Saxagliptin
Advisory Committee Meeting

Endocrinologic and Metabolic Drugs Advisory Committee

April 14, 2015

AstraZeneca

Introduction

Howard Hutchinson, MD

VP Development, Cardiovascular and Metabolic Diseases
AstraZeneca

Saxagliptin Attributes and Robustness of Clinical Program

- **DPP-4 inhibitor approved in US in 2009 as adjunct to diet and exercise to improve glycemic control in Type 2 Diabetes Mellitus (T2DM)**
  - Average HbA1c reduction was 0.4% to 0.8%
- **Original NDA for approval dossier consisted of 8 Phase 3 clinical studies in over 4600 patients**
- **No preclinical or clinical CV safety signals at time of approval**

FDA Post-marketing Requirement (PMR)

- **Randomized, double-blind, controlled trial evaluating the effect of saxagliptin on the incidence of major adverse cardiovascular events (MACE) in patients with T2DM**
- **Secondary objectives to include long-term safety evaluations**
  - Severe infections, hypersensitivity reactions, malignancies, liver abnormalities, bone fractures, pancreatitis, renal abnormalities
- **FDA considered protocol final November 2010**

Onglyza NDA 22350 Approval Letter 31 July 2009

Agenda

Topic	Presenter
Introduction	**Howard Hutchinson, MD** VP Development, Cardiovascular and Metabolic Diseases AstraZeneca Gaithersburg, MD
SAVOR TIMI-53 Study Design & Results	**Benjamin M. Scirica, MD, MPH** TIMI Study Group Brigham and Women's Hospital and Harvard Medical School Boston, MA
Perspectives on the Treatment of Diabetes and the SAVOR Data	**Jay S. Skyler, MD, MACP** Division of Endocrinology, Diabetes, and Metabolism Diabetes Research Institute University of Miami Miller School of Medicine Miami, FL
Conclusion	**Howard Hutchinson, MD**

SAVOR TIMI-53 Study Design & Results

Benjamin M. Scirica, MD, MPH

Senior Investigator, TIMI Study Group
Brigham and Women's Hospital
Associate Professor of Medicine
Harvard Medical School
Boston, MA

Background
SAVOR TIMI 53

- **Previous studies in patients with diabetes have demonstrated that improved glucose control reduces microvascular complications[1-3]**

- **However, uncertainty remains regarding whether any particular glucose-lowering strategy is safe from a CV standpoint or can actually lower macrovascular complications (i.e., MI, stroke, or CV death)[4-8]**

[1] The DCTT Trial. *NEJM*. 1993. [2.] UKPDS 33 *Lancet*. 1998.[3.] ACCORD Eye Study Group. *NEJM*. 2010.[4.] ACCORD main study *NEJM* 2008 [5.] 10-Year follow up of UKPDS. *NEJM.* 2008 [6.] The ORIGIN Trial *NEJM.* 2012.[7.]. VADT *NEJM.* 2009 [8.] The ADVANCE *NEJM.* 2008

Design Considerations
SAVOR TIMI 53

- To definitively exclude unacceptable CV risk as defined by the 2008 FDA guidance to industry (upper 95% CI of HR<1.3 for MACE)
- Not designed to assess glycemic efficacy or microvascular benefits
- Study powered for both a non-inferiority and superiority assessment

Trial Oversight
SAVOR TIMI 53

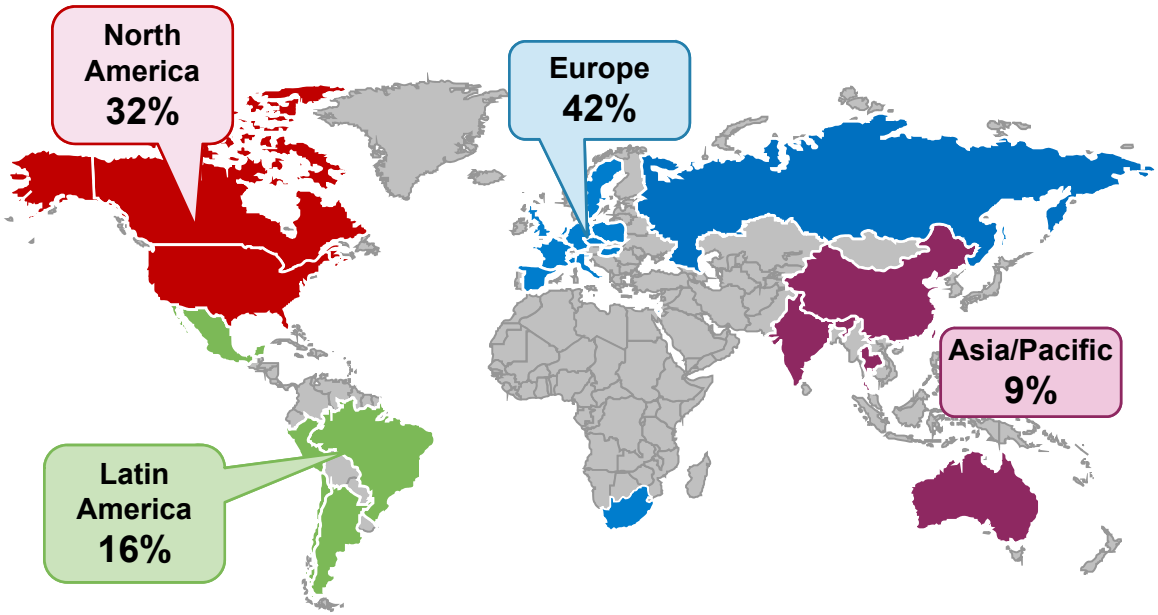
Trial Organization

TIMI Study Group	Chairman: Eugene Braunwald, CV PI: Deepak Bhatt Lead Investigator: Benjamin Scirica
Hadassah Medical Organization	Endocrine PI: Itamar Raz
Sponsor	AstraZeneca/ Bristol-Myers Squibb

Independent Committees:

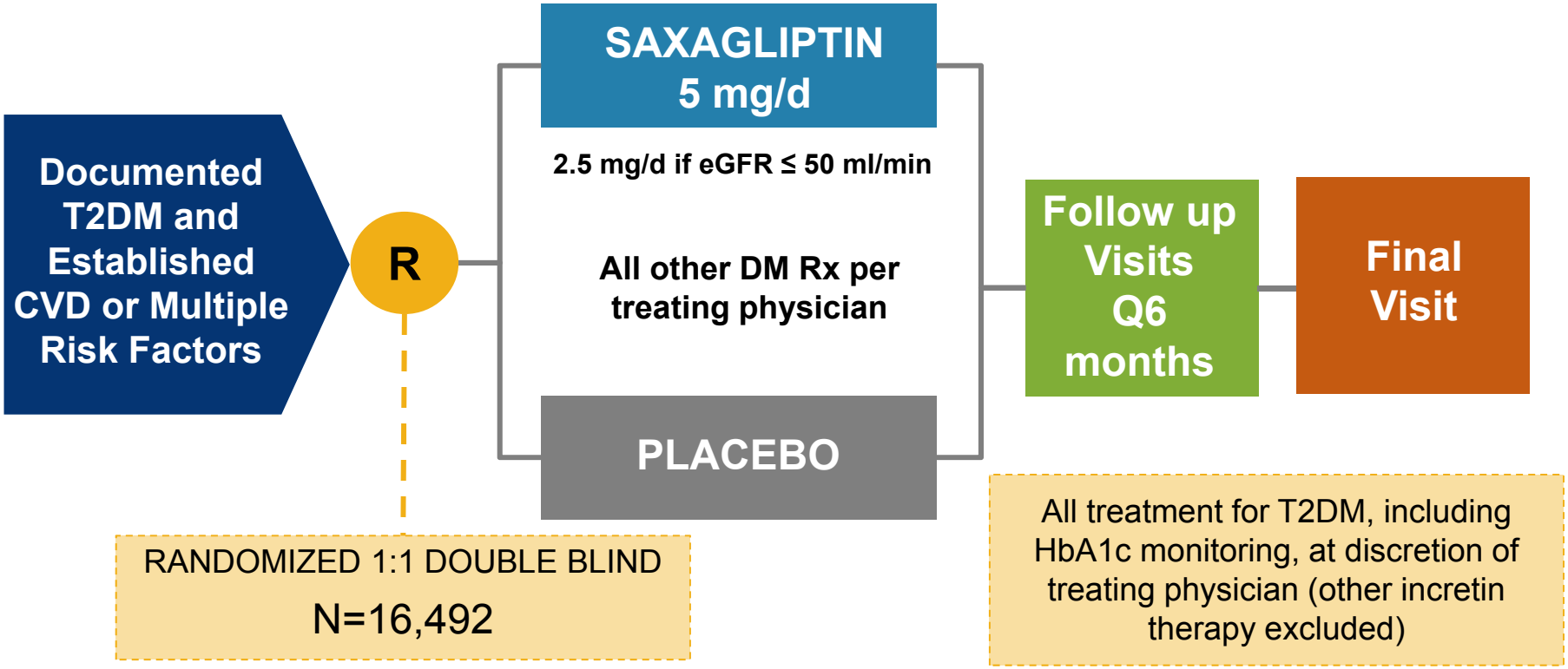
- **Clinical Endpoint Committee**
- **Data Safety Monitoring Board**
- **Executive Committee**
- **Steering Committee**

16,492 patients randomized at 788 sites in 26 countries



Scirica BM, Bhatt DL, Braunwald E, … Raz I. Am Heart J. 2011;162(5):818-825.
Mosenzon O, Raz I, Scirica BM,…Bhatt DL. *Diabetes Metab Res Rev*. 2013;29:417-426.
Scirica BM, Bhatt DL, Braunwald E, … Raz I. *N Engl J Med.* 2013;369(14):1317-26.

Study Design
SAVOR TIMI 53



Primary composite endpoint: CV Death, MI, ischemic stroke
Secondary composite endpoint: CV death, MI, ischemic stroke, hospitalization for heart failure (hHF), unstable angina (UA), or coronary revascularization
Secondary endpoint: All-cause mortality

Scirica BM, Bhatt DL, Braunwald E, … Raz I. *N Engl J Med.* 2013;369(14):1317-26

Statistical Considerations: Power Calculations/Sample Size

- **Assumptions**
  - 2.1% annual event rate
  - 12 month accrual period; 3-year follow-up period
  - 17% ↓ in risk in the saxagliptin group

- **16,500 patients will yield 1040 primary endpoint events, which would provide:**
  - 98% power to exclude excess risk of saxagliptin (i.e., upper 95% CI <1.3)
  - 85% power to test for superiority of saxagliptin
    - At 2.45% 1-sided level for both

Scirica BM, Bhatt DL, Braunwald E, … Raz I. *N Engl J Med.* 2013;369(14):1317-26

Analysis Populations

SAVOR is based on the Intention to Treat (ITT) principle

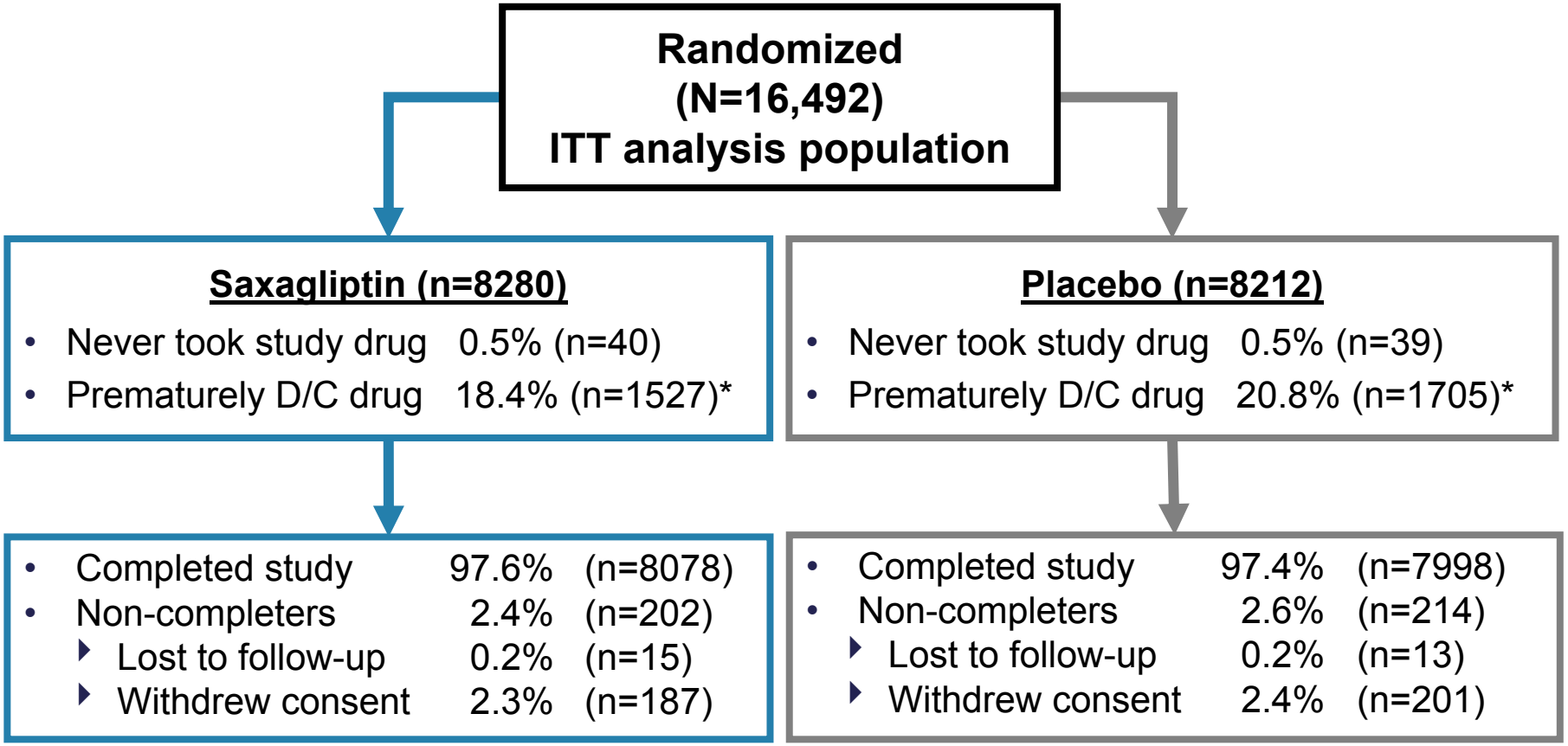
- Evaluate effect of starting saxagliptin or placebo on top of Standard of Care
- Full follow up of endpoints after patients stop study drug
- ITT is the primary analysis population representing the full data

Sensitivity Analyses:

- **Per Protocol (PP):** all randomized patients, excluding patients with important protocol deviations
- **Modified ITT (mITT):** population includes all patients who received at least one dose of study medication; censoring window of 30 days of the last dose of study medication
- ***FDA post-hoc analysis population (mITT/7d):*** *same as predefined mITT with a 7 day censoring window*

Scirica BM, Bhatt DL, Braunwald E, … Raz I. *N Engl J Med.* 2013;369(14):1317-26

Study Disposition
SAVOR TIMI 53



Final vital status was assessed in 99.1%

***Nominal p-value 0.001**

Scirica BM, Bhatt DL, Braunwald E, … Raz I. *N Engl J Med.* 2013;369(14):1317-26

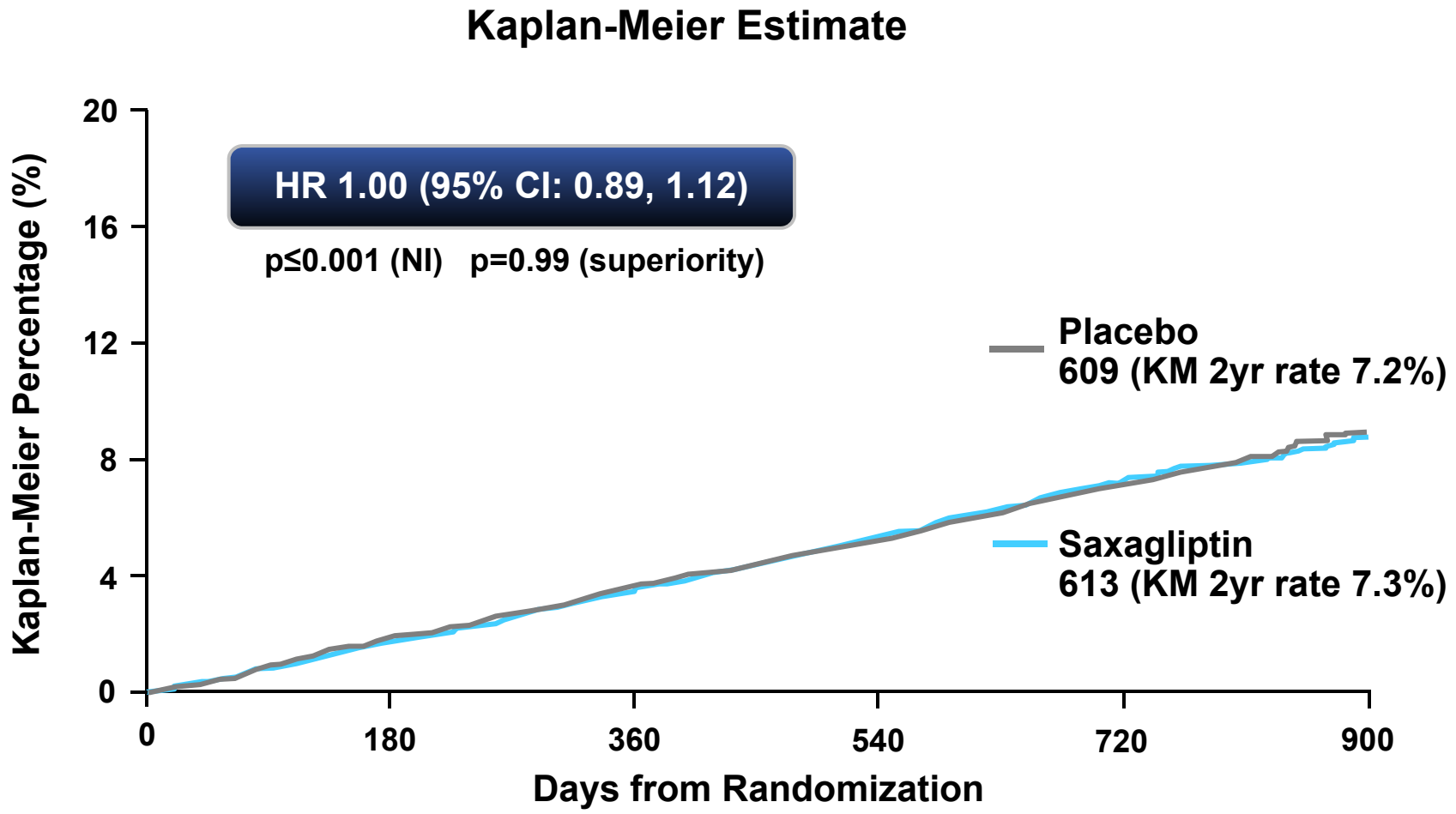
Demographics and Characteristics
SAVOR TIMI 53

Characteristic	Saxagliptin N=8280	Placebo N=8212
Age, yrs	**65**	**65**
Age ≥75 yrs	14.1%	14.1%
Established atherosclerotic disease	**78.4%**	**78.7%**
Hypertension	**81.2%**	**82.4%**
Dyslipidemia	**71.2%**	**71.2%**
Prior heart failure	**12.8%**	**12.8%**
Diabetes duration, yrs	**10.3**	**10.3**
eGFR, mL/min – mean	**72.5**	**72.7**
30–50 mL/min	13.6%	13.6%
<30 mL/min	2.1%	2.0%

Scirica BM, Bhatt DL, Braunwald E, … Raz I. *N Engl J Med.* 2013;369(14):1317-26

Primary Endpoint Analysis

CV Death, MI, Ischemic Stroke



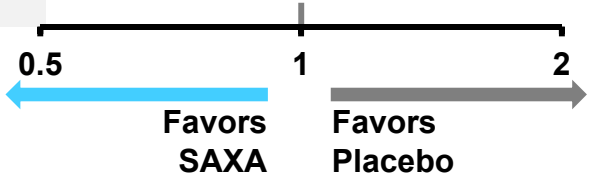
Number of Patients at Risk

Saxagliptin	8280	8071	7836	7313	4920	847
Placebo	8212	7983	7761	7267	4855	851

Sensitivity Analysis: Primary Endpoint

Hazard Ratio of the Time to First Cardiovascular Event for the Primary Composite Endpoint

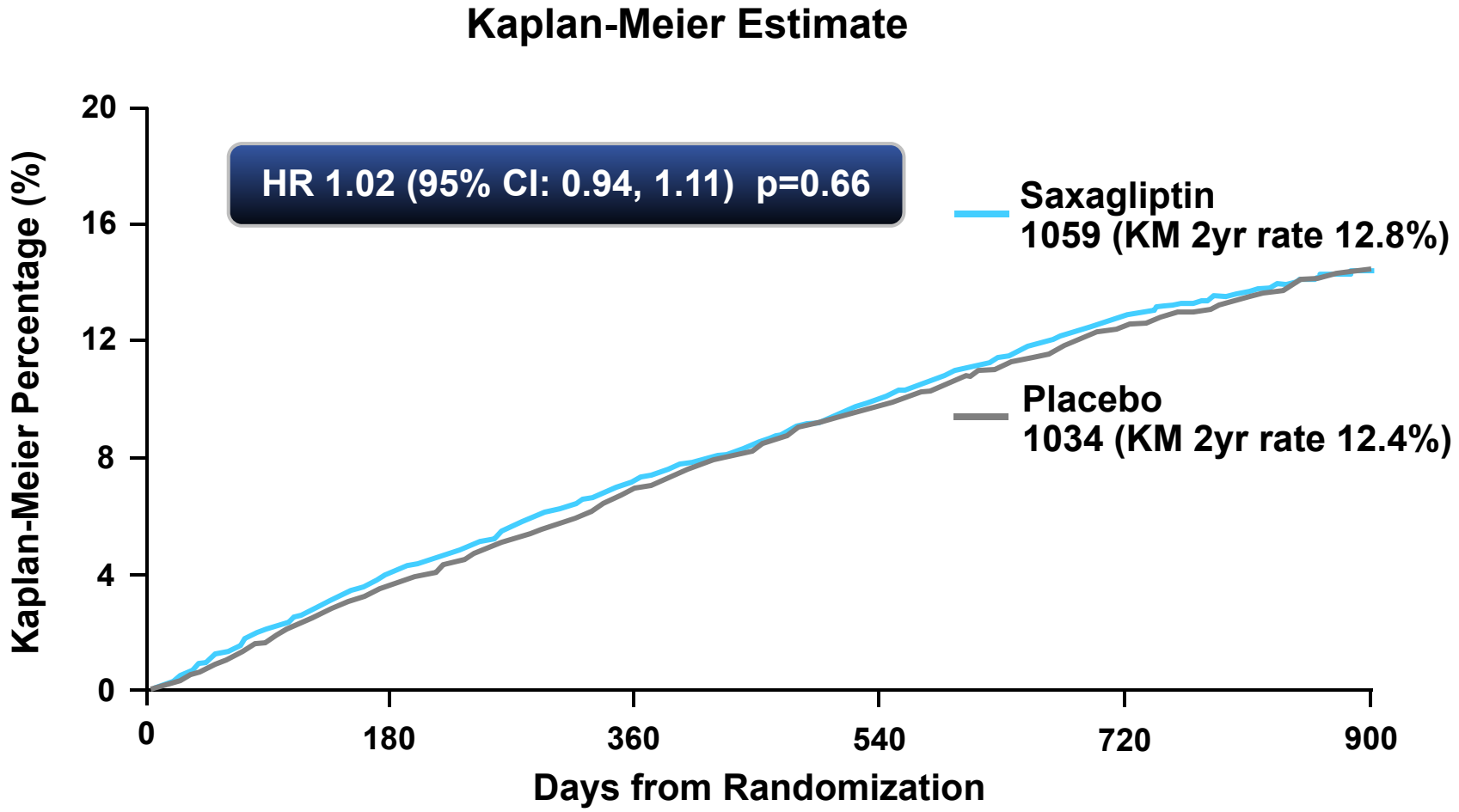
	SAXA		Placebo		Hazard Ratio (95% CI)
	Patients With Events	Event Rate /100 PY	Patients With Events	Event Rate /100 PY	
ITT	**613/8280**	**3.76**	**609/8212**	**3.77**	**1.00 (0.89, 1.12)**
PP	525/7526	3.51	529/7373	3.61	0.98 (0.86, 1.10)
mITT	526/8240	3.52	498/8173	3.40	1.04 (0.92, 1.17)
*mITT/7d**	*511/8240*		*482/8173*		*1.04 (0.92, 1.18)*



Post-hoc FDA Analysis

Secondary Endpoint Analysis

CV Death, MI, Ischemic Stroke, hHF, UA, or Coronary Revasc.



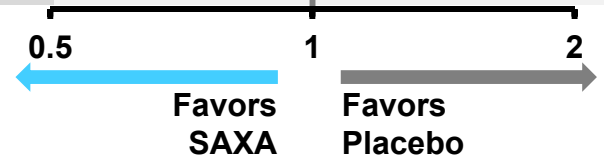
Number of Patients at Risk

Saxagliptin	8280	7880	7539	6963	4660	817
Placebo	8212	7843	7502	6926	4602	813

Sensitivity Analysis: Secondary Endpoint

Hazard Ratio of the Time to First Cardiovascular Events for the Secondary Composite Endpoint

	SAXA		Placebo		Hazard Ratio (95% CI)
	Patients With Events	Event Rate /100 PY	Patients With Events	Event Rate /100 PY	
ITT	**1059/8280**	**6.72**	**1034/8212**	**6.60**	**1.02 (0.94, 1.11)**
PP	910/7526	6.29	902/7373	6.36	0.99 (0.91, 1.09)
mITT	954/8240	6.60	911/8173	6.40	1.04 (0.95, 1.13)

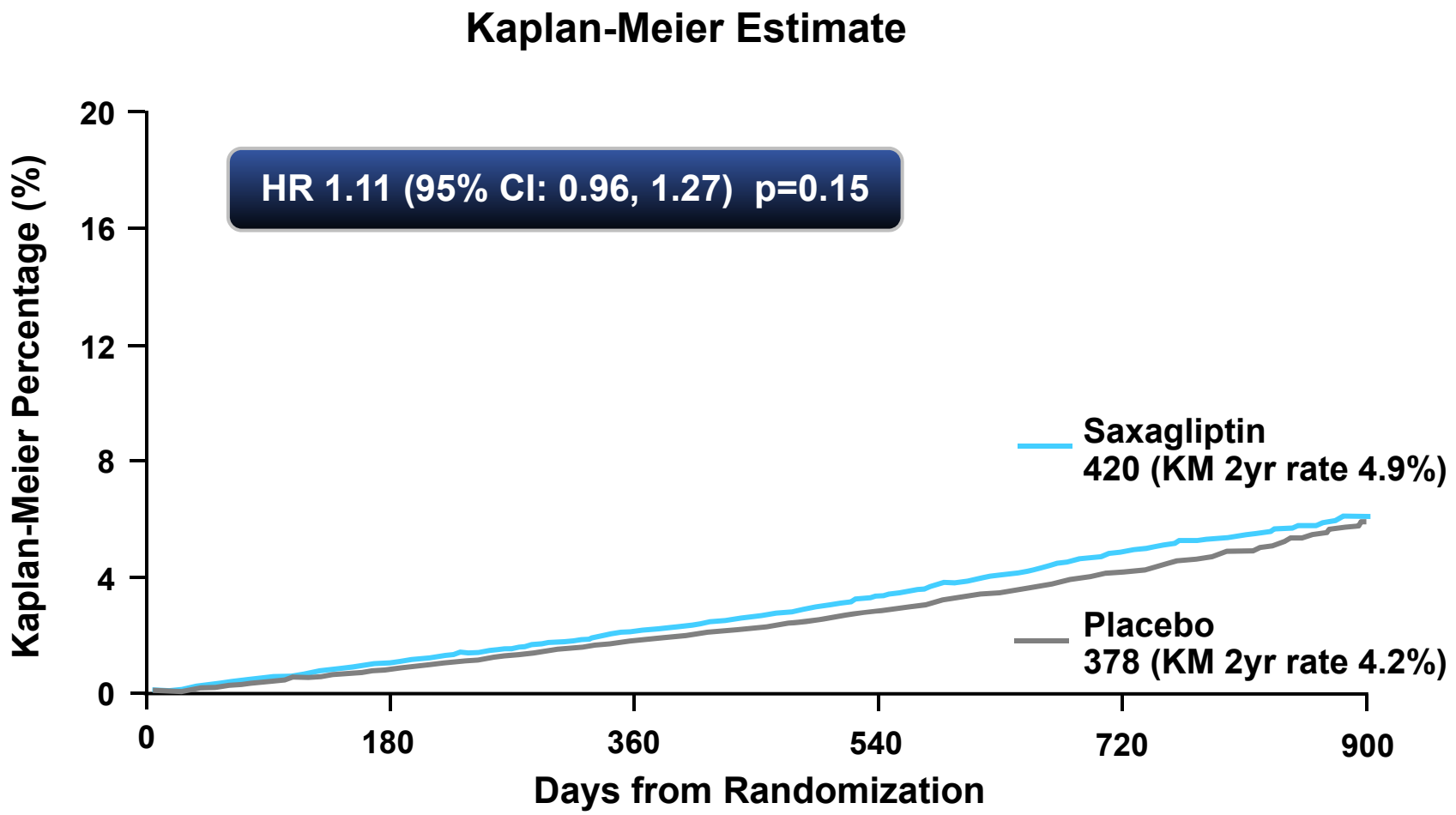


Conclusions on Study Design and CV Composite Endpoints

- **SAVOR designed in accordance with 2008 Guidance and agreement with FDA**
  - Enrolled 16,492 high risk patients with T2DM
  - 32% of patients from United States and Canada
- **Primary and secondary composite endpoints balanced**
  - No increase in the composite of CV death, MI, or stroke
  - Met FDA criteria for CV safety

Analysis and Interpretation of All-Cause Mortality

Cumulative Percent of Time to All-cause Mortality



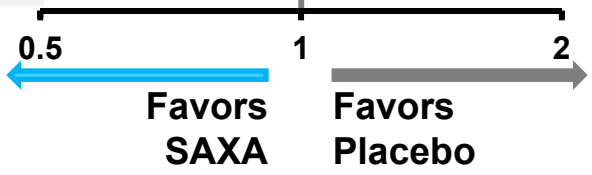
Number of Patients at Risk

Saxagliptin	8280	8182	8070	7636	5181	906
Placebo	8212	8134	8032	7615	5152	902

Sensitivity Analysis: All-cause Mortality

Hazard Ratio of the Time to All-cause Mortality

	SAXA		Placebo		Hazard Ratio (95% CI)
	Patients With Events	Event Rate /100 PY	Patients With Events	Event Rate /100 PY	
ITT	**420/8280**	**2.50**	**378/8212**	**2.26**	**1.11 (0.96, 1.27)**
PP	366/7526	2.39	329/7373	2.18	1.09 (0.94, 1.27)
mITT	297/8240	1.96	248/8173	1.66	1.18 (0.99, 1.39)
*mITT/7d**	*256/8240*	*1.70*	*204/8173*	*1.37*	*1.23 (1.02, 1.48)*



Post-hoc FDA Analysis

Sensitivity Analysis: All-cause Mortality

Hazard Ratio of the Time to All-cause Mortality

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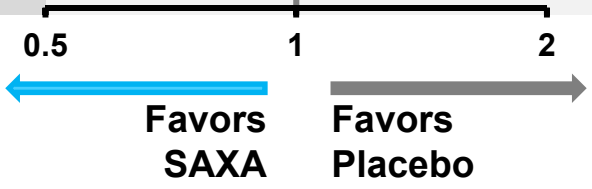
*mITT/7d**	*256/8240*	*1.70*	*204/8173*	*1.37*	*1.23 (1.02, 1.48)*
*Censor at change of diabetes medication or at study drug discontinuation***	*105/8240*	*0.88*	*91/8173*	*0.82*	*1.07 (0.81, 1.42)*



Post-hoc FDA Analysis
****Post-hoc AZ Analysis***

ITT vs. mITT: All-cause Mortality

SAVOR designed as an ITT trial; includes all events

Challenges of using mITT analyses

- **Excludes events**
  - 32% deaths in mITT and 42% in mITT/7d
    - 19% (mITT)/28% (mITT/7d) deaths were excluded even though the fatal SAE started on treatment

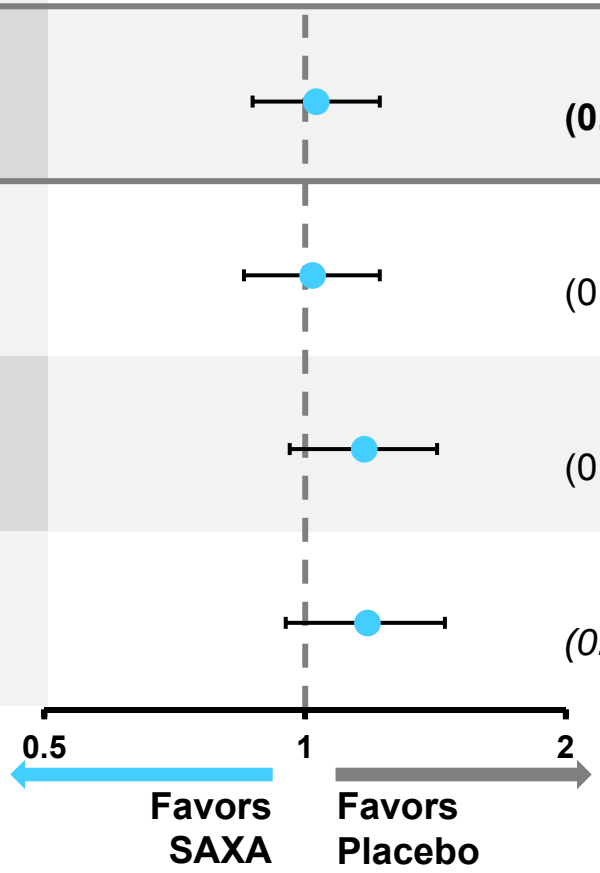
- **mITT introduces potential bias in a non-randomized comparison because:**
  - Patients off drug, regardless of treatment have 4-5 fold increased risk of death
  - Discontinuation rate is greater on placebo
  - More deaths are censored on the placebo group

Because of the selection bias, mITT is at best, a supportive sensitivity analysis

Therefore, ITT is the main population for interpretation for this study

CV Mortality

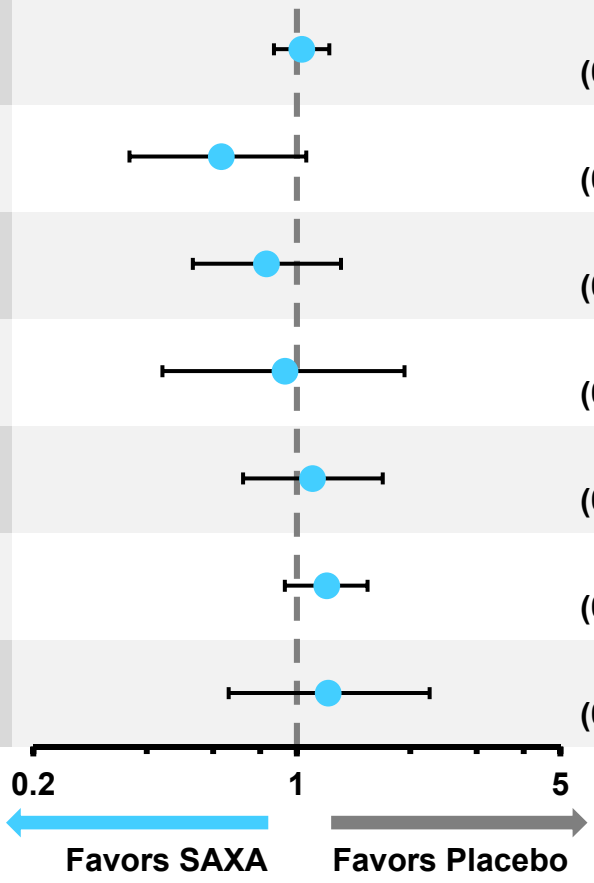
	SAXA		Placebo		Hazard Ratio (95% CI)
	Patients With Events	Event Rate /100 PY	Patients With Events	Event Rate /100 PY	
ITT	**269/8280**	**1.60**	**260/8212**	**1.55**	**1.03 (0.87, 1.22)**
PP	230/7526	1.50	223/7373	1.48	1.02 (0.85, 1.22)
mITT	216/8240	1.42	182/8173	1.22	1.17 (0.96, 1.42)
*mITT/7d**	*196/8240*		*164/8173*		*1.18 (0.95, 1.45)*



Post-hoc FDA Analysis

CV Mortality by Adjudicated Subcategories
ITT

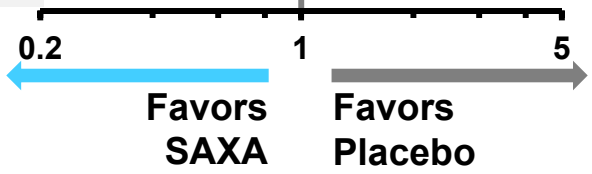
	SAXA N=8280		Placebo N=8212		Hazard Ratio (95% CI)
	Patients With Events	Event Rate /100 PY	Patients With Events	Event Rate /100 PY	
Cardiovascular death	269	1.60	260	1.55	1.03 (0.87, 1.22)
Cerebrovascular	22	0.13	35	0.21	0.63 (0.36, 1.06)
Presumed CV death	35	0.21	42	0.25	0.83 (0.53, 1.31)
Other CV causes	14	0.08	15	0.09	0.93 (0.44, 1.93)
Heart failure	44	0.26	40	0.24	1.10 (0.72, 1.69)
Sudden cardiac death	131	0.78	109	0.65	1.20 (0.93, 1.54)
Acute MI	23	0.14	19	0.11	1.21 (0.66, 2.25)



All events were adjudicated by an independent CEC.

Non-CV Mortality

	SAXA		Placebo		Hazard Ratio (95% CI)
	Patients With Events	Event Rate /100 PY	Patients With Events	Event Rate /100 PY	
ITT	**151/8280**	**0.90**	**118/8212**	**0.71**	**1.27 (1.00, 1.62)**
PP	136/7526	0.89	106/7373	0.70	1.26 (0.98, 1.63)
mITT	81/8240	0.53	66/8173	0.44	1.20 (0.87, 1.67)
*mITT/7d**	*60/8240*		*40/8173*		*1.47 (0.98, 2.20)*



Post-hoc FDA Analysis

Causes of Adjudicated Non-CV Mortality
ITT

	Saxagliptin N=8280 n (%)	Placebo N=8212 n (%)
Non-cardiovascular death	**151 (1.82)**	**118 (1.44)**
Malignancy	53 (0.64)	58 (0.71)
Infection	46 (0.56)	28 (0.34)
Pulmonary failure	13 (0.16)	8 (0.10)
Accident	11 (0.13)	5 (0.06)
Renal failure	10 (0.12)	5 (0.06)
Hemorrhage	8 (0.10)	3 (0.04)
Other	5 (0.06)	1 (0.01)
Hepatic	3 (0.04)	4 (0.05)
Gastrointestinal	1 (0.01)	4 (0.05)
Suicide	1 (0.01)	2 (0.02)

HR for the difference between saxagliptin and placebo for non-CV death overall, 1.27 (95% CI 1.00, 1.62; nominal p-value 0.051).

Investigation of Infectious Death Imbalance

- No increase in overall infections, severe infections or opportunistic infections observed
- No association of a decrease in lymphocytes with infections or infectious death
- Approximately half of all infections leading to death started more than 30 days after stopping therapy

Conclusion: the totality of the evidence does not support an association between saxagliptin treatment and death due to infection

Conclusions: All-cause Mortality

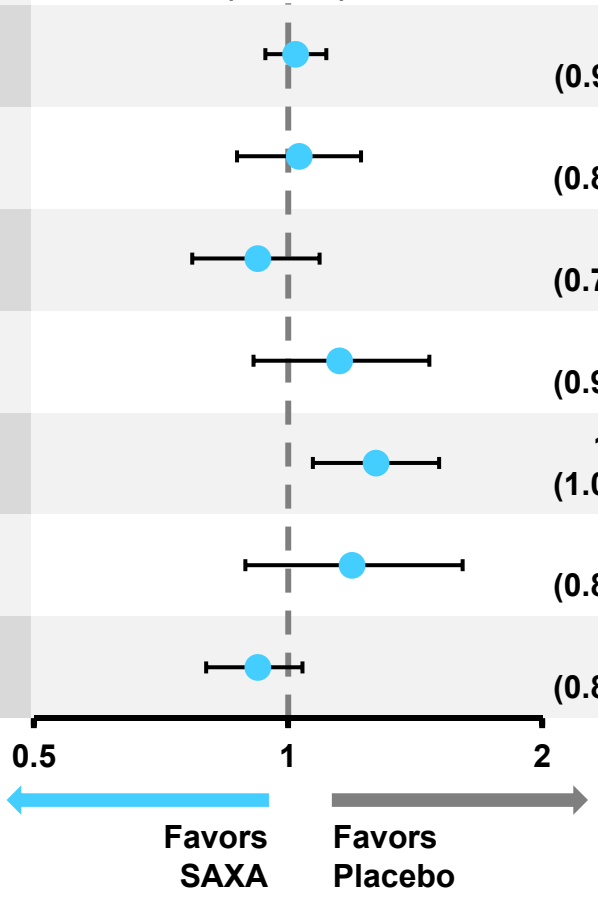
There is no evidence for an increase in all-cause mortality that is attributable to saxagliptin

- **The ITT analysis is the most appropriate analysis**
- **Saxagliptin does not increase the risk for CV death**
- **The evaluation of non-CV death revealed**
  - Malignancies balanced across the two groups
  - Imbalance in fatal infections unlikely to represent a true drug effect
  - Few deaths in other categories

Analysis and Interpretation of Hospitalization for Heart Failure

Time to First Event for Each Individual Components of the Secondary Composite CV Endpoint

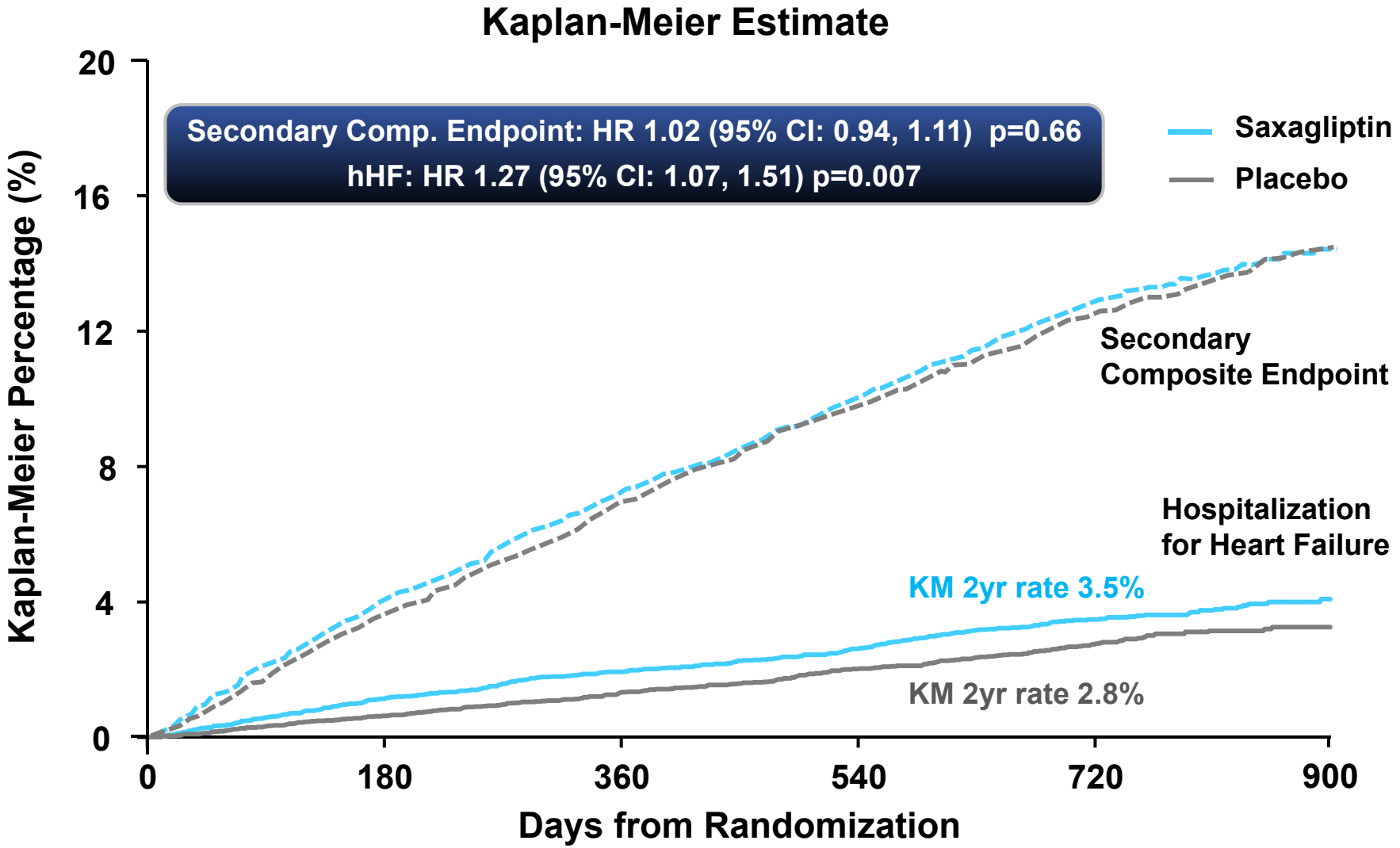
	SAXA N=8280		Placebo N=8212		Hazard Ratio (95% CI)
	Patients With Events	Event Rate /100 PY	Patients With Events	Event Rate /100 PY	
Secondary composite endpoint	1059	6.72	1034	6.60	1.02 (0.94, 1.11)
CV death	269	1.60	260	1.55	1.03 (0.87, 1.22)
Non-fatal MI	240	1.46	260	1.60	0.92 (0.77, 1.09)
Non-fatal ischemic stroke	143	0.87	123	0.75	1.15 (0.91, 1.47)
Hospitalization for heart failure	289	1.76	228	1.39	1.27 * (1.07, 1.51)
Hospitalization for unstable angina pectoris	97	0.59	81	0.49	1.19 (0.89, 1.61)
Hospitalization for coronary revascularisation	423	2.61	459	2.86	0.92 (0.80, 1.04)



*nominal p-value 0.007

Hospitalization for Heart Failure

Time to the First Occurrence of Any Hospitalization for Heart Failure



Hospitalization for Heart Failure
Characteristics

- Baseline characteristics were consistent with known risk factors for HF and similar between groups
- Dyspnea most common presenting symptom (85.8% saxagliptin vs 91.7% placebo)
- Treatment included i.v. diuretics (88.2% of patients in each group) and vasodilator therapy (6.2% and 7.9% of saxagliptin and placebo-treated patients, respectively)
- Evaluation of events 14 days before hHF failed to identify a common precipitating cause

Hospitalization for Heart Failure

First and Subsequent Events

	Saxagliptin N=8280	Placebo N=8212
1st Hospitalization for heart failure (2yr KM Estimate)	**289 (3.5)**	**228 (2.8)**
Subsequent death n (%)	77 (26.6)	60 (26.3)
Subsequent hospitalization for heart failure – patients, n (%)	80 (27.6)	57 (25.0)
All hospitalization for heart failure events*	**413**	**328**

***A patient may have had >1 event**

Hospitalization for Heart Failure
Potential Mechanisms

Potential Mechanisms

- Fluid Retention
- Neurohormonal
- Myocardial Injury
- Worsening ischemia
- Glucose Lowering

Hospitalization for Heart Failure
Potential Mechanisms

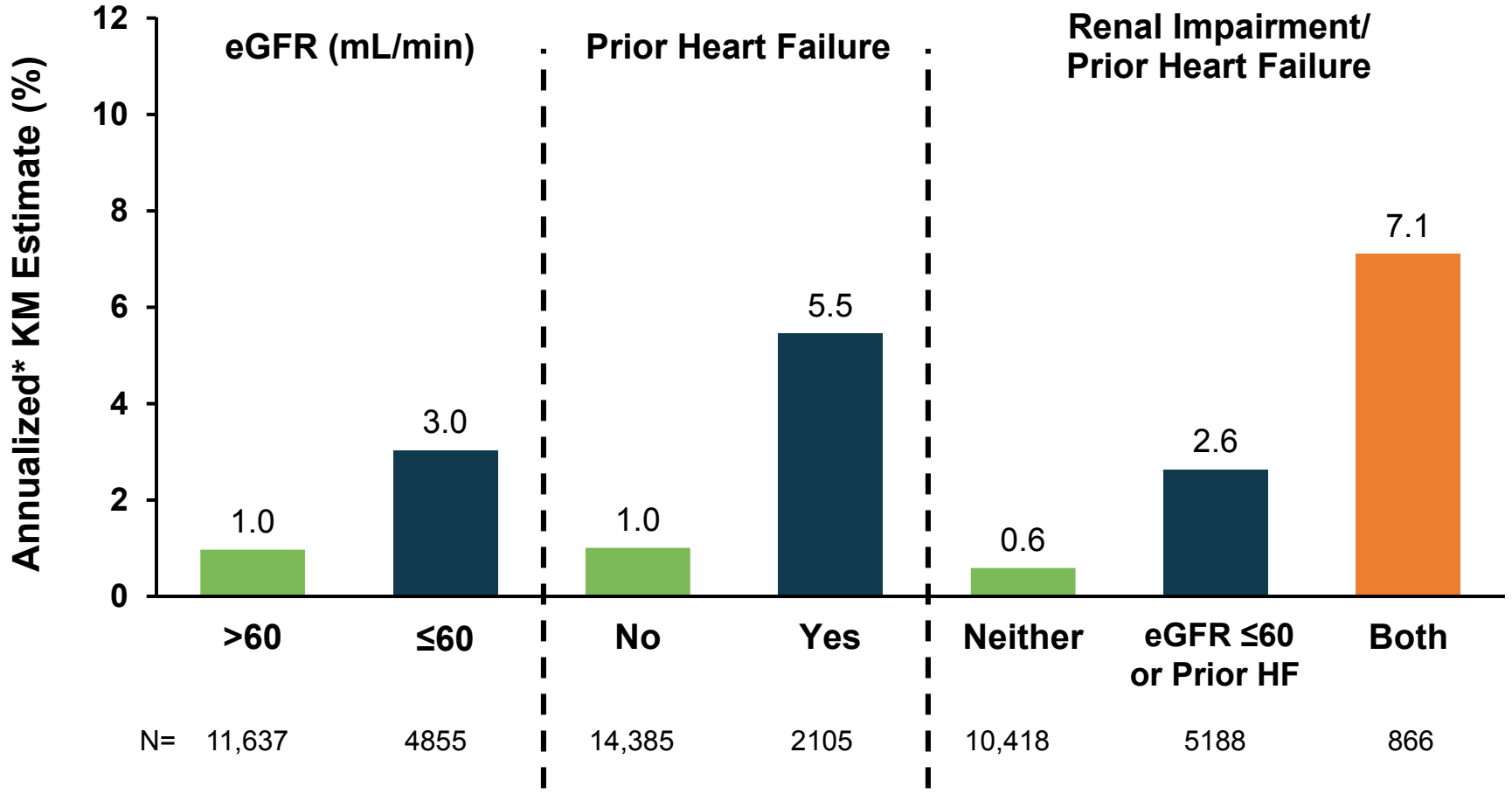
Potential Mechanisms
• Fluid Retention
• Neurohormonal
• Myocardial Injury
• Worsening ischemia
• Glucose Lowering

Observations from SAVOR
• No weight differences
• No difference in edema
• No changes in NT-proBNP
• No changes in hsTnT / hsCRP
• No interaction with ACE inhibitors
• No interaction with hypoglycemia or HbA1c levels
• Few cases with preceding MI

Mechanistic study to examine effects on volume, neurohormonal changes, and cardiac function planned

Hospitalization for Heart Failure

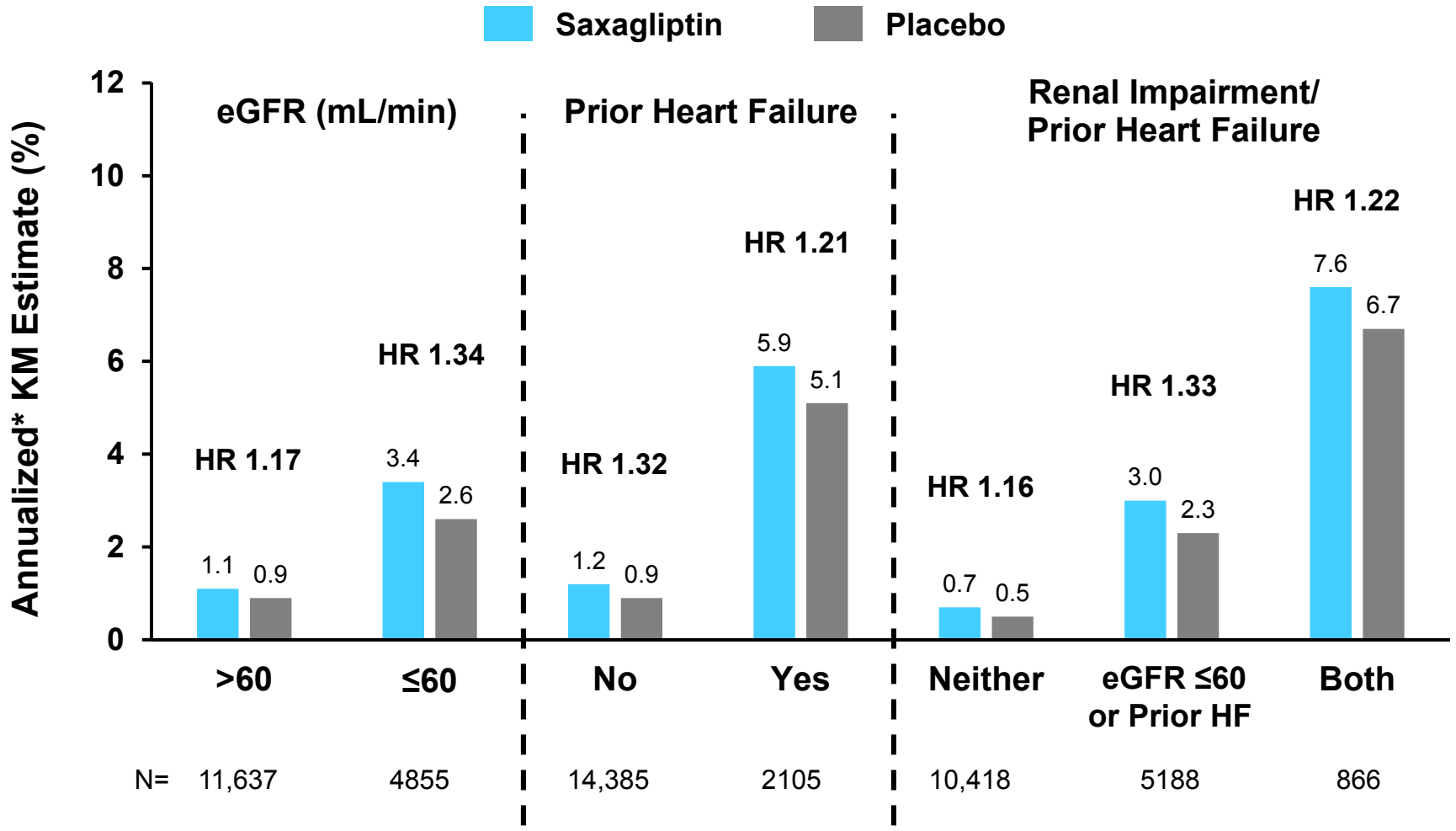
Identifying At-risk Patients Regardless of Treatment



*Based on 2 year KM rates

Hospitalization for Heart Failure

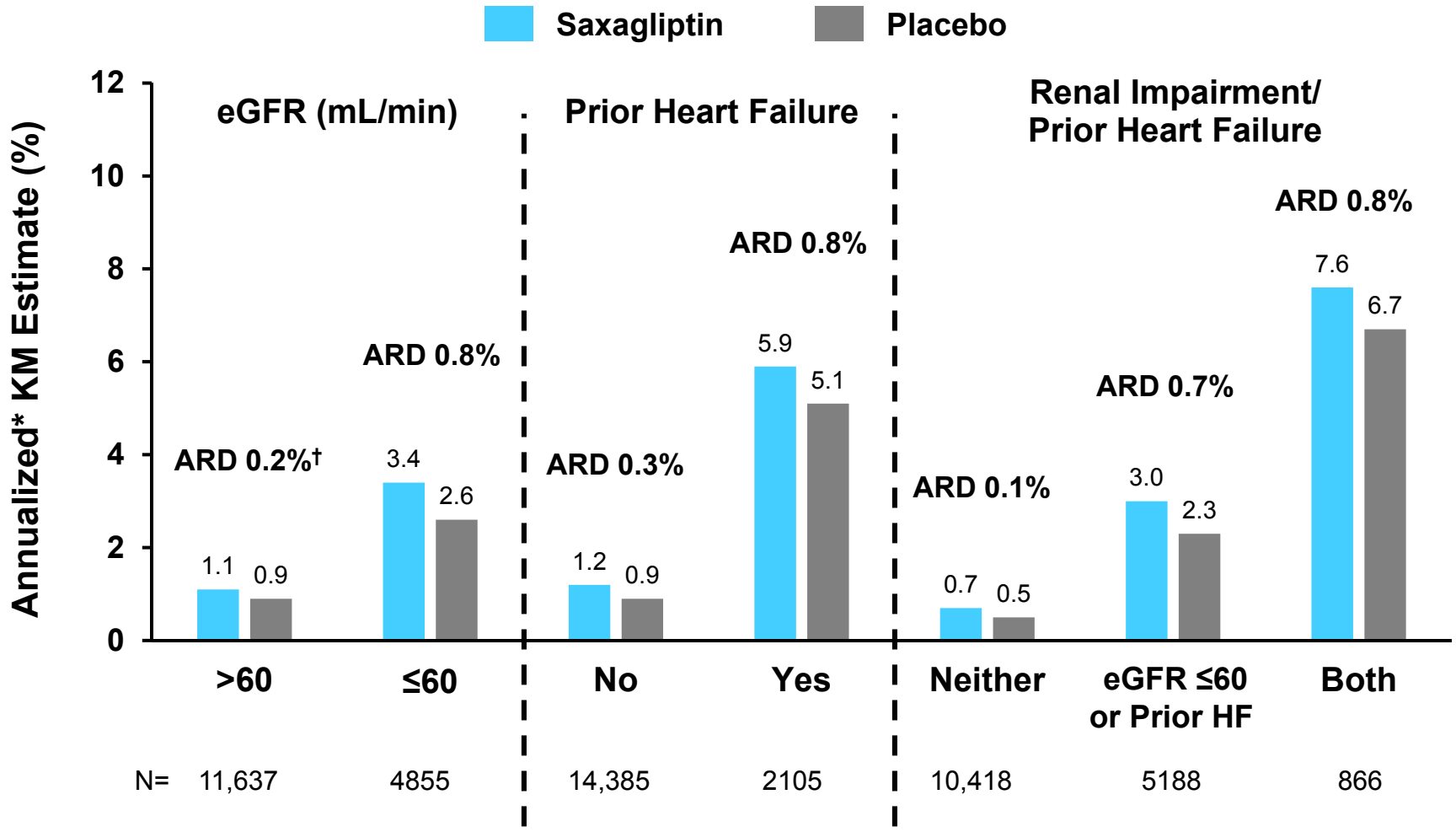
Effect of Saxagliptin in At-risk Patients



*Based on 2 year KM rates

Hospitalization for Heart Failure

Effect of Saxagliptin in At-risk Patients



*Based on 2 year KM rates

†Absolute Risk Difference

Hospitalization for Heart Failure

Competing Risks: Post-hoc Analyses

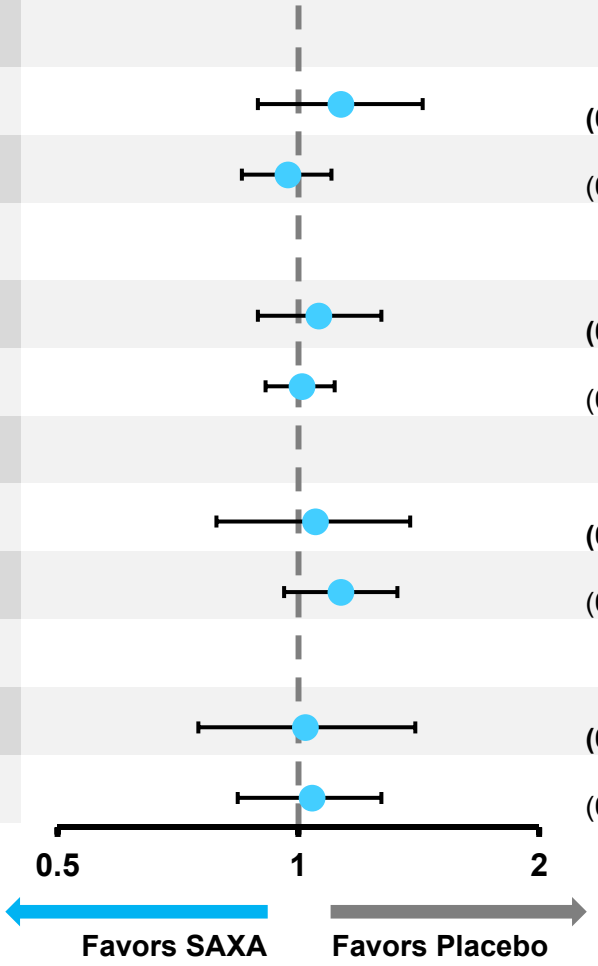
	Total N=16,492 n (%)	Saxagliptin N=8280 n (%)	Placebo N=8212 n (%)	Hazard Ratio (95% CI)
hHF or primary MACE*	1529 (9.3)	784 (9.5)	745 (9.1)	1.05 (0.95, 1.16)
hHF or CV death*	925 (5.6)	493 (6.0)	432 (5.3)	1.14 (1.00, 1.30)
Number of CV Deaths		204	204	
Number of hHF		289	228	
hHF or all-cause mortality*	1180 (7.2)	633 (7.6)	547 (6.7)	1.16 (1.03, 1.30)
Number of deaths		344	319	
Number of hHF		289	228	

*From FDA Analyses

HR for composite endpoints driven primarily by hHF component

Primary Endpoint, Secondary Endpoints and CV Death by Baseline History of Heart Failure

	Total Patients	SAXA N=8280 Patients With Events (%)	SAXA N=8280 Event Rate/ 100 PY	Placebo N=8212 Patients With Events (%)	Placebo N=8212 Event Rate/ 100 PY	Hazard Ratio (95% CI)
Primary Endpoint						
Prior HF	**2105**	**148 (14.0)**	**7.52**	**132 (12.6)**	**6.69**	**1.13 (0.89, 1.43)**
No Prior HF	14385	465 (6.4)	3.24	477 (6.7)	3.36	0.97 (0.85, 1.10)
Secondary Composite Endpoint						
Prior HF	**2105**	**252 (23.9)**	**13.78**	**237 (22.6)**	**12.91**	**1.06 (0.89, 1.27)**
No Prior HF	14385	807 (11.2)	5.79	797 (11.1)	5.77	1.01 (0.91, 1.11)
All Cause Mortality						
Prior HF	**2105**	**105 (9.9)**	**5.11**	**100 (9.5)**	**4.88**	**1.05 (0.79, 1.38)**
No Prior HF	14385	315 (4.4)	2.13	278 (3.9)	1.90	1.13 (0.96, 1.33)
CV Death						
Prior HF	**2105**	**82 (7.8)**	**3.99**	**80 (7.6)**	**3.90**	**1.02 (0.75, 1.40)**
No Prior HF	14385	187 (2.6)	1.27	180 (2.5)	1.23	1.04 (0.84, 1.27)



***All interaction p-values non-significant**

Conclusions: Heart Failure

Increased risk of hHF observed with saxagliptin

- **In the great majority of patients with T2DM and no history of HF and eGFR >60, saxagliptin can be used with little risk of hHF**
- **T2DM patients at higher absolute risk of developing HF can be identified**
  - Even in these patients, the primary and secondary endpoints, including mortality, are balanced between saxagliptin and placebo groups

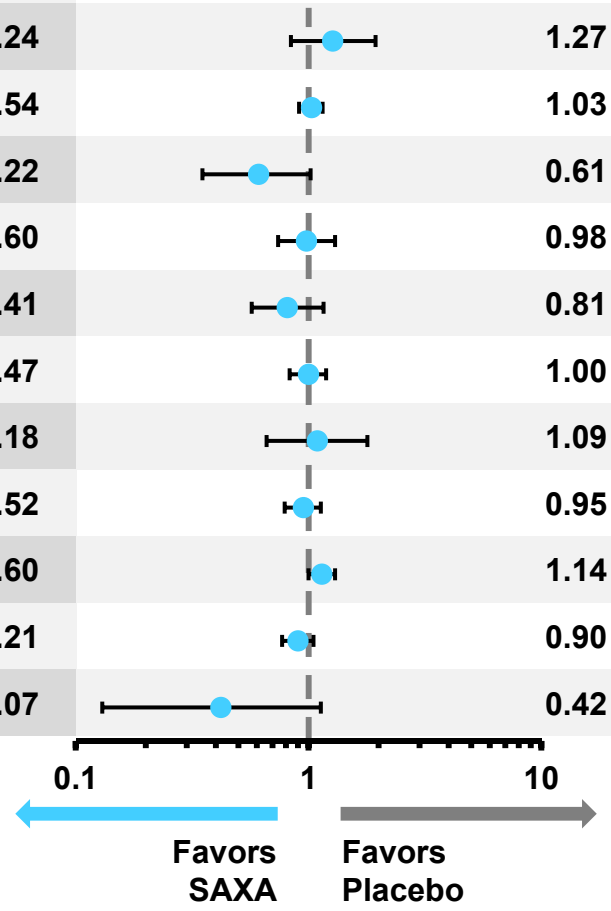
Heart Failure Management

- Heart failure is one of the most common cardiovascular complications in patients with T2DM
- Regardless of diabetes therapies, patients with T2DM should be regularly screened for signs and symptoms of heart failure, and if detected, treated accordingly to optimize heart failure regimen
- Providers must weigh benefit:risk in individual patients when prescribing diabetes medications, which is challenging in patients with or at risk of heart failure
- With its well-characterized profile, saxagliptin is a treatment option, even in patients at high risk

Analysis and Interpretation of Adverse Events of Special Interest

PMR Specified Adverse Events for Assessment

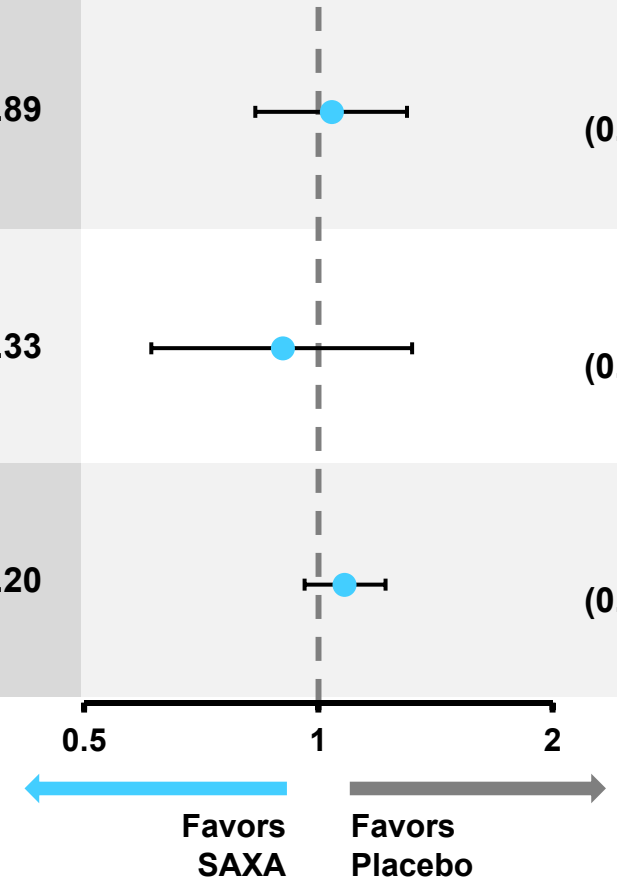
	SAXA N=8280		Placebo N=8212		Hazard Ratio (95% CI)
	Patients With Events	Event Rate /100 PY	Patients With Events	Event Rate /100 PY	
Decrease in lymphocyte count†	50	0.30	39	0.24	1.27 (0.84, 1.94)
Severe infections‡	585	3.63	567	3.54	1.03 (0.91, 1.15)
Opportunistic infections‡	22	0.13	36	0.22	0.61 (0.35, 1.02)
Hypersensitivity reactions‡	98	0.59	99	0.60	0.98 (0.74, 1.30)
Liver abnormalities†	55	0.33	67	0.41	0.81 (0.57, 1.16)
Bone fractures‡	241	1.47	240	1.47	1.00 (0.83, 1.19)
Pancreatitis AEs‡	33	0.20	30	0.18	1.09 (0.66, 1.79)
Skin reactions‡	236	1.44	247	1.52	0.95 (0.79, 1.13)
Renal abnormalities†	481	2.96	421	2.60	1.14 (1.00, 1.30)
Cancer	326	1.99	359	2.21	0.90 (0.77, 1.05)
Pancreatic cancer	5	0.03	12	0.07	0.42 (0.13, 1.13)



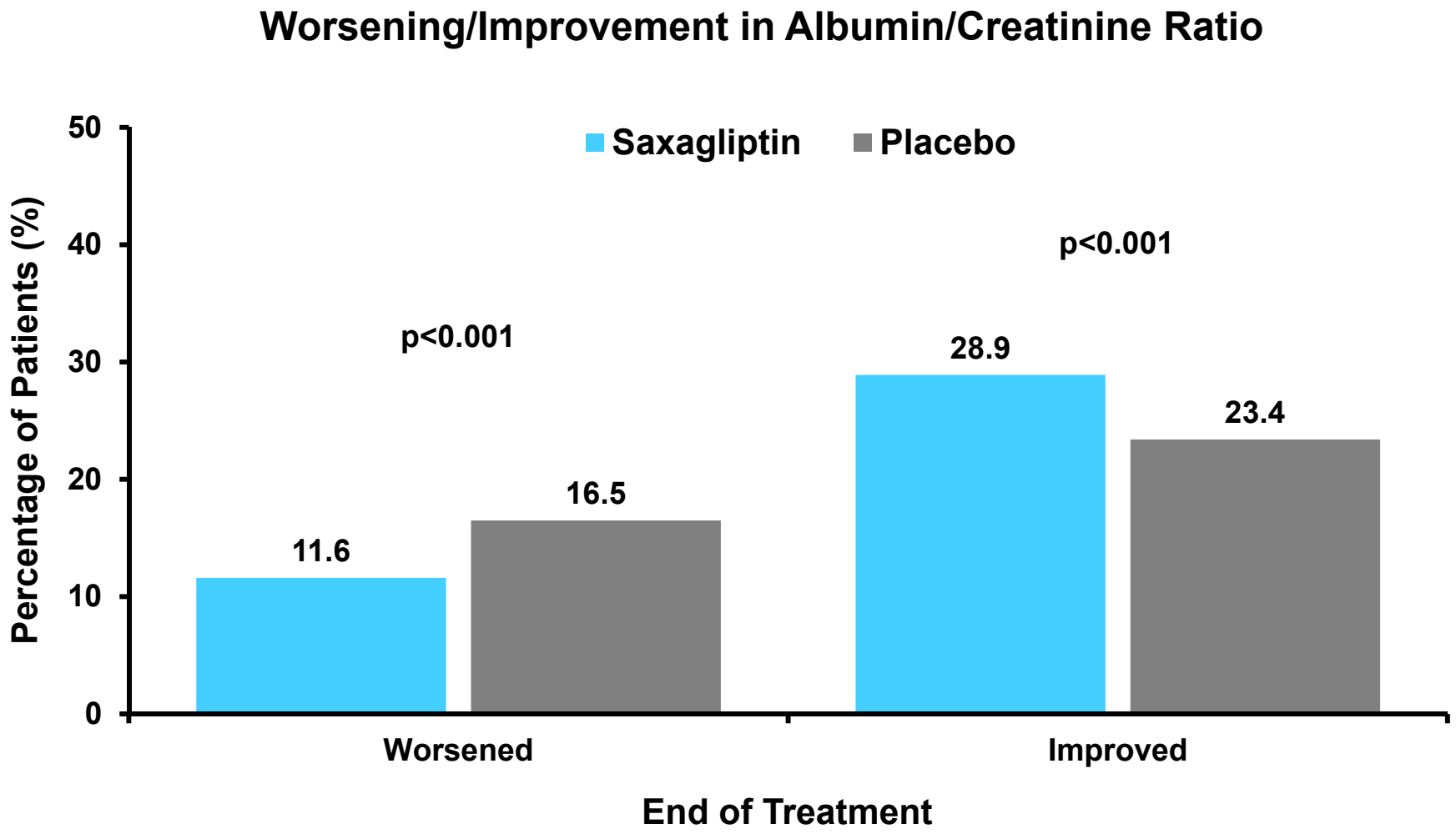
†Case report form, labs, preferred term
‡Case report, preferred term

Pre-Defined Renal Endpoints

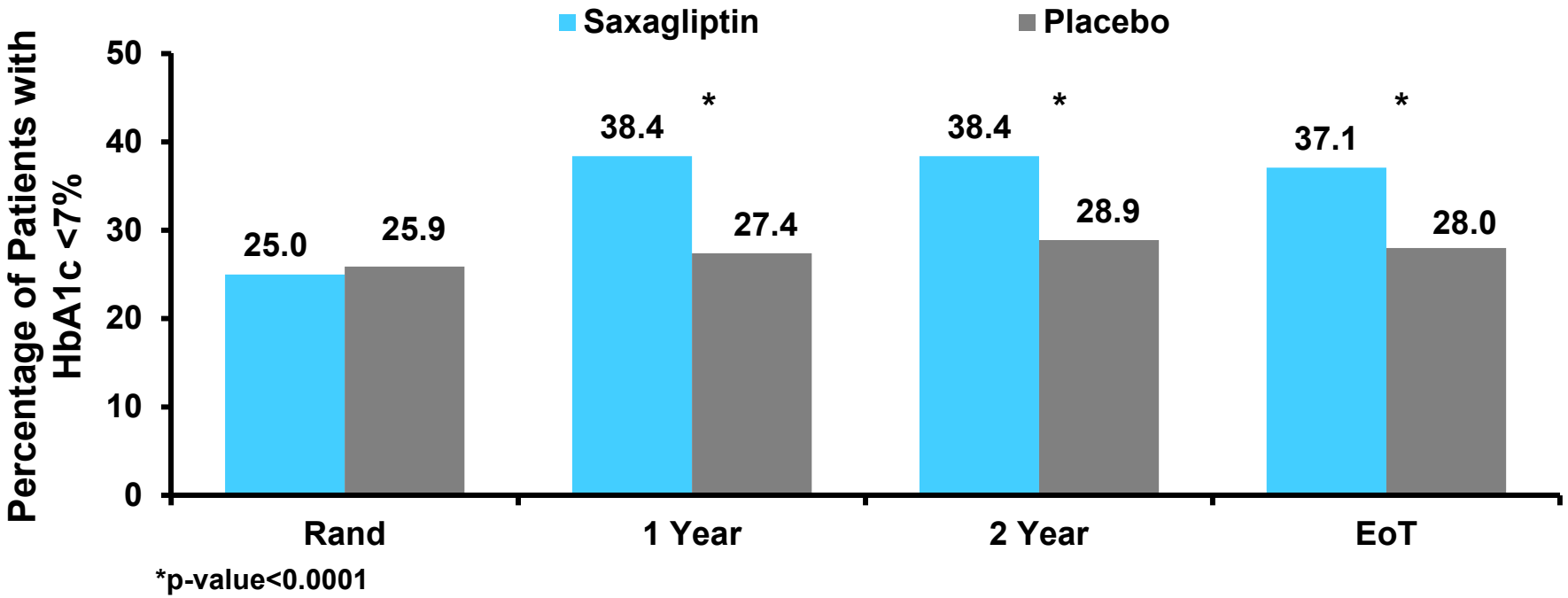
	SAXA N=8280		Placebo N=8212		Hazard Ratio (95% CI)
	Patients With Events	Event Rate/ 100 PY	Patients With Events	Event Rate/ 100 PY	
Doubling of sCr levels	153	0.92	147	0.89	1.04 (0.83, 1.30)
Initiation of chronic dialysis and/or renal transplant and/or a sCr >6.0 mg/dL	51	0.31	55	0.33	0.90 (0.61, 1.32)
Death, doubling of sCr, initiation of chronic dialysis, renal transplant, or a sCr >6.0 mg/dL	573	3.47	525	3.20	1.08 (0.96, 1.22)



Changes in Albuminuria in Patients With Microalbuminuria at Baseline



Glycemic Control Over Time



- 23% ↓ in intensification of anti-hyperglycemic medications with SAXA vs. control (p<0.001)
- 30% ↓ in initiation of insulin therapy for more than 3 months with SAXA vs. control (p<0.001)
- Hypoglycemia more frequent with SAXA (HR 1.16, p<0.001), mostly in patients taking sulfonylureas

SAVOR Conclusions

- **Provided further reassuring information on other potential pre-specified safety concerns of importance for anti-diabetic drugs**
  - Pancreatitis
  - Bone fracture
  - Liver abnormalities
  - Renal abnormalities
  - Severe and opportunistic infections
  - Skin Reactions
  - Malignancy

SAVOR Conclusions

- **When added to standard of care in patients with T2DM at high CV risk, saxagliptin did not alter the risk of CV death, MI, or ischemic stroke**
  - Therefore, the primary safety objective of excluding an unacceptable increase in CV risk, as defined by the FDA guidance, was achieved
  - In addition, we have learned more about saxagliptin through SAVOR-TIMI 53 than is known about most other DM therapies, and therefore can provide clinicians with extensive data on its efficacy and potential risks

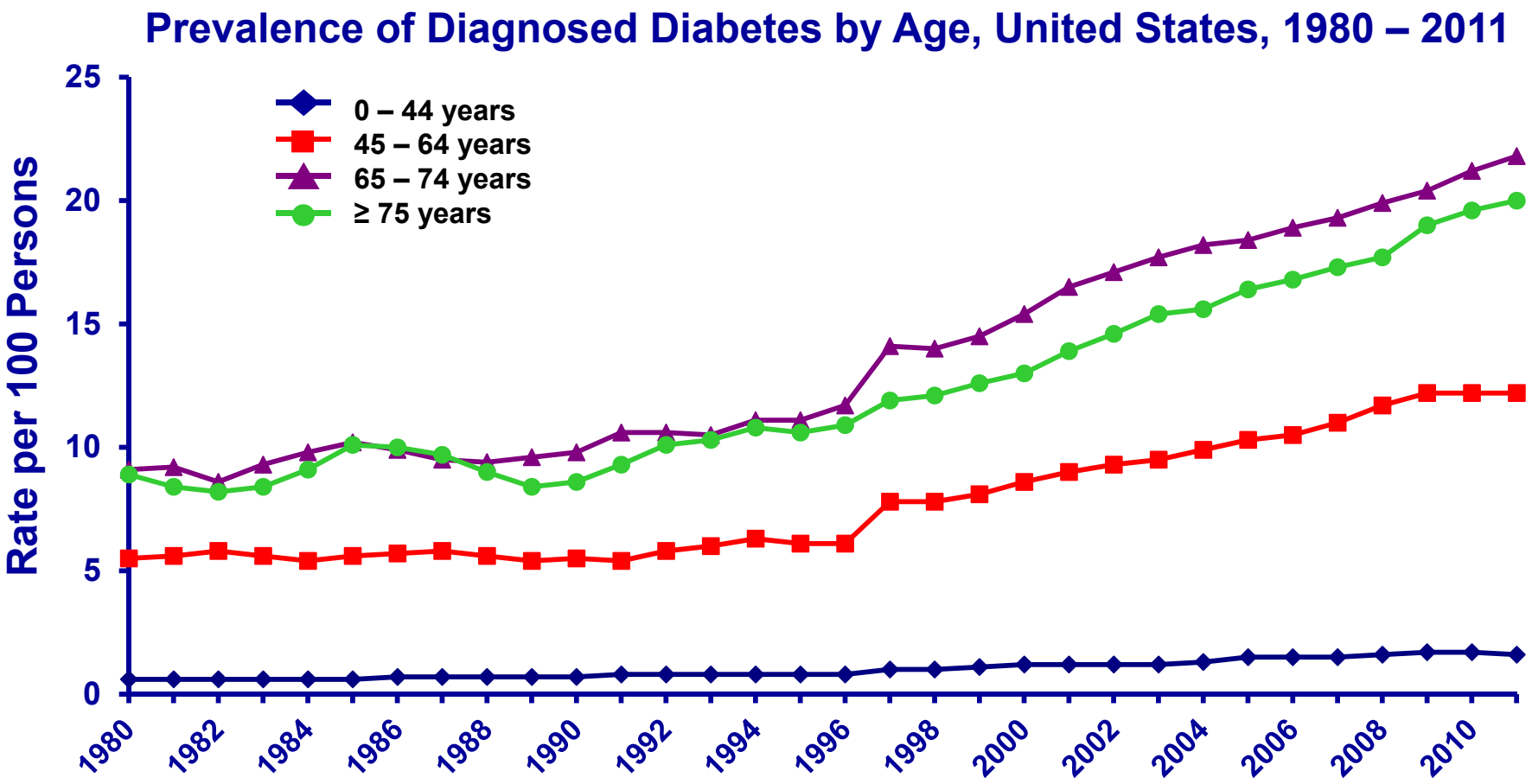
Perspectives on the Treatment of Diabetes and the SAVOR Data

Jay S. Skyler, MD, MACP

Division of Endocrinology, Diabetes, and Metabolism
and Diabetes Research Institute
University of Miami Miller School of Medicine

Burden of Diabetes

The Prevalence of Diabetes is Increasing, Particularly in Adults ≥65 Years of Age



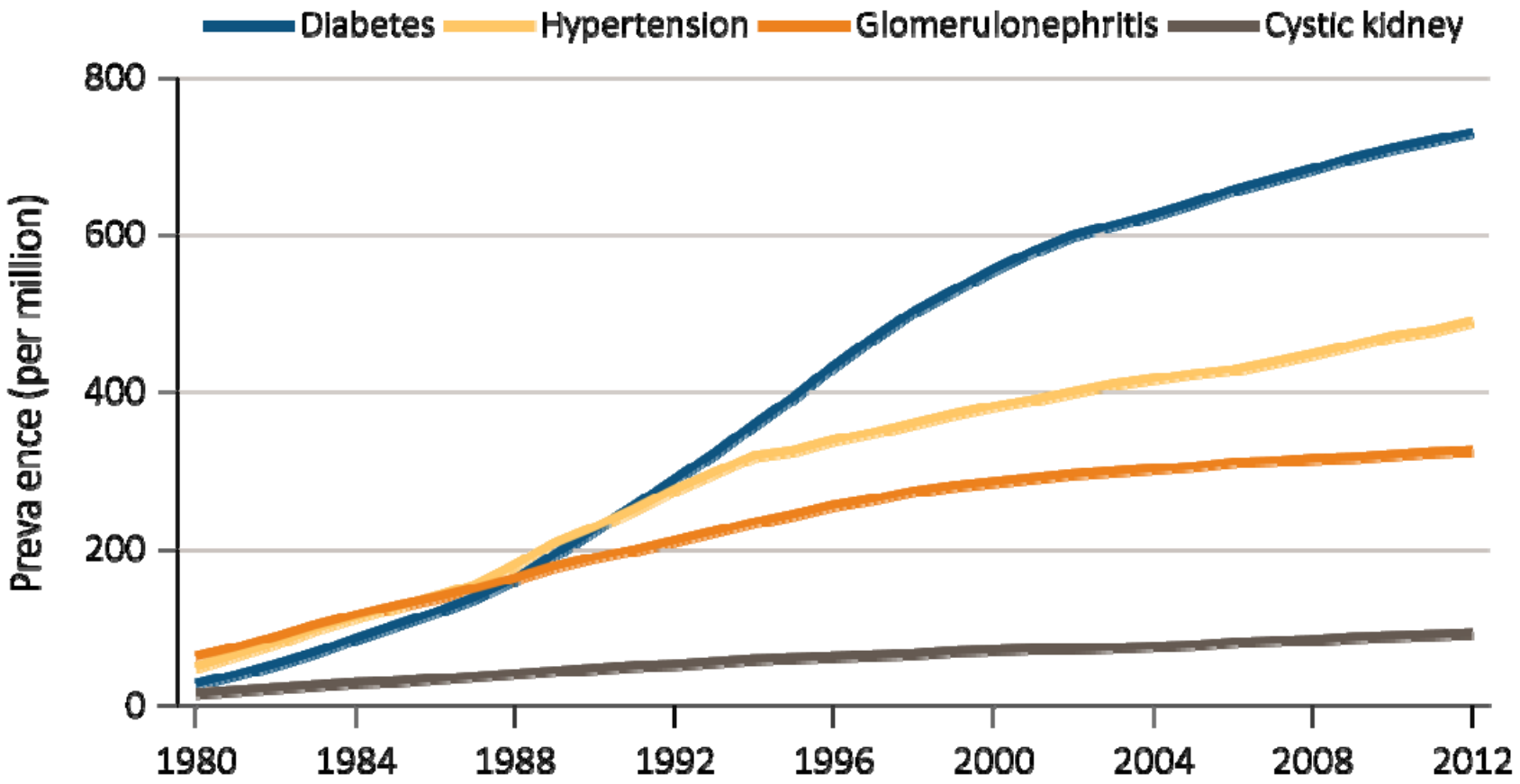
Based on data from the National Health Interview Survey. CDC Diabetes Public Health Resource Web site. Available at: http://www.cdc.gov/diabetes/statistics/prev/national/figbyage.htm.

Burden of Diabetes USA: Morbidity

- **Diabetic Retinopathy**
  #1 Cause of Blindness in Working Age Adults
- **Diabetic Nephropathy**
  #1 Cause of End Stage Renal Disease
- **Diabetic Amputations**
  # 1 Cause of Nontraumatic Lower Extremity Amputations
- **Diabetic Vascular Disease**
  2-to-6-Fold More Likely to Have Heart Disease

Centers for Disease Control and Prevention.
National Diabetes Statistics Report:
Estimates of Diabetes and Its Burden in the United States, 2014.

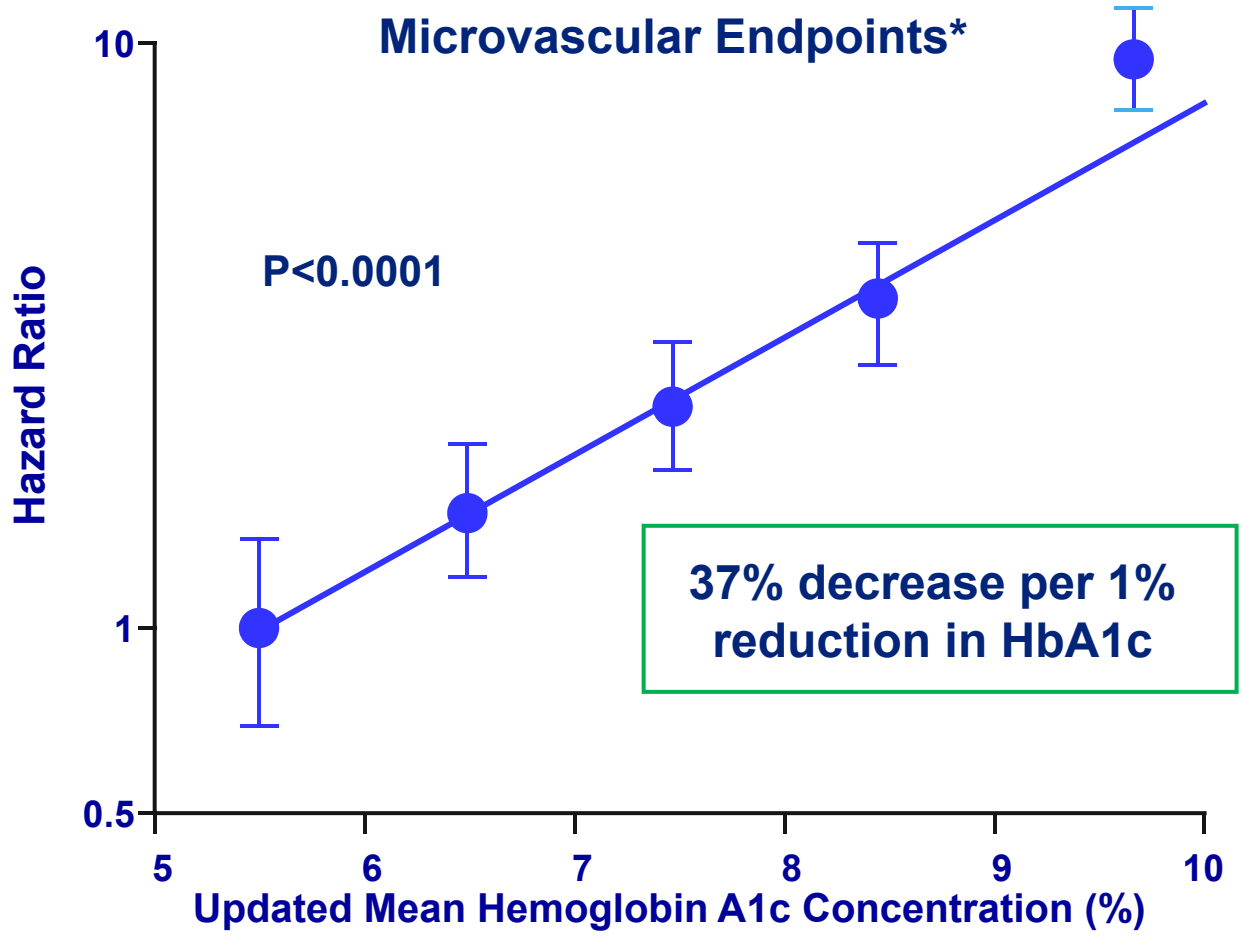
Trends in Adjusted Prevalence of ESRD, per Million, by Primary Cause of ESRD, in the U.S. Population, 1980-2012



United States Renal Data System, 2014 USRDS Annual Data Report.
NIDDK, NIH, Bethesda, MD, 2014.

Impact of Glycemic Control

HbA1c Lowering Associated With Reduction in Microvascular Complications in UKPDS



Stratton, Irene M et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. *British Medical Journal.* 2000; 321: 409

*retinopathy requiring photocoagulation, vitreous hemorrhage, and fatal or non-fatal renal failure

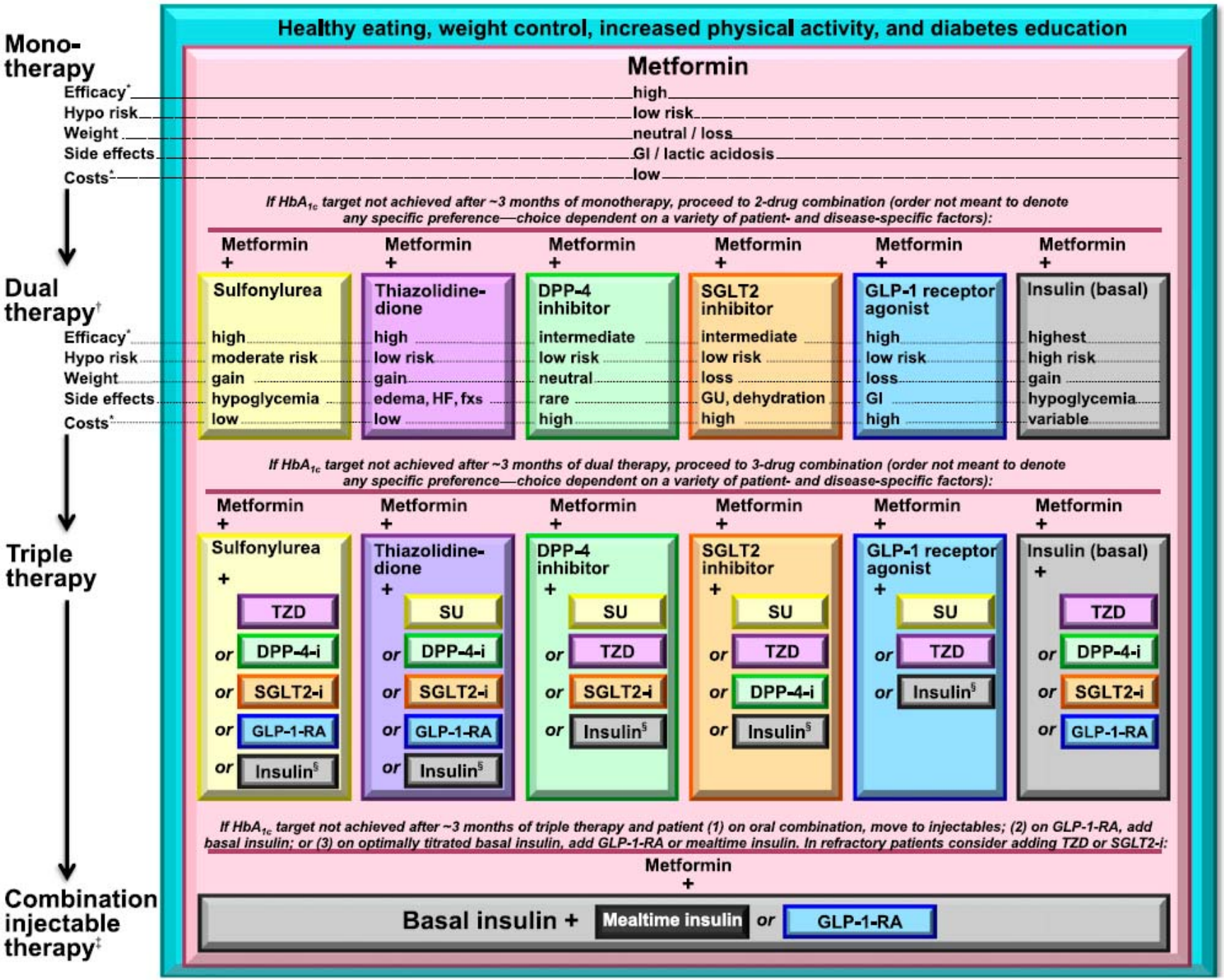
Glycemic Control Improves Microvascular Endpoints

	Microvascular		Cardiovascular Disease		Mortality	
DCCT/EDIC	↓	↓	↔	↓	↔	↓
UKPDS	↓	↓	↔	↓	↔	↓
ACCORD	↓		↔		↑ ?	
ADVANCE	↓	↓	↔		↔	
VADT	↓		↔		↔	

Initial Trial Long Term Follow-up

Adapted from Bergenstal et al. *Am J Med 2010;*123:374e9-e18; updated 2015.

Medications to Treat Diabetes


Healthy eating, weight control, increased physical activity, and diabetes education
Mono-therapy
Metformin
Efficacy* high
Hypo risk low risk
Weight neutral / loss
Side effects GI / lactic acidosis
Costs* low
If HbA1c target not achieved after ~3 months of monotherapy, proceed to 2-drug combination (order not meant to denote any specific preference—choice dependent on a variety of patient- and disease-specific factors):
Dual therapy†
Metformin + Sulfonylurea
Efficacy* high
Hypo risk moderate risk
Weight gain
Side effects hypoglycemia
Costs* low
Metformin + Thiazolidine-dione
high
low risk
gain
edema, HF, fxs
low
Metformin + DPP-4 inhibitor
intermediate
low risk
neutral
rare
high
Metformin + SGLT2 inhibitor
intermediate
low risk
loss
GU, dehydration
high
Metformin + GLP-1 receptor agonist
high
low risk
loss
GI
high
Metformin + Insulin (basal)
highest
high risk
gain
hypoglycemia
variable
If HbA1c target not achieved after ~3 months of dual therapy, proceed to 3-drug combination (order not meant to denote any specific preference—choice dependent on a variety of patient- and disease-specific factors):
Triple therapy
Metformin + Sulfonylurea + TZD or DPP-4-i or SGLT2-i or GLP-1-RA or Insulin§
Metformin + Thiazolidine-dione + SU or DPP-4-i or SGLT2-i or GLP-1-RA or Insulin§
Metformin + DPP-4 inhibitor + SU or TZD or SGLT2-i or Insulin§
Metformin + SGLT2 inhibitor + SU or TZD or DPP-4-i or Insulin§
Metformin + GLP-1 receptor agonist + SU or TZD or Insulin§
Metformin + Insulin (basal) + TZD or DPP-4-i or SGLT2-i or GLP-1-RA
If HbA1c target not achieved after ~3 months of triple therapy and patient (1) on oral combination, move to injectables; (2) on GLP-1-RA, add basal insulin; or (3) on optimally titrated basal insulin, add GLP-1-RA or mealtime insulin. In refractory patients consider adding TZD or SGLT2-i:
Combination injectable therapy‡
Metformin +
Basal insulin + Mealtime insulin or GLP-1-RA

Benefits and Risks of Anti-Diabetes Medications*

Aspect	SU	TZD	DPP-4i	SGLT2i	GLP-1	Insulin
Glycemic efficacy	high	high	moderate	moderate	high	highest
Risk of hypoglycemia	moderate	low	low	low	low	high
Weight	gain	gain	neutral	loss	loss	gain
Side effect(s)	hypo's	edema, HF, fxs	rare	GU, dehydration	GI	hypo's

*Added to Baseline Metformin Therapy

ADA-EASD Type 2 Treatment Guidelines – 2015 Update
Diabetes Care. 2015; 38:140-149

Limitations of Therapeutic Options in T2D

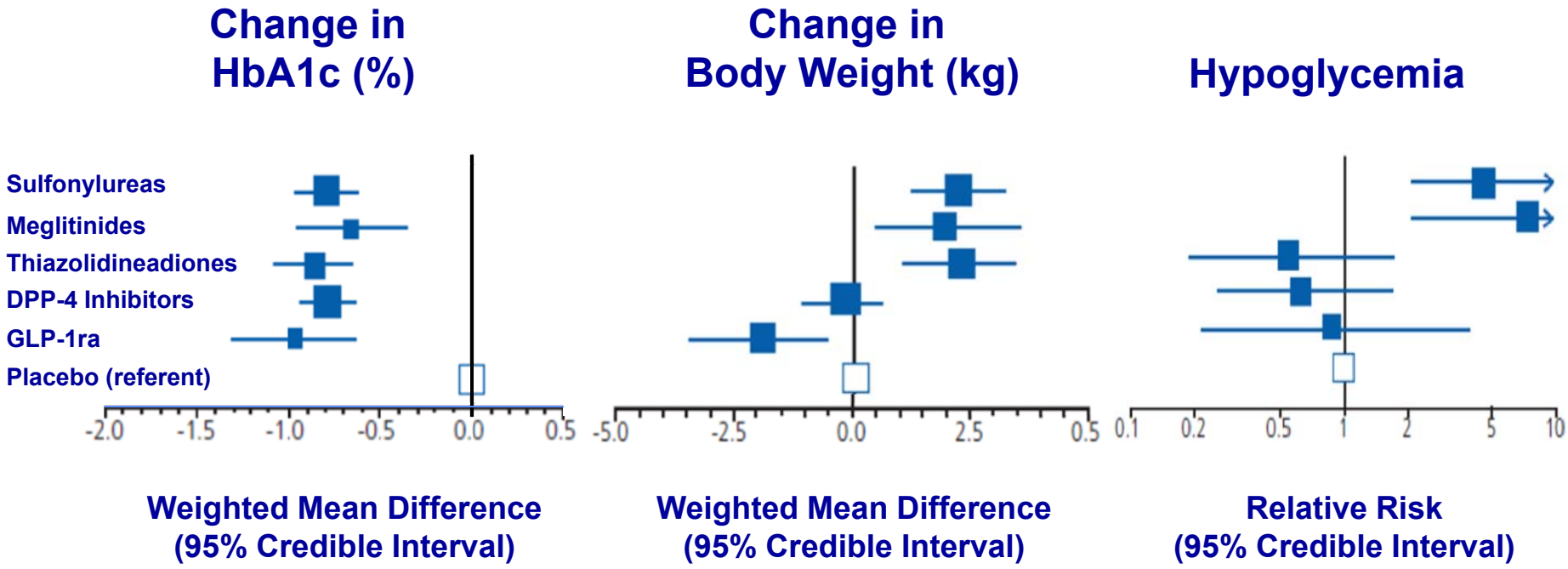
Oral therapies

- Metformin: restricted use in renal impairment and heart failure
- Sulfonylureas: hypoglycemia, weight gain, uncertain CV safety (? harm)
- Thiazolidinediones: weight gain, fluid retention, risk of heart failure
- SGLT2 inhibitors: restricted use in renal impairment, CV safety being explored

Injectible therapies

- Insulin: hypoglycemia, weight gain, fluid retention
- GLP-1 RAs: limited use in renal impairment, CV safety being explored

DPPIV- Inhibitors Improve Glycemic Control Without Increasing Risk of Hypoglycemia or Weight Gain



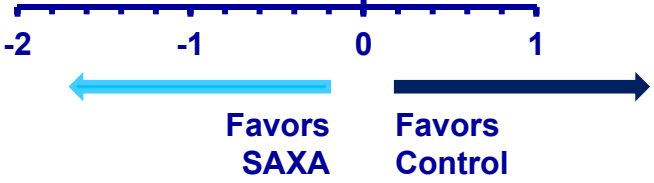
And are efficacious in patients with renal impairment

Adapted from O'Hare, Jones et al. *Br J Diabetes Vasc Dis*. 2015.

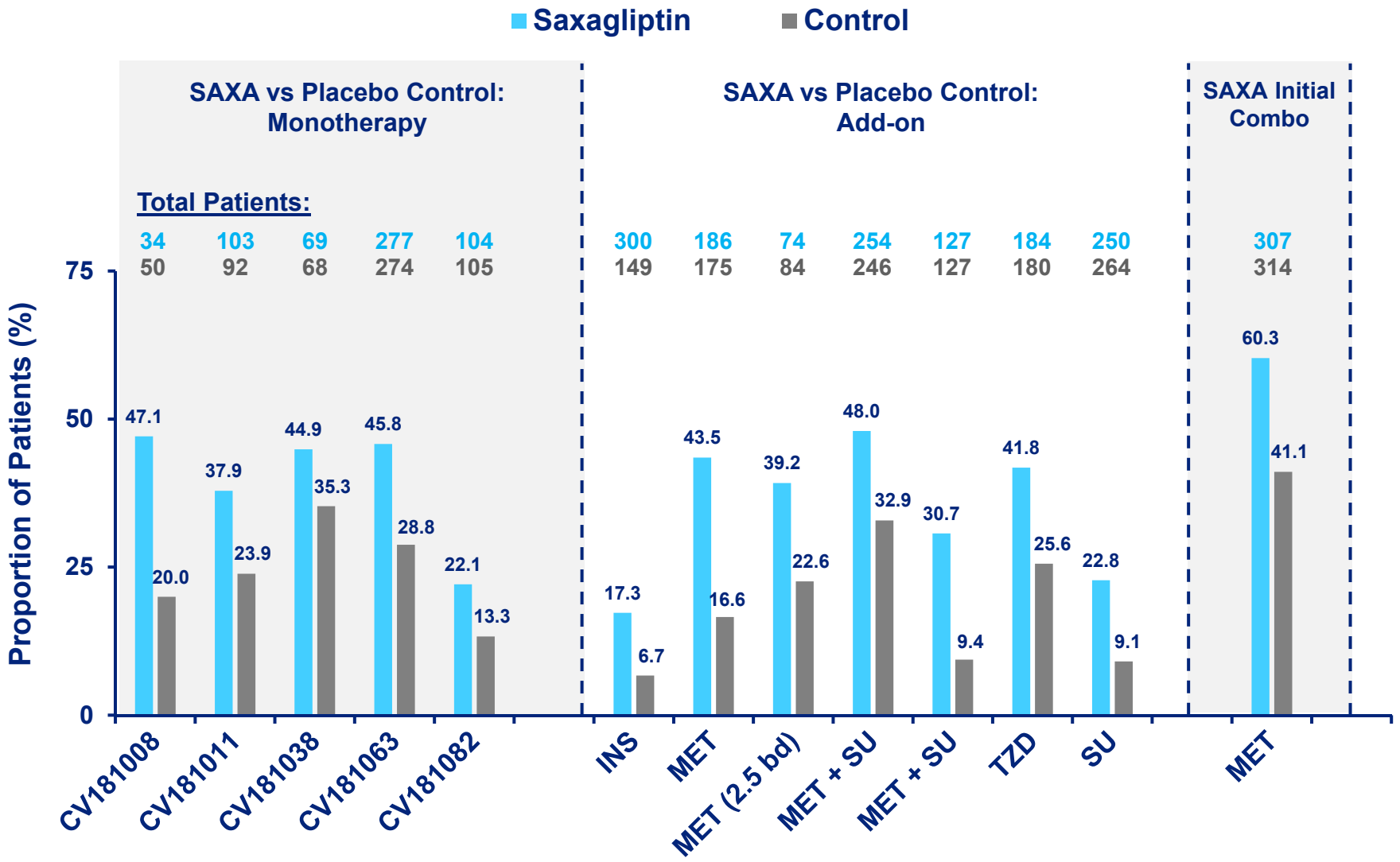
Saxagliptin as a Treatment Option for Type 2 Diabetes

HbA1c Change in Saxagliptin Clinical Program Demonstrates Consistent Efficacy

	SAXA (n)	Control (n)	Mean Diff IV Random, (95% CI)
SAXA vs. placebo control: monotherapy			
Monotherapy: CV181008	42	62	-0.63 (-0.98, -0.28)
Monotherapy: CV181011	103	92	-0.65 (-0.93, -0.37)
Monotherapy: CV181038	69	74	-0.40 (-0.68, -0.12)
Monotherapy: CV181063/D1680C00005	277	274	-0.50 (-0.68, -0.32)
Monotherapy: CV181082/D1680C00008	104	105	-0.46 (-0.73, -0.19)
SAXA vs. placebo control: add-on			
Add-on INS, placebo control: CV181057	300	149	-0.41 (-0.59, -0.23)
Add-on MET+SU, placebo control: CV181064/C00006	275	279	-0.41 (-0.55, -0.27)
Add-on MET+SU, placebo control: D1680L00006	127	127	-0.66 (-0.87, -0.45)
Add-on MET, placebo control: CV181014	186	175	-0.82 (-1.02, -0.62)
Add-on MET, placebo control: CV181080 (2.5 bd)	74	84	-0.34 (-0.58, -0.10)
Add-on TZD, placebo control: CV181013	183	180	-0.64 (-0.85, -0.43)
Add-on SU, modified control: CV181040	250	264	-0.72 (-0.88, -0.56)
SAXA initial combination			
Initial combination MET: CV181039	306	313	-0.54 (-0.73, -0.35)
SAXA renal impairment			
Renal impairment: CV181062/C7(2.5+/-OAD or INS)	81	83	-0.42 (-0.75, -0.09)



Proportion of Patients Reaching HbA1c <7.0% in Saxagliptin Clinical Program



Signs of Preservation of Beta Cell Function

	Placebo n Mean (SD)	Saxagliptin n Mean (SD)	p-value§
HOMA-2β at baseline (%)	n=2312 65.1 (44.50)	n=2408 65.8(47.8)	0.7504
HOMA-2β at 2 yr (%)	n=2173 60.1 (43.1)	n=2278 66.5(48.1)	<.0001
Change in HOMA-2β at 2yr from baseline (%)	n=2173 -4.9 (44.1)	n=2278 1.1 (50.0)	<.0001

Analysis cohort is restricted to those subjects who have both baseline and post baseline HOMA measurements.

§ nonparametric Wilcoxon rank sum test

Leibowitz G et al. *Diabetes Obes Metab*. 2015 Feb 5. doi: 10.1111/dom.12445

SAVOR Design in Perspective

- **SAVOR-TIMI 53 was a large, well conducted CV outcome study that included a large population of patients at high CV risk**
- **Large exposure and overall consistent safety in important patient populations:**
  - Elderly, HF patients, and renal impaired
  - More than 30% of patients enrolled in North America: convincing safety data relevant to a US based physician, including exposure in minority populations.

SAVOR Results in Perspective

- **Overall efficacy consistent with the phase 3 program, including number of patients reaching goal without hypoglycemia**
- **The SAVOR data supports long term beta cell function control as well as improvement in microalbuminuria, an important biomarker of renal health**
- **Overall safety:**
  - Overall SAE and AE were balanced
  - AE's of special interest for DPP4's as a class and overall anti hyperglycemic drugs balanced and reassuring
  - Low risk of hypoglycemia when treated based on label
  - Weight neutral
- **SAVOR satisfied the FDA guidance, i.e. excluding an unacceptable CV risk with saxagliptin**

Conclusions

- The burden of diabetes is growing – more and more people have the disease
- Both microvascular and macrovascular complications are important
- Glycemic control reduces rates of microvascular complications
- Long-term follow-up is needed to show reduction in rates of macrovascular complications
- SAVOR provides evidence that saxagliptin does not increase rates of macrovascular complications
- Risk-benefit is essential in evaluating any treatment
- Saxagliptin has been extensively studied and is an important tool for lowering glycemia, without increasing risk of hypoglycemia or causing weight gain

Conclusion

Howard Hutchinson, MD

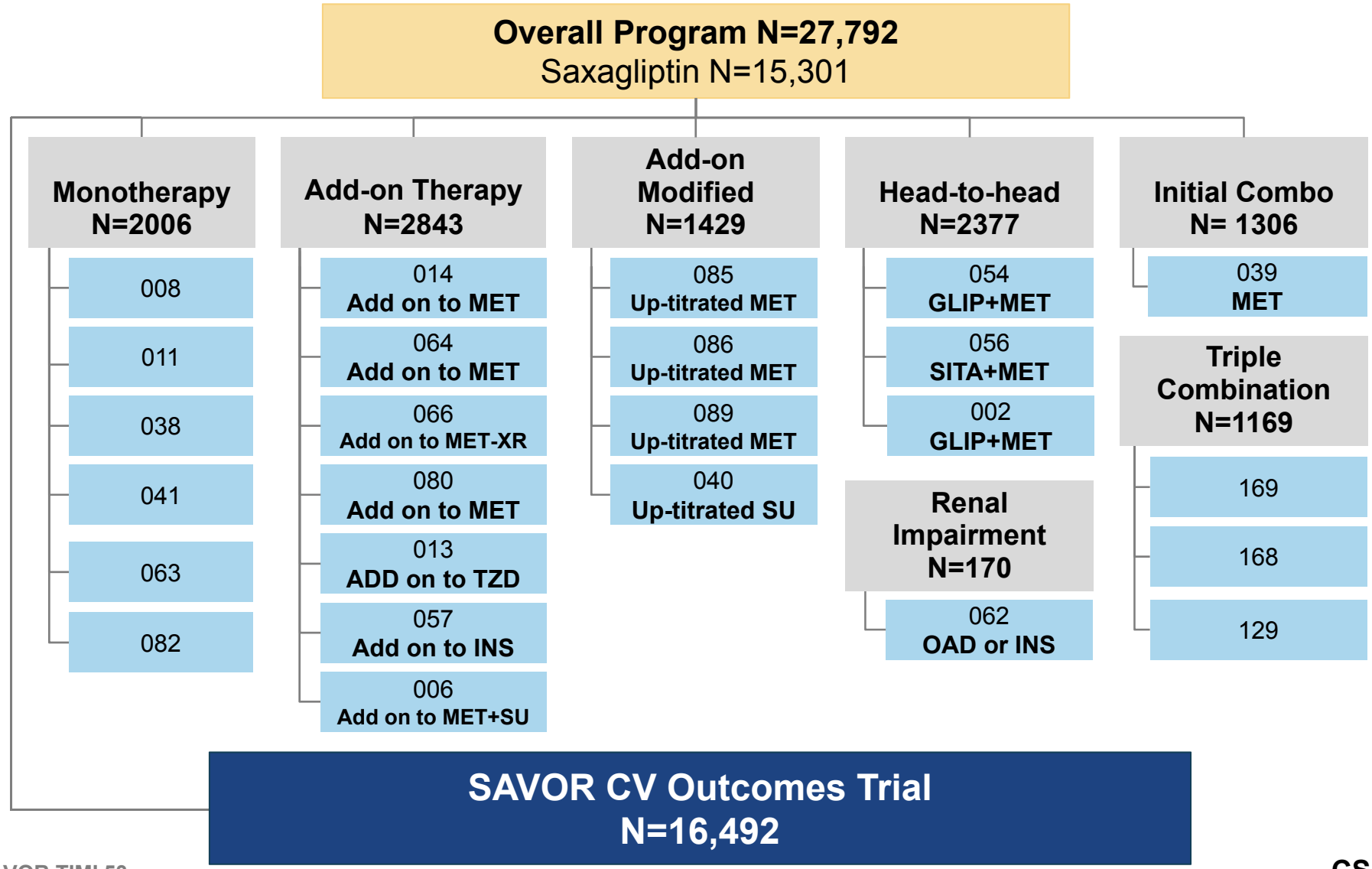
VP Development, Cardiovascular and Metabolic Diseases

AstraZeneca

Summary

- **SAVOR ruled out an unacceptable increase in CV risk as per the 2008 FDA guidance on CV safety of anti-diabetic drugs**
- **Primary and secondary composite endpoints balanced**
- **No increased risk in mortality attributable to saxagliptin**
- **An increased risk for hospitalizations for heart failure was observed**
  - Label update to include new safety information
- **No increase in rates of pancreatitis, bone fractures, malignancy, severe/opportunistic infections, renal or liver abnormalities**

Saxagliptin Clinical Development Program



Benefit/risk: Before SAVOR

Benefits

- **Efficacious in lowering HbA1c**
- **Low incidence of hypoglycemia**
- **Lack of weight gain**
- **Orally administered**

Risks

- **Hypersensitivity reactions**
- **Unknown CV safety**
- **Potential to increase rates of**
  - Pancreatitis
  - Bone fractures
  - Malignancy
  - Severe infections
  - Renal impairment
  - Liver abnormalities

Benefit/risk: After SAVOR

Benefits	Risks

• **Efficacious in lowering HbA1c**
• **Low incidence of hypoglycemia**
• **Lack of weight gain**
• **Orally administered**
• **Acceptable CV safety**
• **Does not increase rates of**
  • Pancreatitis
  • Bone fractures
  • Malignancy
  • Severe infections
  • Renal impairment
  • Liver abnormalities
	• **Hypersensitivity reactions**
	• **Hospitalization for heart failure**

Summary

- **AstraZeneca continues to further characterize the overall benefit-risk profile of saxagliptin**
  - Additional clinical trials
  - Pharmaco-epidemiology studies
  - Post-marketing surveillance
  - Mechanistic study to further investigate the heart failure imbalance
- **The overall benefit-risk profile for saxagliptin remains favorable**
- **Saxagliptin remains an important treatment option for patients with Type 2 Diabetes Mellitus**

Experts Available to the Panel

Benjamin M. Scirica, MD, MPH

- **Associate Professor Medicine, Harvard Medical School**
- **Senior Investigator in the TIMI Study Group**
- **Research focuses on improving risk stratification and treatment of patients with cardiovascular disease (assessment of novel therapeutic cardiometabolic agents, and the development of novel electrocardiography and cardiac biomarkers)**
- **Authored over 80 peer reviewed articles in the area of CV research and large CV outcomes trials**
- **Co-PI or lead investigator for several major trials, including MERLIN, PLATO, TRA2P, AVANT-GARDE and SAVOR**
- **Awarded the following honors:**
  - Lerner Young Investigator Award (2008, Brigham and Women's Hospital)
  - Jean M. Jackson Distinguished Bedside Teacher Award (2012, Brigham and Women's Hospital)

Jay S. Skyler, MD, MAC

- Professor of Medicine, Pediatrics, & Psychology, Division of Endocrinology, Diabetes, & Metabolism, Department of Medicine, University of Miami Miller School of Medicine, Miami, Florida
- Deputy Director for Clinical Research and Academic Programs at the Diabetes Research Institute, University of Miami, Florida
- Research interest focuses on immune intervention and beta cell expansion or replacement
- Past President of the American Diabetes Association, the International Diabetes Immunotherapy Group, and the Southern Society for Clinical Investigation, and Vice-President of the International Diabetes Federation
- Founding Editor of *Diabetes Care*
- Currently Senior Editor of *Diabetes Technology & Therapeutics*
- Author, editor, or co-editor of 21 books or monographs, and has written over 450 articles, book chapters, or editorials
- Awards include the Master of the American College of Physicians (MACP, 2005)

Bertram Pitt, MD

- Professor of Internal Medicine, Emeritus
  University of Michigan School of Medicine
- Research in cardiology area of heart failure
- Author of over 650 peer reviewed publications
- Co-principal or principal investigator of numerous pivotal heart failure trials, including EMPHASIS-HF, EPHESUS, PEARL-HF, SOLVD (NHLBI), TOP CAT (NHLBI), RALES and ARTS-HF
- Awarded the following honors:
  - 2012 Lifetime achievement award-Heart Failure Society of America
  - 2013 Lifetime achievement award-European Society of Heart Failure

Itamar Raz, MD

- Professor of Medicine, Hebrew University, Hadassah Medical School
- Head, Center for the Prevention of Diabetes, Hadassah Medical Center, Israel
- Leader in the field of academic and clinical research in the treatment of diabetes
- Key areas of research center on pathologic mechanisms leading to diabetic complications; centered on the relationship of diabetes to vasoactive peptides, and searching the pathophysiology of beta-cell dysfunction and loss in diabetes
- Authored over 270 publications

Janet Wittes, PhD

- President and Founder Statistics Collaborative, Inc. Washington, DC
- Fellow of the American Statistical Association, the Society for Clinical Trials (SCT), and AAAS
- Her research focuses on design and analysis of randomized clinical trials, sample size recalculation, and analysis of safety data
- Member of many advisory committees (FDA AdComs, NIH, VA, IOM, WHO, Industry)
- Chair or member of DMCs for many multi-center trials sponsored by the NIH, VA, and industry
- Previous major position: Chief, Biostatistics Research Branch, National Heart, Lung, and Blood Institute (NHLBI) (1983–1989)

Saxagliptin
Advisory Committee Meeting

Endocrinologic and Metabolic Drugs

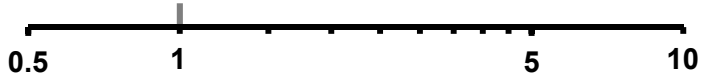
Advisory Committee

April 14, 2015

AstraZeneca

Multivariate Analysis: Baseline Characteristics and Risk of Hospitalization for HF Irrespective of Treatment Group

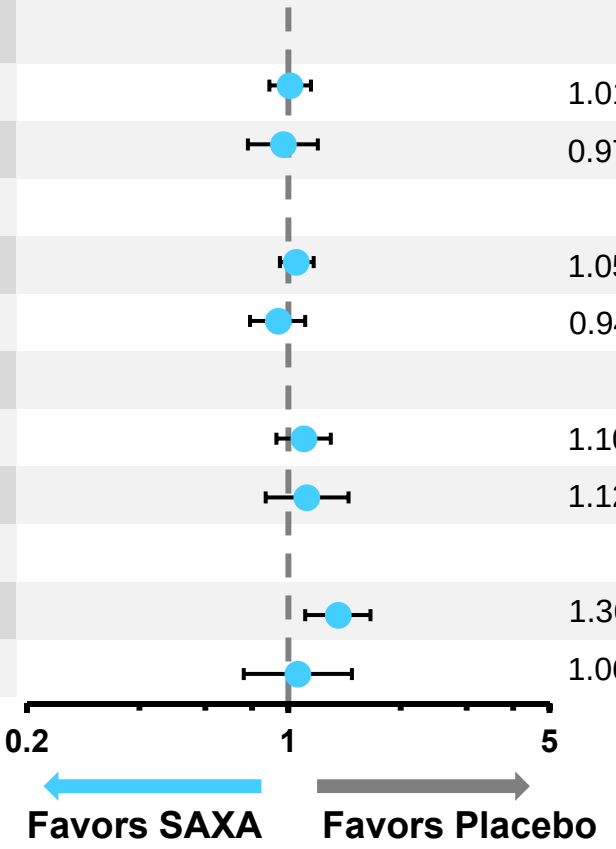
	N	Adjusted Hazard Ratio (95% CI)
History of Heart Failure	1986	4.18 (3.48, 5.03)
Microalb./creat. >33.9 mg/mmol	1638	3.66 (2.90, 4.62)
eGFR ≤60 mL/min	4602	2.00 (1.65, 2.42)
Microalb./creat. ≥3.4 - ≤33.9 mg/mmol	4425	1.89 (1.54, 2.34)
Age ≥75	2192	1.70 (1.38, 2.09)
History of MI	5933	1.47 (1.21, 1.78)
Non-Hispanic	12326	1.56 (1.20, 2.04)
CVD	12343	1.64 (1.18, 2.28)
Saxagliptin	7915	1.29 (1.08, 1.54)
Female	5205	0.76 (0.62, 0.93)
Dyslipidemia	11213	1.27 (1.02, 1.59)



Ranked according to Chi-square value

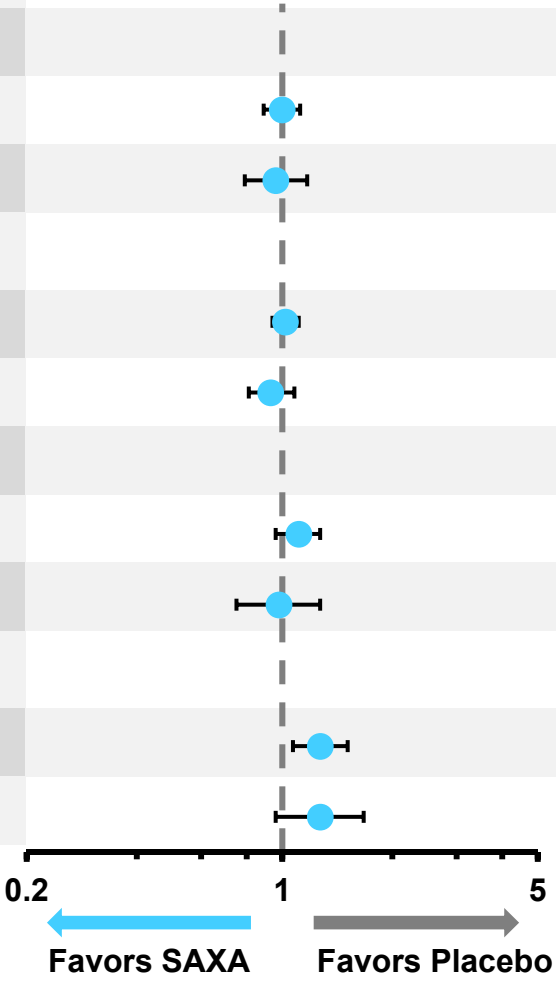
Primary, Secondary Composite, All-cause Mortality and Hospitalization for Heart Failure by Gender

		SAXA N=8280	Placebo N=8212	
		Event Rate/ 100 PY	Event Rate/ 100 PY	Hazard Ratio (95% CI)
Primary composite				
Male	11037	4.21	4.14	1.01 (0.89, 1.15)
Female	5455	2.88	3.03	0.97 (0.78, 1.20)
Secondary composite				
Male	11037	7.69	7.26	1.05 (0.95, 1.17)
Female	5455	4.88	5.32	0.94 (0.79, 1.11)
All-cause mortality				
Male	11037	2.64	2.39	1.10 (0.93, 1.30)
Female	5455	2.21	2.01	1.12 (0.87, 1.45)
Hospitalization for HF				
Male	11037	2.00	1.47	1.36 (1.11, 1.66)
Female	5455	1.30	1.23	1.06 (0.76, 1.48)



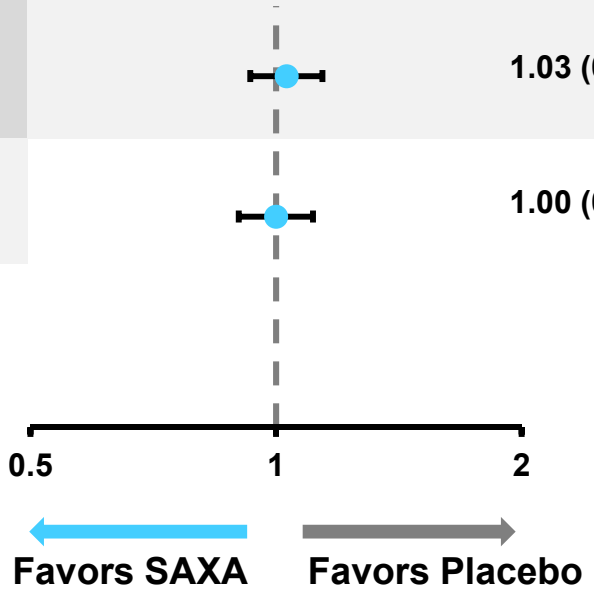
Primary, Secondary Composite, All Cause Mortality and hHF in North America Region

	Total Patients	SAXA Event Rate/ 100PY	Placebo Event Rate/ 100PY	Hazard Ratio (95% CI)
Primary endpoint				
Overall	16492	3.76	3.77	1.00 (0.89, 1.12)
North America	5266	3.82	4.00	0.96 (0.79, 1.17)
Secondary composite endpoint				
Overall	16492	6.72	6.60	1.02 (0.94, 1.11)
North America	5266	7.42	7.96	0.93 (0.81, 1.08)
All-cause mortality				
Overall	16492	2.50	2.26	1.11 (0.96, 1.27)
North America	5266	2.15	2.21	0.98 (0.75, 1.27)
Hospitalization for heart failure				
Overall	16492	1.76	1.39	1.27 (1.07, 1.51)
North America	5266	2.24	1.77	1.27 (0.96, 1.67)



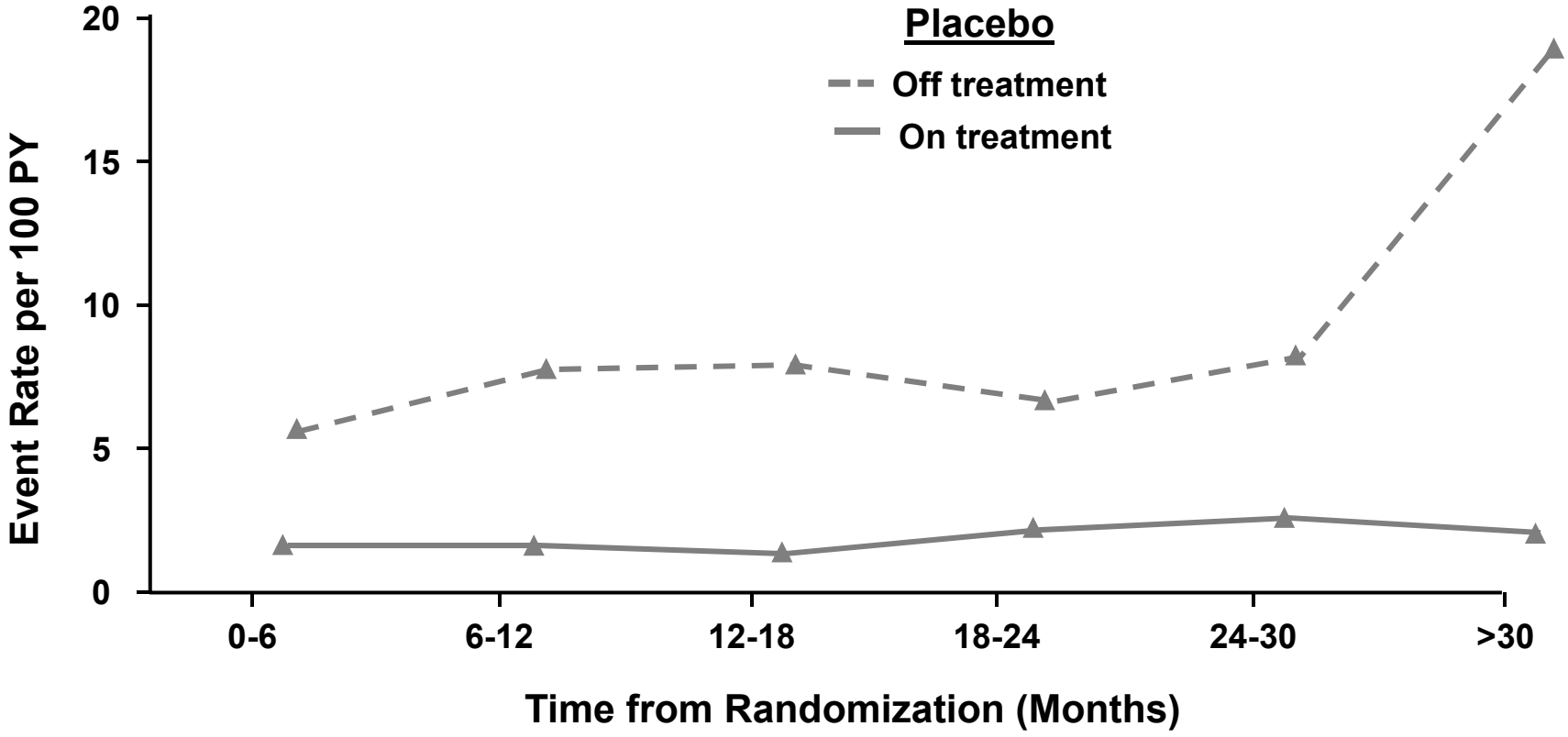
Composite Endpoint of Primary MACE + Non-CV Death

	Saxagliptin N=8280		Placebo N=8212		Hazard Ratio (95% CI)
	Patients with Events	Event Rate /100 PY	Patients with Events	Event Rate /100 PY	
MACE + Non-CV Death	742	4.55	717	4.43	1.03 (0.93, 1.14)
MACE Only	613	3.76	609	3.77	1.00 (0.89, 1.12)



All-cause Mortality Event Rate On/off Treatment: Placebo

mITT

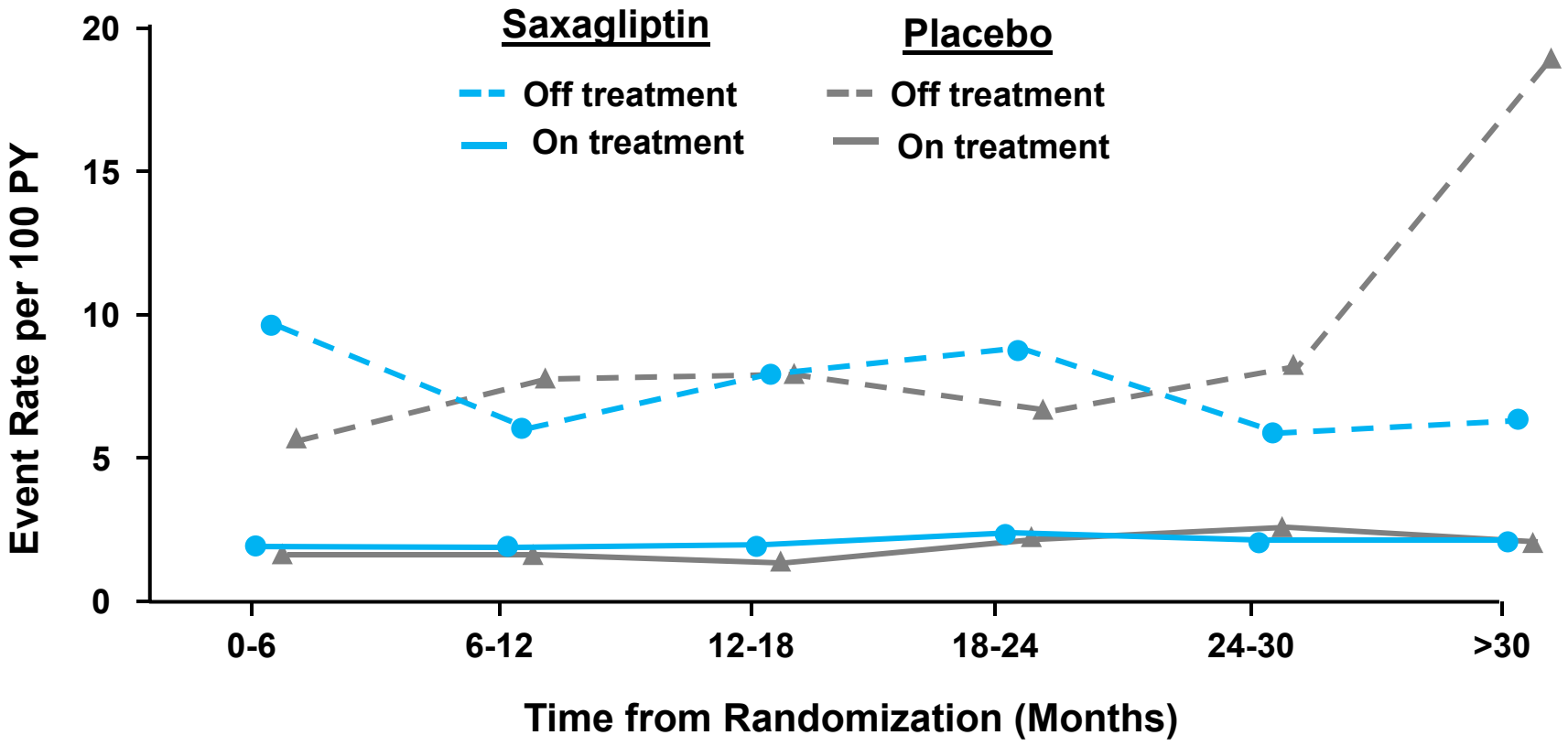


Number of Events

On Placebo	58	58	43	59	29	1
Off Placebo	6	25	38	34	22	3

All-cause Mortality Event Rate On/off Treatment: Saxagliptin and Placebo

mITT



Number of Events

On SAXA	71	68	66	66	25	1
Off SAXA	10	18	35	41	14	1
On Placebo	58	58	43	59	29	1
Off Placebo	6	25	38	34	22	3

Concomitant Diabetes Medications

Diabetes Medication	Baseline		1-Year		2-Year		End of Treatment	
	SAXA N=8280 %	PBO N=8212 %	SAXA N=7999 %	PBO N=7943 %	SAXA N=5101 %	PBO N=5059 %	SAXA N=8041 %	PBO N=8007 %
Metformin	69.9	69.2	69.6	70.1	70.0	69.9	69.4	70.0
Sulfonylureas	40.5	40.0	39.7	40.4	39.2	39.5	39.8	40.2
Thiazolid-inediones	6.2	5.7	5.4	5.2	4.7	4.7	4.9	4.7
Insulin	41.6	41.2	42.3	43.6	42.5	45.8	43.8	46.4
Other anti-hyperglycemic medications	0.6	0.6	0.6	0.5	0.6	0.4	0.7	0.6

Scirica BM, Bhatt DL, Braunwald E et al. *N Engl J Med.* 2013; Supplement

Reasons for Discontinuation of Study Drug

Parameter	Saxagliptin N=8240 n (%)	Placebo N=8280 n (%)
Total Withdrawals	1527 (18.4)	1705 (20.8)
Patient decision	920 (11.1)	1087 (13.2)
AE/SAE due to medication	335 (4.0)	324 (3.9)
Physician choice	98 (1.2)	117 (1.4)
Other	151 (1.8)	150 (1.8)
Criteria violation	18 (0.2)	19 (0.2)
Use of DPP-4/GLP1	5 (<0.1)	8 (<0.1)

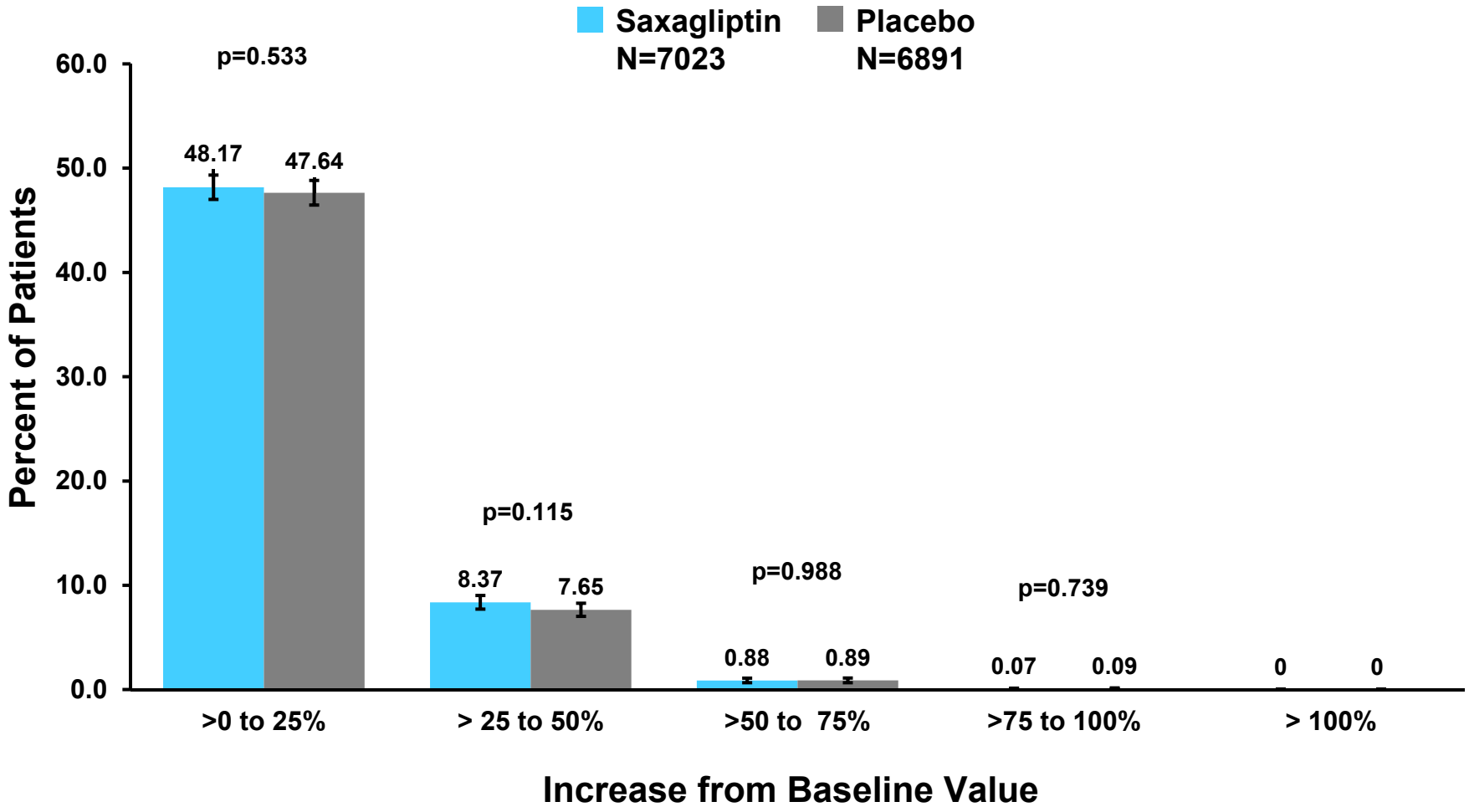
Rationale for Investigating Potential Mechanisms Associated with Heart Failure in SAVOR

- Investigate the association of the administration of saxagliptin and the development of HF
- Determine the mechanisms associated with an increase in blood volume and the development of symptomatic HF
- An understanding of the mechanisms associated with an increase in HF could lead to strategies to prevent and/or decrease the incidence of HF as well as to more effectively treat HF once it occurs

Potential Mechanisms Associated with Heart Failure in SAVOR

- **The early divergence of the KM curves suggests an increase in blood volume possibly due to neurohormonal activation**
  - RAAS
  - Vasopressin
  - Endothelin
  - Norepinephrine
- **Other potential mechanisms include:**
  - Increase in myocardial fibrosis
  - Increase in myocardial cell death
  - Decrease in mitochondrial function and increased reactive oxygen species (ROS)
  - Decrease in renal function

eGFR –Proportion of Patients With Worsening (Last Observation On Treatment)



Investigator-Reported and Adjudication-Confirmed Pancreatitis

Event	Saxagliptin N=8280	Placebo N=8212	p-value (Fisher Exact Test)	HR (95% CI)
Investigator-reported pancreatitis				
Patients with pancreatitis events	33 (0.40)	30 (0.37)	0.80	1.09 (0.66-1.79)
Number of events of pancreatitis	35	35		0.99 (0.90-1.10)
Adjudication-confirmed pancreatitis				
Patients with any pancreatitis event	24 (0.29)	21 (0.26)	0.77	1.13 (0.63-2.06)
Number of events of pancreatitis	26	25		1.03 (0.93-1.15)
Patients with definite acute pancreatitis events	17 (0.2)	9 (0.1)	0.17	1.88 (0.86-4.41)
Patients with acute pancreatitis, definite or possible	22 (0.3)	16 (0.2)	0.42	1.36 (0.72-2.64)
Patients with chronic pancreatitis events	2 (0.02)	6 (0.07)	0.18	0.33 (0.05-1.44)

Data are n (%) unless otherwise indicated. HR and 95% CIs from a Poisson regression model

Raz I, Bhatt DL, Hirshberg B et al. *Diabetes Care.* 2014. www.care.diabetesjournals.org

Characteristics of Adjudicated Pancreatitis Events

Event	Saxagliptin N=8280	Placebo N=8212
Patients with any pancreatitis event*		
Duration of events (days)		
n	21	22
Mean (SD)	13.7 (28.3)	38.5 (103.4)
Median (minimum, maximum)	7.0 (3.0, 135.0)	12.0 (2.0, 494.0)
Action taken to study drug		
Not applicable	4 (15.4)	5 (20.0)
Dose not changed	16 (61.5)	13 (52.0)
Drug interrupted	2 (7.7)	1 (4.0)
Drug withdrawn	4 (15.4)	6 (24.0)
Outcome of the AE		
Resolved	21 (80.8)	21 (84.0)
Recovering	3 (11.5)	1 (4.0)
Not resolved	2 (7.7)	1 (4.0)
Resolved with sequelae	0	1 (4.0)
Fatal	0	1 (4.0)

Data are n (%) unless otherwise indicated. HR and 95% CIs from a Poisson regression model. *Summary is at the event level; denominator is the total number of events for each treatment group. Eight pancreatic cases missing data on duration of events