L'importanza di un trattamento precoce glico-cardio-metabolico nel paziente diabetico tipo 2

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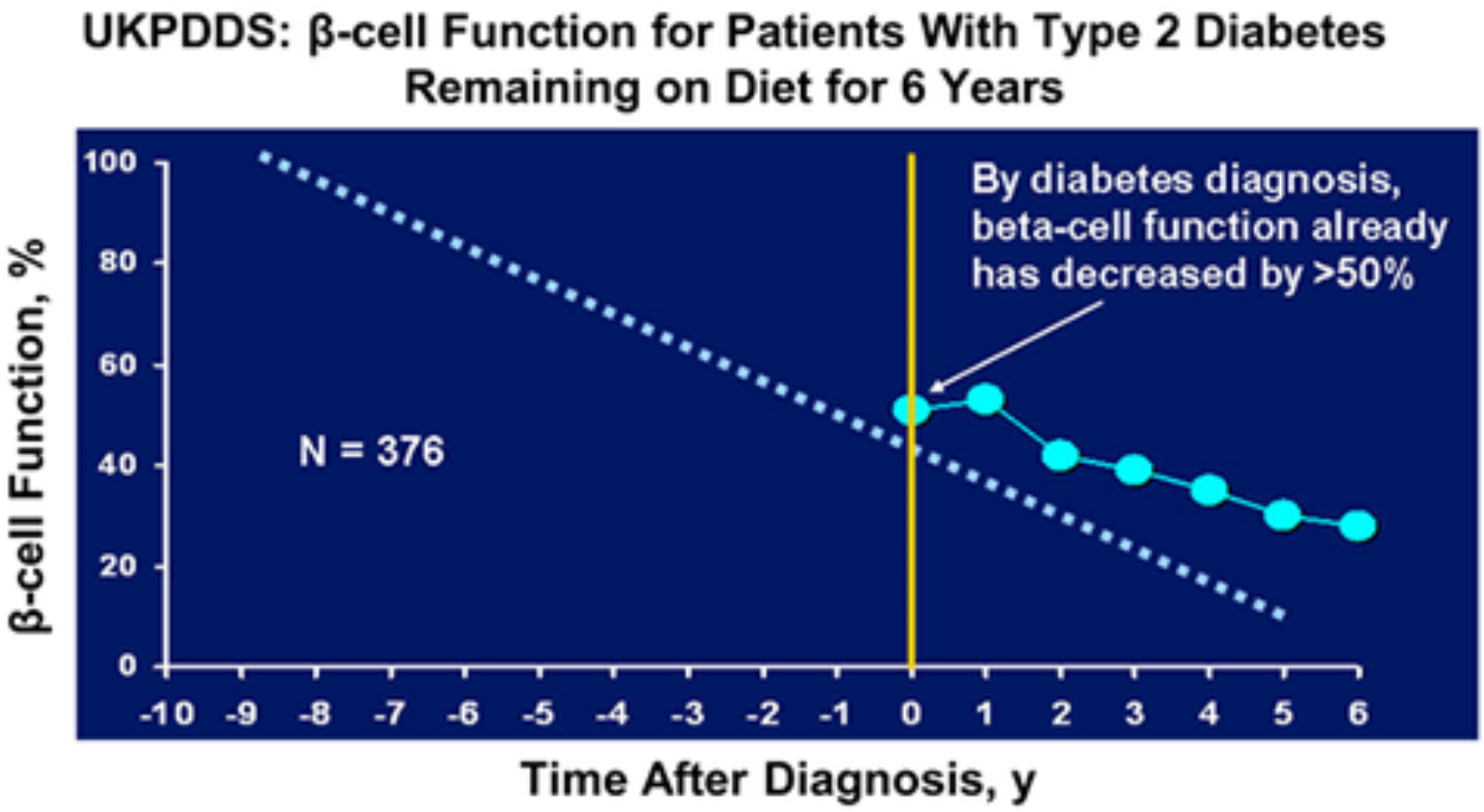
Università degli Studi di Bari "Aldo Moro"

Conflitti di interesse

Ai sensi dell'art. 3.3 sul conflitto di interessi, pag 17 del Regolamento Applicativo Stato-Regioni del 5/11/2009, dichiaro che negli ultimi 2 anni ho avuto rapporti diretti di finanziamento con i seguenti soggetti portatori di interessi commerciali in campo sanitario:

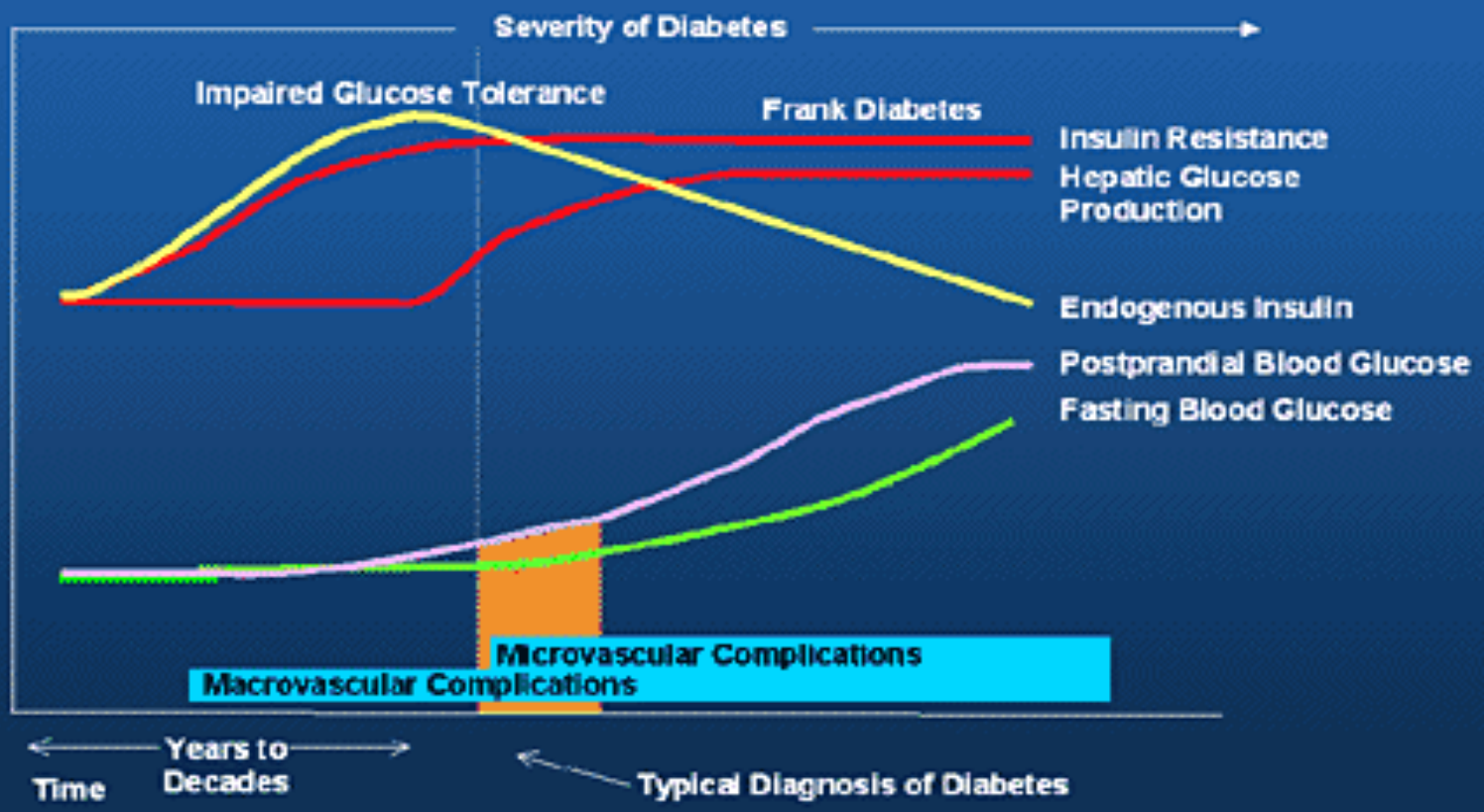
- serono
- ibsa
- novo nordisk
- shire

By the Time of Diagnosis, β-Cell Decline Exceeds 50%

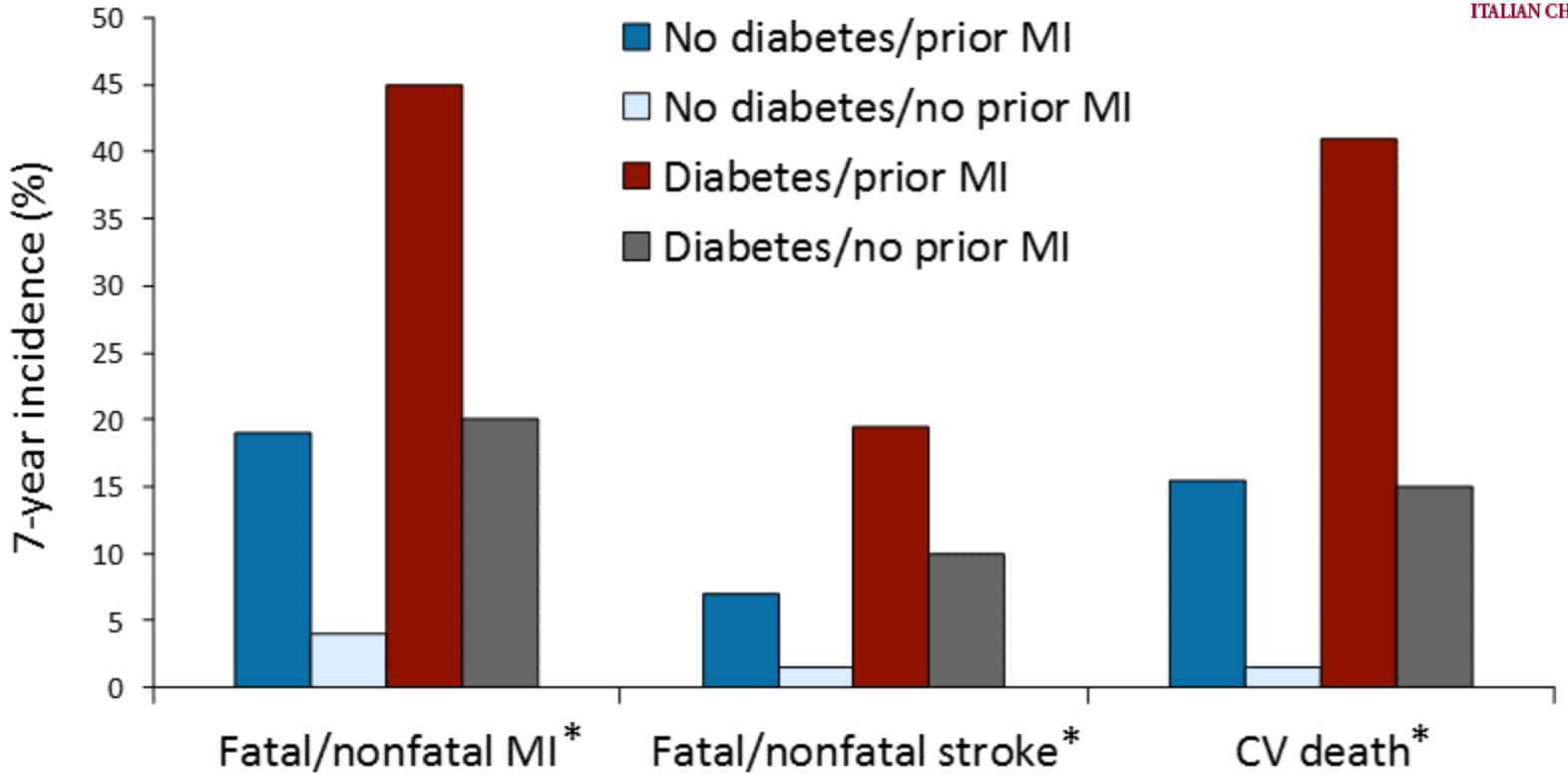


UKPDS Group. *Diabetes*. 1995;44:1249-1258.[1]

Natural History of Type 2 Diabetes



CV Risk in Patients With T2DM and No Prior MI Similar to Risk in People Without DM, but With Prior MI



*P < .001 for diabetes vs no diabetes.

Haffner SM et al. *N Engl J Med*. 1998;339:229-234.

Diabetes and Prior Coronary Heart Disease are Not Necessarily Risk Equivalent for Future Coronary Heart Disease Events

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BACKGROUND: For more than a decade, the presence of diabetes has been considered a coronary heart disease (CHD) "risk equivalent".

OBJECTIVE: The objective of this study was to revisit the concept of risk equivalence by comparing the risk of subsequent CHD events among individuals with or without history of diabetes or CHD in a large contemporary real-world cohort over a period of 10 years (2002 to 2011).

DESIGN: Population-based prospective cohort analysis.

PARTICIPANTS: We studied a cohort of 1,586,061 adult members (ages 30–90 years) of Kaiser Permanente Northern California, an integrated health care delivery system.

MAIN MEASUREMENTS: We calculated hazard ratios (HRs) from Cox proportional hazard models for CHD among four fixed cohorts, defined by prevalent (baseline) risk group: no history of diabetes or CHD (None), prior CHD alone (CHD), diabetes alone (DM), and diabetes and prior CHD (DM+CHD).

KEY RESULTS: We observed 80,012 new CHD events over the follow-up period (~10,980,800 person-years). After multivariable adjustment, the HRs (reference: None) for new CHD events were as follows: CHD alone, 2.8 (95 % CI, 2.7–2.85); DM alone 1.7 (95 % CI, 1.66–1.74); DM+CHD, 3.9 (95 % CI, 3.8–4.0). Individuals with diabetes alone had significantly lower risk of CHD across all age and sex strata compared to those with CHD alone (12.2 versus 22.5 per 1000 person-years). The risk of future CHD for patients with a history of either DM or CHD was similar only among those with diabetes of long duration (≥10 years).

CONCLUSIONS: Not all individuals with diabetes should be unconditionally assumed to be a risk equivalent of those with prior CHD.

INTRODUCTION

The prevalence and burden of diabetes mellitus remains high.[1] After Haffner et al.[2] reported that adults with diabetes had the same risk for future myocardial infarction (MI) as adults with previous MI and without diabetes, the Adult Treatment Panel (ATP) III guidelines in 2001 recommended that all individuals with diabetes be considered as "Coronary heart disease (CHD) risk equivalent".[3] However, the latest 2013 ACC/AHA assessment of risk guidelines considers diabetes as only one of the many variables in its risk assessment equation.[4]

The assertion that all patients with diabetes are CHD equivalent has been controversial.[5,6] Existing evidence is based on relatively small studies with various limitations. Some studies were limited to a single gender,[7–9] while others were based on self-reported diagnosis of diabetes.[10,11] Some lacked the ability to adjust for important confounding risk factors.[12,13] Most of the studies have comprised cohorts from the 1990s,[5] and only a few studies have been able to evaluate the impact of the duration of diabetes.[7,8,14] There is also a paucity of data among relatively young (30–40 years) patients with diabetes. For all these reasons, updated evidence from a contemporary population is needed to inform our understanding of CHD risk in diabetes patients.

We compared the risk of a CHD event among individuals with and without a history of diabetes or CHD among a large (n=1,586,061), ethnically diverse, contemporary real-world cohort of patients in usual care over a period of 10 years (January 1, 2002, through December 31, 2011).

METHODS

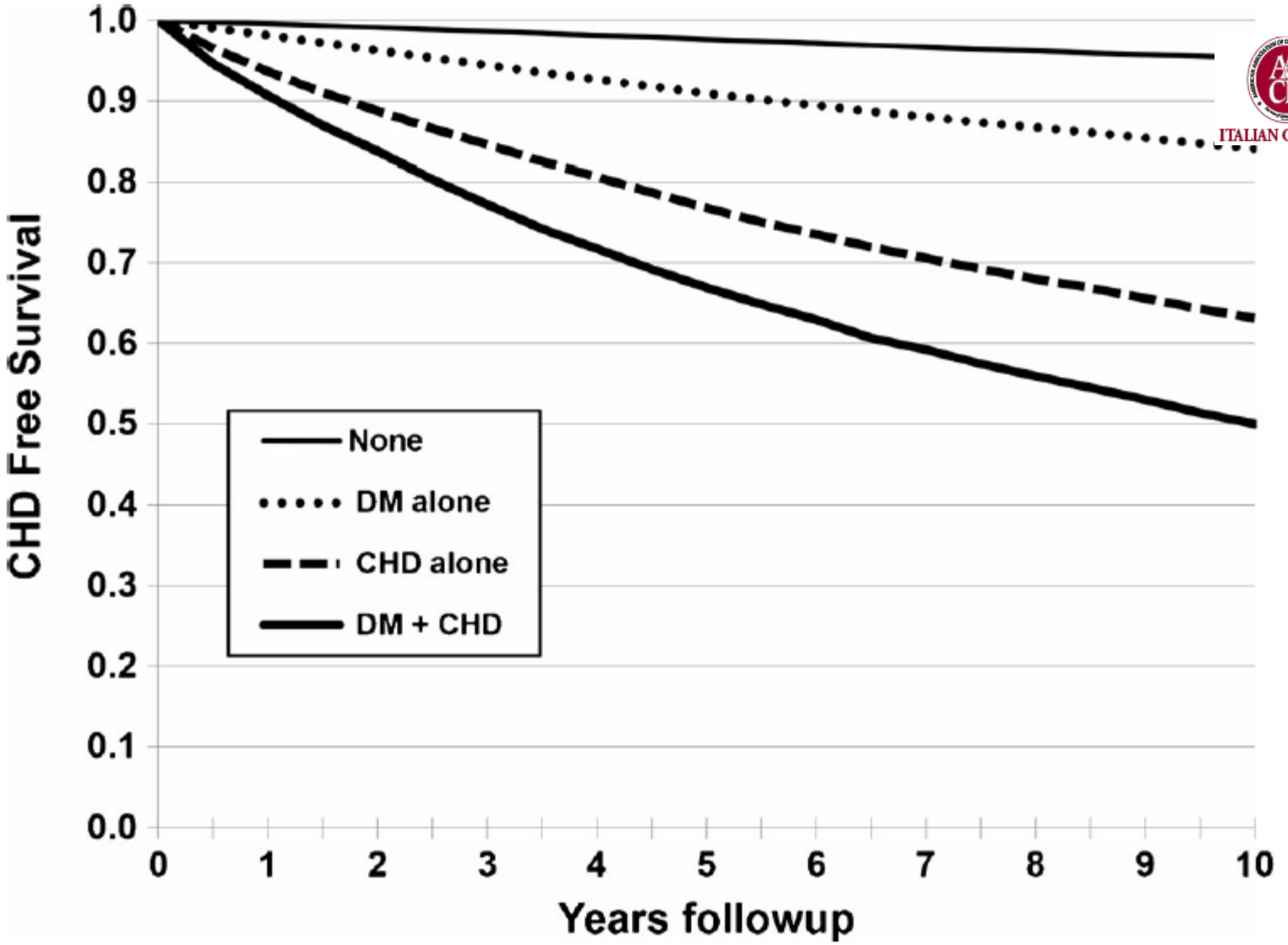
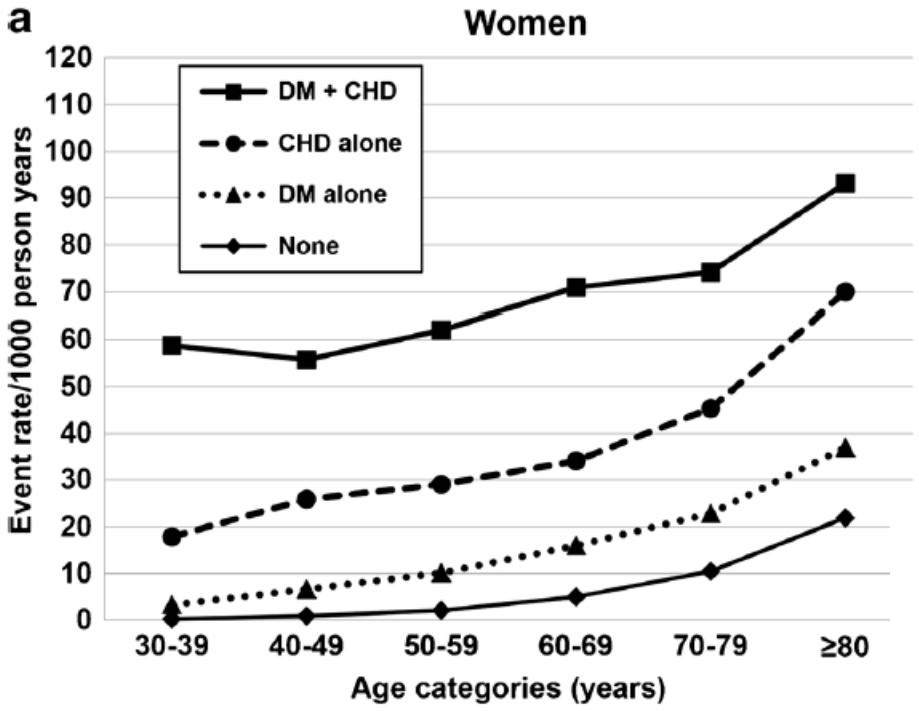


Figure 1 Kaplan–Meier estimates of coronary heart disease defined by baseline history of diabetes or CHD among four cohorts. The four cohorts are defined as: no diabetes or CHD (None); prior CHD alone (CHD); diabetes alone (DM); diabetes and CHD (DM+CHD), from 2002–2011.



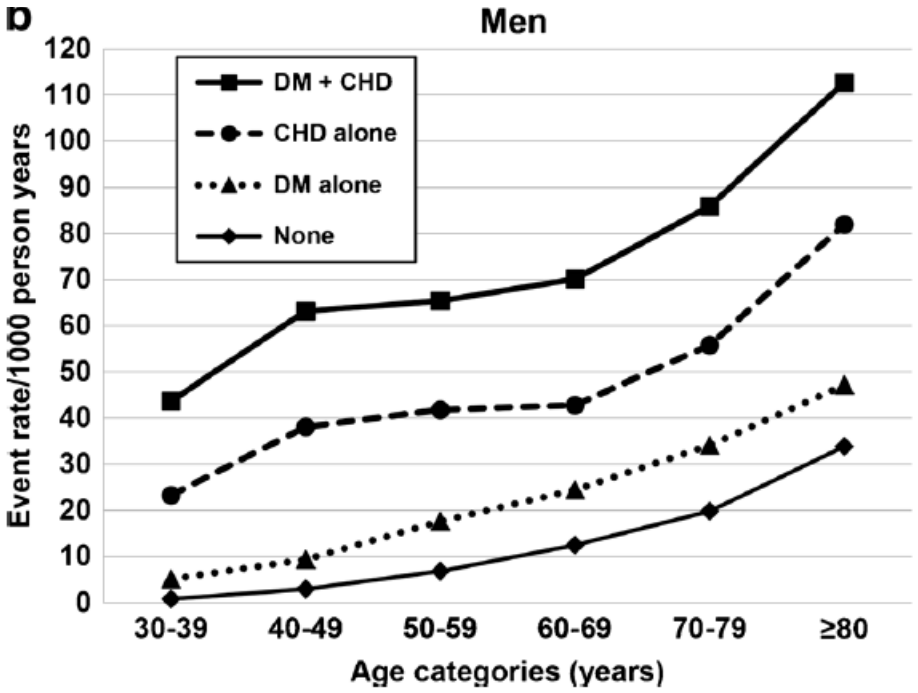


Figure 2 Coronary heart disease rates stratified by sex and age in four cohorts by history of diabetes or CHD. Coronary heart disease rates per 1000 p-y, stratified by sex and age (10-year increments) in four cohorts defined by baseline history of diabetes or CHD: no diabetes or CHD (None); prior CHD alone (CHD); diabetes alone (DM); diabetes and CHD (DM+CHD) *A* Women, *B* Men

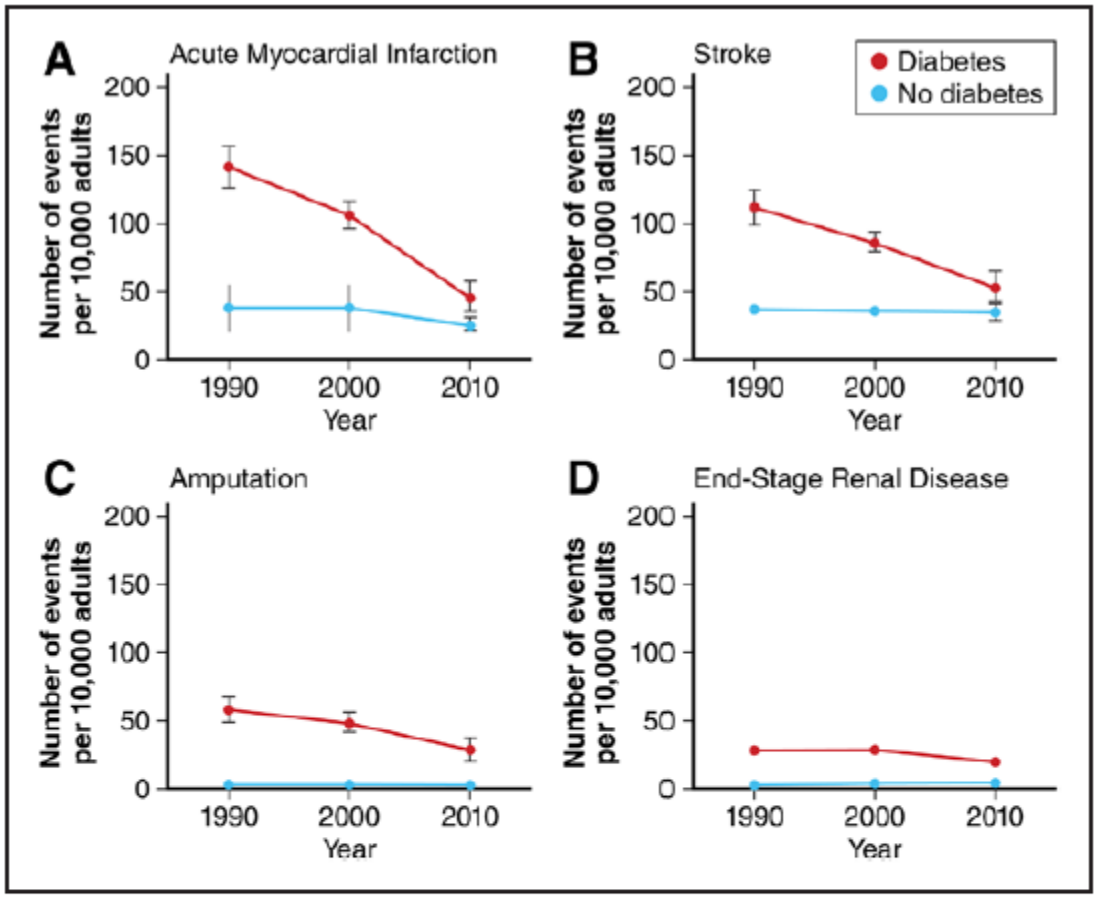


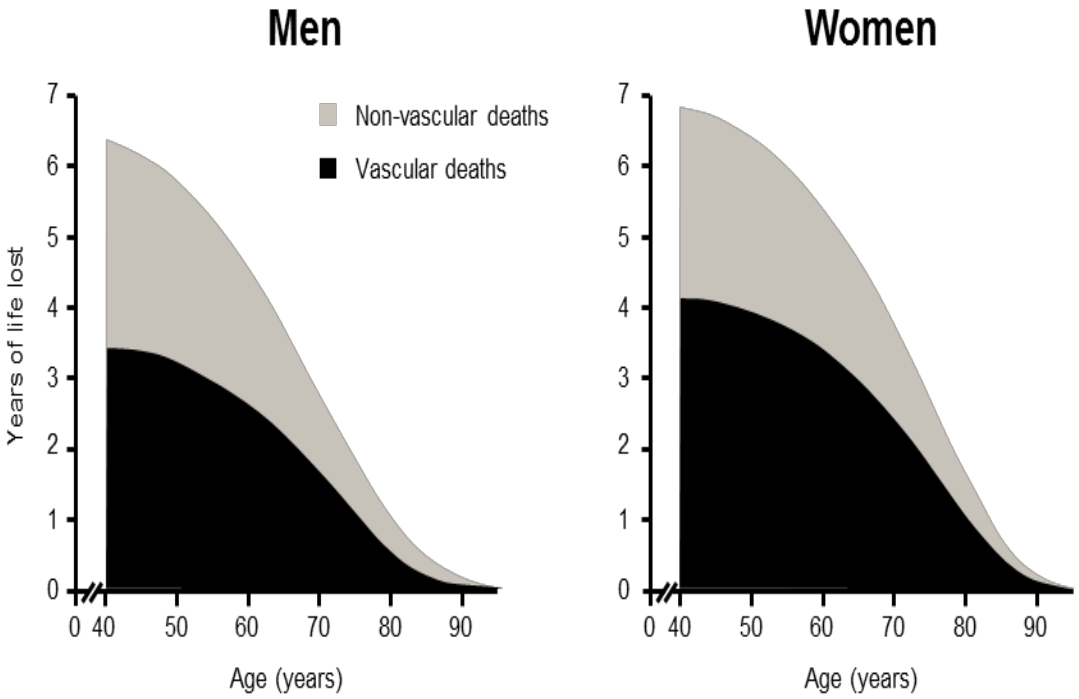
Figure 1. Rates of vascular diseases are decreasing in persons with diabetes mellitus but are still higher than in persons without diabetes mellitus: 20 years of surveillance. Age-standardized rates of selected vascular diseases in individuals with or without diabetes mellitus in the years 1990, 2000, and 2010. **A**, Acute myocardial infarction. **B**, Stroke. **C**, Amputation. **D**, End-stage renal disease. Red indicates individuals with diabetes mellitus; blue, individuals without diabetes mellitus. Error bars indicate 95% confidence intervals. Adapted from Gregg et al with permission of the publisher. Copyright ©2014, Massachusetts Medical Society.

Low Wang et al

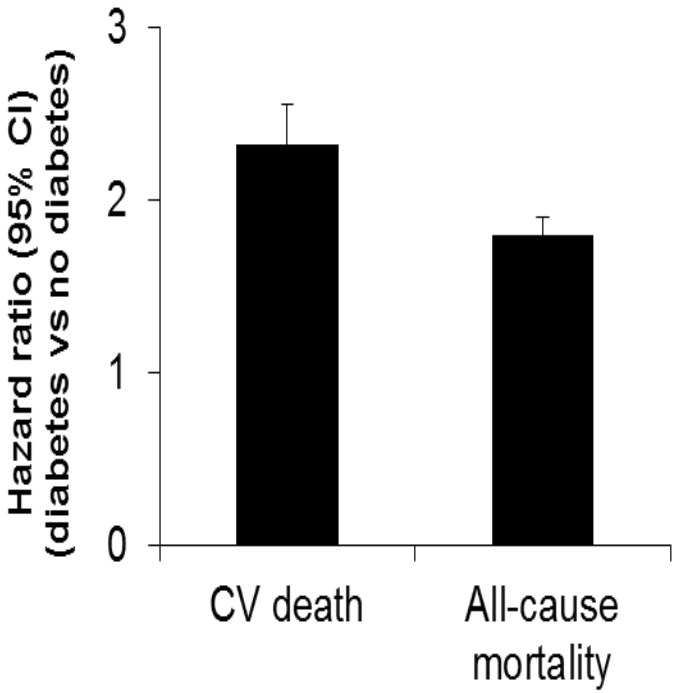
Circulation. 2016;133:2459–2502.

CVD is the leading cause of death in people with T2D

Years of life lost in people with diabetes* compared with non-diabetes peers[1]



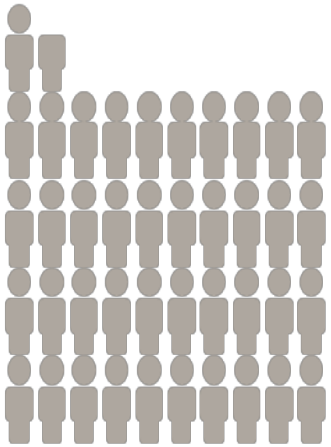
Mortality risk associated with diabetes (n=820,900)[1]



*Information on diabetes type (i.e., type 1 or 2) was generally not available, though the age of the participants suggests that the large majority with diabetes would have type 2. In high income countries, up to 91% of adults with diabetes have type 2[3]
CVD, cardiovascular disease; CI, confidence interval; T2D, type 2 diabetes.

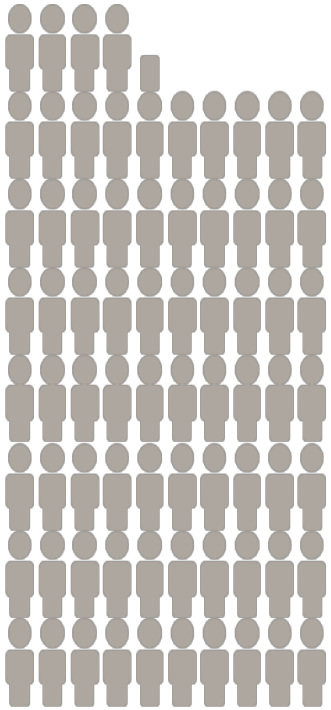
1. Seshasai et al. *N Engl J Med* 2011;364:829-41; 2. Centers for Disease Control and Prevention National Diabetes Fact Sheet 2011. http://www.cdc.gov/diabetes/pubs/pdf/ndfs_2011.pdf; 3. International Diabetes Federation. *IDF Diabetes Atlas, 7th edition.* Brussels, Belgium: International Diabetes Federation, 2015. http://www.diabetesatlas.org

Presented at the American Diabetes Association 76th Scientific Sessions. Session 3-CT-SY24. June 13 2016. New Orleans. LA. USA.



415 million

2015

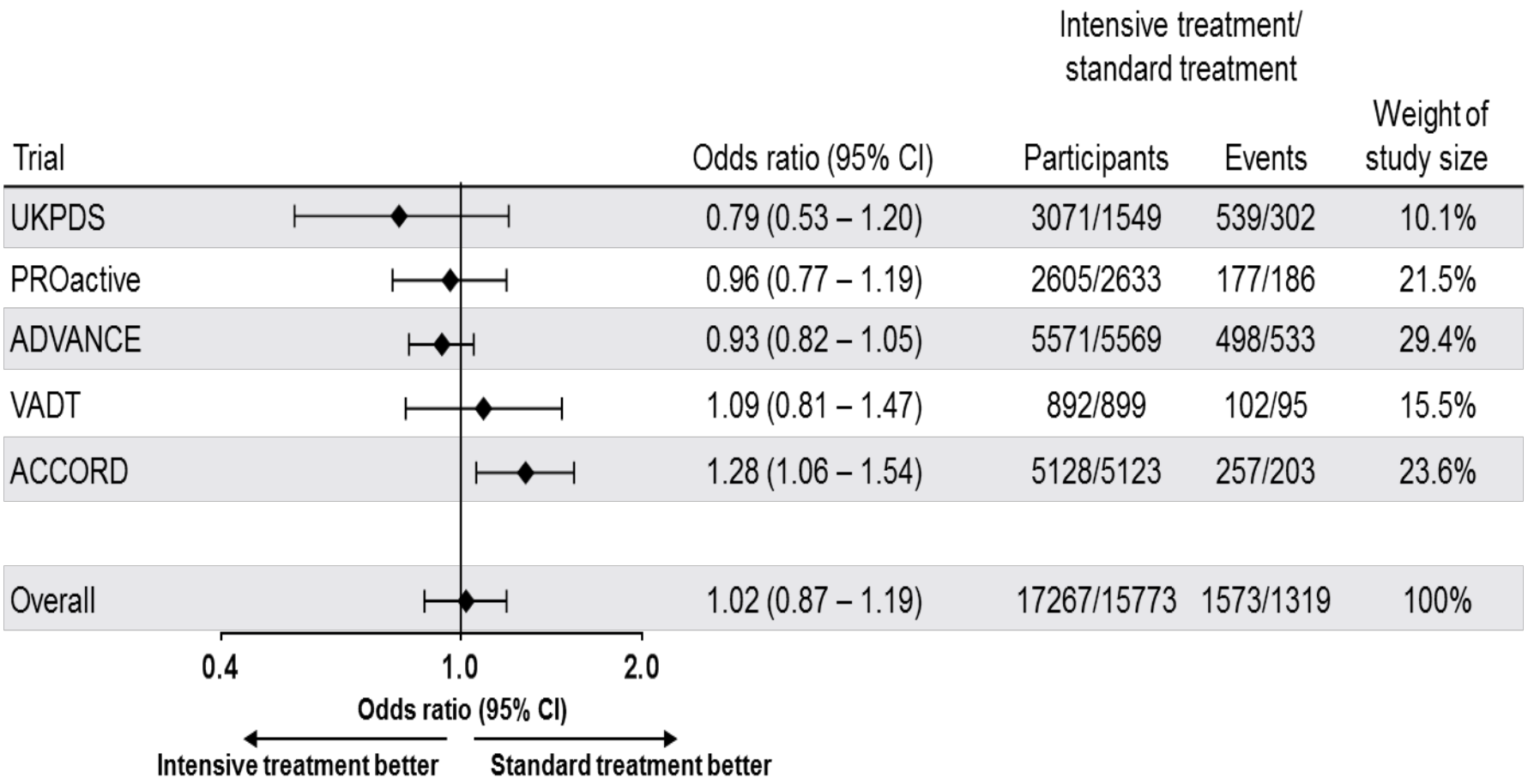


642 million

2040

All Cause Mortality

Intensive vs Standard Glucose Lowering



CI: confidence interval; HR: hazard ratio.

Ray KK et al *Lancet* 2009;373:1765–1772.

Presented at the American Diabetes Association 76th Scientific Sessions, Session 3-CT-SY24. June 13 2016, New Orleans, LA, USA.

December 2008 FDA Guidance on Evaluating CV Risk in New Antidiabetic Therapies for T2DM

ITALIAN CHAPTER

Guidance for Industry

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

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

December 2008
Clinical/Medical

III. RECOMMENDATIONS

To establish the safety of a new antidiabetic therapy to treat type 2 diabetes, sponsors should demonstrate that the therapy will not result in an unacceptable increase in cardiovascular risk. To ensure that a new therapy does not increase cardiovascular risk to an unacceptable extent, the development program for a new type 2 antidiabetic therapy should include the following.

For new clinical studies in the planning stage:

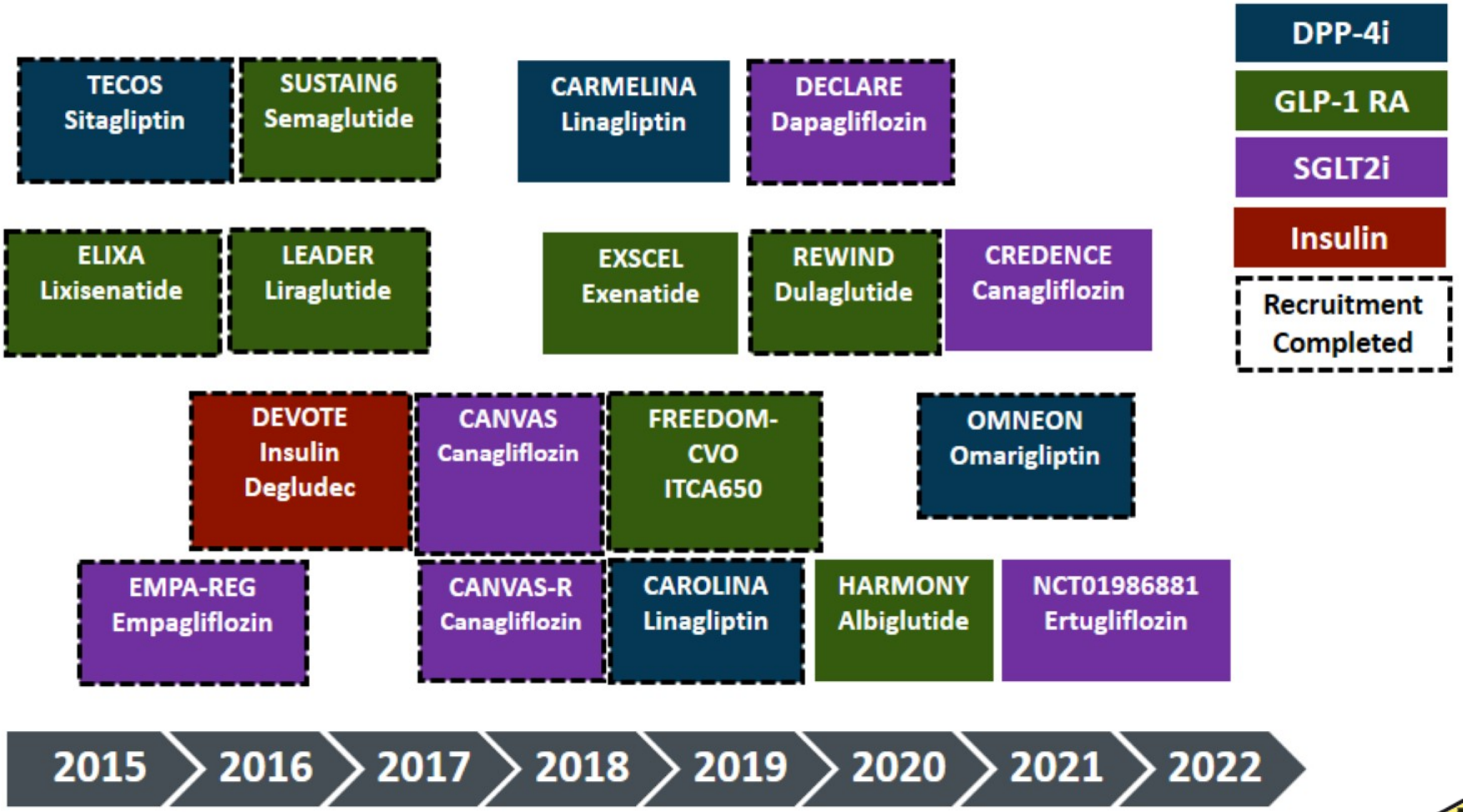
- Sponsors should establish an independent cardiovascular endpoints committee to prospectively adjudicate, in a blinded fashion, cardiovascular events during all phase 2 and phase 3 trials. These events should include cardiovascular mortality, myocardial infarction, and stroke, and can include hospitalization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

- Sponsors should ensure that phase 2 and phase 3 clinical trials are appropriately designed and conducted so that a meta-analysis can be performed at the time of completion of these studies that appropriately accounts for important study design features and patient or study level covariates. To obtain sufficient endpoints to allow a meaningful estimate of risk, the phase 2 and phase 3 programs should include patients at higher risk of cardiovascular events, such as patients with relatively advanced disease, elderly patients, and patients with some degree of renal impairment. Because these types of patients are likely to be treated with the antidiabetic agent, if approved, this population is more appropriate than a younger and healthier population for assessment of other aspects of the test drug's safety.

- Sponsors also should provide a protocol describing the statistical methods for the proposed meta-analysis, including the endpoints that will be assessed. At this time, we believe it would be reasonable to include in a meta-analysis all placebo-controlled trials, add-on trials (i.e., drug versus placebo, each added to standard therapy), and active-

FDA.org

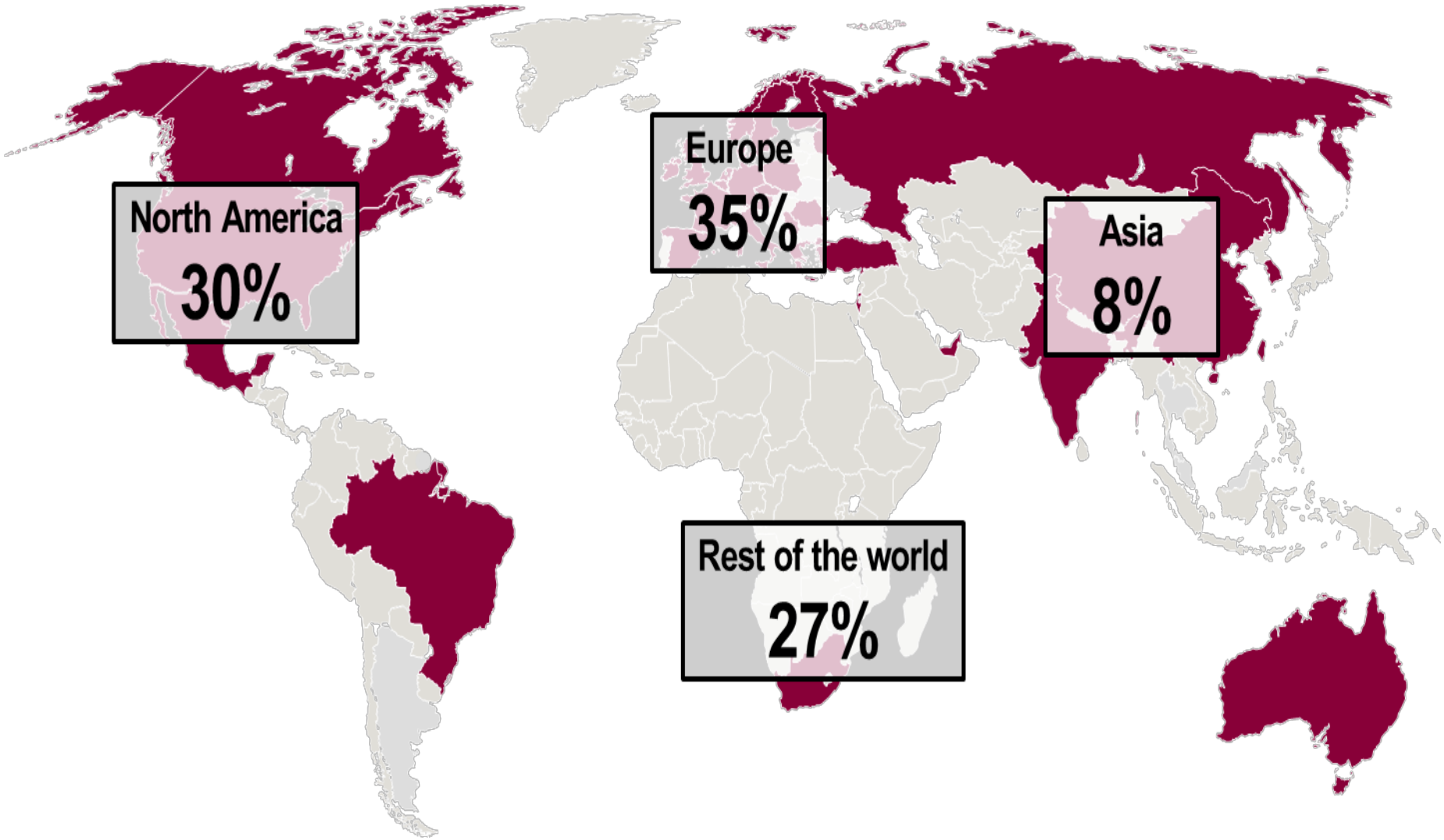
Ongoing CVOTs in Patients With T2DM



Ryden L, et al. *Clin Ther*. 2016. In Press.

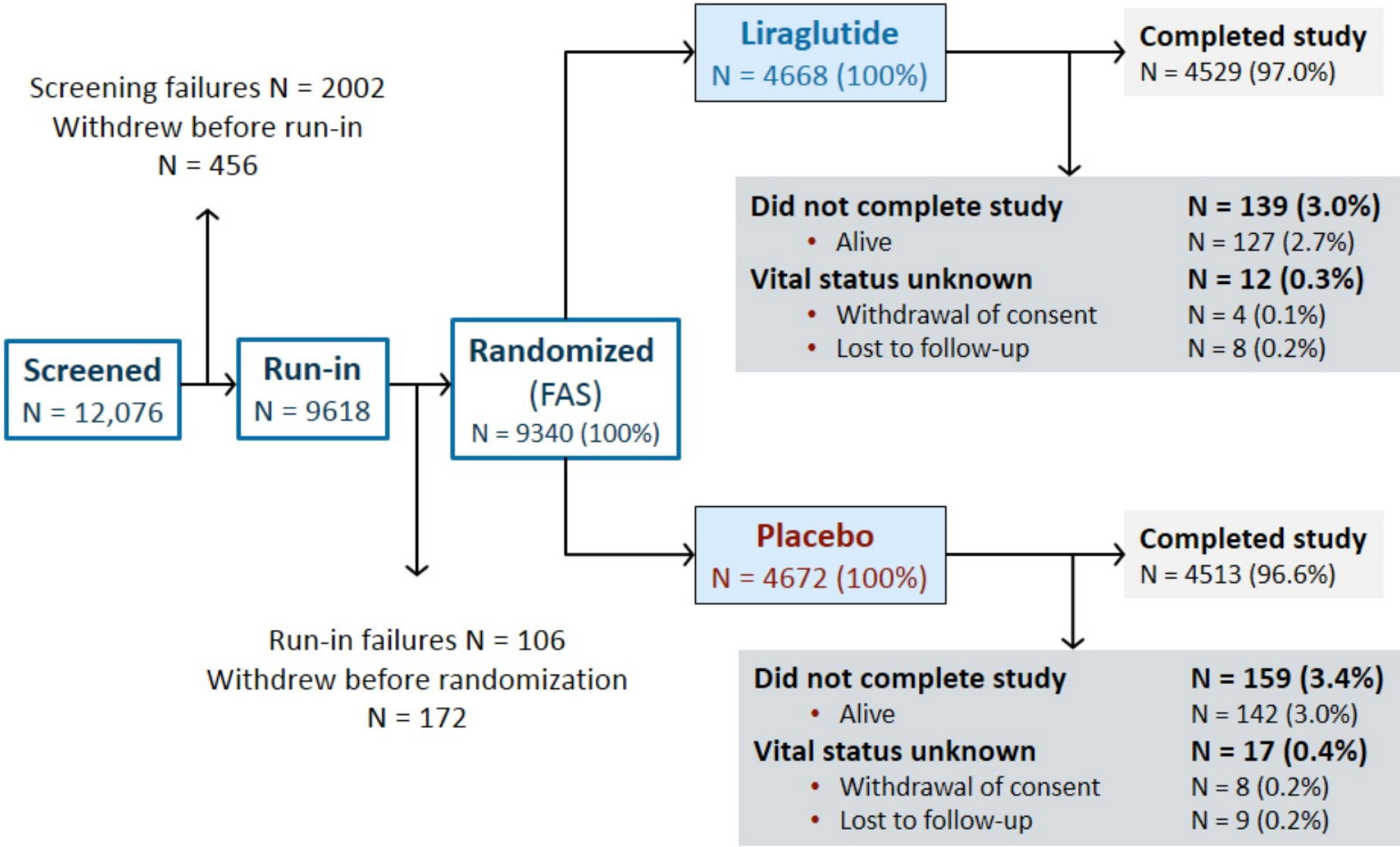
ITALIAN CHAPTER

LEADER: A Global Trial



Presented at the American Diabetes Association 76th Scientific Sessions, Session 3-CT-SY24. June 13 2016, New Orleans, LA, USA.

LEADER: Study Patient Disposition



Marso SP, et al. *N Engl J Med*. 2016;375:311-322.

Baseline characteristics

(mean ± SD unless stated)

	Liraglutide (N=4668)	Placebo (N=4672)
Male sex, N (%)	3011 (64.5)	2992 (64.0)
Age, years	64.2 ± 7.2	64.4 ± 7.2
Diabetes duration, years	12.8 ± 8.0	12.9 ± 8.1
HbA_{1c}, %	8.7 ± 1.6	8.7 ± 1.5
BMI, kg/m^2	32.5 ±6.3	32.5 ± 6.3
Body weight, kg	91.9 ±21.2	91.6 ± 20.8
Systolic blood pressure, mmHg	135.9 ± 17.8	135.9 ± 17.7
Diastolic blood pressure, mmHg	77.2 ± 10.3	77.0 ± 10.1
Heart failure*, N (%)	835 (17.9)	832 (17.8)

*Heart failure includes New York Heart Association class I, II and III. BMI: body mass index; HbA_{1c}: glycated hemoglobin.

Presented at the American Diabetes Association 76th Scientific Sessions, Session 3-CT-SY24. June 13 2016, New Orleans, LA, USA.

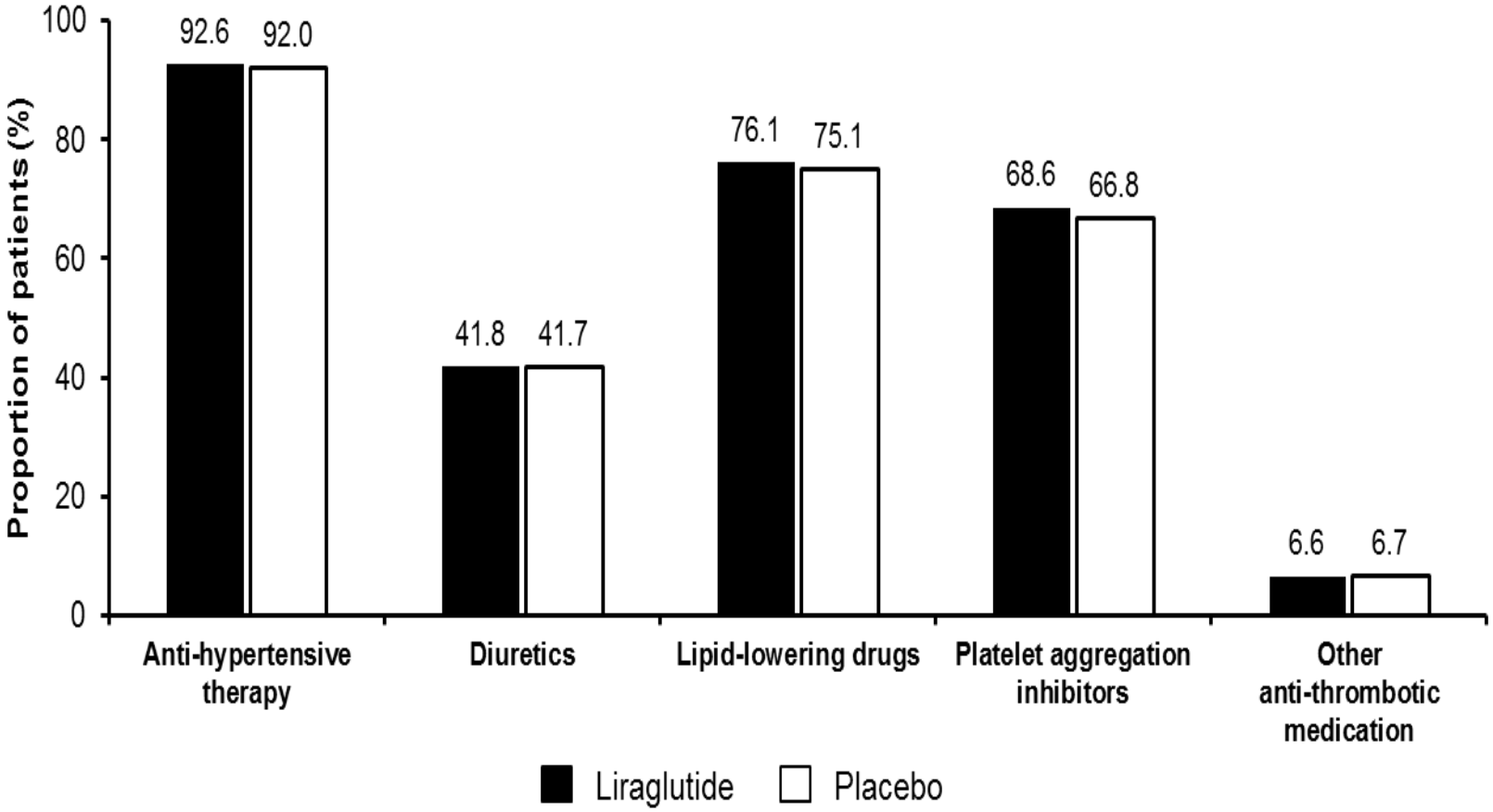
Baseline cardiovascular risk profile

	Liraglutide (N=4668)	Placebo (N=4672)
Established CVD/CKD (age ≥50 years)	**3831 (82.1)**	**3767 (80.6)**
Prior myocardial infarction	1464 (31.4)	1400 (30.0)
Prior stroke or prior TIA	730 (15.6)	777 (16.6)
Prior revascularization	1835 (39.3)	1803 (38.6)
>50% stenosis of coronary, carotid, or lower extremity arteries	1188 (25.4)	1191 (25.5)
Documented symptomatic CHD	412 (8.8)	406 (8.7)
Documented asymptomatic cardiac ischemia	1241 (26.6)	1231 (26.3)
Chronic heart failure NYHA II – III	653 (14.0)	652 (14.0)
Chronic kidney disease (eGFR <60 mL/min/1.73m^2)	1185 (25.4)	1122 (24.0)

Data are number of patients (%).
CHD: coronary heart disease; CKD: chronic kidney disease; CVD: cardiovascular disease; eGFR: estimated glomerular filtration rate; NYHA: New York Heart Association; TIA: transient ischemic attack.

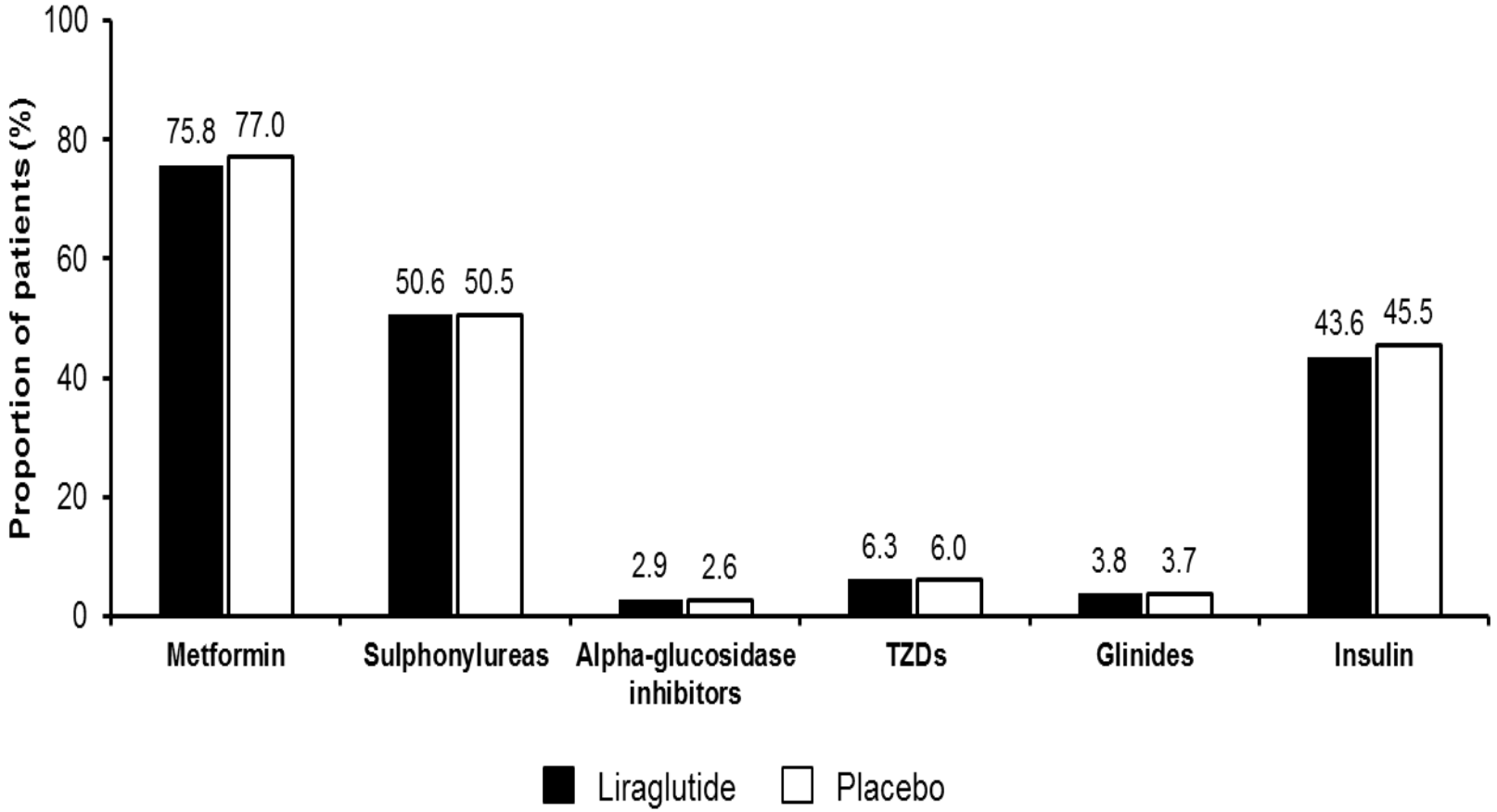
Presented at the American Diabetes Association 76th Scientific Sessions, Session 3-CT-SY24. June 13 2016, New Orleans, LA, USA.

Cardiovascular medication at baseline



Presented at the American Diabetes Association 76th Scientific Sessions, Session 3-CT-SY24. June 13 2016, New Orleans, LA, USA.

Antihyperglycemic medication at baseline



TZD: thiazolidinediones.

Presented at the American Diabetes Association 76th Scientific Sessions, Session 3-CT-SY24. June 13 2016, New Orleans, LA, USA.

Primary and key secondary outcomes

Primary outcome	**Time to first occurrence of composite CV endpoint composed of** • CV death • Non-fatal MI • Non-fatal stroke
Key secondary outcomes	**Time to first occurrence of** • Expanded composite CV endpoint (CV death, non-fatal MI, non-fatal stroke, coronary revascularization, unstable angina pectoris requiring hospitalization or hospitalization for heart failure) • All-cause death • Each individual component of expanded composite CV endpoint • A composite renal and eye microvascular outcome*

*Nephropathy and retinopathy

CV: cardiovascular; MI: myocardial infarction

Marso SP et al. *N Engl J Med* 2016;375:311–322

LEADER: Primary Outcome*

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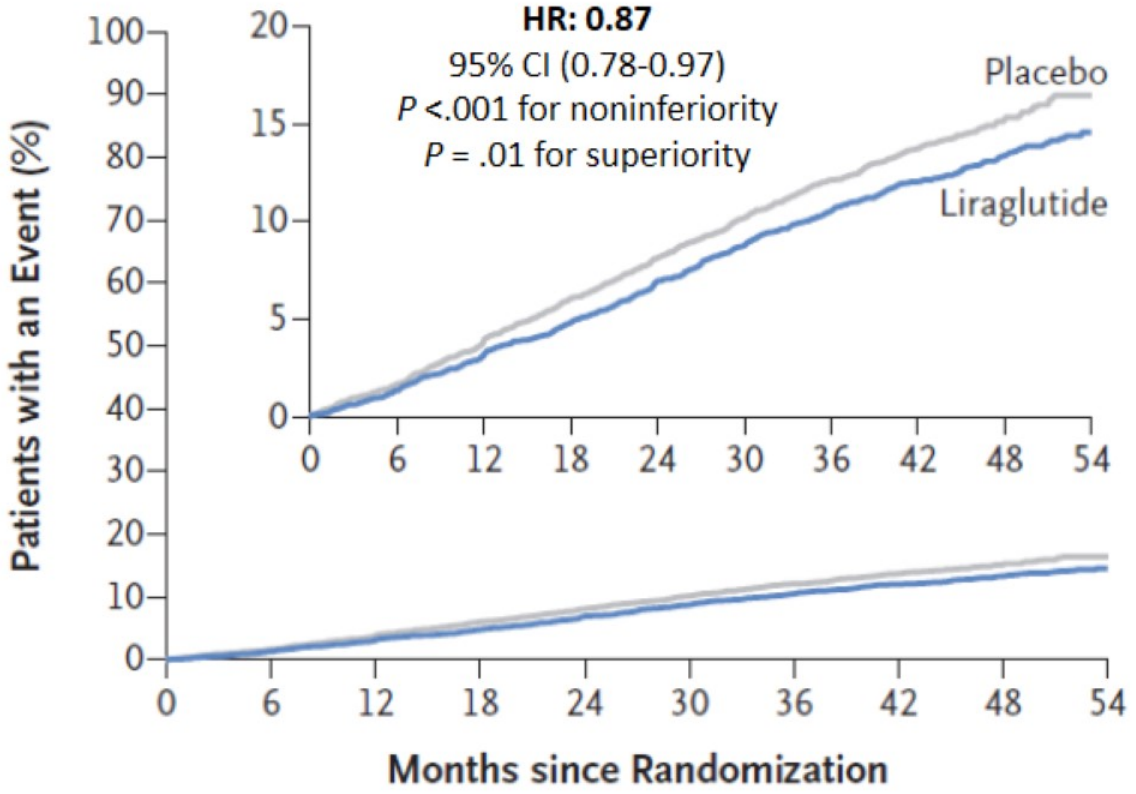


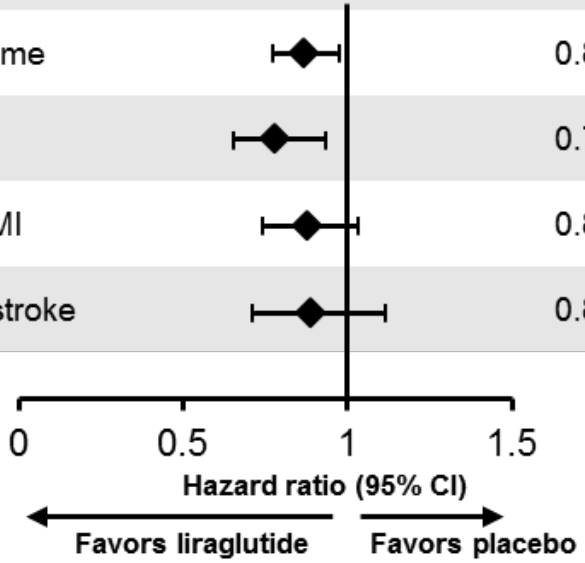
No. at Risk

Liraglutide	4668	4593	4496	4400	4280	4172	4072	3982	1562	424
Placebo	4672	4588	4473	4352	4237	4123	4010	3914	1543	407

*3-point MACE consisting of CV death, nonfatal MI, or nonfatal stroke

Components of the primary outcome

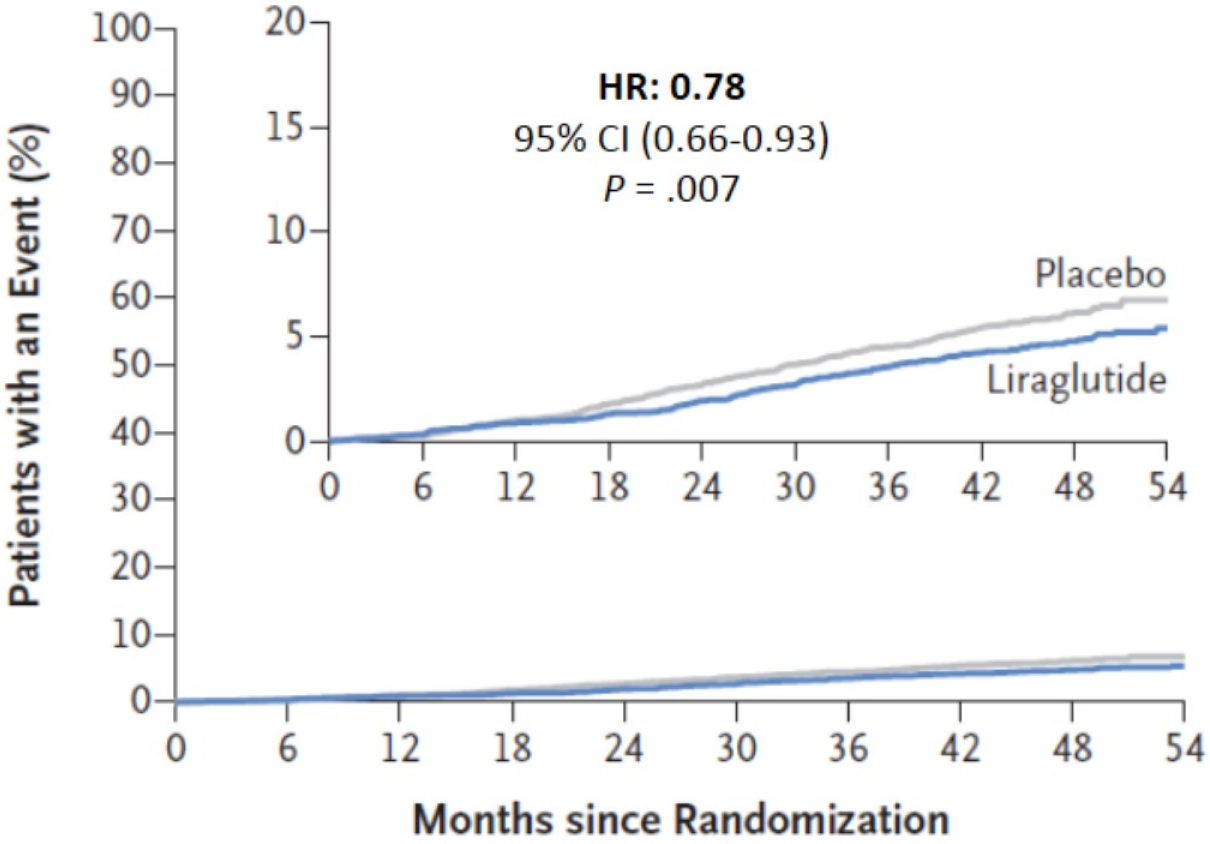
	Hazard ratio (95% CI)	*p*-value	Liraglutide N	Liraglutide %	Liraglutide R	Placebo N	Placebo %	Placebo R
Total number of patients			**4668**	**100.0**	**–**	**4672**	**100.0**	**–**
Primary outcome	0.87 (0.78 ; 0.97)	0.01	608	13.0	3.4	694	14.9	3.9
CV death	0.78 (0.66 ; 0.93)	0.007	219	4.7	1.2	278	6.0	1.6
Non-fatal MI	0.88 (0.75 ; 0.03)	0.11	281	6.0	1.6	317	6.8	1.8
Non-fatal stroke	0.89 (0.72 ; 1.11)	0.30	159	3.4	0.9	177	3.8	1.0



Hazard ratios and *p*-values were estimated with the use of a Cox proportional-hazards regression model with treatment as a covariate
%: percentage of group; CI: confidence interval; CV: cardiovascular; MI: myocardial infarction; N: number of patients; R: incidence rate per 100 patient-years of observation

Marso SP et al. *N Engl J Med* 2016;375:311–322

LEADER: CV Death

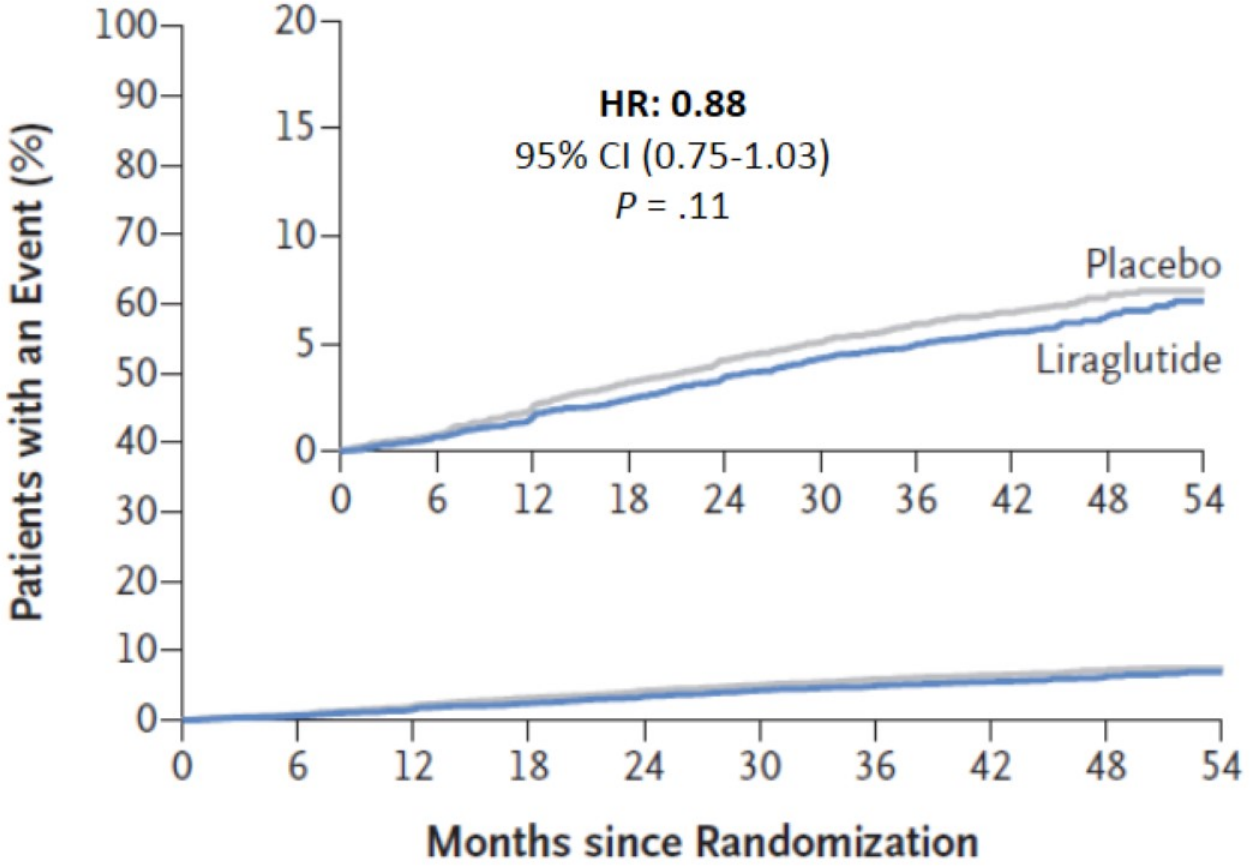


No. at Risk

Liraglutide	4668	4641	4599	4558	4505	4445	4382	4322	1723	484
Placebo	4672	4648	4601	4546	4479	4407	4338	4267	1709	465

From Marso SP, et al; for the LEADER Steering Committee on behalf of the LEADER Trial Investigators. *N Engl J Med*. 2016. [Epub ahead of print].

LEADER: Time to Nonfatal MI



No. at Risk

Liraglutide	4668	4609	4531	4454	4359	4263	4181	4102	1619	440
Placebo	4672	4613	4513	4407	4301	4202	4103	4020	1594	424

From Marso SP, et al; for the LEADER Steering Committee on behalf of the LEADER Trial Investigators. *N Engl J Med*. 2016. [Epub ahead of print].

LEADER: Time to Nonfatal Stroke

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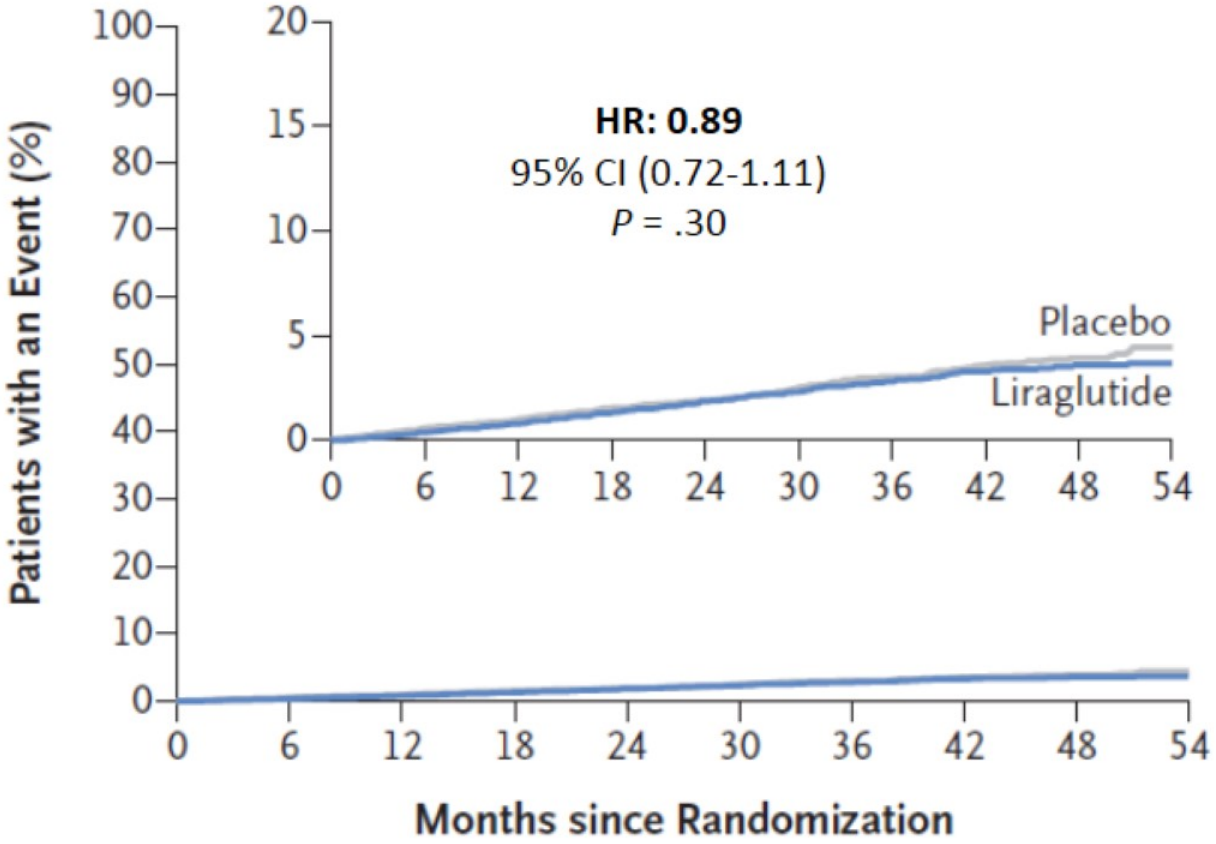


No. at Risk

Liraglutide	4668	4624	4564	4504	4426	4351	4269	4194	1662	465
Placebo	4672	4622	4558	4484	4405	4314	4228	4141	1648	445

Recurrent CV event analysis

Total CV death, non-fatal myocardial infarction or non-fatal stroke

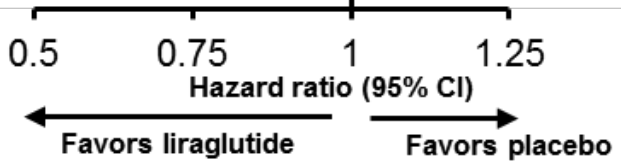
Treatment	Number of patients (N)	Number of patients with a CV event (%)	Number of CV events	Hazard ratio (CI)	*p*-value
Liraglutide	4668	608 (13.0)	735	0.86 (0.78–0.95)	0.004
Placebo	4672	694 (14.9)	870		

Post-hoc analysis. Analysis based on an Andersen–Gill intensity model with treatment group as an explanatory variable and number of previous events as a time-dependent covariate
CI: confidence interval; EAC: event adjudication committee

Presented at the American Diabetes Association 77th Scientific Sessions, Session 1-AC-SY13. June 11 2017, San Diego, CA, USA

Primary outcome – analyses adjusted for use of CV medication at baseline

	Hazard ratio (95% CI)	Liraglutide N	Liraglutide %	Placebo N	Placebo %
Adjusted for beta-blockers	0.86 (0.77 ; 0.96)	608	13.0	694	14.9
Adjusted for ACE inhibitors	0.87 (0.78 ; 0.97)	608	13.0	694	14.9
Adjusted for statins	0.87 (0.78 ; 0.97)	608	13.0	694	14.9
Adjusted for platelet aggregation inhibitors	0.87 (0.78 ; 0.97)	608	13.0	694	14.9



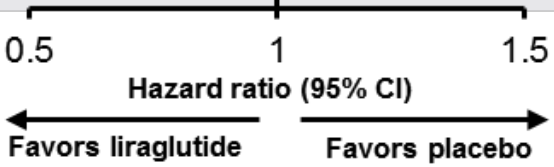
Post-hoc analysis. Time to first event is analysed using Cox proportional-hazards regression model with treatment and covariate as factors

ACE: angiotensin converting enzyme; CI: confidence interval; CV: cardiovascular; N: number of patients with an event between randomization date and follow-up date

Presented at the American Diabetes Association 77th Scientific Sessions, Session 1-AC-SY13. June 11 2017, San Diego, CA, USA

Primary outcome by insulin use at baseline

	Hazard ratio (95% CI)	Liraglutide N	Liraglutide %	Placebo N	Placebo %
Total number of patients		4668		4672	
Primary outcome	0.87 (0.78 ; 0.97)	608	13.0	694	14.9
Insulin use at baseline (Y/N)					
Yes	0.88 (0.75 ; 1.03)	295	14.5	347	16.3
No	0.86 (0.74 ; 1.01)	313	11.9	347	13.7



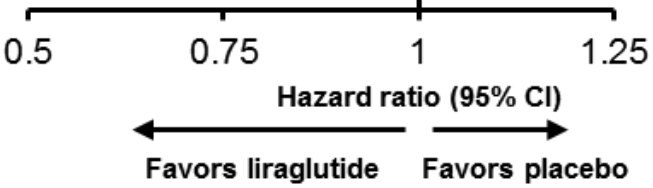
Post-hoc analysis

%: proportion of patients; CI: confidence interval; N: number of patients

Presented at the American Diabetes Association 77th Scientific Sessions, Session 1-AC-SY13. June 11 2017, San Diego, CA, USA

Primary outcome in patients never treated with insulin during the trial

	Hazard ratio (95% CI)	Liraglutide N	Liraglutide R	Placebo N	Placebo R
Total number of patients		4668		4672	
Primary outcome	0.87 (0.78 ; 0.97)	608	3.4	694	3.9
Patients not on insulin at baseline		2630		2541	
Primary outcome	0.82 (0.68 ; 0.98)	229	2.9	217	3.5

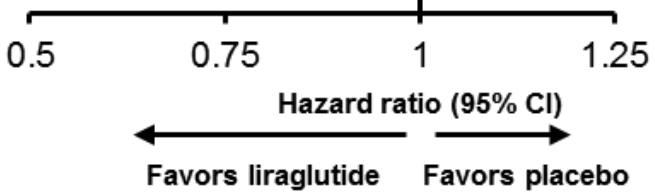


Post-hoc analysis – insulin-naïve patients censored if initiating insulin
CI: confidence interval; N: number of patients; R: incidence rate per 100 patient years

Presented at the American Diabetes Association 77th Scientific Sessions, Session 1-AC-SY13. June 11 2017, San Diego, CA, USA

Primary outcome in patients never treated with SU or TZD during the trial

	Hazard ratio (95% CI)	Liraglutide N	Liraglutide R	Placebo N	Placebo R
Total number of patients		4668		4672	
Primary outcome	0.87 (0.78 ; 0.97)	608	3.4	694	3.9
Patients not on SU at baseline		2126		2146	
Primary outcome	0.79 (0.67 ; 0.94)	242	3.6	277	4.5
Patients not on TZD at baseline		2185		2222	
Primary outcome	0.87 (0.78 ; 0.97)	569	3.6	643	4.2

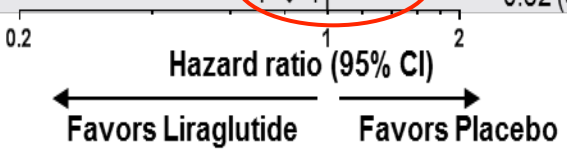


Post-hoc analysis – censoring patients at the time of initiation of SU or TZD
CI: confidence interval; N: number of patients; R: incidence rate per 100 patient years; SU: sulfonylurea; TZD: thiazolidinedione

Presented at the American Diabetes Association 77th Scientific Sessions, Session 1-AC-SY13. June 11 2017, San Diego, CA, USA

Primary outcome: Subgroup analyses

Subgroup	Hazard ratio (95% CI)	p-value for interaction	No. of patients	Liraglutide no. of events/no. of patients (%)	Placebo no. of events/no. of patients (%)
Primary analysis	**0.87 (0.78–0.97)**		**9340**	**608/4668 (13.0)**	**694/4672 (14.9)**
Sex		0.84			
Female	0.88 (0.72–1.08)		3337	183/1657 (11.0)	209/1680 (12.4)
Male	0.86 (0.75–0.98)		6003	425/3011 (14.1)	485/2992 (16.2)
Age		0.27			
<60 years	0.78 (0.62–0.97)		2321	140/1197 (11.7)	166/1124 (14.8)
>/= 60 years	0.90 (0.79–1.02)		7019	468/3471 (13.5)	528/3548 (14.9)
Geographic region		0.20			
Europe	0.82 (0.68–0.98)		3296	207/1639 (12.6)	252/1657 (15.2)
North America	1.01 (0.84–1.22)		2847	212/1401 (15.1)	216/1446 (14.9)
Asia	0.62 (0.37–1.04)		711	24/360 (6.7)	37/351 (10.5)
Rest of the world	0.83 (0.68–1.03)		2486	165/1268 (13.0)	189/1218 (15.5)
Race		0.32			
White	0.90 (0.80–1.02)		7238	494/3616 (13.7)	543/3622 (15.0)
Black or African American	0.87 (0.59–1.27)		777	47/370 (12.7)	59/407 (14.5)
Asian	0.70 (0.46–1.04)		936	40/471 (8.5)	56/465 (12.0)
Other	0.61 (0.37–1.00)		389	27/211 (12.8)	36/178 (20.2)
Ethnic group		0.30			
Hispanic or Latino	0.74 (0.54–1.02)		1134	68/580 (11.7)	86/554 (15.5)
Not Hispanic or Latino	0.89 (0.79–1.00)		8206	540/4088 (13.2)	608/4118 (14.8)
Body mass index		0.15			
</=30 kg/m^2	0.96 (0.81–1.15)		3574	241/1743 (13.8)	261/1831 (14.3)
>30 kg/m^2	0.82 (0.71–0.94)		5757	367/2920 (12.6)	431/2837 (15.2)



Prespecified Cox proportional-hazard regression analyses were performed for subgroups of patients with respect to the primary outcome (first occurrence of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke). P values signify tests of homogeneity for between-group differences with no adjustment for multiple testing. The percentages of patients with a first primary outcome between the randomization date and the date of last follow-up are shown. Race or ethnic group was self-reported. CI: confidence interval.

Presented at the American Diabetes Association 76th Scientific Sessions, Session 3-CT-SY24. June 13 2016, New Orleans, LA, USA.

Circulation

RESEARCH LETTER

Effect of Liraglutide on Cardiovascular Events in Patients With Type 2 Diabetes Mellitus and Polyvascular Disease

Results of the LEADER Trial

Subodh Verma, MD, PhD
Deepak L. Bhatt, MD, MPH
Stephen C. Bain, MD
John B. Buse, MD, PhD
Johannes F.E. Mann, MD

The presence of polyvascular disease, defined as atherosclerosis involving >1 distinct vascular territory, is a strong, independent predictor of cardiovascular events.[1–4] In the LEADER trial (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results),[5] the human glucagon-like peptide 1 analog liraglutide reduced cardiovascular events in patients with type 2 diabetes mellitus at high cardiovascular risk. In this post hoc analysis of LEADER, we evalu-

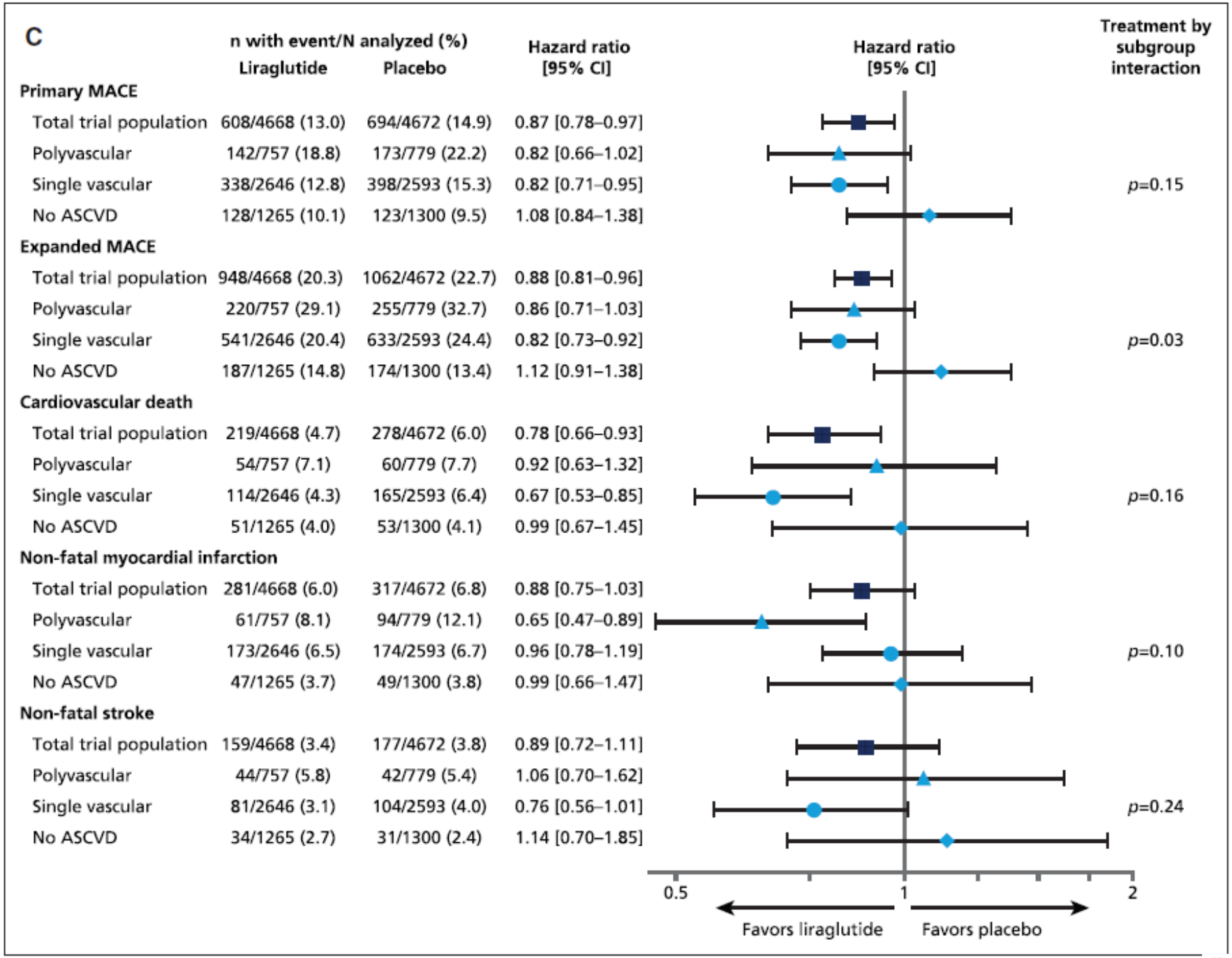
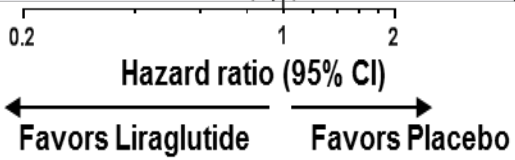


Figure Continued.

Verma et al
Circulation. 2018;137:2179–2183.

Primary outcome: Subgroup analyses

Subgroup	Hazard ratio (95% CI)	p-value for interaction	No. of patients	Liraglutide no. of events/no. of patients (%)	Placebo no. of events/no. of patients (%)
Primary analysis	**0.87 (0.78–0.97)**		**9340**	**608/4668 (13.0)**	**694/4672 (14.9)**
Glycated hemoglobin		0.58			
</=8.3%	0.89 (0.76–1.05)		4768	289/2340 (12.4)	333/2428 (13.7)
>8.3%	0.84 (0.72–0.98)		4572	319/2328 (13.7)	361/2244 (16.1)
Duration of diabetes		0.42			
</=11 years	0.82 (0.70–0.97)		4429	265/2216 (12.0)	316/2213 (14.3)
>11 years	0.90 (0.78–1.04)		4892	340/2441 (13.9)	376/2451 (15.3)
Risk of CVD		0.04			
Age >/=50 years and established CVD/CKD	0.83 (0.74–0.93)		7598	536/3831 (14.0)	629/3767 (16.7)
Age >/=60 years and risk factors for CVD	1.20 (0.86–1.67)		1742	72/837 (8.6)	65/905 (7.2)
Chronic heart failure		0.53			
Yes	0.94 (0.72–1.21)		1305	112/653 (17.2)	119/652 (18.3)
No	0.85 (0.76–0.96)		8035	496/4015 (12.4)	575/4020 (14.3)
Antidiabetic therapy		0.73			
1 OAD	0.75 (0.58–0.98)		1818	99/922 (10.7)	125/896 (14.0)
>1 OAD	0.95 (0.78–1.16)		2997	191/1515 (12.6)	196/1482 (13.2)
Insulin with OAD(s)	0.89 (0.74–1.06)		3422	223/1674 (13.3)	259/1748 (14.8)
Insulin without OAD	0.86 (0.63–1.17)		737	71/361 (19.7)	86/376 (22.9)
None	0.73 (0.42–1.25)		366	24/196 (12.2)	28/170 (16.5)
Renal function		0.01			
<60 mL/min/1.73 m^2	0.69 (0.57–0.85)		2158	172/1116 (15.4)	223/1042 (21.4)
>/=60 mL/min/1.73 m^2	0.94 (0.83–1.07)		7182	436/3552 (12.3)	471/3630 (13.0)

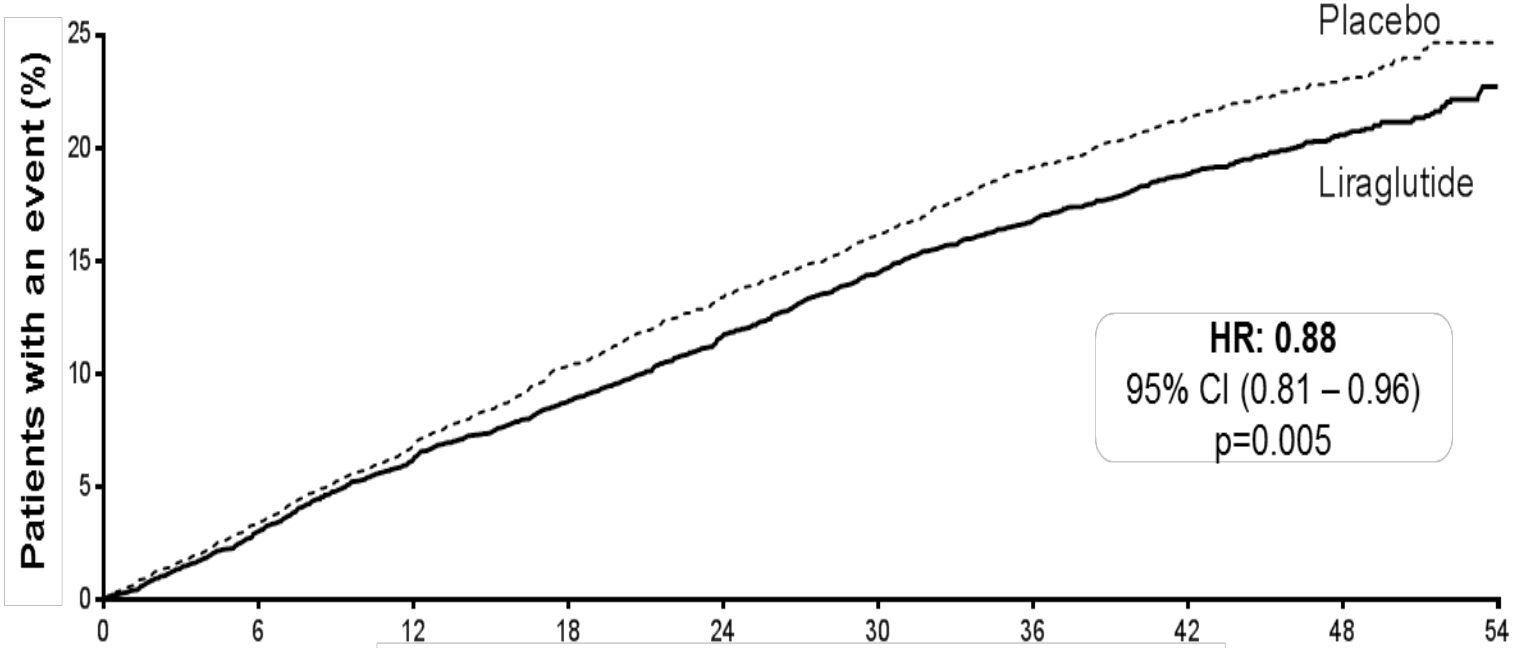


Prespecified Cox proportional-hazard regression analyses were performed for subgroups of patients with respect to the primary outcome (first occurrence of death from CV causes, nonfatal MI, or nonfatal stroke). P values signify tests of homogeneity for between-group differences with no adjustment for multiple testing. The percentages of patients with a first primary outcome between the randomization date and the date of last follow-up are shown. There were missing data for BMI in 5 patients in the liraglutide group and 4 in the placebo group and for the duration of diabetes in 11 patients in the liraglutide group and 8 in the placebo group.

Presented at the American Diabetes Association 76th Scientific Sessions, Session 3-CT-SY24. June 13 2016, New Orleans, LA, USA.

Expanded MACE

CV death, non-fatal MI, non-fatal stroke, coronary revascularization, or hospitalization for unstable angina pectoris or heart failure



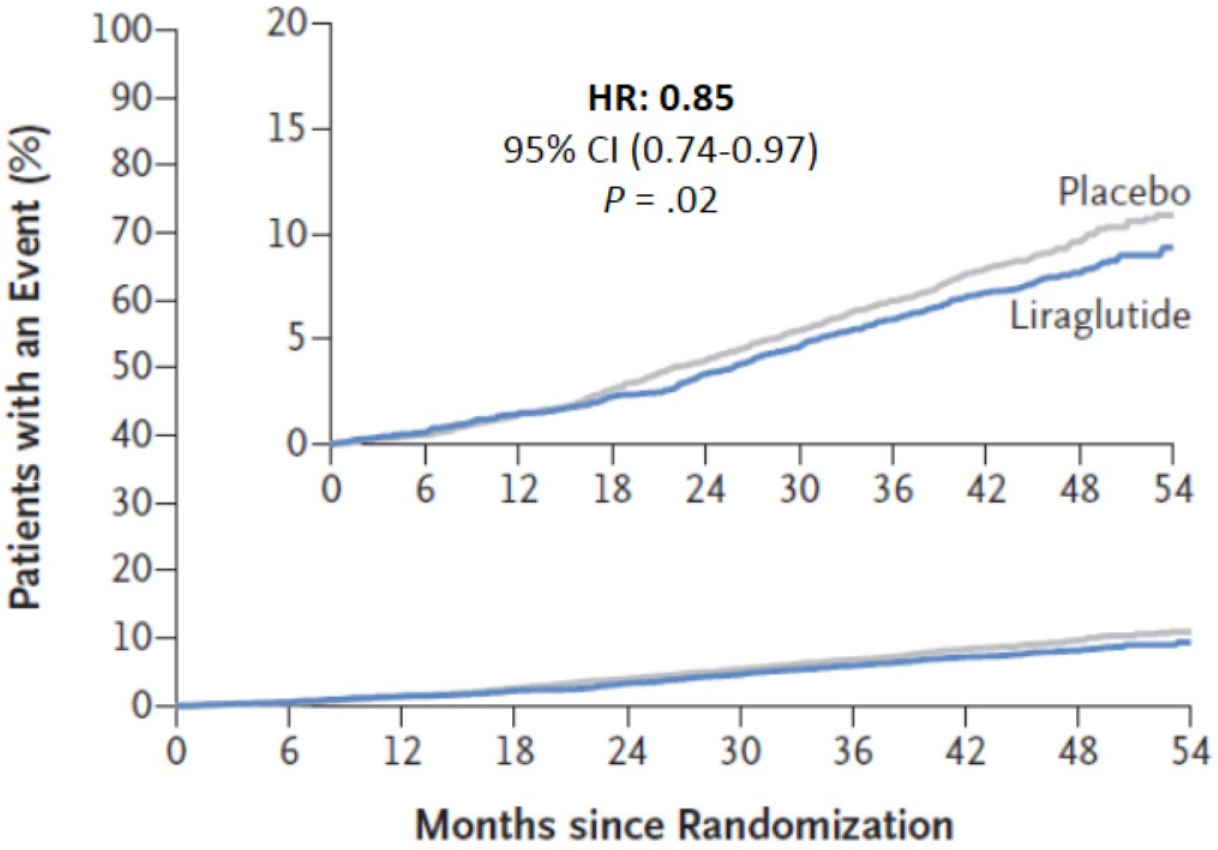
Patients at risk										
Liraglutide	4668	4515	4356	4221	4063	3914	3793	3682	1452	395
Placebo	4672	4506	4336	4157	4002	3857	3697	3581	1410	366

The cumulative incidences were estimated with the use of the Kaplan–Meier method, and the hazard ratios with the use of the Cox proportional-hazard regression model. The data analyses are truncated at 54 months, because less than 10% of the patients had an observation time beyond 54 months.
CI: confidence interval; CV: cardiovascular; HR: hazard ratio; MACE: major adverse cardiovascular event; MI: myocardial infarction.

Presented at the American Diabetes Association 76th Scientific Sessions, Session 3-CT-SY24. June 13 2016, New Orleans, LA, USA.

LEADER: All-Cause Death

ITALIAN CHAPTER

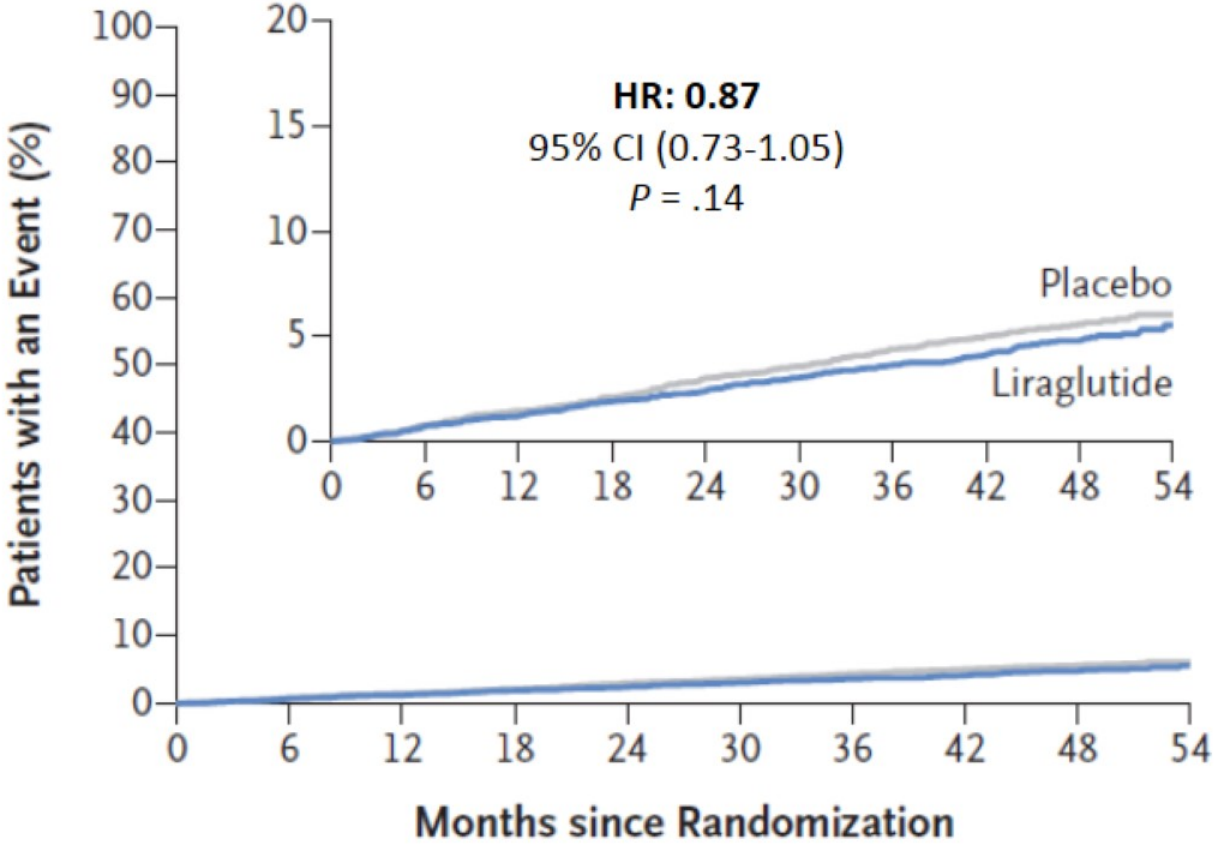


No. at Risk

Liraglutide	4668	4641	4599	4558	4505	4445	4382	4322	1723	484
Placebo	4672	4648	4601	4546	4479	4407	4338	4268	1709	465

From Marso SP, et al; for the LEADER Steering Committee on behalf of the LEADER Trial Investigators. *N Engl J Med*. 2016. [Epub ahead of print].

LEADER: Hospitalization for HF

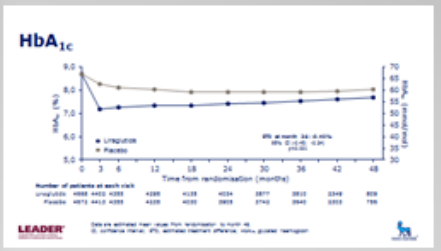
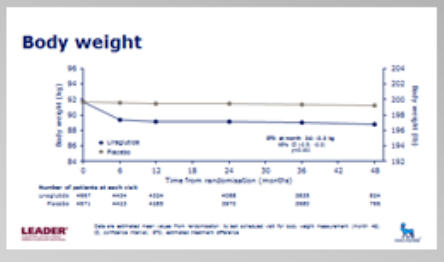
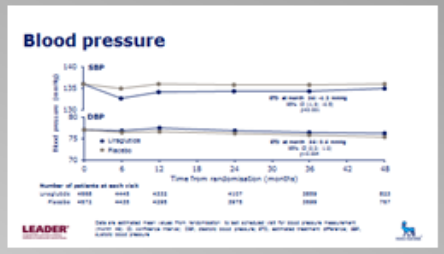
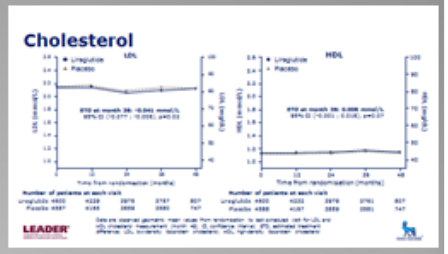


No. at Risk

Liraglutide	4668	4612	4550	4483	4414	4337	4258	4185	1662	467
Placebo	4672	4612	4540	4464	4372	4288	4187	4107	1647	442

From Marso SP, et al; for the LEADER Steering Committee on behalf of the LEADER Trial Investigators. *N Engl J Med*. 2016. [Epub ahead of print].

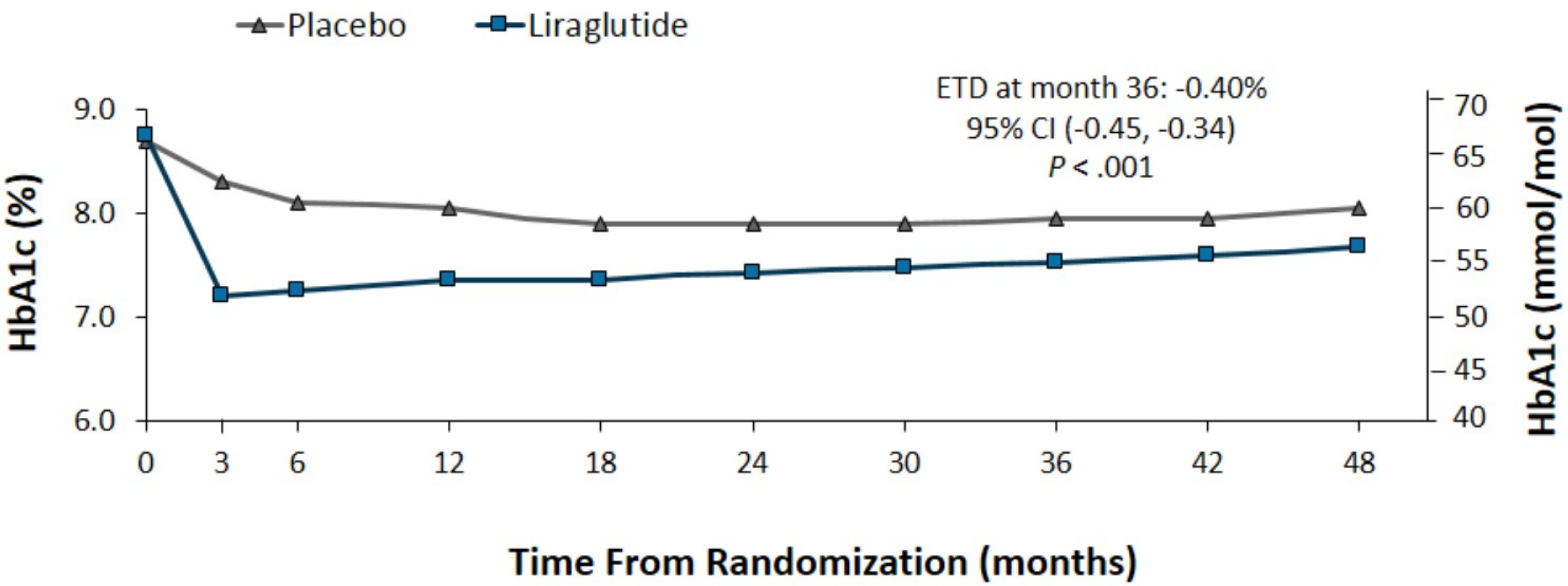
Summary of efficacy results at 3 years

HbA_{1c}	Body Weight	SBP	Lipids
			
Treatment Difference **–0.4%** 95% CI (–0.45; –0.34) *p*<0.001	Treatment Difference **–2.3 kg** 95% CI (–2.54; –1.99) *p*<0.001	Treatment Difference **–1.2 mmHg** 95% CI (–1.9; –0.5) *p*<0.001	**Small decreases** in TC, LDL-C and TGs **Small increase** in HDL-C

Mean change from baseline is to Month 36
BP: blood pressure; DBP: diastolic blood pressure; HbA_{1c}: glycated hemoglobin; HDL-C: low-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol;
SBP: systolic blood pressure; TG: triglycerides; TC: total cholesterol

Marso SP et al. *N Engl J Med* 2016;375:311–322; Presented at ADA 2016

LEADER: Change in HbA1c Over Time



Number of patients at each visit

Liraglutide	4668	4402	4355	4295	4135	4034	3877	3810	2349	809
Placebo	4672	4413	4355	4235	4030	3905	3742	3640	2303	756

Marso SP, et al. *N Engl J Med*. 2016;375:311-322.

ITALIAN CHAPTER

Is Hemoglobin A1C the right outcome for studies of diabetes?

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[†]Section of Cardiovascular Medicine and the Robert Wood Johnson Foundation Clinical Scholars Program, Department of Internal Medicine, Yale School of Medicine, Department of Health Policy and Management, Yale School of Public Health, and the Center for Outcomes Research and Evaluation, Yale–New Haven Hospital, New Haven, CT

JAMA. 2017 March 14; 317(10): 1017–1018.

The goals of treatment of type 2 diabetes are to reduce the risk of diabetic complications and, as a result, improve the quality and, possibly, quantity of life. For several decades, authoritative guidelines instructed clinicians to strictly control glucose levels of patients with diabetes to accomplish these goals. In addition, in the 1990s, the FDA began to approve drugs for the treatment of diabetes based upon hemoglobin A1c (HbA1c) as the outcome. The prevailing belief was that risk reduction could be achieved by a clinical focus on reaching target values of HbA1c, agnostic to the strategies employed. This belief, analogous to early notions about lipid lowering, persisted despite the failure of trials evaluating tight glycemic targets to reduce the risk of heart disease or improve survival.[1]

Results from recent cardiovascular outcomes trials of patients with type 2 diabetes are shifting this approach. In these trials, drugs that lowered HbA1c to similar levels had different effects on patient outcomes.[2–6] For example, empagliflozin compared with placebo decreased cardiovascular events and mortality.[5] Levels of HbA1c were similar between the groups because investigators were encouraged to adjust background therapies to achieve glycemic control according to local guidelines. Similarly, semaglutide compared with placebo lowered the risk of major cardiovascular events, despite minimal differences in HbA1c between the groups.[4] The results imply that the type of drug used to achieve glycemic control matters, because the total effect of a drug is not entirely conveyed by its effect on glucose levels. As a result, the diabetes field is moving away from its historic reliance on surrogate markers and toward outcome studies to identify drugs that actually achieve the goals of diabetes care.

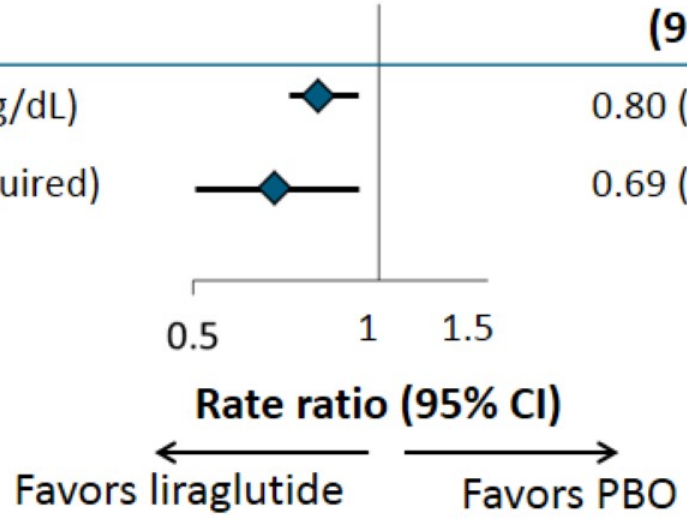
Type 2 diabetes
More than hyperglycaemia

Most important
Treat the patient!
Not the HbA_{1c}

LEADER: Risk for Hypoglycemia

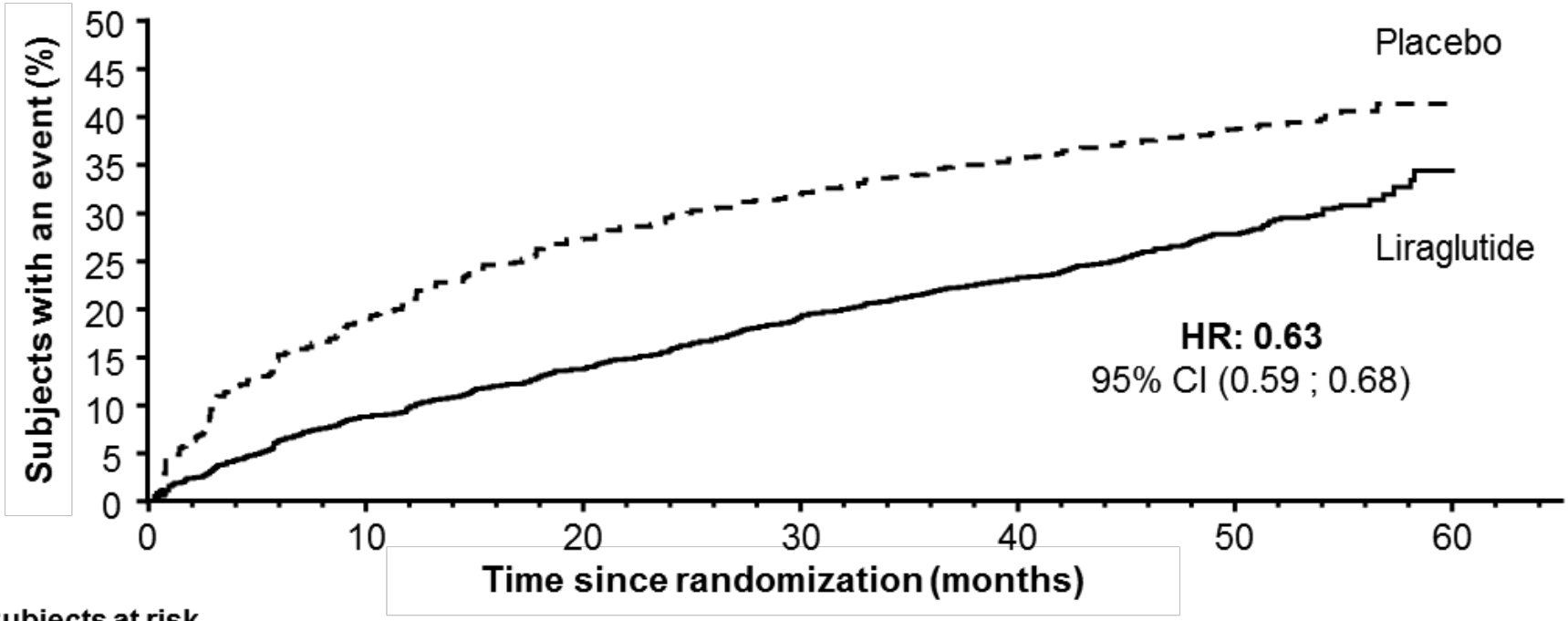
ITALIAN CHAPTER

	Rate ratio (95% CI)	*P Value*
Confirmed hypoglycemia (PG ≤56 mg/dL)	0.80 (0.74-0.88)	<.001
Severe hypoglycemia (assistance required)	0.69 (0.51-0.93)	.016



Marso SP, et al. *N Engl J Med*. 2016 Jun 13 [Epub ahead of print].

Time to first initiation of insulin or any new OAD

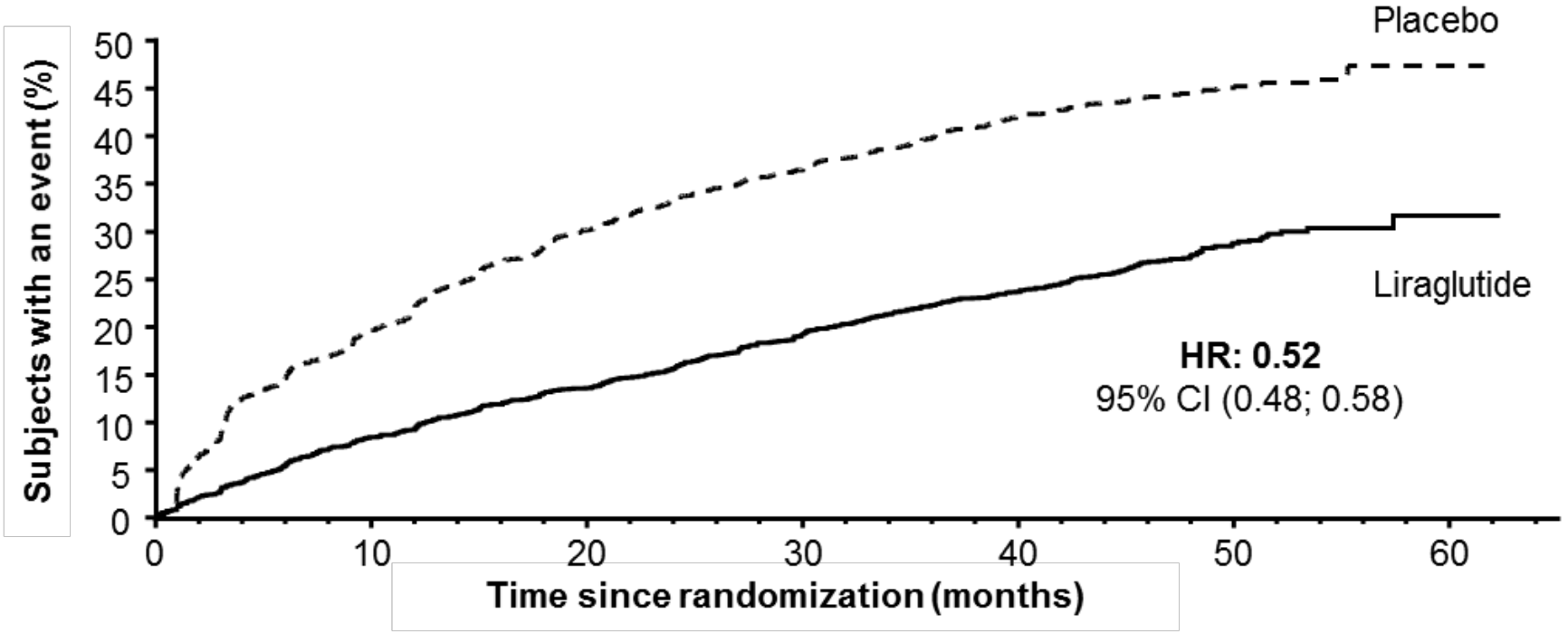


Subjects at risk							
Liraglutide	4668	4068	3786	3452	3183	705	5
Placebo	4672	3575	3111	2803	2548	541	9

Time to first event analyzed using a Cox regression with treatment group as fixed factor. Only events that occurred between randomization date and follow-up date were used for defining first event. Subjects without an event were censored at time of last contact (phone or visit)
CI: confidence interval; HR: hazard ratio; OAD: oral antidiabetic drug

Presented at the American Diabetes Association 77th Scientific Sessions, Session 1-AC-SY13. June 11 2017, San Diego, CA, USA

Time to insulin initiation – patients insulin-naïve at baseline



Subjects at risk							
Liraglutide	2633	2386	2238	2057	1906	448	3
Placebo	2548	2026	1728	1534	1374	336	7

Kaplan–Meier plot of time to insulin initiation in patients who were insulin-naïve at baseline; Cox proportional-hazards regression model adjusted for treatment; patients without an event are censored at time of last contact (phone or visit)
CI: confidence interval; HR: hazard ratio

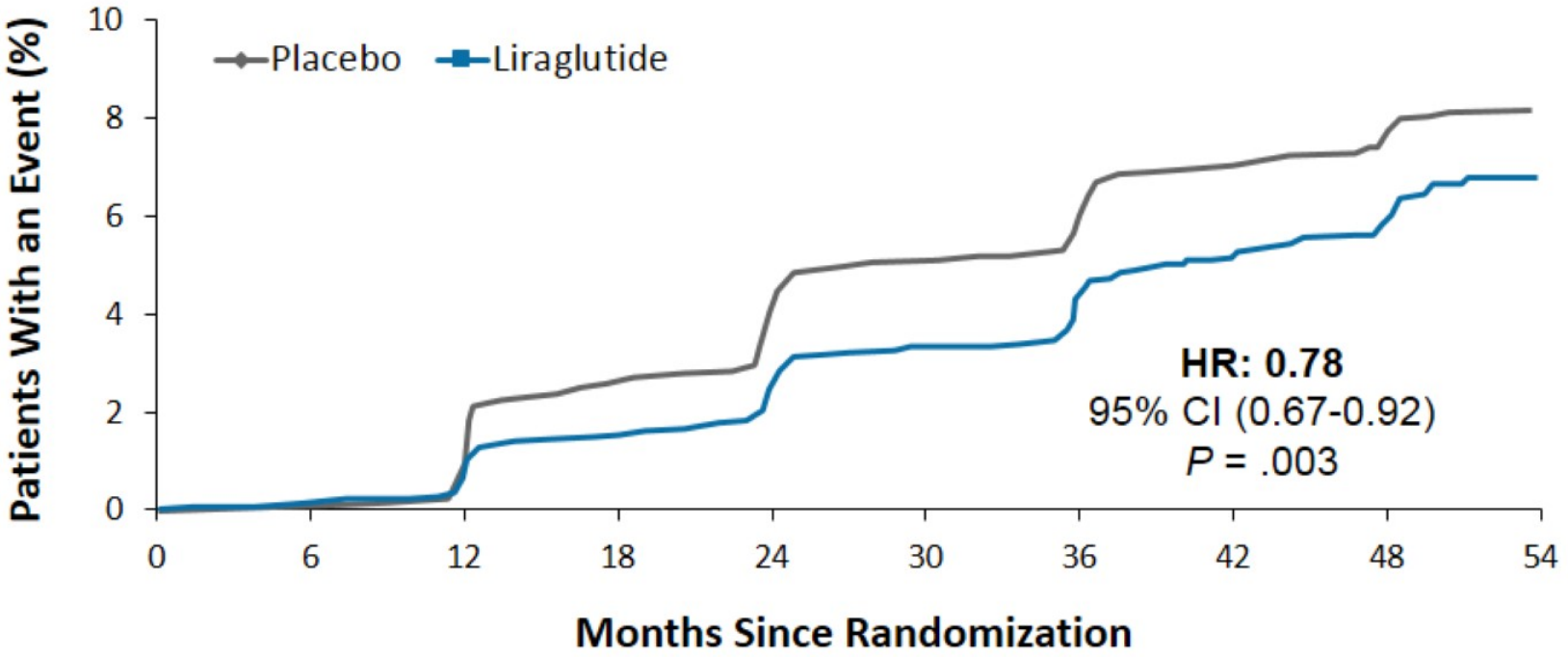
Presented at the American Diabetes Association 77th Scientific Sessions, Session 1-AC-SY13. June 11 2017, San Diego, CA, USA

Microvascular event definitions

Event type		Event definition – one or more of the below
Microvascular events	**Renal**	• New onset of persistent macroalbuminuria • Persistent doubling of serum creatinine • Need for continuous renal replacement therapy • Death due to renal disease
	Eye	• Need for retinal photocoagulation or treatment with intravitreal agents • Vitreous hemorrhage • Diabetes-related blindness

Presented at the American Diabetes Association 76th Scientific Sessions, Session 3-CT-SY24. June 13 2016, New Orleans, LA, USA.

LEADER: Time to First Renal Event*



Patients at risk

Liraglutide	4668	4635	4561	4492	4400	4304	4210	4114	1632	454
Placebo	4672	4643	4540	4428	4316	4196	4094	3990	1613	433

*Macroalbuminuria, doubling of serum creatinine, ESRD, or renal death

Mann JF. ADA 76th Scientific Sessions, Session 3-CT-SY24. June 13 2016, New Orleans, LA.

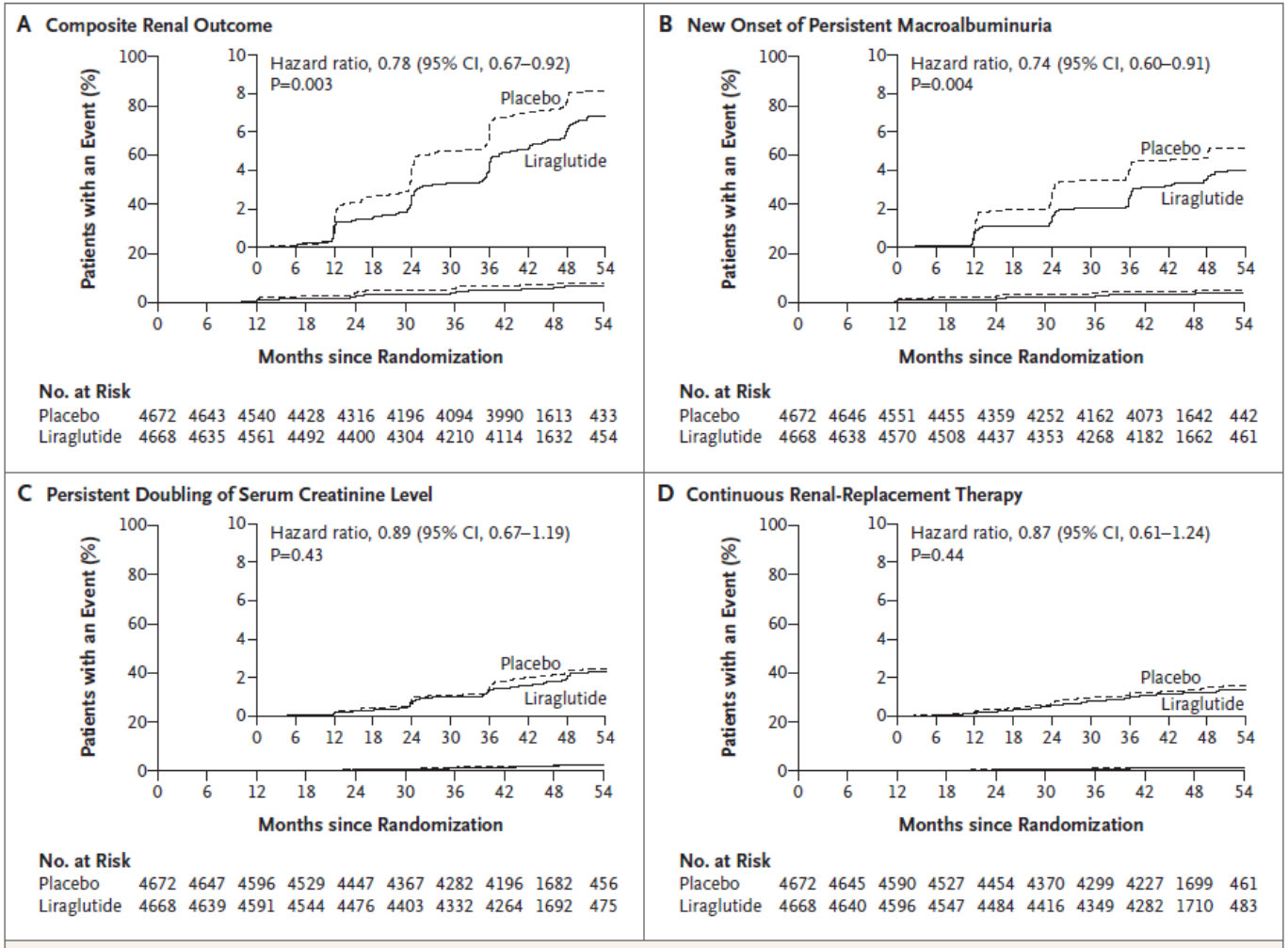


Figure 1. Composite Renal Outcome and Components of the Composite Outcome.

The primary composite renal outcome in the time-to-event analysis was a composite (Panel A) of the first occurrence of persistent macroalbuminuria (Panel B), persistent doubling of the serum creatinine level and an estimated glomerular filtration rate of 45 ml or less per minute per 1.73 m^2 of body-surface area (referred to as persistent doubling of the serum creatinine level; Panel C), the need for continuous renal-replacement therapy (for end-stage renal disease; Panel D), or death due to renal disease (data not shown). The component of death due to renal disease occurred in 13 patients (8 patients in the liraglutide group and 5 in the placebo group). Cumulative incidences were estimated with the use of the Kaplan–Meier method, and the hazard ratios were calculated with the use of the Cox proportional-hazard regression model. The insets show the same data on an enlarged y axis. The data analyses are truncated at 54 months because less than 10% of the participants had an observation time beyond 54 months. All the events were adjudicated. One patient with macroalbuminuria at baseline had an event of new-onset persistent macroalbuminuria that was confirmed by adjudication after the patient had regression to microalbuminuria earlier in the trial.

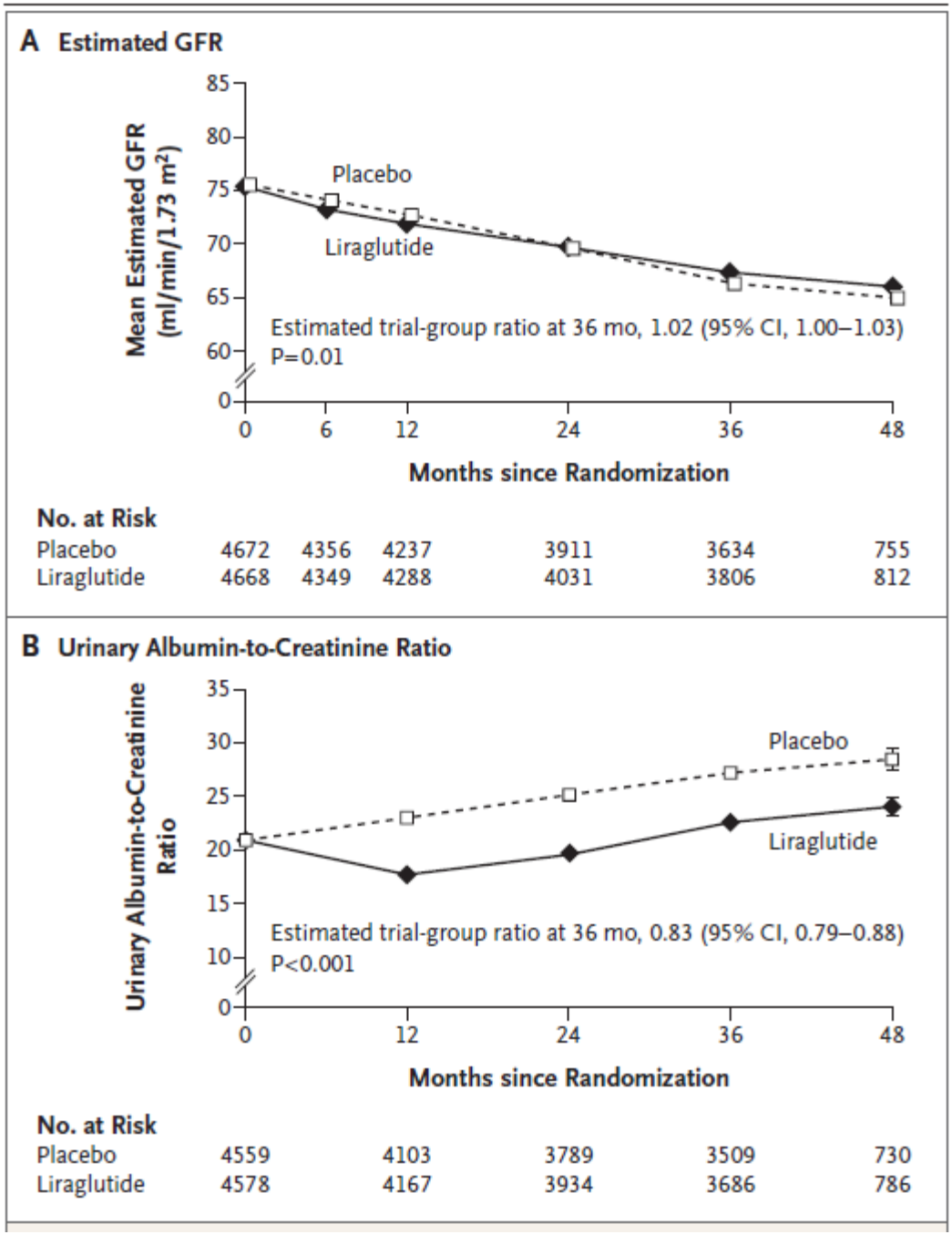


Figure 3. Changes in the Estimated GFR and Urinary Albumin-to-Creatinine Ratio.

Panel A shows the estimated GFR, and Panel B the urinary albumin-to-creatinine ratio (with albumin measured in milligrams and creatinine measured in grams). Geometric means were estimated for the urinary albumin-to-creatinine ratio with the use of a linear mixed model for log-transformed assessment, with accounting for repeated measures. Trial-group ratios were estimated with the use of a mixed-effect model for repeated measures on log-transformed values. Interaction between visit and, respectively, trial group, sex, geographic region, and use of antidiabetic therapy at baseline were included as fixed effects, and interaction between visit and baseline log-estimated GFR or baseline urinary albumin-to-creatinine ratio and age at baseline were included as covariates. The values for the urinary albumin-to-creatinine ratio that were outside the range of quantification were imputed (see the Supplementary Methods section in the Supplementary Appendix).

Nat Rev Nephrol. 2017 ; 13(10):605-628.

Marcel H. A. Muskiet1*,

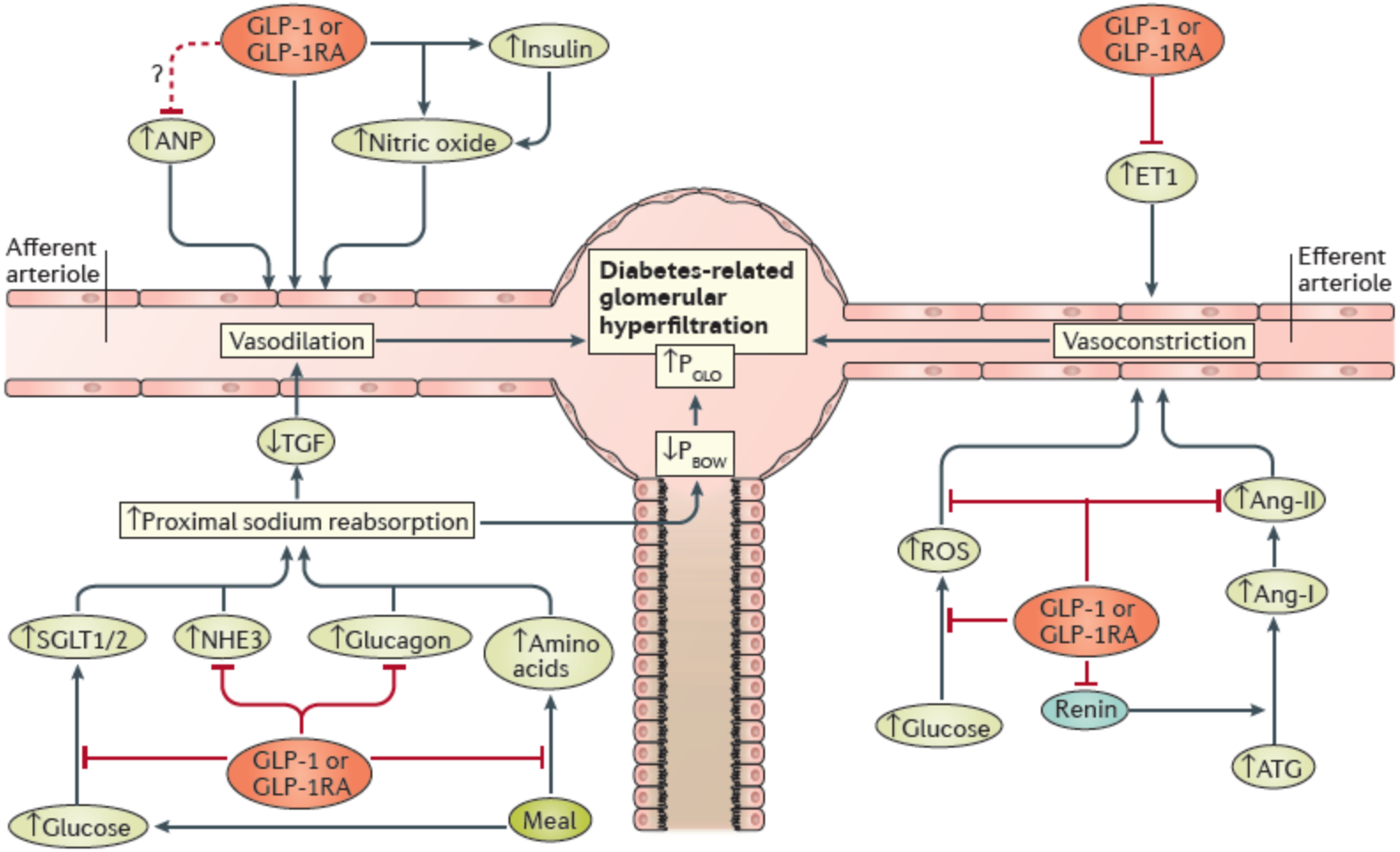
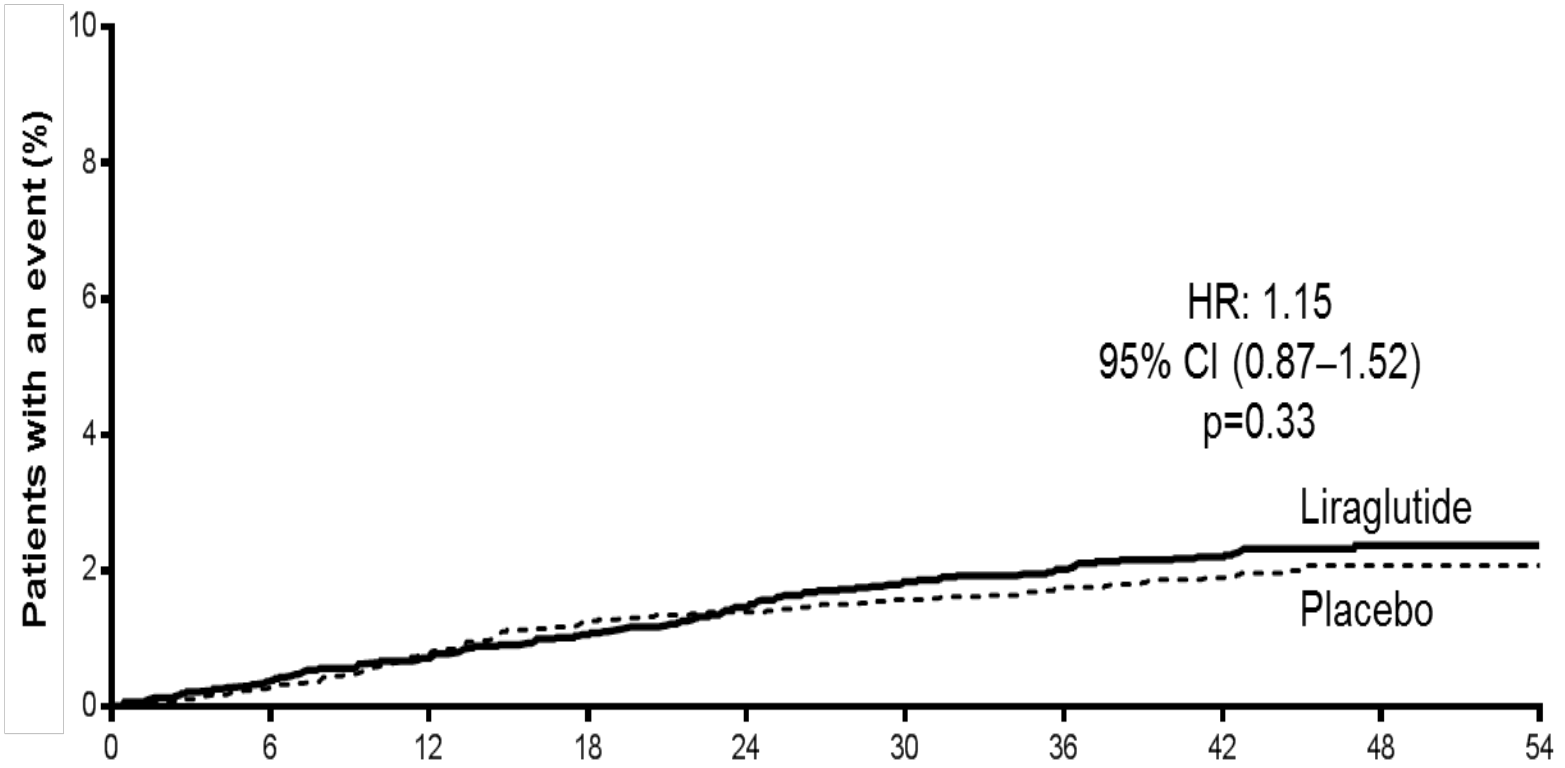


Figure 4 | **Effects of glucagon-like peptide 1 (GLP-1) and GLP-1 receptor agonists (GLP-1RAs) on renal haemodynamics in diabetes mellitus.** Several vascular and tubular factors are implicated in fasting and postprandial glomerular hyperfiltration in the setting of diabetes. These factors result in a net reduction in afferent renal arteriolar resistance, a net increase in efferent renal arteriolar resistance and/or a reduction in hydraulic pressure in Bowman space (P_{BOW}), and thereby an increase in glomerular hydraulic pressure (P_{GLO}) and single nephron glomerular filtration rate. GLP-1RAs are associated with direct GLP-1R-mediated and, at least in part, nitric oxide-dependent vasodilation of the afferent renal arteriole, as well as indirect inhibition of vascular and tubular factors that are putative mediators of glomerular hyperfiltration in diabetes. The integrated effect of incretin-based therapy on renal haemodynamics seems to be the result of direct vasodilative actions and inhibition of pathways of glomerular hyperfiltration. Theoretically, this effect is dependent on baseline phenotypic characteristics and co-medication. Ang-I, angiotensin I; Ang-II, angiotensin II; ANP, atrial natriuretic peptide; ATG, angiotensinogen; ET1, endothelin 1; NHE3, sodium–hydrogen exchanger isoform 3; ROS, reactive oxygen species; SGLT, sodium–glucose co-transporter; TGF, tubuloglomerular feedback.

Time to first eye event

Photocoagulation or treatment with intravitreal agents, vitreous hemorrhage or blindness



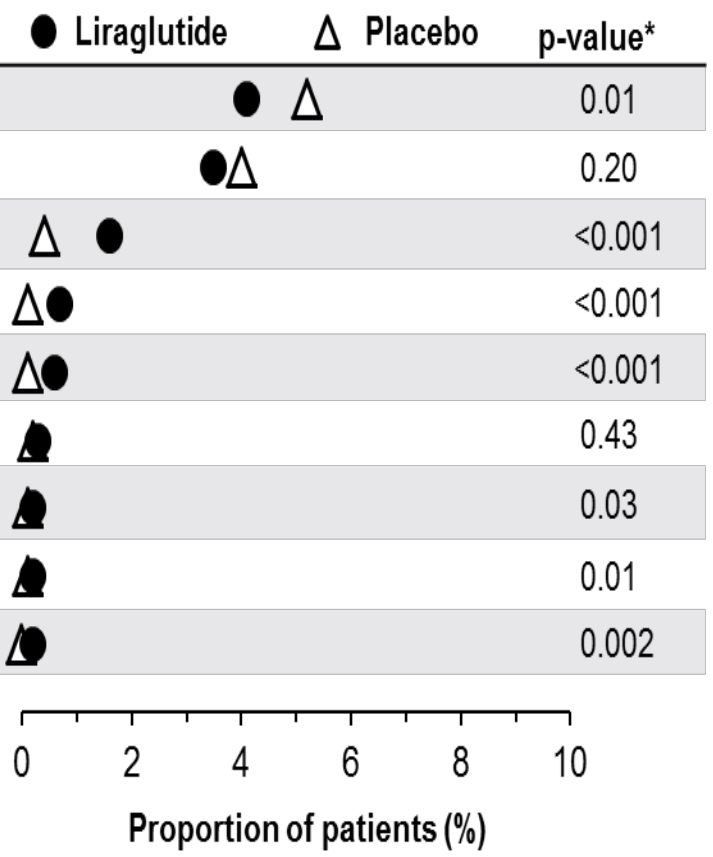
Patients at risk										
Liraglutide	4668	4624	4566	4509	4442	4366	4297	4231	1689	473
Placebo	4672	4636	4565	4489	4417	4339	4264	4188	1681	454

The cumulative incidences were estimated with the use of the Kaplan–Meier method, and the hazard ratios with the use of the Cox proportional-hazard regression model. The data analyses are truncated at 54 months, because less than 10% of the patients had an observation time beyond 54 months. CI: confidence interval; HR: hazard ratio.

Presented at the American Diabetes Association 76th Scientific Sessions, Session 3-CT-SY24. June 13 2016, New Orleans, LA, USA.

AEs leading to permanent treatment discontinuation

	Number of patients	
	Liraglutide	Placebo
Serious adverse event	192	245
Severe adverse event	164	188
Nausea	77	18
Vomiting	31	2
Diarrhea	27	5
Lipase increased	15	11
Abdominal pain	11	3
Decreased appetite	11	3
Abdominal discomfort	10	0



*Exploratory analysis with no adjustment of p-values for multiplicity.
Permanent discontinuation of the treatment regimen was indicated by the investigator in the adverse event form. P-values were calculated by means of Pearson's chi-square test.

Presented at the American Diabetes Association 76th Scientific Sessions, Session 3-CT-SY24. June 13 2016, New Orleans, LA, USA.

LEADER: Incidence of Pancreatitis*

	Liraglutide		Placebo		
	N	%	N	%	*P* value
Acute pancreatitis	18	0.4	23	0.5	.44
Chronic pancreatitis	0	0.0	2	0.0	.16

*Confirmed by adjudication

ITALIAN CHAPTER

Marso SP, et al. *N Engl J Med*. 2016;375:311-322.

Summary

- Liraglutide reduced the risk of major CV events in patients with T2DM at high CV risk
  - Both risk of first event and recurrent events
- The reduction in CV events with liraglutide appeared independent of:
  - Baseline insulin or CV medication use
  - Initiation of insulin or SU/TZD during the trial
  - Experiencing an episode of severe hypoglycemia
- It appears unlikely that the CV risk reduction with liraglutide can be fully explained by the observed differences in HbA_{1c}, body weight, SBP and lipids

CV: cardiovascular; HbA_{1c}: glycated hemoglobin; SBP: systolic blood pressure; SU: sulfonylurea; T2DM: type 2 diabetes mellitus

Presented at the American Diabetes Association 77th Scientific Sessions, Session 1-AC-SY13. June 11 2017, San Diego, CA, USA

LEADER: Summary (2)

- Liraglutide reduced the risk for 3-point MACE by 13%
  - All 3 components of MACE contributed to the risk reduction
- Liraglutide reduced composite microvascular endpoints
  - Driven by reduced new and persistent macroalbuminuria
- Liraglutide resulted in reductions in HbA_{1c}, body weight, and hypoglycemia
- Liraglutide was generally well tolerated. In line with previous trials, liraglutide was associated with gastrointestinal side effects, increases in pancreatic enzymes and heart rate

HbA_{1c}: glycated hemoglobin; MACE: major adverse cardiovascular event.

Presented at the American Diabetes Association 76th Scientific Sessions, Session 3-CT-SY24. June 13 2016, New Orleans, LA, USA.

LEADER: Summary (3)

- No increase in pancreatitis but an increase in acute gallstone disease
- No increase in hospitalization for heart failure
- Liraglutide reduced the risk of all-cause death by 15%
- Liraglutide reduced the risk of CV death by 22%

CV: cardiovascular.

Presented at the American Diabetes Association 76th Scientific Sessions, Session 3-CT-SY24. June 13 2016, New Orleans, LA, USA.

Potential Mechanism of Liraglutide on CV Outcomes

- **Pattern of CV benefit observed in LEADER trial different from that observed in EMPA-REG OUTCOME trial**
  - The time to benefit emerged later in LEADER vs EMPA-REG OUTCOME
  - Greater consistency in effects on the components of the composite primary outcome in LEADER
- **Benefits observed in EMPA-REG OUTCOME likely more closely linked to hemodynamic changes**
- **Benefits observed in LEADER are perhaps related to the modified progression of atherosclerotic vascular disease**

ITALIAN CHAPTER

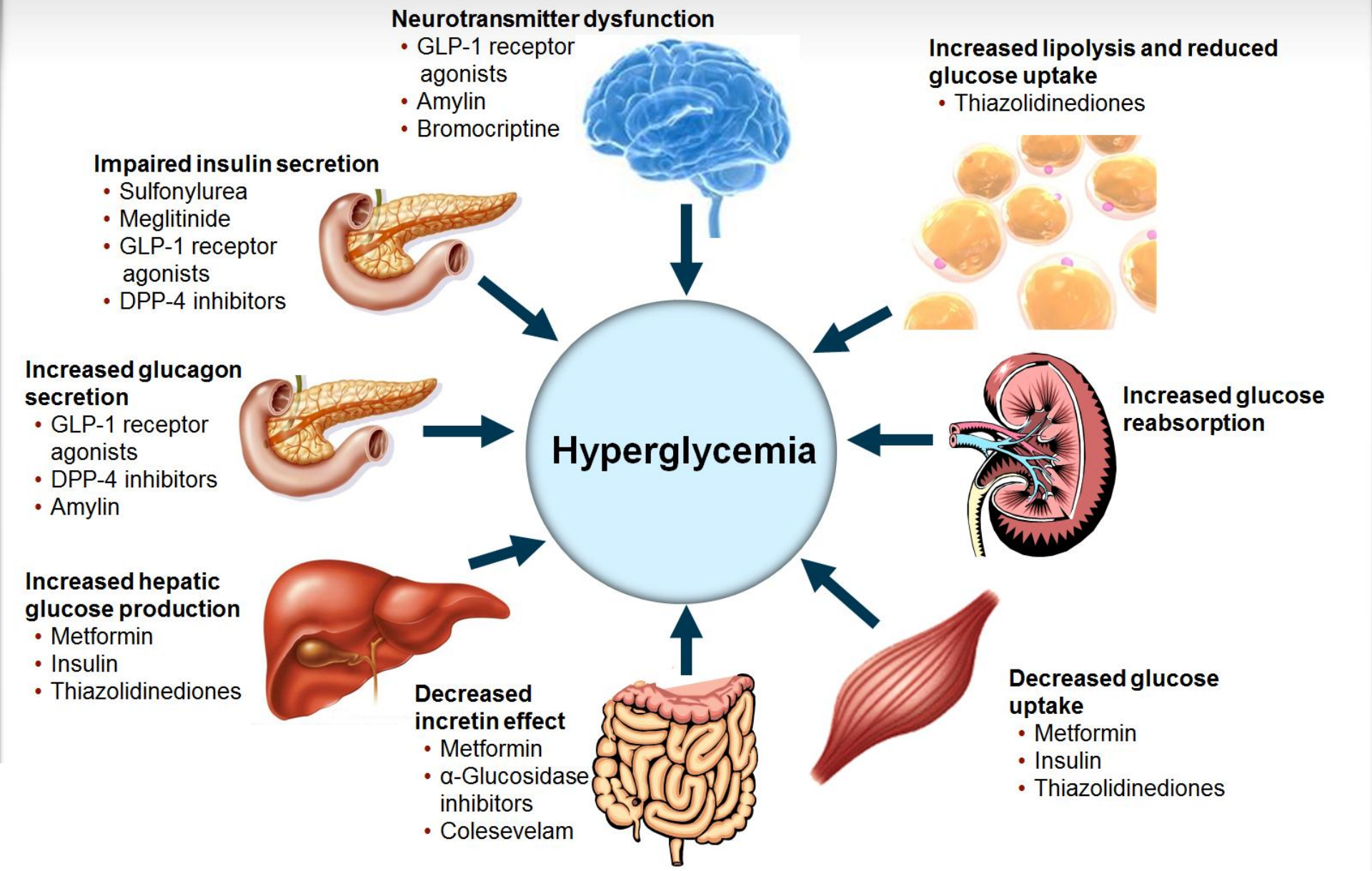
Marso SP, et al. *N Engl J Med*. 2016;375:311-322.

ITALIAN CHAPTER

Summary

- Data from the LEADER trial provides a further impetus for earlier use of GLP-1 RAs, especially in T2DM patients at high CV risk, but probably also for other patient subgroups

Hyperglycemia in Type 2 Diabetes



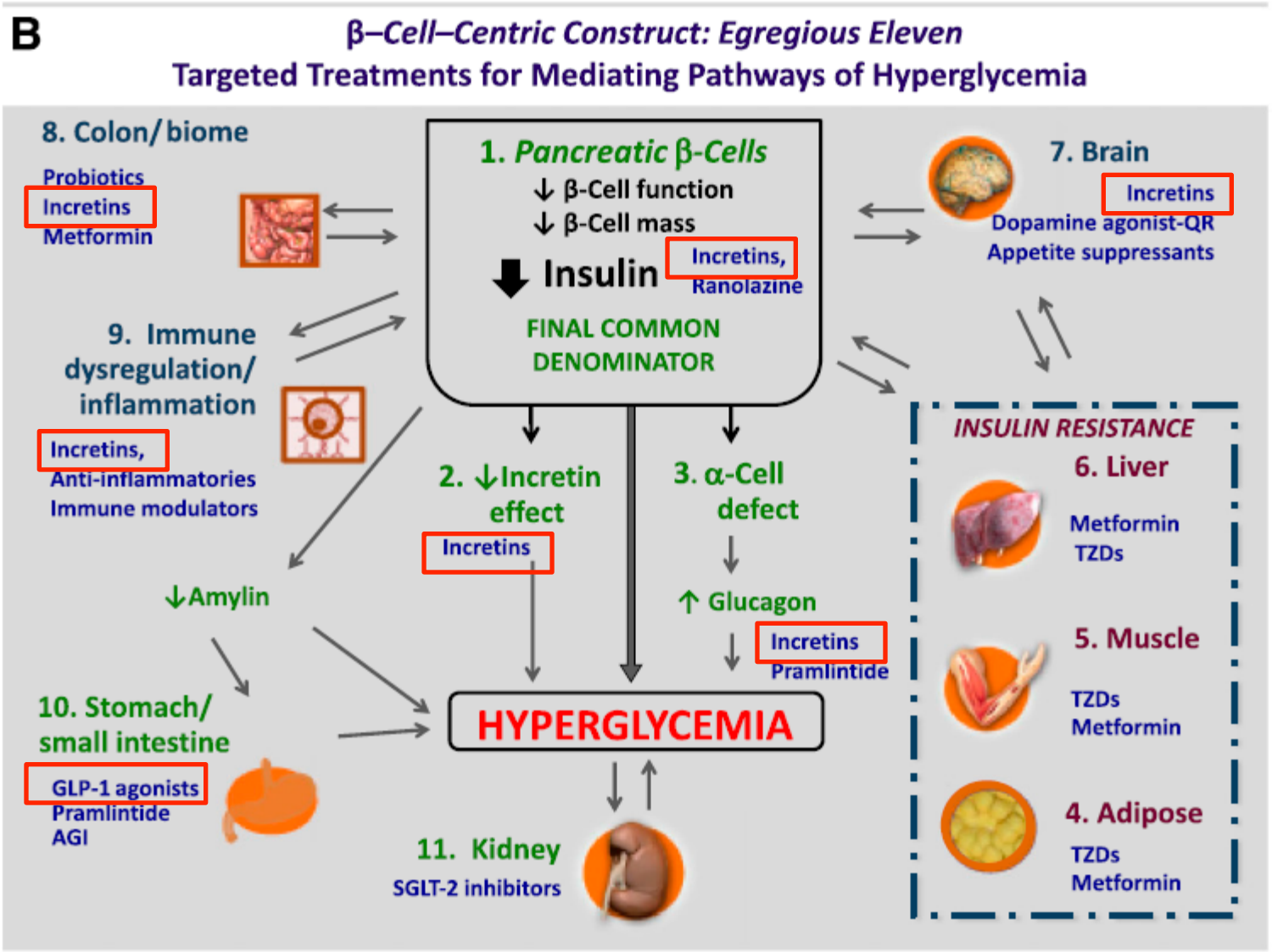
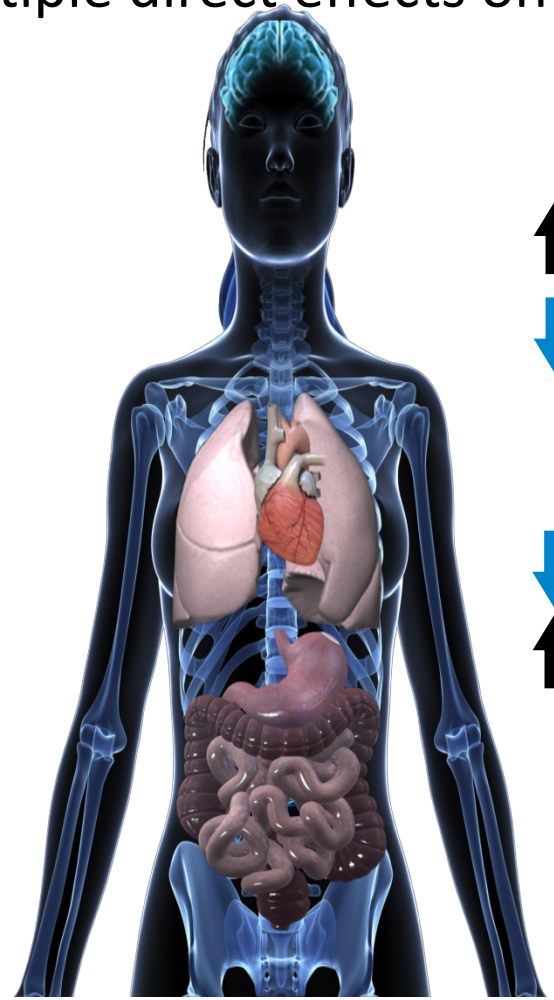


Figure 3—β-Cell–centric construct: the egregious eleven. Dysfunction of the β-cells is the final common denominator in DM. *A*: Eleven currently known mediating pathways of hyperglycemia are shown. Many of these contribute to β-cell dysfunction (liver, muscle, adipose tissue [shown in red to depict additional association with IR], brain, colon/biome, and immune dysregulation/inflammation [shown in blue]), and others result from β-cell dysfunction through downstream effects (reduced insulin, decreased incretin effect, α-cell defect, stomach/small intestine via reduced amylin, and kidney [shown in green]). *B*: Current targeted therapies for each of the current mediating pathways of hyperglycemia. GLP-1, glucagon-like peptide 1; QR, quick release.

Liraglutide has multiple direct effects on human physiology[1]



Pancreas[2–4]

↑ Insulin secretion (glucose-dependent) and β-cell sensitivity

↑ Insulin synthesis

↓ Glucagon secretion (glucose-dependent)

Liver[4]

↓ Hepatic glucose output

Brain[5,6]

↑ Satiety

↓ Energy intake

Cardiovascular system[7,8]

↓ Systolic blood pressure

↑ Heart rate

1. Holst JJ et al. *Trends Mol Med* 2008;14:161–168; 2. Flint A et al. *Adv Ther* 2011;28:213–226; 3. Degn K et al. *Diabetes* 2004;53:1187–1194; 4. Baggio LL, Drucker DJ. *Gastroenterology* 2007;132:2131–2157; 5. Horowitz M et al. *Diabetes Res Clin Pract* 2012;97:258–266; 6. Niswender K et al. *Diabetes Obes Metab* 2013;15:42–54; 7. Fonseca V et al. *Diabetes* 2010;59(Suppl 1):A79 (296-OR); 8. Meier JJ et al. *Nat Rev Endocrinol* 2012;8:728–742

Nat Rev Nephrol. 2017 ; 13(10):605-628.

Marcel H. A. Muskiet1,*

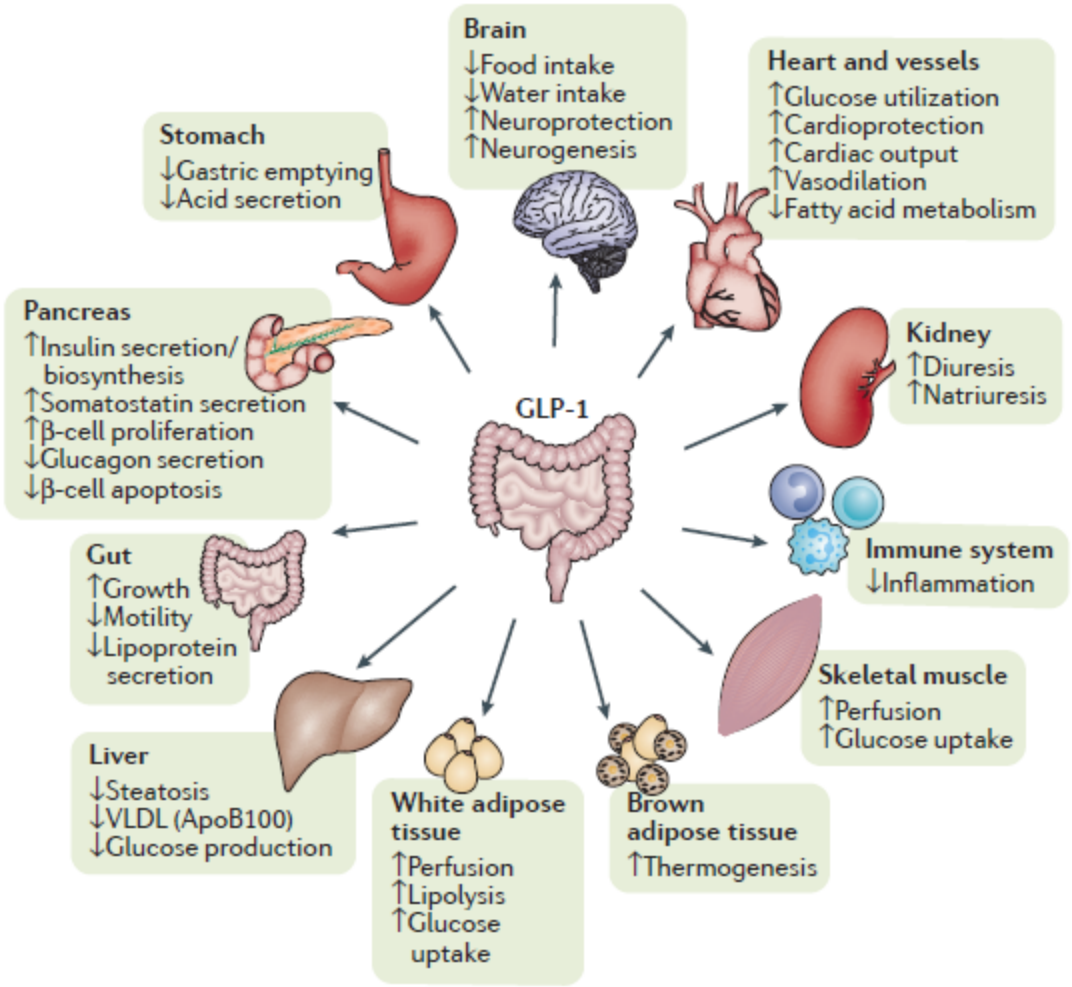
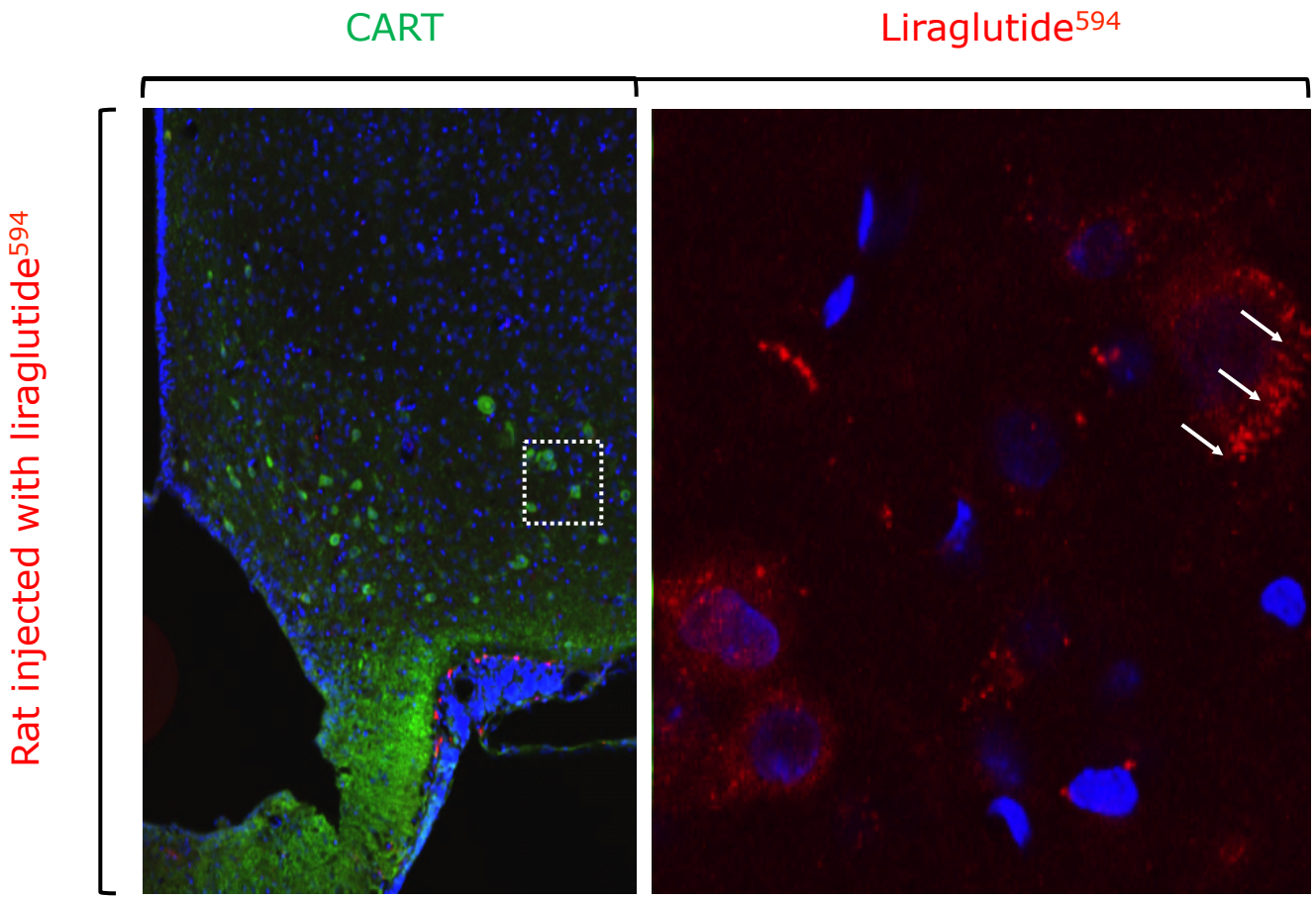


Figure 3 | **Putative actions of glucagon-like peptide 1 (GLP-1).** The best elucidated physiological roles of GLP-1 are those related to pancreatic islet cell function. However, GLP-1 and GLP-1 receptor agonists also have pleiotropic effects on various other tissues and organs, with various potential physiological, pathophysiological and pharmacological implications. VLDL, very low density lipoprotein.

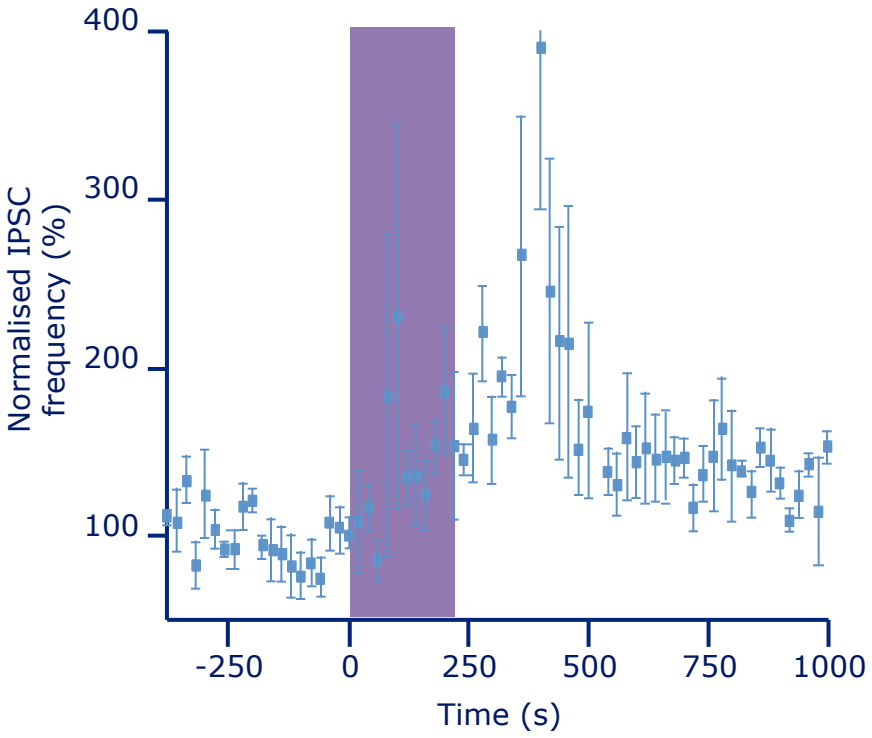
Liraglutide^{594} was localised in CART/POMC neurons in rat brain

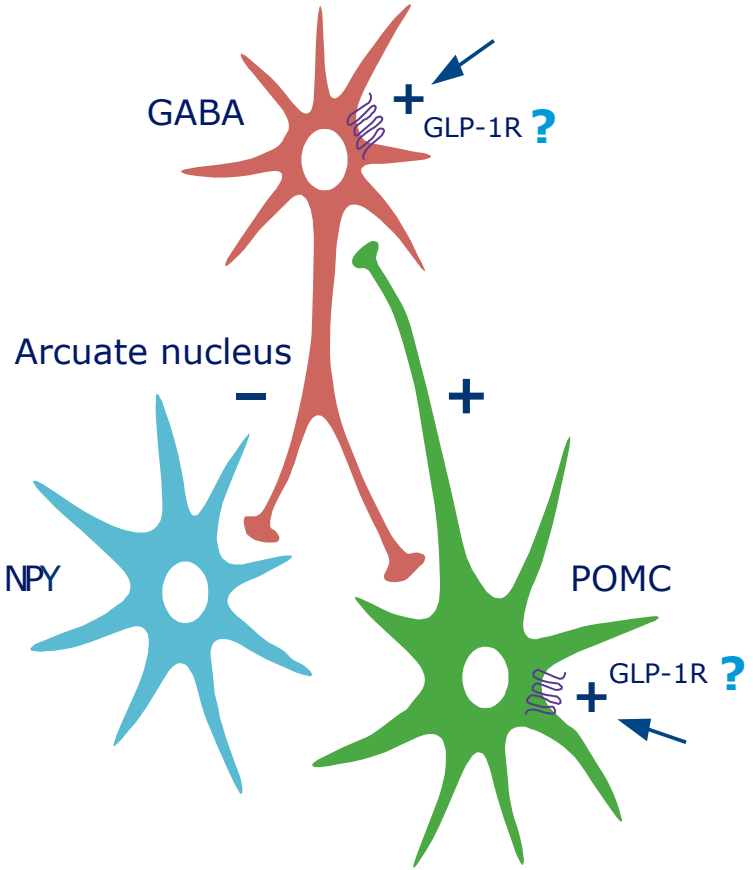


Liraglutide^{594}, Alexa Fluor®594 C5-maleimide-liraglutide; CART, cocaine- and amphetamine-regulated transcript; POMC, pro-opiomelanocortin

Secher *et al. J Clin Invest* 2014;124:4473–88

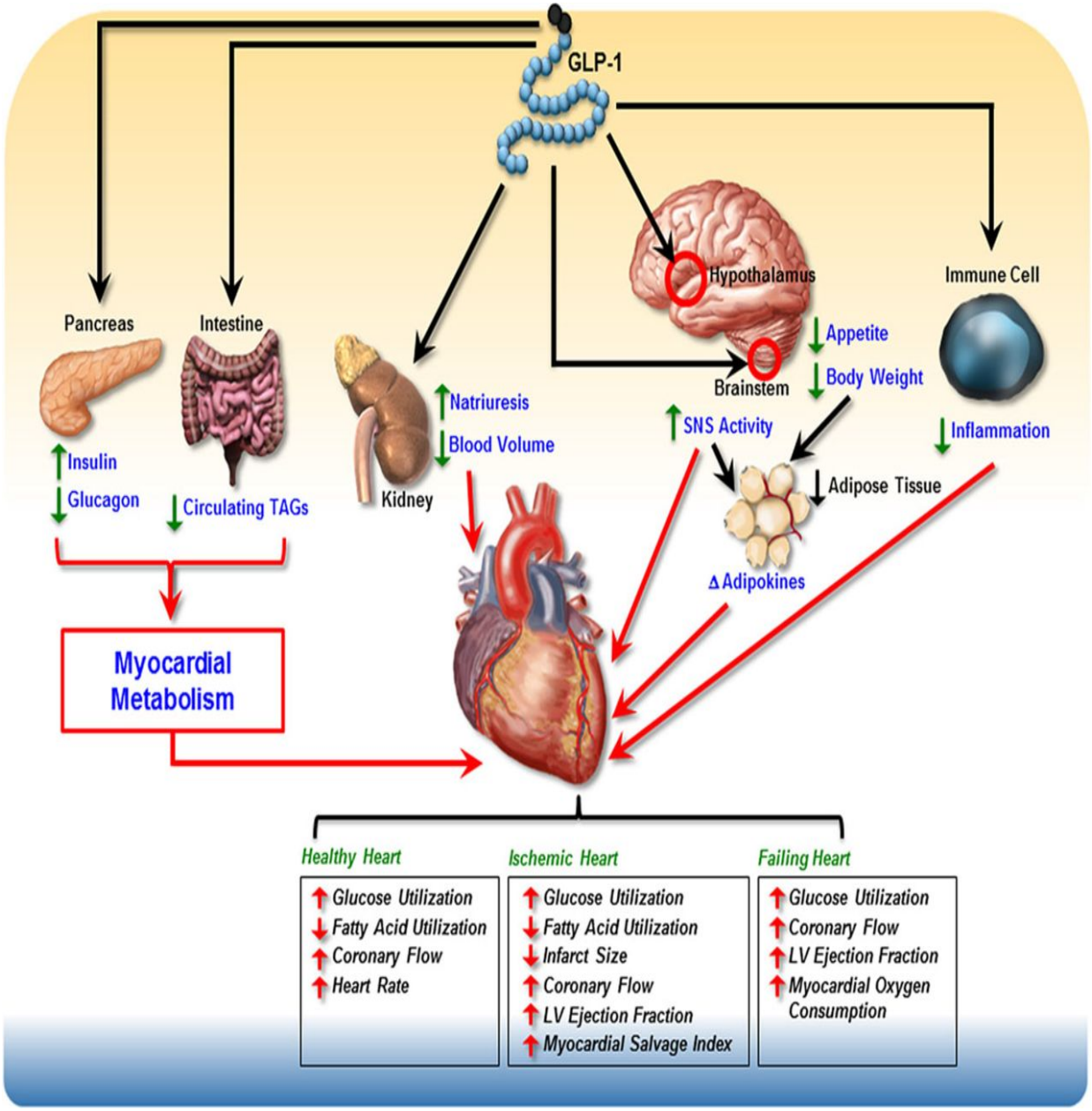
GLP-1 mediated regulation of GABAergic effects on POMC neurons





IPSC frequency (%) from voltage clamp recordings of POMC neurons showed an increased GABAergic IPSC frequency in the presence of GLP-1(7-36)amide. GLP-1, glucagon-like peptide-1; IPSC, inhibitory postsynaptic current; POMC, pro-opiomelanocortin; GABAergic, gamma-aminobutyric acid-ergic; GLP-1(7-36)amide, glucagon-like peptide-1(7-36)amide

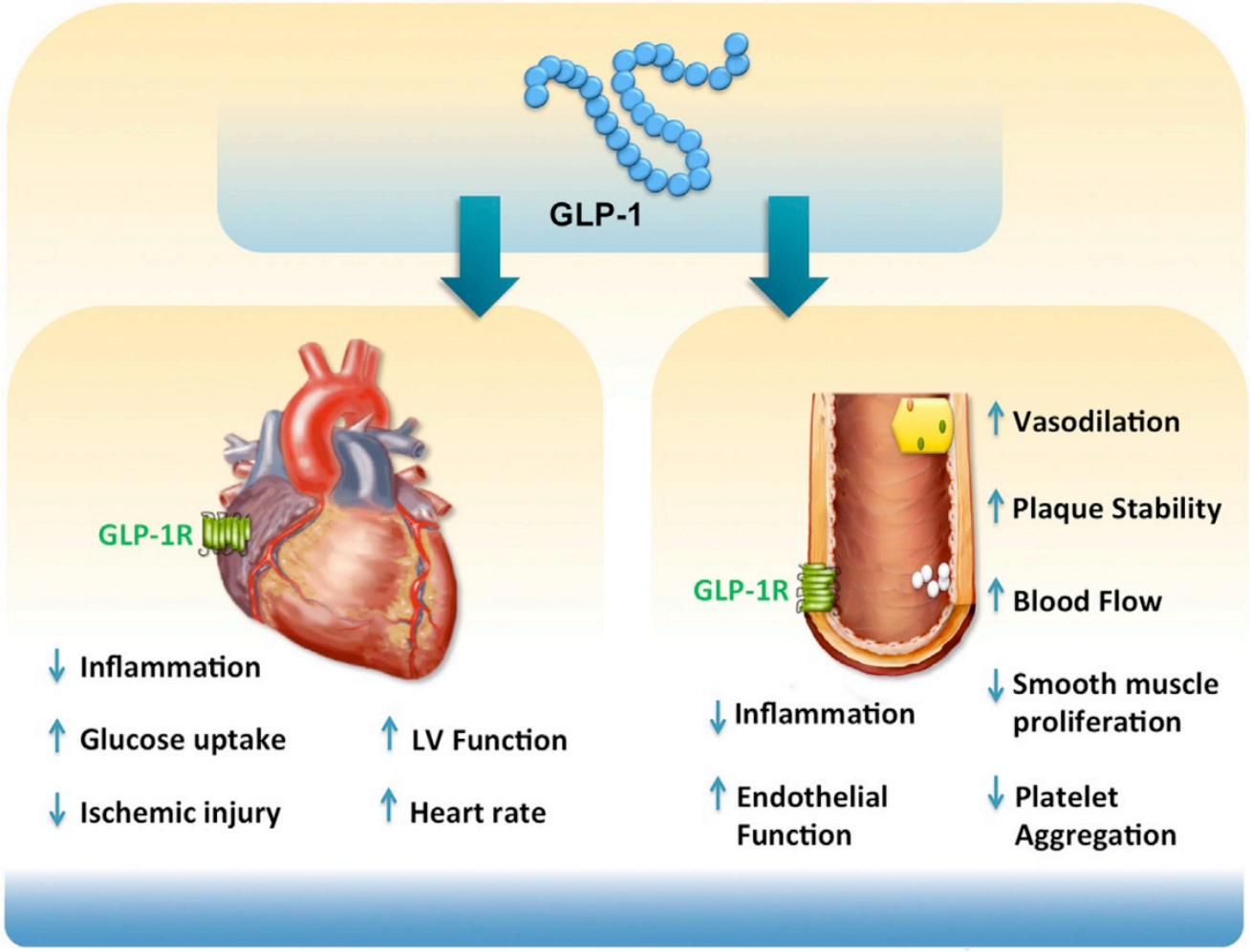
Secher *et al. J Clin Invest* 2014;124:4473–88



Ussher JR, Drucker DJ. *Circ Res* 2014;114:1788–803.

Presented at the American Diabetes Association 76th Scientific Sessions, Session 3-CT-SY24. June 13 2016, New Orleans, LA, USA.

Potential mechanisms for CVD benefit



Drucker DJ. *Cell Metab* 2016;24:15–30

Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes

Steven P. Marso, M.D., Stephen C. Bain, M.D., Agostino Consoli, M.D., Freddy G. Eliaschewitz, M.D., Esteban Jódar, M.D., Lawrence A. Leiter, M.D., Ildiko Lingvay, M.D., M.P.H., M.S.C.S., Julio Rosenstock, M.D., Jochen Seufert, M.D., Ph.D., Mark L. Warren, M.D., Vincent Woo, M.D., Oluf Hansen, M.Sc., Anders G. Holst, M.D., Ph.D., Jonas Pettersson, M.D., Ph.D., and Tina Vilsbøll, M.D., D.M.Sc., for the SUSTAIN-6 Investigators*

ABSTRACT

BACKGROUND

Regulatory guidance specifies the need to establish cardiovascular safety of new diabetes therapies in patients with type 2 diabetes in order to rule out excess cardiovascular risk. The cardiovascular effects of semaglutide, a glucagon-like peptide 1 analogue with an extended half-life of approximately 1 week, in type 2 diabetes are unknown.

METHODS

We randomly assigned 3297 patients with type 2 diabetes who were on a standard-care regimen to receive once-weekly semaglutide (0.5 mg or 1.0 mg) or placebo for 104 weeks. The primary composite outcome was the first occurrence of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke. We hypothesized that semaglutide would be noninferior to placebo for the primary outcome. The noninferiority margin was 1.8 for the upper boundary of the 95% confidence interval of the hazard ratio.

RESULTS

At baseline, 2735 of the patients (83.0%) had established cardiovascular disease, chronic kidney disease, or both. The primary outcome occurred in 108 of 1648 patients (6.6%) in the semaglutide group and in 146 of 1649 patients (8.9%) in the placebo group (hazard ratio, 0.74; 95% confidence interval [CI], 0.58 to 0.95; P<0.001 for noninferiority). Nonfatal myocardial infarction occurred in 2.9% of the patients receiving semaglutide and in 3.9% of those receiving placebo (hazard ratio, 0.74; 95% CI, 0.51 to 1.08; P=0.12); nonfatal stroke occurred in 1.6% and 2.7%, respectively (hazard ratio, 0.61; 95% CI, 0.38 to 0.99; P=0.04). Rates of death from cardiovascular causes were similar in the two groups. Rates of new or worsening nephropathy were lower in the semaglutide group, but rates of retinopathy complications (vitreous hemorrhage, blindness, or conditions requiring treatment with an intravitreal agent or photocoagulation) were significantly higher (hazard ratio, 1.76; 95% CI, 1.11 to 2.78; P=0.02). Fewer serious adverse events occurred in the semaglutide group, although more patients discontinued treatment because of adverse events, mainly gastrointestinal.

CONCLUSIONS

In patients with type 2 diabetes who were at high cardiovascular risk, the rate of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke was significantly lower among patients receiving semaglutide than among those receiving placebo, an outcome that confirmed the noninferiority of semaglutide. (Funded by Novo Nordisk; SUSTAIN-6 ClinicalTrials.gov number, NCT01720446.)

From the Research Medical Center, Kansas City, MO (S.P.M.); School of Medicine, Swansea University, Swansea, United Kingdom (S.C.B.); Department of Medicine and Aging Science and Center of Excellence on Aging and Translational Medicine, G. d'Annunzio University, Chieti-Pescara, Italy (A.C.); CPClin Research Center/Hospital Israelita Albert Einstein, São Paulo (F.G.E.); Hospital Universitario Quirón Salud Madrid, Facultad de Ciencias de la Salud, Universidad Europea de Madrid, Madrid (E.J.); Li Ka Shing Knowledge Institute and Keenan Research Centre for Biomedical Science, St. Michael's Hospital, University of Toronto, Toronto (L.A.L.), and the University of Manitoba, Winnipeg (V.W.) — both in Canada; University of Texas Southwestern Medical Center (I.L.) and Dallas Diabetes Research Center at Medical City (J.R.) — both in Dallas; University of Freiburg Medical Center, Faculty of Medicine, University of Freiburg, Freiburg, Germany (J.S.); Physicians East, Greenville, NC (M.L.W.); and Novo Nordisk, Søborg (O.H., A.G.H., J.P.), and the Center for Diabetes Research, Gentofte Hospital, University of Copenhagen, Hellerup (T.V.) — both in Denmark. Address reprint requests to Dr. Marso at Cardiovascular Services, HCA Midwest Health, Research Medical Center, 2316 E. Meyer Blvd., Kansas City, MO 64132, or at smarso@gmail.com.

*A complete list of the investigators in the Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes (SUSTAIN-6) is provided in the Supplementary Appendix, available at NEJM.org.

This article was published on September 16, 2016, at NEJM.org.

DOI: 10.1056/NEJMoa1607141

ITALIAN CHAPTER

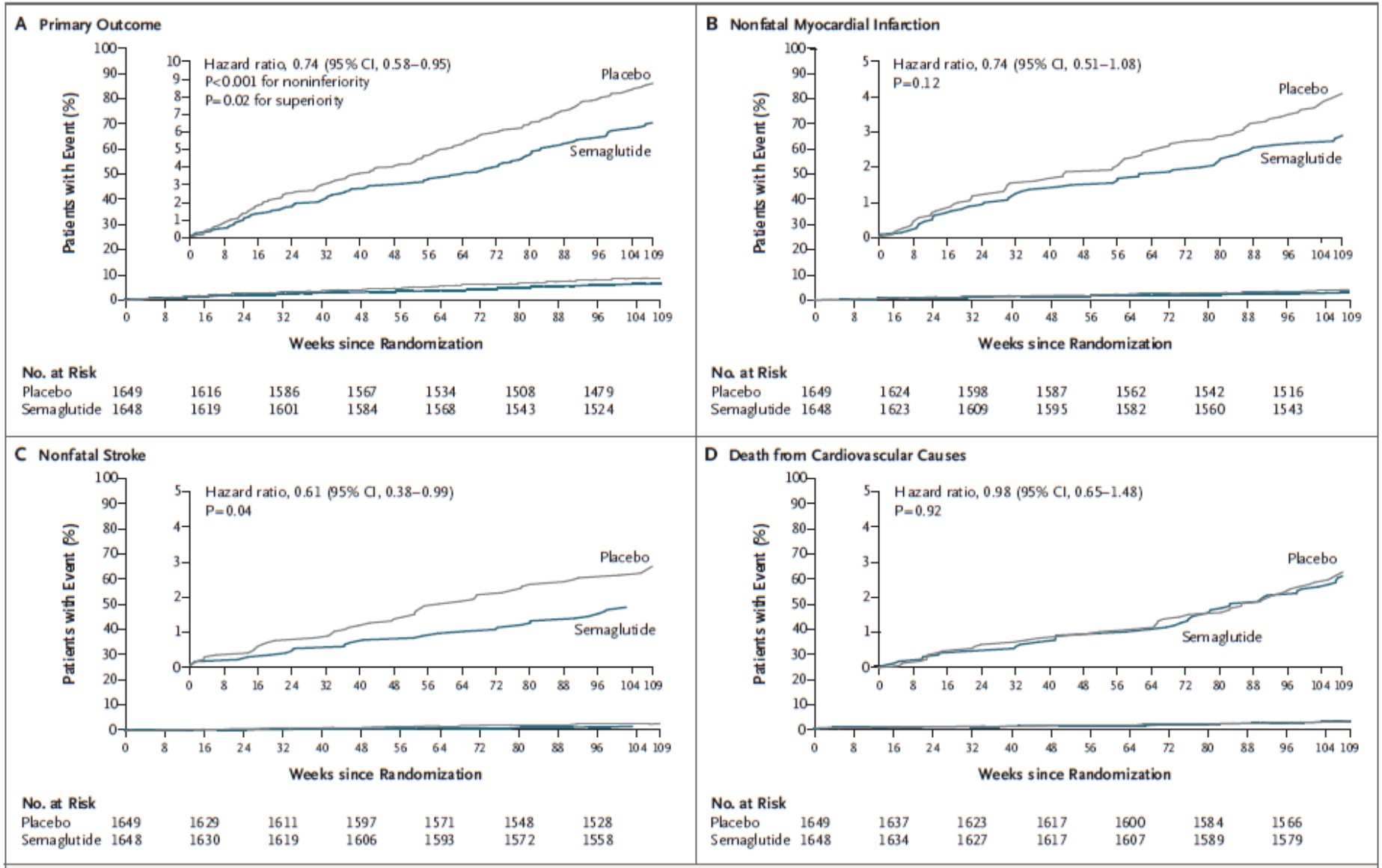


Figure 1. Cardiovascular Outcomes.

Shown are Kaplan–Meier plots of the primary outcome (a composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke) (Panel A), nonfatal myocardial infarction (Panel B), nonfatal stroke (Panel C), and death from cardiovascular causes (Panel D). The trial included a planned observation period of 109 weeks for all patients (a 104-week treatment period with a 5-week follow-up period). In Panel C, there were no events in the semaglutide group after week 104. Insets show the same data on an expanded y axis.

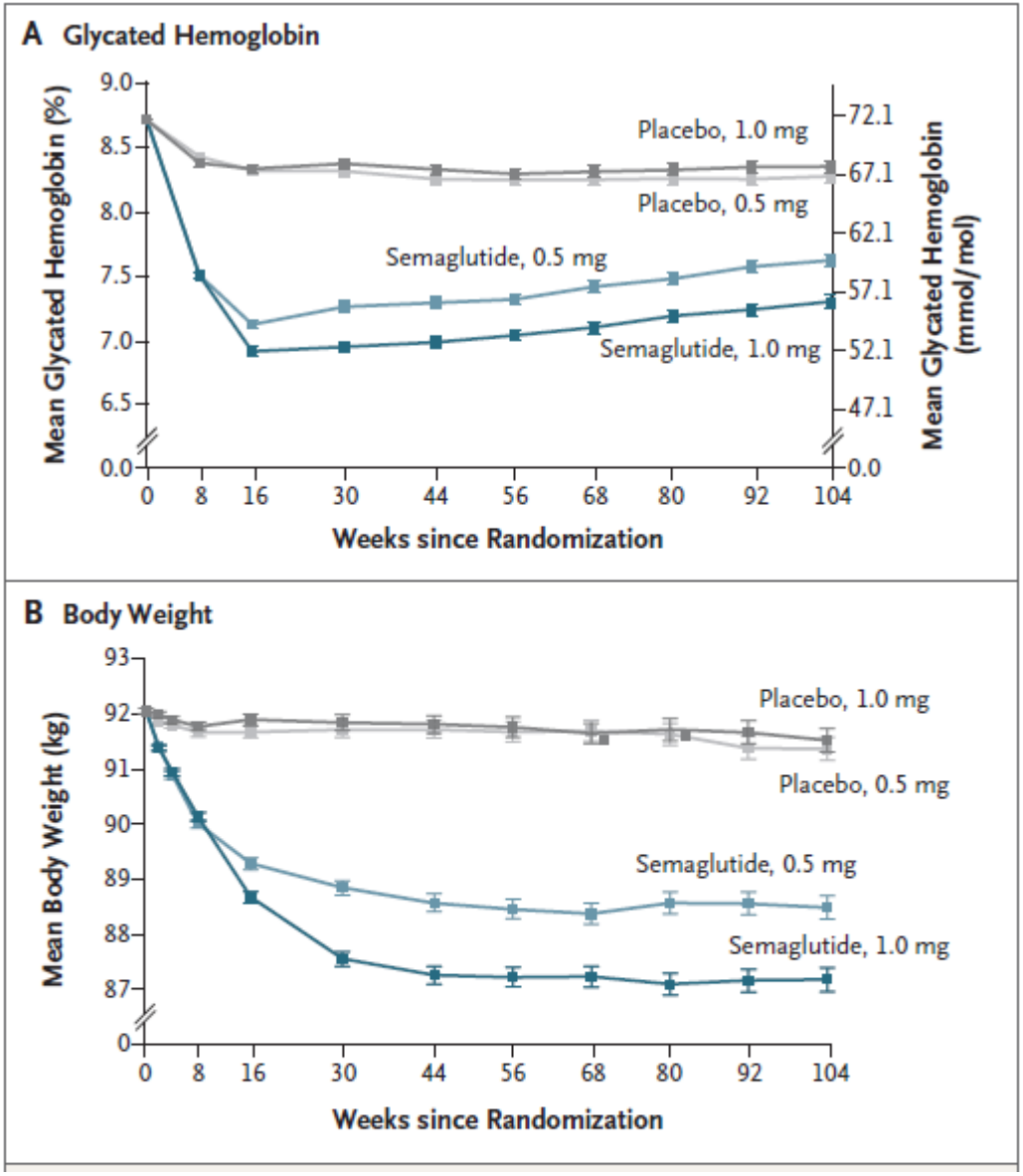


Figure 2. Glycated Hemoglobin and Body Weight.

Shown are the mean values for glycated hemoglobin (Panel A) and body weight (Panel B) during the trial period. The I bars represent standard errors. Data were estimated on the basis of scheduled visits in the full analysis set with the use of a mixed model for repeated measures with treatment group (semaglutide doses of 0.5 mg and 1.0 mg and corresponding placebo doses) and all possible combinations of stratification factors used for randomization as fixed factors.

Steven P. Marso,

This article was published on September 16, 2016, at NEJM.org.

SUSTAIN 6

ITALIAN CHAPTER

- **Long-term, randomized, double-blind, placebo-controlled, multicenter CV outcome trial**
  - Semaglutide, a once-weekly GLP-1 RA vs placebo, in addition to standard care, in patients with T2DM
- **Over a 2-year period in more than 3000 patients, the primary endpoint of noninferiority in a 3-point MACE was met, as well as a statistically significant reduction in CV risk**

Novo Nordisk, 2016.

JAMA | Original Investigation

Effect of Oral Semaglutide Compared With Placebo and Subcutaneous Semaglutide on Glycemic Control in Patients With Type 2 Diabetes

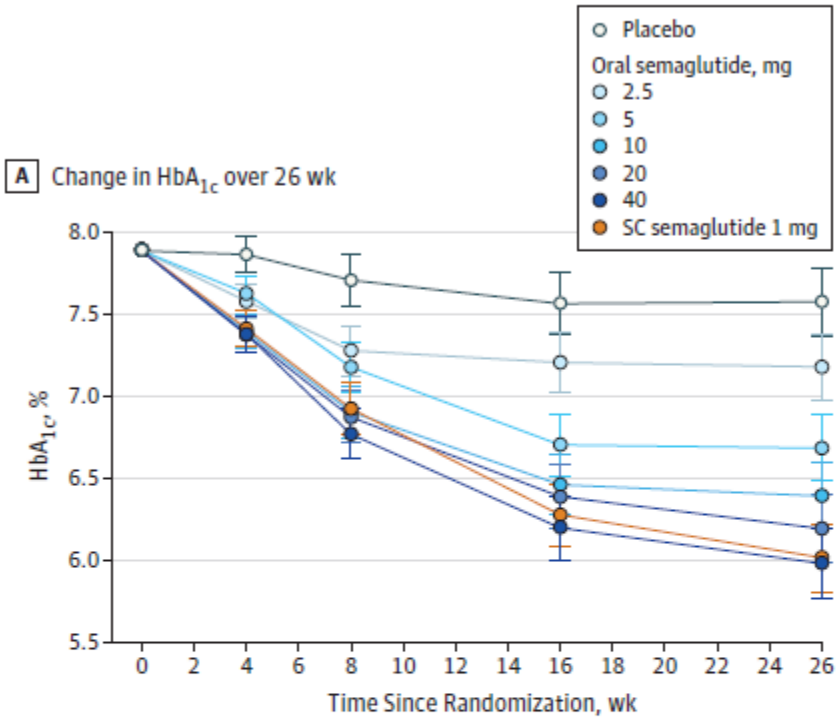
A Randomized Clinical Trial

Melanie Davies, MD; Thomas R. Pieber, MD; Marie-Louise Hartoft-Nielsen, MD; Oluf K. H. Hansen, MSc; Serge Jabbour, MD; Julio Rosenstock, MD

JAMA October 17, 2017 Volume 318, Number 15

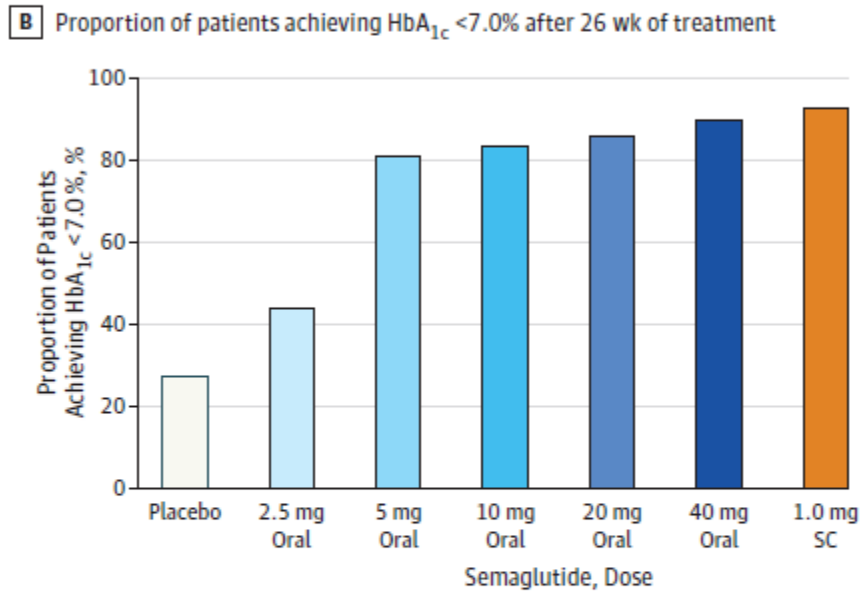
CONCLUSIONS AND RELEVANCE Among patients with type 2 diabetes, oral semaglutide resulted in better glycemic control than placebo over 26 weeks. These findings support phase 3 studies to assess longer-term and clinical outcomes, as well as safety.

Figure 3. Hemoglobin A_{1c} (HbA_{1c}) Efficacy Parameters From Baseline to Week 26 Among Patients With Type 2 Diabetes and Insufficient Glycemic Control



No. of patients[a]

Placebo	69	69	64	57	51
Oral semaglutide, mg					
2.5	68	68	64	61	56
5	69	69	63	61	58
10	66	66	61	61	57
20	70	70	60	53	48
40	68	68	63	55	46
SC semaglutide 1 mg	67	67	66	61	48

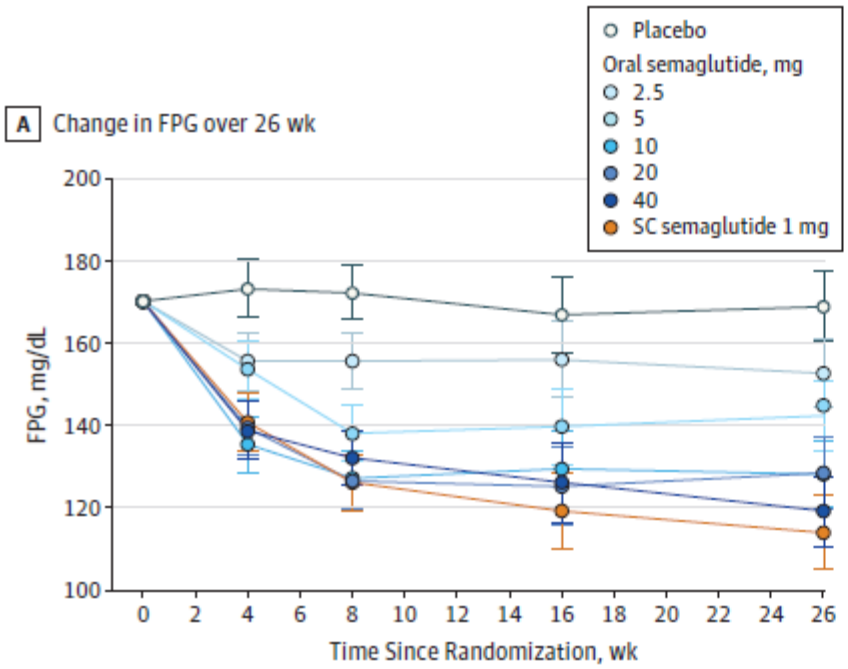


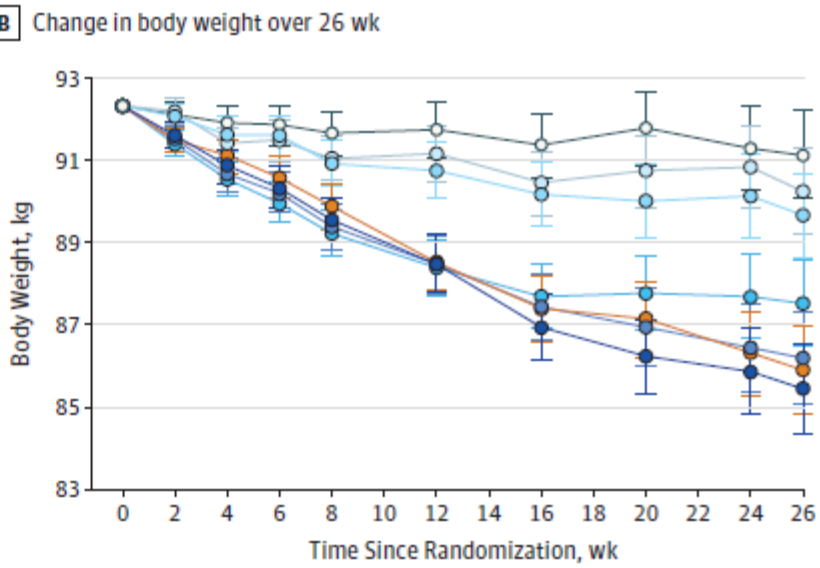
No. of patients[a]							
	69	68	69	67	70	68	68

RMM indicates repeated measures model; SC, subcutaneous. A, Data are estimated means from RMM with treatment, stratum, country, and baseline value all nested within visit. Error bars indicate 95% CIs. B, The proportion of patients achieving an HbA_{1c} level of less than 7.0% after 26 weeks of treatment was significant for the oral semaglutide 2.5-mg group vs placebo ($P = .01$) and for all other oral semaglutide dosages and SC semaglutide ($P < .001$). Missing HbA_{1c} values are imputed from RMM analysis before calculating the proportions of patients reaching the target.

[a] No. of patients with an assessment (panel A) and imputed value (panel B).

Figure 4. Fasting Plasma Glucose (FPG) Level and Body Weight Efficacy Parameters From Baseline to Week 26 Among Patients With Type 2 Diabetes and Insufficient Glycemic Control





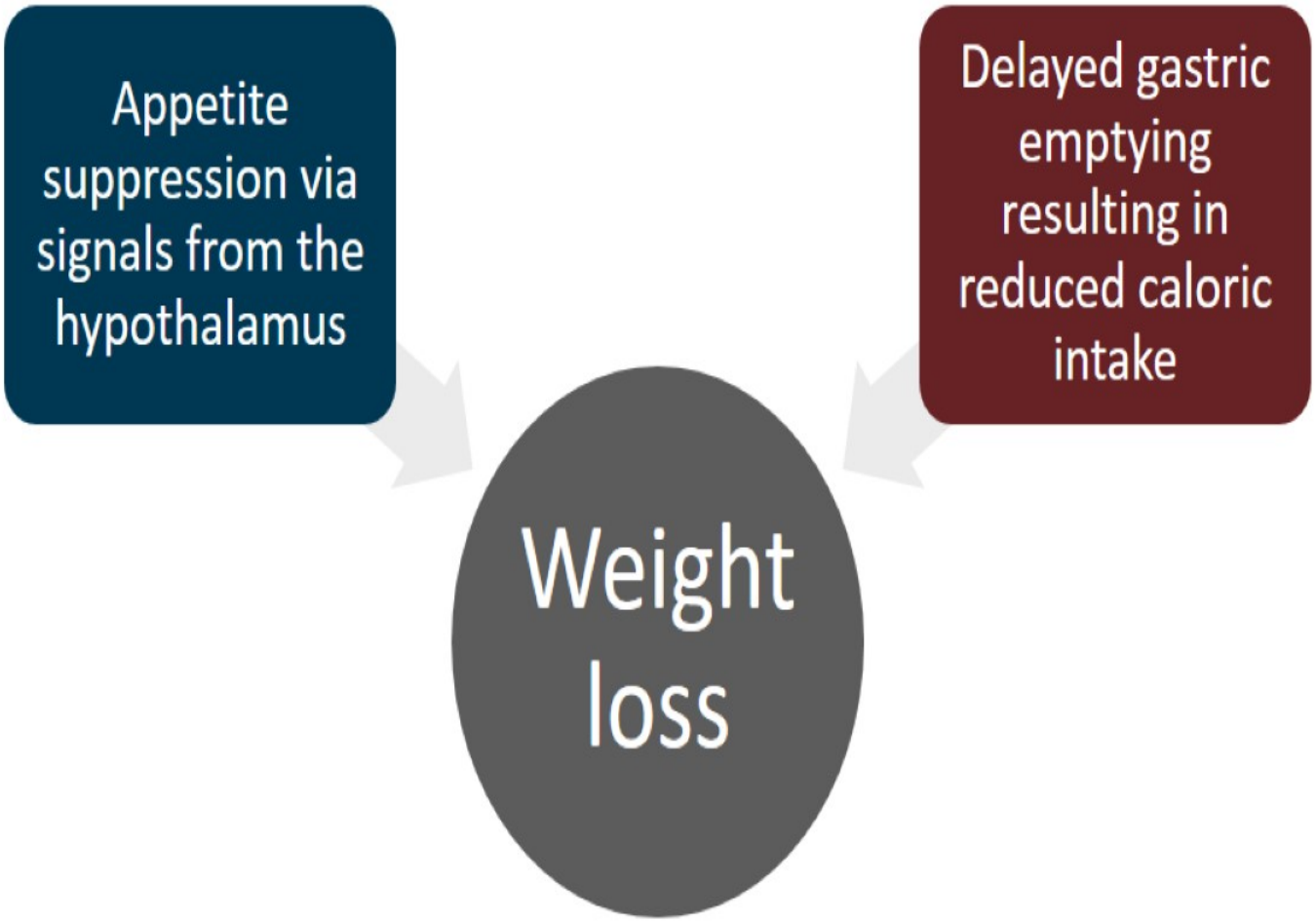
No. of patients[a]					
Placebo	68	68	61	57	50
Oral semaglutide, mg					
2.5	66	66	60	58	55
5	66	66	60	59	55
10	66	66	61	61	57
20	69	69	60	53	47
40	66	66	60	54	45
SC semaglutide 1 mg	63	63	62	57	43

No. of patients[a]					
Placebo	71	68	64	57	51
Oral semaglutide, mg					
2.5	70	68	64	60	56
5	70	68	63	61	57
10	69	65	62	60	57
20	70	66	57	51	47
40	71	66	63	50	46
SC semaglutide 1 mg	69	66	65	57	46

RMM indicates repeated measures model; SC, subcutaneous. Data are estimated means from the RMM with treatment, stratum, country, and baseline value all nested within visit. Error bars are 95% CIs.

[a] No. of patients with an assessment.

Mechanisms of Action of Liraglutide for Weight Loss



Van Gaal L, et al. *Diabetes Care*. 2016;39(suppl 2):S260-S267.

GLYCEMIC CONTROL ALGORITHM

LIFESTYLE THERAPY
(Including Medically Assisted Weight Loss)

Entry A1C < 7.5%

MONOTHERAPY*

- ✓ Metformin
- ✓ GLP-1 RA
- ✓ SGLT-2i
- ✓ DPP-4i
- ! TZD
- ✓ AGi
- ! SU/GLN

If not at goal in 3 months proceed to Dual Therapy

Entry A1C ≥ 7.5%

DUAL THERAPY*

MET or other 1st-line agent +

- ✓ GLP-1 RA
- ✓ SGLT-2i
- ✓ DPP-4i
- ! TZD
- ! Basal Insulin
- ✓ Colesevelam
- ✓ Bromocriptine QR
- ✓ AGi
- ! SU/GLN

If not at goal in 3 months proceed to Triple Therapy

TRIPLE THERAPY*

MET or other 1st-line agent + 2nd-line agent +

- ✓ GLP-1 RA
- ✓ SGLT-2i
- ! TZD
- ! Basal insulin
- ✓ DPP-4i
- ✓ Colesevelam
- ✓ Bromocriptine QR
- ✓ AGi
- ! SU/GLN

If not at goal in 3 months proceed to or intensify insulin therapy

Entry A1C > 9.0%

SYMPTOMS

NO	YES
DUAL Therapy OR TRIPLE Therapy	INSULIN ± Other Agents

ADD OR INTENSIFY INSULIN

Refer to Insulin Algorithm

LEGEND

- ✓ Few adverse events and/or possible benefits
- ! Use with caution

* Order of medications represents a suggested hierarchy of usage; length of line reflects strength of recommendation

PROGRESSION OF DISEASE

 DOI 10.4158/EP161682.CS

ALGORITMO PER IL CONTROLLO GLICEMICO

INDIVIDUALIZZA GLI OBIETTIVI

HbA1c ≤ 6.5% in pazienti senza gravi comorbilità e a basso rischio ipoglicemico

HbA1c > 6.5% in pazienti con gravi comorbilità e a rischio ipoglicemico

INTERVENTO SULLO STILE DI VITA
(compreso calo ponderale medicalmente assistito)

HbA1c iniziale < 7.5%

MONOTERAPIA*

- ✓ Metformina
- ✓ GLP-1 RA
- ✓ SGLT-2 in
- ✓ DPP-4 in
- ⚠ TZD
- ✓ AGI
- ⚠ SU/Glinidi

Se non a target in 3 mesi, vai a terapia duplice

HbA1c iniziale > 7.5%

TERAPIA DUPLICE*

MET o altro farmaco di 1° linea +

- ✓ GLP-1 RA
- ✓ SGLT-2 in
- ✓ DPP-4 in
- ⚠ TZD
- ⚠ Insulina basale
- ✓ Coleveselam
- ✓ Bromocriptina QR
- ✓ AGI
- ⚠ SU/Glinidi

Se non a target in 3 mesi, vai a terapia triplice

TERAPIA TRIPLICE*

MET o altro farmaco di 1° linea + farmaco di 2° linea +

- ✓ GLP-1 RA
- ✓ SGLT-2 in
- ⚠ TZD
- ⚠ Insulina basale
- ✓ DPP-4 in
- ✓ Coleveselam
- ✓ Bromocriptina QR
- ✓ AGI
- ⚠ SU/Glinidi

Se non a target in 3 mesi, vai a insulina o intensificala

HbA1c iniziale > 9.0%

SINTOMI

NO	SÌ
TERAPIA DUPLICE o TERAPIA TRIPLICE	INSULINA ± altro agente

AGGIUNGI O INTENSIFICA INSULINA
(vedi algoritmo insulina)

LEGENDA
- ✓ Pochi effetti collaterali e/o possibili benefici
- ⚠ Da usare con cautela

* L'ordine dei farmaci rappresenta la gerarchia suggerita;
La lunghezza del segmento riflette la forza della raccomandazione

PROGRESSIONE DI MALATTIA

Diabetologia
https://doi.org/10.1007/s00125-018-4729-5

CONSENSUS REPORT

Management of hyperglycaemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD)

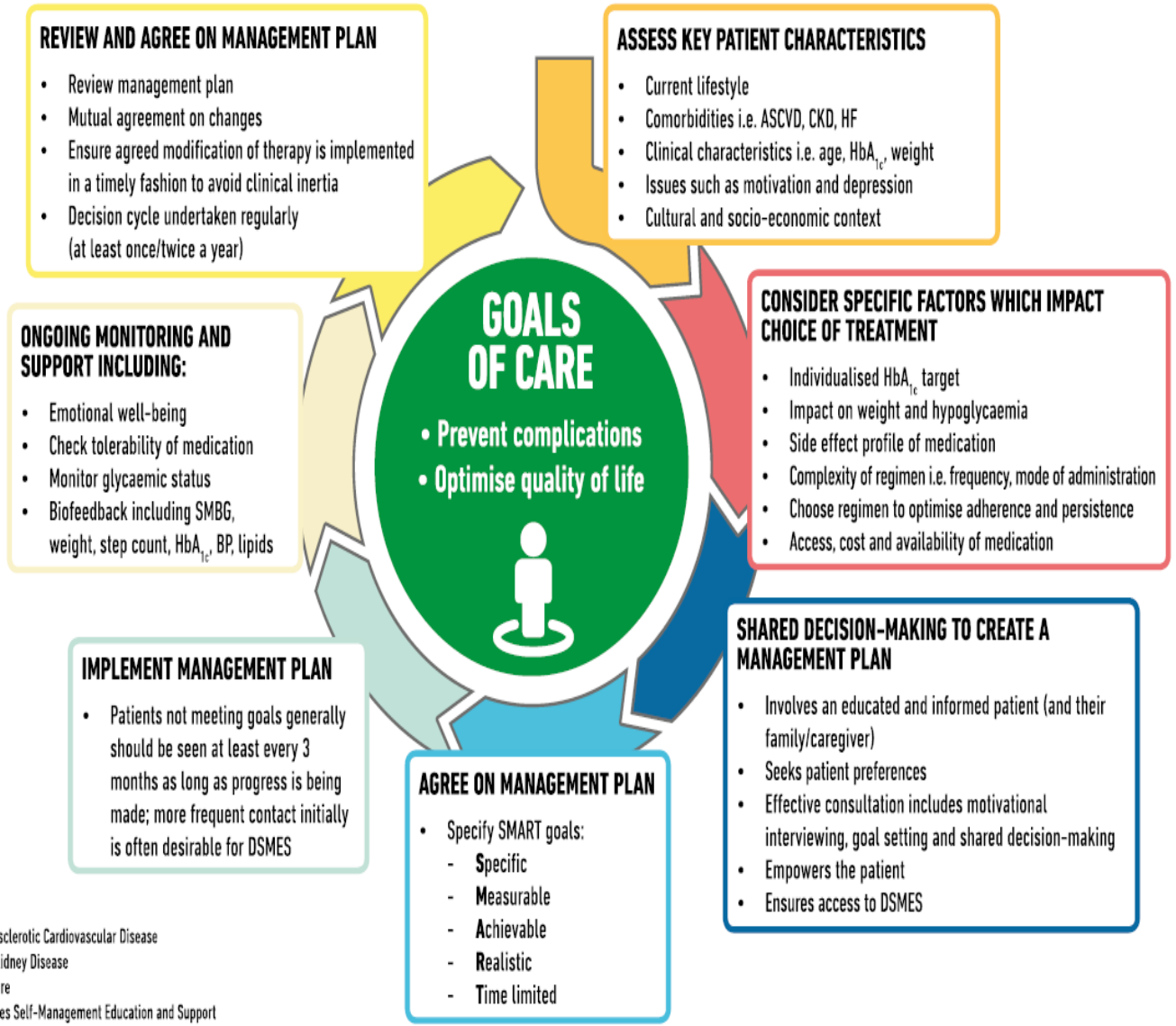
Melanie J. Davies[1,2] · David A. D'Alessio[3] · Judith Fradkin[4] · Walter N. Kernan[5] · Chantal Mathieu[6] · Geltrude Mingrone[7,8] · Peter Rossing[9,10] · Apostolos Tsapas[11] · Deborah J. Wexler[12,13] · John B. Buse[14]

Abstract

The American Diabetes Association and the European Association for the Study of Diabetes convened a panel to update the prior position statements, published in 2012 and 2015, on the management of type 2 diabetes in adults. A systematic evaluation of the literature since 2014 informed new recommendations. These include additional focus on lifestyle management and diabetes self-management education and support. For those with obesity, efforts targeting weight loss, including lifestyle, medication and surgical interventions, are recommended. With regards to medication management, for patients with clinical cardiovascular disease, a sodium–glucose cotransporter-2 (SGLT2) inhibitor or a glucagon-like peptide-1 (GLP-1) receptor agonist with proven cardiovascular benefit is recommended. For patients with chronic kidney disease or clinical heart failure and atherosclerotic cardiovascular disease, an SGLT2 inhibitor with proven benefit is recommended. GLP-1 receptor agonists are generally recommended as the first injectable medication.

Keywords Cardiovascular disease · Chronic kidney disease · Costs · Glucose-lowering therapy · Guidelines · Heart failure · Hypoglycaemia · Patient-centred care · Type 2 diabetes mellitus · Weight management

DECISION CYCLE FOR PATIENT-CENTRED GLYCAEMIC MANAGEMENT IN TYPE 2 DIABETES



ASCVD = Atherosclerotic Cardiovascular Disease
CKD = Chronic Kidney Disease
HF = Heart Failure
DSMES = Diabetes Self-Management Education and Support
SMBG = Self-Monitored Blood Glucose

Fig. 1 Decision cycle for patient-centred glycaemic management in type 2 diabetes

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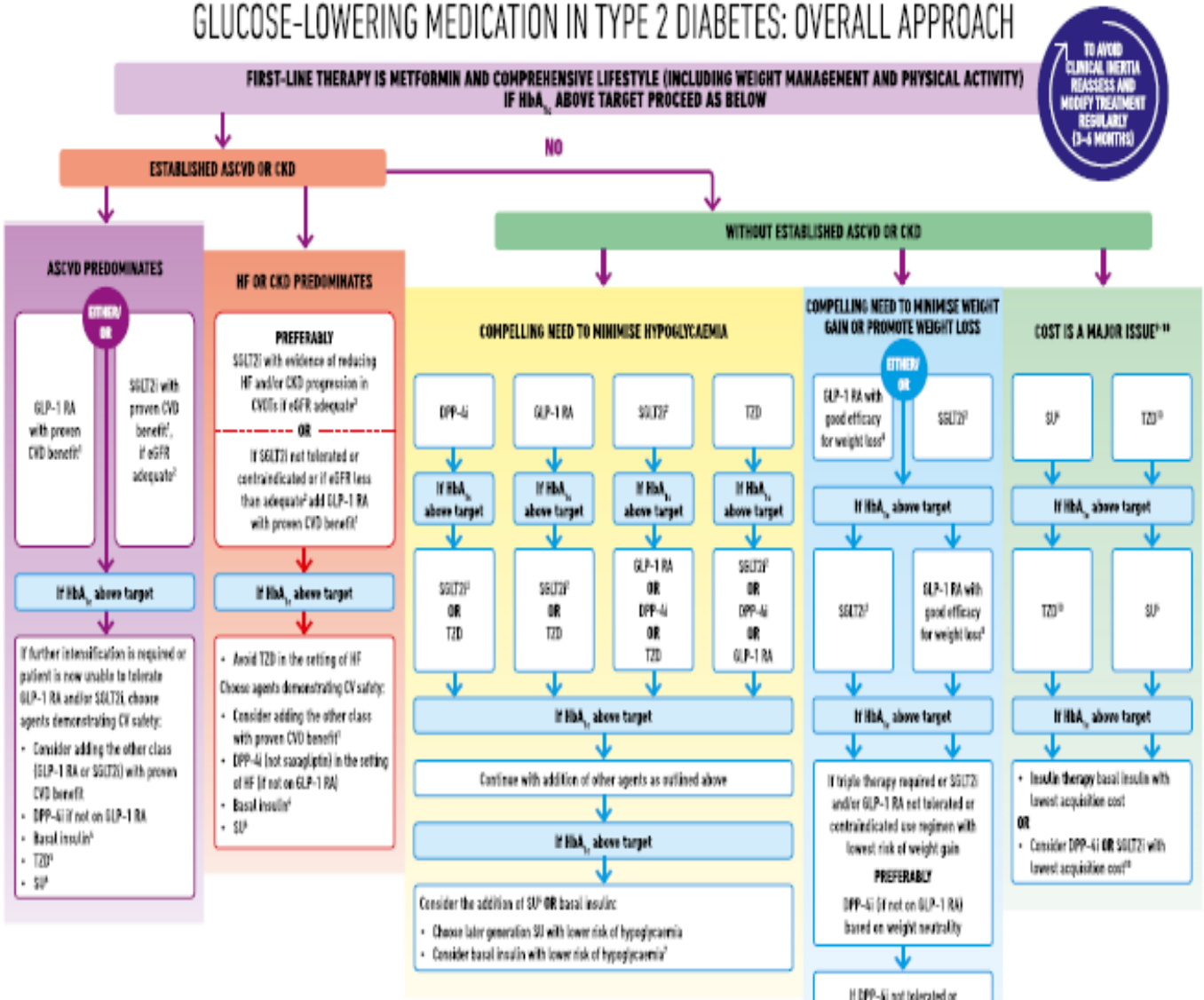

1. Proven CVD benefit means it has label indication of reducing CVD events. For GLP-1 RA strongest evidence for liraglutide > semaglutide > exenatide extended release. For SGLT2i evidence modestly stronger for empagliflozin > canagliflozin.
2. Be aware that SGLT2i vary by region and individual agent with regard to indicated level of eGFR for initiation and continued use
3. Both empagliflozin and canagliflozin have shown reduction in HF and reduction in CKD progression in CVOTs
4. Degludec or U100 glargine have demonstrated CVD safety
5. Low dose may be better tolerated though less well studied for CVD effects
6. Choose later generation SU with lower risk of hypoglycaemia
7. Degludec / glargine U300 < glargine U100 / detemir < NPH insulin
8. Semaglutide > Liraglutide > dulaglutide > exenatide > lixisenatide
9. If no specific comorbidities (i.e. no established CVD, low risk of hypoglycaemia and lower priority to avoid weight gain or no weight-related comorbidities)
10. Consider country- and region-specific cost of drugs. In some countries TZDs relatively more expensive and DPP-4i relatively cheaper

Fig. 2 Glucose-lowering medication in type 2 diabetes: overall approach

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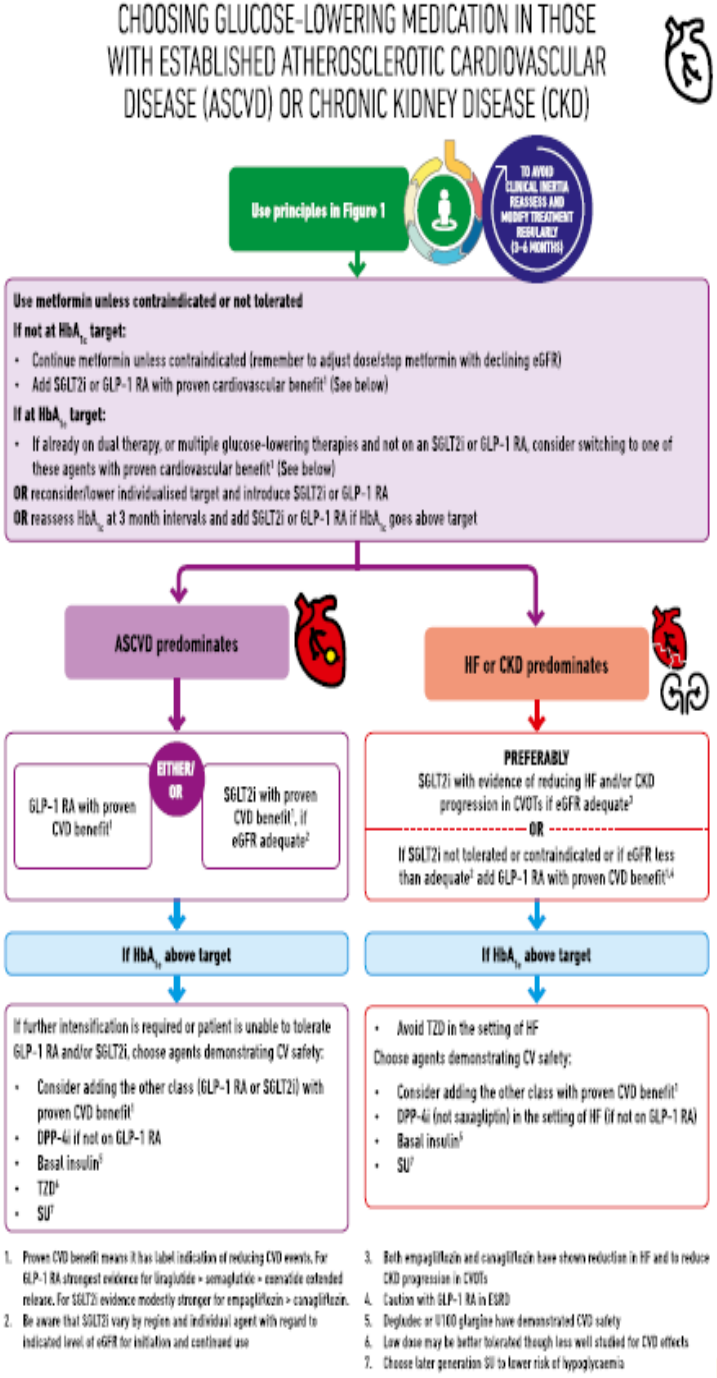

Fig. 3 Choosing glucose-lowering medication in those with established atherosclerotic cardiovascular disease (ASCVD) or chronic ki (CKD)

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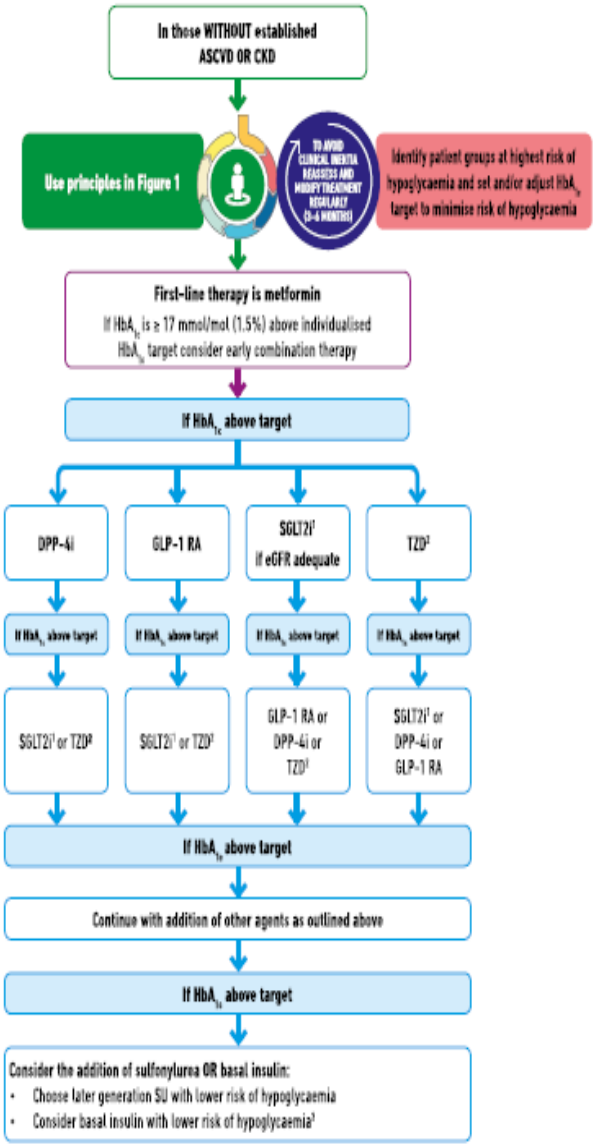
CHOOSING GLUCOSE-LOWERING MEDICATION IF COMPELLING NEED TO MINIMISE HYPOGLYCAEMIA



1. Be aware that SGLT2i vary by region and individual agent with regard to indicated level of eGFR for initiation and continued use
2. Low dose TZDs are better tolerated
3. Degludec / glargine U300 < glargine U100 / detemir < NPH insulin

Fig. 5 Choosing glucose-lowering medication if compelling need to minimise hypoglycaemia

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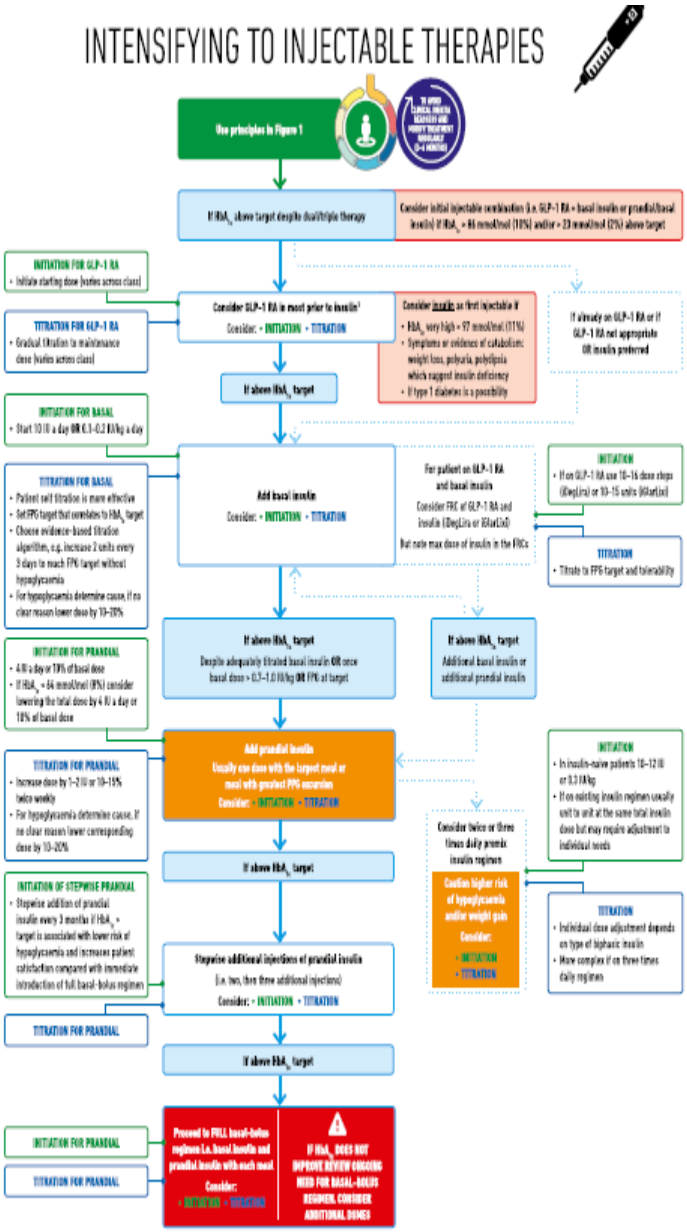

Fig. 7 Intensifying to injectable therapies

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Is It Time to Change the Type 2 Diabetes Treatment Paradigm? Yes! GLP-1 RAs Should Replace Metformin in the Type 2 Diabetes Algorithm

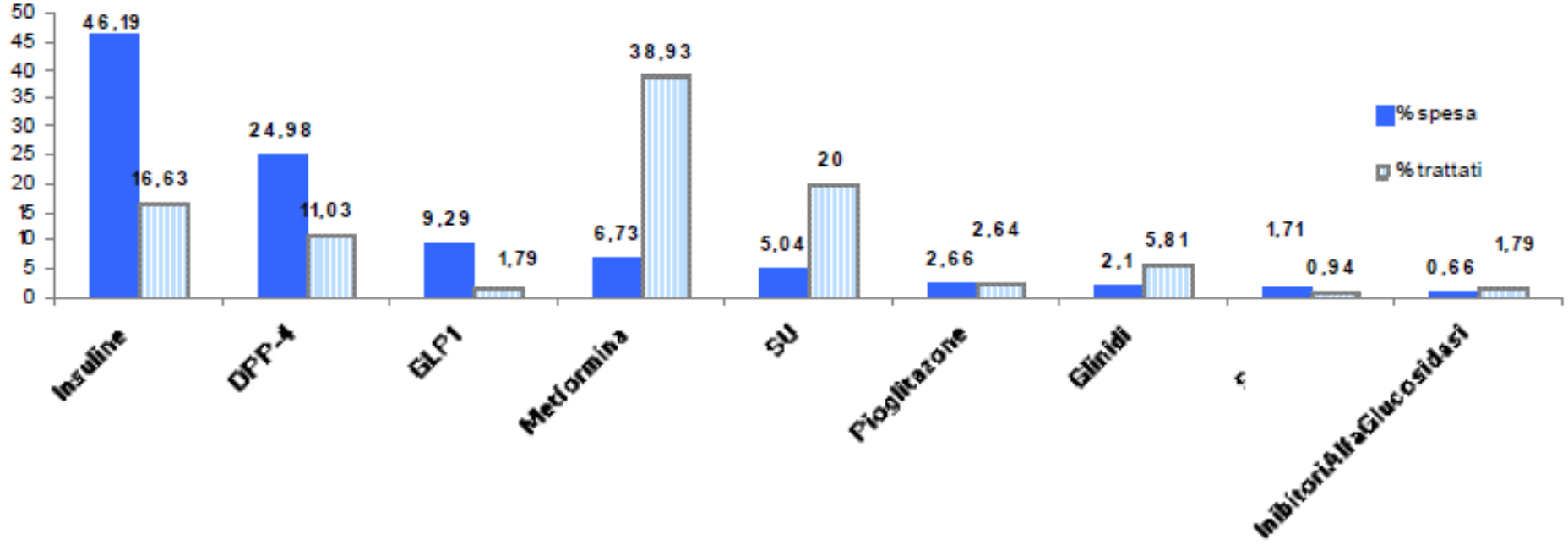
Muhammad Abdul-Ghani[1,2] and Ralph A. DeFronzo[1]

Diabetes Care 2017;40:1121–1127 | https://doi.org/10.2337/dc16-2368

Table 2—Benefits of GLP-1 RAs far outweigh those of metformin

	GLP-1 RAs	Metformin
Pathophysiological defects in T2D (see Fig. 1)	Corrects six of the defects	Corrects only one of the defects
Glucose-lowering efficacy	Strong	Strong
Durability of HbA_{1c} reduction	Strong	None
Weight loss	3–4 kg	1–2 kg
Blood pressure	~2–3 mmHg reduction	Neutral
Lipid profile	Lowers triglycerides, increases HDL cholesterol	Neutral
Cardiovascular protection (MACE)	Reduction by 13–26%	Neutral
Renal protection	Reduction by 22%	Neutral
Tolerability	~10–15% GI side effects	~10–15% GI side effects
Dosing	Weekly subcutaneous injection	Once to twice daily oral administration
Cost	High	Low

Figura 1- Ipoglicemizzanti (% di pazienti trattati e % spesa) nei primi 8 mesi del 2016 nell'ULSS 20



...grazie!