REWIND

Dulaglutide CV Outcomes Trial

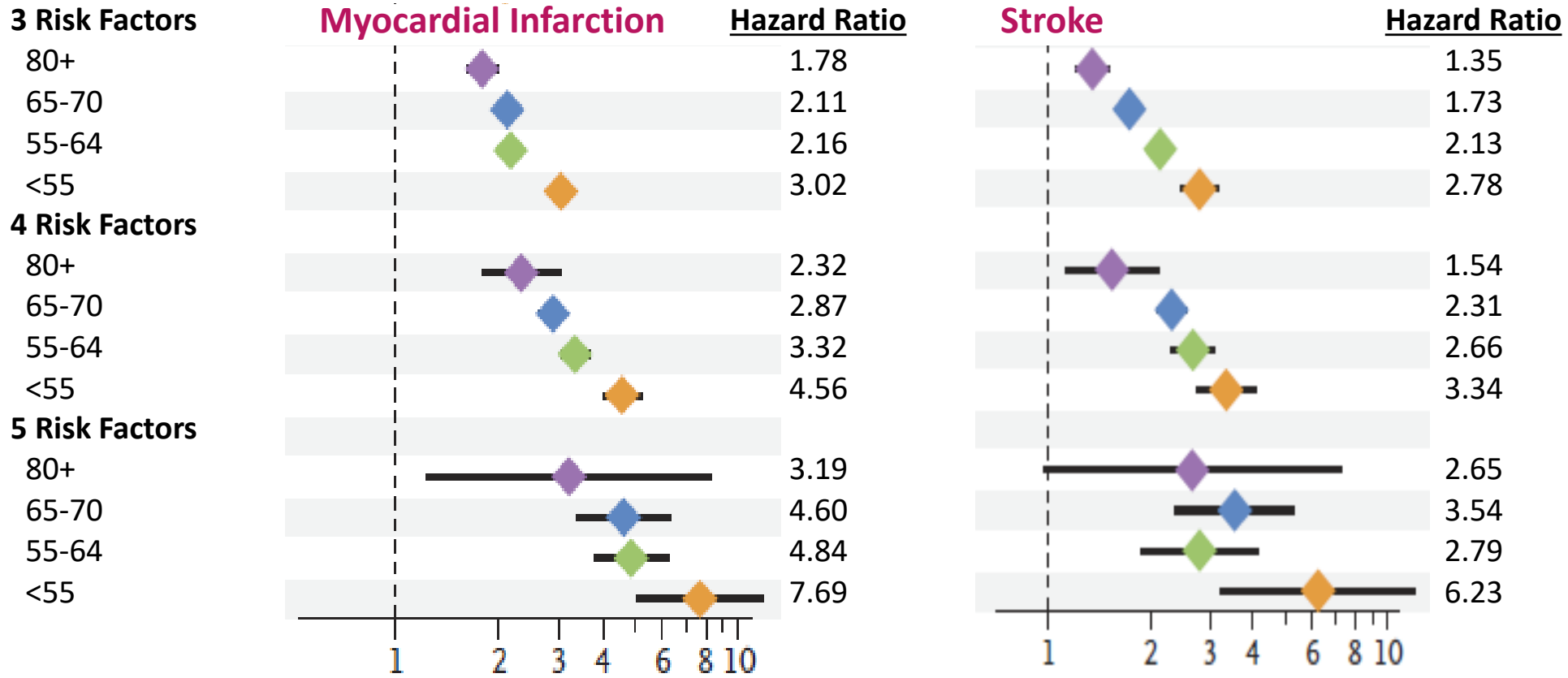
Researching CV **E**vents with a **W**eekly **IN**cretin in **D**iabetes

Population Health Research Institute
HEALTH THROUGH KNOWLEDGE

REWIND
Dulaglutide CV Outcomes Trial

Introduction

- People with type 2 diabetes (DM) → 1.5 to 2-fold higher risk of CV (cardiovascular) outcomes or death than unaffected people
- The risk rises with # of risk factors (Rawshani et al. NEJM 2018;633)



REWIND
Dulaglutide CV Outcomes Trial

Introduction

- Large RCTs have reported that 3 GLP-1 RAs (glucagon-like peptide receptor 1 agonists) reduced CV events in people with type 2 DM whose mean HbA1c was ≥ 8.0% & whose annual risk of CV events was ≥ 4%
- The CV effects of GLP-1 RAs in people with type 2 DM with a broader range of CV risk & with HbA1c levels more reflective of those in the general population is not known
- Dulaglutide is a GLP-1 RA comprising 2 modified human GLP-1 molecules linked to an IgG4 heavy chain with $t_{1/2}$ = 5 d
  - Dosed weekly at 0.75 mg or 1.5 mg sc
  - Reduces glucose, BP, weight
  - May have CV benefits similar to other GLP1 RAs

REWIND
Dulaglutide CV Outcomes Trial

Background: Previous GLP-1 RA Trials

	ELIXA	LEADER	SUSTAIN 6	EXSCEL	HARMONY
N	6068	9340	3297	14752	9463
Drug Tested	Lixisenatide/d	Liraglutide/d	Semaglutide/wk	Exenatide/wk	Albiglutide/wk
Prior CVD	100%	81%	83%	73%	100%
Mean Age	60 y	64 y	54 y	62 y	64 y
Women	30%	36%	39%	38%	31%
Median F/U	2.1 y	3.8 y	2.1 y	3.2 y	1.6 y

REWIND
Dulaglutide CV Outcomes Trial

Background: Previous GLP-1 RA Trials

	ELIXA	LEADER	SUSTAIN 6	EXSCEL	HARMONY
N	6068	9340	3297	14752	9463
Drug Tested	Lixisenatide/d	Liraglutide/d	Semaglutide/wk	Exenatide/wk	Albiglutide/wk
Prior CVD	100%	81%	83%	73%	100%
Mean Age	60 y	64 y	54 y	62 y	64 y
Women	30%	36%	39%	38%	31%
Median F/U	2.1 y	3.8 y	2.1 y	3.2 y	1.6 y

REWIND
Dulaglutide CV Outcomes Trial

Background: Previous GLP-1 RA Trials

	ELIXA	LEADER	SUSTAIN 6	EXSCEL	HARMONY
N	6068	9340	3297	14752	9463
Drug Tested	Lixisenatide/d	Liraglutide/d	Semaglutide/wk	Exenatide/wk	Albiglutide/wk
Prior CVD	100%	81%	83%	73%	100%
Mean Age	60 y	64 y	54 y	62 y	64 y
Women	30%	36%	39%	38%	31%
Median F/U	2.1 y	3.8 y	2.1 y	3.2 y	1.6 y
DM Duration	9.2 y	12.8 y	13.9 y	13.1 y	14.2 y
Baseline A1c	7.7%	8.7%	8.7%	8.1%	8.8%
Baseline eGFR	76	~75	~75	76	79
Insulin Use	39%	45%	58%	46%	59%
Adherence	~75%	84%	88%	76%	86%

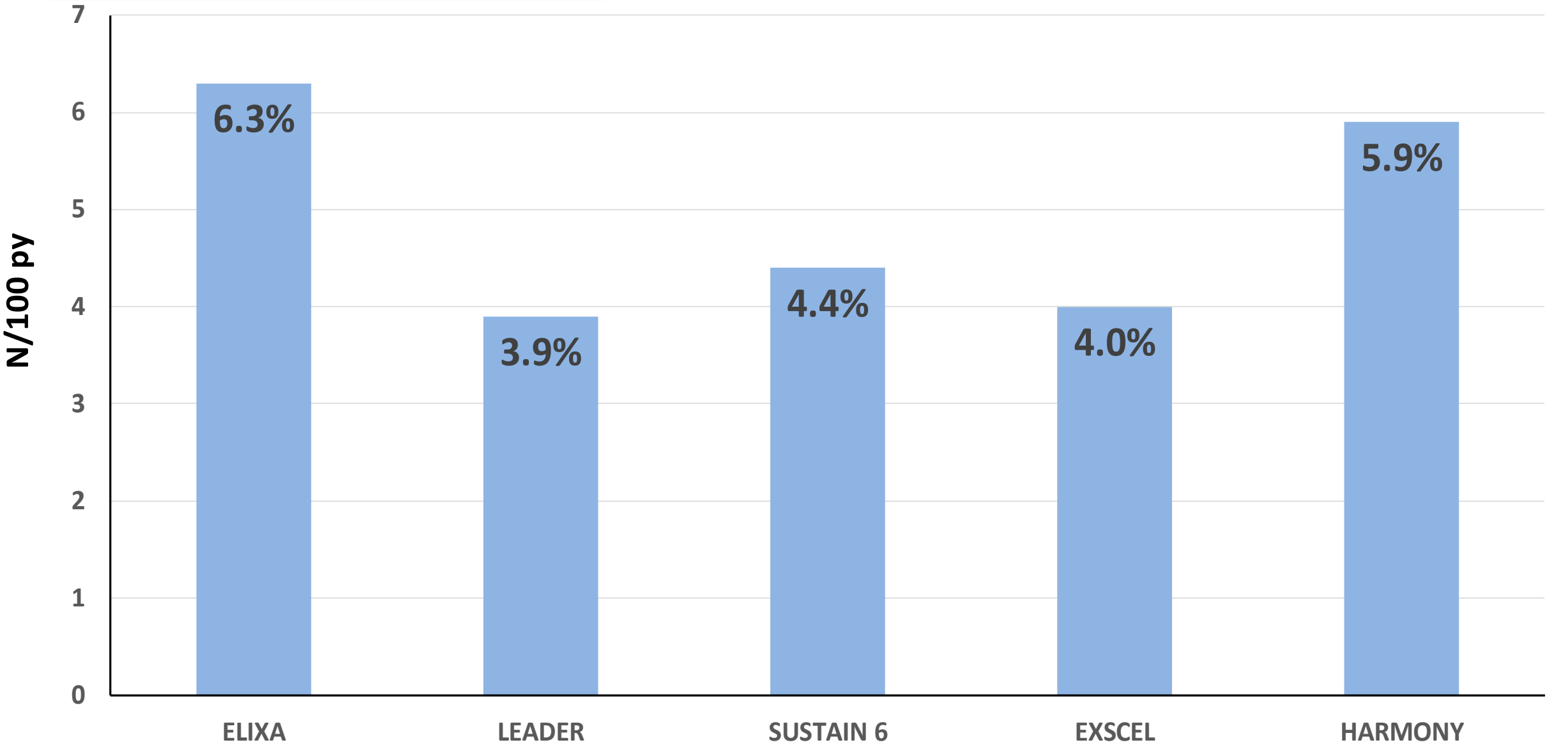
REWIND
Dulaglutide CV Outcomes Trial

Background: Previous GLP-1 RA Trials

	ELIXA	LEADER	SUSTAIN 6	EXSCEL	HARMONY
N	6068	9340	3297	14752	9463
Drug Tested	Lixisenatide/d	Liraglutide/d	Semaglutide/wk	Exenatide/wk	Albiglutide/wk
Prior CVD	100%	81%	83%	73%	100%
Mean Age	60 y	64 y	54 y	62 y	64 y
Women	30%	36%	39%	38%	31%
Median F/U	2.1 y	3.8 y	2.1 y	3.2 y	1.6 y
DM Duration	9.2 y	12.8 y	13.9 y	13.1 y	14.2 y
Baseline A1c	7.7%	8.7%	8.7%	8.1%	8.8%
Baseline eGFR	76	~75	~75	76	79
Insulin Use	39%	45%	58%	46%	59%
Adherence	~75%	84%	88%	76%	86%

REWIND
Dulaglutide CV Outcomes Trial

Annual Placebo MACE Rates by Trial

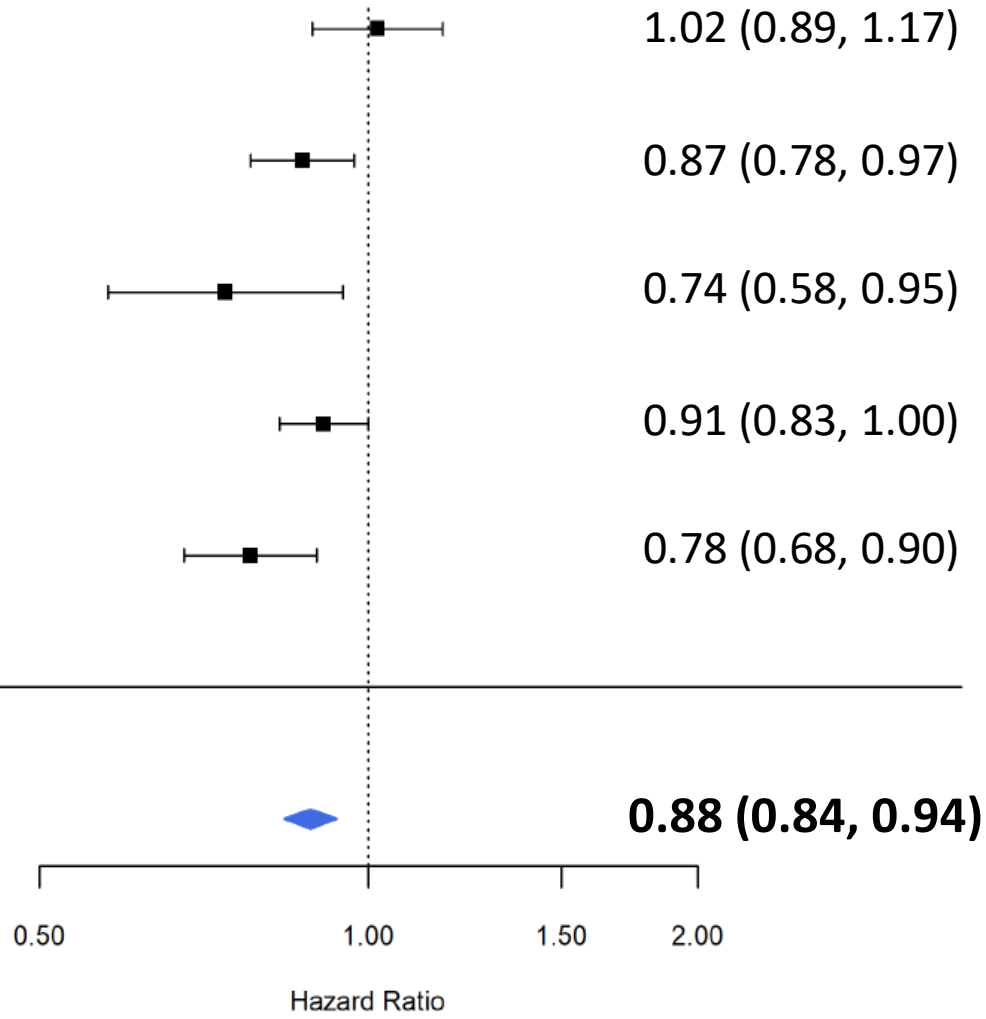


REWIND
Dulaglutide CV Outcomes Trial

Meta-analysis of MACE (GLP-1 RA CVOTs)

Zelniker et al. Circulation 2019:2022

Trials	Patients	Events	Treatment	Placebo	Weights	HR (95% CI)
ELIXA	6068	805	406/3034	399/3034	16.7	1.02 (0.89, 1.17)
LEADER	9340	1302	608/4668	694/4672	26.3	0.87 (0.78, 0.97)
SUSTAIN 6	3297	254	108/1648	146/1649	5.1	0.74 (0.58, 0.95)
EXSCEL	14752	1744	839/7356	905/7396	36.0	0.91 (0.83, 1.00)
HARMONY	9463	766	338/4731	428/4732	15.9	0.78 (0.68, 0.90)



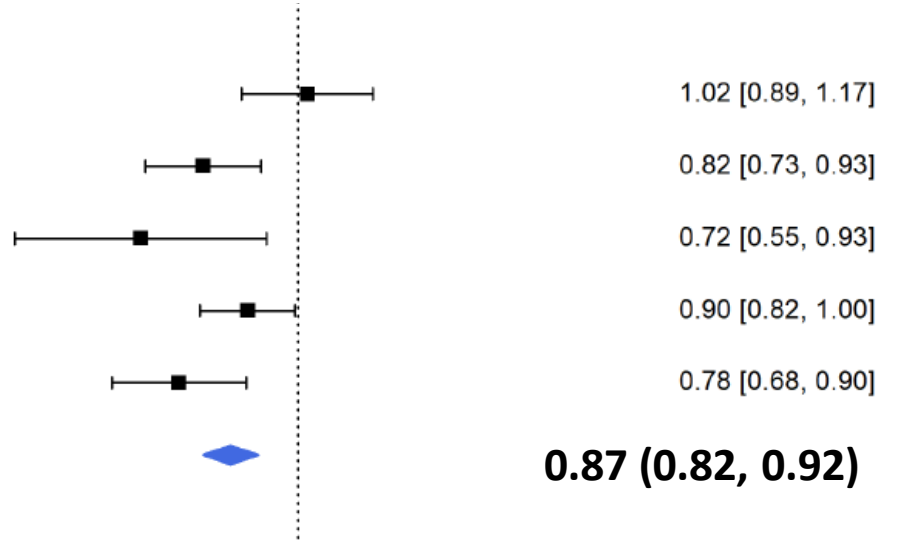
Fixed Effects for MACE Outcome (P-value < 0.001) **0.88 (0.84, 0.94)**

REWIND
Dulaglutide CV Outcomes Trial

Meta-analysis of MACE (GLP-1 RA CVOTs)

Zelniker et al. Circulation 2019:2022

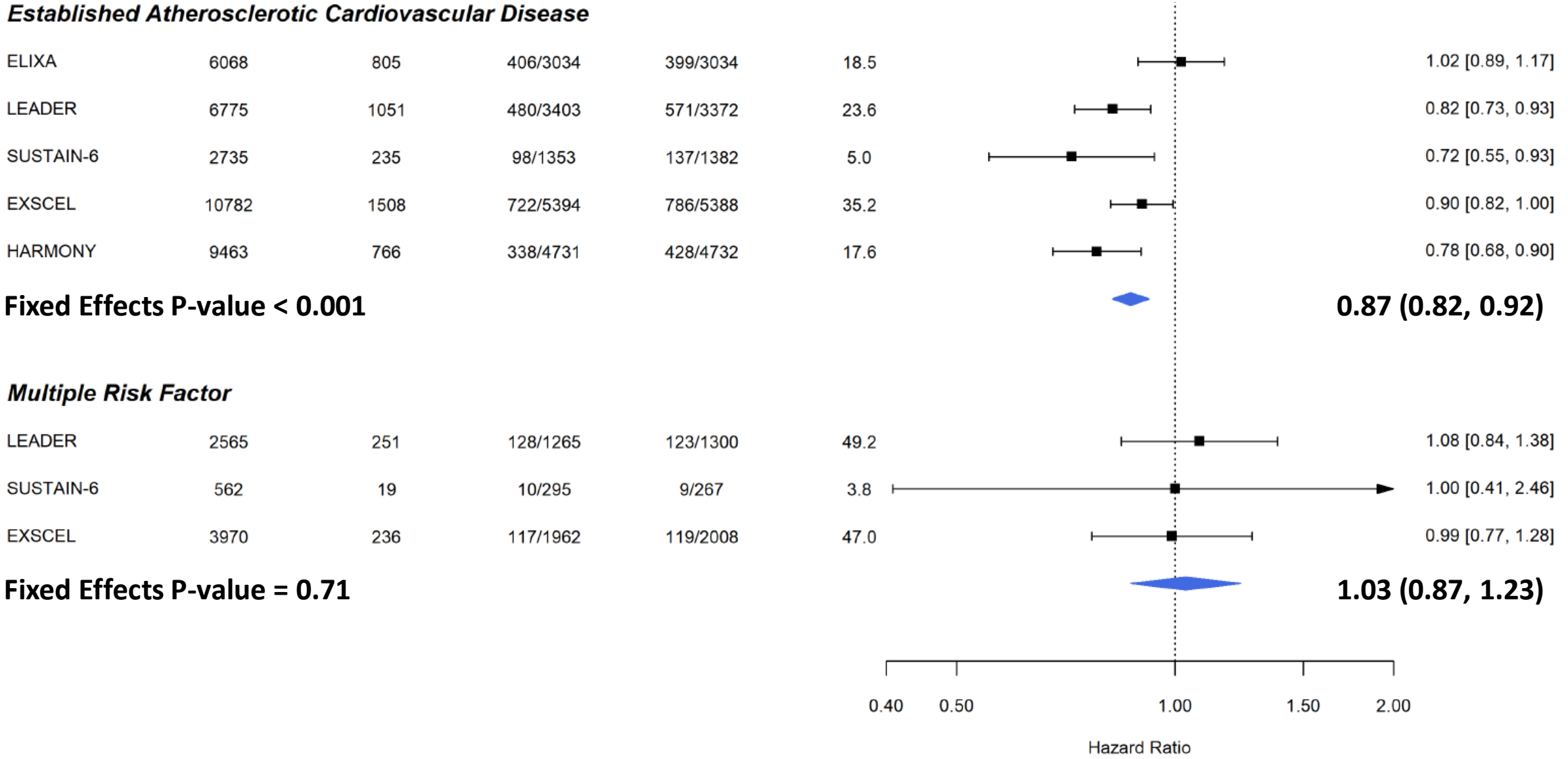
Established Atherosclerotic Cardiovascular Disease						
ELIXA	6068	805	406/3034	399/3034	18.5	1.02 [0.89, 1.17]
LEADER	6775	1051	480/3403	571/3372	23.6	0.82 [0.73, 0.93]
SUSTAIN-6	2735	235	98/1353	137/1382	5.0	0.72 [0.55, 0.93]
EXSCEL	10782	1508	722/5394	786/5388	35.2	0.90 [0.82, 1.00]
HARMONY	9463	766	338/4731	428/4732	17.6	0.78 [0.68, 0.90]
Fixed Effects P-value < 0.001						**0.87 (0.82, 0.92)**



REWIND
Dulaglutide CV Outcomes Trial

Meta-analysis of MACE (GLP-1 RA CVOTs)

Zelniker et al. Circulation 2019:2022



REWIND
Dulaglutide CV Outcomes Trial

Research Question

In men & women with established or newly detected type 2 diabetes who have additional CV risk factors…

… does adding a weekly sc. injection of the GLP-1 RA dulaglutide (1.5 mg) to the medical regimen safely reduce serious CV outcomes more than adding a wkly sc. placebo injection?

REWIND
Dulaglutide CV Outcomes Trial

Key Inclusion Criteria

Type 2 DM - New or previously diagnosed (with stable glucose drugs X 3 mo)

- On 0-2 oral glucose drugs +/- basal insulin or GLP-1 RA

A1C ≤ 9.5% (81 mmol/mol)

BMI ≥ 23 kg/m^2

Age ≥ 50 & vascular disease

(prior MI, stroke, revascularization, or unstable angina + ECG changes or PCI or positive imaging)

≥ 55 & subclinical vascular disease

(positive stress test/image, >50% stenosis, ABI<0.9; eGFR <60; hypertension + LVH, or albuminuria)

≥ 60 & 2 CV risk factors

(tobacco, lipid drug, LDL-C ≥ 3.4 (130 mg/dl), HDL-C < 1.0 (40 mg/dl) for men & < 1.3 (50 mg/dl) for women or TG ≥ 2.3 (200 mg/dl), ≥ 1 BP drug or SBP ≥ 140 or DBP ≥ 95. waist:hip ratio >1.0 for men & > 0.8 for women)

REWIND
Dulaglutide CV Outcomes Trial

Trial Outcomes

Primary Composite: First Occurrence of a MACE Outcome

- Nonfatal MI (including silent), nonfatal stroke, or CV death

Secondary Outcomes

- Microvascular composite outcome
  - *Retinopathy:* *laser Rx/anti VEGF, vitrectomy*
  - *Nephropathy:* *clinical proteinuria, 30% eGFR fall, renal replacement Rx*
- Hospitalization for unstable angina
- Hospitalization or urgent visit for heart failure
- Each component of the primary outcome
- Total mortality

REWIND
Dulaglutide CV Outcomes Trial

Other Trial Outcomes

- HbA1c
- Weight & Waist/Hip Ratio
- Expanded Composite CV Outcome: MACE or Hosp for UA
- Revascularization (coronary, carotid, or peripheral)
- Any hospitalization
- Any fracture
- Cholelithiasis
- Erectile dysfunction in men (IIEF)
- Cognitive decline (DSST & MOCA)

REWIND
Dulaglutide CV Outcomes Trial

Trial Leadership

Academic: Population Health Research Institute (PHRI) & Global Network

HC Gerstein, HM Colhoun, GR Dagenais R Diaz, P Pais, J Probstfield, MC Riddle, L Rydén, D Xavier, A Avezum, J Basile, N Chung, I Conget, WC Cushman, E Franek, N Hancu, M Hanefeld, S Holt, P Jansky, M Keltai, F Lanas, LA Leiter, P Lopez-Jaramillo, EGC Munoz, V Pirags, N Pogosova, PJ Raubenheimer, JE Shaw, W Sheu, T Temelkova-Kurktschiev

Sponsor: Eli Lilly & Company

M Lakshmanan, JS Riesmeyer, C Atisso

Data Collection & Site Management: ICON

Statistical & Organizational: PHRI

L Dyal, S Hall, P Rao-Melacini, G Wong

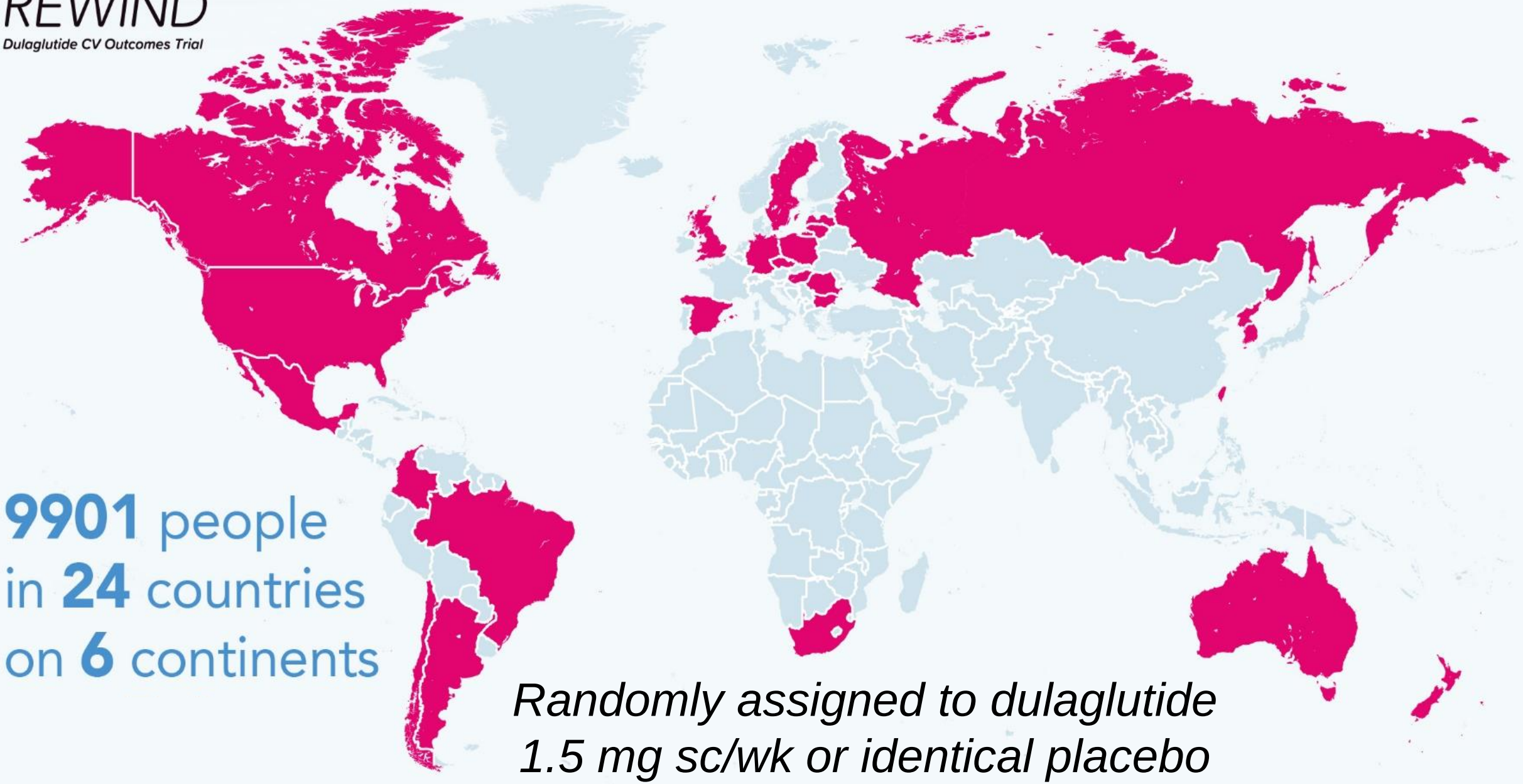
Independent Data Monitoring Committee (IDMC)

J Wittes, B Byington, S Griffin, C Hennekens, P Moayyedi

REWIND

Dulaglutide CV Outcomes Trial

Recruitment at 371 sites from Aug 2011-Aug 2013



9901 people
in **24** countries
on **6** continents

Randomly assigned to dulaglutide 1.5 mg sc/wk or identical placebo

REWIND
Dulaglutide CV Outcomes Trial

Baseline Characteristics

	All Participants N=9901	Dulaglutide N=4949	Placebo N=4952
Age (years)	**66.2**	66.2	66.2
Females (%)	**46.4**	46.6	46.1
White (%)	**75.7**	75.9	75.6
Current Tobacco (%)	**14.2**	14.0	14.4
Prior CV Disease (%)	**31.5**	31.5	31.4
Prior MI or Ischemic Stroke (%)	**20.6**	20.8	20.3
Prior Hypertension (%)	**93.2**	93.0	93.3
Prior Heart Failure (%)	**8.6**	8.5	8.7

History of MI, ischemic stroke, unstable angina with ECG changes, myocardial ischemia on imaging or stress test, or revascularization (coronary, carotid or peripheral)

REWIND
Dulaglutide CV Outcomes Trial

Diabetes-related Characteristics

	All Participants N=9901	Dulaglutide N=4949	Placebo N=4952
HbA1c (%)	**7.3**	7.3	7.4
DM Duration (y)	**10.5**	10.5	10.6
Retinopathy (%)	**9.0**	9.1	8.9
eGFR <60 ml/min/1.73m² (%)	**22.2**	21.8	22.6
Albuminuria (%)*	**35.0**	34.5	35.5
Metformin (%)	**81.2**	81.3	81.1
Sulfonylurea (%)	**46.0**	45.9	46.1
Insulin (%)	**23.9**	24.0	23.7
DPP4i (%)	**5.7**	5.4	6.0
Thiazolidinedione (%)	**1.7**	2.0	1.4
Other incl. SGLT2i (%)	**0.3**	0.3	0.4

**** ACR ≥ 3.39 mg/mmol or 30 mg/g***

REWIND
Dulaglutide CV Outcomes Trial

Baseline Measures – SI Units

	All Participants N=9901	Dulaglutide N=4949	Placebo N=4952
BMI (kg/m^2)	**32.3**	32.3	32.3
Systolic BP (mm Hg)	**137.2**	137.1	137.3
Diastolic BP (mm Hg)	**78.5**	78.4	78.5
Heart Rate (bpm)	**71.5**	71.4	71.6
Serum Creat (umol/l)	**84.1**	83.7	84.5
Median eGFR (ml/min/1.73m^2)	**74.9**	75.3	74.7
Median ACR (mg/mmol)	**1.82**	1.80	1.88
Cholesterol (mmol/L)	**4.52**	4.52	4.52
LDL (mmol/L)	**2.56**	2.56	2.56
HDL (mmol/L)	**1.18**	1.18	1.18
Median Triglycerides (mmol/L)	**1.60**	1.60	1.60

REWIND
Dulaglutide CV Outcomes Trial

Baseline Measures – Conventional Units

	All Participants N=9901	Dulaglutide N=4949	Placebo N=4952
BMI (kg/m^2)	**32.3**	32.3	32.3
Systolic BP (mm Hg)	**137.2**	137.1	137.3
Diastolic BP (mm Hg)	**78.5**	78.4	78.5
Heart Rate (bpm)	**71.5**	71.4	71.6
Serum Creat (mg/dl)	**0.95**	0.95	0.96
Median eGFR (ml/min/1.73m^2)	**74.9**	75.3	74.7
Median ACR (mg/g)	**16.1**	15.9	16.6
Cholesterol (mg/dl)	**174.5**	174.5	174.5
LDL (mg/dl)	**98.8**	98.8	98.8
HDL (mg/dl)	**45.6**	45.6	45.6
Median Triglycerides (mg/dl)	**141.6**	141.6	141.6

REWIND
Dulaglutide CV Outcomes Trial

Baseline use of CV Drugs

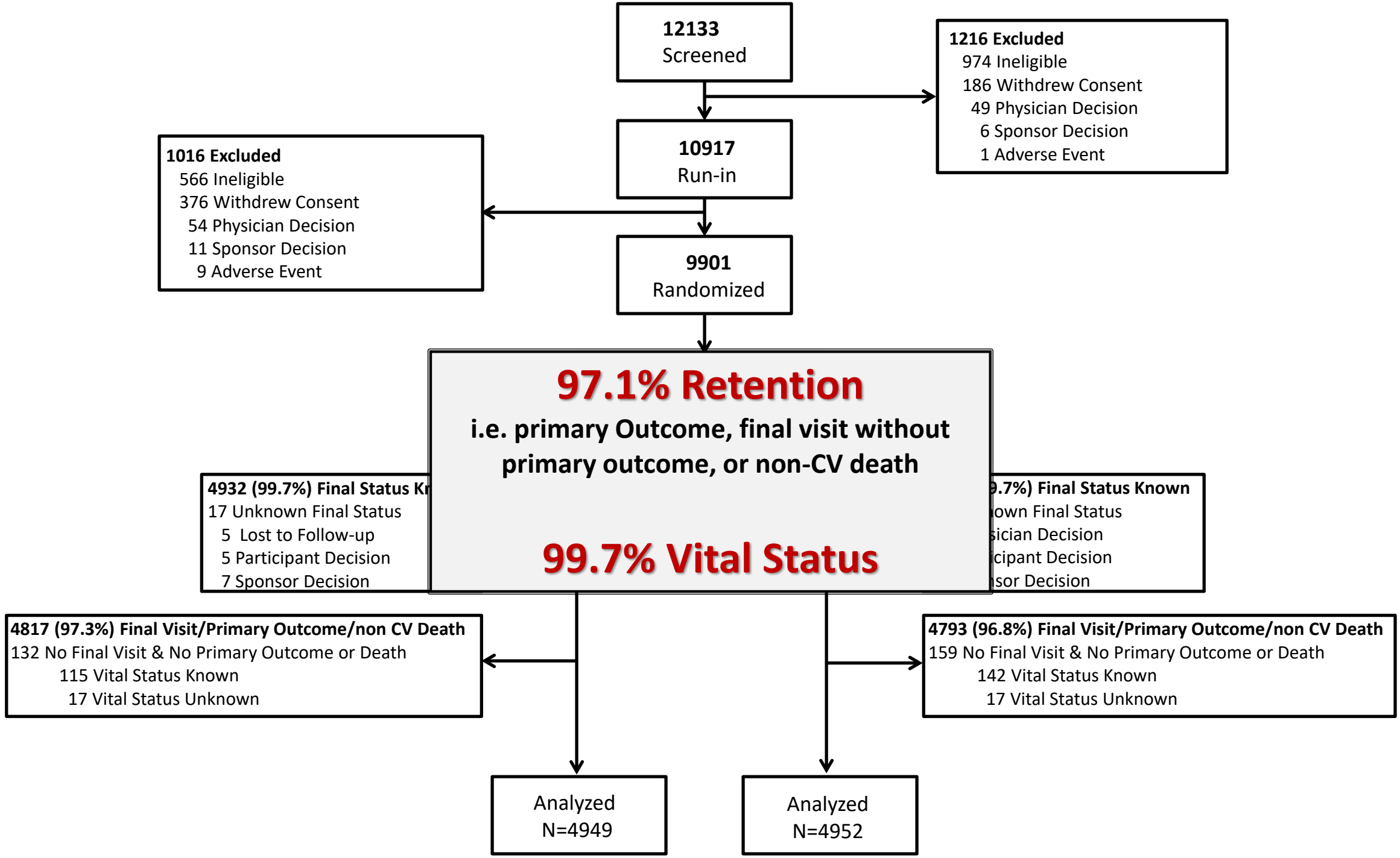
	All Participants N=9901	Dulaglutide N=4949	Placebo N=4952
ACE/ARB (%)	**81.5**	81.0	82.0
Beta Blocker (%)	**45.6**	45.2	45.9
Other Blood Pressure (%)	**56.6**	55.9	57.2
Statin (%)	**66.1**	66.3	66.0
Fibrate (%)	**9.1**	9.1	9.0
Antiplatelet (%)	**54.0**	53.8	54.1

REWIND
Dulaglutide CV Outcomes Trial

Follow-up Time, Retention, Adherence

Median follow-up period = 5.4 years (IQR 5.1, 5.9)

Person years of follow-up = 51820


12133
Screened
1216 Excluded
974 Ineligible
186 Withdrew Consent
49 Physician Decision
6 Sponsor Decision
1 Adverse Event
10917
Run-in
1016 Excluded
566 Ineligible
376 Withdrew Consent
54 Physician Decision
11 Sponsor Decision
9 Adverse Event
9901
Randomized
97.1% Retention
i.e. primary Outcome, final visit without primary outcome, or non-CV death
99.7% Vital Status
4932 (99.7%) Final Status Kn
17 Unknown Final Status
5 Lost to Follow-up
5 Participant Decision
7 Sponsor Decision
9.7%) Final Status Known
own Final Status
sician Decision
cipant Decision
sor Decision
4817 (97.3%) Final Visit/Primary Outcome/non CV Death
132 No Final Visit & No Primary Outcome or Death
115 Vital Status Known
17 Vital Status Unknown
4793 (96.8%) Final Visit/Primary Outcome/non CV Death
159 No Final Visit & No Primary Outcome or Death
142 Vital Status Known
17 Vital Status Unknown
Analyzed
N=4949
Analyzed
N=4952

REWIND
Dulaglutide CV Outcomes Trial

Study Drug Adherence

In 9901 Participants followed for a Median of 5.4 years

	Dulaglutide N = 4949	Placebo N =4952
% F/U Time on Study Drug	82.2%	83.1%

REWIND
Dulaglutide CV Outcomes Trial

Study Drug Adherence

In 9901 Participants followed for a Median of 5.4 years

	Dulaglutide N = 4949	Placebo N =4952
% F/U Time on Study Drug	82.2%	83.1%
Study Drug @ Last Visit	73.2%	71.1%

REWIND
Dulaglutide CV Outcomes Trial

Study Drug Adherence

In 9901 Participants followed for a Median of 5.4 years

	Dulaglutide N = 4949	Placebo N =4952
% F/U Time on Study Drug	82.2%	83.1%
Study Drug @ Last Visit	73.2%	71.1%
Never Stopped at All	57.7%	56.2%

REWIND
Dulaglutide CV Outcomes Trial

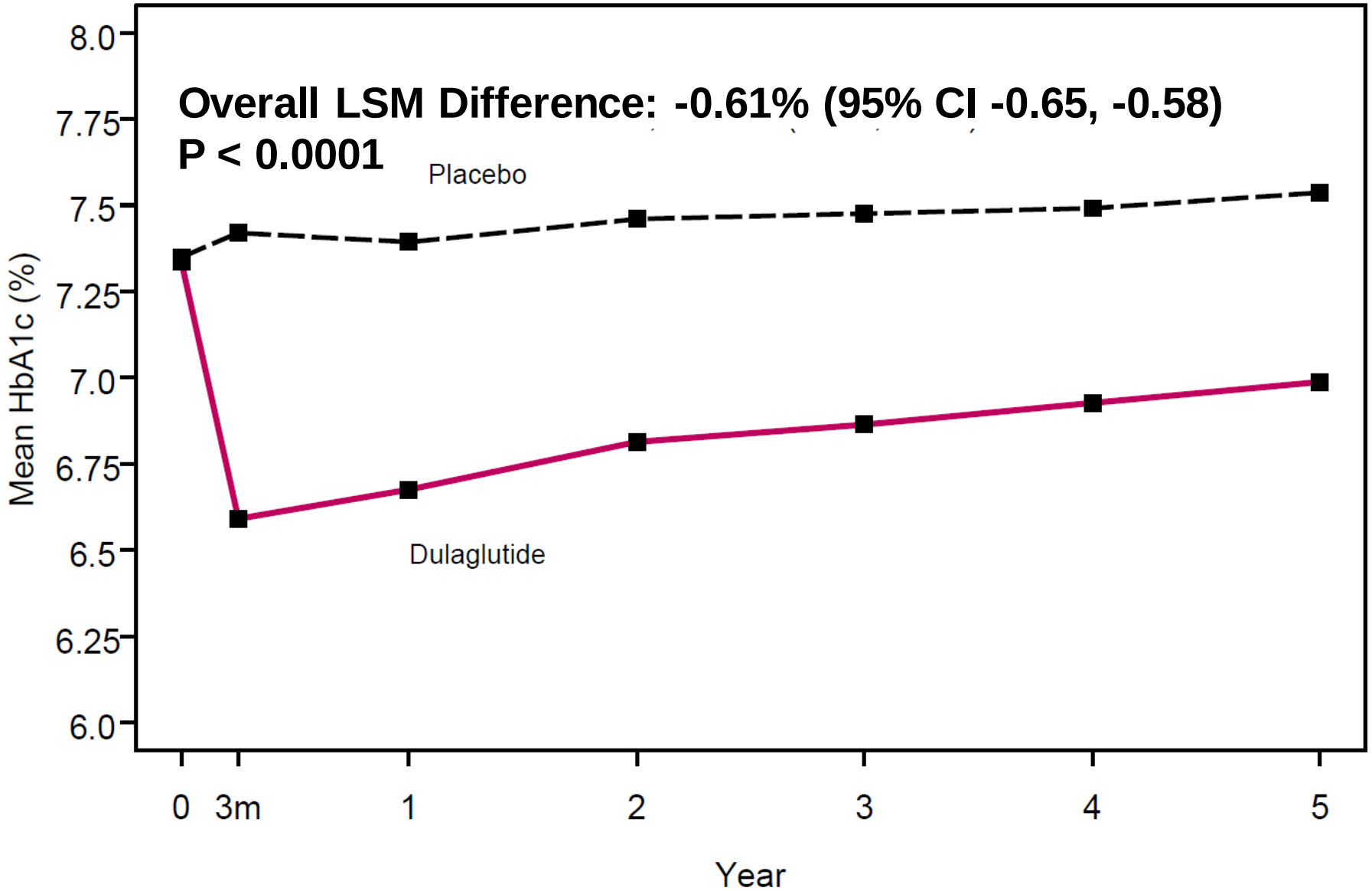
Study Drug Adherence

In 9901 Participants followed for a Median of 5.4 years

	Dulaglutide N = 4949	Placebo N =4952
% F/U Time on Study Drug	82.2%	83.1%
Study Drug @ Last Visit	73.2%	71.1%
Never Stopped at All	57.7%	56.2%
Stopped due to an AE	11.0%	7.5%

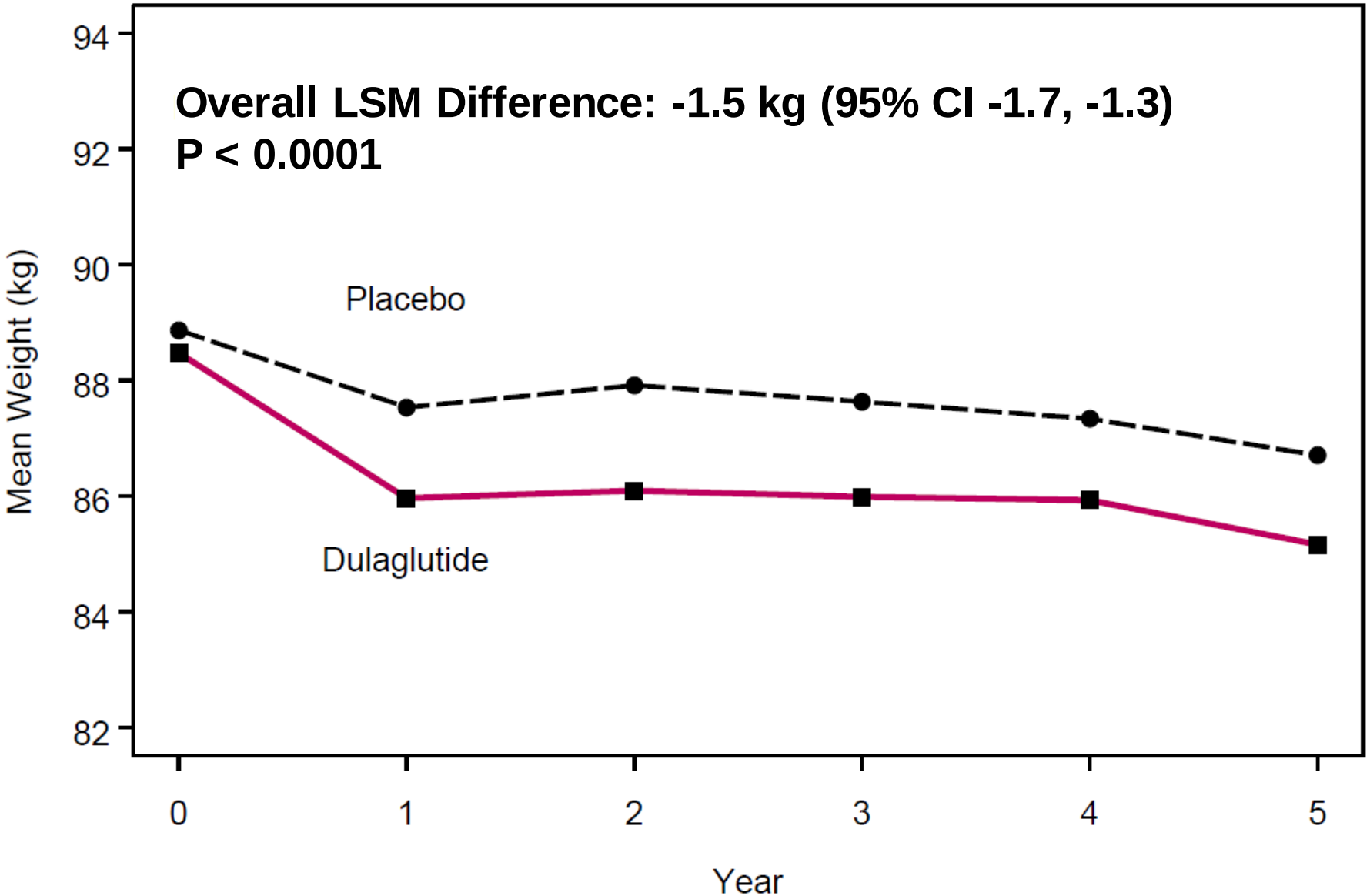
REWIND
Dulaglutide CV Outcomes Trial

Dulaglutide's Effect on HbA1c



REWIND
Dulaglutide CV Outcomes Trial

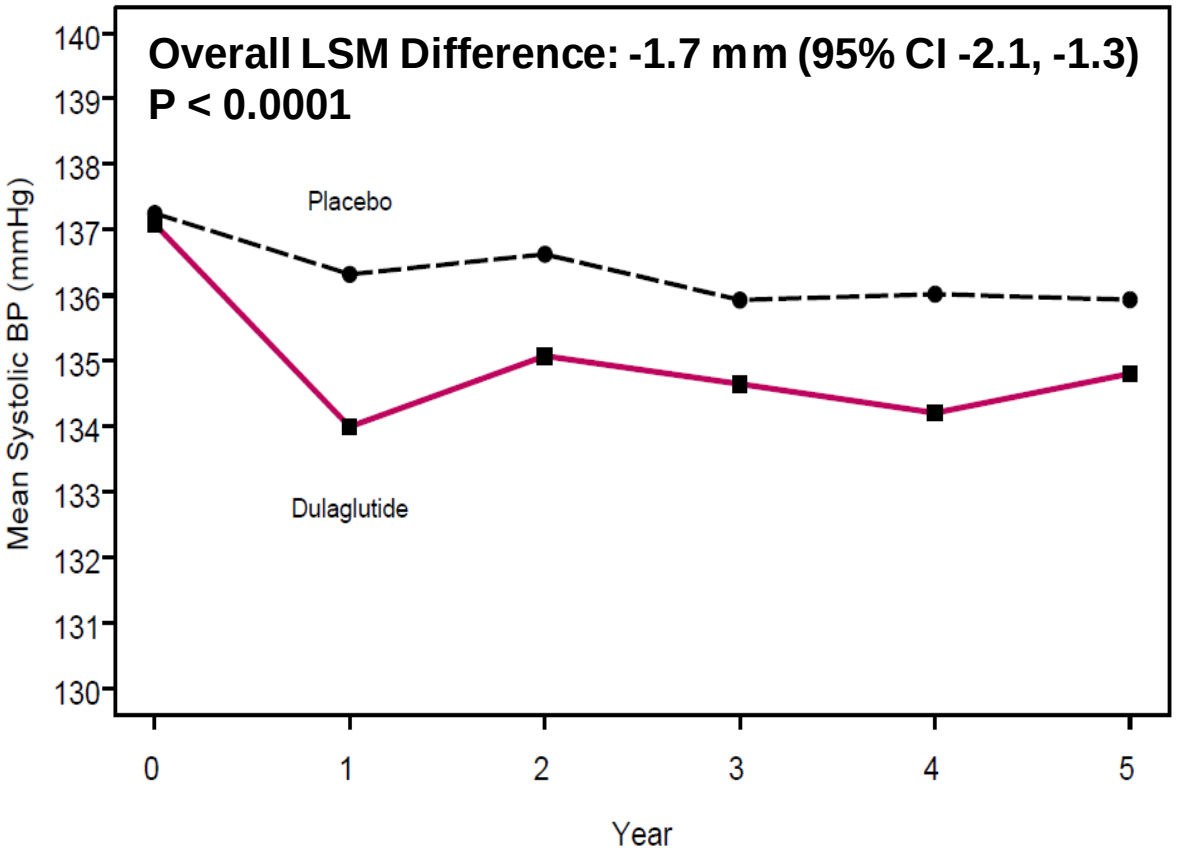
Dulaglutide's Effect on Weight



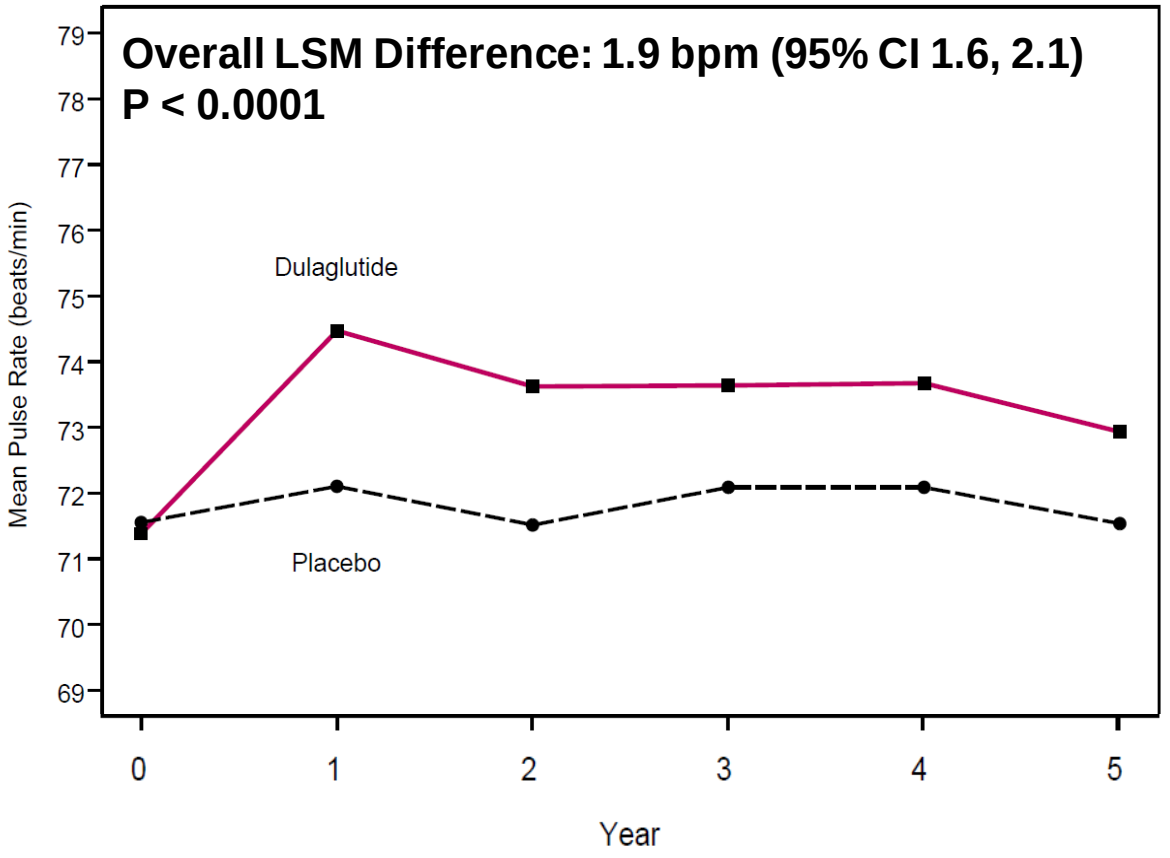
REWIND
Dulaglutide CV Outcomes Trial

Dulaglutide's Effect on SBP & Heart Rate

Systolic Blood Pressure

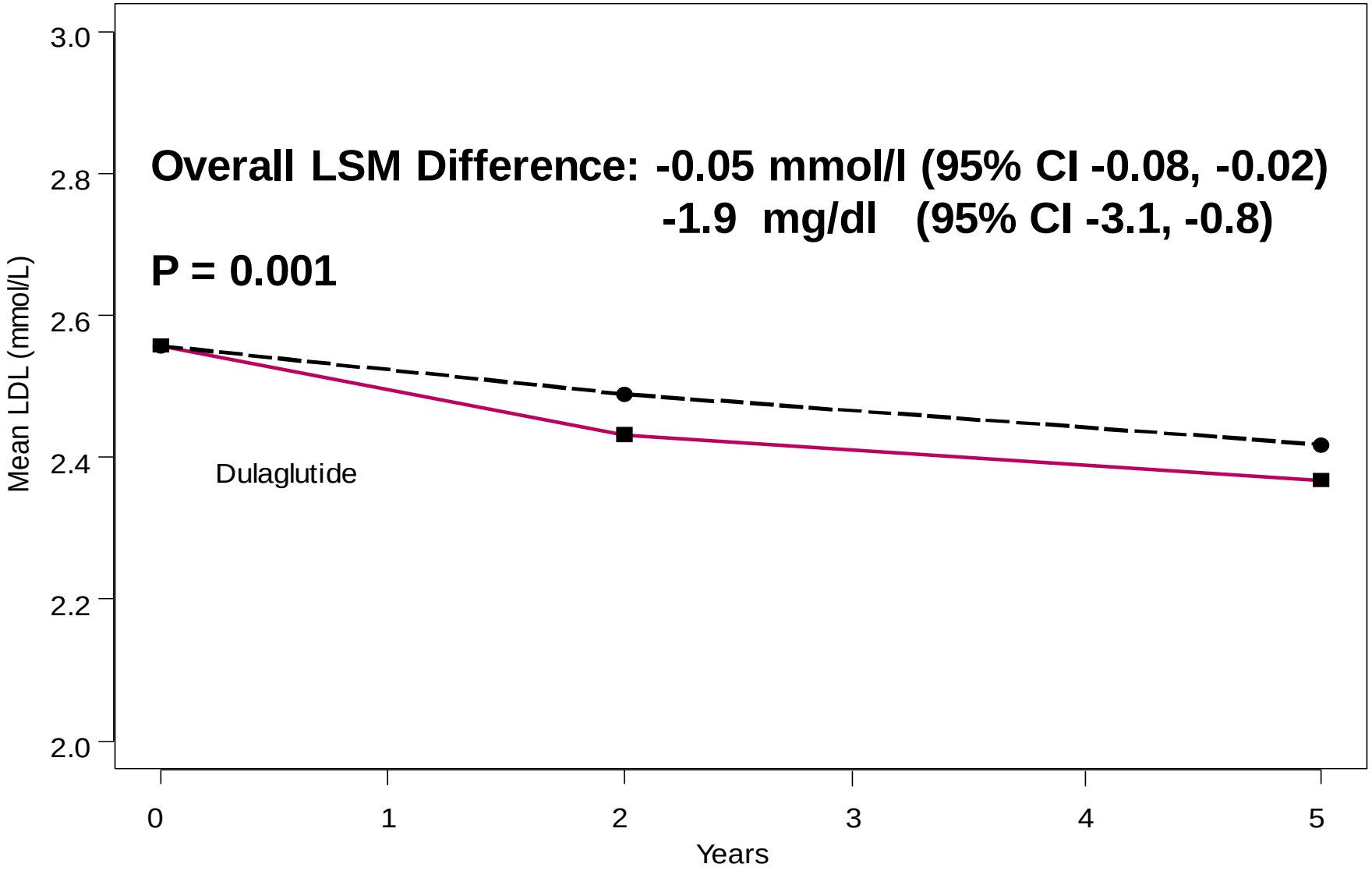


Heart Rate



REWIND
Dulaglutide CV Outcomes Trial

Dulaglutide's Effect on LDL Cholesterol



REWIND
Dulaglutide CV Outcomes Trial

Summary of Effect on Clinical Measures

Measurement	Dulaglutide	Placebo	Difference	P
HbA1c (%)	-0.46	0.16	-0.61	<0.0001
LDL (mmol/l)	-0.15	-0.09	-0.05	0.001
Weight (kg)	-2.95	-1.49	-1.46	<0.0001
Body Mass Index	-1.08	-0.55	-0.53	<0.0001
Waist:Hip (Men)	-0.007	-0.004	-0.003	0.04
Waist:Hip (Women)	-0.005	0.0	-0.005	0.009
Systolic BP (mm Hg)	-3.15	-1.44	-1.70	<0.0001
Mean BP (mm)	-2.34	-1.85	-0.49	<0.0001
Heart Rate (bpm)	2.95	1.09	1.87	<0.0001

REWIND
Dulaglutide CV Outcomes Trial

Research Question

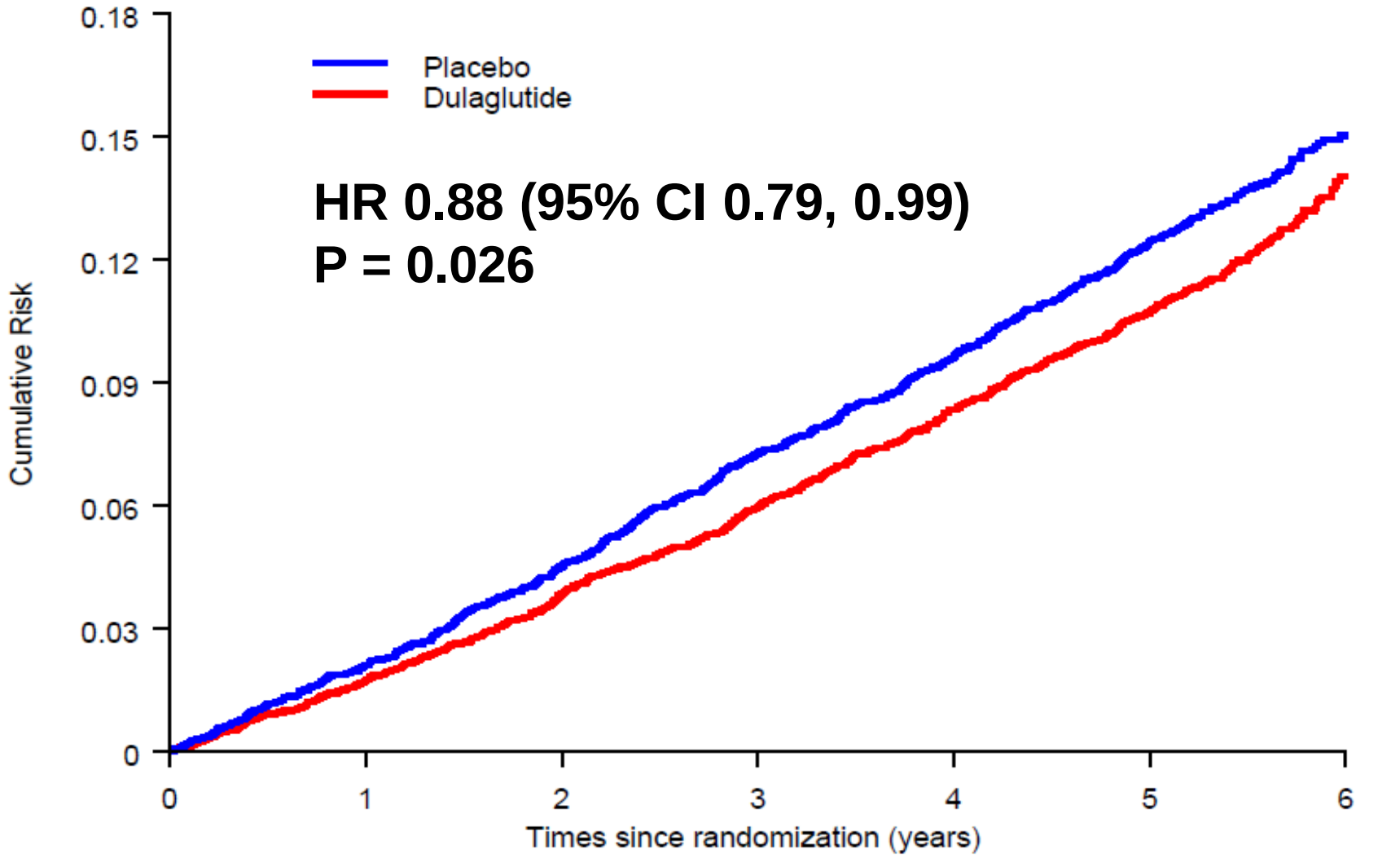
In men & women with established or newly detected type 2 diabetes who have additional CV risk factors…

… does adding a wkly sc. injection of the GLP-1 RA dulaglutide (1.5 mg) to the medical regimen safely reduce serious CV outcomes more than adding a wkly sc. placebo injection?

REWIND
Dulaglutide CV Outcomes Trial

Dulaglutide's Effect on the CV Composite

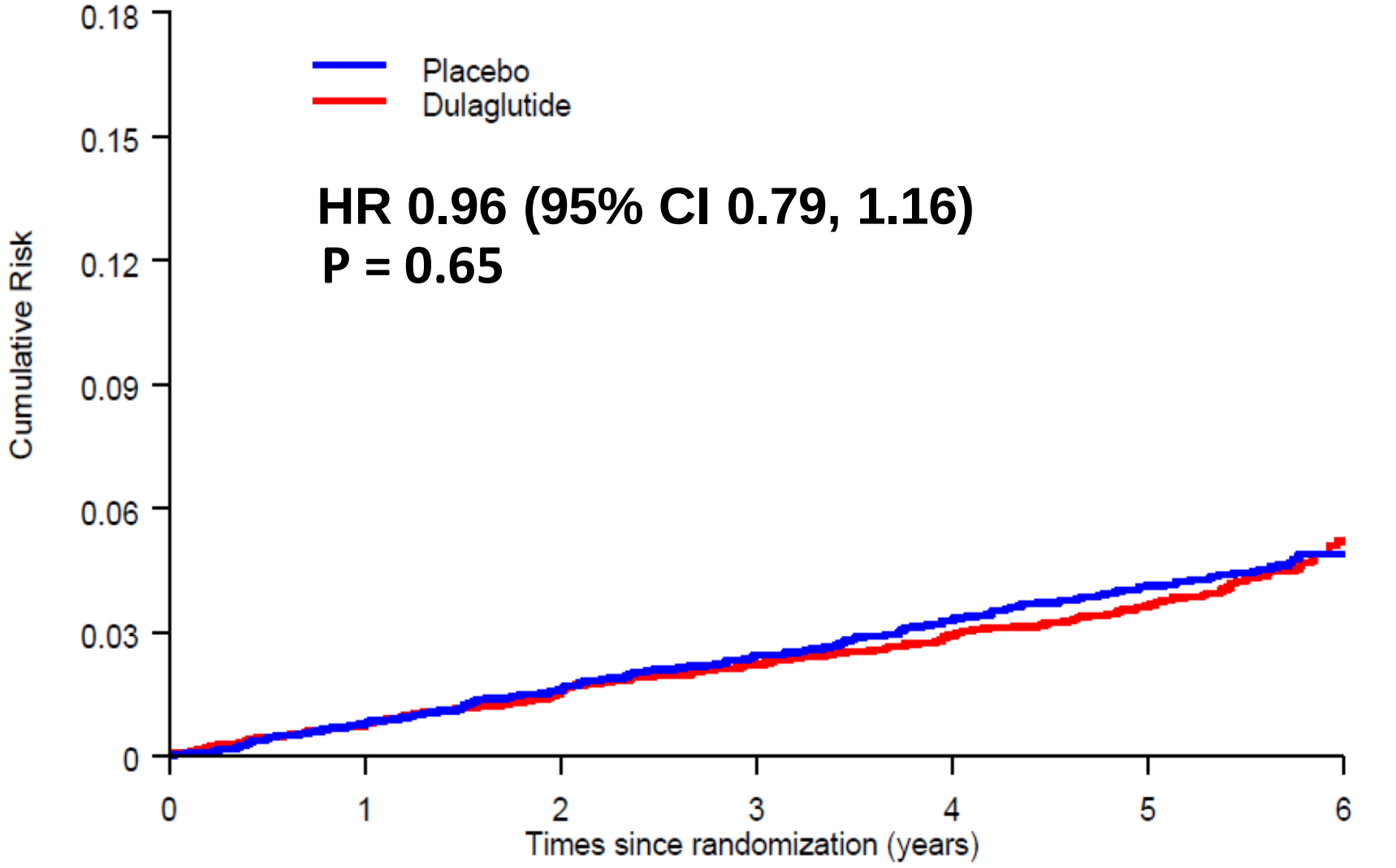
Primary Outcome: 1st Occurrence of Nonfatal MI, Nonfatal Stroke, CV Death



No. at Risk							
Placebo	4952	4791	4625	4437	4275	3575	742
Dulaglutide	4949	4815	4670	4521	4369	3686	741

REWIND
Dulaglutide CV Outcomes Trial

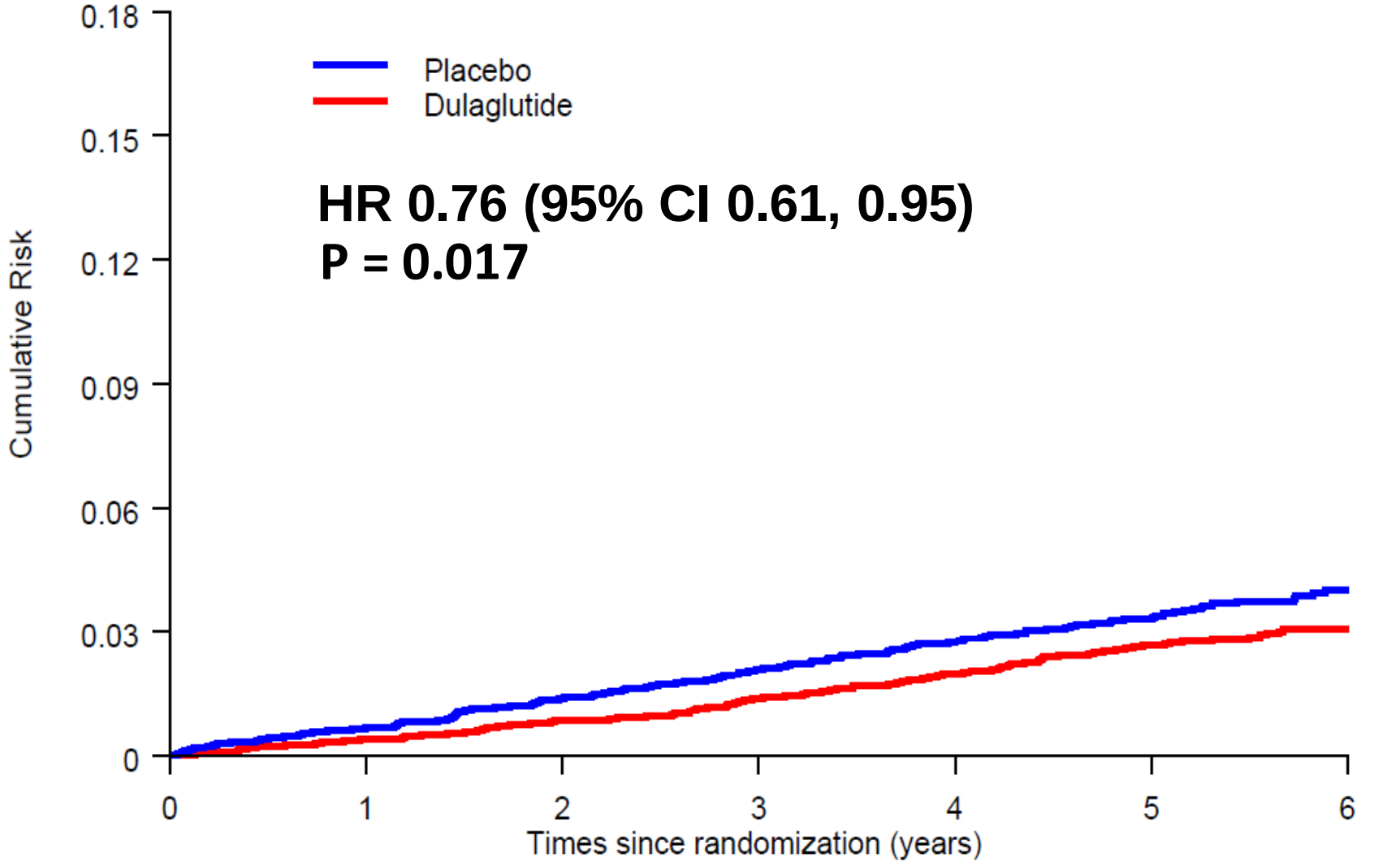
Dulaglutide's Effect on Nonfatal MI



No. at Risk							
Placebo	4952	4819	4680	4518	4372	3672	766
Dulaglutide	4949	4833	4705	4574	4443	3772	767

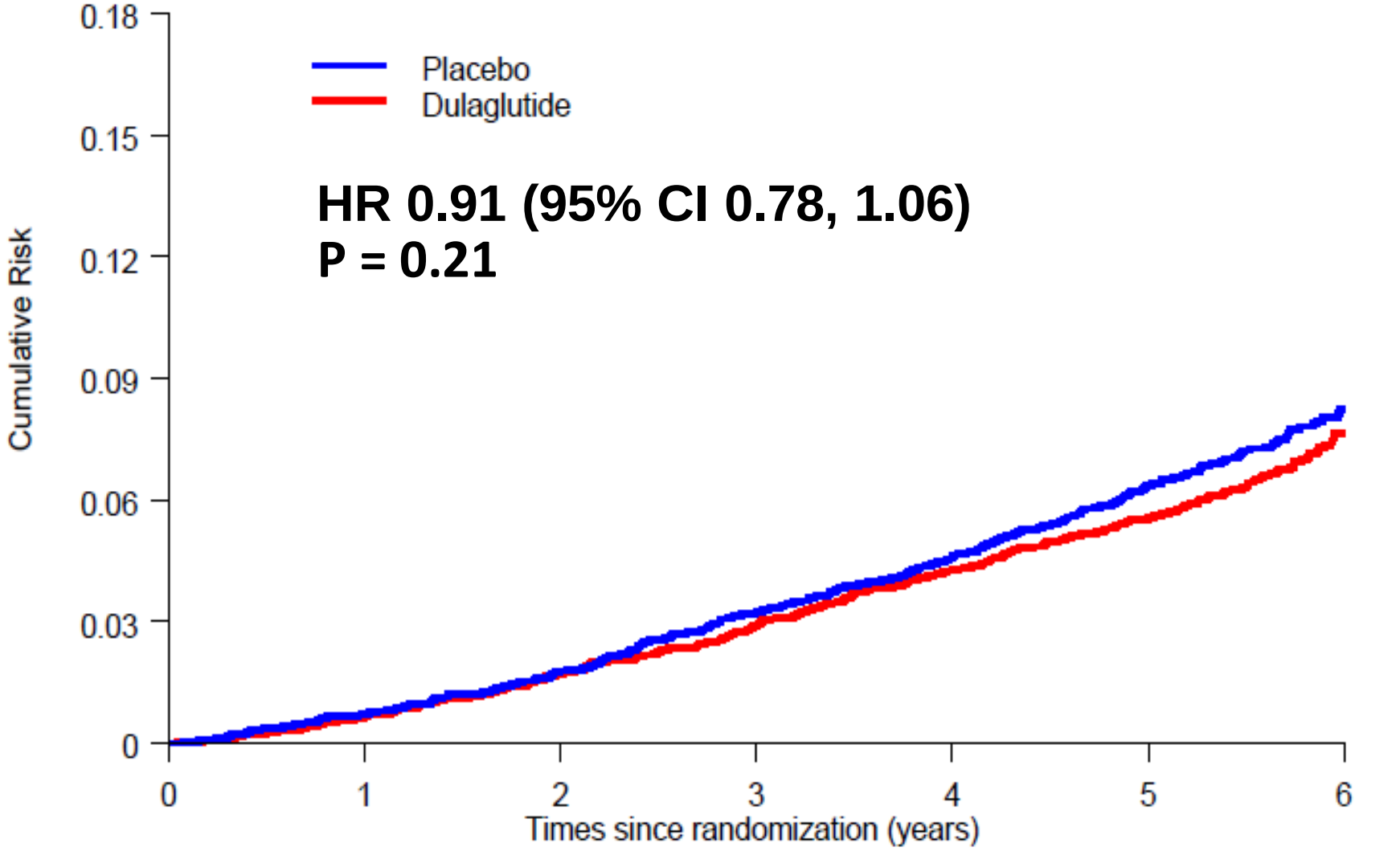
REWIND
Dulaglutide CV Outcomes Trial

Dulaglutide's Effect on Nonfatal Stroke



REWIND
Dulaglutide CV Outcomes Trial

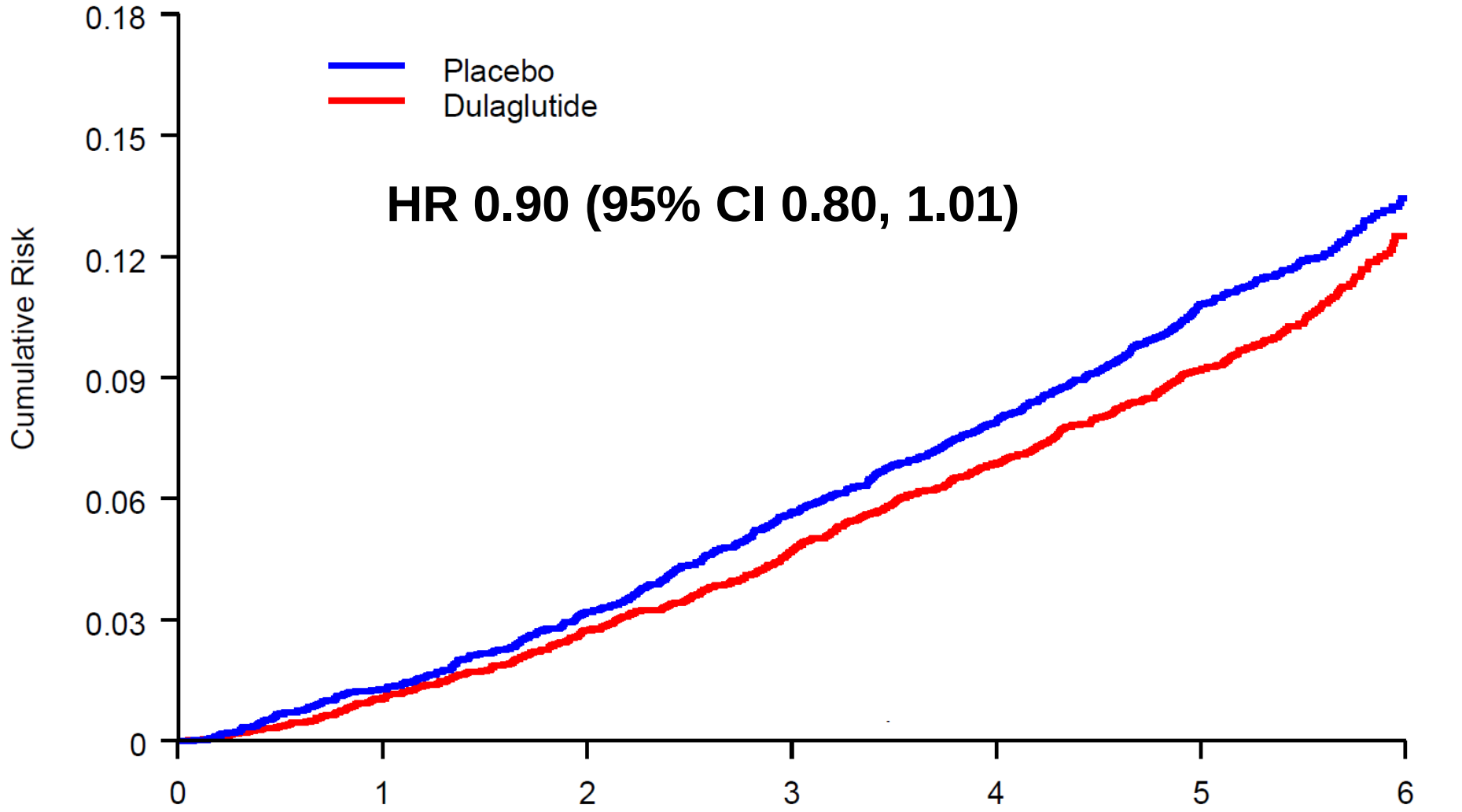
Dulaglutide's Effect on CV Death



No. at Risk							
Placebo	4952	4854	4748	4617	4499	3813	802
Dulaglutide	4949	4866	4773	4663	4556	3887	807

REWIND
Dulaglutide CV Outcomes Trial

Dulagutide's Effect on All-Cause Death

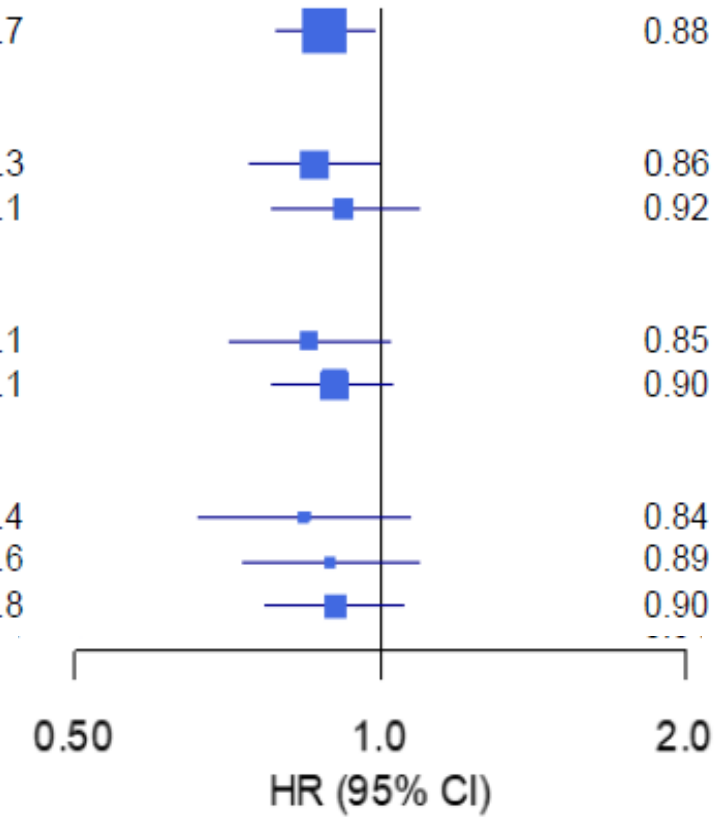


No. at Risk							
Placebo	4952	4854	4748	4617	4499	3813	802
Dulaglutide	4949	4866	4773	4663	4556	3887	807

REWIND
Dulaglutide CV Outcomes Trial

CV Composite in Prespecified Subgroups

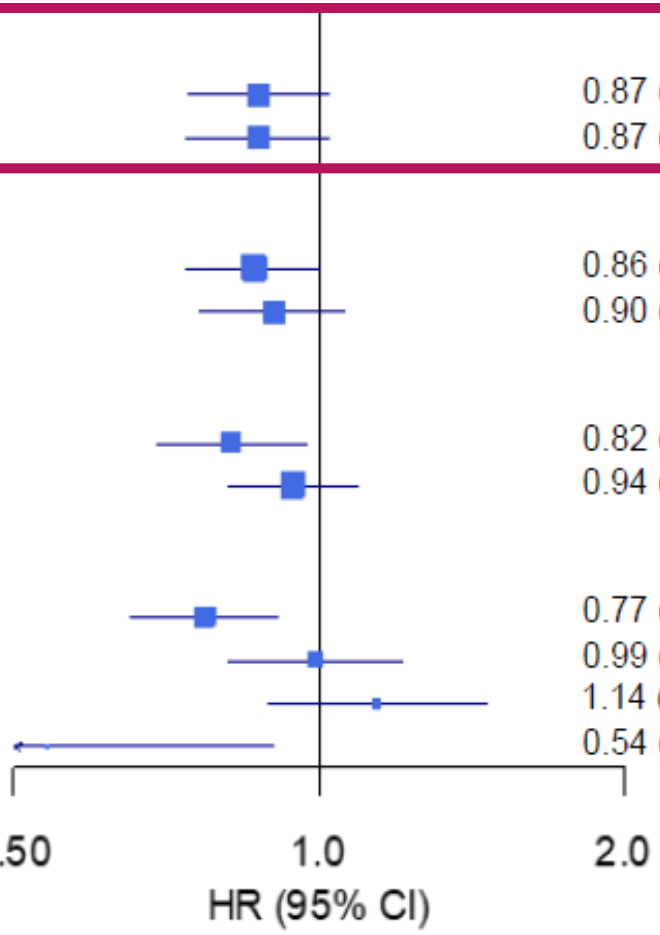
Subgroups	Dulaglutide Events/Total (%)	Dulaglutide Rate/100 py	Placebo Events/Total (%)	Placebo Rate/100 py	Hazard Ratio 95% CI	P value for Interaction
Overall	594 /4949 (12.0)	2.4	663 /4952 (13.4)	2.7	0.88 (0.79-0.99)	.
Age						
≥ 66 years	331 /2314 (14.3)	2.9	384 /2350 (16.3)	3.3	0.86 (0.74-1.00)	
< 66 years	263 /2635 (10.0)	1.9	279 /2602 (10.7)	2.1	0.92 (0.78-1.09)	0.571
Sex						
Female	218 /2306 (9.5)	1.8	249 /2283 (10.9)	2.1	0.85 (0.71-1.02)	
Male	376 /2643 (14.2)	2.8	414 /2669 (15.5)	3.1	0.90 (0.79-1.04)	0.598
Duration of Diabetes						
< 5 years	128 /1227 (10.4)	2.0	146 /1192 (12.2)	2.4	0.84 (0.66-1.06)	
5 - 10 years	174 /1446 (12.0)	2.3	196 /1476 (13.3)	2.6	0.89 (0.73-1.09)	
≥ 10 years	292 /2276 (12.8)	2.5	321 /2284 (14.1)	2.8	0.90 (0.77-1.06)	0.877



REWIND
Dulaglutide CV Outcomes Trial

CV Composite in Prespecified Subgroups

Subgroups	Dulaglutide Events/Total (%)	Dulaglutide Rate/100 py	Placebo Events/Total (%)	Placebo Rate/100 py	Hazard Ratio 95% CI	P value for Interaction
History of CVD						
Prior CVD	280 /1560 (17.9)	3.7	315 /1554 (20.3)	4.2	0.87 (0.74-1.02)	
No Prior CVD	277 /3093 (8.9)	1.7	317 /3128 (10.1)	2.0	0.87 (0.74-1.02)	0.970
Baseline HbA1c						
≥ 7.2%	328 /2610 (12.6)	2.5	373 /2603 (14.3)	2.9	0.86 (0.74-1.00)	
< 7.2%	263 /2329 (11.3)	2.2	289 /2334 (12.4)	2.4	0.90 (0.76-1.06)	0.746
BMI (kg/m^2)						
≥ 32	254 /2281 (11.1)	2.1	308 /2302 (13.4)	2.6	0.82 (0.69-0.96)	
< 32	340 /2667 (12.7)	2.5	355 /2650 (13.4)	2.7	0.94 (0.81-1.09)	0.214
Region						
Europe	248 /2174 (11.4)	2.2	315 /2165 (14.5)	2.9	0.77 (0.65-0.90)	
Latin America	191 /1511 (12.6)	2.6	190 /1510 (12.6)	2.6	0.99 (0.81-1.21)	
USA/Canada	132 /1032 (12.8)	2.4	117 /1039 (11.3)	2.1	1.14 (0.89-1.47)	
Asia Pacific	23 / 232 (9.9)	1.9	41 / 238 (17.2)	3.5	0.54 (0.32-0.89)	0.008



REWIND
Dulaglutide CV Outcomes Trial

CV Composite in Other Subgroups

	Dulaglutide (N/100 py)	Placebo (N/100 py)	HR (95%CI)	P Int
Overall	**2.35**	**2.66**	**0.88 (0.79, 0.99)**	
White	2.40	2.67	0.90 (0.79, 1.02)	0.77
Black	2.30	2.98	0.77 (0.51, 1.17)	
Asian	1.97	2.80	0.71 (0.40, 1.24)	
Other	2.23	2.42	0.92 (0.67, 1.28)	

REWIND
Dulaglutide CV Outcomes Trial

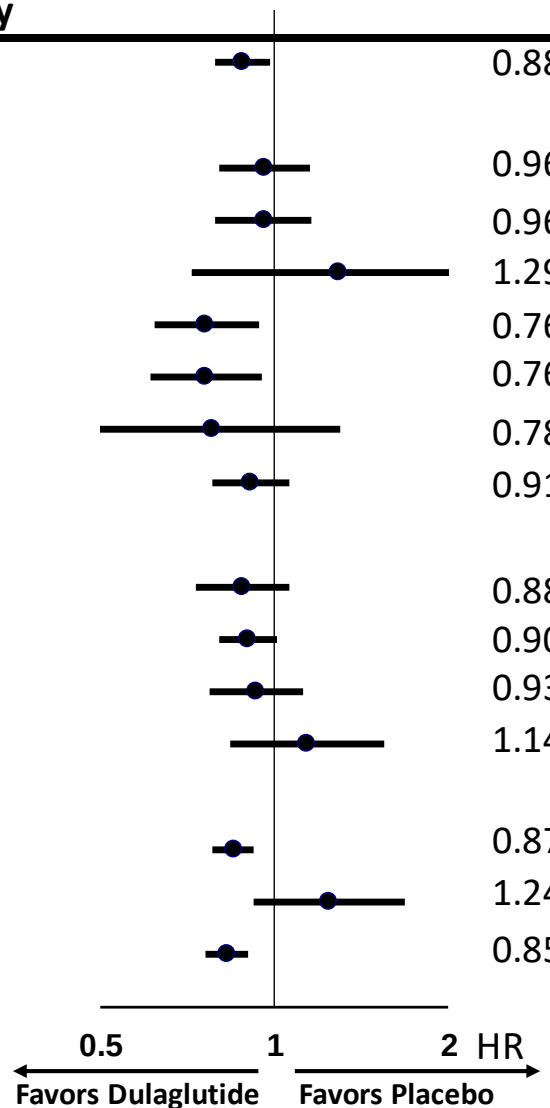
CV & Diabetes Medications at Last Visit

	Dulaglutide N = 4949	Placebo N = 4952
Metformin (%)	70	73
Sulfonylurea (%)	33	38
Insulin (%)	27	36
SGLT2i (%)	5	7
GLP-1 RA (%)	1	1
Thiazolidinedione (%)	2	2
Statin (%)	67	68
ARB or ACEi (%)	76	78
ASA (%)	50	51
Beta Blocker (%)	47	47

REWIND
Dulaglutide CV Outcomes Trial

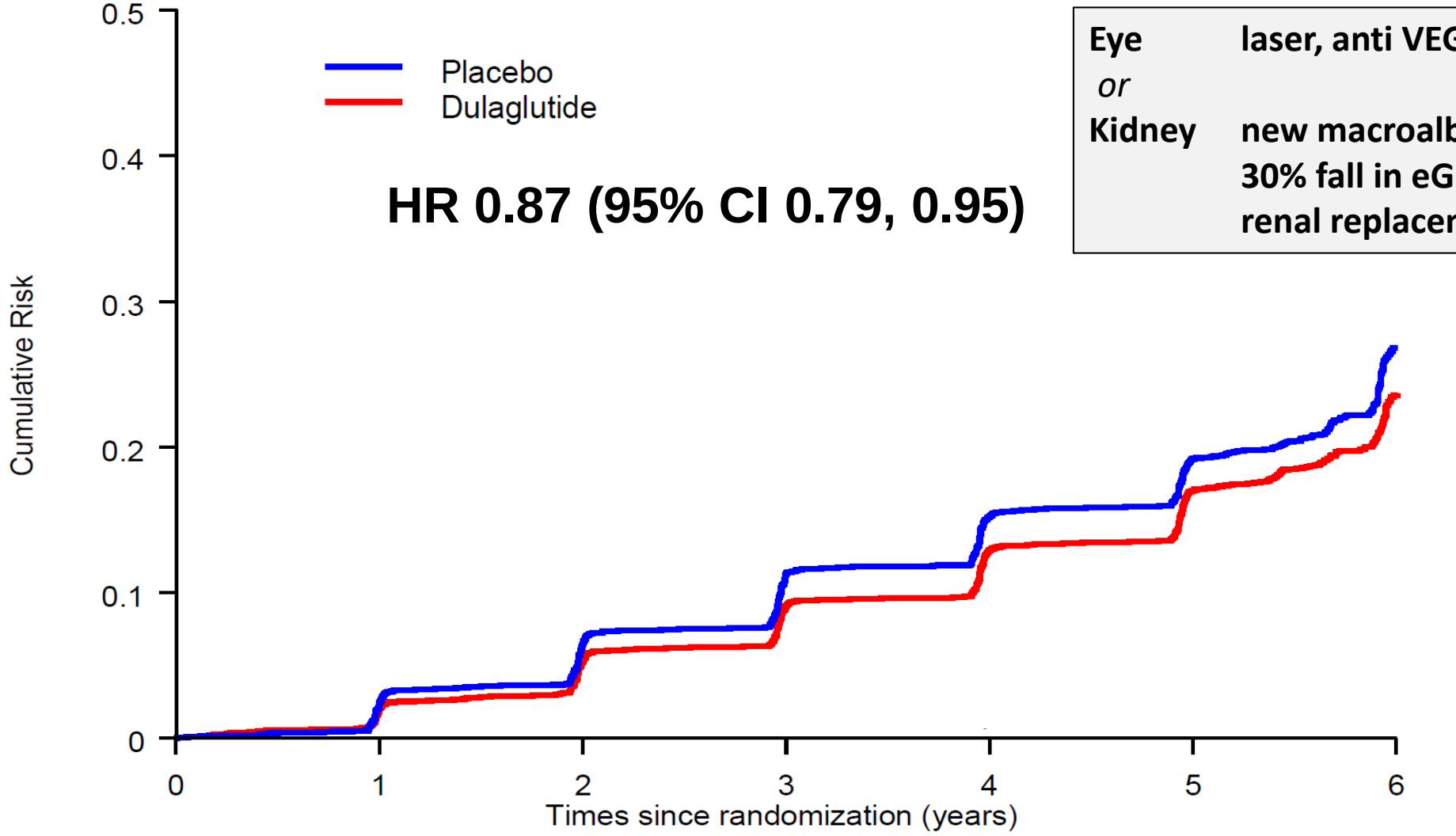
Summary: Dulaglutide & Outcomes

	Dulaglutide (N=4949)		Placebo (N=4952)		HR (95%CI)
	N (%)	N/100 py	N (%)	N/100 py	
Primary Composite	594 (12.0)	2.35	663 (13.4)	2.66	0.88 (0.79, 0.99)
MI	223 (4.5)	0.87	231 (4.7)	0.91	0.96 (0.79, 1.15)
Nonfatal MI	205 (4.1)	0.80	212 (4.3)	0.84	0.96 (0.79, 1.16)
Fatal MI	26 (0.5)	0.10	20 (0.4)	0.08	1.29 (0.72, 2.30)
Stroke	158 (3.2)	0.61	205 (4.1)	0.81	0.76 (0.62, 0.94)
Nonfatal Stroke	135 (2.7)	0.52	175 (3.5)	0.69	0.76 (0.61, 0.95)
Fatal Stroke	26 (0.5)	0.10	33 (0.7)	0.13	0.78 (0.47, 1.30)
CV Death	317 (6.4)	1.22	346 (7.0)	1.34	0.91 (0.78, 1.06)
Non-CV Death	219 (4.4)	0.84	246 (5.0)	0.95	0.88 (0.73, 1.06)
All Death	536 (10.8)	2.06	592 (12.0)	2.29	0.90 (0.80, 1.01)
Heart Failure	213 (4.3)	0.83	226 (4.6)	0.89	0.93 (0.77, 1.12)
Unstable Angina	88 (1.8)	0.34	77 (1.6)	0.30	1.14 (0.84, 1.54)
Composite Microvascular	910 (18.4)	3.76	1019 (20.6)	4.31	0.87 (0.79, 0.95)
Eye Outcome	95 (1.9)	0.40	76 (1.5)	0.30	1.24 (0.92, 1.68)
Renal Outcome	848 (17.1)	3.47	970 (19.6)	4.07	0.85 (0.77, 0.93)



REWIND
Dulaglutide CV Outcomes Trial

Microvascular Composite Outcome



Eye	**laser, anti VEGF, vitrectomy**
or	
Kidney	**new macroalbuminuria,** *or* **30% fall in eGFR,** *or* **renal replacement Rx**

No. at Risk							
Placebo	4952	4737	4441	4112	3846	3132	635
Dulaglutide	4949	4770	4530	4251	3989	3270	656

REWIND
Dulaglutide CV Outcomes Trial

Baseline Renal Characteristics

	All Participants N=9901	Dulaglutide N=4949	Placebo N=4952
Age (years)	**66.2**	66.2	66.2
Females (%)	**46.4**	46.6	46.1
White (%)	**75.7**	75.9	75.6
Prior CV Disease (%)	**31.5**	31.5	31.4
ACE/ARB (%)	**81.5**	81.0	82.0
Mean HbA1c (%)	**7.3**	7.3	7.4
Mean Blood Pressure (mm Hg)	**137/79**	137/78	137/79
Mean eGFR (ml/min/1.73m^2)	**77**	77	77
Median Urine ACR (mg/mmol)	**1.82**	1.80	1.88

REWIND
Dulaglutide CV Outcomes Trial

Baseline Renal Characteristics

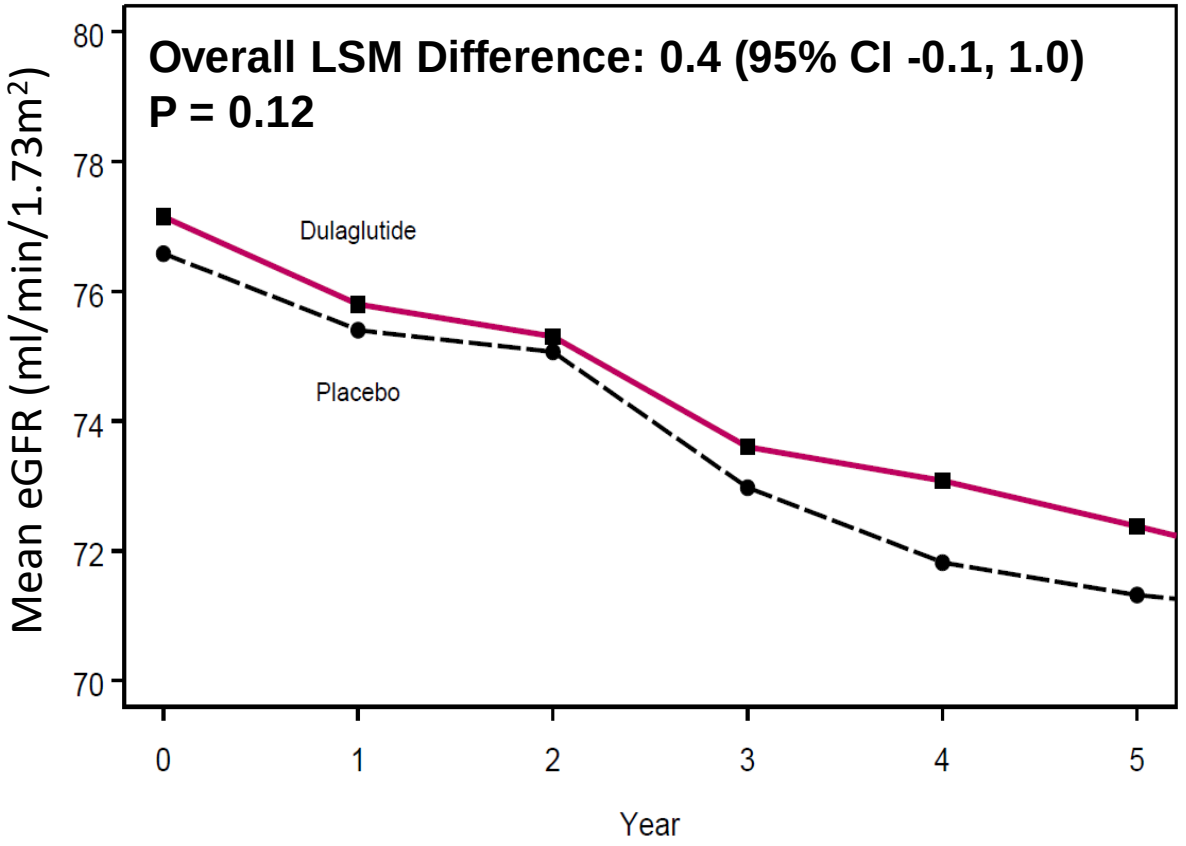
	All Participants N=9901	Dulaglutide N=4949	Placebo N=4952
eGFR ≥ 90 (%)	**25.6**	26.2	25.0
eGFR 60-89 (%)	**49.5**	49.2	49.9
eGFR 30-59 (%)	**21.1**	20.8	21.5
eGFR < 30 (%)	**1.1**	1.0	1.1
Albuminuria[a] (%)	**35.0**	34.5	35.5
Microalbuminuria[b] (%)	**27.0**	26.8	27.3
Macroalbuminuria[c] (%)	**8.0**	7.7	8.3
eGFR < 60 & albuminuria (%)	**10.5**	10.0	11.0
eGFR < 60 & no albuminuria (%)	**10.5**	10.5	10.5
eGFR ≥ 60 & albuminuria (%)	**24.0**	23.9	24.1
eGFR ≥ 60 & no albuminuria (%)	**47.0**	47.5	46.5

[a]ACR ≥3.39 mg/mmol (30 mg/g); [b]ACR 3.39 - 33.9 mg/mmol (30-300 mg/g); [c]ACR > 33.9 mg/mmol (300 mg/g)

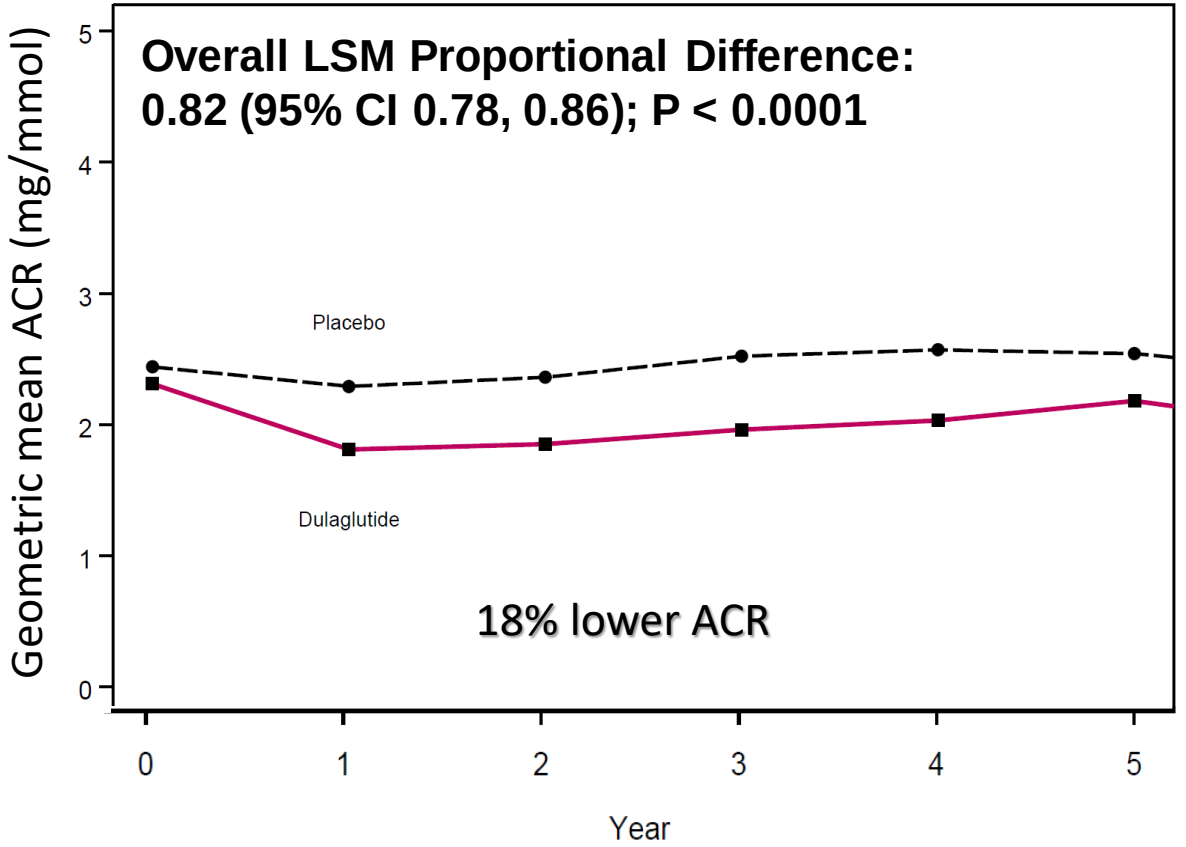
REWIND
Dulaglutide CV Outcomes Trial

Effect on eGFR & Urine Alb/Creatinine

Estimated GFR



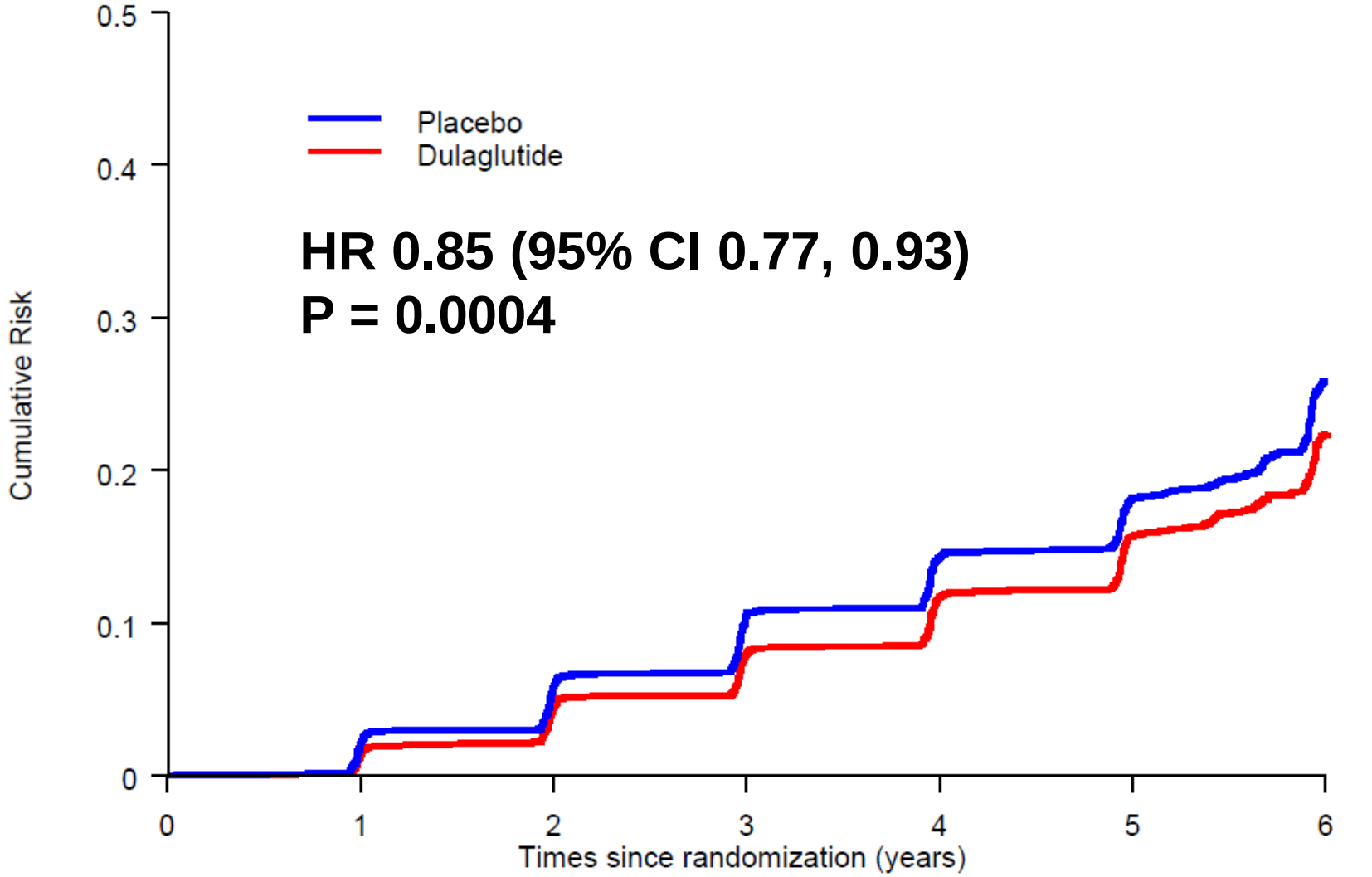
Urine Albumin/Creatinine



REWIND
Dulaglutide CV Outcomes Trial

Renal Composite Outcome

New Macroalbuminuria, 30% fall in eGFR, or Renal Replacement Rx

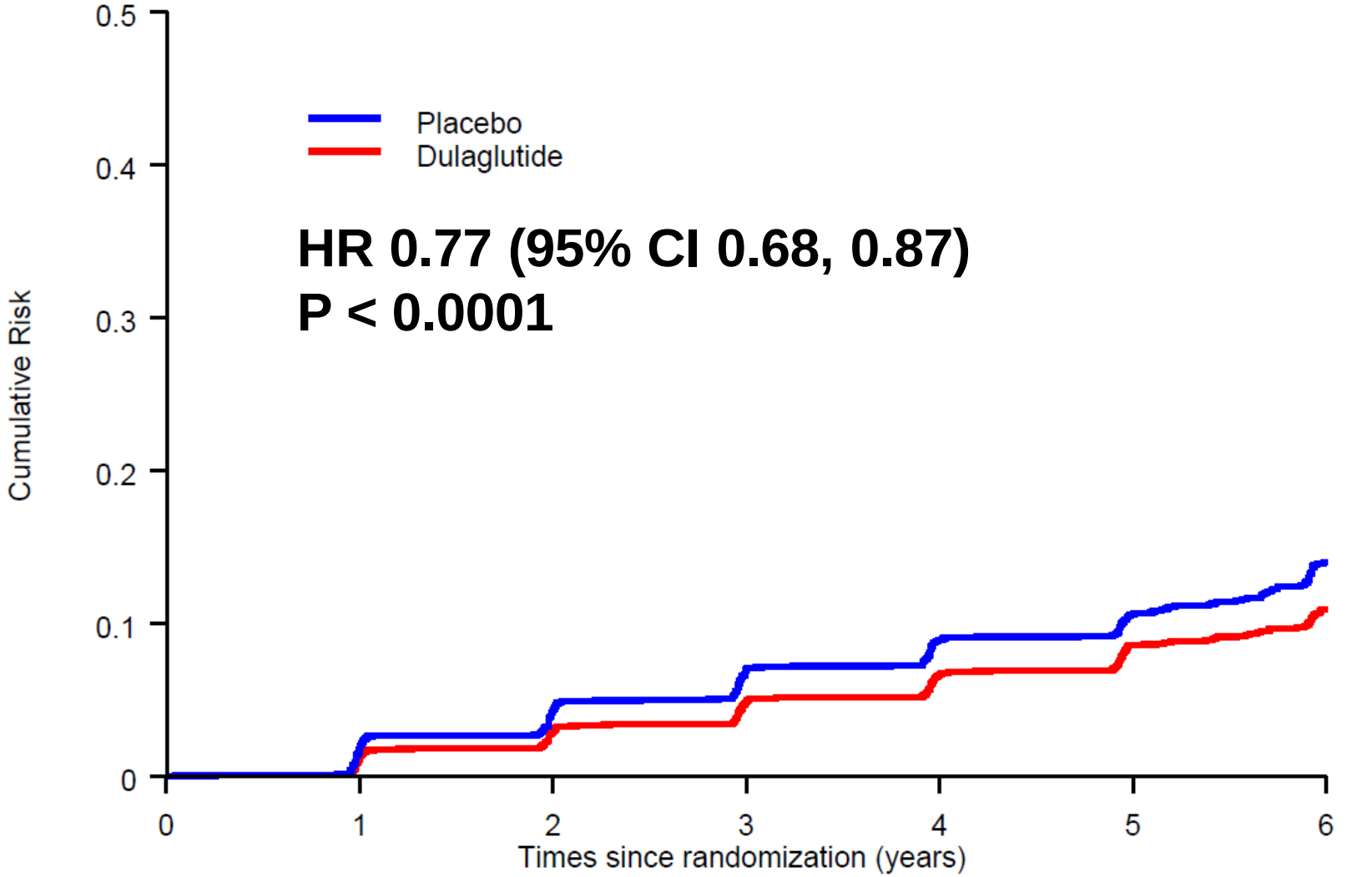


No. at Risk							
Placebo	4952	4756	4475	4145	3887	3169	641
Dulaglutide	4949	4798	4571	4303	4045	3320	667

REWIND
Dulaglutide CV Outcomes Trial

Development of New Macroalbuminuria

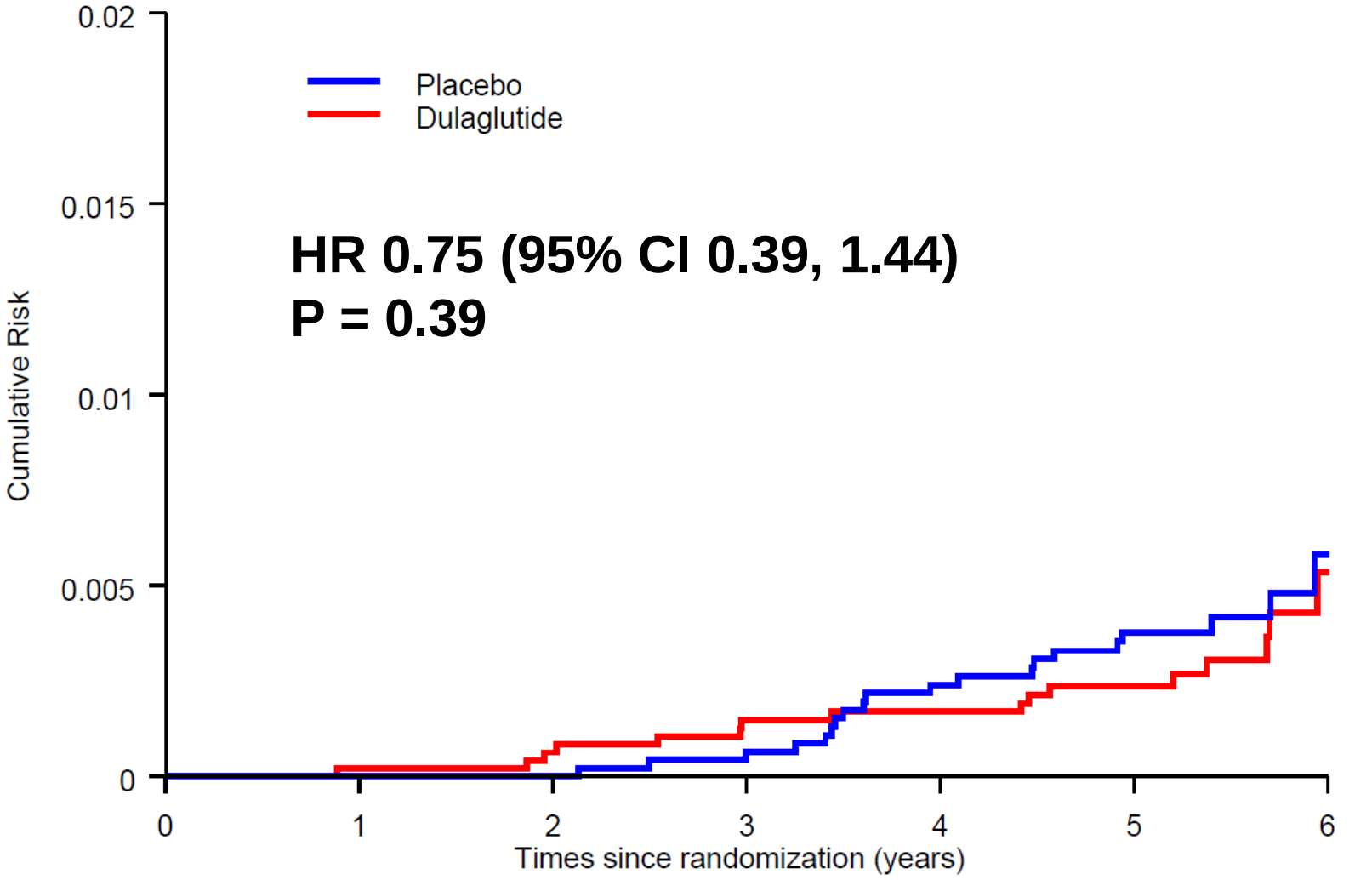
New Urine Albumin/Creatinine > 33.9 mg/mmol (300 mg/g)



No. at Risk							
Placebo	4952	4762	4542	4308	4127	3440	723
Dulaglutide	4949	4805	4636	4438	4263	3576	740

REWIND
Dulaglutide CV Outcomes Trial

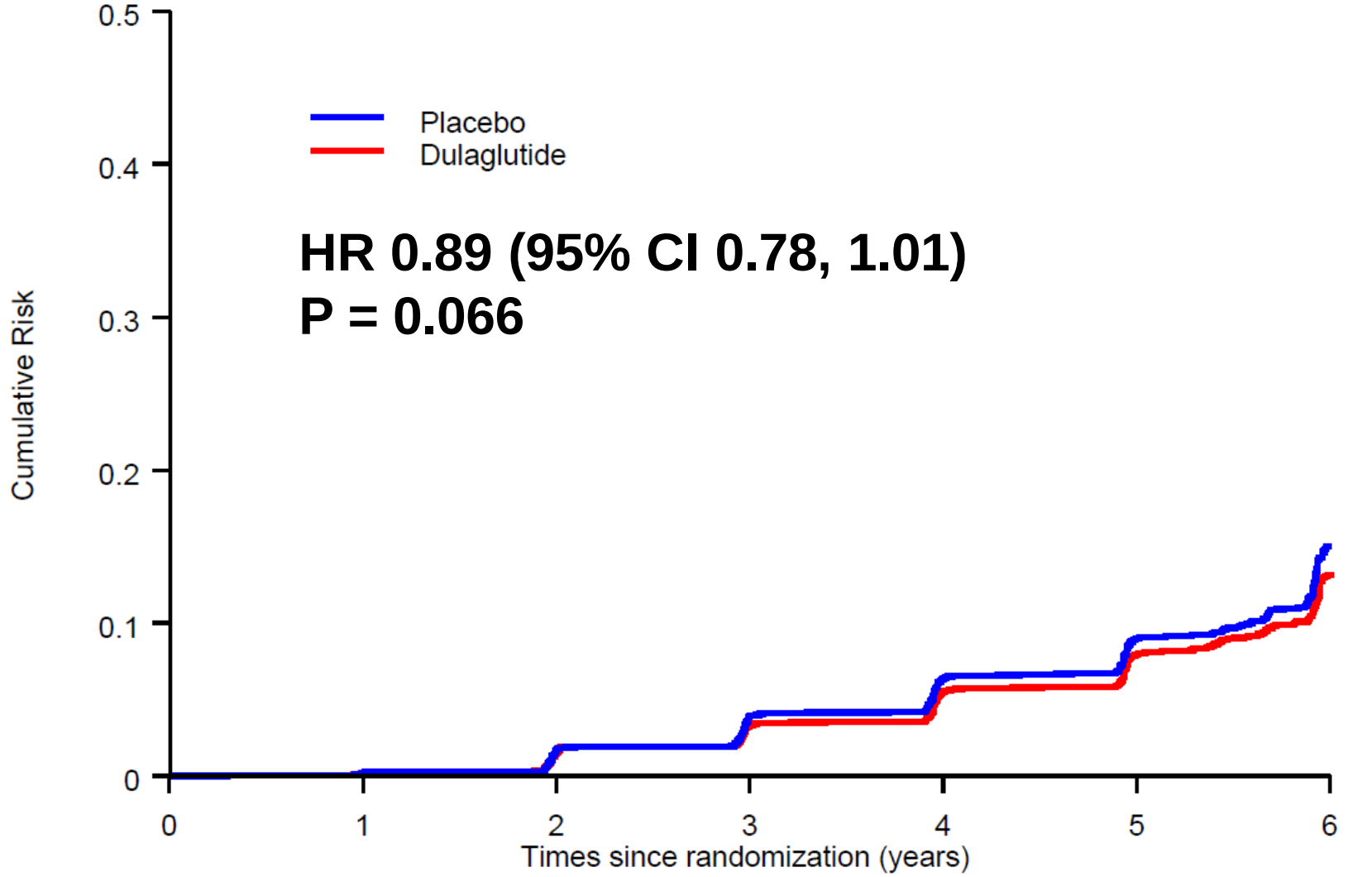
Renal Replacement Therapy



No. at Risk							
Placebo	4952	4854	4748	4614	4490	3805	797
Dulaglutide	4949	4865	4771	4659	4552	3882	807

REWIND
Dulaglutide CV Outcomes Trial

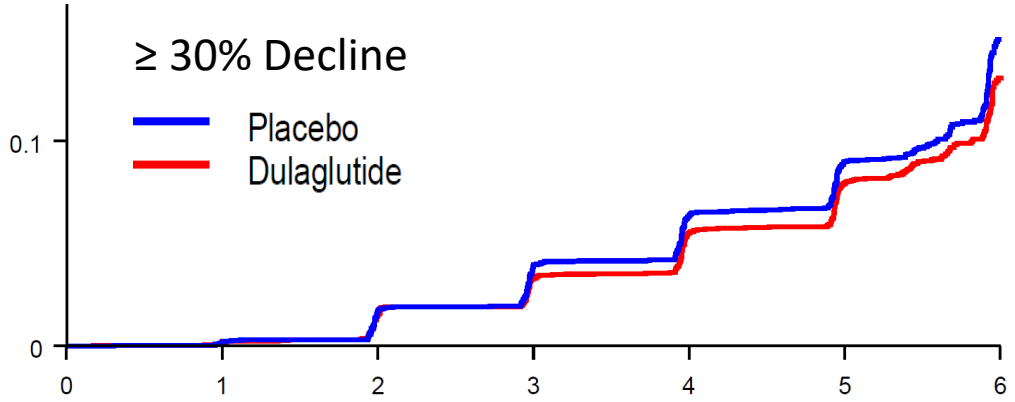
Sustained eGFR Decline ≥ 30%



No. at Risk							
Placebo	4952	4848	4672	4440	4220	3489	708
Dulaglutide	4949	4858	4707	4517	4315	3598	728

REWIND
Dulaglutide CV Outcomes Trial

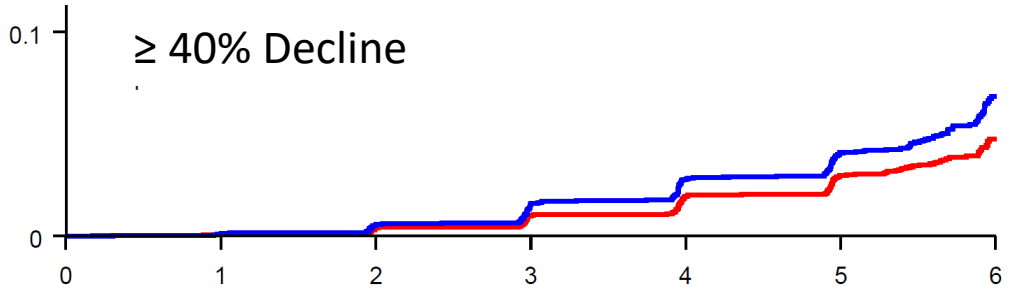
Sustained eGFR Decline ≥ 30, 40 & 50%



Sustained eGFR decline ≥ 30%

HR 0.89 (0.78, 1.01)

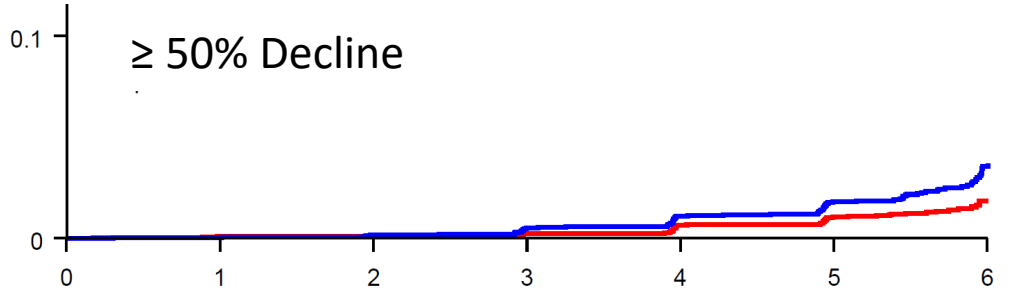
0.066



Sustained eGFR decline ≥ 40%

HR 0.70 (0.57, 0.85)

0.0004



Sustained eGFR decline ≥ 50%

HR 0.56 (0.41, 0.76)

0.0002

Sensitivity Analyses

REWIND
Dulaglutide CV Outcomes Trial

Dulaglutide & Renal Outcome: Subgroups

Subgroup	HR (95%CI)	P Int
Overall Effect	**0.85 (0.77, 0.93)**	**-**
eGFR < 60	0.88 (0.73, 1.05)	0.65
eGFR ≥ 60	0.83 (0.75, 0.93)	
No Albuminuria[a]	0.87 (0.75, 1.01)	0.66
Albuminuria	0.84 (0.74, 0.95)	
No ACEi/ARB use	0.97 (0.77, 1.22)	0.23
ACEi/ARB use	0.83 (0.75, 0.92)	

[a]ACR ≥3.39 mg/mmol (30 mg/g)

REWIND
Dulaglutide CV Outcomes Trial

Summary: Dulaglutide & Renal Outcomes

	Dulaglutide (N/100 py)	Placebo (N/100 py)	HR (95%CI)	P
Renal Composite Outcome	3.47	4.07	0.85 (0.77, 0.93)	0.0004
Components of Composite				
First Macroalbuminuria[a]	1.76	2.29	0.77 (0.68, 0.87)	<0.0001
Sustained Decline in eGFR of ≥ 30%	1.79	2.00	0.89 (0.78, 1.01)	0.066
Chronic Renal Replacement	0.06	0.08	0.75 (0.39, 1.44)	0.39
Serious Renal Adverse Event[b]	0.32	0.36	0.90 (0.67, 1.20)	0.46

[a]ACR > 33.9 mg/mmol (300 mg/g); [b]any reported AE linked to acute renal failure

REWIND
Dulaglutide CV Outcomes Trial

Summary: Dulaglutide & Renal Outcomes

	Dulaglutide (N/100 py)	Placebo (N/100 py)	HR (95%CI)	P
Renal Composite Outcome	3.47	4.07	0.85 (0.77, 0.93)	0.0004
Components of Composite				
First Macroalbuminuria[a]	1.76	2.29	0.77 (0.68, 0.87)	<0.0001
Sustained Decline in eGFR of ≥ 30%	1.79	2.00	0.89 (0.78, 1.01)	0.066
Chronic Renal Replacement	0.06	0.08	0.75 (0.39, 1.44)	0.39
Serious Renal Adverse Event[b]	0.32	0.36	0.90 (0.67, 1.20)	0.46
Sensitivity Analyses				
a) Sustained eGFR Decline ≥ 40%	0.66	0.93	0.70 (0.57, 0.85)	0.0004
Renal composite with this decline	2.36	3.10	0.76 (0.68, 0.84)	<0.0001
b) Sustained eGFR Decline ≥ 50%	0.24	0.42	0.56 (0.41, 0.76)	0.0002
Renal composite with this decline	1.99	2.66	0.74 (0.66, 0.84)	<0.0001

[a]ACR > 33.9 mg/mmol (300 mg/g); [b]any reported AE linked to acute renal failure

REWIND
Dulaglutide CV Outcomes Trial

Adverse Events of Special Interest

	Dulaglutide N = 4949	Placebo N= 4952	P
1st Study Drug Stopping	42.3%	43.8%	0.38
Acute Pancreatitis	0.5%	0.3%	0.11
Based on Imaging & Enzymes	0.1%	0.1%	0.71
Any Cancer	7.1%	7.0%	0.98
MTC or C-Cell Hyperplasia	1	0	0.32
Thyroid Cancer	0.1%	0.1%	0.21
Pancreatic Cancer	0.4%	0.2%	0.22

REWIND
Dulaglutide CV Outcomes Trial

Adverse Events of Special Interest

	Dulaglutide N = 4949	Placebo N= 4952	P
Serious Hepatic Event (%)	0.5	0.8	0.057
Serious Renal/Urinary Event (%)	1.7	1.9	0.46
Immune Reactions (%)	0.2	0.4	0.022
Serious GI Event*	2.4	2.4	0.87
SVT/CV Conduction Disorders (%)	4.4	3.9	0.26
Severe Hypoglycemia (%)	1.3	1.5	0.38

REWIND
Dulaglutide CV Outcomes Trial

Adverse Events of Special Interest

	Dulaglutide N = 4949	Placebo N= 4952	P
Serious Hepatic Event (%)	0.5	0.8	0.057
Serious Renal/Urinary Event (%)	1.7	1.9	0.46
Immune Reactions (%)	0.2	0.4	0.022
Serious GI Event*	2.4	2.4	0.87
SVT/CV Conduction Disorders (%)	4.4	3.9	0.26
Severe Hypoglycemia (%)	1.3	1.5	0.38
** All GI adverse events*	*47.4%*	*34.1%*	*<0.0001*

REWIND
Dulaglutide CV Outcomes Trial

Reported Serious Adverse Events

	Dulaglutide N = 4949	Placebo N= 4952	P*
Blood/Lymphatic System Disorders	1.2%	1.0%	0.33
Cardiac Disorders	11.1%	11.3%	0.71
Congenital, Familial & Genetic Disorders	0.2%	0.1%	0.22
Ear & Labyrinth Disorders	0.2%	0.3%	0.26
Endocrine Disorders	0.5%	0.2%	0.05
Eye Disorders	0.8%	1.1%	0.17
Gastrointestinal Disorders	4.8%	4.6%	0.70
General & Administration Site Conditions	1.8%	2.2%	0.17
Hepatobiliary Disorders	2.4%	2.1%	0.45
Immune System Disorders	0.0%	0.1%	0.16
Infections & Infestations	9.8%	10.4%	0.34
Injury, Poisoning & Procedural Complications	5.3%	5.3%	0.92

*P from chi square test

REWIND
Dulaglutide CV Outcomes Trial

Reported Serious Adverse Events

	Dulaglutide N = 4949	Placebo N= 4952	P*
Metabolism & Nutrition Disorders	3.4%	4.0	0.11
MSK & Connective Tissue Disorders	4.6%	4.4%	0.59
Neoplasms Benign, Malignant & Unspecified	6.7%	6.7%	0.97
Nervous System Disorders	4.4%	5.1%	0.13
Psychiatric Disorders	0.7%	0.9%	0.26
Renal & Urinary Disorders	3.2%	3.6%	0.24
Reproductive System & Breast Disorders	1.1%	0.8%	0.18
Respiratory, Thoracic, Mediastinal Disorders	3.0%	3.5%	0.16
Skin & Subcutaneous Tissue Disorders	0.7%	1.0%	0.06
Social Circumstances	1	1	
Vascular Disorders	2.9%	3.1%	0.60
Product Issues	0.1%	0.2%	0.11

*P from chi square test

REWIND
Dulaglutide CV Outcomes Trial

REWIND Findings in Context

	ELIXA	LEADER	SUSTAIN 6	EXSCEL	HARMONY
N	6068	9340	3297	14752	9463
Drug Tested	Lixi/d	Lira/d	Sema/wk	Exena/wk	Albig/wk
Prior CVD	100%	81%	83%	73%	100%
Mean Age	60 y	64 y	54 y	62 y	64 y
Women	30%	36%	39%	38%	31%
Median F/U	2.1 y	3.8 y	2.1 y	3.2 y	1.6 y
DM Duration	9.2 y	12.8 y	13.9 y	13.1 y	14.2 y
Baseline A1c	7.7%	8.7%	8.7%	8.1%	8.8%
Baseline eGFR	76	~75	~75	76	79
Insulin Use	39%	45%	58%	46%	59%

REWIND
Dulaglutide CV Outcomes Trial

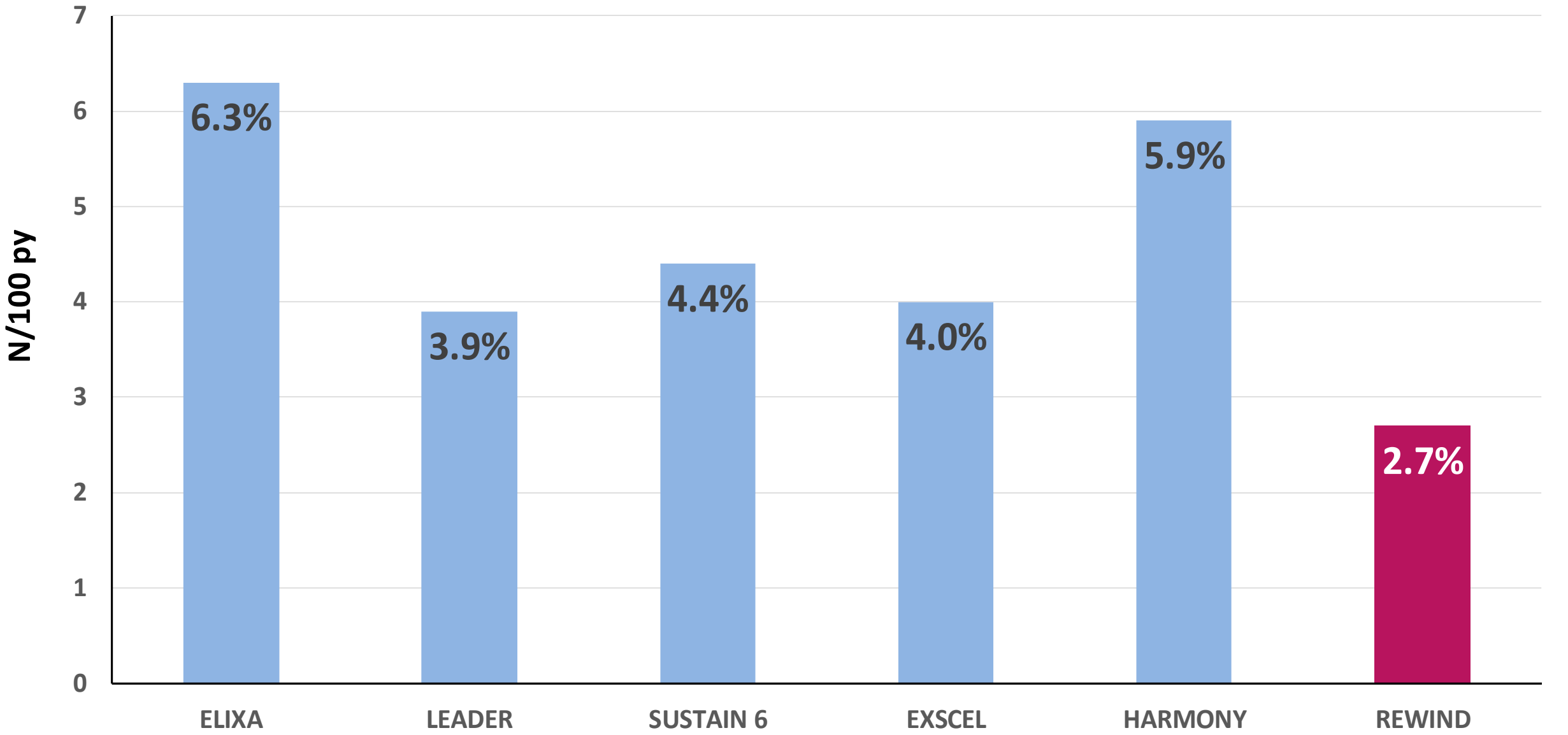
REWIND Findings in Context

	ELIXA	LEADER	SUSTAIN 6	EXSCEL	HARMONY	REWIND
N	6068	9340	3297	14752	9463	9901
Drug Tested	Lixi/d	Lira/d	Sema/wk	Exena/wk	Albig/wk	Dula/wk
Prior CVD	100%	81%				31%
Mean Age	60 y	64 y				66 y
Women	30%	36%				46%
Median F/U	2.1 y	3.8 y				5.4 y
DM Duration	9.2 y	12.8 y				10.5 y
Baseline A1c	7.7%	8.7%				7.3%
Baseline eGFR	76	~75	~75	76	79	77
Insulin Use	39%	45%	58%	46%	59%	24%

Participants were similar to the sorts of ambulatory patients with type 2 DM & CV risk factors who are routinely seen in clinical practice

REWIND
Dulaglutide CV Outcomes Trial

Annual Placebo MACE Rates by Trial



REWIND
Dulaglutide CV Outcomes Trial

Summary

- *In middle age & older men & women similar to people with type 2 DM in the general population with …*
  - *a broad range of glycemic control &*
  - *high use of at least one CV protective drug*

  … adding dulaglutide (1.5mg sc/wk) safely reduces CV outcomes for > 5 yrs
- *Similar benefits occur in:*
  - *men & women*
  - *higher & lower BMI*
  - *prior & no prior CVD*
  - *higher & lower A1c*

Population Health Research Institute
HEALTH THROUGH KNOWLEDGE

REWIND
Dulaglutide CV Outcomes Trial

Summary

- *Dulaglutide therapy for a median of 5.4 years also durably reduced*
  - *HbA1c by ~0.6%,*
  - *Weight by 1.5 kg, &*
  - *Systolic BP by 1.7 mm Hg*
- *Dulaglutide was taken for 82% of follow-up time & was well-tolerated with more GI AEs (as expected)*

REWIND
Dulaglutide CV Outcomes Trial

Conclusion

The addition of dulaglutide could be considered for both primary & secondary CV prevention in middle-aged patients with type 2 diabetes & cardiovascular risk factors

Population Health Research Institute
HEALTH THROUGH KNOWLEDGE

REWIND
Dulaglutide CV Outcomes Trial

Thanks to….

9901 REWIND participants & their families

All of the REWIND investigators, coordinators, & research staff worldwide

Population Health Research Institute
HEALTH THROUGH KNOWLEDGE

REWIND
Dulaglutide CV Outcomes Trial

Resources

Presentation Slides for download: *www.phri.ca/rewind*

2 Online Publications: *www.thelancet.com*

Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial

Dulaglutide and renal outcomes in type 2 diabetes: an exploratory analysis of the REWIND randomised, placebo-controlled trial

Population Health Research Institute
HEALTH THROUGH KNOWLEDGE