Multi-factor approach to reduce cardiovascular risk in diabetes

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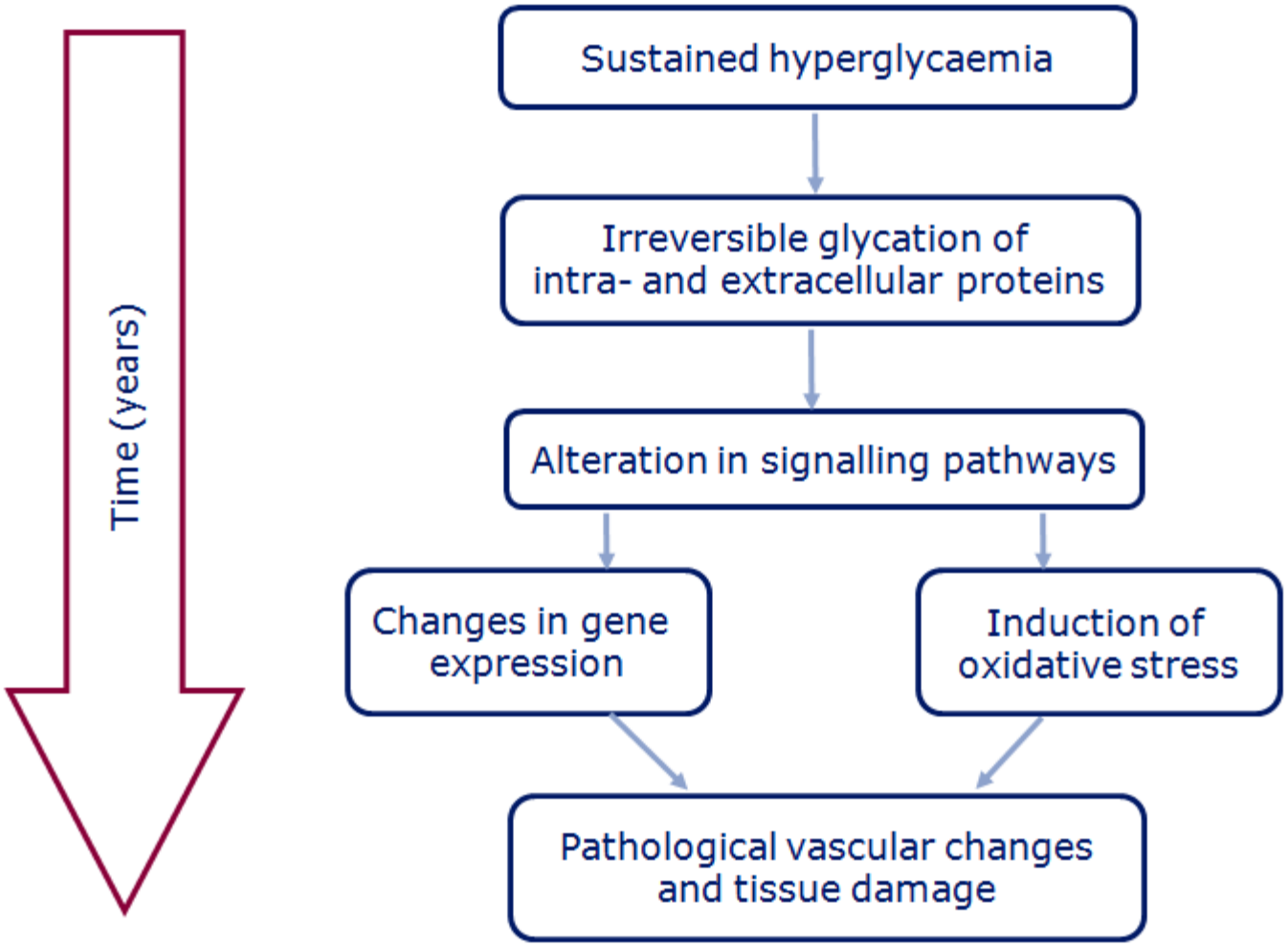
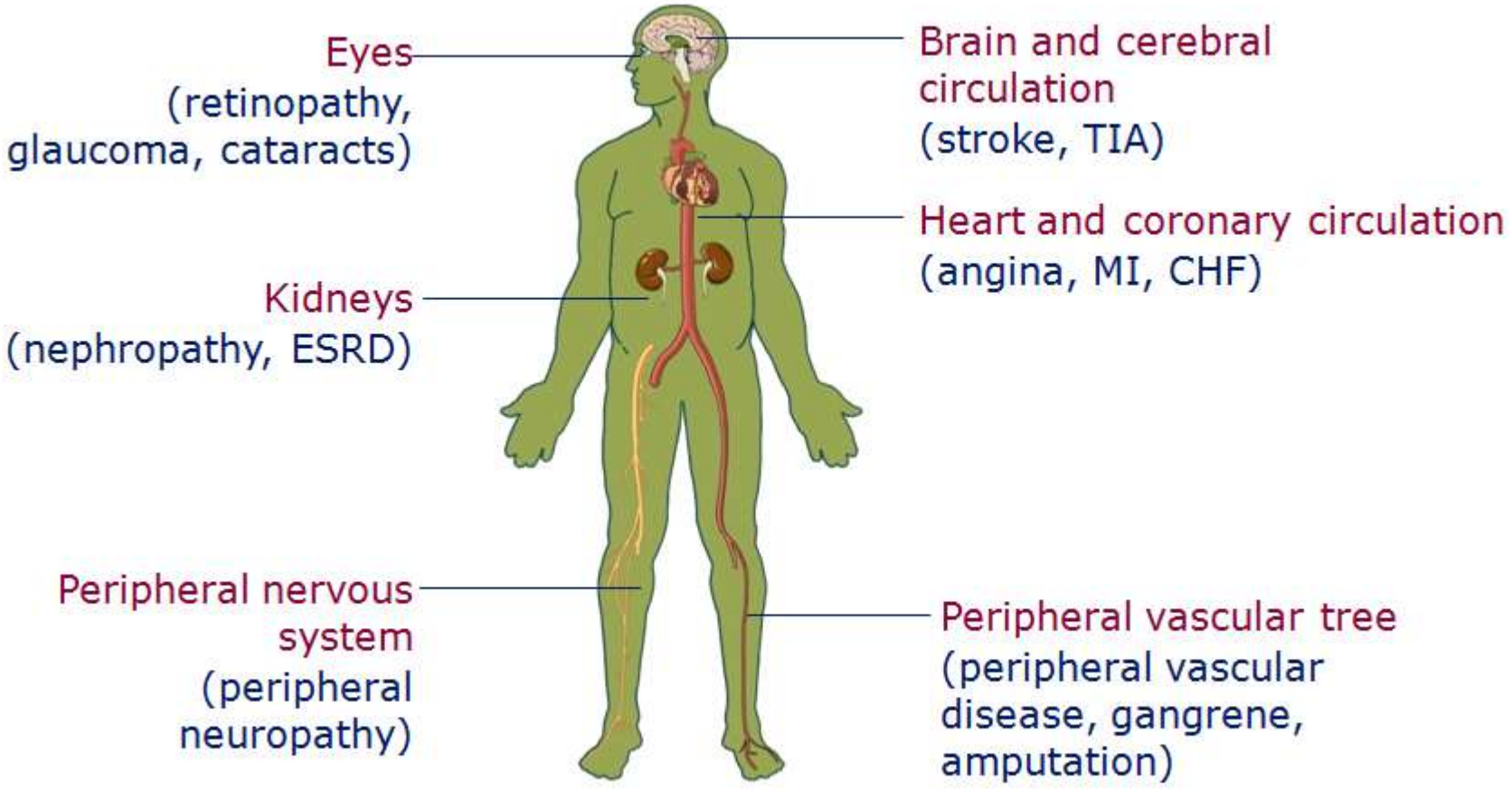
Type 2 diabetes progression: vascular changes and tissue damage



Adapted from DeFronzo *et al. International Textbook of Diabetes*. 3rd edn. New York, NY: John Wiley & Sons; 2004:1141

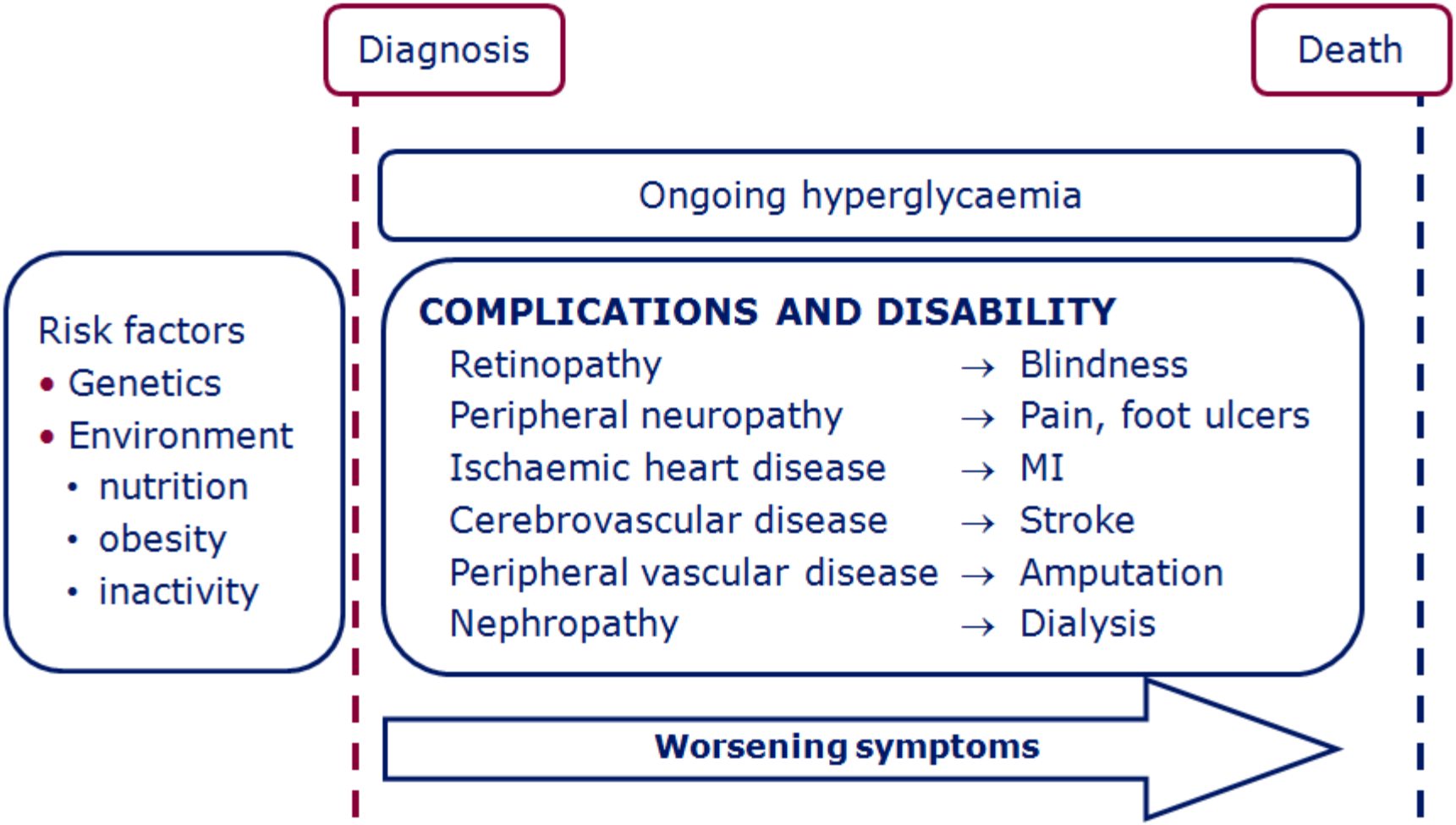
Tissue damage leads to serious long-term complications in type 2 diabetes



CHF, congestive heart failure; ESRD, end-stage renal disease; MI, myocardial infarction; TIA, transient ischaemic attack

Adapted from *Diabetes Atlas* 4th edn. International Diabetes Federation. 2009

Micro- and macrovascular complications are associated with type 2 diabetes



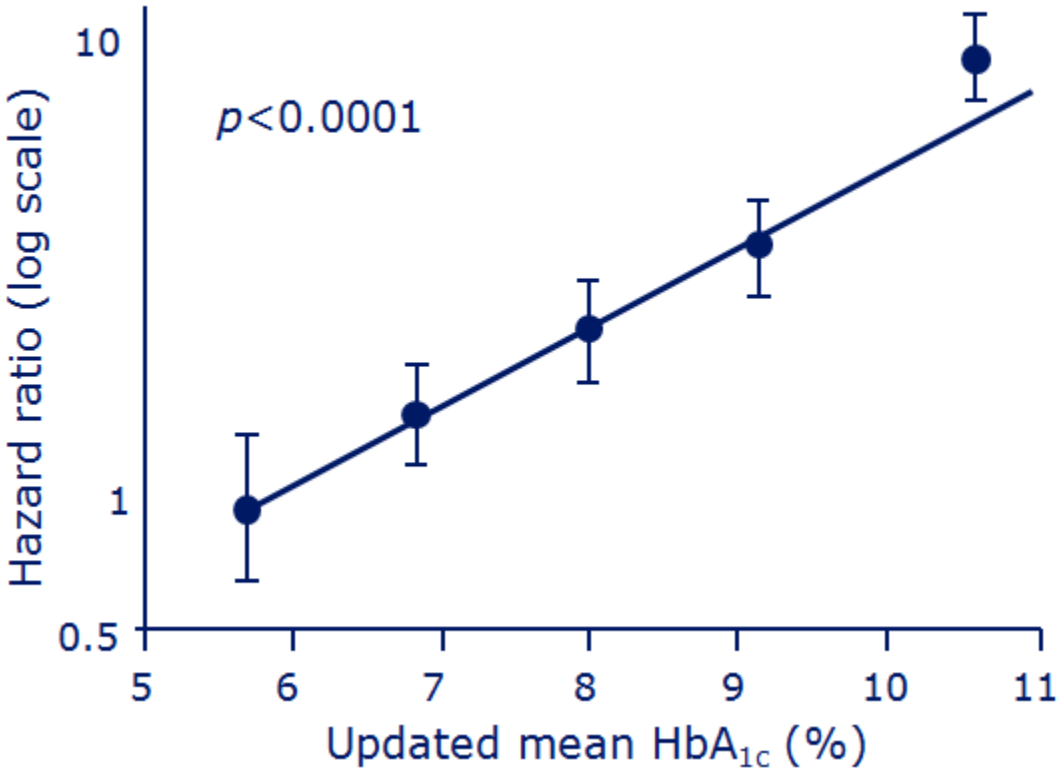
Adapted from Brown *et al*. *Diabetes Obes Metab* 2000;2(Suppl. 2):S11–18

Microvascular complications of type 2 diabetes

- Visual impairment
  - e.g., retinopathy, glaucoma, cataracts
- Peripheral neuropathy
  - e.g., motor, sensory, autonomic nerve damage
- Nephropathy
  - e.g., microalbuminuria/proteinuria, ESRD

UKPDS: glycaemic control – effects on microvascular endpoints*

37% reduction in microvascular endpoints per 1% HbA_{1c} reduction

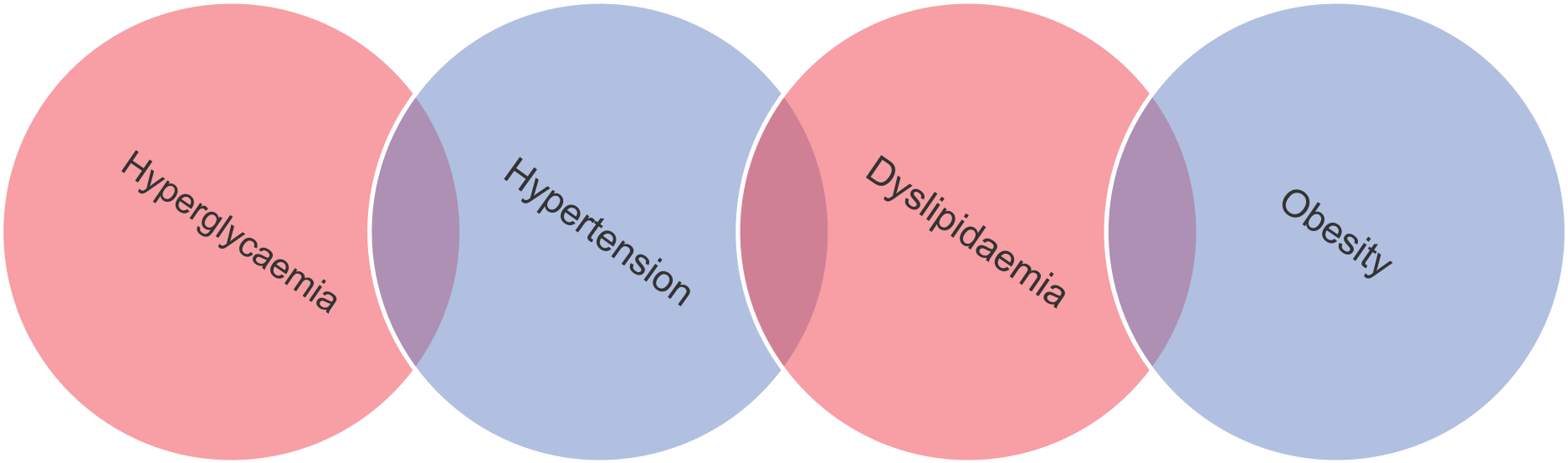


*Estimated hazard ratios (95% CI) between updated mean HbA_{1c} and microvascular endpoints (retinopathy, nephropathy, and neuropathy). Data are adjusted for age at diagnosis of diabetes, sex, ethnic group, smoking, presence of albuminuria, SBP, HDL-C, LDL-C and TG

HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; TG, triglycerides

Adapted from Stratton *et al*. *BMJ* 2000;321:405–12

Modifiable CV risk factors are common in patients with T2D[1,2]



Almost a third of diabetes patients were current smokers[2]

1. Svensson et al. Diab Vasc Dis Res 2013;10:520–9. 2. Das et al. Am Heart J 2006;151:1087–93.

ABCs of Type 2 Diabetes: AACE/ACE 2011 and ADA 2011

Target Treatment Goals	AACE/ACE 2011	ADA 2011
A1C	≤ 6.5%	< 7.0%
Blood pressure	<130/80 mm Hg	<130/80 mm Hg
Cholesterol (lipids)	• LDL-C < 100 mg/dL (< 70 mg/dL for patients with diabetes and coronary artery disease) • HDL-C > 40 mg/dL in men; > 50 mg/dL in women • Triglycerides <150 mg/dL	• LDL-C < 100 mg/dL (< 70 mg/dL for patients with diabetes and coronary artery disease) • HDL-C > 40 mg/dL in men; > 50 mg/dL in women; • Triglycerides < 150 mg/dL

Handelsman Y, et al. American Association of Clinical Endocrinologists Medical Guidelines for Clinical Practice for Developing a Diabetes Mellitus Comprehensive Care Plan. *Endocr Pract*. 2011;17(Suppl 2):1-53.

Standards of Medical Care in Diabetes—2011. *Diabetes Care.* 34(Supplement 1): S11-S61.

Glycemic Control Recommendations for Type 2 Diabetes: AACE/ACE 2011 and ADA 2011

Target Treatment Goals	AACE/ACE 2011	ADA 2011
A1C	≤ 6.5%	< 7.0%
Fasting glucose	Fasting plasma glucose: < 110 mg/dL	Preprandial capillary plasma glucose: 70 – 130 mg/dL
Postprandial glucose	2-hr postprandial glucose: < 140 mg/dL	Peak postprandial capillary plasma glucose: < 180 mg/dL

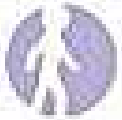
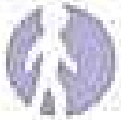
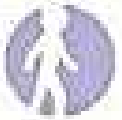
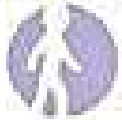
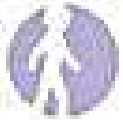
Handelsman Y, et al. American Association of Clinical Endocrinologists Medical Guidelines for Clinical Practice for Developing a Diabetes Mellitus Comprehensive Care Plan. *Endocr Pract*. 2011;17(Suppl 2):1-53.

Standards of Medical Care in Diabetes—2011. *Diabetes Care*. 34(Supplement 1): S11-S61.

Physical exercise: **recommendations**

Adults with diabetes should be advised to perform at least **150 min/week of moderate-intensity aerobic physical activity** (50–70% of maximum heart rate), spread over at least 3 days/week with no more than 2 consecutive days without exercise. Class A

In the absence of contraindications, adults with type 2 diabetes should be encouraged to perform **resistance training at least twice per week**. Class A

Example 1: Moderate Intensity Activity and Muscle Strengthening Activity						
Sunday	**Monday**	**Tuesday**	**Wednesday**	**Thursday**	**Friday**	**Saturday**
30 minute brisk walk 	30 minute brisk walk 	30 minute brisk walk 	Weight training 	30 minute brisk walk 	30 minute brisk walk 	Weight training 
Total: 150 minutes moderate-intensity aerobic activity + 2 days muscle-strengthening activity						

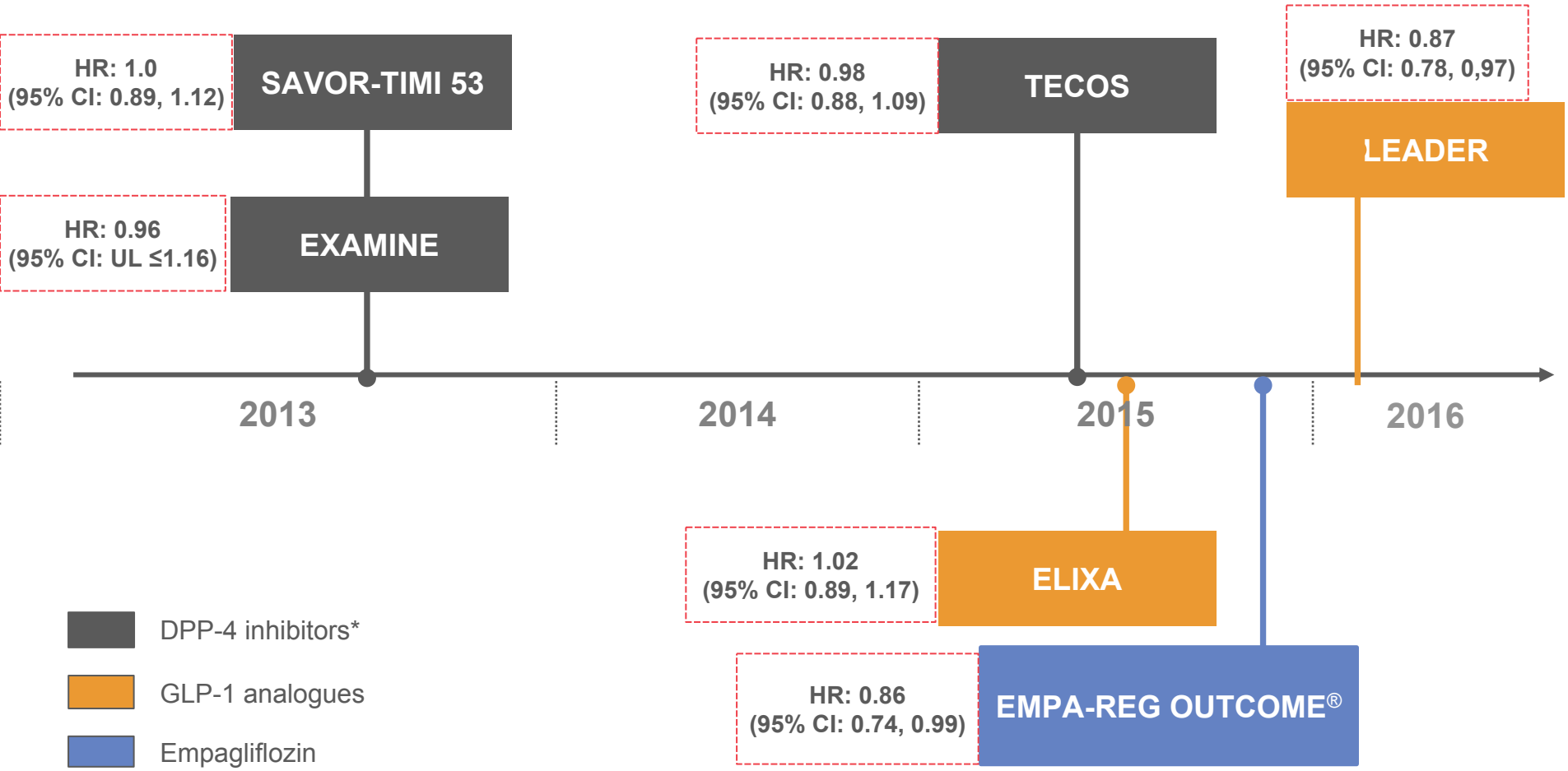
Caloric restriction

➢ **Caloric restriction** is a drastic intervention on eating habits aimed to reduce the caloric intake of about 25%.

- ✓ Energy intake of about 1800 kcal/die, rich in fruit, vegetable, nuts, soy and meat
- ✓ Reduced intake of carbohydrates and hydrogenated oils

Fontana L et al. JAMA 2009

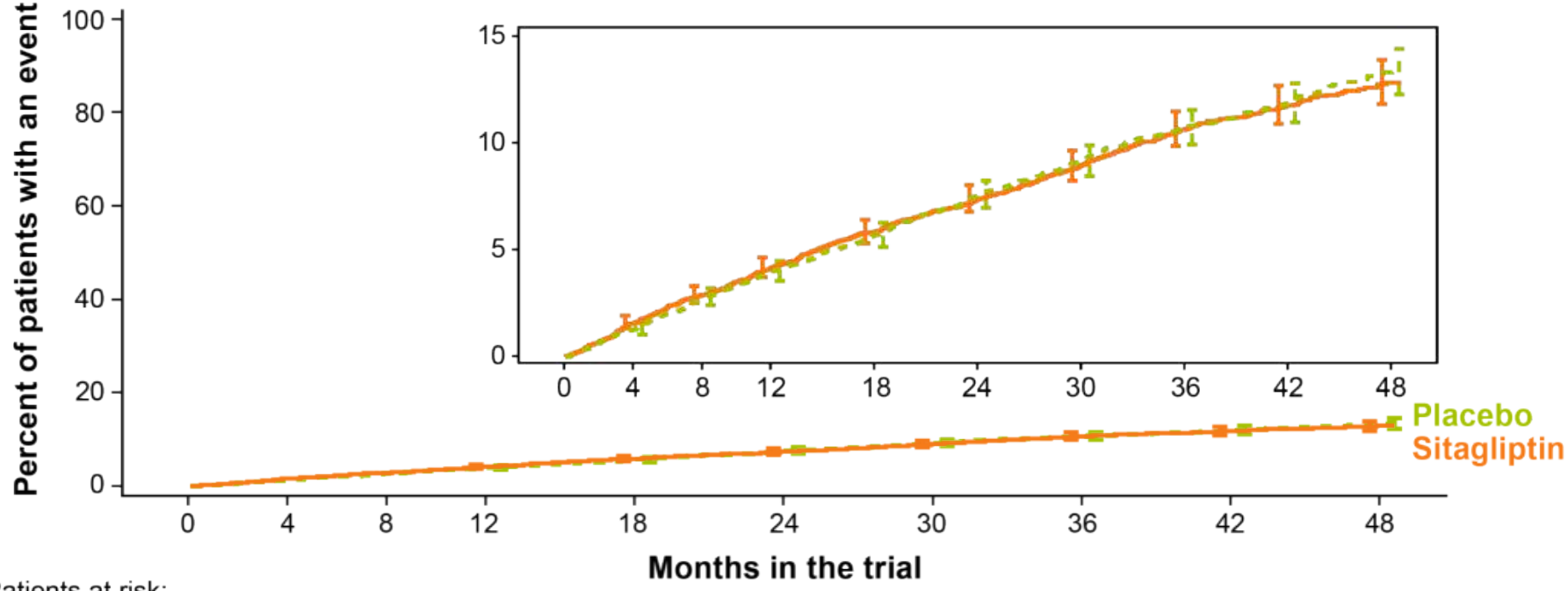
Recent trials of newer glucose-lowering agents on the primary CV outcome



CV, cardiovascular; HR, hazard ratio; DPP-4, dipeptidyl peptidase-4
*Saxagliptin, alogliptin, sitagliptin

Adapted from: https://s3-eu-west-1.amazonaws.com/presentations/easd/empa-reg-slide-kit.pptx

Primary Composite Cardiovascular Outcome*
PP Analysis for Non-inferiority

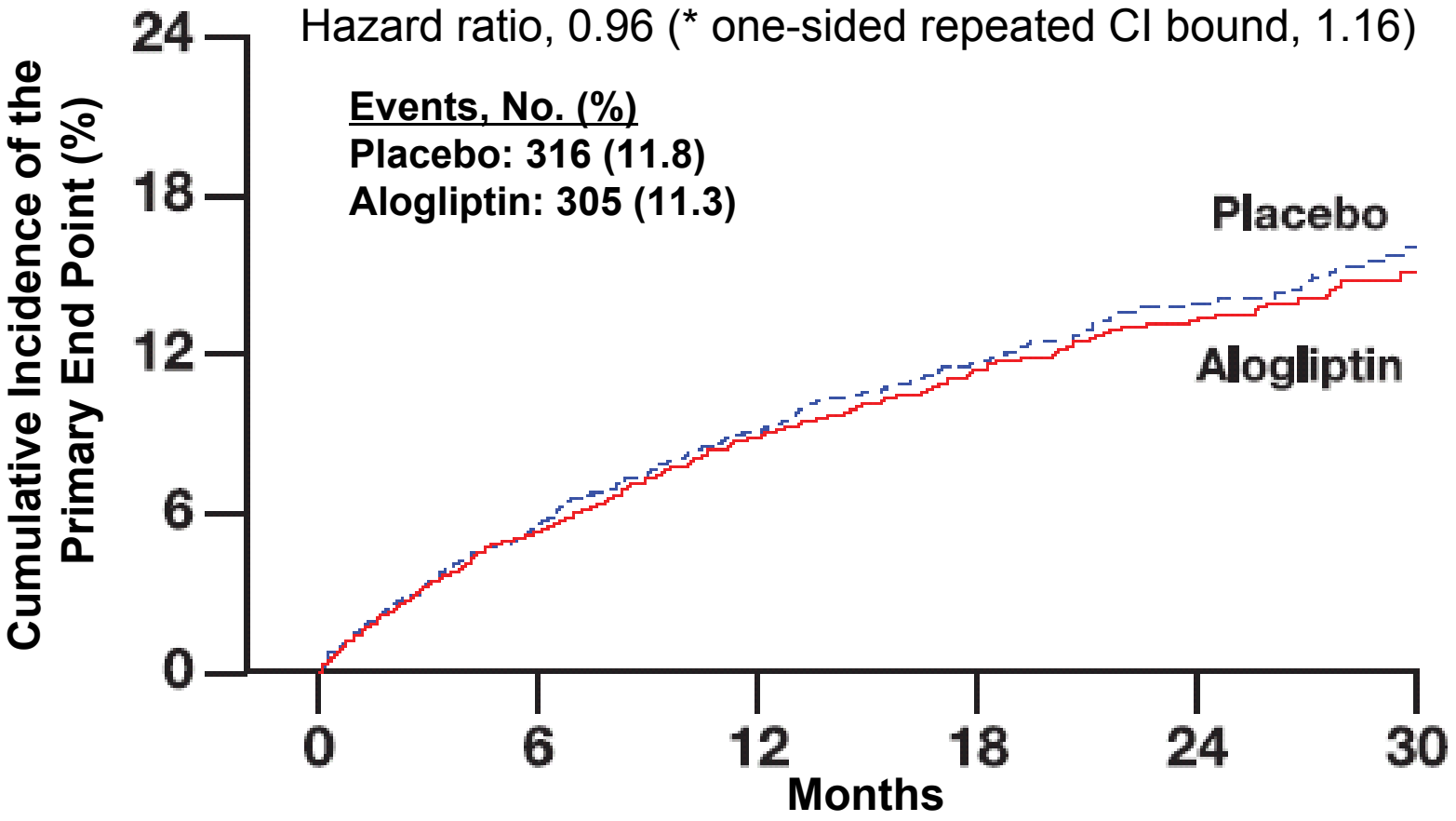


Patients at risk:										
Sitagliptin	7,257	6,857	6,519	6,275	5,931	5,616	3,919	2,896	1,748	1,028
Placebo	7,266	6,846	6,449	6,165	5,803	5,421	3,780	2,743	1,690	1,005

** CV death, nonfatal MI, nonfatal stroke, hospitalization for unstable angina*

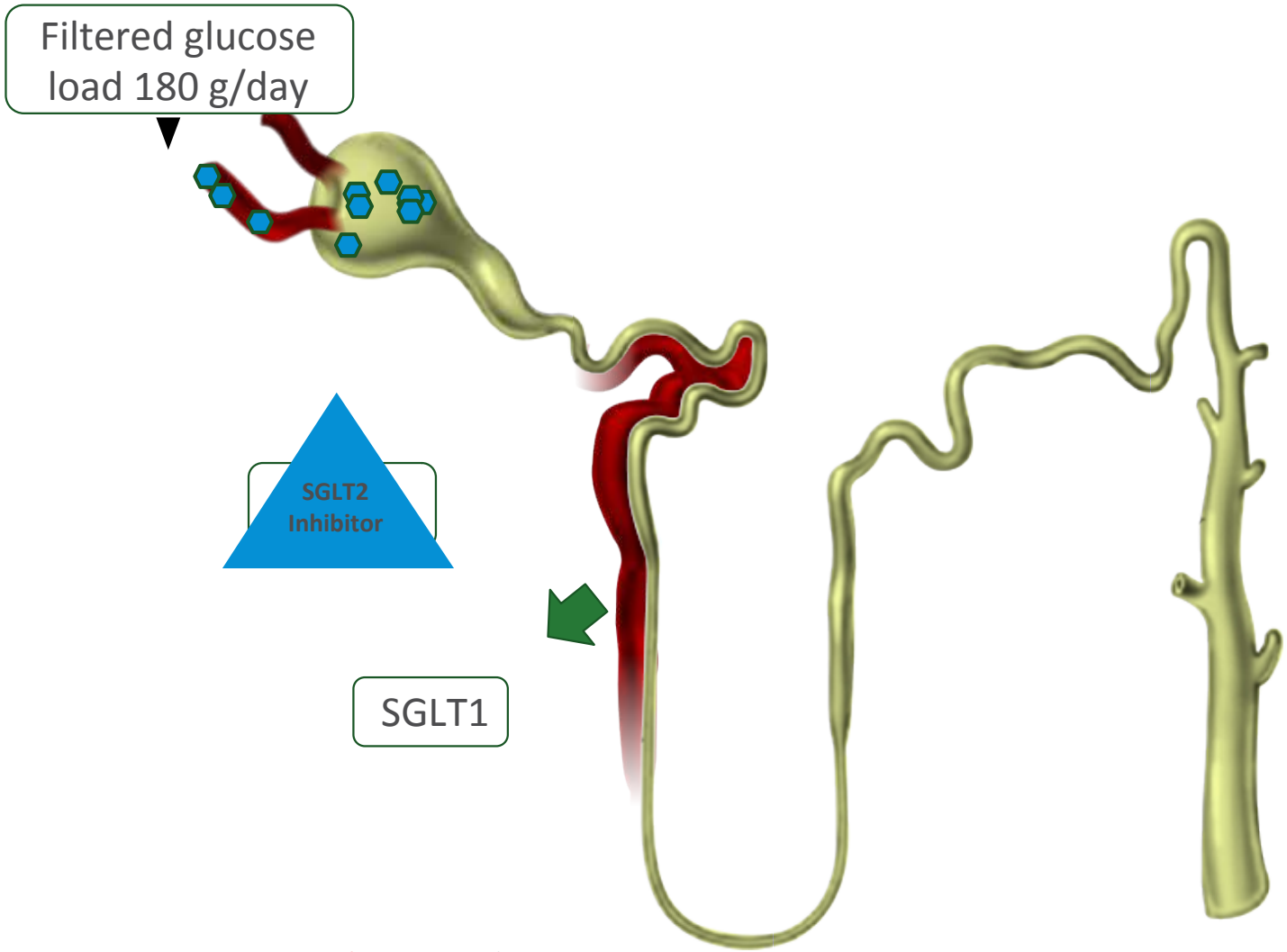
 al. NEJM 2015; DOI: 10.1056/NEJMoa1501352

Alogliptin and MACE



* Using alpha=0.01.

Urinary glucose excretion via SGLT2 inhibition

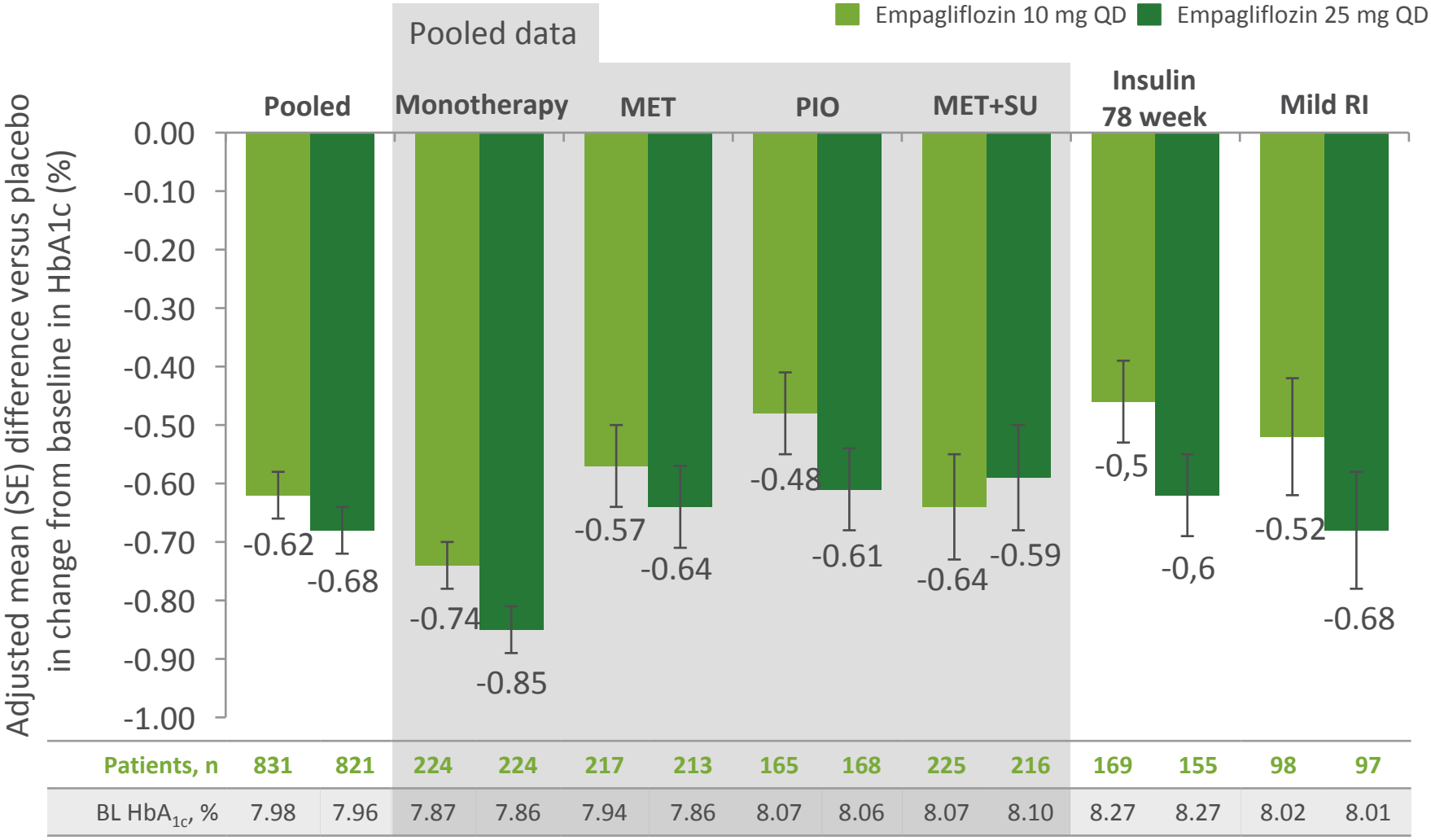


SGLT2 inhibitors reduce glucose re-absorption in the proximal tubule, leading to urinary glucose excretion* and osmotic diuresis

*Loss of ~80 g of glucose/day (~240 cal/per day).
Gerich JE. *Diabet Med*. 2010;27:136–142.

Phase III pooled efficacy and cardiovascular risk factor analysis

Placebo-corrected change* from baseline in HbA_{1c}



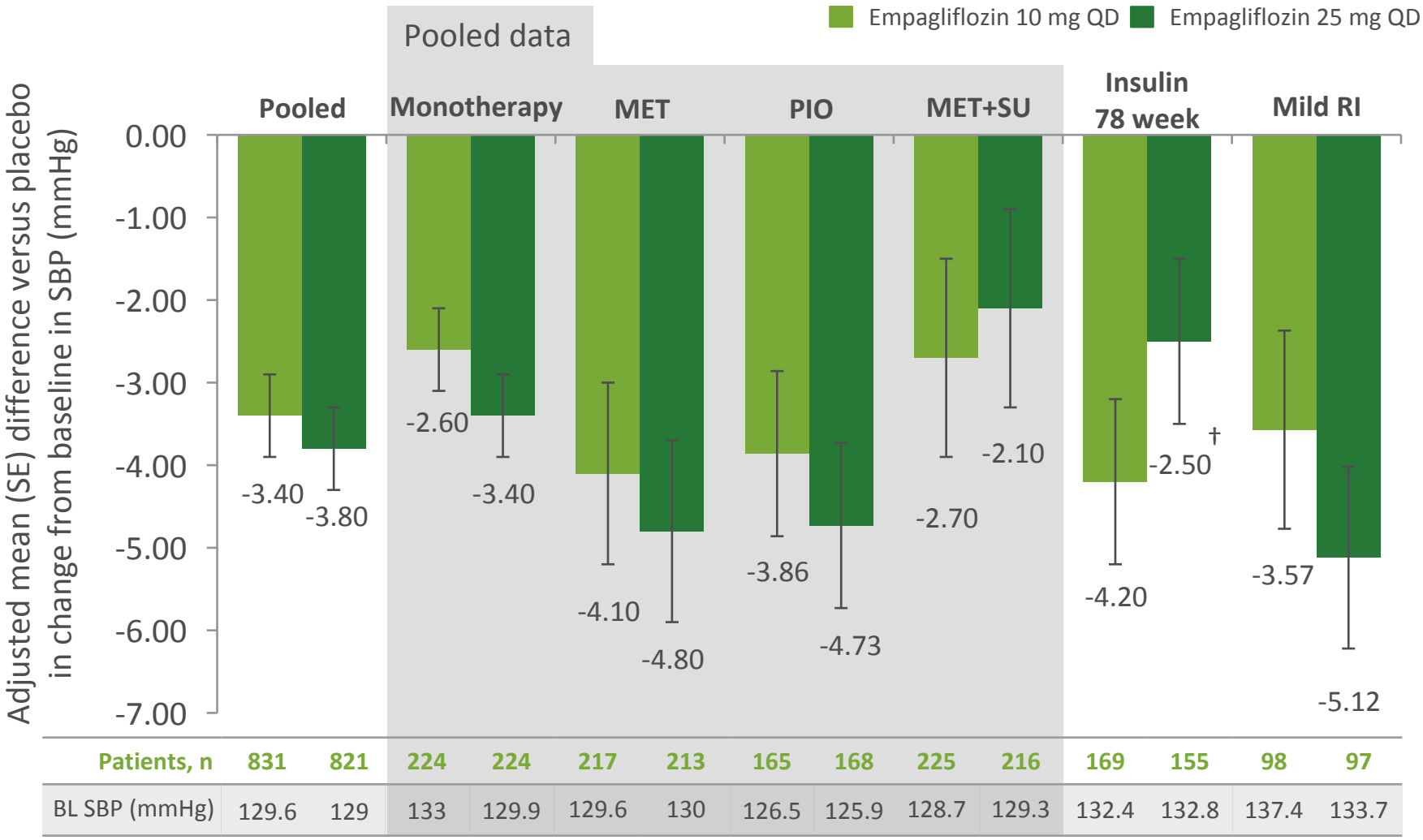
	Pooled		Monotherapy		MET		PIO		MET+SU		Insulin 78 week		Mild RI	
Patients, n	831	821	224	224	217	213	165	168	225	216	169	155	98	97
BL HbA_{1c}, %	7.98	7.96	7.87	7.86	7.94	7.86	8.07	8.06	8.07	8.10	8.27	8.27	8.02	8.01

BL, baseline; MET, metformin; PIO, pioglitazone; QD, once daily; RI, renal impairment; SE, standard error; SU, sulphonylurea.
*All statistically significant unless otherwise marked.

Hach T, et al., Häring H-U, et al., Rosenstock J, et al., Barnett A, et al. *Diabetes*. 2013;(Suppl 1) (P69-LB, P1092, P1102, P1104, respectively);
Kovacs C, et al. *Diabetes Obes Metab*. 2013 Aug 1. doi: 10.1111/dom.12188; Häring H-U, et al. *Diabetes Care*. 2014. doi:10.2337/dc12-2673.
Barnett A, et al. Lancet Diabetes Endocrinol. 2014 May;2(5):369-84. doi: 10.1016/S2213-8587(13)70208-0
Rosenstock J, et al Poster: 931, 49th Annual Meeting of the European Association for the Study of Diabetes, 23–27 September 2013

Pooled data from 4 pivotal Phase III trials

Phase III pooled efficacy and cardiovascular risk factor analysis
Placebo-corrected change* from baseline in SBP

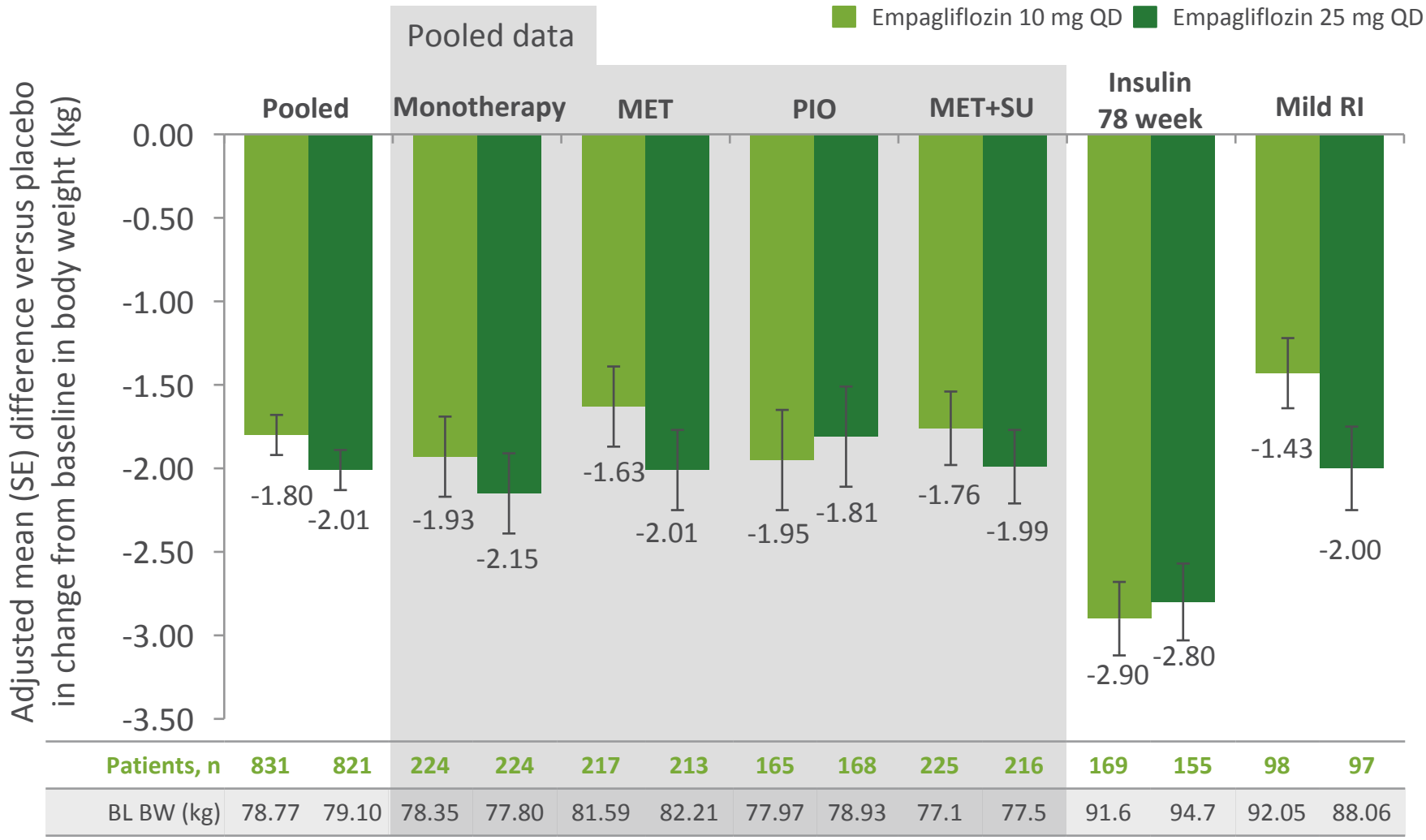


BL, baseline ; MET, metformin; PIO, pioglitazone; QD, once daily; RI, renal impairment; SBP, systolic blood pressure; SE, standard error; SU, sulphonylurea.
*All statistically significant unless otherwise marked. †Not statistically significant.

Hach T, et al., Häring H-U, et al., Rosenstock J, et al., Barnett A, et al. *Diabetes*. 2013;(Suppl 1) (P69-LB, P1092, P1102, P1104, respectively);
Kovacs C, et al. *Diabetes Obes Metab*. 2013 Aug 1. doi: 10.1111/dom.12188; Häring H-U, et al. *Diabetes Care*. 2014. doi:10.2337/dc12-2673.
Barnett A, et al. Lancet Diabetes Endocrinol. 2014 May;2(5):369-84. doi: 10.1016/S2213-8587(13)70208-0
Rosenstock J, et al Poster: 931, 49th Annual Meeting of the European Association for the Study of Diabetes, 23–27 September 2013

Pooled data from 4 pivotal Phase III trials

Phase III pooled efficacy and cardiovascular risk factor analysis
Placebo-corrected change* from baseline in body weight

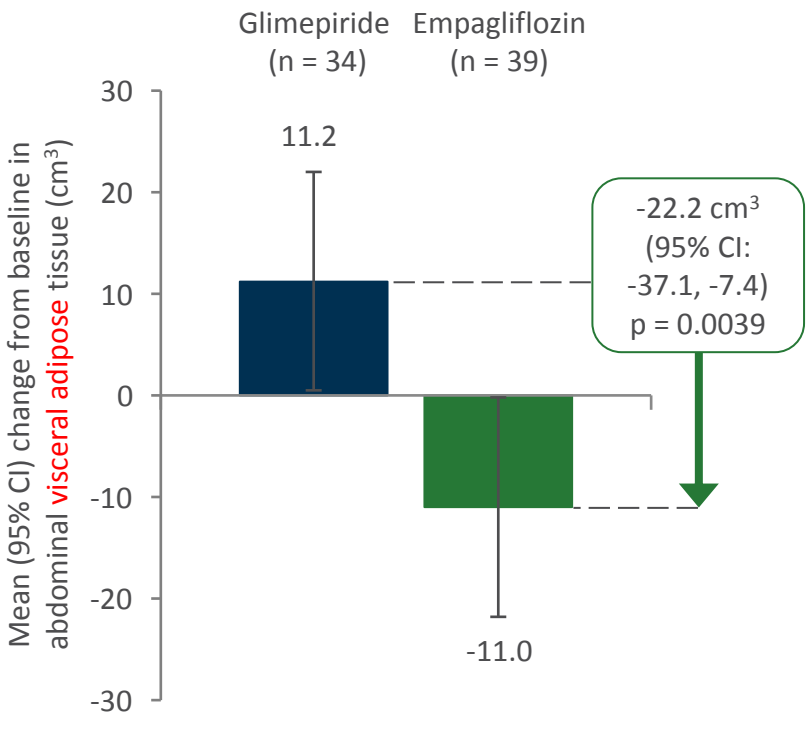


Pooled data from 4 pivotal Phase III trials

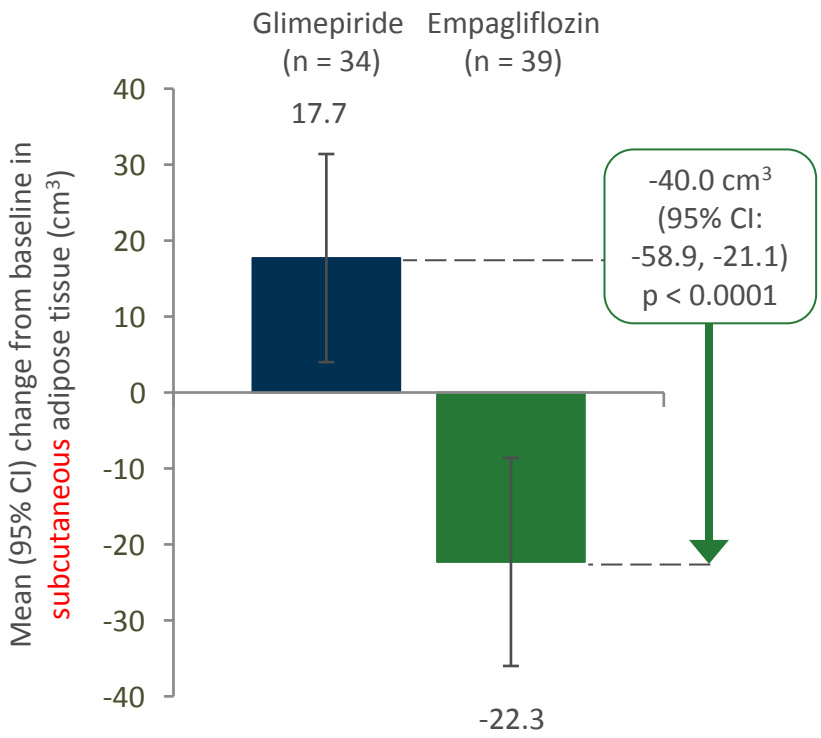
BL, baseline; BW, body weight; MET, metformin; PIO, pioglitazone; QD, once daily; RI, renal impairment; SE, standard error; SU, sulphonylurea.
*All statistically significant unless otherwise marked.

Hach T, et al., Häring H-U, et al., Rosenstock J, et al., Barnett A, et al. *Diabetes*. 2013;(Suppl 1) (P69-LB, P1092, P1102, P1104, respectively);
Kovacs C, et al. *Diabetes Obes Metab*. 2013 Aug 1. doi: 10.1111/dom.12188; Häring H-U, et al. *Diabetes Care*. 2014. doi:10.2337/dc12-2673.
Barnett A, et al. Lancet Diabetes Endocrinol. 2014 May;2(5):369-84. doi: 10.1016/S2213-8587(13)70208-0
Rosenstock J, et al Poster: 931, 49th Annual Meeting of the European Association for the Study of Diabetes, 23–27 September 2013

104-week study with empagliflozin H2H versus glimepiride
Change from baseline in visceral and subcutaneous fat at Week 104*



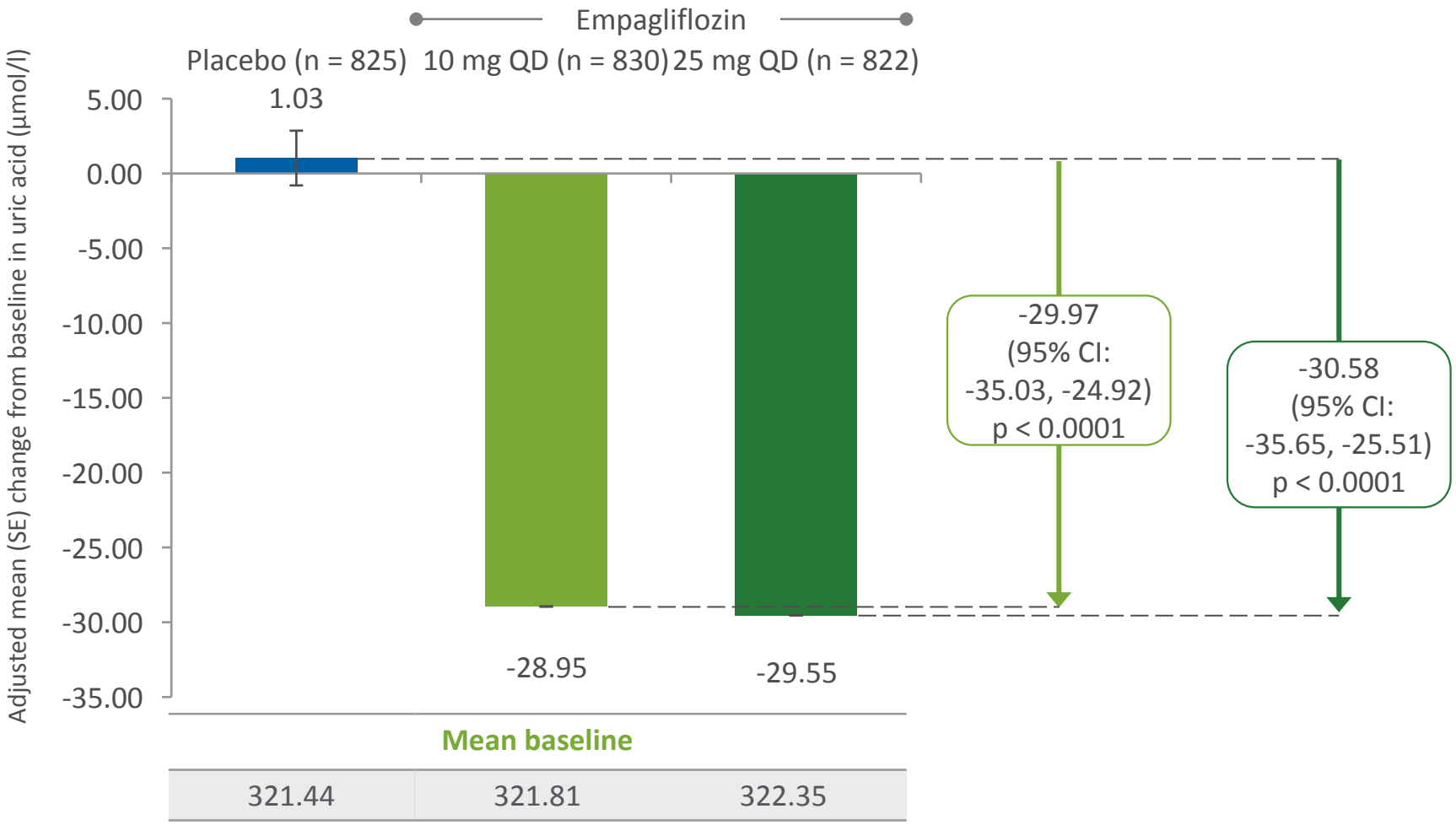
	Glimepiride	EMPA 25 mg QD
Mean baseline (95% CI)	175.1 (142.4, 207.9)	156.2 (137.1, 175.3)



	Glimepiride	EMPA 25 mg QD
Mean baseline (95% CI)	339.5 (297.9, 381.1)	346. (310.6, 381.3)

CI, confidence interval; EMPA, empagliflozin; H2H, head-to-head; QD, once daily.
*Dedicated sub-study using magnetic resonance imaging; patient participation was optional.
Ridderstråle M, et al. *Lancet Diabetes Endocrinol.* 2014;2:691–700.

Phase III pooled efficacy and cardiovascular risk factor analysis
Change from baseline in uric acid



CI, confidence interval; QD, once daily; NS, not significant; SE, standard error.
ANCOVA. TS.
Adapted from: Hach T, et al. *Diabetes*. 2013;(Suppl 1) (P69-LB).

Pooled data from 4 pivotal Phase III trials

Primary Results of EMPA-REG OUTCOME®

Summary of primary results. Please refer to manuscript for full details

EMPA-REG OUTCOME®

42 countries

590 sites

11,531 pts screened

7020 pts randomized

>97 % completed trial

>99 % vital status available

Patients with T2D at high CV risk

Placebo

Empagliflozin 10 mg

Empagliflozin 25 mg

On top of standard of care

Target: ≥691 CV events

CV, cardiovascular.

Pre-specified primary and key secondary outcomes

- Primary outcome
  - **3-point MACE:** Time to first occurrence of CV death, non-fatal MI or non-fatal stroke
- Key secondary outcome
  - **4-point MACE:** Time to first occurrence of CV death, non-fatal MI, non-fatal stroke or hospitalisation for unstable angina

CV, cardiovascular; MI, myocardial infarction; MACE, Major Adverse Cardiovascular Event

Baseline characteristics: CV complications

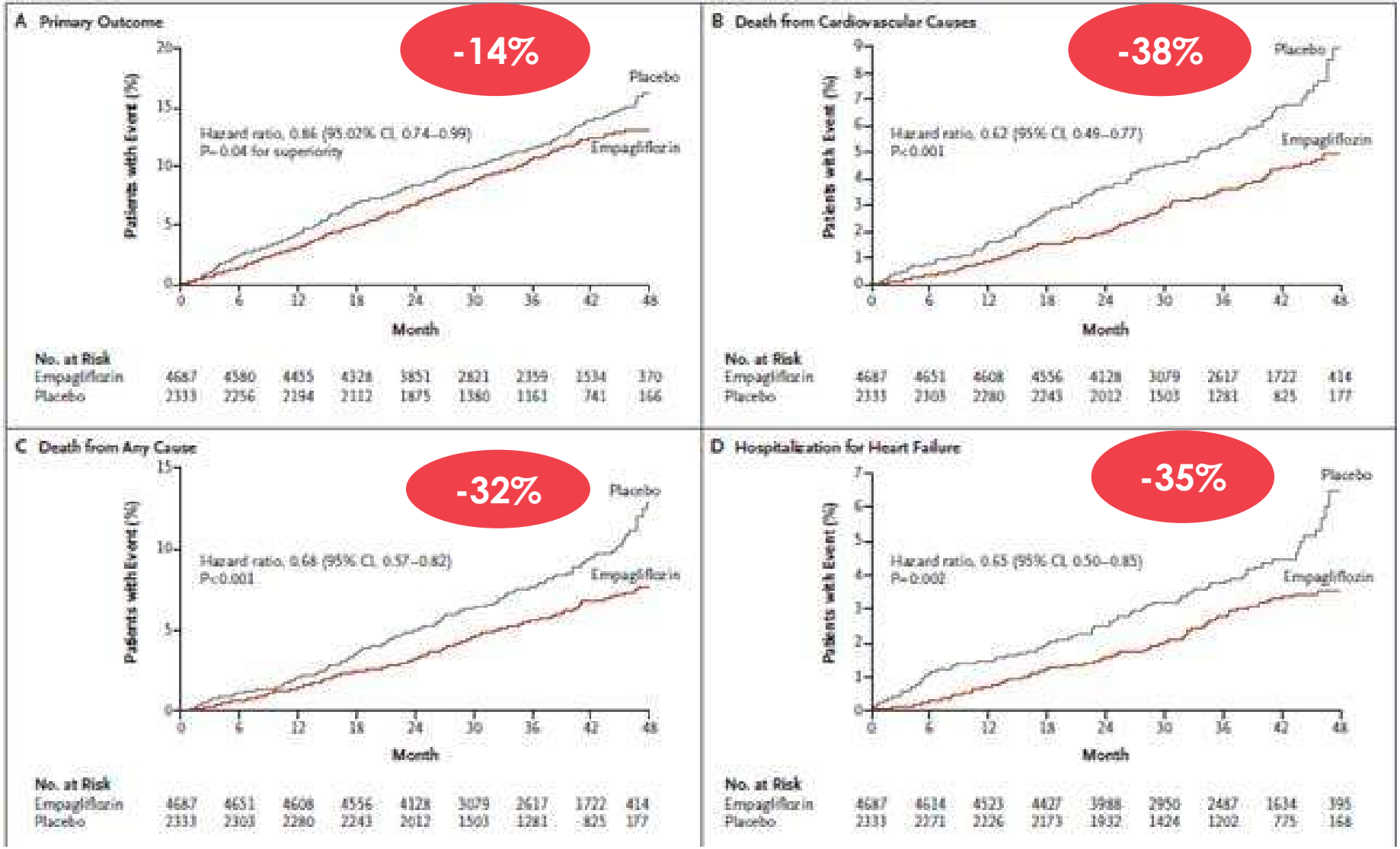
	Placebo (n=2333)	Empagliflozin 10 mg (n=2345)	Empagliflozin 25 mg (n=2342)
Any CV risk factor	2307 (98.9%)	2333 (99.5%)	2324 (99.2%)
Coronary artery disease	1763 (75.6%)	1782 (76.0%)	1763 (75.3%)
Multi-vessel coronary artery disease	1100 (47.1%)	1078 (46.0%)	1101 (47.0%)
History of MI	1083 (46.4%)	1107 (47.2%)	1083 (46.2%)
Coronary artery bypass graft	563 (24.1%)	594 (25.3%)	581 (24.8%)
History of stroke	553 (23.7%)	535 (22.8%)	549 (23.4%)
Peripheral artery disease	479 (20.5%)	465 (19.8%)	517 (22.1%)
Single vessel coronary artery disease	238 (10.2%)	258 (11.0%)	240 (10.2%)
Cardiac failure*	244 (10.5%)	240 (10.2%)	222 (9.5%)

Data are n (%) in patients treated with ≥1 dose of study drug

*Based on narrow standardised MedDRA query "cardiac failure"

Cardiovascular outcomes

Cardiovascular outcomes



Safety and tolerability

EMPA-REG OUTCOME®: conclusions

- Empagliflozin reduced risk for 3-point MACE by 14%
- Empagliflozin reduced hospitalisation for heart failure by 35%
- Empagliflozin reduced CV death by 38%
- Empagliflozin improved survival by reducing all-cause mortality by 32%

CV, cardiovascular

EMPA-REG OUTCOME®: Summary

- Empagliflozin was associated with a reduction in HbA1c without an increase in hypoglycaemia, reductions in weight and blood pressure, and small increases in LDL cholesterol and HDL cholesterol

- Empagliflozin was associated with an increase in genital infections but was otherwise well tolerated

MACE, Major Adverse Cardiovascular Event; HDL, high density lipoprotein; LDL, low density lipoprotein

Number needed to treat (NNT) to prevent one death across landmark trials in patients with high CV risk

Simvastatin[1] for 5.4 years

30

High CV risk
5% diabetes, 26% hypertension

Ramipril[2] for 5 years

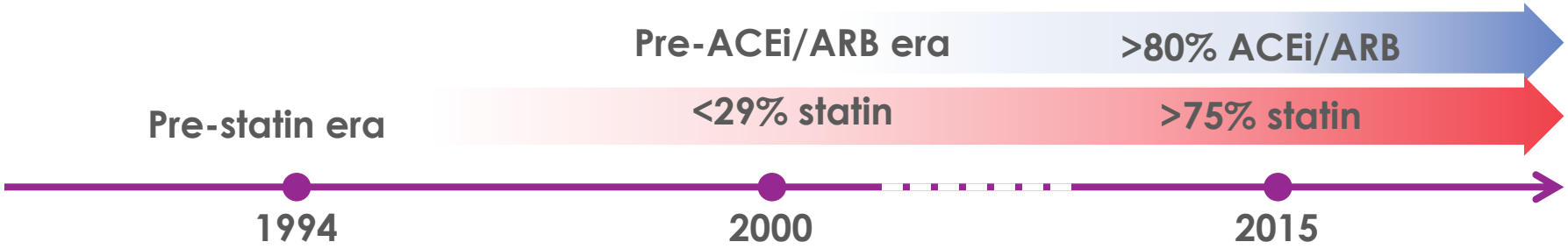
56

High CV risk
38% diabetes, 46% hypertension

Empagliflozin for 3 years

39

T2DM with high CV risk
92% hypertension



1. 4S investigator. Lancet 1994; 344: 1383-89, http://www.trialresultscenter.org/study2590-4S.htm;
2. HOPE investigator N Engl J Med 2000;342:145-53, http://www.trialresultscenter.org/study2606-HOPE.htm

GIT
↓Gastric emptying
↑Acid secretion
↓GI motility

Brain
↓Apetite
↑Satiety
↑Energy expenditure

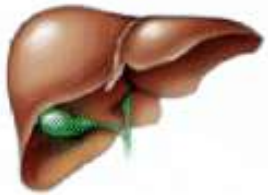
Heart
↓Blood pressure
↑Heart rate
↑Myocardial contractility
↑Cardioprotection

GLP-1
or
GLP-1R AGONISTS

Pancreas
↑Insulin secretion
↓Glucagon secretion
↑Insulin biosynthesis
↑ß-cell survival
↑ß-cell proliferation

↑Insulin sensitivity

Kidney
↑Natriuresis



Liver
↓Hepatic glucose production

Adipose tissue
↑Lyposis
↑FFA synthesis
↑Glucose uptake

Muscle
↑Glycogen synthesis
↑Glucose oxidation

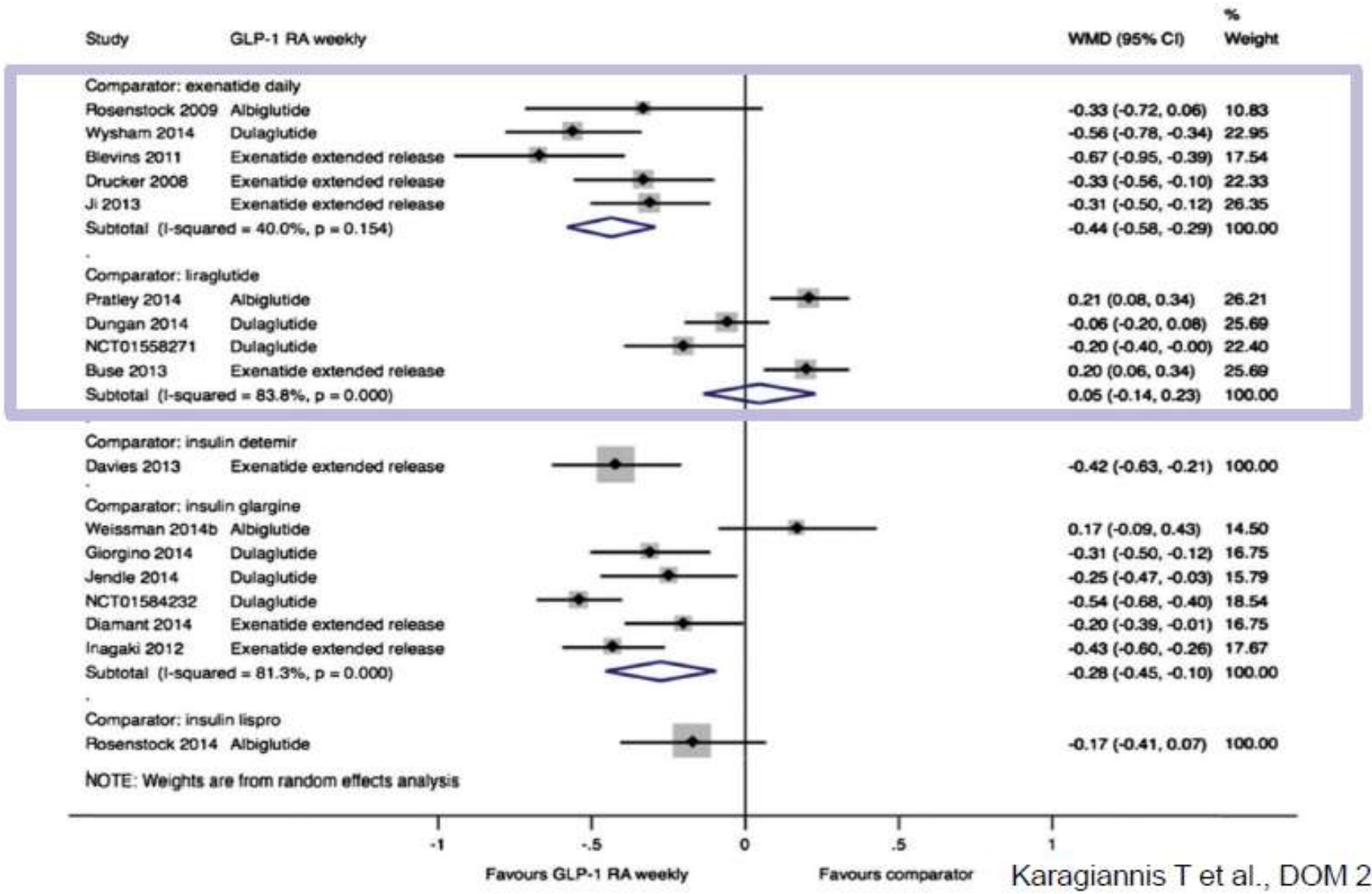
Characterization of various GLP1-RA

	Half-life	Dosing	Titration	injection meal related	Duration of Action	Reconstitution required ? Extra action for device…
Lixisenatide[1,2]	3 hours	Once daily	yes	yes	Short	no
Exenatide BID[4]	2-4 hours	Twice daily	yes	yes	Short	no
Liraglutide[3]	13 hours	Once daily	Yes	no	ntermed.	no
Exenatide QW[5,6]	2 weeks	Once weekly	no	no	Long	yes
Albiglutide[7,8]	6–8 days	Once weekly	yes	no	Long	yes
Dulaglutide	4-5 days	Once weekly	No?/ tbd	no	Long	No (invisible needle)

1 Lyxumia Summary of product characteristics. Accessed 14 May 2013. 2. Fineman et al. Diabetes Obno/ tbdes Metab 2012;14:675-688. 3. Victoza Summary of product characteristics. Accessed 14 May 2013. 4. BYETTA Summary of product characteristics. Accessed 14 May 2013. 5. BYDUREON Summary of product characteristics. Accessed 14 May 2013. 6. Murphy CE. Ann Pharmacother 2012;46:812-821. 7. Eperzan Summary of Opinion (EMA). Accessed 14 Feb 2014. 8. Meier JJ. Nat Rev Endocrinol 2012;8:728-742. 9. Barrington P et al. Obes Metab 2011;13:434–438.

Change in HbA1c:

Once weekly GLP-1RA vs other Injectable therapies

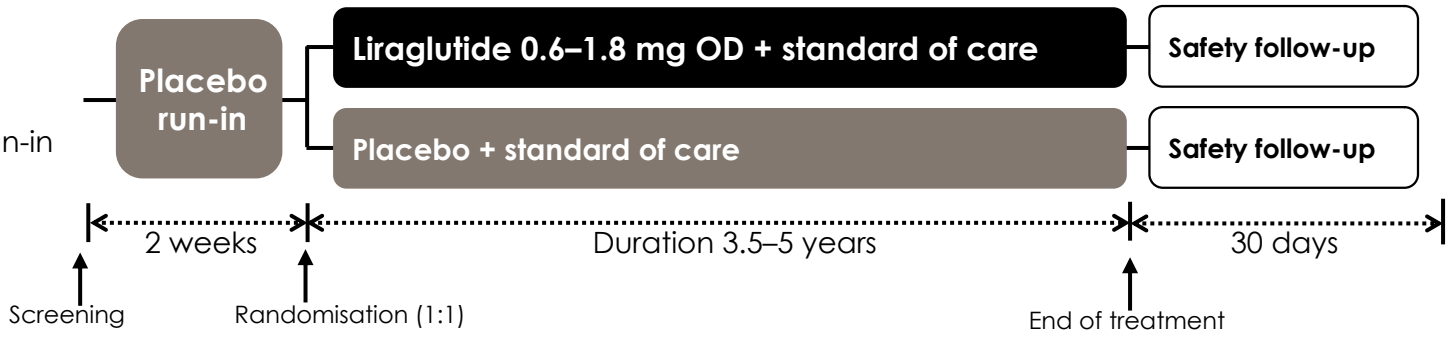


Karagiannis T et al., DOM 2015

LEADER: Study design

9340 patients

- Double blinded
- 2-week placebo run-in



Key inclusion criteria

- T2DM, HbA_{1c} ≥7.0%
- Antidiabetic drug naïve; OADs and/or basal/premix insulin
- Age ≥50 years and established CV disease or chronic renal failure

  or
- Age ≥60 years and risk factors for CV disease

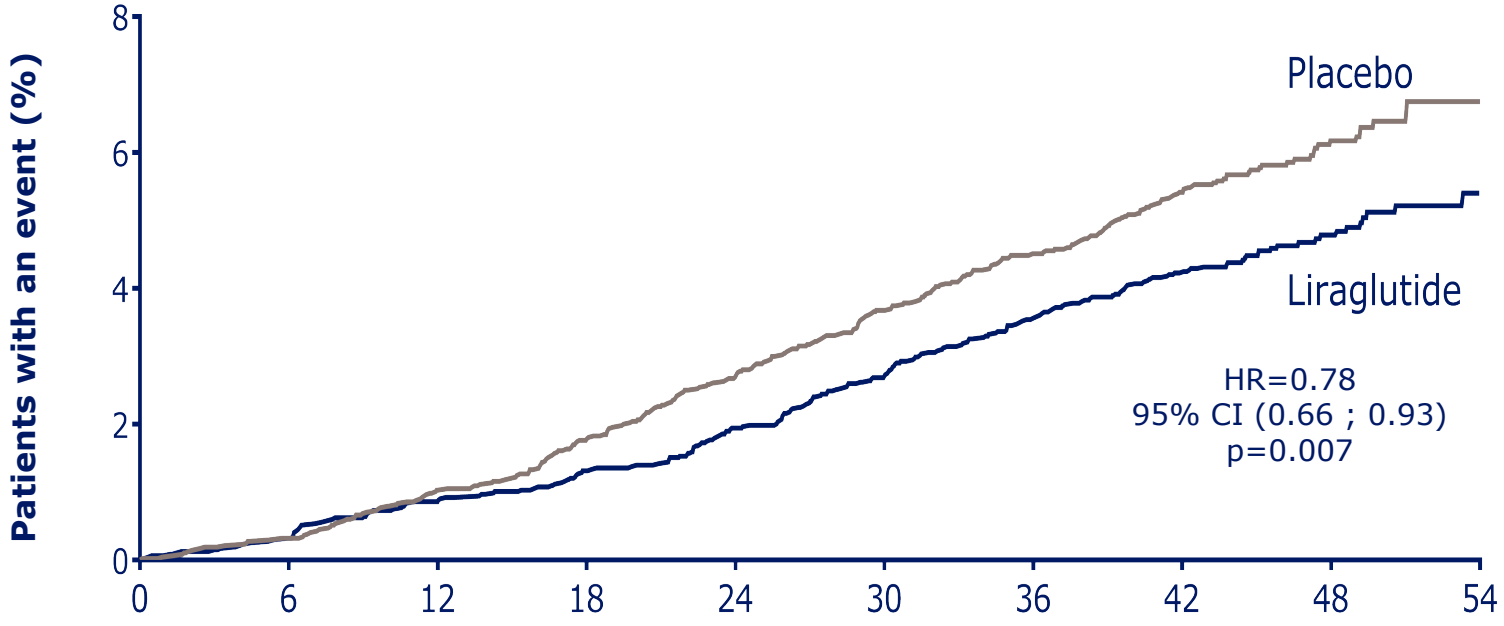
Key exclusion criteria

- T1DM
- Use of GLP-1RAs, DPP-4i, pramlintide, or rapid-acting insulin
- Familial or personal history of MEN-2 or MTC

CV, cardiovascular; HbA_{1c}, glycosylated haemoglobin; OAD, oral antidiabetic drug; OD, once daily; T2DM, type 2 diabetes mellitus.

Marso SP et al. *N Engl J Med* 2016. DOI: 10.1056/NEJMoa1603827.

CV death



Patients at risk

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

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.
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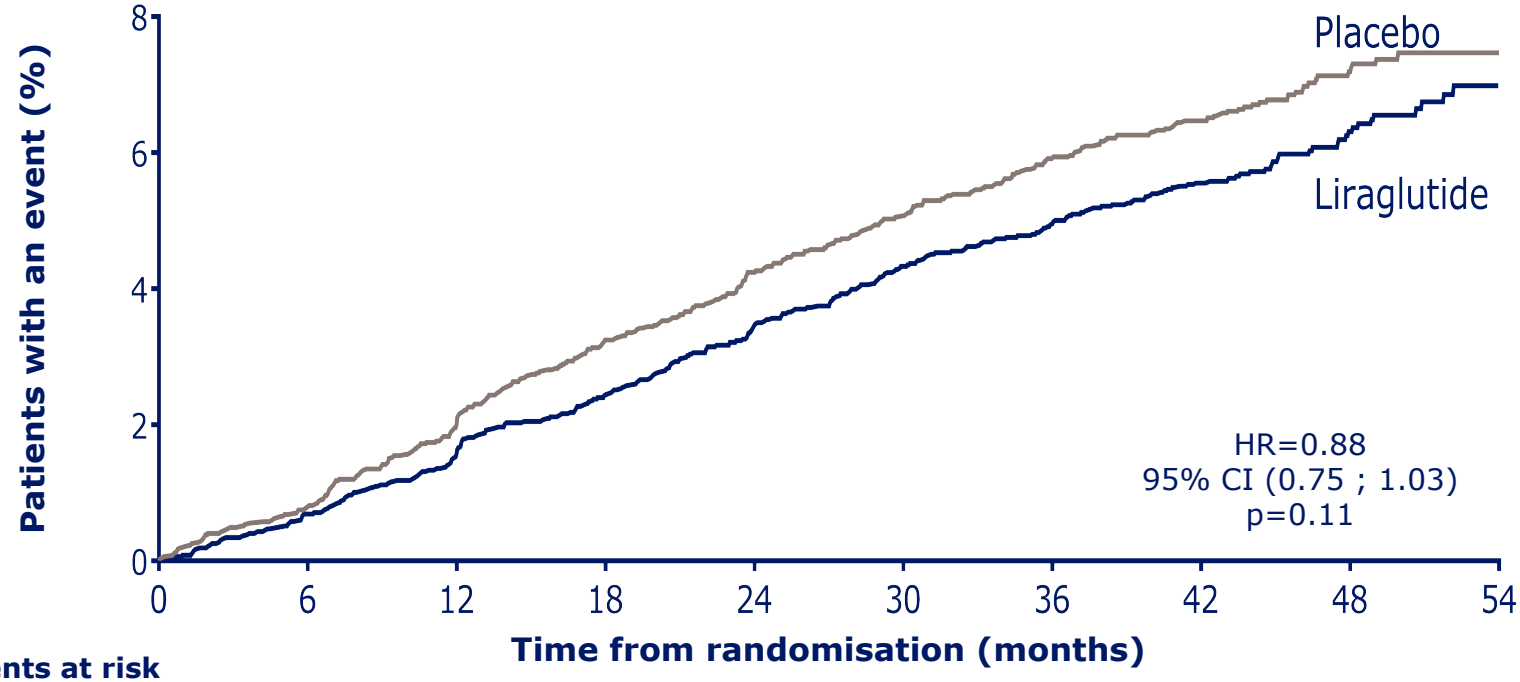
Non-fatal myocardial infarction



Patients at risk

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

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.
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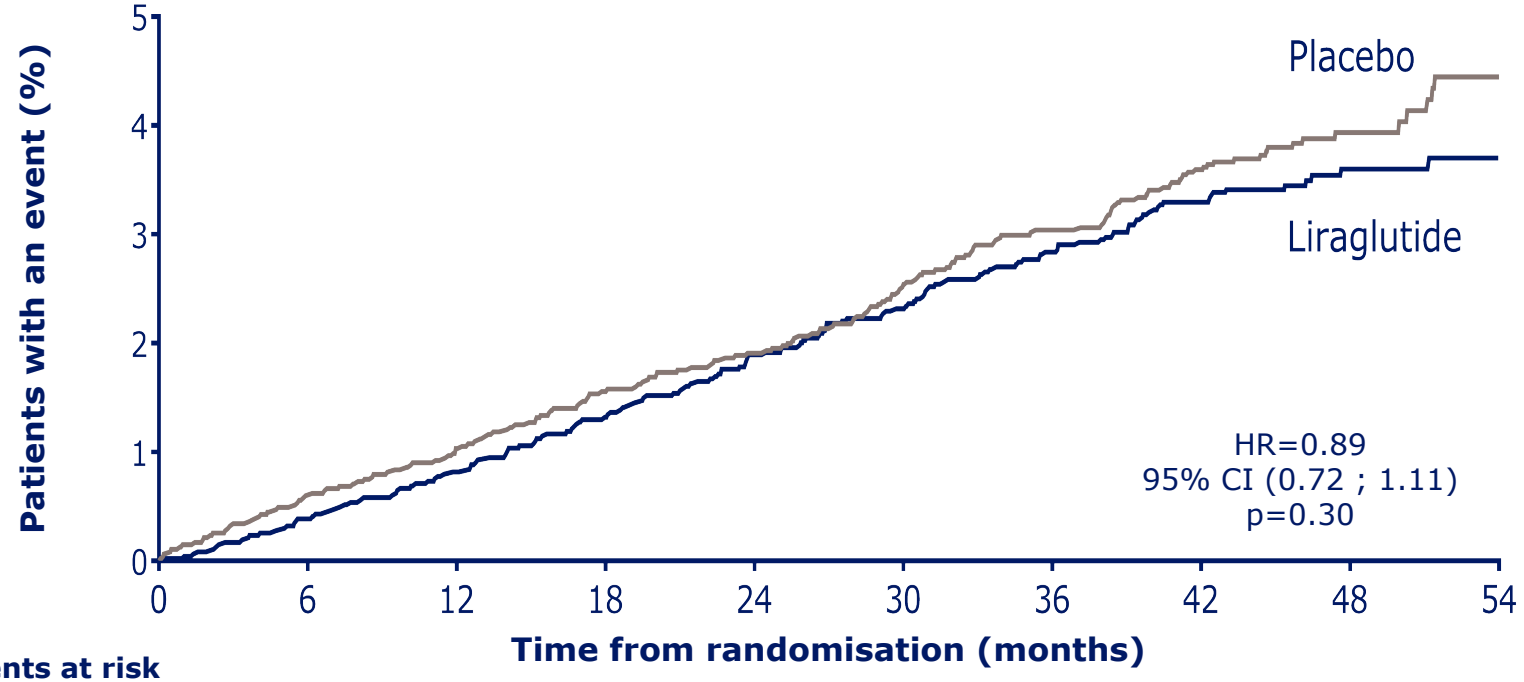
Non-fatal stroke



Patients at risk

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

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.
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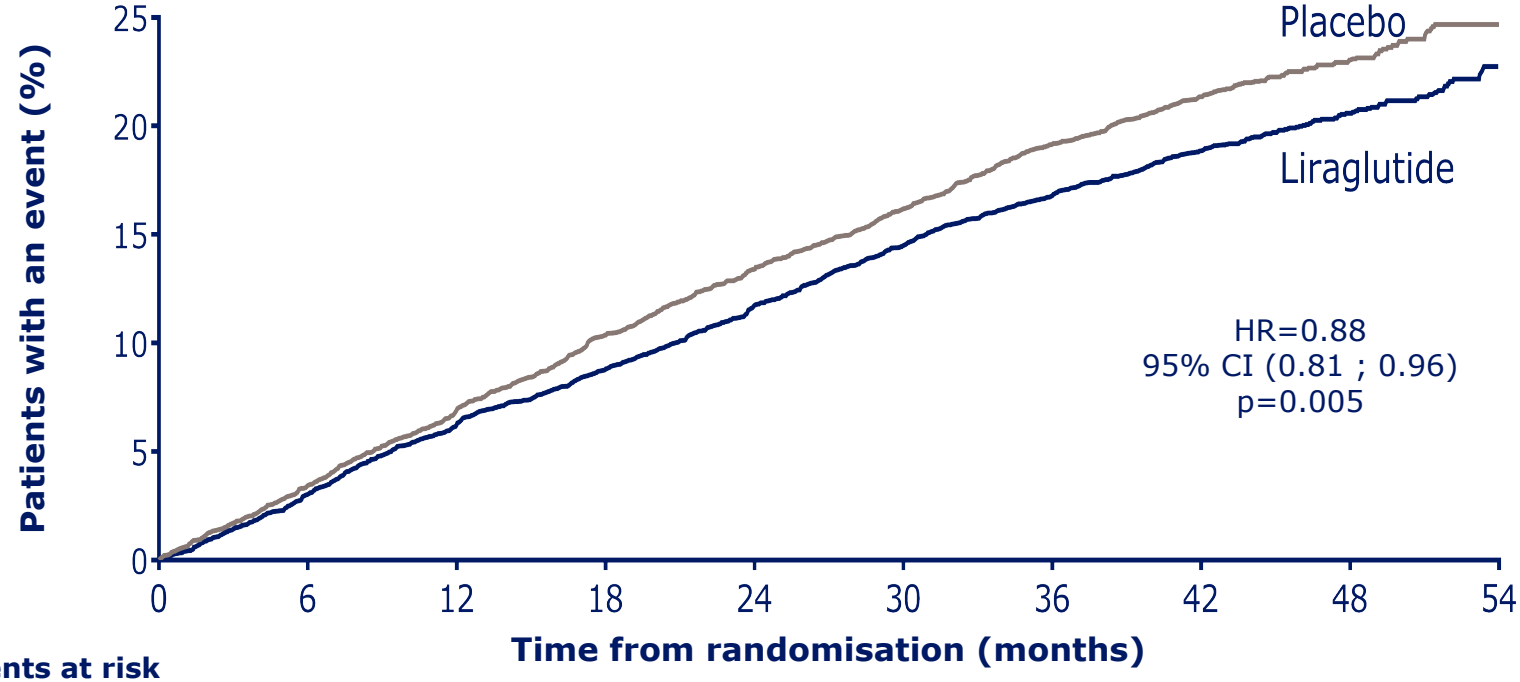
Expanded MACE
All-cause death
Hospitalisation for HF

Expanded MACE

CV death, non-fatal MI, non-fatal stroke, coronary revascularisation, or hospitalisation 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; HR, hazard ratio; MACE, major adverse cardiovascular event.
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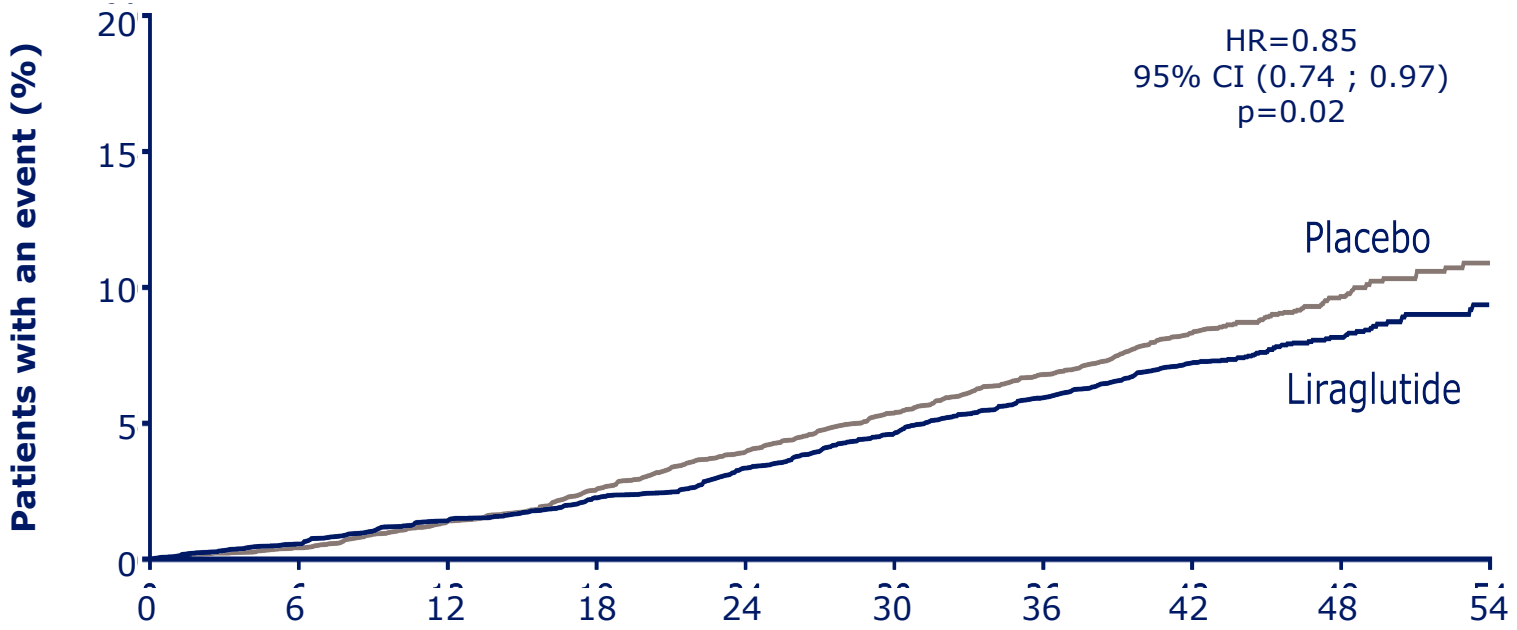
All-cause death



Patients at risk

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

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.
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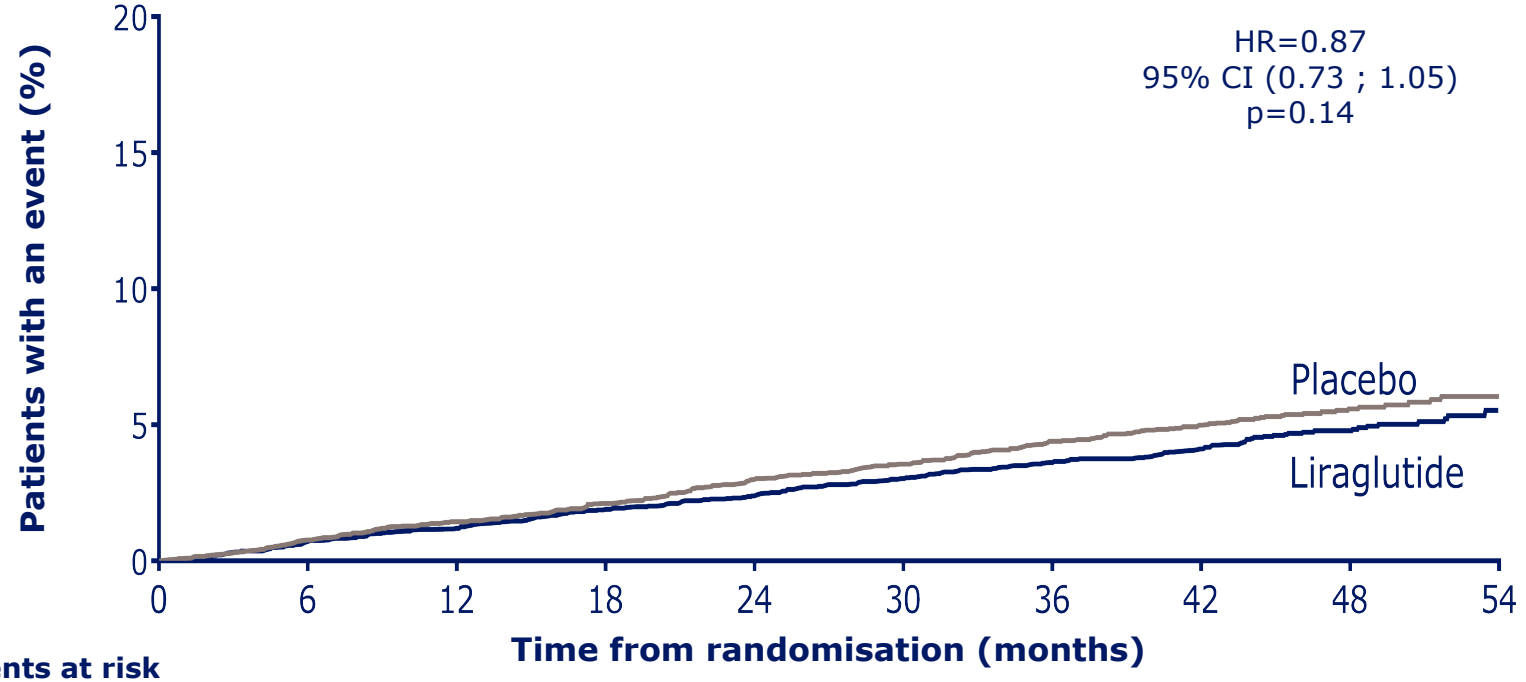
Hospitalisation for heart failure



Patients at risk

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

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.
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Conclusion

In patients with type 2 diabetes at high risk of cardiovascular events on standard therapy, liraglutide- as compared to placebo-treated patients had lower rates of cardiovascular events and all-cause death

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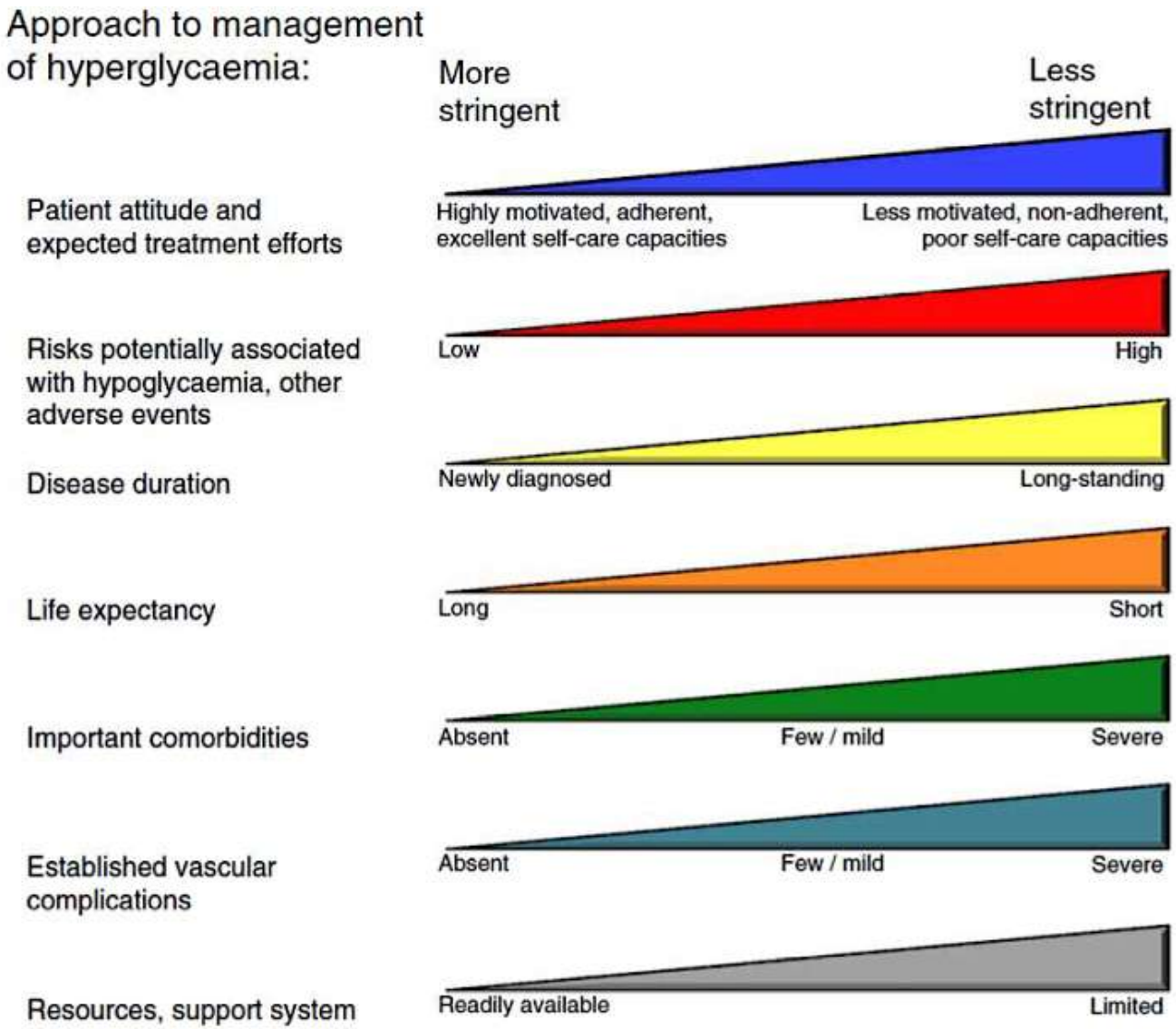
ADA/EASD position statement 2012
Towards the personalization of glycaemic targets



Inzucchi S. et al, Diabetes Care. Vol 35 (2012)