Endocrinologic and Metabolic Drugs Advisory Committee Meeting
October 24-25, 2018

Introductory Remarks

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Acting Division Director
Division of Metabolism and Endocrinology Products
Food and Drug Administration

Guidance for Industry

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

Regulatory Framework

- Food and Drug Administration Amendments Act
- FDA could require post-approval study to:
  - Assess known serious risk
  - Assess signals of serious risk
  - Identify an unexpected serious risk when available data indicate the potential for a serious risk

FDA = Food and Drug Administration

Postmarketing Requirement Language

"There have been signals of serious risk for cardiovascular events with some medications developed for the treatment of type 2 diabetes mellitus, and available data have not definitively excluded the potential for this serious risk with [DRUG PRODUCT]. We have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess a signal of serious risk of major adverse cardiovascular events with antidiabetic medications, including [DRUG PRODUCT]."

How to Move Forward

- Several completed trials
  - SAVOR-TIMI
  - EXAMINE
  - EMPA-REG OUTCOME
  - ELIXA
  - LEADER
  - SUSTAIN-6
  - CANVAS Program
  - EXSCEL
- Now what?

Day 1

- FDA Presentations
  - Dr. Lisa Yanoff
    - History of the 2008 Cardiovascular Guidance and Overview of the Guidance Recommendations
  - Dr. Patrick Archdeacon
    - Review of Cardiovascular Assessments Prior to the 2008 Guidance
  - Drs. Tania Condarco and Mahtab Niyyati
    - Review of Design and Results of Cardiovascular Outcome Trials

CV = cardiovascular

Day 1 (cont.)

- Outside Speakers
  - Dr. Robert Ratner
    - Where Do We Stand on CV Safety in Diabetes?
  - Dr. Marc Sabatine
    - TIMI Study Group Presentation
  - Dr. Jennifer Green
    - Impact and Importance of the 2008 Guidance in Diabetes Care

TIMI = Thrombolysis in Myocardial Infarction

Day 2 - Agenda

- Open Public Hearing

- Committee Discussion

Discussion Topic 1

Discuss the impact of the recommendations in the 2008 Guidance for Industry: Diabetes Mellitus – Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes on the assessment of cardiovascular risk for drugs indicated to improve glycemic control in patients with type 2 diabetes mellitus.

Discussion Topic 2

For each recommendation described in the 2008 guidance, discuss its value in the evaluation of the safety of new antidiabetic drugs. The recommendations we would like you to consider are:

a. Establishment of an independent cardiovascular endpoints committee for prospective adjudication.

b. Inclusion of patients at higher risk for cardiovascular events in phase 2 and phase 3 trials to obtain sufficient endpoints to allow for a meaningful estimate of risk.

c. Exclusion of 1.8 from the upper bound of the two-sided 95% confidence interval for the estimated risk ratio prior to approval.

d. Exclusion of 1.3 from the upper bound of the two-sided 95% confidence interval for the estimated risk ratio to conclude that there is no unacceptable increase in cardiovascular risk.

Discussion Topic 3

Discuss how cardiovascular safety findings from members of a drug class should or should not be applied to all members of the drug class.

Voting Question

The 2008 Guidance for Industry: Diabetes Mellitus – Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes provided recommendations on excluding an unacceptable increase in cardiovascular risk for all new therapies to improve glycemic control in patients with type 2 diabetes regardless of the presence or absence of a signal for cardiovascular risk in the development program.

Voting Question (cont.)

Should an unacceptable increase in cardiovascular risk be excluded for all new drugs to improve glycemic control in patients with type 2 diabetes, regardless of the presence or absence of a signal for cardiovascular risk in the development program?

a. If 'Yes', provide your rationale. Include in your discussion what changes, if any, you would recommend to the 2008 guidance and why, and what kind of assessment would be appropriate and when it should be conducted.

b. If 'No', provide your rationale. Include in your discussion what might constitute a signal of cardiovascular risk that would warrant conduct of a cardiovascular outcome trial or other form of cardiovascular risk assessment.


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EMDAC Advisory Committee Meeting
October 24, 2018

History of the 2008 Cardiovascular Guidance and Overview of the Guidance Recommendations

Lisa Yanoff, MD

Acting Deputy Director, Division of Metabolism and Endocrinology Products
Office of New Drugs, Center for Drug Evaluation and Research
US Food and Drug Administration

Outline

- History of the 2008 Cardiovascular (CV) Guidance
  - Reminder of current diabetes drug approval standard
  - Review of data raising concern about drug-specific CV harm
  - Discussion of the 2008 EMDAC meeting
- Overview of the Current Guidance Recommendations

Type 2 Diabetes Mellitus

- 30 million people in the United States with diabetes
  - 95% type 2 diabetes
- 2-4 fold higher risk of cardiovascular death
- Most deaths due to cardiovascular disease/stroke
- Other important long-term complications
  - Peripheral vascular disease
  - Microvascular (retinopathy, nephropathy, and neuropathy)

https://www.cdc.gov/diabetes/data/statistics/statistics-report.html
N Engl J Med. 1998; 339:229-34; JAMA. 2002; 287:2570-81; Lanct. 2005; 365:1333-46

Available Therapies: Type 2 Diabetes

- **Alpha-glucosidase inhibitors:** Acarbose, Miglitol
- **Amylin analog:** Pramlintide
- **Biguanide:** Metformin
- **Bile acid sequestrant**: Colesevelam
- **Dopamine agonist**: Bromocriptine
- **Dipeptidyl peptidase-4 inhibitors**: Sitagliptin, Saxagliptin**,** Linagliptin, Alogliptin
- **Glinides**: Repaglinide, Nateglinide
- **Glucagon-like peptide-1 receptor agonists**: Exenatide, Exenatide LAR, Liraglutide, Albiglutide, Dulaglutide, Lixisenatide, Semaglutide
- **Insulin**
- **Sodium-glucose cotransporter-2 inhibitors**: Canagliflozin, Dapagliflozin, Empagliflozin, Ertugliflozin
- **Sulfonylureas:** Glimepiride, Glyburide, Glipizide
- **Thiazolidinediones:** Pioglitazone, Rosiglitazone

Establishing Benefit of a Drug

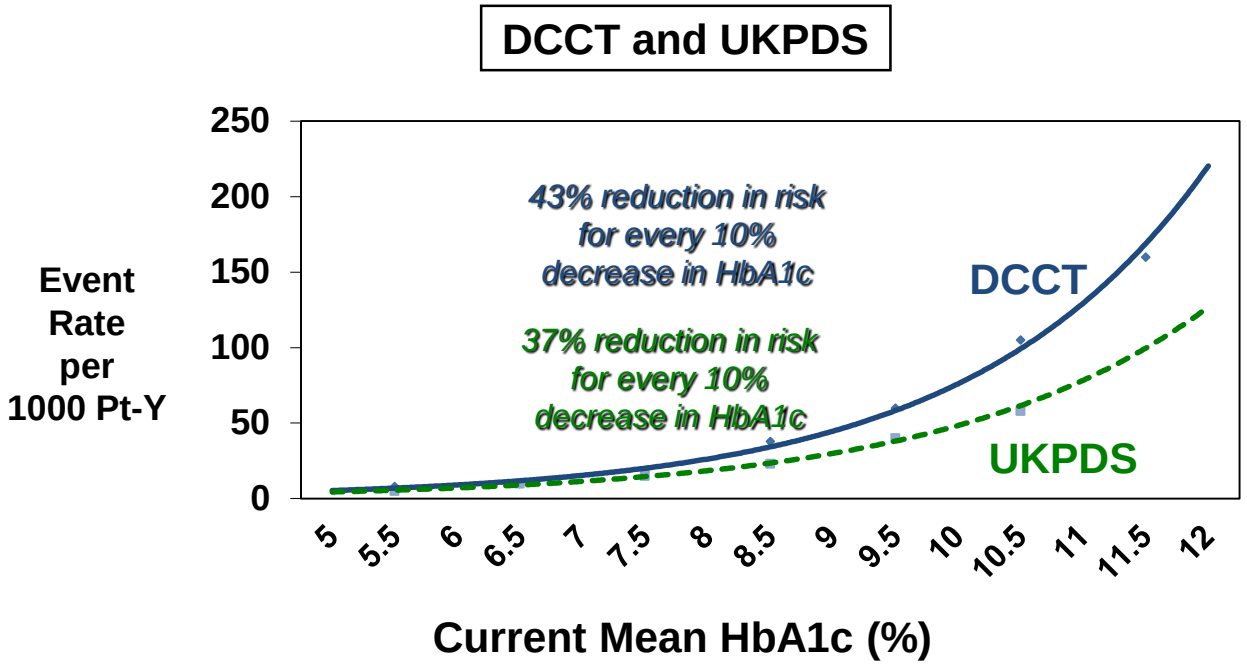
- Approval for anti-diabetic agents was/is based on glycemic lowering
  - Indication: as an adjunct to diet and exercise to improve glycemic control in…
- Efficacy for glycemic control established by demonstrating that the new drug is more effective than placebo at lowering hemoglobin a1c (HbA1c)
- New drug is also usually assessed in various treatment scenarios

Establishing Benefit of a Drug

- HbA1c (hemoglobin a1c / glycated hemoglobin)
  - Irreversible attachment of glucose to hemoglobin
  - Directly proportional to the ambient glucose concentration
  - Correlates with average blood glucose over the preceding 2 or 3 months.
  - Standardized assay
- HbA1c reduction is surrogate for benefit on microvascular disease
  - Clinical trials have established that glycemic lowering results in a reduction in the onset and progression of microvascular complications (DCCT, UKPDS)

DCCT: Diabetes Control and Complications Trial; UKPDS: United Kingdom Prospective Diabetes Study

Relationship between Glycemia and Complications



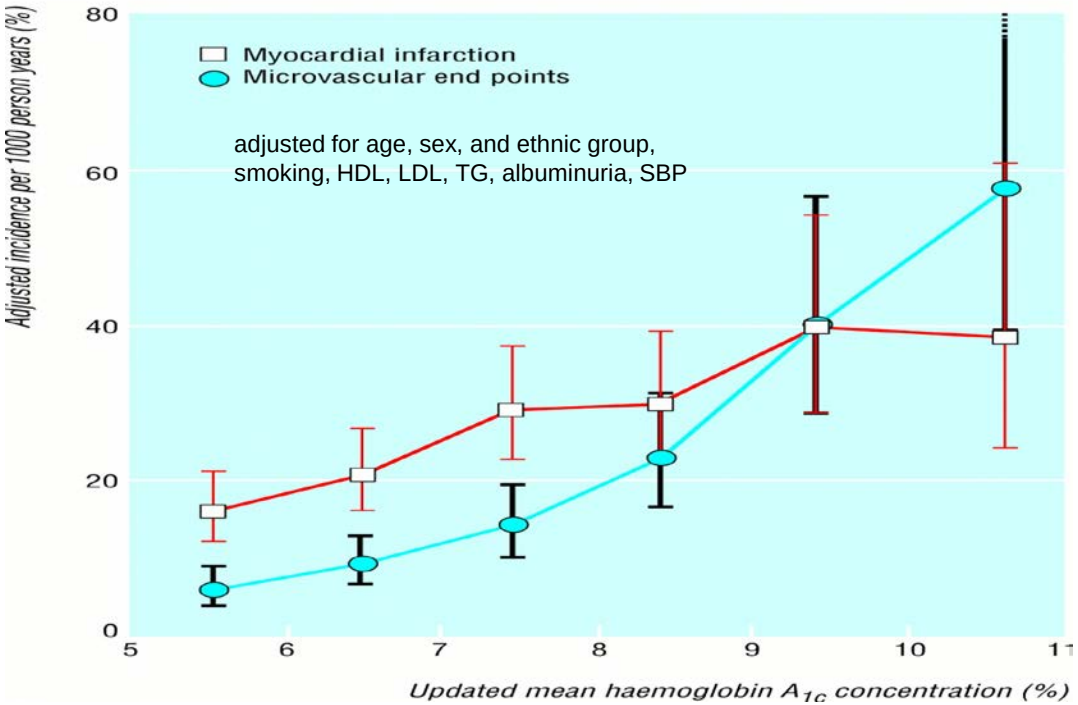
Establishing Benefit of a Drug

- Symptomatic benefit from glycemic lowering
- Diabetes product labels do not explicitly state that they are indicated for a reduction in microvascular disease
  - Microvascular benefit, is not overtly claimed in labeling, based on the surrogate endpoint

Macrovascular benefit? Or risk?

- A1c is not considered to be a useful surrogate for macrovascular/cardiovascular disease (CVD) reduction for diabetes drug approval.
  - Interactions with traditional risk factors such as age, body weight, renal function, hyperlipidemia, or inflammatory status
  - CVD risk appears to begin even with glucose in prediabetes range with a more gradual increase in risk as higher glycemia is reached (as compared to microvascular disease)
- Some evidence had been emerging that certain anti-diabetes therapies may increase the risk of CVD.

UKPDS – Association of HbA1c and Complications



Stratton IM et al. *BMJ*. 2000; 321:405-412.

Macrovascular benefit? Or risk?

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CV Safety of Diabetes Drugs

- 1970 - tolbutamide – increased risk of cardiovascular mortality
  - University Group Diabetes Program (UGDP) reported that patients treated with diet plus tolbutamide had a rate of cardiovascular mortality approximately 2 1/2 times that of patients treated with diet alone.
- Code of Federal Regulations (CFR) 310.517:- Labeling for oral hypoglycemic drugs of the sulfonylurea class
  - ”Special Warning on Increased Risk of Cardiovascular Mortality”

Diabetes. 1970; 19 (Supp 2): 747-830 *Lancet*. 1998; 352:837-53 and 854-65

CV Safety of Diabetes Drugs

- 1998 – UK Prospective Diabetes Study (UKPDS)
- Substudy: 537 patients randomized to metformin add-on to sulfonylurea (SU) therapy (vs. continuing SU alone) at fasting glucose >110 mg/dL
- Median HbA1c over 4 years: 7.7% in the cohort with +metformin; 8.2% in those on SU alone.
- **Increase in diabetes-related death with metformin add-on to sulfonylurea**

Lancet, 1998, 854-865

CV Safety of Diabetes Drugs

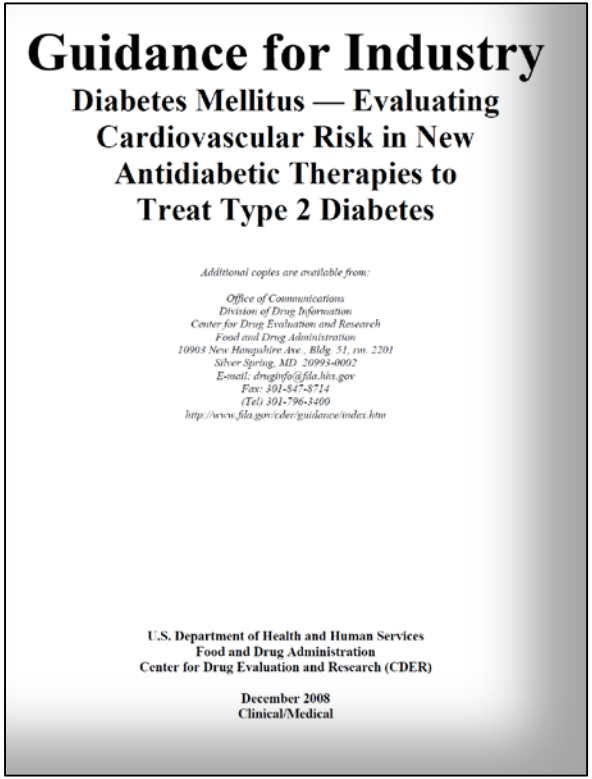
- 2005/2006 - the dual PPAR muraglitazar showed unexpected evidence of increased cardiovascular mortality; not FDA approved
- 2007-A meta-analysis of rosiglitazone trials suggested that increased the risk of myocardial infarction by 43% and cardiovascular mortality by 64% compared to placebo and other anti-diabetic agents
- 2008 – ACCORD intensive therapy – death rate increased
- **Concern about determining *overall* clinical benefit of diabetes drugs based on glycemic control / HbA1c**

PPAR: peroxisome proliferator-activated receptor
ACCORD: Action to Control Cardiovascular Risk in Diabetes

July 2008 Advisory Committee

- On July 1 and 2, 2008, the Endocrinologic and Metabolic Drugs Advisory Committee met to discuss the role of cardiovascular assessment in the premarketing and postmarketing settings.

- After considering the discussion at this meeting as well as other available data and information, we have determined that concerns about cardiovascular risk should be more thoroughly addressed during drug development.



Voting Question to the 2008 Panel

It should be assumed that an anti-diabetic therapy with a concerning CV safety signal during Phase 2/3 development will be required to conduct a long-term cardiovascular trial. For those drugs or biologics without such a signal, should there be a requirement to conduct a long-term cardiovascular trial? (vote yes/no requested)

- **If "yes", please discuss when such a study should be conducted:**
  - **Pre-approval**
  - **Post-approval. If a long-term CV trial is required post-approval, please discuss whether this study should be ongoing at the time of approval (i.e., trial already initiated at time of approval).**

July 2008 Advisory Committee Opinion

- Majority of the committee recommended more extensive, standardized, assessment of cardiovascular risk in the pre and post marketing phase
- Goal to rule out risk but not to necessarily demonstrate CV benefit

HbA1c as a Surrogate Endpoint

- The use of HbA1c as a surrogate endpoint for drug approval was upheld
- Reduction in HbA1c supports a reduction in the risk of onset and progression of microvascular disease.
  - a surrogate can be validated for one but not all clinical endpoints of interest, in this case validated for microvascular but not macrovascular disease
- In 2018, FDA's view of the value of approving diabetes drugs based on glycemic control remains largely unchanged.

Guidance CV Risk 'Goalposts'

- To establish safety of a new antidiabetic drug to treat type 2 diabetes, sponsors should demonstrate that the therapy will not result in an unacceptable increase in cardiovascular risk (MACE)
  - Pre-marketing, exclude hazard ratio greater than 1.8
  - Post-marketing, exclude hazard ratio greater than 1.3
- Diabetes development programs pre-guidance did not have a sufficient number of CV events to assess risk
  - To exclude a 1.3 margin you need 611 events, 2.0 margin: 88 events

MACE: major adverse cardiovascular events

Event-Driven Trials

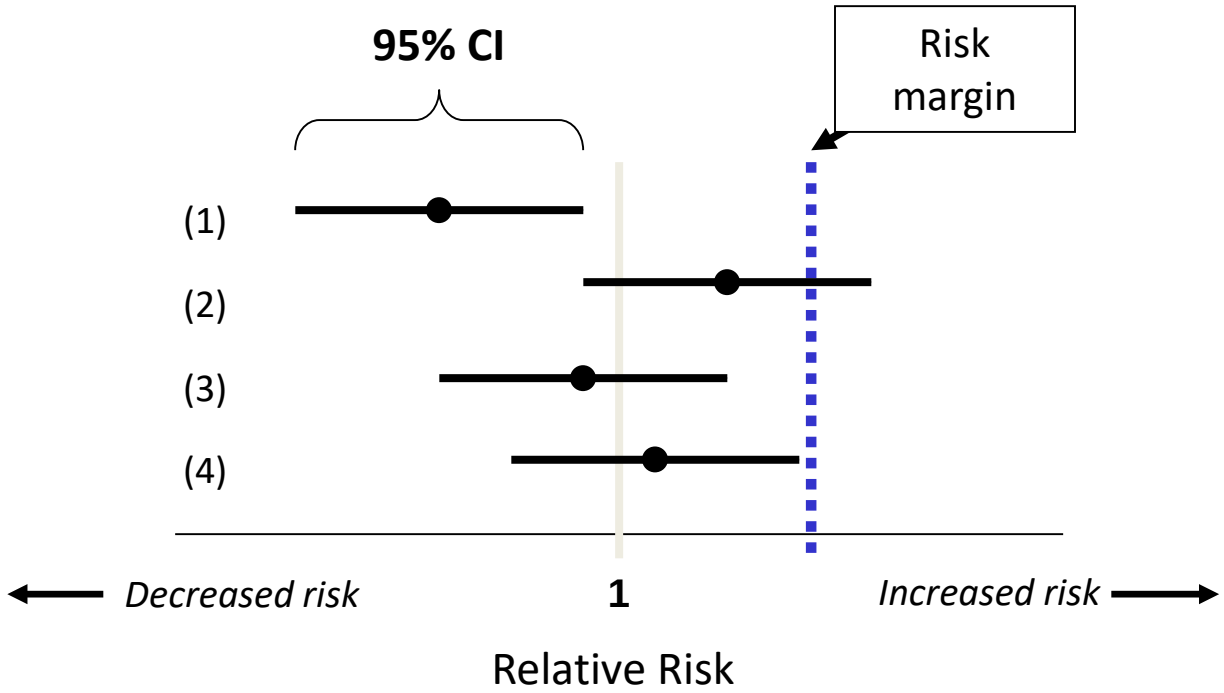
- Event-driven trials are information-based designs
  - The statistical information is fixed in advance rather than using the number of subjects to determine the trial size
  - Statistical information = number of events
  - The trial continues until the prespecified number of events are observed
- To observe the needed events to preserve statistical power you need to observe a certain number of patient years
  - The expected number of patient years can be anticipated by considering the likely rate of events being assessed, but actual value will depend on the observed event rate

How ‘Big’ do Trials Need to Be?

Number of Events for 90% Power	Upper 95% CI Excluded	Maximum Point Estimate of HR	Patient-Years Needed (3% annual event rate)
88	2.0	1.32	2,933
122	1.8	1.26	4,067
256	1.5	1.17	8,533
611	1.3	1.11	20,367
4,627	1.1	1.04	154,233

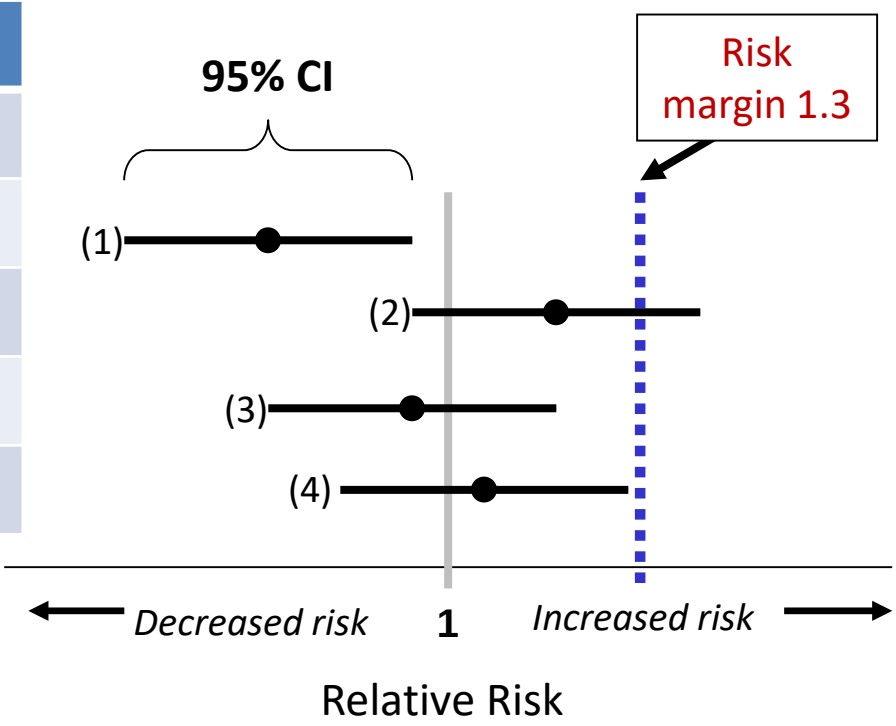
CI: Confidence Interval; HR: Hazard Ratio

Illustration of Non-Excessive Risk



Excluding Risk Margin of 1.3

# of MACE Events		HR (95% CI)
Drug	Comparator	
(1) 265	346	0.77 (0.66, 0.89)
(2) 326	285	1.14 (0.98, 1.33)
(3) 296	315	0.94 (0.81, 1.09)
(4) 316	295	1.07 (0.92, 1.25)



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Trial Integrity, Reliability, Validity

- Establish an independent cardiovascular endpoints committee
- Include patients at higher risk of cardiovascular disease (older, co-morbidities, etc.)
- Provide longer-term data (e.g., ≥ 2 years)
  - Diabetes is a chronic disease
  - Could be an increased risk in the short term but overall favorable benefit risk over the long term
  - Very large, but short trials would not identify drug related risk

Overall Goal of Guidance

- Guidance aims to provide for…
  - Continuing reliance on the HbA1c surrogate for initial approval
  - Improved assessment of cardiovascular risk both pre- and post-marketing, to provide patients with an informed choice of therapy with regard to overall benefit risk

Thank You for Your Attention


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Review of Cardiovascular Assessments Prior to the 2008 Guidance

Endocrinologic and Metabolic Drugs Advisory Committee Meeting
October 24, 2018

Patrick Archdeacon, MD
Acting Clinical Team Lead
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration

Overview

- Demographics & disease characteristics
- Exposure (how many patients and for how long)
- Cardiovascular (CV) data collection and event ascertainment

Demographics & Disease Characteristics

Patient Demographics-Exenatide (Combined Phase 3 trials)

Baseline Demographic or Characteristic	Means of 3 pivotal trials
Age, years	54.7
Duration of diabetes, years	7.5
HbA1c(%)	8.4

Baseline Demographic or Characteristic	
Established CV disease	Excluded*
Clinically significant renal disease	Excluded

* Patients with AMI, unstable angina, angioplasty, coronary bypass within12 months excluded

Adapted from Primary Clinical Review of NDA 21-773

NDA = New Drug Application

HbA1c = hemoglobin A1c

Patient Demographics-Sitagliptin
(Combined Pivotal Phase 3 trials)

Baseline Demographic or Characteristic	Mean of 4 pivotal trials
Age, years	54.8
Duration of diabetes, years	5.3
HbA1c(%)	8.0

Baseline Demographic or Characteristic	
Established CV disease	Excluded*
eGFR ≤50 mL/min/1.73 m^2	Excluded**

*Patients with acute coronary syndrome/intervention within six months were excluded
** The overall development program included a 91 patient study of patients with chronic kidney disease
Adapted from Primary Clinical Review of NDA 21-995

eGFR = estimated glomerular filtration rate

Patient Demographics-Saxagliptin (Combined Pivotal Phase 2/3 trials)

Baseline Demographic or Characteristic	Means of 8 pivotal trials
Age, years	54.5
Duration of diabetes, years	5.2
HbA1c(%)	8.2

Baseline Demographic or Characteristic	
History of Coronary Artery Disease – Range of pivotal trials	3%-13%
eGFR ≤50 mL/min/1.73 m^2	Excluded

Adapted from the Primary Clinical Review from NDA 22-350

Comparison of Program Demographics/Characteristics

Baseline Demographic or Characteristic of Pivotal Trials	Exenatide	Sitagliptin	Saxagliptin
Age, years	54.7	54.8	54.5
Duration of diabetes, years	7.5	5.3	5.2
HbA1c(%)	8.4	8.0	8.2

Adapted from Primary Clinical Reviews of NDAs 21-773, 21-995, and 22-350

Exposure

Exposures in Original NDAs

	Total Exposed	Exposed Populations from Controlled Core Phase 2±3 Trials				
		Randomized	> 6 weeks	> 22 weeks	>24 weeks	≥ 52 weeks
Exenatide	1857	963	913	807	800	0*
Sitagliptin	3276	1538	1477	966		444
Saxagliptin	4042	3422			2462	1080

Adapted from Clinical Study Reports for Studies 112, 113, and 115 of NDA 21-773 and Primary Clinical Reviews of NDAs 21-773, 21-995 and 22-350

* 334 patients randomized to exenatide continued in long term extensions of the core clinical trials beyond 50 weeks, but no patients randomized to placebo were continued beyond 28 weeks

CV Data Collection and Event Ascertainment

Implementation of CV Data Curation Recommendations

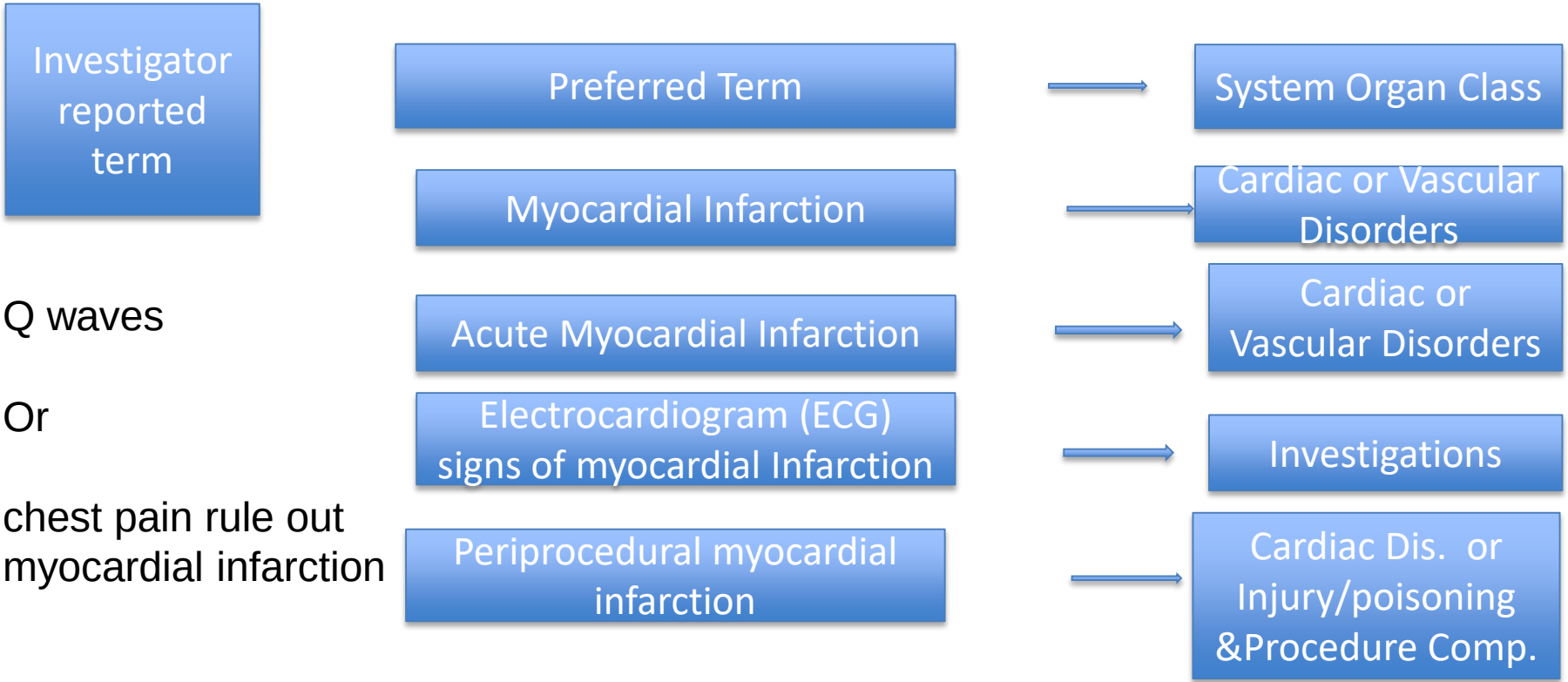
While the guidance is not proscriptive about how the recommendations must be implemented, cardiovascular outcome trials (CVOTs) conducted to date have adopted similar practices for identifying and gathering data and adjudicating cases

- CV Event Adjudication Committee (CVEAC) charters
- Event detection triggers
- Dedicated CV case report forms (CRFs)
- Event package data presentation
- Event adjudication

CV Event Ascertainment Pre-2008

- Investigator reported (severity of the event based on investigator's judgement)
- Not necessarily systematically collected or adjudicated
- Reporting and data collection variable across sites, regions

Pre-2008 CV Event Capture



CV Assessment – Exenatide

System Organ Class	Clinical Pharmacology Studies		Clinical Studies					Other Studies	
			Controlled				Uncon-trolled		
Cardiac Disorder			Short term		Long Term				
	E n=328	P n=200	E n=204	P n=61	E n=963	P n=483	E n=660	E n=109	P n=61
Serious	0 (0)	0 (0)	0 (0)	0 (0)	8 (1%)	9 (2%)	10 (2%)	0 (0)	0 (0)
Non-serious	11 (3%)	0 (0)	2 (1)	0 (0)	26 (3%)	25 (5%)	19 (3%)	2 (0)	0 (0)

Source: Primary Clinical review of NDA 21-773

E = exenatide
P = placebo

CV Assessment – Sitagliptin
(Pooled Phase 3 safety population)

System Organ Class	Sitagliptin n=1564	Comparator n=778
Cardiac disorders		
Serious	9 (0.6%)	3 (0.4%)
Non-serious	29 (1.9%)	18 (2.3%)

Source: Primary Clinical review of NDA 21-995

CV Event Ascertainment Saxagliptin

- Review of saxagliptin NDA included an effort to assess the available data in the context of the CVOT guidance recommendations
  - Broad MACE SMQ
  - Custom MACE SMQ
- This approach also applied to the two other products (liraglutide and alogliptin) under review at time of publication of the CVOT guidance

SMQ = Standardized Medical Dictionary of Regulatory Activity Query
MACE = Major Adverse Cardiovascular Event

Broad and Custom MACE SMQs

	Broad SMQ	Custom Query
Myocardial Infarction Terms		
Acute coronary syndrome	X	
Acute myocardial infarction	X	X
Agonal rhythm		
Blood creatine phosphokinase abnormal	X	
Blood creatine phosphokinase increased	X	
Blood creatine phosphokinase MB abnormal	X	
Blood creatine phosphokinase MB increased	X	
Cardiac arrest		
Cardiac death		
Cardiac enzymes increased	X	
Cardio-respiratory arrest		
Coronary artery embolism	X	
Coronary artery occlusion	X	
Coronary artery reocclusion	X	
Coronary artery thrombosis	X	X
Coronary bypass thrombosis	X	
Electrocardiogram Q wave abnormal	X	
Electrocardiogram ST segment abnormal	X	
Electrocardiogram ST segment elevation	X	
Electrocardiogram ST-T segment elevation	X	

.....

	Broad SMQ	Custom Query
Troponin T increased	X	
Vascular graft occlusion	X	
Ventricular asystole		
Stroke Terms		
Agnosia	X	
Amaurosis fugax	X	
Angiogram cerebral abnormal	X	
Aphasia	X	
Balint's syndrome	X	
Basal ganglia hemorrhage	X	
Basilar artery occlusion	X	
Basilar artery stenosis	X	
Basilar artery thrombosis	X	X
Brain stem hemorrhage	X	
Brain stem infarction	X	X
Brain stem ischemia	X	
Brain stem stroke	X	X
Brain stem thrombosis	X	X
Capsular warning syndrome	X	
Carotid aneurysm rupture	X	

CV Assessment - Saxagliptin

	Saxagliptin N=3356	Comparator N=1251	Odds Ratio* (95% CI)
Broad MACE			
Short-term period	58 (1.8%)	25 (2.0%)	0.90 (0.6, 1.5)
Combined short-term and long-term period	100 (3.1%)	41 (3.2%)	0.96 (0.7, 1.4)
Custom MACE			
Short-term period	4 (0.1%)	7 (0.6%)	0.21(0.04, 0.8)
Combined short-term and long-term period	23 (0.7%)	17 (1.3%)	0.52 (0.3, 1.0)

* Common odds ratio stratified on study

Source: Cross Discipline Team Lead Review NDA 22-350

CI = confidence interval

Conclusions on Diabetes Programs Pre-2008

- Studies primarily designed to demonstrate effect on HbA1c
- Patients were younger with limited comorbidities
- Typically, duration of diabetes was under 10 years.
- Limited long-term (> 1 year) exposure data
- Limited control arm data
- Lack of systematic, prospective collection of CV event data severely limits CV event ascertainment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Review of Design and Results of Cardiovascular Outcome Trials

Endocrinologic and Metabolic Drugs Advisory Committee Meeting
October 24, 2018

Tania Condarco, MD
Clinical Team Lead (Acting)
Mahtab Niyyati, MD
Clinical Reviewer
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research

Overview

- Overview of pre- and post-marketing cardiovascular assessment conducted post-guidance
- Discuss trial design and results of CVOTs conducted to fulfill the 2008 CV guidance
- Compare trial characteristics pre- and post-guidance

CVOT: Cardiovascular outcome trial; CV: cardiovascular

Overview

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Pre-market CV Safety Assessment

	Phase 2/3 Meta-analysis
	Dapagliflozin
Randomized patients	9,339
Number of events accrued	178^
Hazard ratio	0.81
CI*	0.59, 1.09

*95% confidence interval (CI), ^MACE+, Source: Canagliflozin, Division Director review, Mary Parks, March 29, 2013; Dapagliflozin, Statistical review, Eugenio Andraca-Carrera, February 2011

Pre-market CV Safety Assessment

	Phase 2/3 Meta-analysis	Phase 2/3 + interim CVOT analysis
	Dapagliflozin	**Canagliflozin**
Randomized patients	9,339	**9,723**
Number of events accrued	178^	**201^**
Hazard Ratio	0.81	**0.91**
CI*	0.59, 1.09	**0.68, 1.22**

161 events (interim analysis)

40 events (Phase 2/3)

*95% confidence interval (CI),^MACE+, Source: Canagliflozin, Division Director review, Mary Parks, March 29, 2013; Dapagliflozin, Statistical review, Eugenio Andraca-Carrera, February 2011

Pre-market CV Safety Assessment

	Phase 2/3 Meta-analysis	Phase 2/3 + interim CVOT analysis	Interim analysis CVOT
	Dapagliflozin	Canagliflozin	Alogliptin
Randomized patients	9,339	9,723	**2,134**
No. of events accrued	178^	201^	**83~**
HR	0.81	0.91	**0.81**
CI*	0.59, 1.09	0.68, 1.22	**0.44, 1.5**

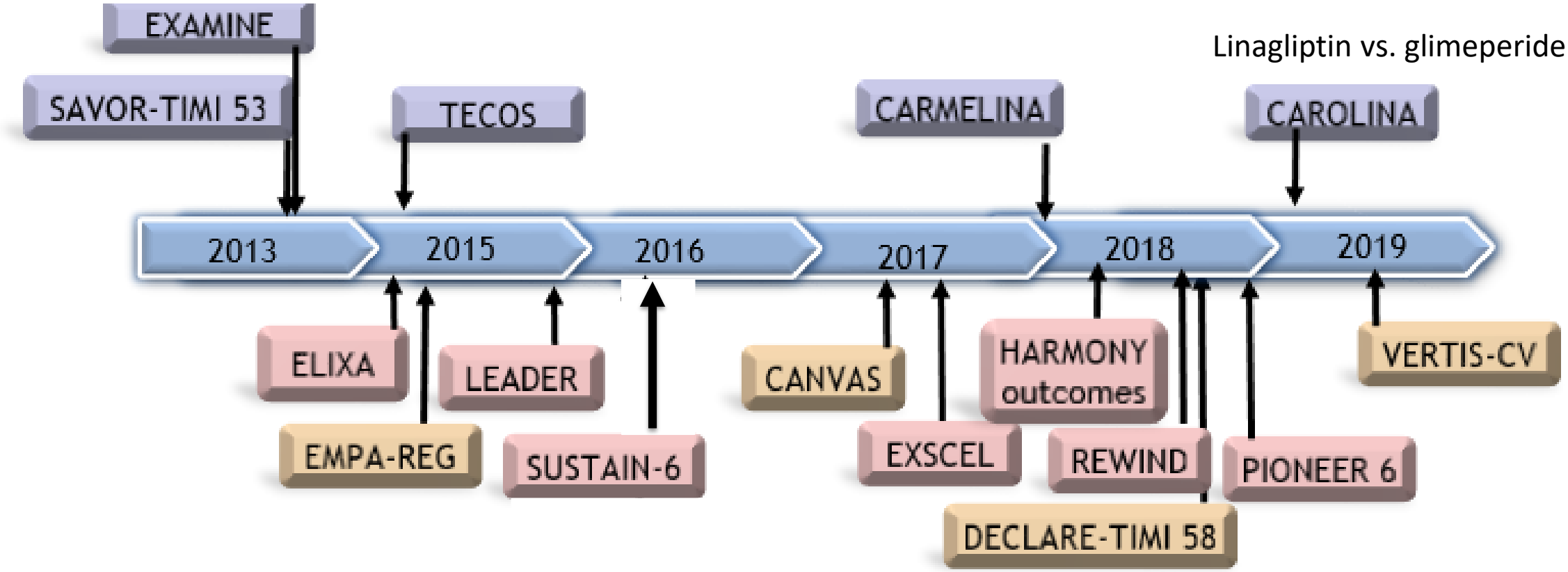
*95% confidence interval (CI), ^MACE+, ~MACE. No=number, HR: hazard ratio. Source: Canagliflozin, Division Director review, Mary Parks, March 29, 2013; Dapagliflozin, Statistical review, Eugenio Andraca-Carrera, February 2011

Pre-market CV Safety Assessment

	Phase 2/3 Meta-analysis	Phase 2/3 + interim CVOT analysis	Interim analysis CVOT	Smaller-CVOT
	Dapagliflozin	Canagliflozin	Alogliptin	Semaglutide
Randomized patients	9,339	9,723	2,134	**3,297**
No. of events accrued	178^	201^	83~	**254~**
HR	0.81	0.91	0.81	**0.74**
CI*	0.59, 1.09	0.68, 1.22	0.44, 1.5**	**0.58-0.95**

*95% confidence interval (CI),**99.5% CI, ^MACE+, ~MACE. No. Number, HR: hazard ratio Source: Canagliflozin, Division Director review, Mary Parks, March 29, 2013; Dapagliflozin, Statistical review, Eugenio Andraca-Carrera, February 2011

Trials Addressing 2008 Guidance



DPP4-inhibitors

SGLT2 inhibitors

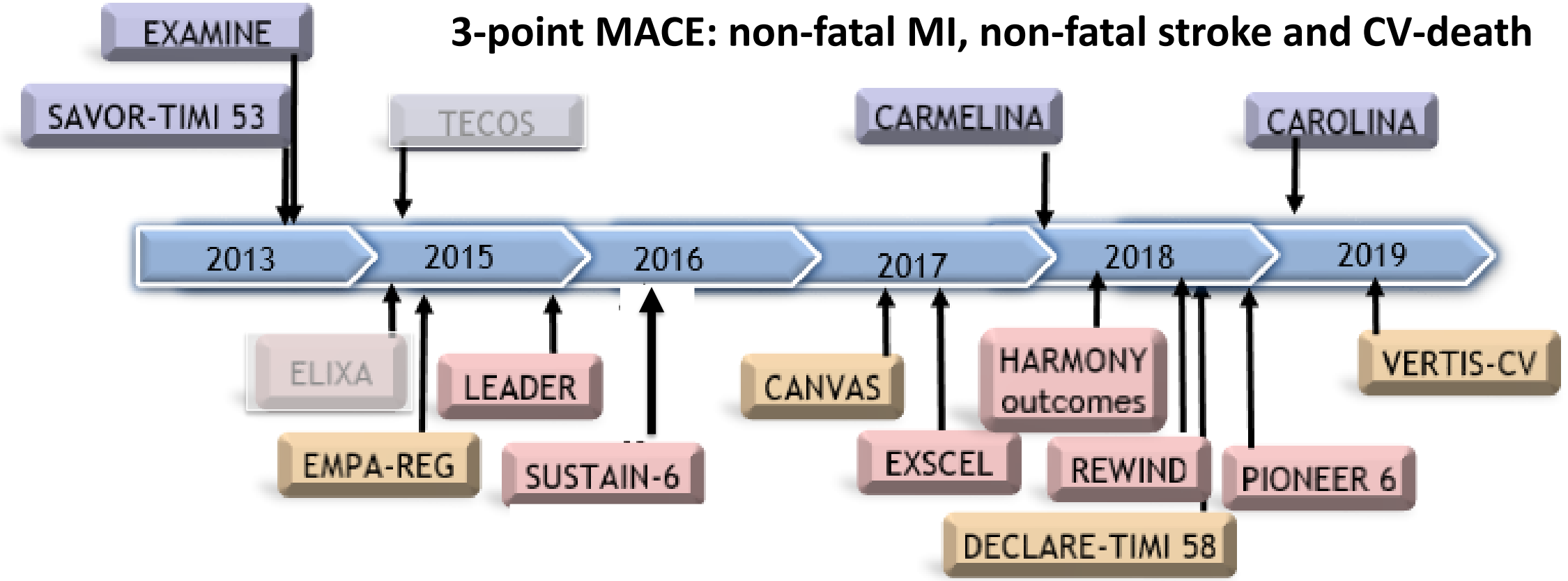
GLP-1 receptor agonists

Drug + **standard of care** vs. placebo + **standard of care**

Drug + **standard of care** vs. active comparator + **standard of care**

Completion/expected completion dates as per clinicaltrials.gov, DPP4: Dipeptidyl peptidase-4; SGLT2: sodium glucose cotransporter 2
GLP-1: glucagon-like peptide-1

Trials Addressing 2008 Guidance



DPP4-inhibitors

SGLT2 inhibitors

GLP-1 receptor agonists

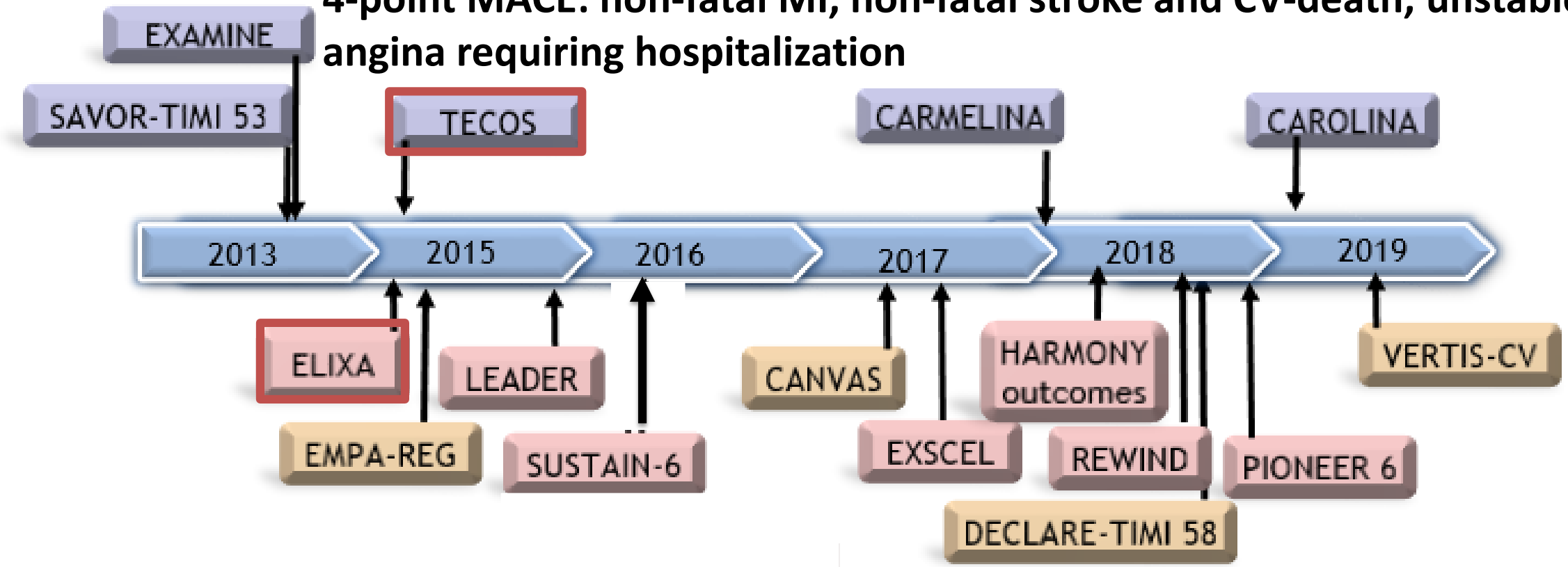
Drug + **standard of care** vs. placebo + **standard of care**

Drug + **standard of care** vs. active comparator + **standard of care**

Completion/expected completion dates as per clinicaltrials.gov, DPP4: Dipeptidyl peptidase-4; SGLT2: sodium glucose cotransporter 2
GLP-1: glucagon-like peptide-1

Trials Addressing 2008 Guidance

4-point MACE: non-fatal MI, non-fatal stroke and CV-death, unstable angina requiring hospitalization



DPP4-inhibitors

SGLT2 inhibitors

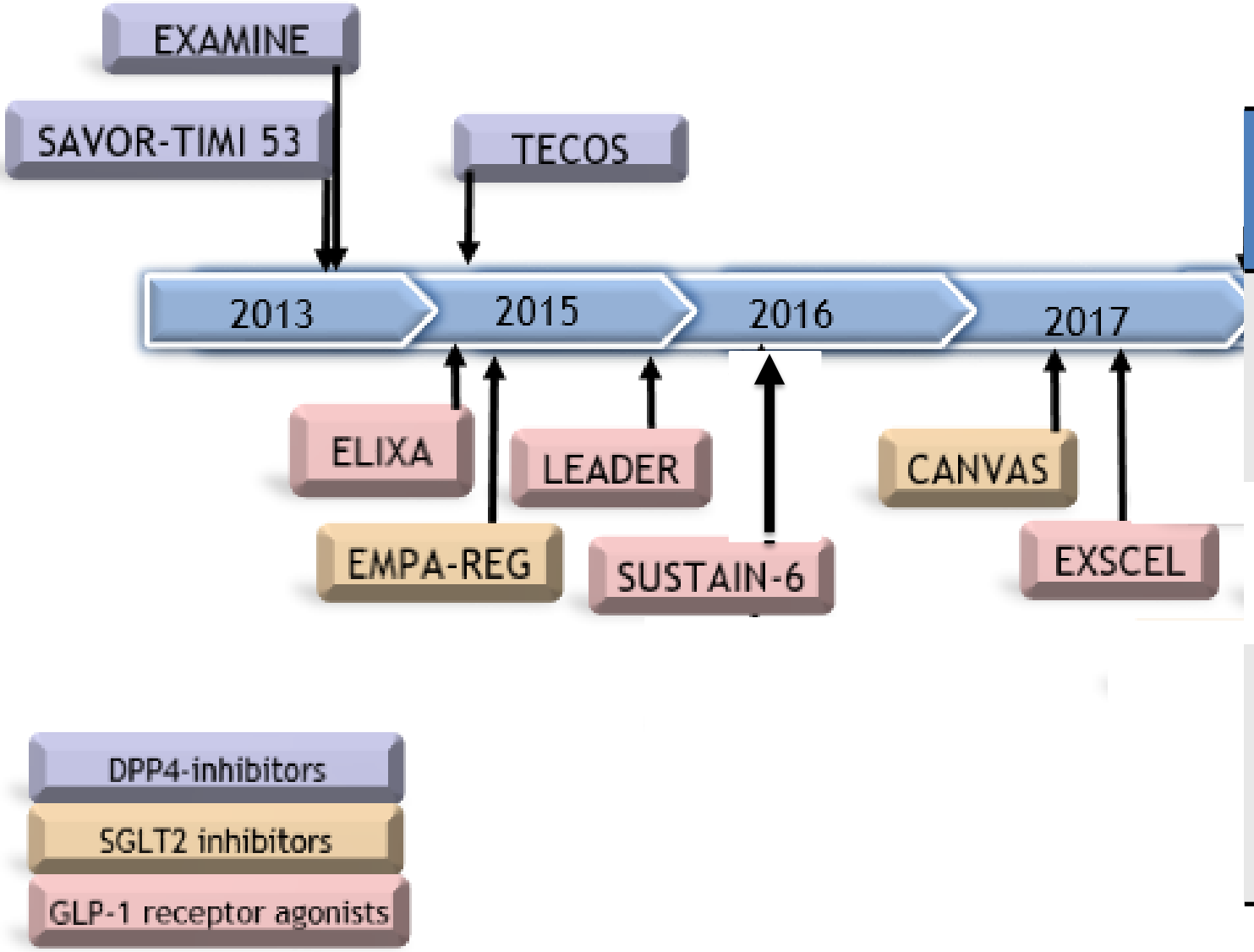
GLP-1 receptor agonists

Drug + **standard of care** vs. placebo + **standard of care**

Drug + **standard of care** vs. active comparator + **standard of care**

Completion/expected completion dates as per clinicaltrials.gov, DPP4: Dipeptidyl peptidase-4; SGLT2: sodium glucose cotransporter 2 GLP-1: glucagon-like peptide-1

Trials Addressing 2008 Guidance



	Average follow up (Years)
DPP4i	
TECOS	3.0
SAVOR	2.1
EXAMINE	1.5
SGLT2i	
EMPA-REG	3.1
CANVAS program*	3.6
GLP-1 RA	
ELIXA	2.1
LEADER	3.8
SUSTAIN-6	2.1
EXSCEL	3.2

Completion/expected completion dates as per clinicaltrials.gov, DPP4i: Dipeptidyl peptidase-4 inhibitor; SGLT2i: sodium glucose cotransporter 2 Inhibitor, GLP-1: glucagon-like peptide-1 , * CANVAS R and CANVAS are part of the CANVAS PROGRAM

Demographic Characteristics

	DPP-4i			GLP1 RA				SGLT2i	
	TECOS	SAVOR	EXAMINE	EXSCEL	LEADER	SUSTAIN 6	ELIXA	EMPA-REG	CANVAS Program
Randomized patients	14,735	16,492	5,380	14,572	9,340	3,297	6,068	7,020	10,142

CV: cardiovascular, HTN: hypertension; Dz: disease, CANVAS program: refers to both CANVAS and CANVAS-R

Indian J Endocrinol Metab 2017 Jan-Feb; 21(1): 4–10; N Engl J Med 2017; 377:644-657; N Engl J Med 2017 Sep 28;377(13):1228-1239; Expert Rev Clin Pharmacol. 2017 Apr;10(4):429-442; Diabetes Care 2018;41:14–3

Demographic Characteristics

	DPP-4i			GLP1 RA				SGLT2i	
	TECOS	SAVOR	EXAMINE	EXSCEL	LEADER	SUSTAIN 6	ELIXA	EMPA-REG	CANVAS Program
Randomized patients	14,735	16,492	5,380	14,572	9,340	3,297	6,068	7,020	10,142
Established CV Dz. (%)	100	78	100	70	81	83	100	99	66

CV: cardiovascular, HTN: hypertension; Dz: disease, CANVAS program: refers to both CANVAS and CANVAS-R

Indian J Endocrinol Metab 2017 Jan-Feb; 21(1): 4–10; N Engl J Med 2017; 377:644-657; N Engl J Med 2017 Sep 28;377(13):1228-1239; Expert Rev Clin Pharmacol. 2017 Apr;10(4):429-442; Diabetes Care 2018;41:14–3

Demographic Characteristics

	DPP-4i			GLP1 RA				SGLT2i	
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Randomized patients	14,735	16,492	5,380	14,572	9,340	3,297	6,068	7,020	10,142
Established CV Dz. (%)	100	78	100	70	81	83	100	99	66
Age (mean)	66	65	61	62	64	65	60	60	63
HbA1c (%)	7.2	8	8	8	8.7	8	7.7	8.1	8.2
Diabetes duration (mean yrs.)	12	10	7	12	13	14	9	> 10 (57%)	8

CV: cardiovascular, HTN: hypertension; Dz: disease, CANVAS program: refers to both CANVAS and CANVAS-R

Indian J Endocrinol Metab 2017 Jan-Feb; 21(1): 4–10; N Engl J Med 2017; 377:644-657; N Engl J Med 2017 Sep 28;377(13):1228-1239; Expert Rev Clin Pharmacol. 2017 Apr;10(4):429-442; Diabetes Care 2018;41:14–3

Demographic Characteristics

	DPP-4i			GLP1 RA				SGLT2i	
	TECOS	SAVOR	EXAMINE	EXSCEL	LEADER	SUSTAIN 6	ELIXA	EMPA-REG	CANVAS Program
Randomized patients	14,735	16,492	5,380	14,572	9,340	3,297	6,068	7,020	10,142
Established CV Dz. (%)	100	78	100	70	81	83	100	99	66
Age (mean)	66	65	61	62	64	65	60	63	63
HbA1c (%)	7.2	8	8	8	8.7	8.7	7.7	8	8.2
Diabetes duration (mean yrs.)	12	12	7	12	13	14	9	> 10 (57%)	14
BMI (kg/m^2)	30	31	29	32	33	33	30	31	32
HTN (%)	86	82	83	NA	90	93	76	94	90
Moderate/severe renal impairment (%)	10	16	27	21	25	29	22	26	18*

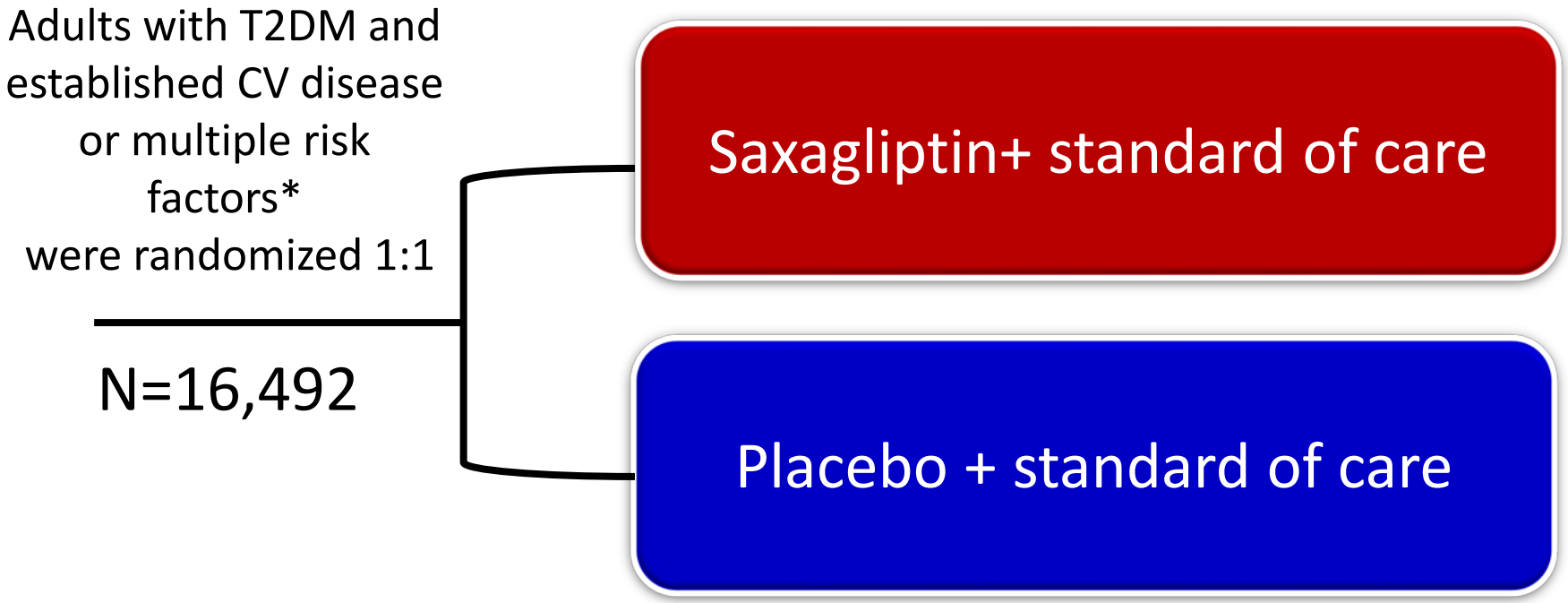
*Refers to nephropathy, CV: cardiovascular, HTN: hypertension; Dz: disease, CANVAS program: refers to both CANVAS and CANVAS-R, NA: not available; Indian J Endocrinol Metab 2017 Jan-Feb; 21(1): 4–10; N Engl J Med 2017; 377:644-657; N Engl J Med 2017 Sep 28;377(13):1228-1239; Expert Rev Clin Pharmacol. 2017 Apr;10(4):429-442; Diabetes Care 2018;41:14–3

Overview

- Overview of pre- and post-marketing cardiovascular assessment conducted post-guidance
- Discuss trial design and results of CVOTs conducted to fulfill the 2008 CV guidance
- Compare trial characteristics pre- and post-guidance

CVOT: Cardiovascular outcome trial; CV: cardiovascular

Trial Design – SAVOR



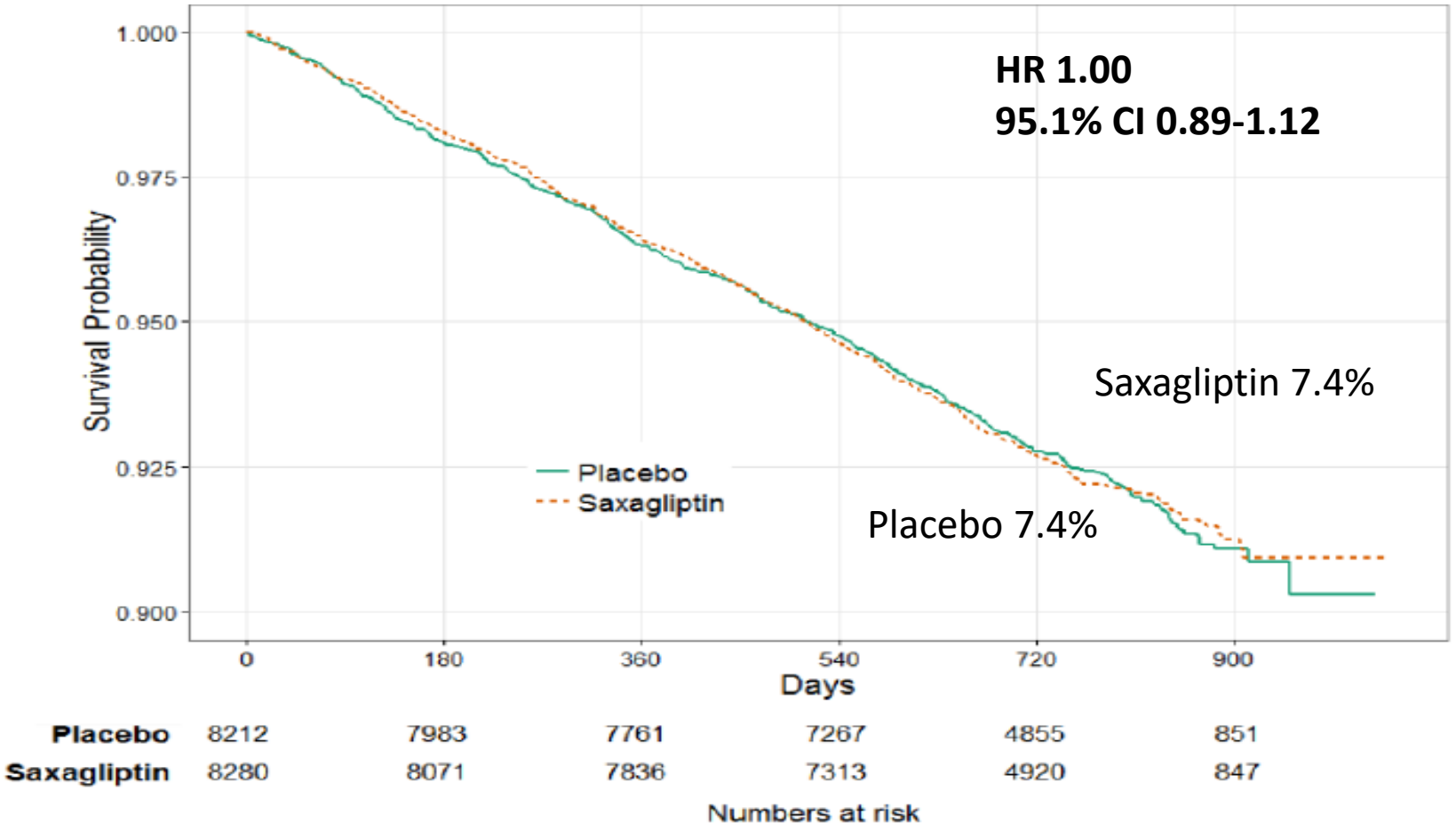
*Enrollment criteria included: patients ≥ 40 years old with established CV disease (CAD/PAD/CVD) OR multiple risk factors i.e., ≥ 60 y women/ ≥55 y men with at least one of the following: dyslipidemia, HTN, active smoking.

-For subjects receiving the 5 mg/day dose who developed renal impairment (i.e., eGFR ≤50 mL/min) during the trial, a single dose reduction to 2.5 mg daily was allowed.

Trial Results – SAVOR

N= 16,492

1,222 primary MACE events*



*MACE composite of cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke

Source: modified FDA briefing material for the saxagliptin Advisory Committee dated April 14, 2015

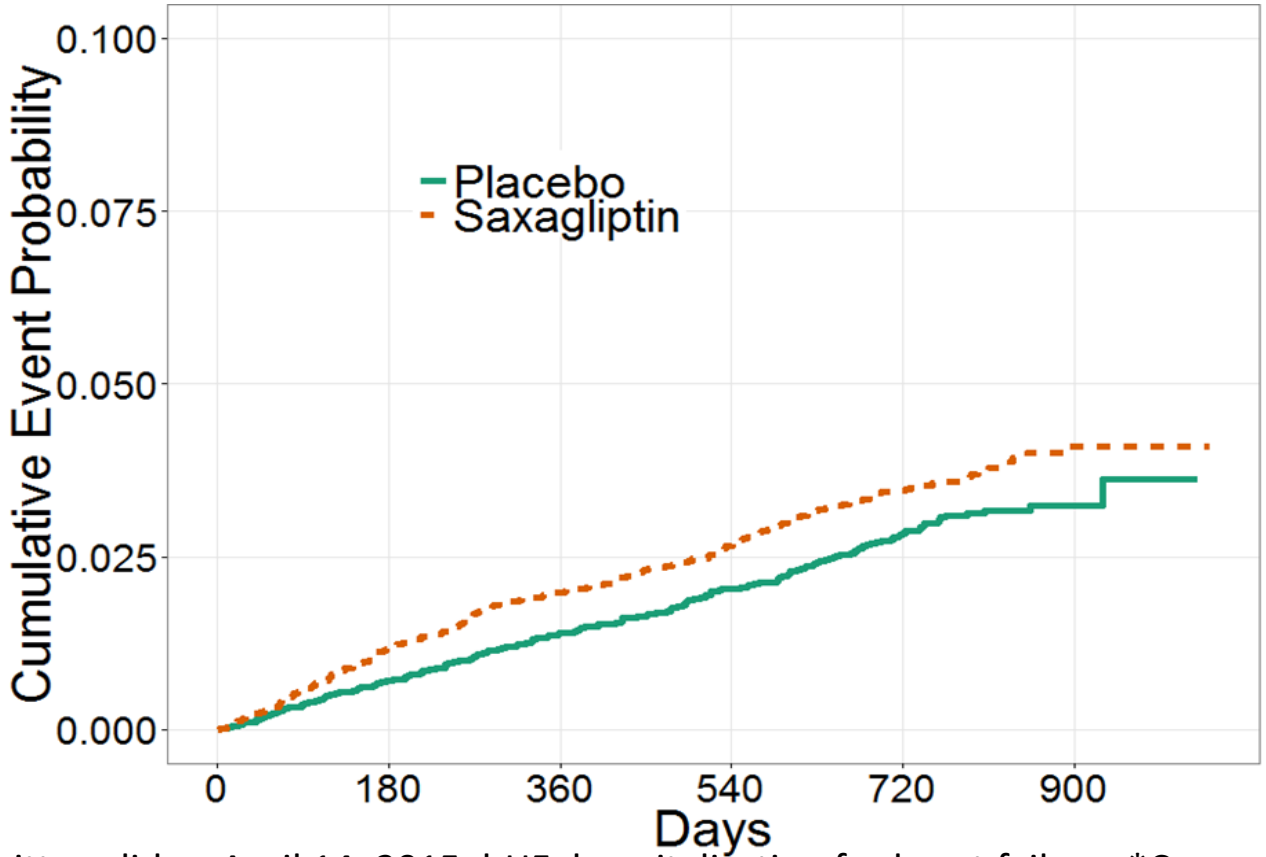
Components of MACE – SAVOR

	Saxagliptin N=8,280	Placebo N=8,212	Hazard Ratio (95.1%)
MACE composite N (%)	613 (7.4)	609 (7.4)	1.00 (0.89, 1.12)
CV death	245 (3.0)	234 (2.8)	
Non-fatal MI	233 (2.8)	260 (3.2)	
Non-fatal ischemic stroke	135 (1.6)	115 (1.4)	

CV: cardiovascular; MI: myocardial infarction
Source: modified from saxagliptin Prescribing Information

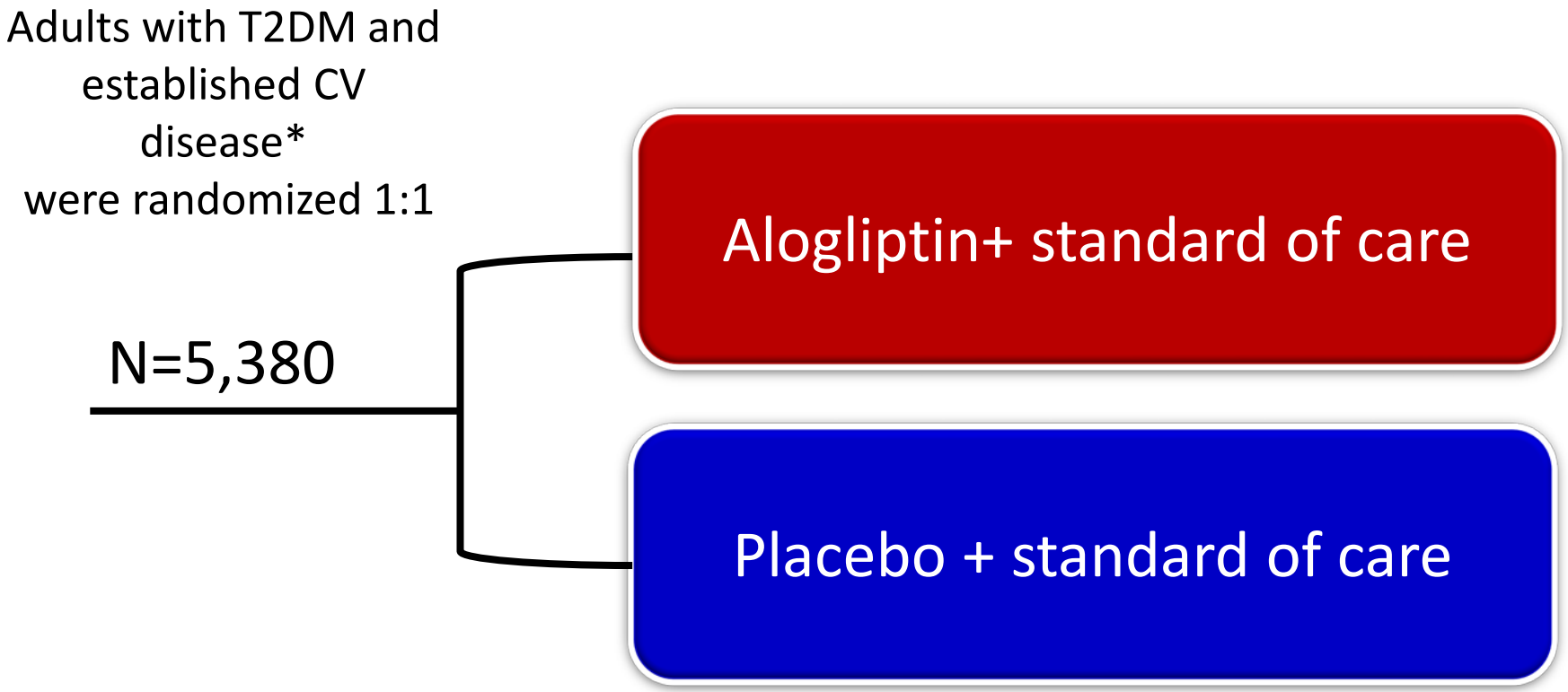
Safety Findings – SAVOR-Heart Failure

	Saxagliptin N=8,280	Placebo N=8,212	Hazard Ratio (95.1% CI)
hHF (%)	289 (3.5)	228 (2.8)	1.27 (1.07, 1.51)*



Source: SAVOR Advisory Committee slides, April 14, 2015, hHF: hospitalization for heart failure; *Cox proportional hazards model-based hazard ratio estimate

Trial Design – EXAMINE

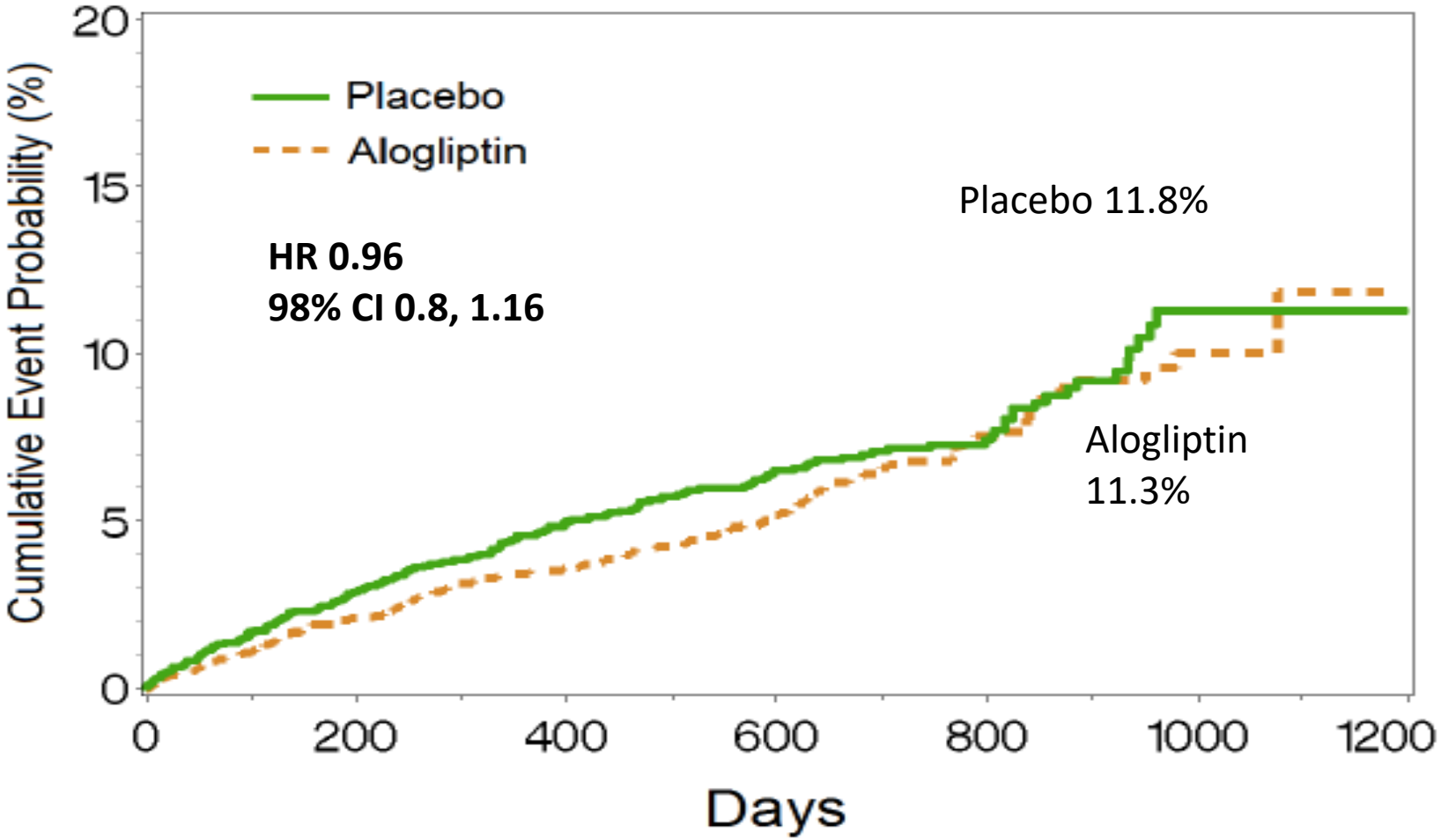


*Enrollment criteria included: patients with a history of acute coronary syndrm (myocardial infarctin or unstable angina requiring hospitalization) within 15 to 90 days before randomization.

-At randomization subjects were assigned to alogliptin 25 mg, 12.5 mg, or 6.25 mg depending on renal function. Following randomization, alogliptin dose adjustments were allowed based on changes in renal function.

Trial Results – EXAMINE

N= 5,380
621 primary MACE*



*MACE composite of cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke
Source: modified FDA alogliptin Advisory Committee statistical slides dated April 14, 2015

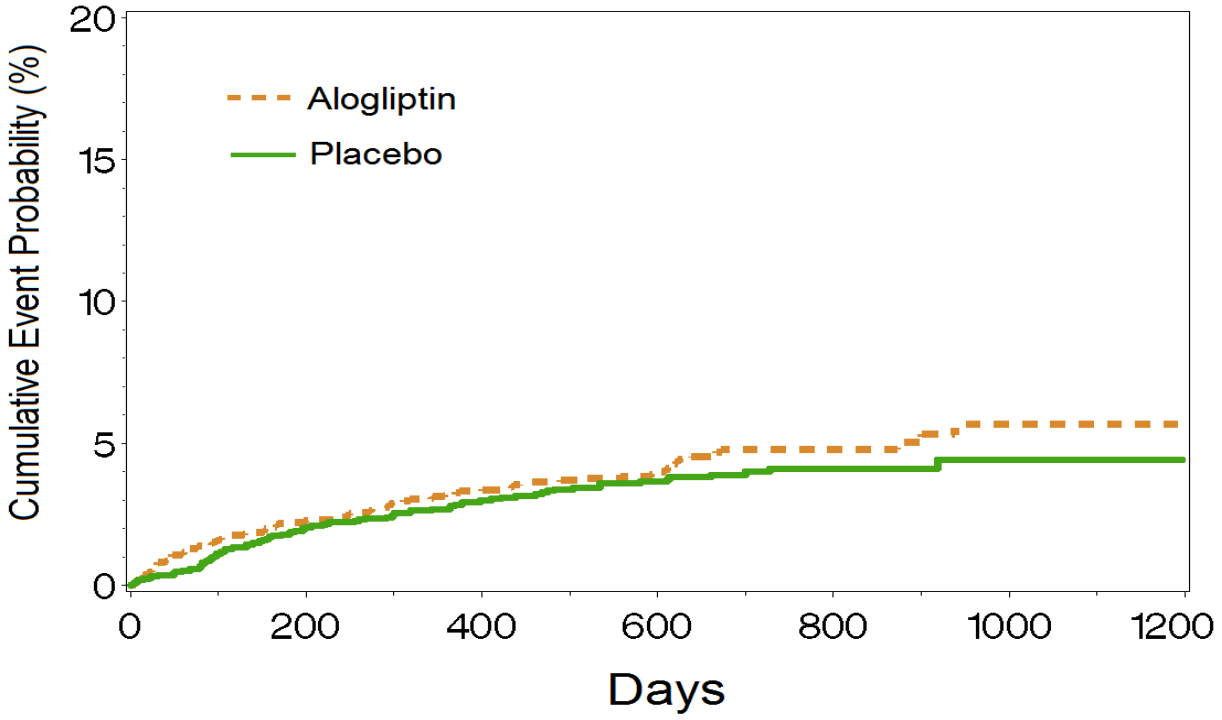
Components of MACE – EXAMINE

	Alogliptin N=2,701	Placebo N=2,679	Hazard Ratio (98%)
MACE composite N (%)	305 (11.3)	316 (11.8)	0.96 (0.80, 1.16)
CV death N (%)	89 (3.3)	111 (4.1)	
Non-fatal MI N (%)	187 (6.9)	173 (6.5)	
Non-fatal ischemic stroke N (%)	29 (1.1)	32 (1.2)	

CV: cardiovascular; MI: myocardial infarction
Source: modified from alogliptin Prescribing Information

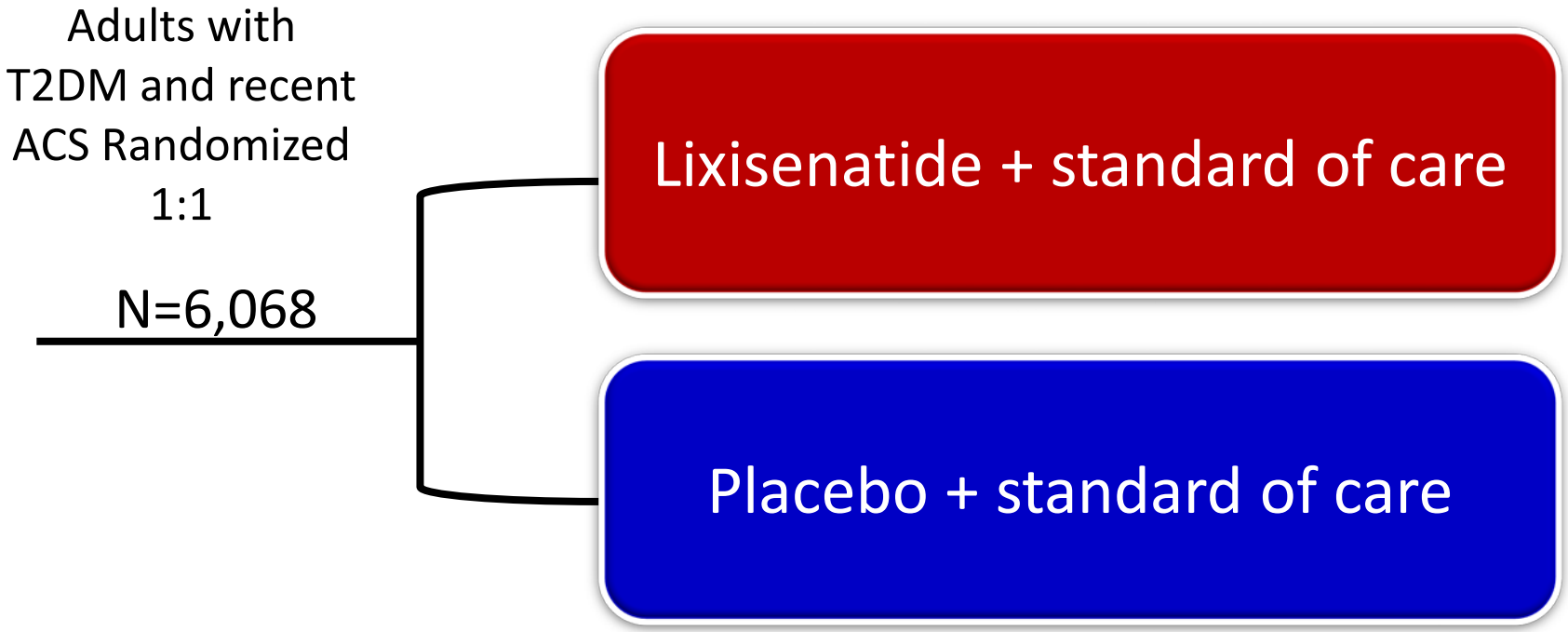
Safety Findings – EXAMINE-Heart Failure

	Alogliptin N=2,701	Placebo N=2,679	Hazard Ratio (95% CI)
hHF (%)	106 (2.6)	89 (2.2)	1.19 (0.90, 1.58)



Source: modified FDA alogliptin Advisory Committee statistical slides dated April 14, 2015; hHF: hospitalization for heart failure

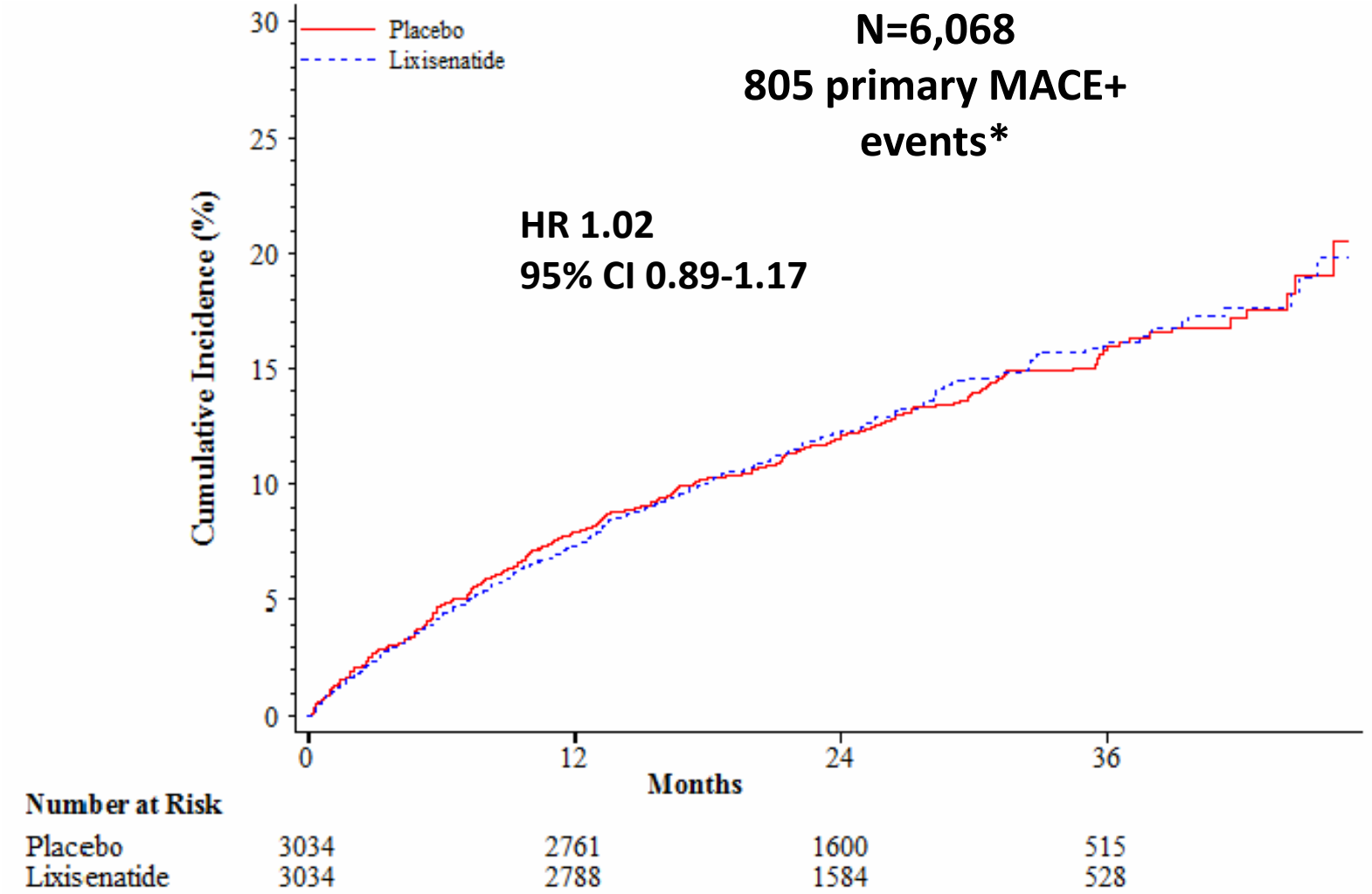
Trial Design – ELIXA



*Enrollment criteria included: patients with a history of acute coronary syndrome (a ST segment elevation myocardial infarction [STEMI] or a non-ST segment elevation myocardial infarction [NSTEMI], or unstable angina) within 180 days before randomization.

-Dose of investigational drug was titrated from a starting dose of 10 mcg during the first 2 weeks to 20 mcg

Trial Results – ELIXA



Placebo 13.2%

Lixisenatide 13.4%

* MACE+ composite of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, or hospitalization for unstable angina

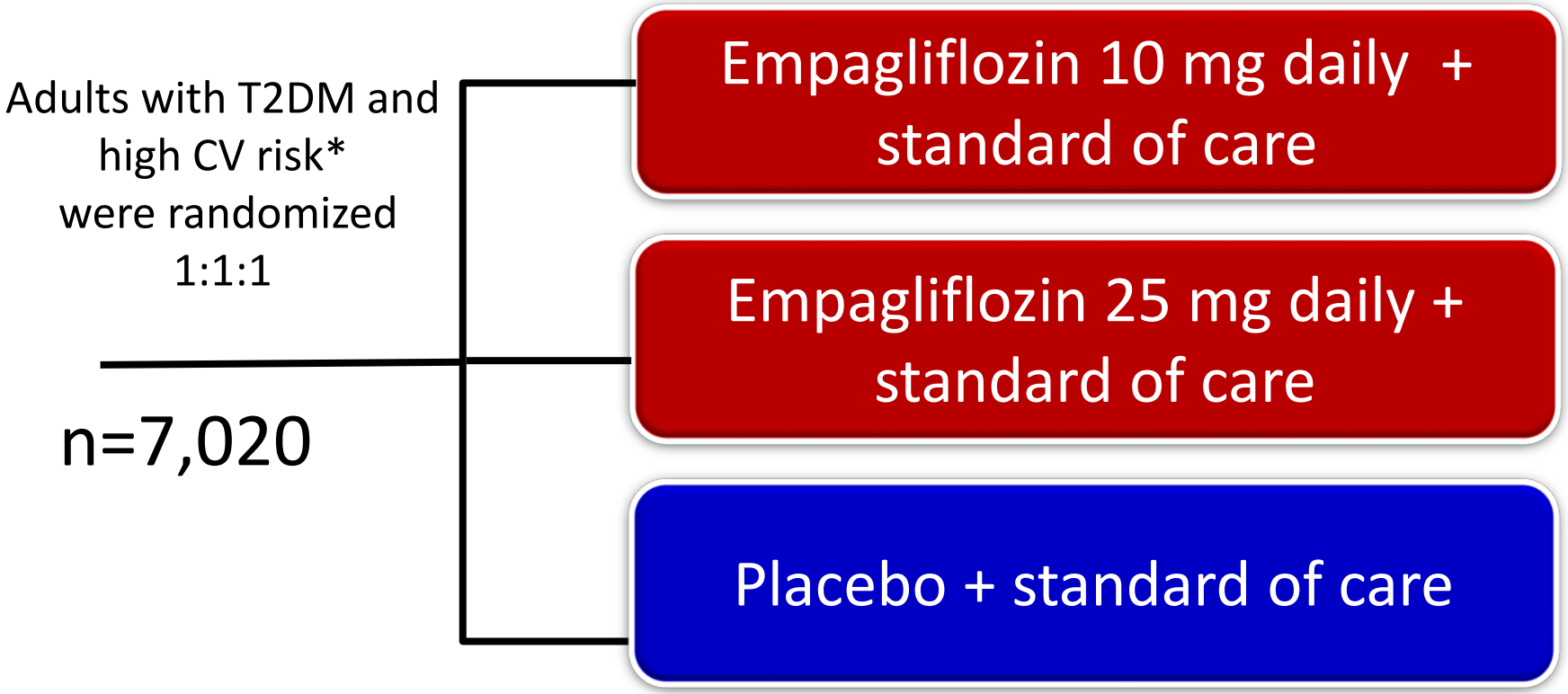
Source: Advisory committee slides dated May 25, 2015

Components of MACE+ – ELIXA

	Lixisenatide N=3,034	Placebo N=3,034	Hazard Ratio (95%)
MACE composite N (%)	406 (13.4)	399 (13.2)	1.02 (0.89, 1.17)
CV death N (%)	88 (2.9)	93 (3.1)	
Non-fatal MI N (%)	255 (8.4)	247 (8.1)	
Non-fatal ischemic stroke N (%)	54 (1.8)	49 (1.6)	
Hospitalization for unstable angina N (%)	9 (0.3)	10 (0.3)	

CV: cardiovascular; MI: myocardial infarction, Source: modified from lixisenatide Prescribing Information

Trial Design – EMPA-REG OUTCOME



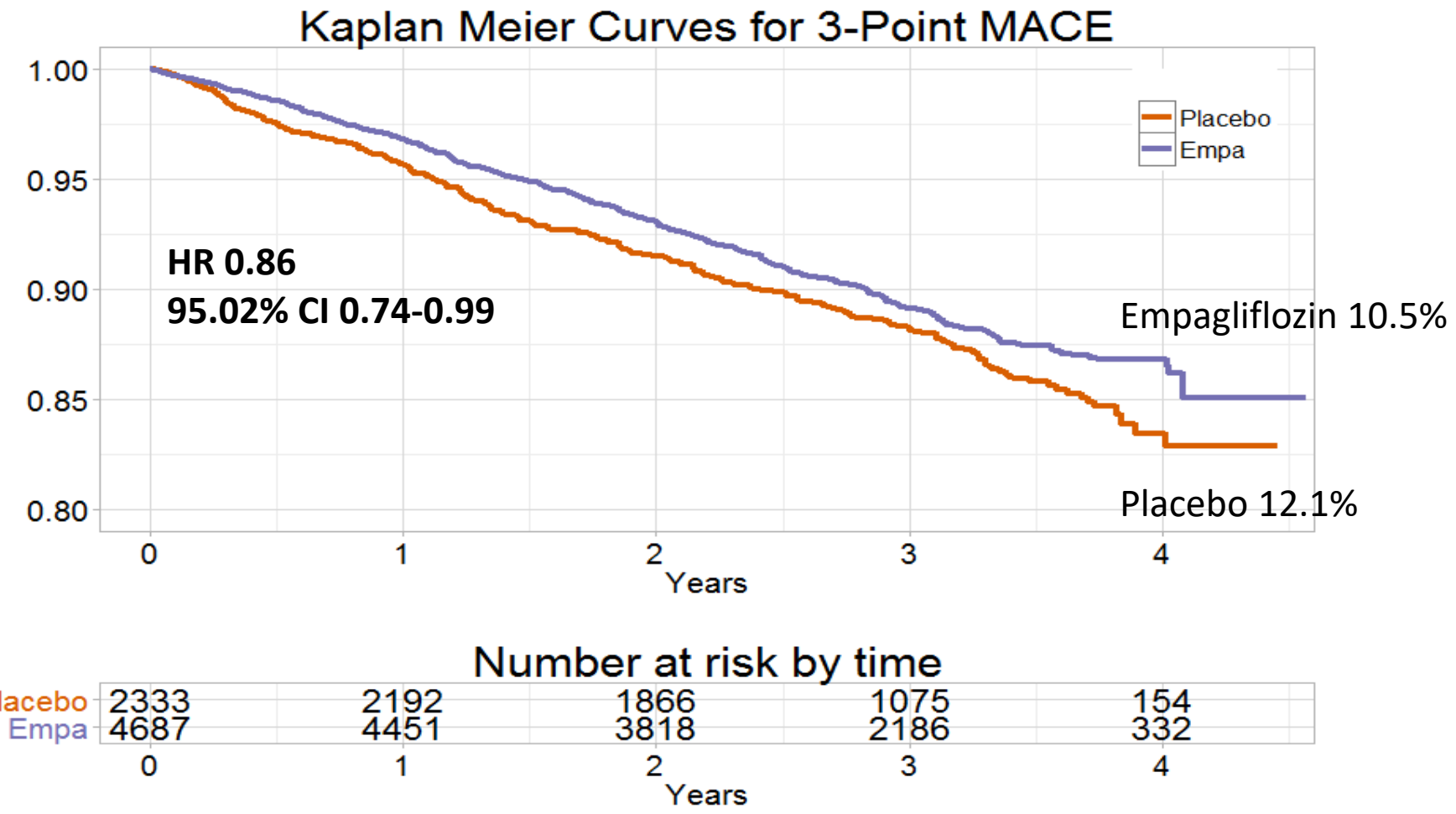
*Enrollment criteria included: patients with confirmed history of MI > 2 months before informed consent, evidence of multi-vessel coronary artery disease (CAD) or single vessel CAD and positive noninvasive stress test or discharge from hospital with documented diagnosis of unstable angina within 12 months before study, unstable angina > 2 months before informed consent with confirmed evidence of CAD, ischemic or hemorrhagic stroke, and peripheral arterial disease.

-Empagliflozin was started at 10 mg or 25 mg once daily with no dose escalation.

Trial Results – EMPA-REG OUTCOME

N= 7,020

772 primary MACE events*



*composite of cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke

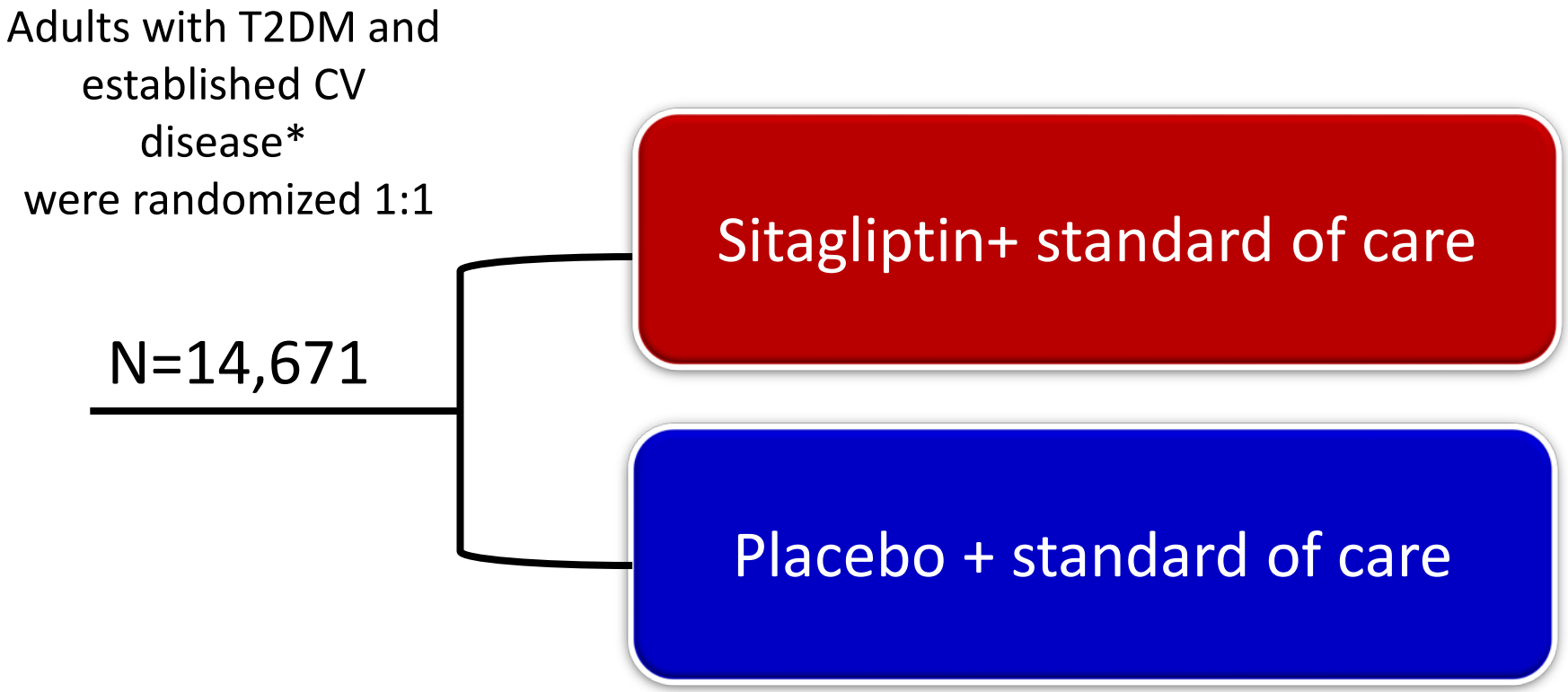
Source: modified FDA empagliflozin Advisory Committee statistical slides dated June 28, 2016

Components of MACE – EMPA-REG OUTCOME

	Empagliflozin N=4,687	Placebo N=2,333	Hazard Ratio (95%)
MACE composite N (%)	490 (10.5)	282 (12.1)	0.86 (0.74, 0.99)
CV death N (%)	172 (3.7)	137 (5.9)	0.62 (0.49, 0.77)
Non-fatal MI N (%)	213 (4.5)	121 (5.2)	0.87 (0.70, 1.09)
Non-fatal ischemic stroke N (%)	150 (3.2)	60 (2.6)	1.24(0.92, 1.67)

CV: cardiovascular; MI: myocardial infarction
Source: from empagliflozin Prescribing Information

Trial Design – TECOS



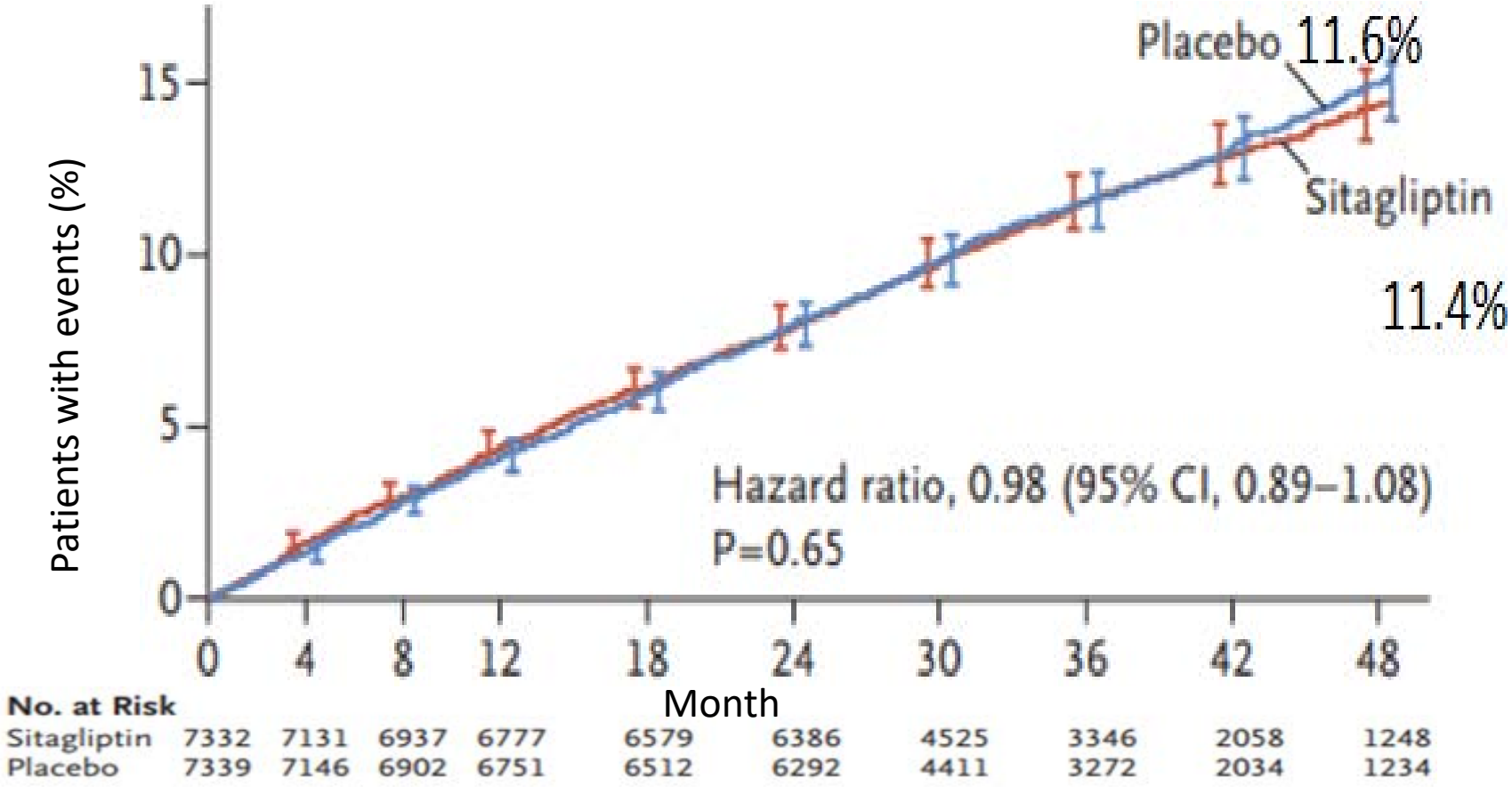
*Enrollment criteria included: patients ≥ 50 years old with history of established CV disease i.e., major coronary artery disease, ischemic cerebrovascular disease, or atherosclerotic peripheral arterial disease.

Sitagliptin was given in a dose of 100 mg daily for patients with an eGFR ≥50 mL/min/1.73m2, and for patients with eGFR ≥ 30 to <50 mL/min/1.73 m2, the dose of sitagliptin was 50 mg daily.

Trial Results – TECOS

N= 14,671

1,690 primary MACE+ events*



*composite of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, or unstable angina requiring hospitalization.

Source: Modified figure N Engl J Med 2015;373:232-242

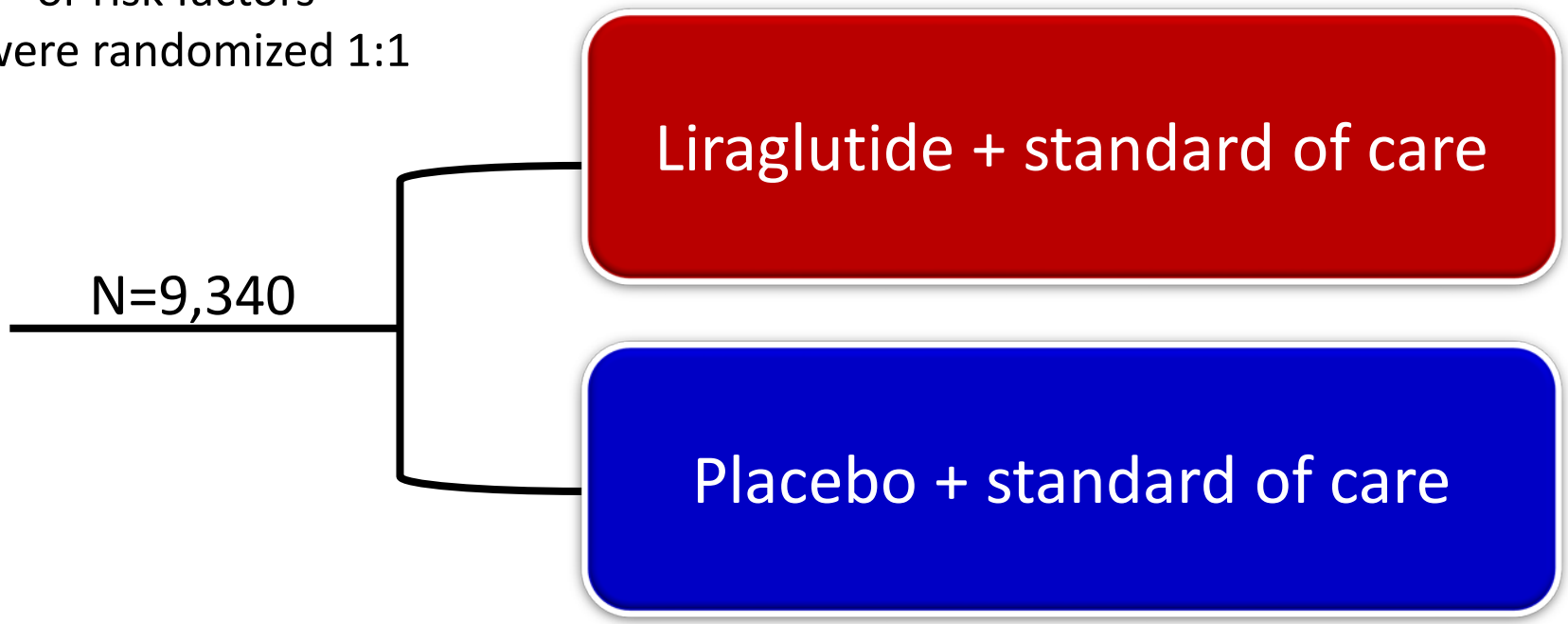
Components of MACE+: TECOS

	Sitagliptin N=7,332	Placebo N=7,339	Hazard Ratio (95%)
MACE composite N (%)	839 (11.4)	851 (11.6)	0.98 (0.89, 1.08)
CV death N (%)	311 (4.2)	291 (4)	
Non-fatal MI N (%)	275 (3.8)	286 (3.9)	
Non-fatal ischemic stroke N (%)	145 (2)	157 (2.1)	
Hospitalization for unstable angina N (%)	108 (1.5)	117 (1.6)	

CV: cardiovascular; MI:myocardial infarction
Source: N Engl J Med 2015;373:232-242

Trial Design – LEADER

Adults with T2DM and
Established CV disease
or risk factors*
were randomized 1:1



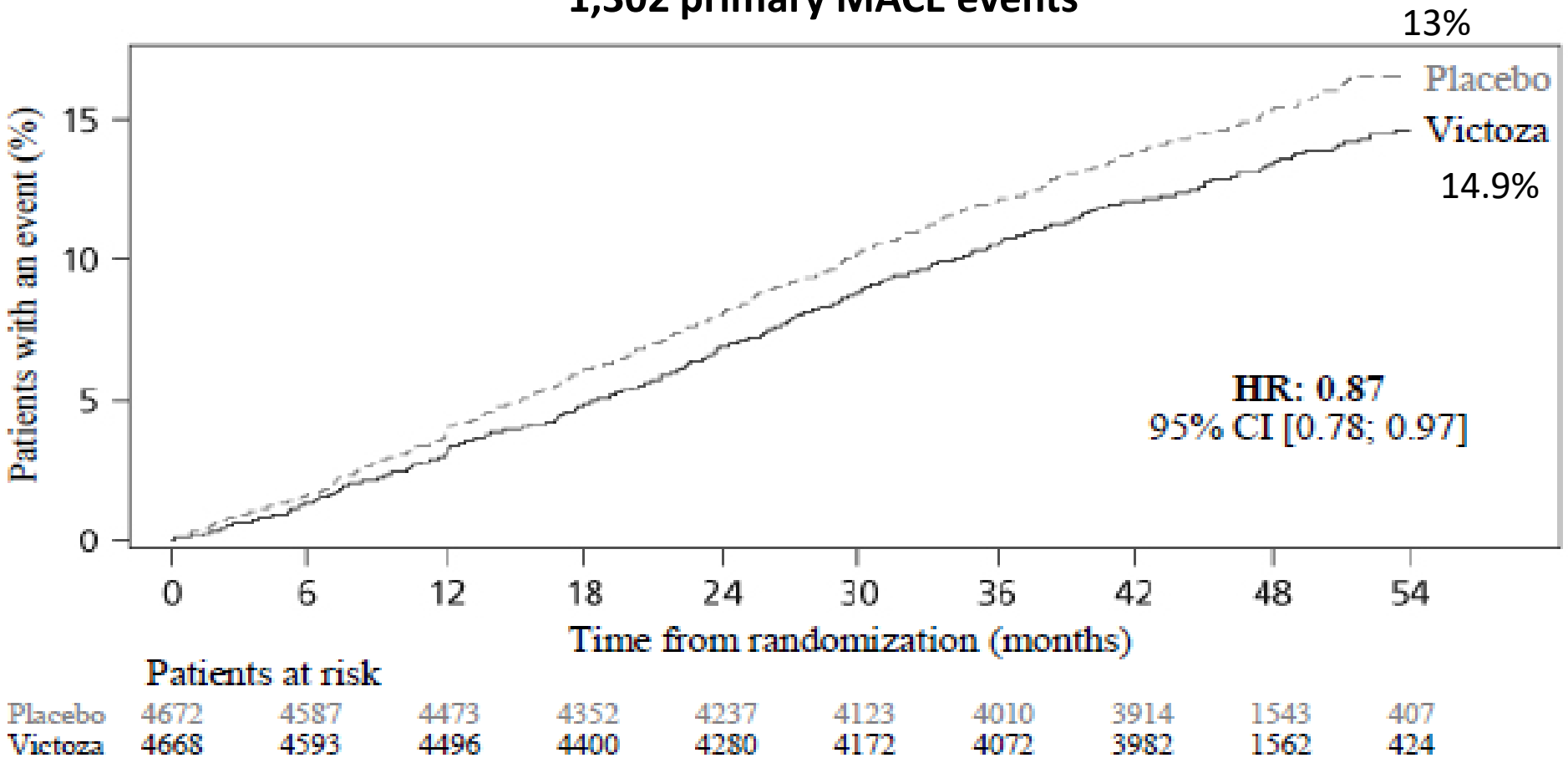
*Enrollment criteria included: patients 50 years of age or older and had established, stable, cardiovascular, cerebrovascular, peripheral artery disease, chronic kidney disease or NYHA class II and III heart failure (80%) or patients 60 years of age or older with other specified risk factors for cardiovascular disease (20%).

Dose of investigational drug was titrated 0.6 mg weekly to a maximum tolerated dose of 1.8 mg as add-on to standard of care treatment

Trial Results – LEADER

N=9,340

1,302 primary MACE events*



*composite of cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke

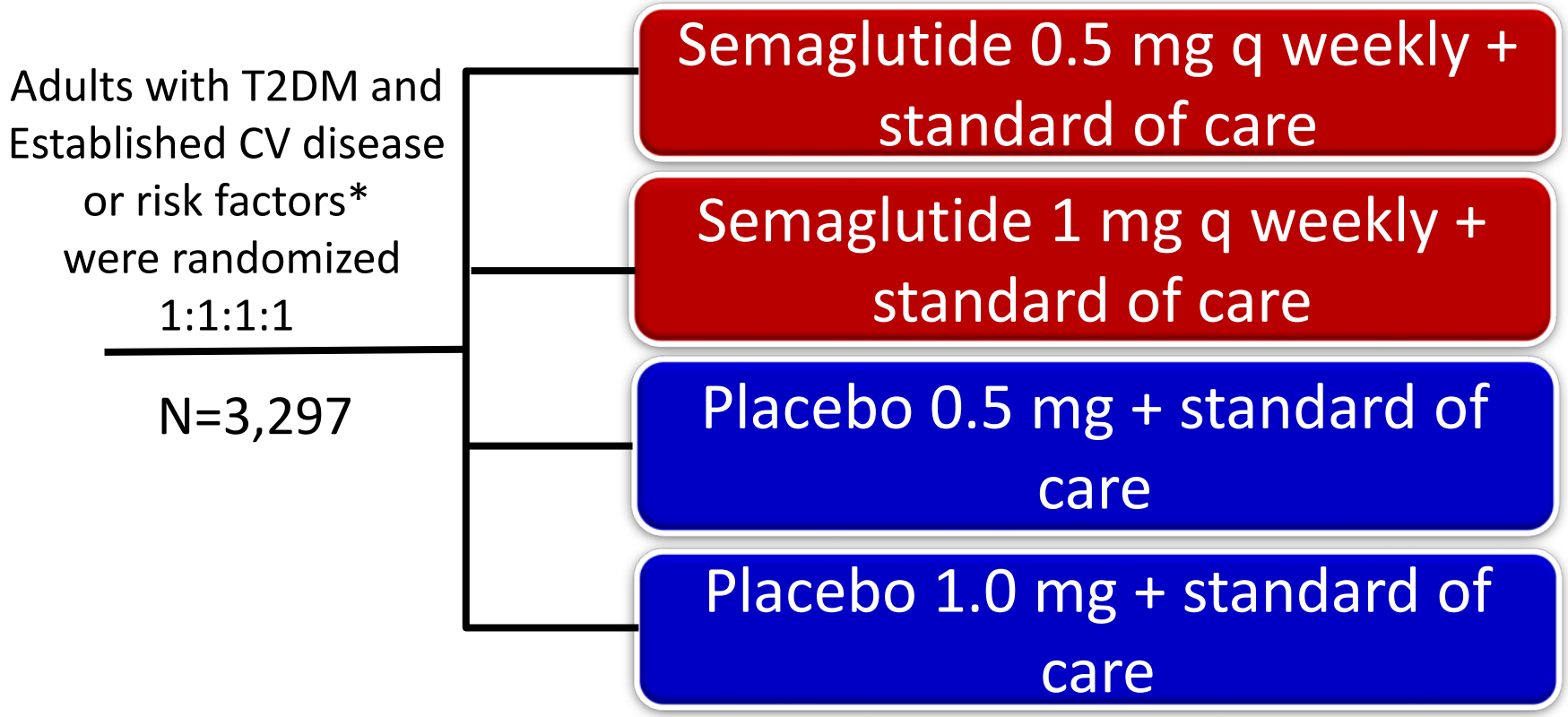
Source: adapted from Victoza Prescribing Information

Components of MACE – LEADER

	Liraglutide N=4,668	Placebo N=4,672	Hazard Ratio (95%)
MACE composite N (%)	608 (13)	694 (14.9)	0.87 (0.78, 0.97)
CV death N (%)	219 (4.7)	278 (6)	0.78 (0.66, 0.93)
Non-fatal MI N (%)	281 (6)	317 (6.8)	0.88 (0.75, 1.03)
Non-fatal ischemic stroke N (%)	159 (4.7)	278 (6)	0.89 (0.72, 1.11)

CV: cardiovascular; MI: myocardial infarction
Source: Victoza Prescribing Information

Trial Design – SUSTAIN 6



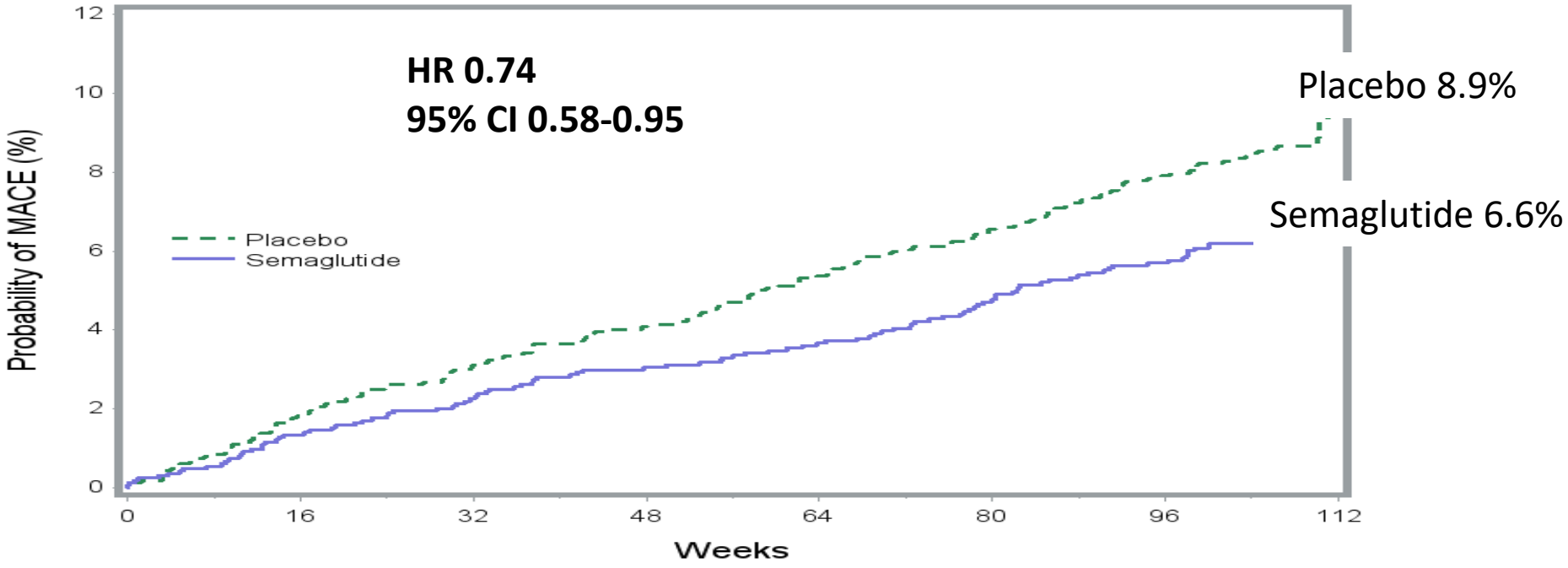
*Enrollment criteria included: patients ≥50 years with established, stable, cardiovascular, cerebrovascular, peripheral artery disease, chronic kidney disease or NYHA class II and III heart failure (83%) or patients ≥ 60 years with other risk factors for cardiovascular disease (17%).

-Dose of drug started at 0.25 mg once weekly for 4 weeks. The dose was increased to 0.5 mg once weekly (and kept for the 0.5 mg group) or titrated up after 4 weeks to 1 mg (for the 1 mg group)

Trial Results – SUSTAIN 6

N= 3,297

254 primary MACE events*



Subjects at risk

Semaglutide:	1648	1619	1601	1584	1568	1543	1524	179
Placebo:	1649	1616	1586	1567	1534	1508	1479	171

*composite of cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke

Source: modified FDA semaglutide Advisory Committee statistical slides dated October 18, 2017

Components of MACE – SUSTAIN-6

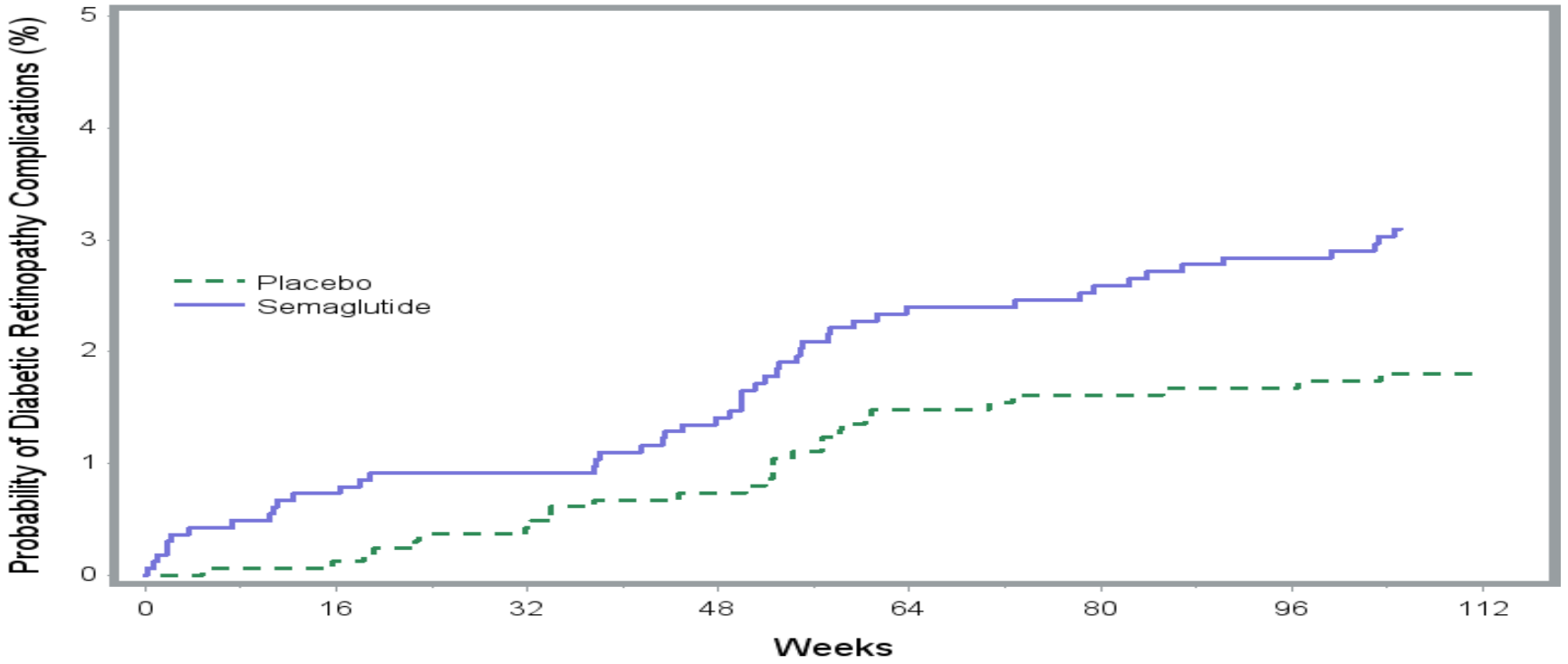
	Semaglutide N=1,648	Placebo N=1,649	Hazard Ratio (95%)
MACE composite N (%)	108 (6.6)	146 (8.9)	0.74 (0.58-0.95)
CV death N (%)	37 (2.2)	40 (2.4)	
Non-fatal MI N (%)	46 (2.8)	64 (3.9)	
Non-fatal ischemic stroke N (%)	25 (1.5)	42 (2.5)	

CV: cardiovascular; MI: myocardial infarction

Source: modified from Clinical Review, New Drug Application 209637, page 181

Safety Findings – SUSTAIN 6-Retinopathy

	Semaglutide N=1,648	Placebo N=1,649	Hazard Ratio (95% CI)
Retinopathy (%)	50 (1.5)	29 (0.9)	1.76 (1.11, 2.78)

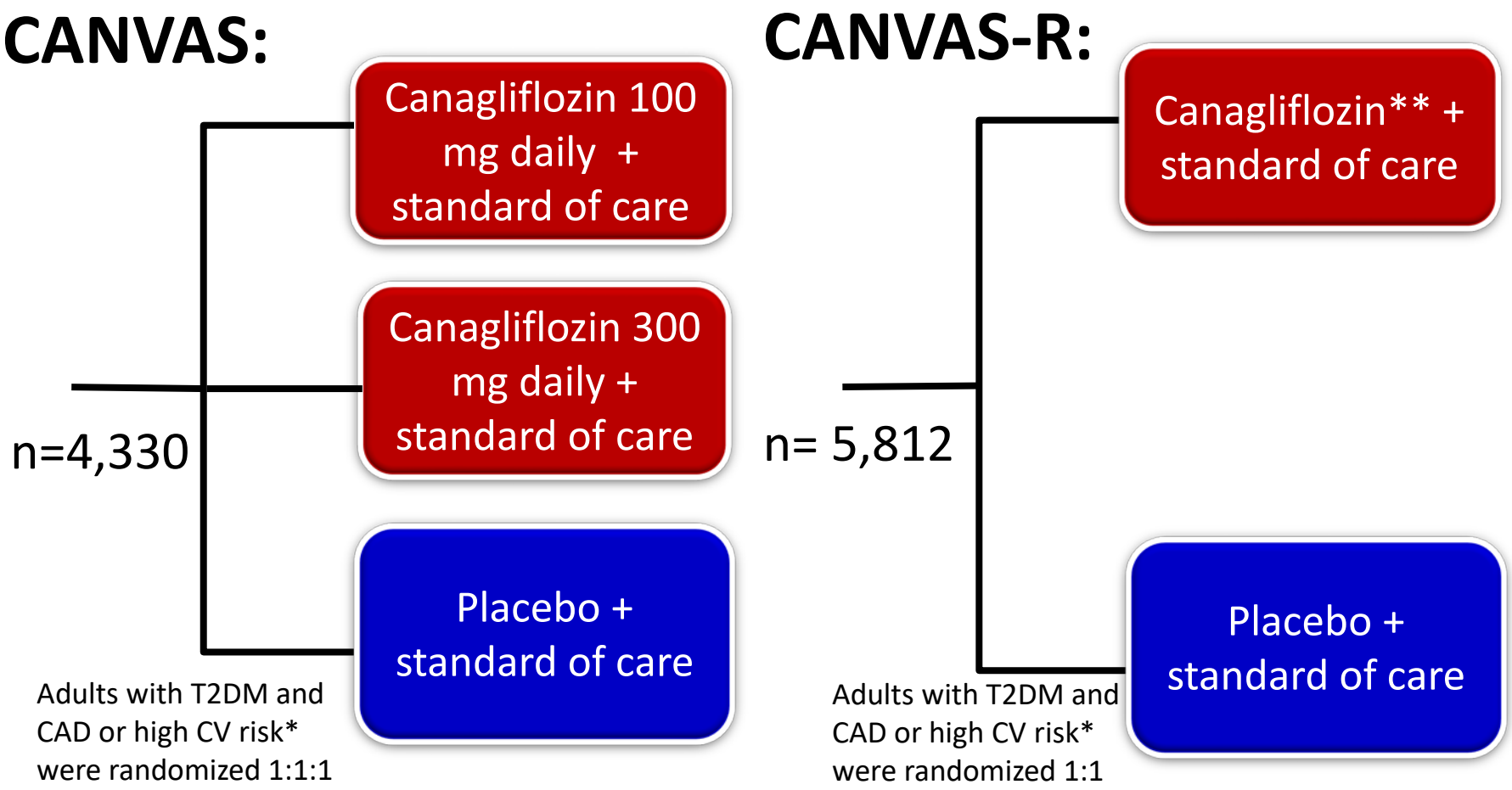


Subjects at risk

Semaglutide:	1648	1622	1612	1595	1570	1548	1535	180
Placebo:	1649	1636	1617	1605	1576	1558	1539	178

Source: Semaglutide Advisory Committee slides, October 18, 2017

Trial Design – CANVAS and CANVAS-RENAL (R)



* Main enrollment criteria in both trials were identical: patients ≥ 30 y with a history of CV event or ≥ 50 y with a high risk for CV event (2 or more of the following: diabetes duration of at least 10 years, systolic blood pressure > 140 mmHg on => 1 antihypertensive drugs, current smoking, micro- or macroalbuminuria or HDL < 38.7 mg/dL.

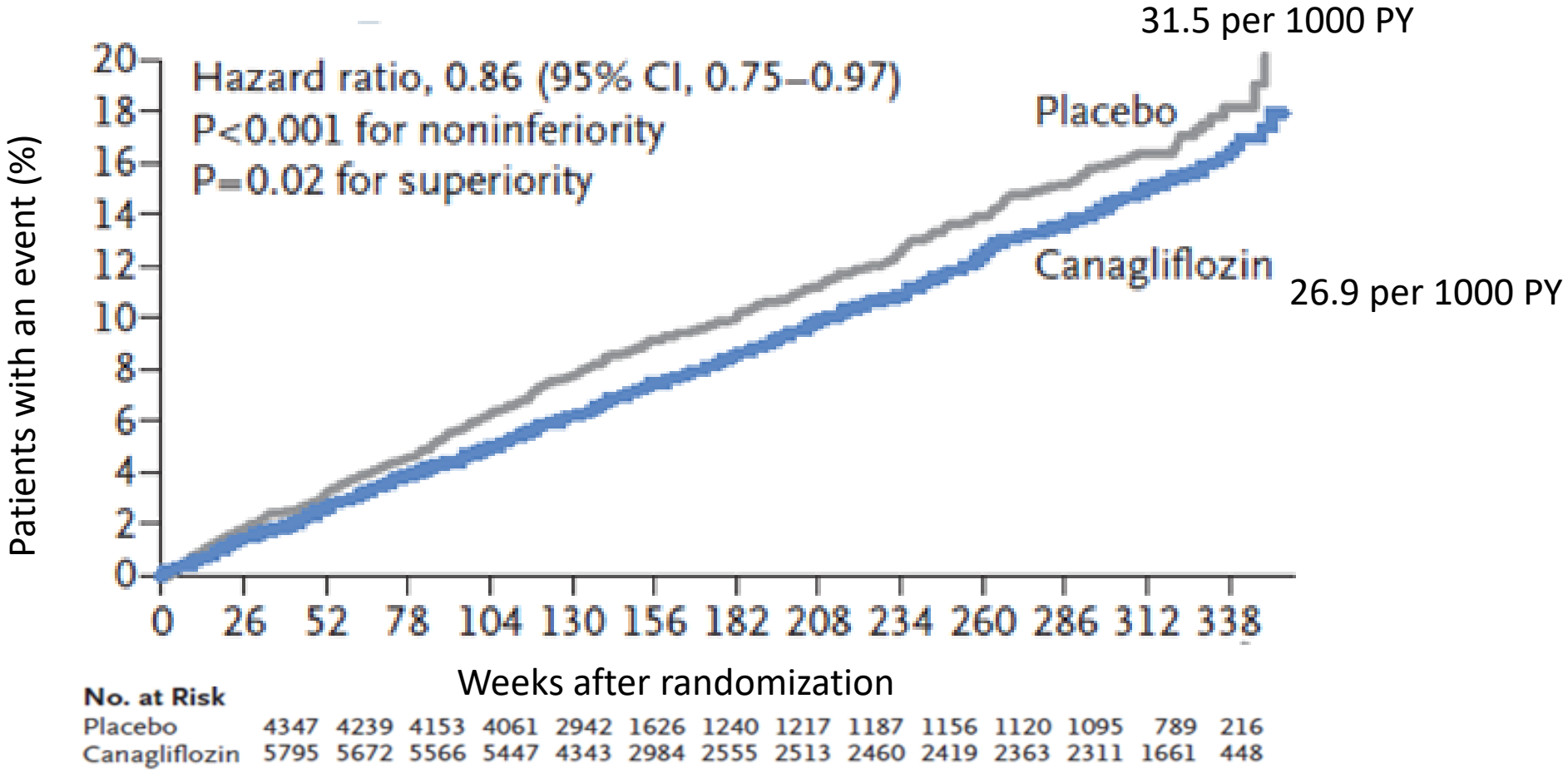
**Canagliflozin was started at 100 mg daily with an option to increase to 300 mg starting from week 13.

Source: N Engl J Med 2017; 377:644-657.

Trial Results – CANVAS and CANVAS-R

N= 10,142

1,011 primary MACE events*



*Pre-specified integrated analysis of the two trials for primary MACE: composite of cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke, PY: patient years

Source: Modified figure N Engl J Med 2017; 377:644-657.

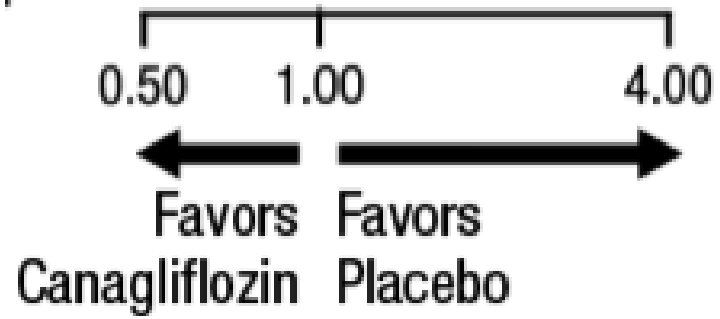
Components of MACE – CANVAS Program

	Canagliflozin N=5,795	Placebo N=4,347	Hazard Ratio (95%)
	Events per 1000 PY		
MACE composite	26.9	31.5	0.86 (0.75-0.97)
CV death per	11.6	12.8	
Non-fatal MI	9.7	11.6	
Non-fatal ischemic stroke	7.1	8.4	

CV: cardiovascular; MI: myocardial infarction, PY: patient years, Source: N Engl J Med 2017; 377:644-657.

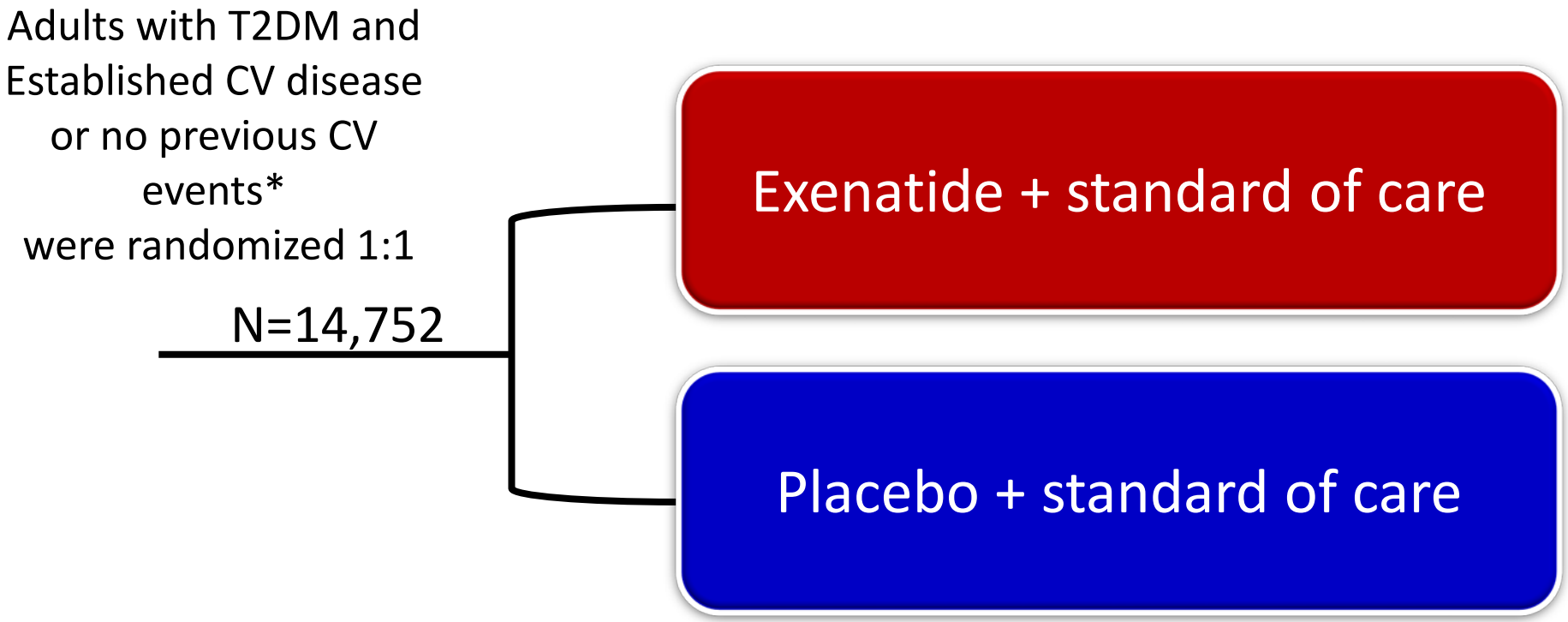
Safety Findings – CANVAS Program- Amputations

	Canagliflozin Event rate per 1000 patient-years	Placebo Event rate per 1000 patient-years	Hazard ratio (95% CI)
All amputation	6.30	3.37	1.97 (1.41–2.75)
Minor amputation	4.48	2.44	1.94 (1.31–2.88)
Toe	3.44	2.16	
Transmetatarsal	1.03	0.29	
Major amputation	1.82	0.93	2.03 (1.08–3.82)
Ankle	0.04	0.07	
Below-knee	1.16	0.64	
Above-knee	0.62	0.21	



Source: N Engl J Med 2017; 377:644-657.

Trial Design – EXSCEL

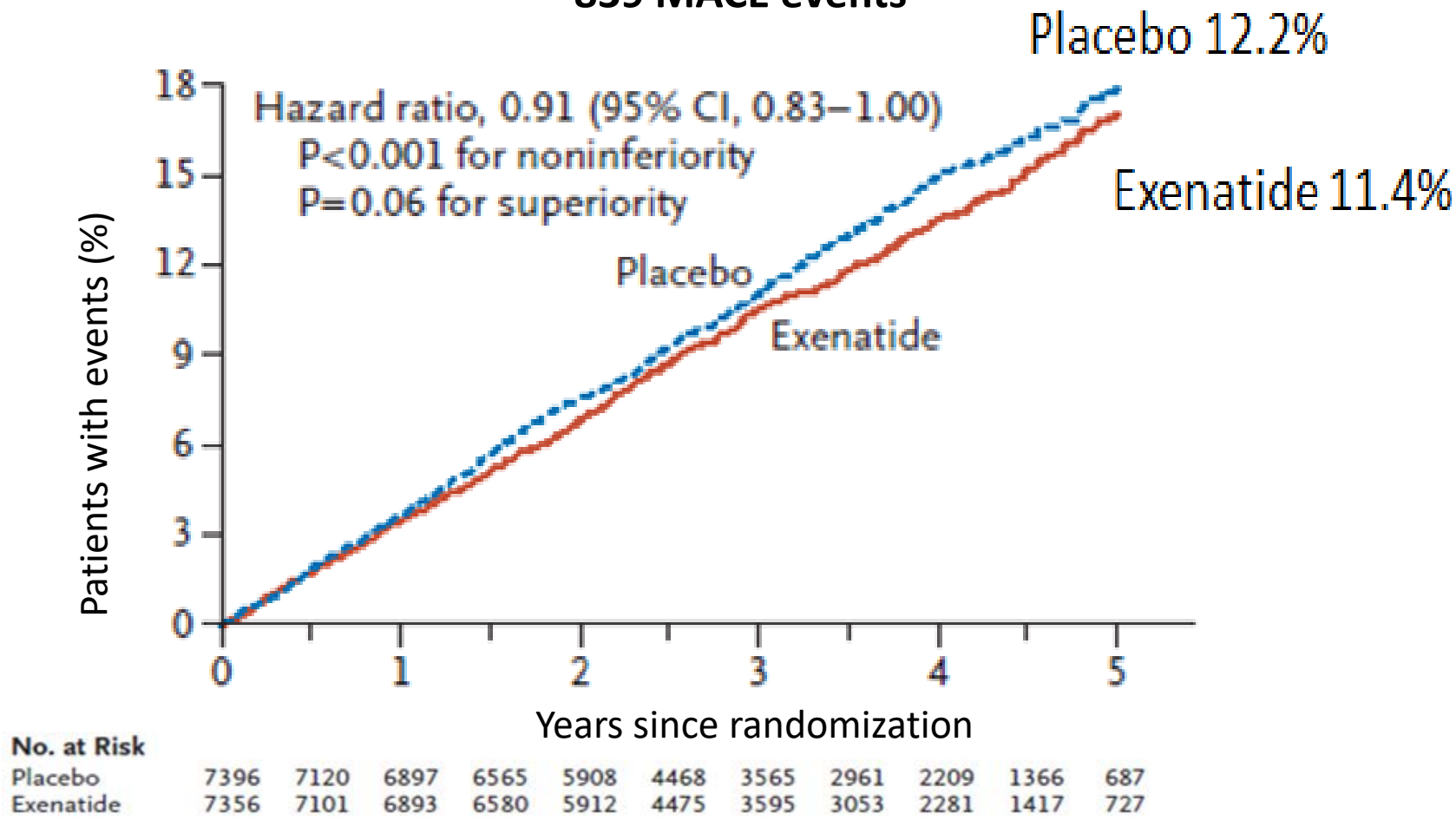


*Enrollment criteria included: 70% of the enrolled patients had previous cardiovascular (CV) event (coronary artery disease, ischemic cerebrovascular disease, peripheral arterial disease) and 30% with no previous CV event.

Exenatide dose was 2 mg add-on to standard of care treatment

Trial Results – EXSCEL

N=14,572
839 MACE events*



*composite of cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke

Source: Modified figure N Engl J Med 2017; 377: 1288-39.

Components of MACE – EXSCEL

	Exenatide N=7,356	Placebo N=7,396	Hazard Ratio (95%)
MACE composite N (%)	839 (11.4)	905 (12.2)	0.91 (0.83-1)
CV death N (%)	229 (3.1)	258 (3.5)	
Non-fatal MI N (%)	455 (6.2)	470 (6.4)	
Non-fatal ischemic stroke N (%)	155 (2.1)	177 (2.4)	

CV: cardiovascular; MI: myocardial infarction

Source: N Engl J Med 2017; 377: Supplementary appendix; Table S3, page 40

Conclusions Regarding CVOTs

- All met the guidance cardiovascular safety recommendations
- CV trends were generally consistent within each drug class
- Safety signals seen in CVOTs (not in phase 3):
  - Heart Failure – SAVOR and EXAMINE
  - Diabetic retinopathy – SUSTAIN-6
  - Lower limb amputation –CANVAS

Overview

- Overview of pre- and post-marketing cardiovascular assessment conducted post-guidance
- Discuss trial design and results of CVOTs conducted to fulfill the 2008 CV guidance
- Compare trial characteristics pre- and post-guidance

CVOT: Cardiovascular outcome trial; CV: cardiovascular

Demographic Characteristics: Pre-guidance

	Alogliptin	Saxagliptin	Liraglutide
	Phase 3	**Phase 3**	**Phase 3**
Randomized patients	4,702	4,607	6,638
Established CV Dz. (%)	ACS Excluded^	3-13%**	Excluded~
Age (mean)	53-57*	52-55*	52-58^^
HbA1c (%)	7.9-8.1*	8-8.5*	8.3-8.6
Diabetes duration (mean yrs.)	5.9-7.8*	5-7*	6.8-9.7#
Moderate/severe renal impairment (%)	Excluded	Excluded	Excluded

CV: cardiovascular, Dz: disease; ^within 6-12 months of enrollment*mean range in add-on trials** investigator reported coronary artery disease; ~Macroangiopathy (definition not specified) reported in 5.3- 15.8% of patients;^^mean range #mean range in add-on to 2 oral hypoglycemic agents

Demographic Characteristics: Pre- and Post-Guidance

	Alogliptin		Saxagliptin		Liraglutide	
	Phase 3	EXAMINE	Phase 3	SAVOR	Phase 3	LEADER
Randomized patients	4,702	5,380	4,607	16,492	6,638	9,340
Established CV Dz. (%)	ACS Excluded^	100	3-13%**	78	Excluded~	81
Age (mean)	53-57*	61	52-55*	65	52-58^^	64
HbA1c (%)	7.9-8.1*	7.6	8-8.5*	8	8.3-8.6	8.7
Diabetes duration (mean yrs.)	5.9-7.8*	9.1	5-7*	12	6.8-9.7#	13
Moderate/severe renal impairment (%)	Excluded	27	Excluded	16	Excluded	25

CV: cardiovascular, Dz: disease; ^within 6-12 months of enrollment*mean range in add-on trials** investigator reported coronary artery disease; ~Macroangiopathy (definition not specified) reported in 5.3- 15.8% of patients;^^mean range #mean range in add-on to 2 oral hypoglycemic agents

Pre- and Post-guidance Cardiovascular Risk Assessment: Alogliptin

	Phase-3 N=4,702	EXAMINE N=5,380
Number of events accrued	**18***	**621**
Mean follow up time (years)	0.5-1	1.5

*Custom Query consists of a subset of Broad SMQ. Abbreviations: N=number of patients, CI=confidence interval
Source: Adapted from Cross-Discipline Team Lead Review dated May 27, 2009

Pre- and Post-guidance Cardiovascular Risk Assessment: Saxagliptin

	Phase 3 N=4,607	SAVOR N=16,492
Number of events accrued	**40***	**1222**
Mean follow up time (years)	0.5-1	2.1

*Custom Query consists of a subset of Broad SMQ. Abbreviations: CI=confidence interval
Source: adapted from the Advisory Committee Joint Clinical and Statistical Briefing Document dated April 1, 2009

Pre- and Post-guidance Cardiovascular Risk Assessment: Liraglutide

	Phase 3 N=6,638	LEADER N=9,340
Number of events accrued	**38***	**1,302**
Mean follow up time (years)	0.5-1	3.8

*Custom Query consists of a subset of Broad SMQ. Abbreviations: CI=confidence interval
Source: adapted from the Clinical Briefing Document for the April 2, 2009 Advisory Committee Meeting

Summary

- Three classes of DM therapies have conducted CV outcome trials
- CV trials provide a focused CV assessment in at-risk population
- All CV trials demonstrated no excess CV risk
- Some CV trials have shown a CV benefit
- CV trials captured unexpected non-CV safety signals for few drugs
- Pre-guidance programs provided limited assessment of CV safety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Endocrinologic and Metabolic Drugs Advisory Committee Meeting
October 24-25, 2018

Introductory Remarks

William Chong, MD
Acting Division Director
Division of Metabolism and Endocrinology Products
Food and Drug Administration

Guidance for Industry

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

Day 2 - Agenda

- Open Public Hearing

- Committee Discussion

Discussion Topic 1

Discuss the impact of the recommendations in the 2008 Guidance for Industry: Diabetes Mellitus – Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes on the assessment of cardiovascular risk for drugs indicated to improve glycemic control in patients with type 2 diabetes mellitus.

Discussion Topic 2

For each recommendation described in the 2008 guidance, discuss its value in the evaluation of the safety of new antidiabetic drugs. The recommendations we would like you to consider are:

a. Establishment of an independent cardiovascular endpoints committee for prospective adjudication.

b. Inclusion of patients at higher risk for cardiovascular events in phase 2 and phase 3 trials to obtain sufficient endpoints to allow for a meaningful estimate of risk.

c. Exclusion of 1.8 from the upper bound of the two-sided 95% confidence interval for the estimated risk ratio prior to approval.

d. Exclusion of 1.3 from the upper bound of the two-sided 95% confidence interval for the estimated risk ratio to conclude that there is no unacceptable increase in cardiovascular risk.

Discussion Topic 3

Discuss how cardiovascular safety findings from members of a drug class should or should not be applied to all members of the drug class.

Voting Question

The 2008 Guidance for Industry: Diabetes Mellitus – Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes provided recommendations on excluding an unacceptable increase in cardiovascular risk for all new therapies to improve glycemic control in patients with type 2 diabetes regardless of the presence or absence of a signal for cardiovascular risk in the development program.

Voting Question (cont.)

Should an unacceptable increase in cardiovascular risk be excluded for all new drugs to improve glycemic control in patients with type 2 diabetes, regardless of the presence or absence of a signal for cardiovascular risk in the development program?

a. If 'Yes', provide your rationale. Include in your discussion what changes, if any, you would recommend to the 2008 guidance and why, and what kind of assessment would be appropriate and when it should be conducted.

b. If 'No', provide your rationale. Include in your discussion what might constitute a signal of cardiovascular risk that would warrant conduct of a cardiovascular outcome trial or other form of cardiovascular risk assessment.


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