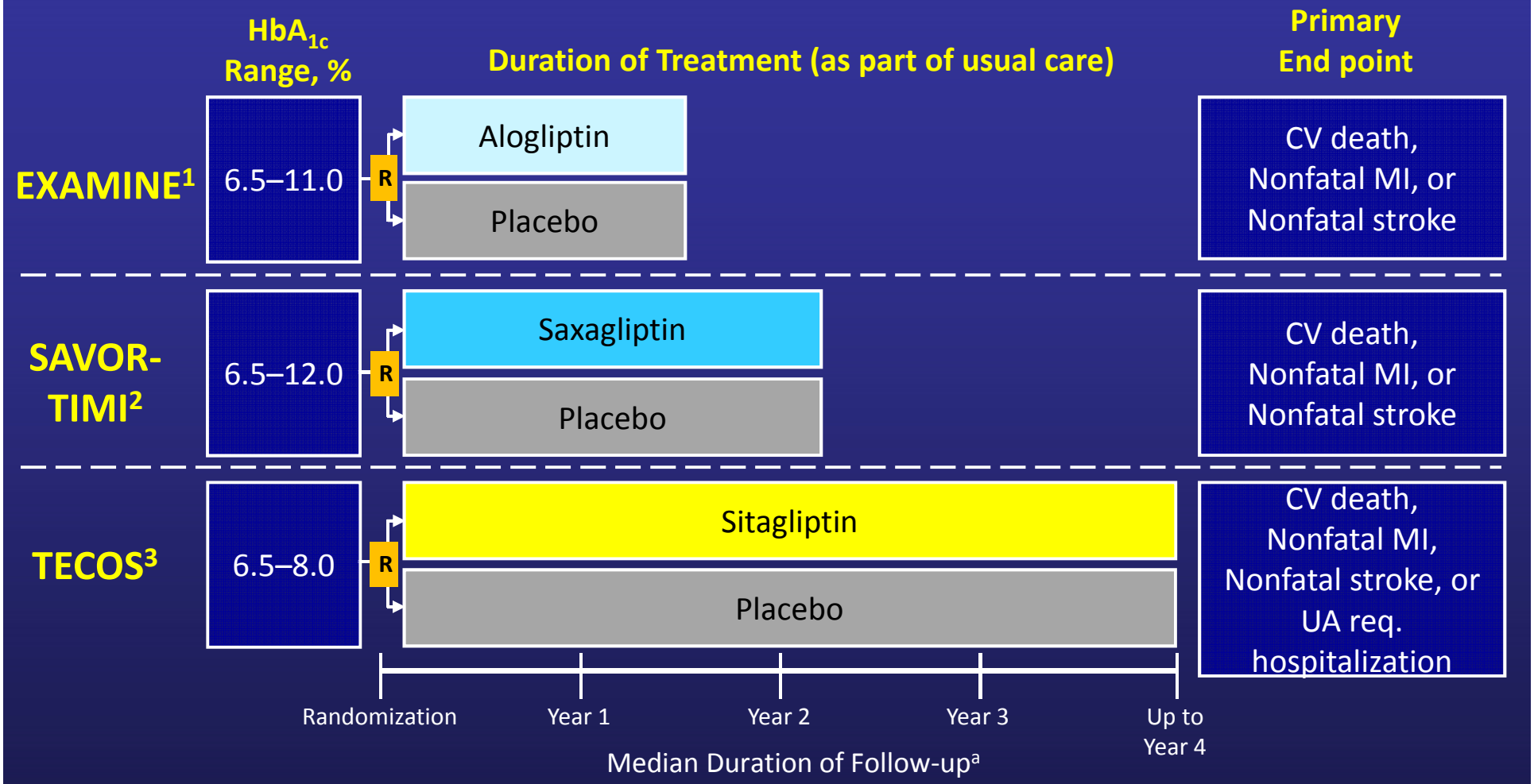

**1.** White W et al. *N Engl J Med*. 2013;369:1327–1335. **2.** Scirica BM et al. *N Engl J Med*. 2013;369:1317–1326. **3.** Green JB et al. *Am Heart J* 2013;166:983–989.e7. **4.** CARMELINA: Cardiovascular and renal microvascular outcome study with linagliptin in patients with type 2 diabetes mellitus at high vascular risk. ClinicalTrials.gov web site. http://clinicaltrials.gov/ct2/show/ NCT01703298. Accessed September 12, 2014.

# EXAMINE, SAVOR-TIMI, and TECOS

| | EXAMINE[1] | SAVOR-TIMI[2] | TECOS[3] |
|---|---|---|---|
| | *Alogliptin vs Placebo* | *Saxagliptin vs Placebo* | *Sitagliptin vs Placebo* |
| **Sample size, N** | 5,380 | 16,492 | ~14,000 |
| **Median duration of diabetes, y** | ≈7.2 | 10.3 | 11.0 |
| **Baseline $HbA_{1c}$, %** | 8.0 | 8.0 | 7.3 |
| **Number of events** | 621 | 1,222 | >1,300 |
| **Median duration of exposure, y** | 1.5 | 2.1 | Up to 4.0 |

**1.** White WE et al. *N Engl J Med.* 2013:369:1327–1335. **2.** Scirica BM et al. *N Engl J Med.* 2013:369:1317–1326. **3.** Green JB et al. *Am Heart J* 2013;166:983–989.e7.

# EXAMINE, SAVOR-TIMI, and TECOS




[a]Approximate median duration of follow-up for TECOS, based on the expected event rate at study initiation.

**1.** White WB et al. *N Engl J Med.* 2013;369:1327–1335. **2.** Scirica BM et al. *N Engl J Med* 2013;369:1317–1326. **3.** Green JB et al. *Am Heart J.* 2013;166:983–989.e7.

# EXAMINE: Results Summary[1]

- Alogliptin was noninferior for the primary composite end point of CV death, nonfatal MI, and nonfatal stroke
  - Alogliptin 11.3% vs placebo 11.8%; HR (upper bound of 95% CI) = 0.96 (1.16)
- Treatment with alogliptin did not significantly increase the incidence of pancreatitis or pancreatic cancer compared with placebo
- Alogliptin and placebo groups did not differ significantly with respect to the incidence of serious adverse events, including hypoglycemia, cancer, angioedema, elevated serum aminotransferase values, and changes in eGFR
  - Alogliptin 33.6% vs placebo 35.5%; *P*=0.14

**1.** White WB, et al. *N Engl J Med.* 2013;369:1327–1335.

# SAVOR-TIMI: Results Summary[1]

- Saxagliptin was noninferior for the primary composite end point of CV death, nonfatal MI, and nonfatal stroke
  - Saxagliptin 7.3% vs placebo 7.2%; HR (95% CI) = 1.00 (0.89–1.12)
- Treatment with saxagliptin did not significantly increase the incidence of pancreatitis or pancreatic cancer compared with placebo
- Saxagliptin was associated with an increase in hypoglycemia compared with placebo (15.3% vs 13.4%; *P*<0.001)
- Treatment with saxagliptin did not significantly increase the incidence of thrombocytopenia, lymphocytopenia, infections, cancers, hypersensitivity or skin reactions, bone fractures, or liver abnormalities

**1.** Scirica BM et al. *N Engl J Med.* 2013;369:1317–1326.

# EXAMINE and SAVOR-TIMI: Hospitalization for Heart Failure

## EXAMINE[1,2]

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

EXAMINE: In a post-hoc analysis, there was a trend (*P*=NS) for increased hospitalization for HF with alogliptin compared with placebo[2]

## SAVOR-TIMI[3]

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

SAVOR-TIMI: Hospitalization for HF was significantly increased with saxagliptin compared with placebo[3]

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

[a]Post-hoc analysis.

**1.** Reproduced with permission from White WB et al. *N Engl J Med* 2013;369:1327–1335. **2.** 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.

# DPP-4 Inhibitor CV Outcome Trials Were *Not* Designed to Demonstrate CV Risk Reductions Based on Differences in Glycemic Control

**EXAMINE and SAVOR-TIMI[1,2]**

- Differences in $HbA_{1c}$ in the DPP-4 inhibitor arms vs placebo arms were small because usual care was pursued in both study arms by the use of additional antihyperglycemic medications

**TECOS[3]**

- Design permits rapid equalization of glycemic control between groups
- Glycemic equality between groups will permit assessment of the CV effects of sitagliptin independently of its glucose-lowering effects

**1.** White WB et al. *N Engl J Med.* 2013;369:1327–1335. **2.** Scirica BM et al. *N Engl J Med* 2013;369:1317–1326. **3.** Green JB et al. *Am Heart J.* 2013;166:983–989.e7.

# Trial Evaluating Cardiovascular Outcomes With Sitagliptin (TECOS)

# TECOS: Study Objective[1]

- To assess cardiovascular outcomes and clinical safety of long-term treatment with sitagliptin used as part of usual care compared with usual care without sitagliptin in patients with type 2 diabetes and a history of cardiovascular disease and inadequate glycemic control

- TECOS will primarily test the hypothesis that sitagliptin, when used as part of usual diabetes care, is noninferior to usual care without sitagliptin with regard to the risk of significant confirmed cardiovascular outcomes

- If sitagliptin is found to be noninferior to usual care without sitagliptin, an assessment of superiority will be performed

TECOS = Trial Evaluating Cardiovascular Outcomes With Sitagliptin.

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

# TECOS: Study Design[1]

- Randomized, double-blind, placebo-controlled safety study
- Approximately 14,000 patients with type 2 diabetes
- Event-driven trial that will continue until 1,300 confirmed CV events have occurred
- Integrated study design with no interruption of usual care[a]
  - Sitagliptin vs placebo will be added to the ongoing care regimen
- Desired outcome of glycemic equipoise between treatment arms to assess CV effects of sitagliptin independent of glucose-lowering effects
- Once-daily sitagliptin 50-mg or 100-mg oral tablet at randomization, dose dependent on renal function
  - Dose could be reduced to 50 mg or 25 mg once daily during the study

[a]Usual care defined as stable-dose monotherapy or dual combination therapy with metformin, pioglitazone, or a sulfonylurea. Also includes stable dose of insulin, either alone or in combination with a stable dose of metformin for at least 3 months.

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

TECOS

# TECOS: Selected Inclusion Criteria[1]

Inclusion criteria included:

- Aged ≥50 years with type 2 diabetes
- Documented vascular disease in the coronary, cerebral, or peripheral arteries
- Patients with inadequate control ($HbA_{1c}$ of 6.5%–8.0%) for at least 3 months despite:
  - Stable-dose monotherapy or dual combination therapy with metformin, pioglitazone, and/or a sulfonylurea
  - Stable dose of insulin as monotherapy or in combination with stable dose of metformin

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

# TECOS: Exclusion Criteria Include:[1]

- Type 1 diabetes mellitus or ketoacidosis
- ≥2 episodes of severe hypoglycemia requiring assistance ≤12 months prior to enrollment
- Use of approved or investigational DPP-4 inhibitor, GLP-1 analogue, or TZD other than pioglitazone ≤3 months prior to enrollment
- eGFR <30 mL/min/1.73 $m^2$
- Planned or anticipated revascularization procedure
- Cirrhosis of the liver
- Pregnancy or planned pregnancy
- Known allergy or intolerance to sitagliptin

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

# TECOS: Study Population and Enrollment

## Study population[1]

- ≈14,000 patients from 39 countries
  - Aimed to enroll participants: ≈1/3 each from Europe, Australasia, and the Americas
  - Required to enroll ≥2,000 patients receiving metformin monotherapy

## Study enrollment

- Enrollment began December 2008[1]
- Enrollment is completed, with 14,724 patients[2]

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

2. Bethel MA et al. Baseline characteristics of patients enrolled in the trial evaluating cardiovascular outcomes with sitagliptin (TECOS). Poster presented at: World Diabetes Congress 2013; December 2–6, 2013; Melbourne, Australia. Abstract PD-0700.

# TECOS: Statistical Analyses and Population[1]

## Statistical analyses

- Noninferiority – assuming HR of 1.00
  - Upper limit of (95% CI) <1.3 — 611 patients with primary CV end points
- Superiority – assuming HR of 0.85
  - Upper limit of (95% CI) <1.0 — 1,300 patients with primary CV end points

## Analysis population for the between-treatment difference in time to first primary cardiovascular end point

- Noninferiority
  - PP population primary; ITT population supportive
- Superiority
  - ITT population primary; PP population supportive

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

# TECOS: Dosage and Administration[1]

- Once-daily oral sitagliptin 100 mg or placebo dosed orally; once daily in the morning
  - Starting dose of once-daily sitagliptin 50 mg for patients with eGFR 30–<50 mL/min/1.73 $m^2$
- eGFR values assessed at least annually to determine whether adjustment of study drug dose is necessary
  - If eGFR falls to <30 mL/min/1.73 $m^2$, dose will be reduced to once-daily sitagliptin 25 mg
  - If eGFR shows sustained recovery, dose will be uptitrated
- Dosing changes based on 2 consecutive serum creatinine measurements

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

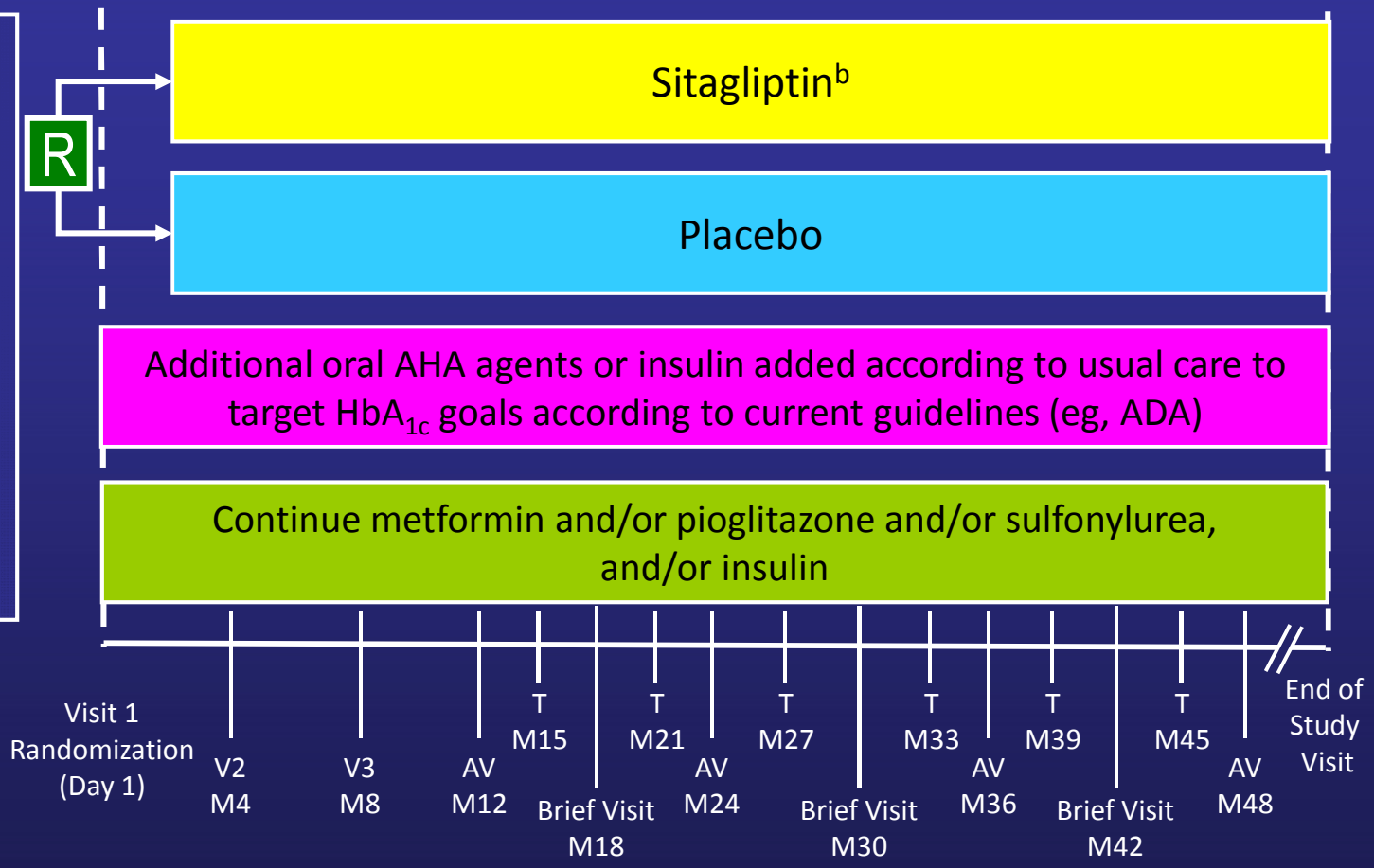
# TECOS: Summary of Study Design[1]

Patients aged ≥50 years with T2DM, pre-existing CVD, and:

- $HbA_{1c}$ 6.5%–8.0% (48–64 mmol/mol) and dose-stable for ≥3 months on:
  - Metformin, pioglitazone, or sulfonylurea as monotherapy or any dual combination therapy[a]

OR

- Insulin alone or in combination with metformin




[a]Minimum of 2,000 patients on metformin monotherapy.

[b]If eGFR is ≥50 mL/min/1.73 $m^2$, dose of sitagliptin = 100 mg/d; if eGFR is 30 to <50 mL/min/1.73 $m^2$, dose of sitagliptin = 50 mg/d; if <30 mL/min/1.73 $m^2$ during the study, dose reduced to 25 mg/d.

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

# TECOS: Outcomes[1]

- Primary outcome was time from randomization to the first adjudicated[a]:
  - CV-related death
  - Nonfatal MI
  - Nonfatal stroke
  - Unstable angina requiring hospitalization
- Secondary outcomes
  - Composite end point of: time to first adjudicated confirmed CV-related death, nonfatal MI, 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 include:
  - 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
  - Counts of outpatient visits and hospitalizations

[a]CV events will be adjudicated by an independent committee, blinded to study therapy.

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

# TECOS: Analysis[1]

- Primary outcome analysis is designed to demonstrate noninferiority of usual care with sitagliptin vs usual care without sitagliptin
  - If sitagliptin is found noninferior to placebo, an assessment of superiority will be performed
- Median follow-up of approximately 4 years is anticipated
  - Study will continue until 1,300 confirmed cardiovascular events have occurred

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

# TECOS: Other Events[1]

- Adjudicated events
  - Malignancies
  - Pancreatitis
- Other selected events
  - Peripheral vascular disease
  - Glycemic extremes
    - Hypoglycemia, hyperglycemia, diabetic ketoacidosis, hyperosmolar hyperglycemic nonketotic coma
  - Diabetic eye disease
  - Diabetic neuropathy
  - Diabetic nephropathy
  - Renal failure, ESRD, dialysis, renal transplant
  - Metabolic conditions associated with diabetes
  - Hospitalization due to diabetes complications
  - Infections
  - GI conditions

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

# TECOS: Subgroup Analyses[1]

- Prespecified subgroups for the primary composite CV end point (Per protocol population)
  - Antihyperglycemic therapy at entry
  - Baseline $HbA_{1c}$
  - Duration of diabetes
  - Baseline renal function
  - History of previous CVD
  - Race
  - Region
  - Sex
  - Age

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

# TECOS: Baseline Patient Characteristics[1]

| Baseline Characteristics | Enrolled N=14,724 |
|---|---|
| Mean age (±SD), years | 66 (8) |
| Men/women, % | 71/29 |
| Race, % | |
| Caucasian | 68 |
| Asian (Other) | 15 |
| Asian (Oriental) | 7 |
| Hispanic | 6 |
| Black | 3 |
| Other | 1 |

1. Bethel MA et al. Baseline characteristics of patients enrolled in the trial evaluating cardiovascular outcomes with sitagliptin (TECOS). Poster presented at: World Diabetes Congress 2013; December 2–6, 2013; Melbourne, Australia. Abstract PD-0700.

# TECOS: Baseline Disease Characteristics[1]

| Baseline Characteristics[a] | Enrolled N=14,724 |
|---|---|
| Duration of diabetes, years | 11.0 (8.2) |
| $HbA_{1c}$, % | 7.3 (0.7) |
| Systolic BP, mmHg | 135 (17) |
| Diastolic BP, mmHg | 77 (12) |
| HDL cholesterol, mmol/L | 1.1 (0.3) |
| LDL cholesterol, mmol/L | 2.3 (1.2) |
| Current smoker[b], % | 11 |
| Statin use, % | 80 |
| Aspirin use, % | 78 |

[a]Values are mean (±SD) unless specified.

[b]Compared with nonsmokers and prior smokers.

1. Bethel MA et al. Baseline characteristics of patients enrolled in the trial evaluating cardiovascular outcomes with sitagliptin (TECOS). Poster presented at: World Diabetes Congress 2013; December 2–6, 2013; Melbourne, Australia. Abstract PD-0700.

# TECOS: Baseline Characteristics[a]—CV Risk Factors by Region[1]

| | North America n=2,593 | Western Europe n=2,076 | Eastern Europe n=4,018 | Asia Pacific n=4,566 | Latin America n=1,471 |
|---|---|---|---|---|---|
| $HbA_{1c}$ , % | 7.2 (0.6) | 7.2 (0.6) | 7.2 (0.6) | 7.3 (0.6)[b] | 7.2 (0.9) |
| Systolic BP, mmHg | 130.1 (16.9) | 138.0 (17.5)[b] | 136.5 (14.5)[b] | 133.9 (17.3)[b] | 138.5 (19.6)[b] |
| Diastolic BP, mmHg | 72.0 (10.6) | 76.3 (17.3)[b] | 80.6 (8.8)[b] | 77.1 (10.4)[b] | 78.8 (10.9)[b] |
| HDL cholesterol, mmol/L | 1.08 (0.31) | 1.14 (0.32)[b] | 1.21 (0.37)[b] | 1.09 (0.28) | 1.11 (0.36)[b] |
| LDL cholesterol, mmol/L | 2.0 (0.8) | 2.3 (1.9)[b] | 2.7 (1.1)[b] | 2.2 (0.9)[b] | 2.7 (1.0)[b] |
| Statin use, % | 89 | 87 | 69[b] | 84[a] | 68[b] |
| Aspirin use, % | 83 | 77[b] | 72[b] | 84 | 74[b] |
| Current smoker, %[c] | 13 | 13 | 13 | 9[a] | 8[b] |

[a]Values are mean (±SD) unless specified.

[b]P<0.01 compared with North America.

[b]Compared with nonsmokers and prior smokers.

1. Bethel MA et al. Baseline characteristics of patients enrolled in the trial evaluating cardiovascular outcomes with sitagliptin (TECOS). Poster presented at: World Diabetes Congress 2013; December 2–6, 2013; Melbourne, Australia. Abstract PD-0700.

# TECOS: Baseline Characteristics—CV Risk Factors by Region *(continued)*[1]

- Compared to North America:
  - Statin use was lower in Eastern Europe, Asia Pacific, and Latin America
  - Aspirin use was lower in all regions, except Asia Pacific
  - Smoking levels were lower in Asia Pacific and Latin America
  - Mean $HbA_{1c}$ levels were higher in Asia Pacific
  - Mean systolic and diastolic blood pressures were higher in all regions
  - Mean LDL cholesterol levels were higher in all regions
  - Mean HDL cholesterol levels were higher in Western Europe, Eastern Europe, and Latin America

1. Bethel MA et al. Baseline characteristics of patients enrolled in the trial evaluating cardiovascular outcomes with sitagliptin (TECOS). Poster presented at: World Diabetes Congress 2013; December 2–6, 2013; Melbourne, Australia. Abstract PD-0700.

# TECOS: Baseline Characteristics Conclusions

- In patients enrolled in TECOS with T2DM and known CV disease[1]:
  - CV risk factor levels are reasonably well controlled
  - Regional differences exist in the use of evidence-based CV risk reduction strategies
  - Regional differences exist in achieved blood pressure and lipid levels
- Given the apparent regional diversity in baseline CV risk, the planned final analysis will incorporate these differences when exploring possible heterogeneity of the effects of sitagliptin on CV outcomes[1]
- TECOS is event-driven and the study will continue until the required number of confirmed events have accumulated[2]
- Results expected in 2015[1]

1. Bethel MA et al. Baseline characteristics of patients enrolled in the trial evaluating cardiovascular outcomes with sitagliptin (TECOS). Poster presented at: World Diabetes Congress 2013; December 2–6, 2013; Melbourne, Australia. Abstract PD-0700.
2. Green JB et al. Am Heart J. 2013;166:983–989.e7.

# TECOS: Top Line results

On 27 April 2015, MSD announced that the Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) of MSD's DPP-4 inhibitor, JANUVIA® (sitagliptin), achieved its primary endpoint of non-inferiority for the composite cardiovascular (CV) endpoint.

Among secondary endpoints, there was no increase in hospitalization for heart failure in the sitagliptin group versus placebo.

The complete results of TECOS will be presented on June 8, 2015 at the 75th Scientific Sessions of the American Diabetes Association.

# Summary

- The effect of specific antihyperglycemic medications on CV risk in patients with T2DM cannot be predicted based solely on reduction in $HbA_{1c}$[1]
- The FDA has implemented regulatory requirements to assess the CV safety of antihyperglycemic medications to treat T2DM[2]
- EXAMINE (alogliptin) and SAVOR-TIMI (saxagliptin) demonstrated noninferiority compared with placebo for the primary composite ***safety*** end point[3,4]
  - In a post-hoc analysis, alogliptin showed a nonstatistically significant trend for increased hospitalization for heart failure[5]
  - Saxagliptin showed a small but statistically significant increase in hospitalization for heart failure[3]
- Noninferiority was also demonstrated for alogliptin and saxagliptin compared with placebo for other safety end points, including incidence of cancer and pancreatitis[3,4]

**1.** McMurray JJV et al. *Lancet Diabetes Endocrinol*. 2014; DOI 10.1016/S2213-8587(14)70031-2; **2.** 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; **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.** Sanon VP et al. *Clin Diabetes.* 2014;32:121–126.

# Summary *(continued)*[1]

- TECOS is designed to assess CV safety by measuring risk of CV events with sitagliptin used as part of usual care compared with usual care without sitagliptin in patients with T2DM and a history of CV disease
- TECOS will assess the primary outcome of time from randomization to the first adjudicated
  - CV-related death
  - Nonfatal MI
  - Nonfatal stroke
  - Unstable angina requiring hospitalization
- Hospitalization for heart failure is a predefined outcome and will be adjudicated
- TECOS has been designed to show glycemic equality between groups, and may permit assessment of the effect of sitagliptin on CV outcomes independently of its glucose-lowering effects

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