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<http://glucose.ai>

# What's new in diabetes?

## Type 1 diabetes

- focus on glucose variability as metric
- techniques to reduce variability: new insulins, CGMS / flash glucose monitoring, closed-loop sensor/pump systems

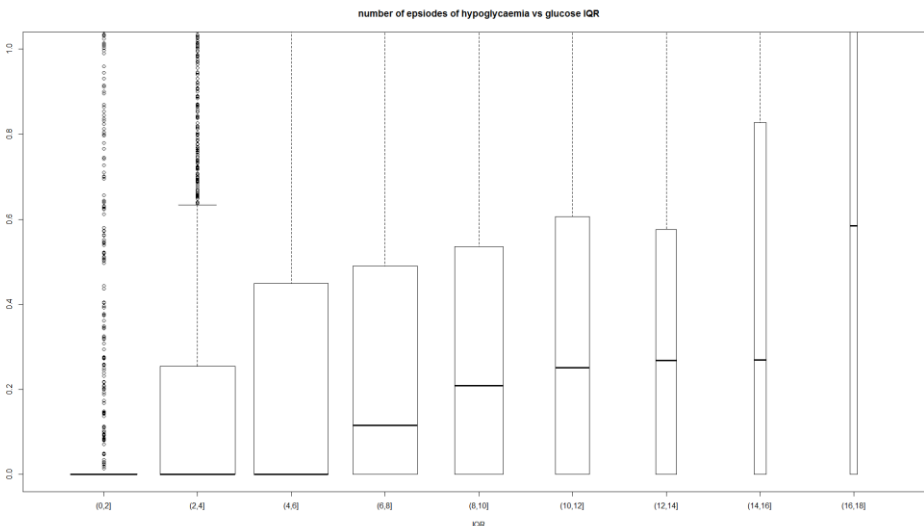
## Type 2 diabetes

- focus on glucose variability as key metric
- move from surrogate to outcome driven therapeutic choices

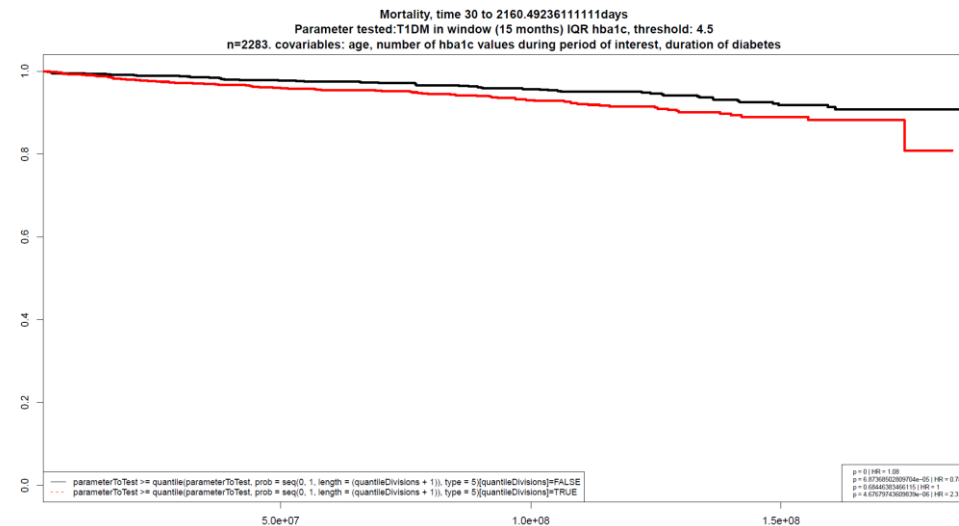
# Type 1 Diabetes

# Type 1 diabetes: Glucose Variability

- median glucose (HbA1c associated with complications) – has traditionally driven management decisions
- multiscale glucose variability associates with short and long term outcomes (hypoglycaemia / mortality)



CBG variability vs inpatient hypoglycaemia rate



HbA1c variability vs 5y mortality (1)

# **Type 1 diabetes:** Strategies to reduce glycaemic variability

- improve patient view of glucose throughout 24h period  
(CGMS / flash monitoring)
- improve insulin requirement / delivery matching
  - structured education / DAFNE
- improve insulin kinetics / delivery mechanism
  - new insulins
  - insulin pump / closed loop systems
- intelligent ML based systems to assist decision making

# Type 1 diabetes: flash monitoring



MY ACCOUNT

BASKET

Abbott

PRODUCTS

DISCOVER

SUPPORT



## FREESTYLE LIBRE SENSOR

1

**£57.95**  
Incl. VAT

BUY NOW

Please note that quantities are limited to 10 Sensor per customer per purchase.

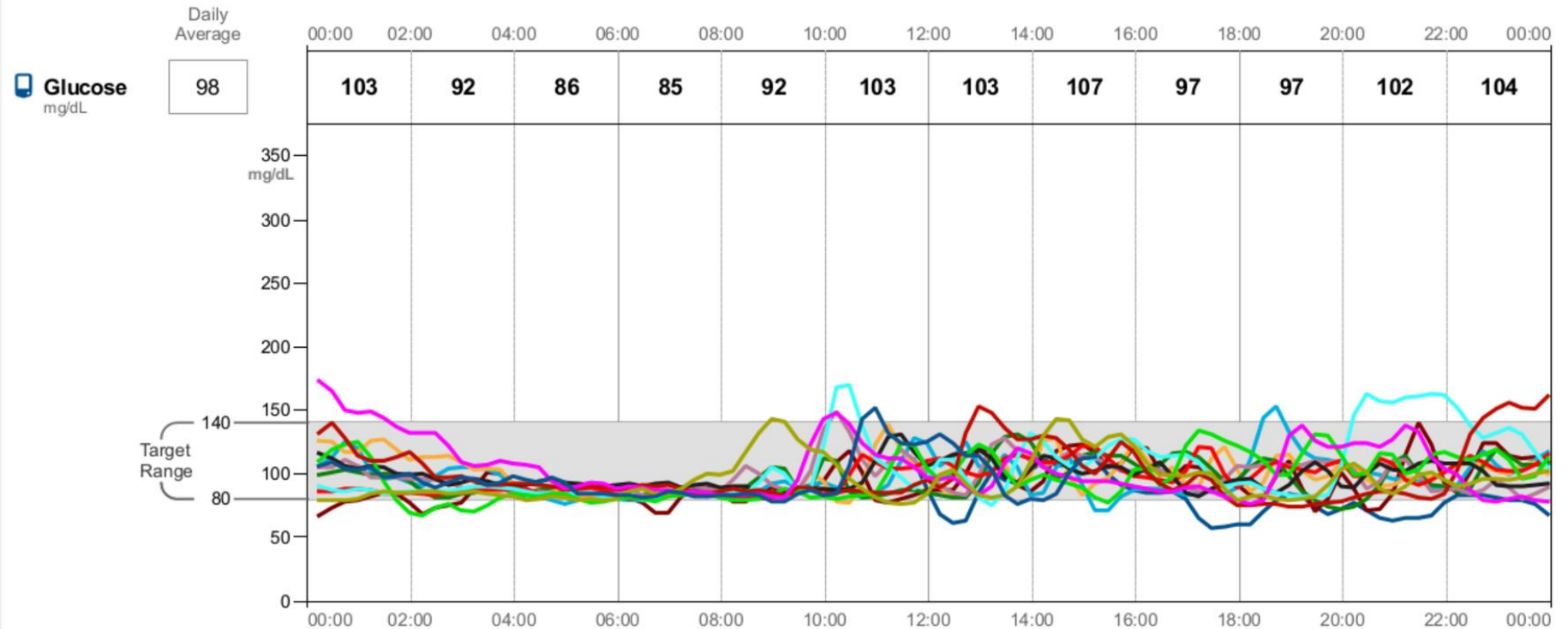


# Daily Patterns (with glucose readings)

26 May 2016 - 8 June 2016 (14 days)

FreeStyle Libre Pro 

Estimated A1c **5.0% or 31 mmol/mol**



Hourly Pattern with glucose reading for every day at different time. Check late nights and early mornings, there seems to be a little rise.

# improved understanding of glycaemia leads to better decision making by patients and doctors

## Glucose Pattern Insights

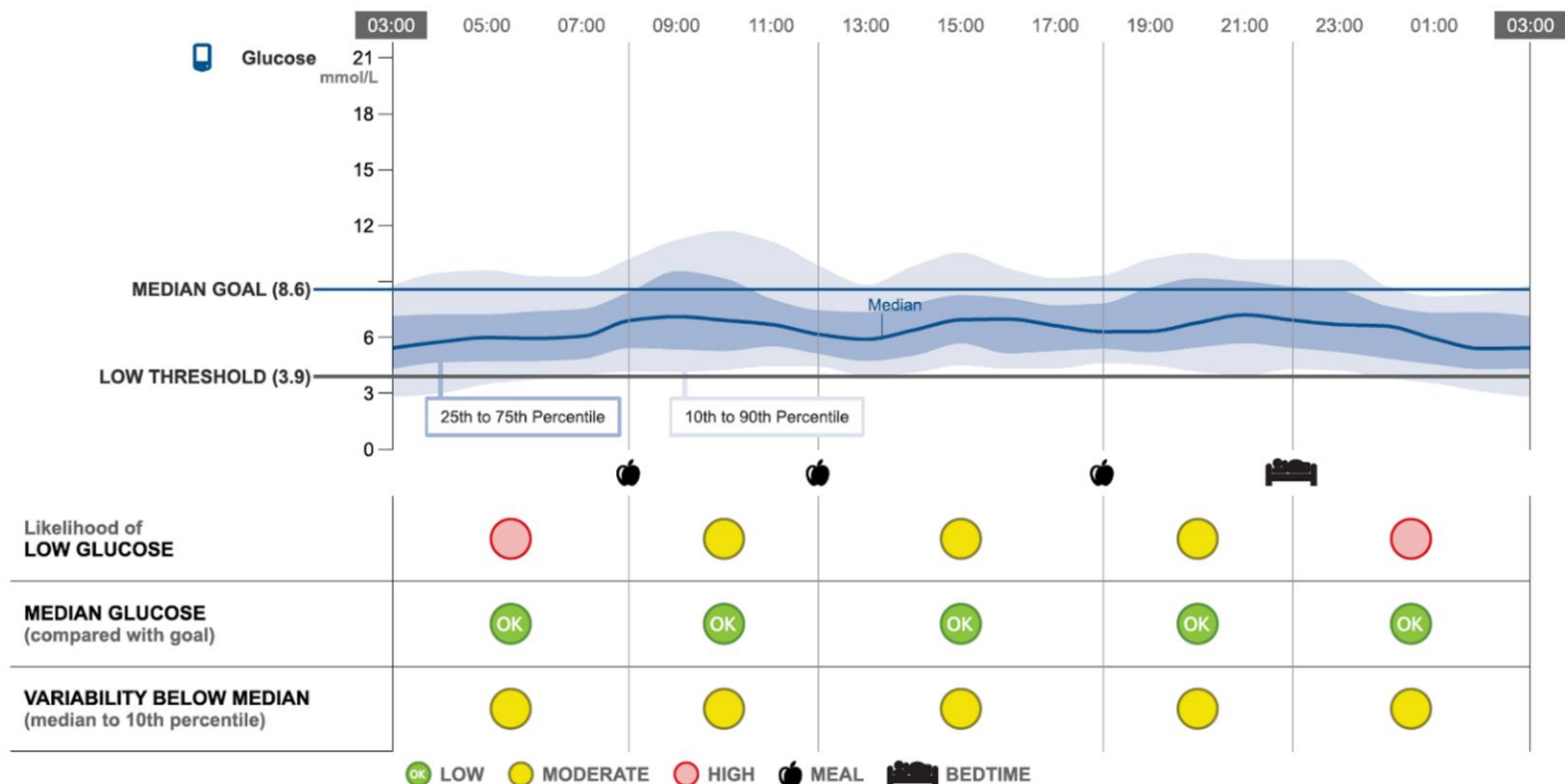
13 September 2014 - 10 October 2014 (28 days)

LOW-GLUCOSE ALLOWANCE SETTING: Medium

MEDIAN GOAL SETTING: 8.6 mmol/L (A1c: 7.0% or 53 mmol/mol)

FreeStyle Libre 

Estimated A1c **5.8% or 40 mmol/mol**





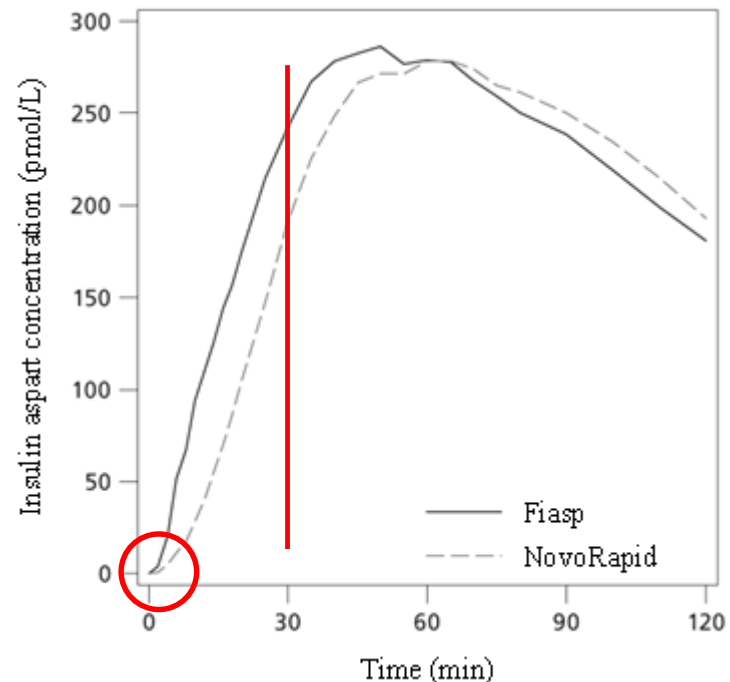
# Type 1 diabetes: new insulins

- faster acting short-acting insulins  
reduce interval required pre-meal for dosing  
quicker time to peak reduces post-prandial glucose

faster asparte (FIAsp)

x2 AUC in first 30 mins

faster onset of action



# Type 1 diabetes: new insulins

- longer acting long-acting insulins
  - lower intra-individual variability of day-to-day action
  - less overnight hypoglycaemia
  - dose timing flexibility
  - ? less DKA in intermittent insulin users

insulin glargine U300 (Tuojeo)

insulin degludec (Tresiba)

# Type 1 diabetes: pump technologies

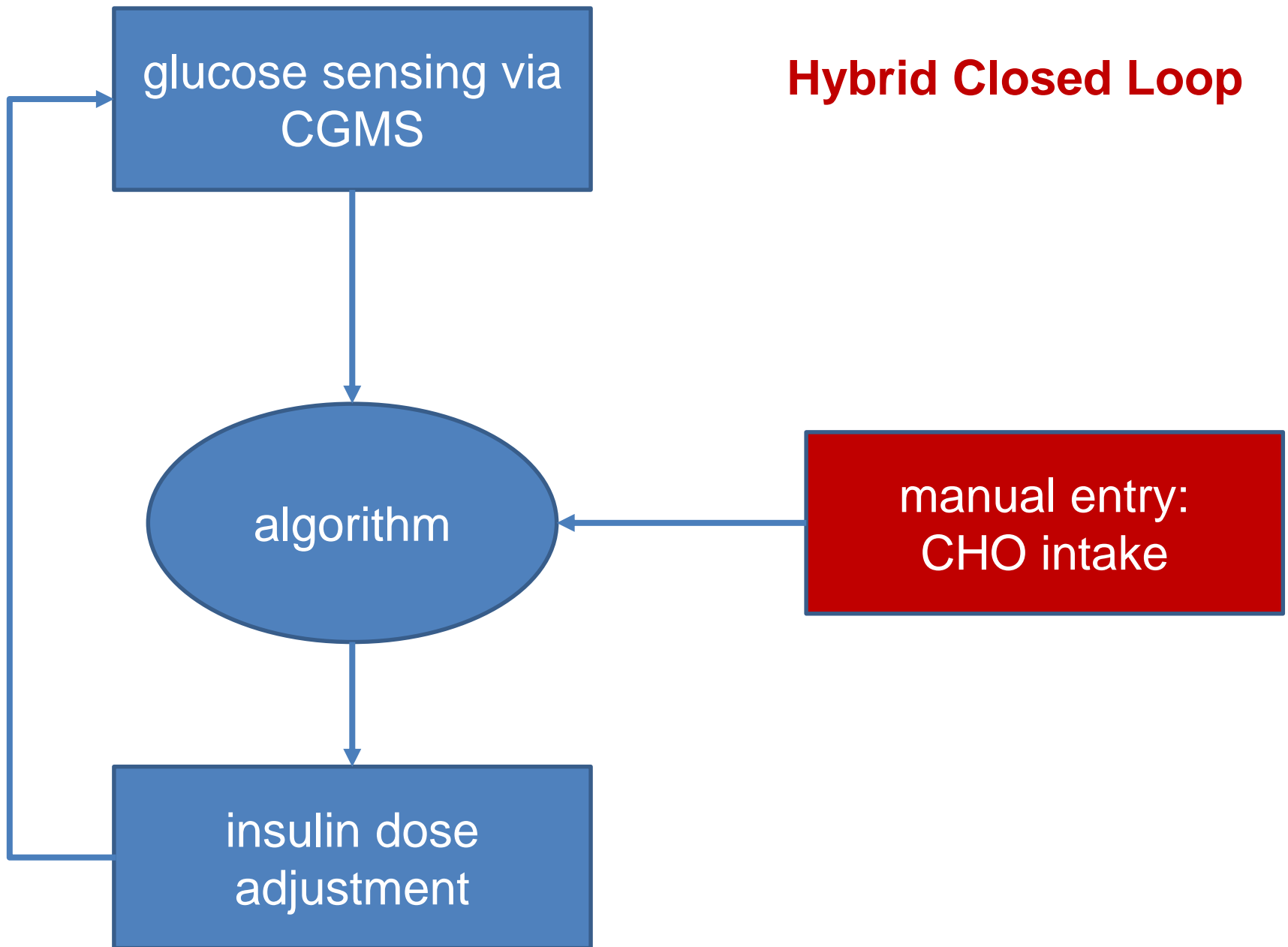
- Medtronic 670G – FDA approved

BREAKING NEWS: FDA APPROVES THE MINIMED 670G SYSTEM,  
WORLD'S FIRST HYBRID CLOSED LOOP SYSTEM

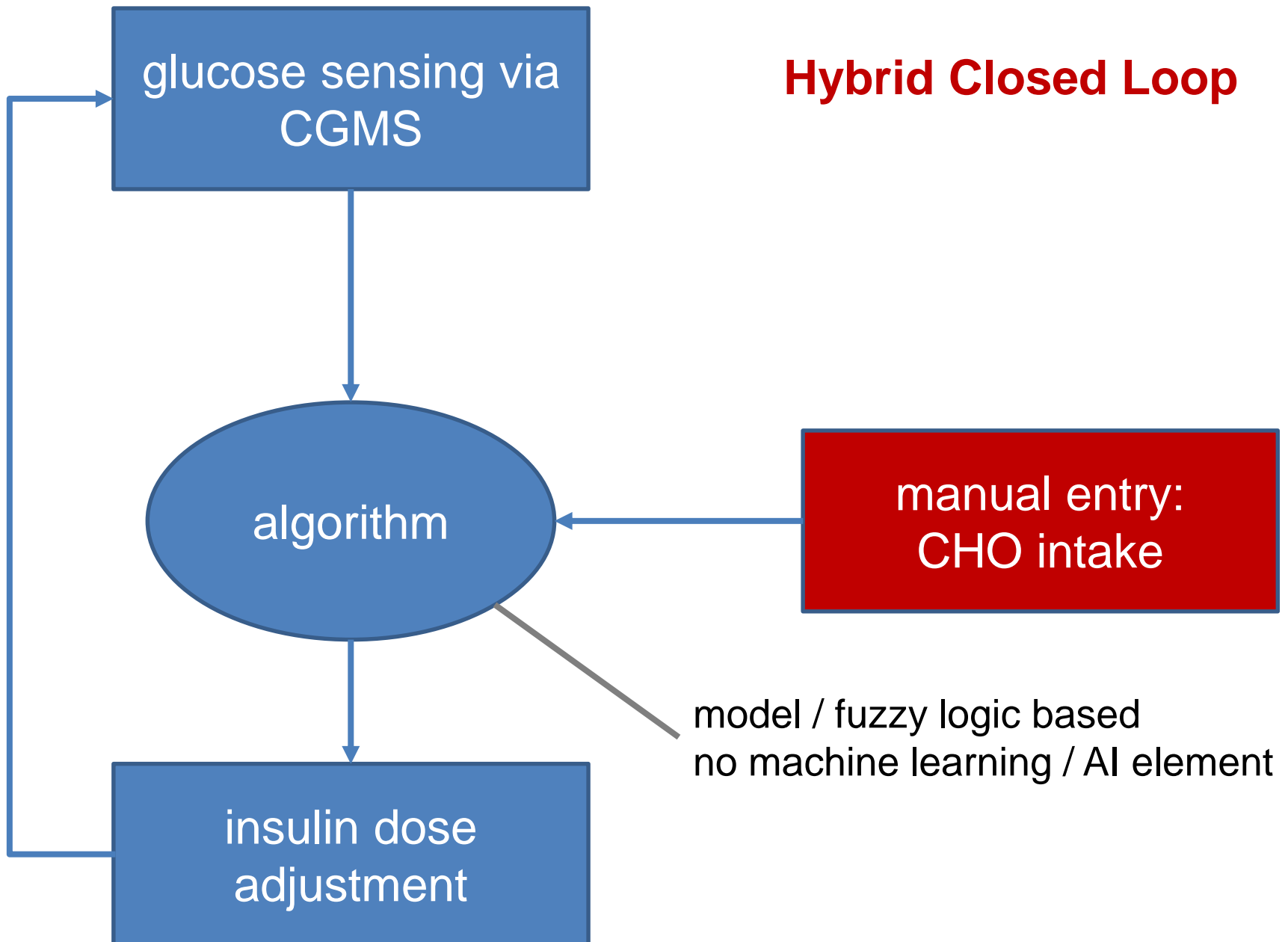
Posted by [Sara Tilleskjaer](#) On September 29, 2016 In [Meaningful Innovation](#)



## Hybrid Closed Loop

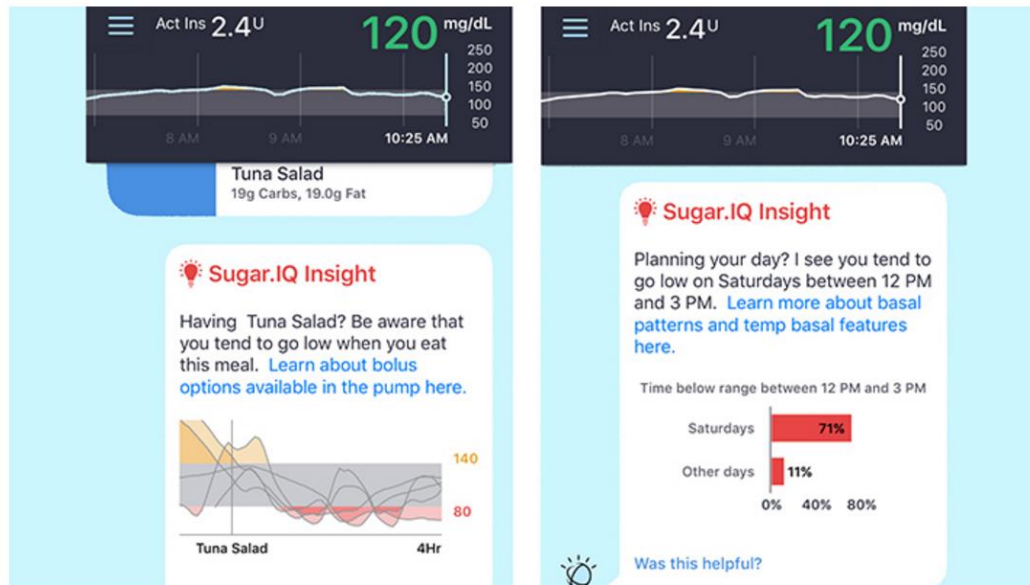


## Hybrid Closed Loop



# Type 1 diabetes: machine learning / AI

- Medtronic / IBM Watson – sugar.IQ

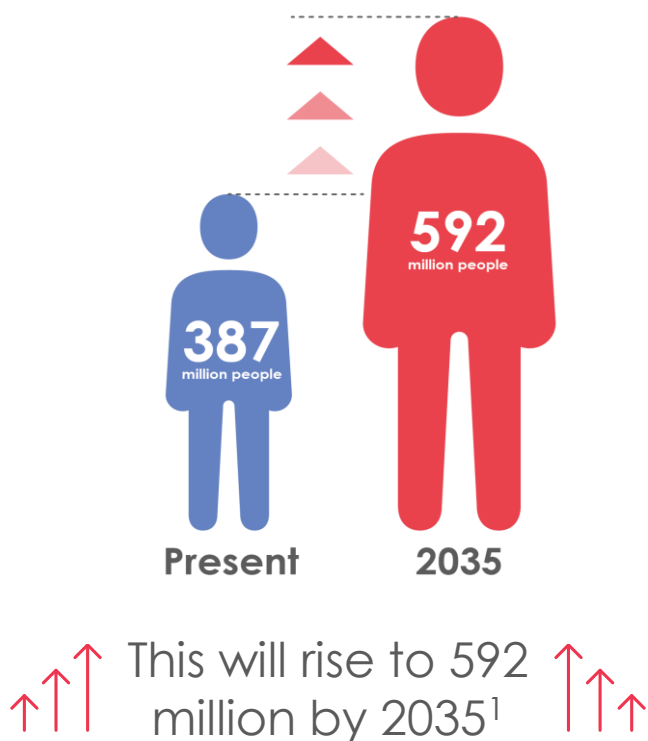


- pattern recognition using multiple data sources:
- CBG / CGMS, accelerometer data, CHO / nutritional data, location, weather etc

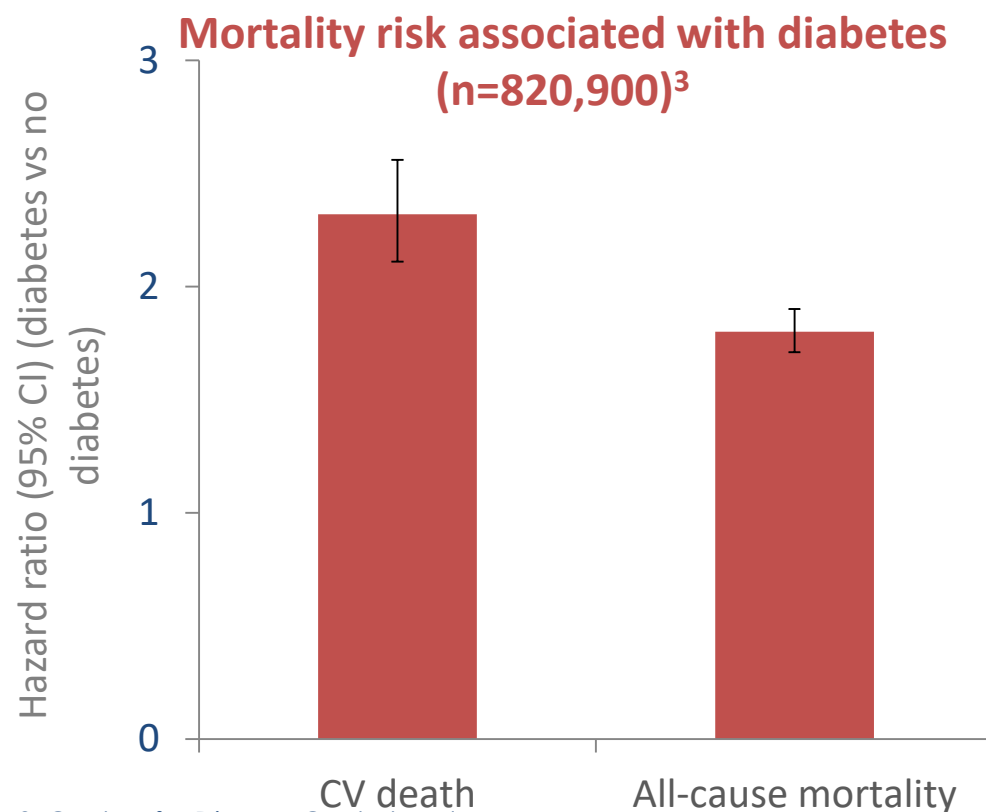
# Type 2 Diabetes

# Type 2 diabetes is increasingly prevalent

- Globally, 387 million people are living with diabetes<sup>1</sup>



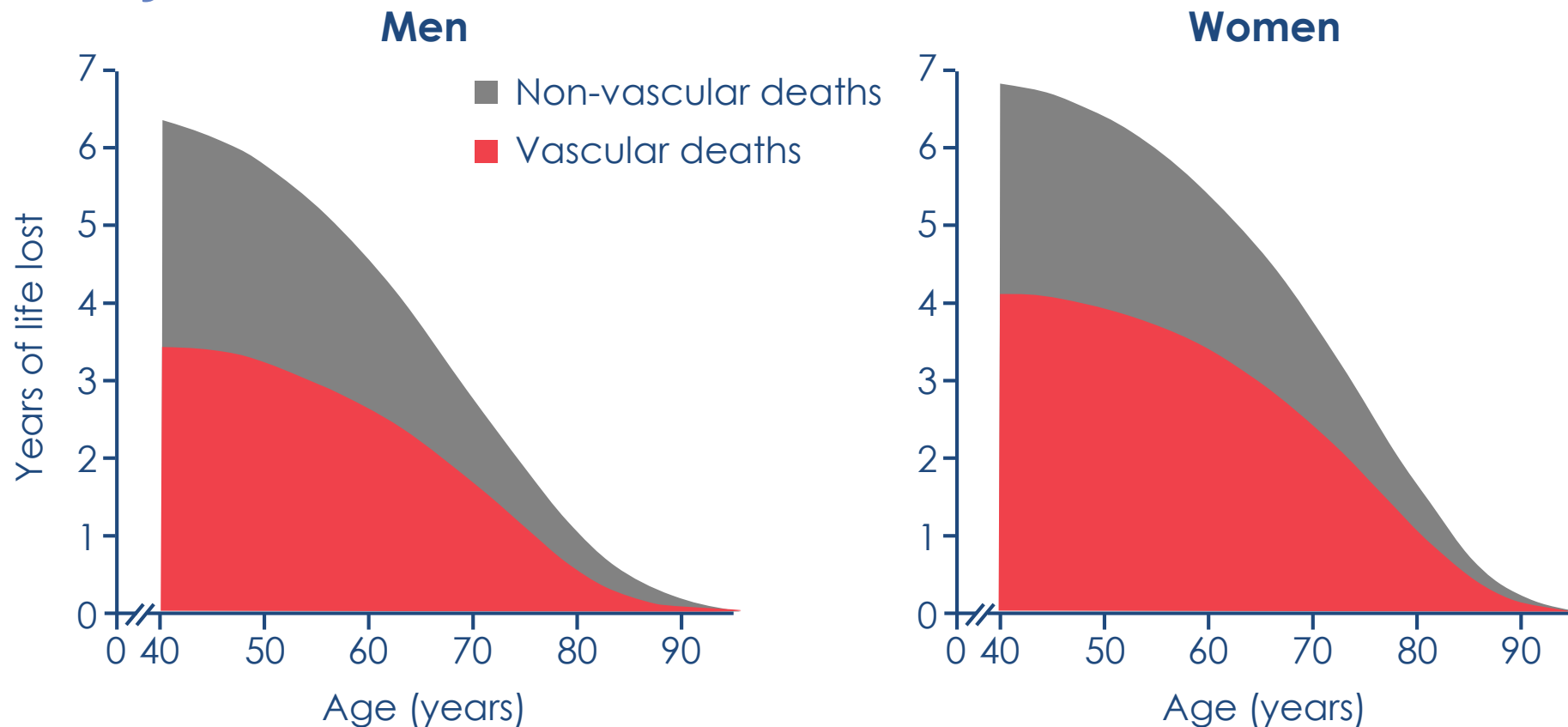
- At least 68% of people >65 years with diabetes die of heart disease<sup>2</sup>



1. IDF Diabetes Atlas 6th Edition 2014 <http://www.idf.org/diabetesatlas>; 2. Centers for Disease Control and Prevention, National Diabetes Fact Sheet, 2011 Available at [http://www.cdc.gov/diabetes/pubs/pdf/ndfs\\_2011.pdf](http://www.cdc.gov/diabetes/pubs/pdf/ndfs_2011.pdf); 3. Seshasai SRK et al. N Engl J Med 2011;364:829-41 Supplementary Appendix



# Diabetes is associated with significant loss of life years

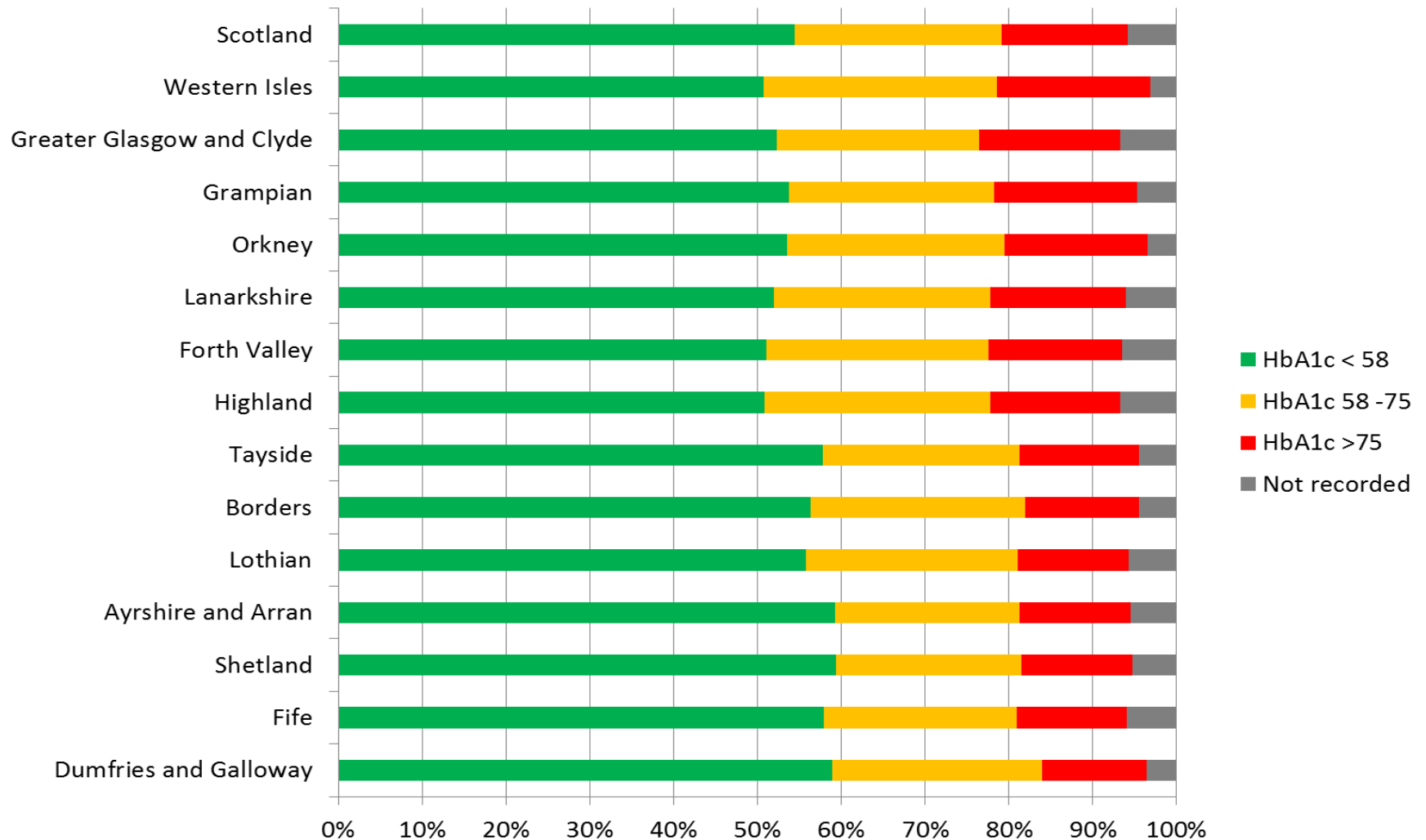


On average, a 50-year-old individual with diabetes and no history of vascular disease will die 6 years earlier compared to someone without diabetes

# How well do we manage glycaemia in T2DM?

Scottish Diabetes Survey 2015

Number of Patients with Type 2 with HbA1c Controlled



# Type 2 diabetes: guidelines

- many in existence
- all basically similar ie  
metformin + others in various orders

## UKPDS: Metformin in Overweight Patients

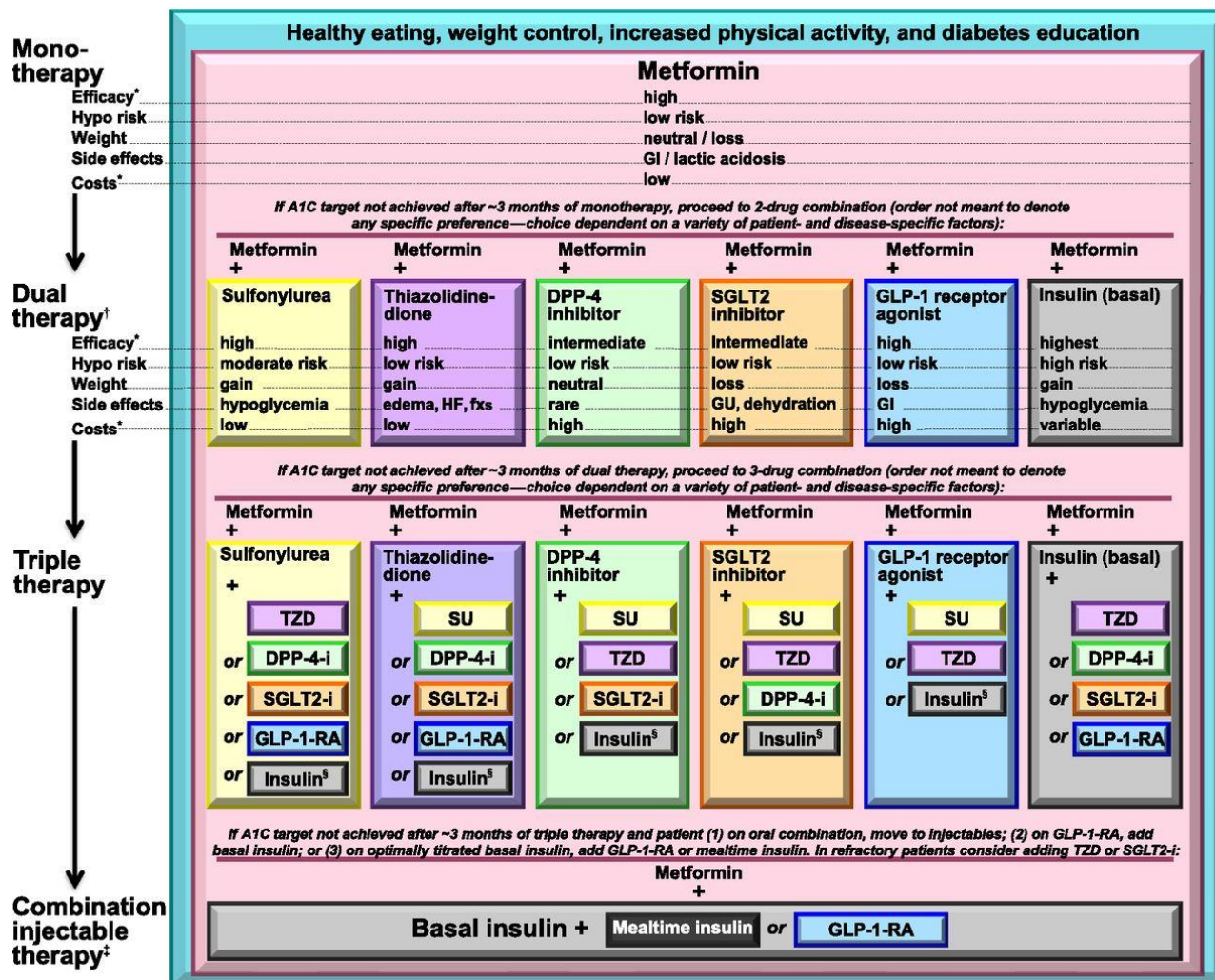
	Metformin HbA <sub>1c</sub> = 7.4%		Sulfonylurea/Insulin HbA <sub>1c</sub> = 8.0%	
	Change in Risk*	P value	Change in Risk*	P value
Any diabetes-related endpoint	↓ 32%	0.0023	↓ 7%	NS
Diabetes-related deaths	↓ 42%	0.017	↓ 20%	NS
Myocardial infarction	↓ 39%	0.01	↓ 21%	NS
Stroke	↓ 41%	NS	↑ 14%	NS
Microvascular disease	↓ 29%	NS	↓ 16%	NS

\*Compared with conventional therapy.

UKPDS Group. *Lancet* 1998;352:854–865.

- what is the mortality evidence for other agents?

# Antihyperglycemic therapy in type 2 diabetes: general recommendations (15).



American Diabetes Association Dia Care 2015;38:S41-S48

# NICE NG28 – Algorithm for blood glucose lowering therapy in adults with type 2 diabetes

If the person is symptomatically hyperglycaemic, consider insulin or an SU. Review treatment when blood glucose control has been achieved.

## ADULT WITH TYPE 2 DIABETES WHO CAN TAKE METFORMIN

If HbA1c rises to 48 mmol/mol (6.5%) on lifestyle interventions:

- Offer standard-release metformin
- Support the person to aim for an HbA1c level of 48 mmol/mol (6.5%)

### FIRST INTENSIFICATION

If HbA1c rises to 58 mmol/mol (7.5%):

- Consider dual therapy with:
  - metformin and a DPP-4i
  - metformin and pioglitazone<sup>a</sup>
  - metformin and an SU
  - metformin and an SGLT-2<sup>p</sup>
- Support the person to aim for an HbA1c level of 53 mmol/mol (7.0%)

### SECOND INTENSIFICATION

If HbA1c rises to 58 mmol/mol (7.5%):

- Consider:
  - triple therapy with:
    - o metformin, a DPP-4i and an SU
    - o metformin, pioglitazone<sup>a</sup> and an SU
    - o metformin, pioglitazone<sup>a</sup> or an SU, and an SGLT-2<sup>p</sup>
  - insulin-based treatment
- Support the person to aim for an HbA1c level of 53 mmol/mol (7.0%)

If standard-release metformin is not tolerated or contraindicated, consider a trial of modified-release metformin

If triple therapy is not effective, not tolerated or contraindicated, consider combination therapy with metformin, an SU and a GLP-1 mimetic<sup>c</sup> for adults with type 2 diabetes who:

- have a BMI of 35 kg/m<sup>2</sup> or higher (adjust accordingly for people from black, Asian and other minority ethnic groups) and specific psychological or other medical problems associated with obesity or
- have a BMI lower than 35 kg/m<sup>2</sup>, and for whom insulin therapy would have significant occupational implications, or weight loss would benefit other significant obesity-related comorbidities

## METFORMIN CONTRAINDICATED OR NOT TOLERATED

If HbA1c rises to 48 mmol/mol (6.5%) on lifestyle interventions:

- Consider one of the following<sup>d</sup>:
  - a DPP-4i, pioglitazone<sup>a</sup> or an SU
- Support the person to aim for an HbA1c level of 48 mmol/mol (6.5%) for people on a DPP-4i or pioglitazone or 53 mmol/mol (7.0%) for people on an SU

### FIRST INTENSIFICATION

If HbA1c rises to 58 mmol/mol (7.5%):

- Consider dual therapy<sup>e</sup> with:
  - a DPP-4i and pioglitazone<sup>a</sup>
  - a DPP-4i and an SU
  - pioglitazone<sup>a</sup> and an SU
- Support the person to aim for an HbA1c level of 53 mmol/mol (7.0%)

### SECOND INTENSIFICATION

If HbA1c rises to 58 mmol/mol (7.5%):

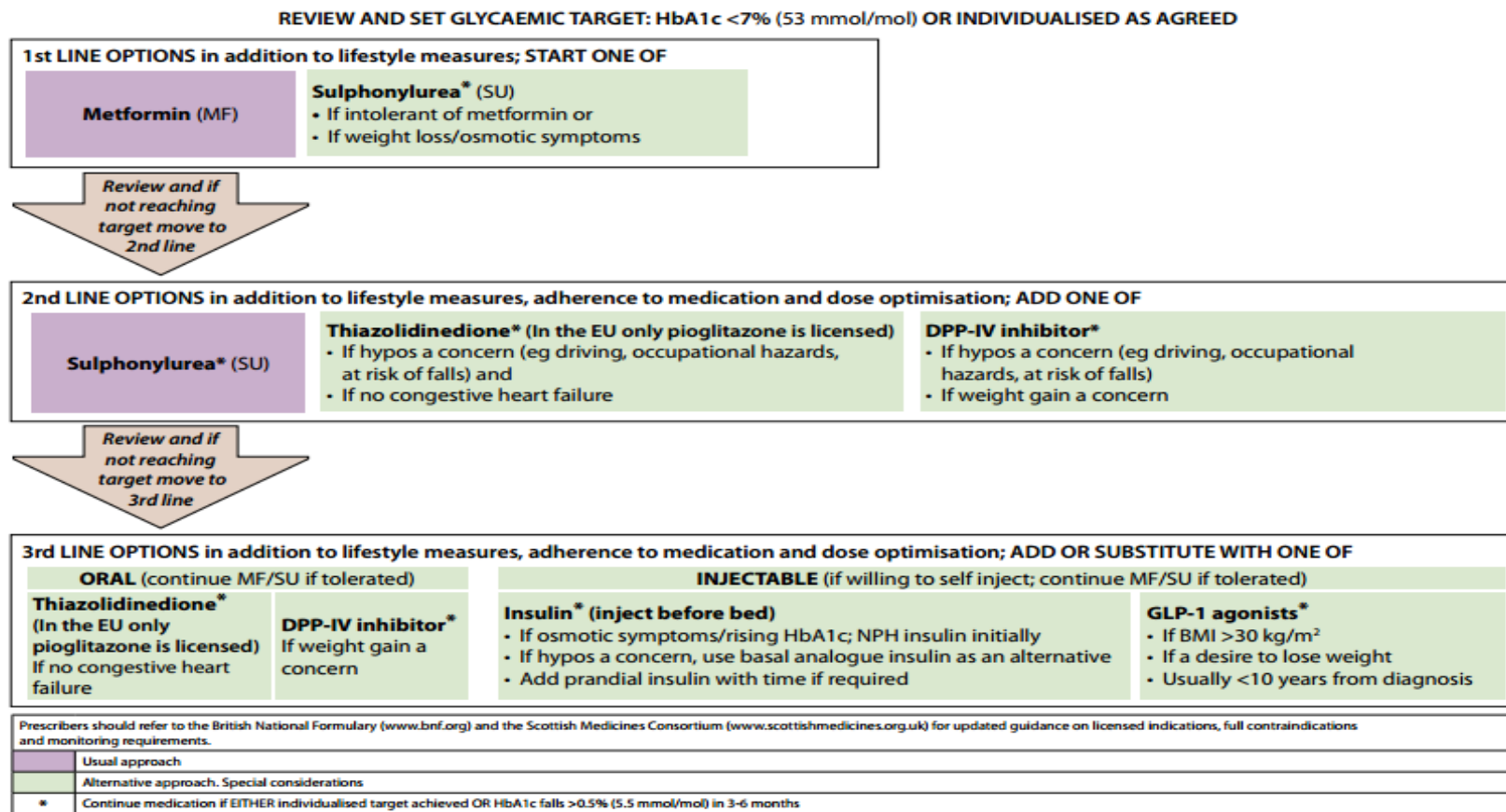
- Consider insulin-based treatment
- Support the person to aim for an HbA1c level of 53 mmol/mol (7.0%)

## Insulin-based treatment

- When starting insulin, use a structured programme and continue metformin for people without contraindications or intolerance. Review the continued need for other blood glucose lowering therapies<sup>f</sup>.
- Offer NPH insulin once or twice daily according to need.
- Consider starting both NPH and short-acting insulin either separately or as pre-mixed (biphasic) human insulin (particularly if HbA1c is 75 mmol/mol (9.0%) or higher).
- Consider, as an alternative to NPH insulin, using insulin detemir or glargine<sup>g</sup> if the person: needs assistance to inject insulin, lifestyle is restricted by recurrent symptomatic hypoglycaemic episodes or would otherwise need twice-daily NPH insulin in combination with oral blood glucose lowering drugs.
- Consider pre-mixed (biphasic) preparations that include short-acting insulin analogues, rather than pre-mixed (biphasic) preparations that include short-acting human insulin preparations, if: the person prefers injecting insulin immediately before a meal, hypoglycaemia is a problem or blood glucose levels rise markedly after meals.
- Only offer a GLP-1 mimetic<sup>c</sup> in combination with insulin with specialist care advice and ongoing support from a consultant-led multidisciplinary team<sup>h</sup>.
- Monitor people on insulin for the need to change the regimen.
- An SGLT-2i in combination with insulin with or without other antidiabetic drugs is an option<sup>p</sup>.

**NICE updated its guidance for type 2 diabetes in Dec 2015 (NG28)**  
**This sets an initial HbA1c target of 6.5%, with a target of 7.0% at further intensification steps with 3/6 month patient reviews**

# SIGN recommendations for pharmacological management of glycaemic control in people with T2D



## Reference

SIGN clinical guideline 116. Management of diabetes. March 2010

Available at: <http://www.sign.ac.uk/guidelines/fulltext/116/> (accessed September 2014).

Prepared 13/2/17



## MANAGEMENT OF TYPE 2 DIABETES

Refer to GGC Formulary for preferred agents and restrictions including updates

3 month trial of lifestyle changes. Refer to structured education programme (DESMOND or equivalent).  
Set glycaemic target HbA1c < 53mmol/mol or individualised

If HbA1c > 53mmol/mol or individualised target is not met

### FIRST LINE OPTIONS – Please see Tables A and B overleaf

**ADD METFORMIN** (refer to guidance on p. 4 to ensure titration to maximum tolerated dose)  
or **SULFONYLUREA** if intolerant of Metformin

If HbA1c > 53mmol/mol or individualised target is not met

### SECOND LINE OPTIONS – Please see Tables A and B overleaf

**ADD  
SULFONYLUREA**

**ADD GLITAZONE**

**ADD GLIPTIN**

**ADD SGLT-2**

Withdraw treatment after 6 months if HbA1c has decreased by < 6 mmol/mol.

If HbA1c > 59 mmol/mol or individualised target is not met

### THIRD LINE OPTIONS – Please see Tables A and B overleaf

#### ORAL ADMINISTRATION

Only likely to be effective if HbA1c is < 86 mmol/mol

**ADD  
GLITAZONE**

**ADD GLIPTIN**

**ADD SGLT-2**

If HbA1c > 59 mmol/mol or if individualised target is not met withdraw treatment and consider injectable therapy

#### SUBCUTANEOUS ADMINISTRATION

**ADD INSULIN**

**ADD GLP-1 AGONIST**  
Only if BMI > 30kg/m<sup>2</sup>

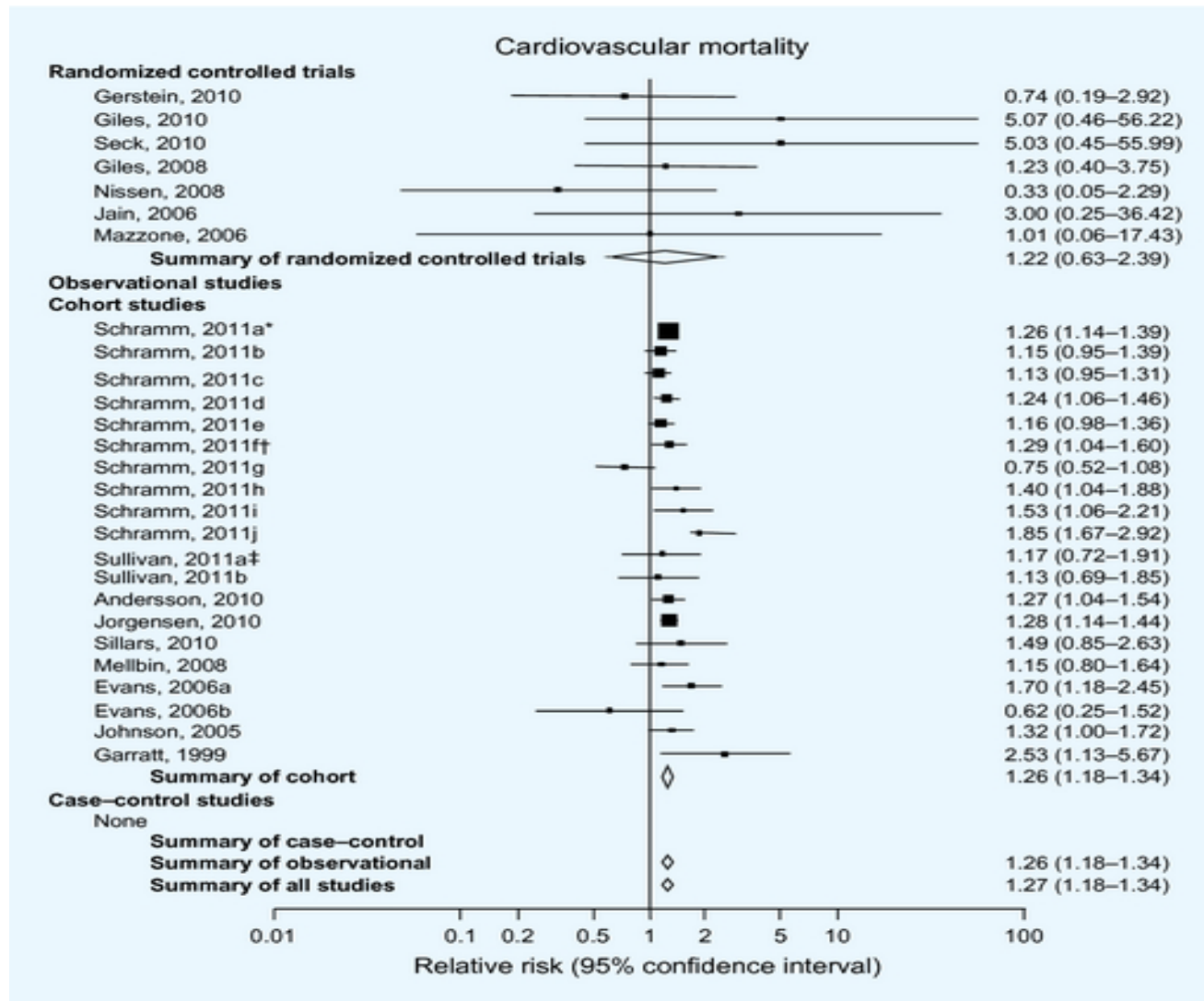
**Treatment targets:** HbA1c  
reduction of 6 mmol / mol  
**AND individualised weight  
loss target**

If HbA1c > 59  
mmol/mol or  
individualised target is  
not met intensify  
insulin treatment

Review regularly at 6  
months; unless both  
targets are achieved refer  
for specialist review.

If HbA1c target not met  
consider insulin therapy

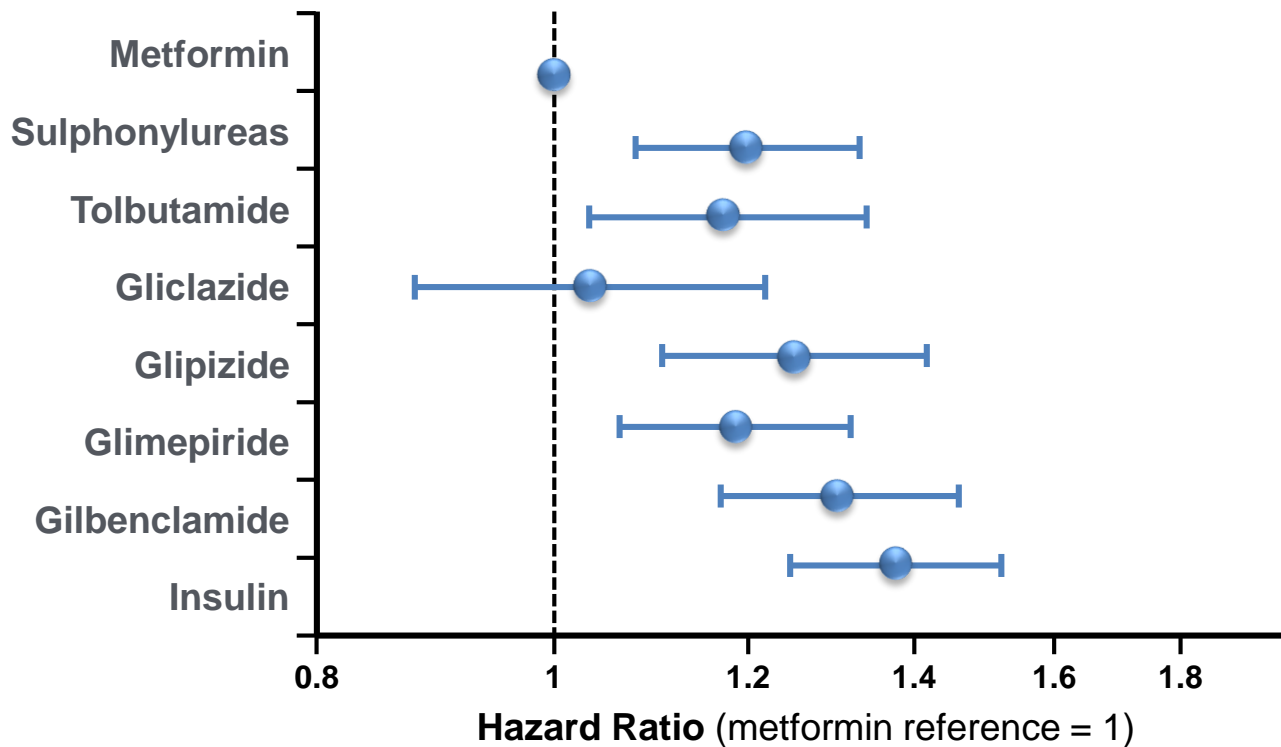
# Sulphonylureas and risk of cardiovascular disease: systematic review and meta-analysis





# Glucose-lowering treatments and associated CV risk

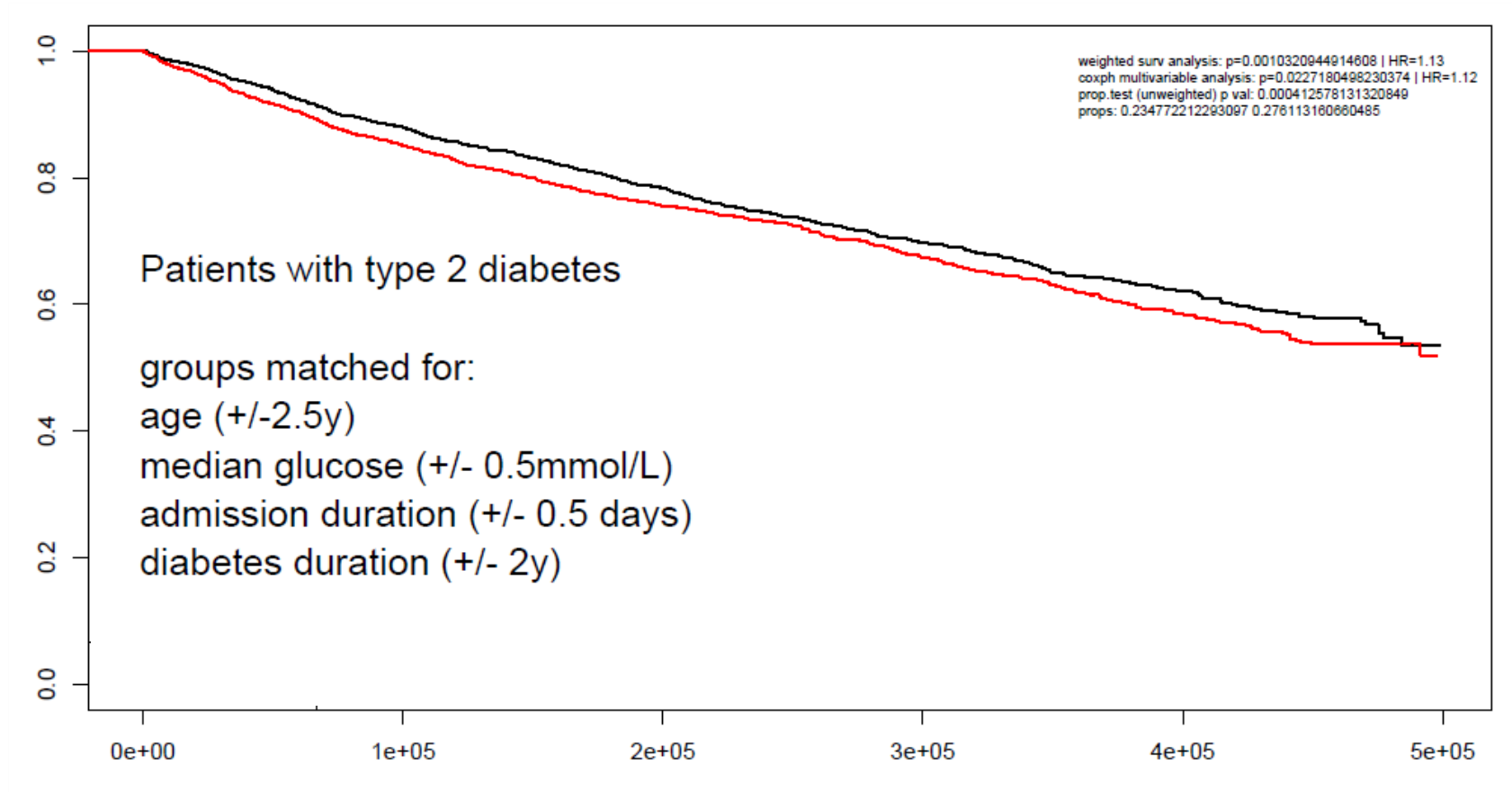
Risk of cardiovascular mortality and non-fatal myocardial infarction  
(6171 events)



CV: cardiovascular

Adapted from Jørgensen CH, et al. *Cardiovasc Diabetol* 2010;9:54.

## Inpatient with preadmission SU/metformin



# Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial

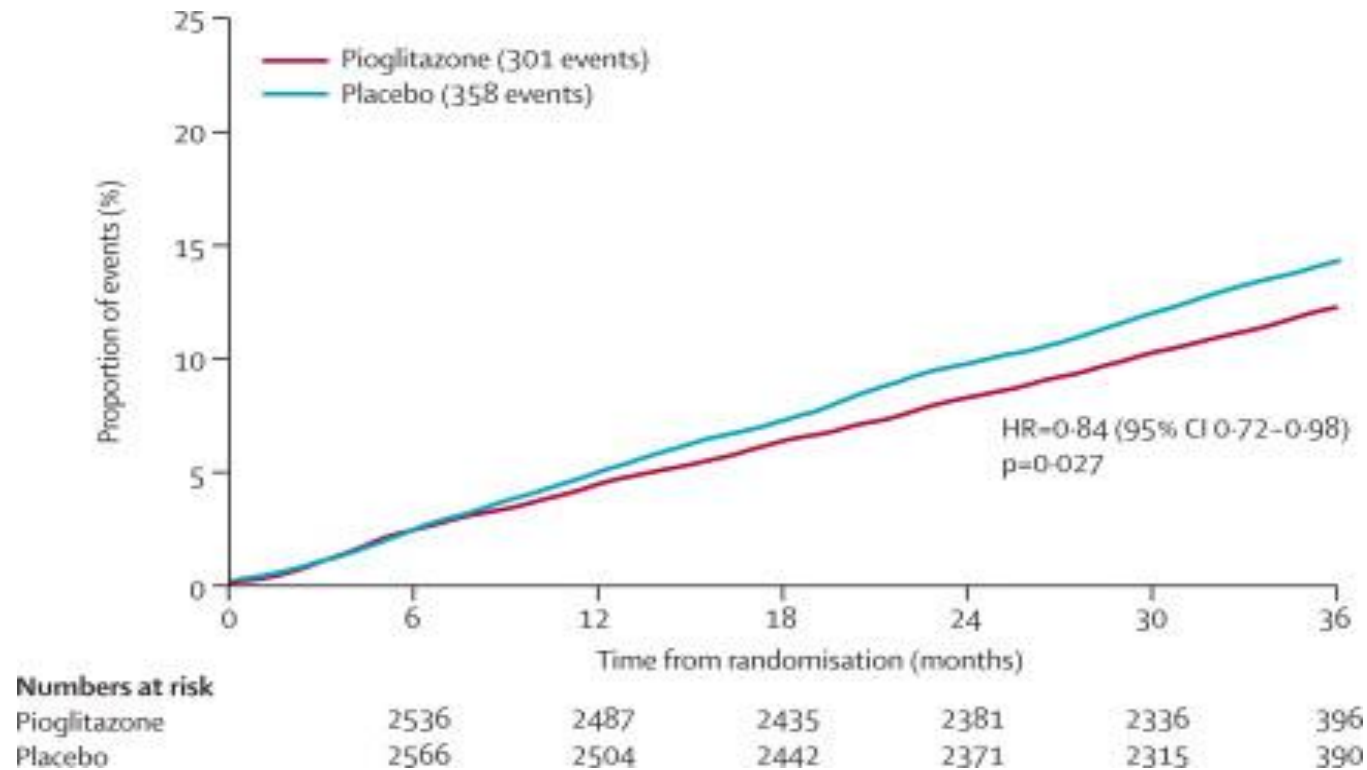


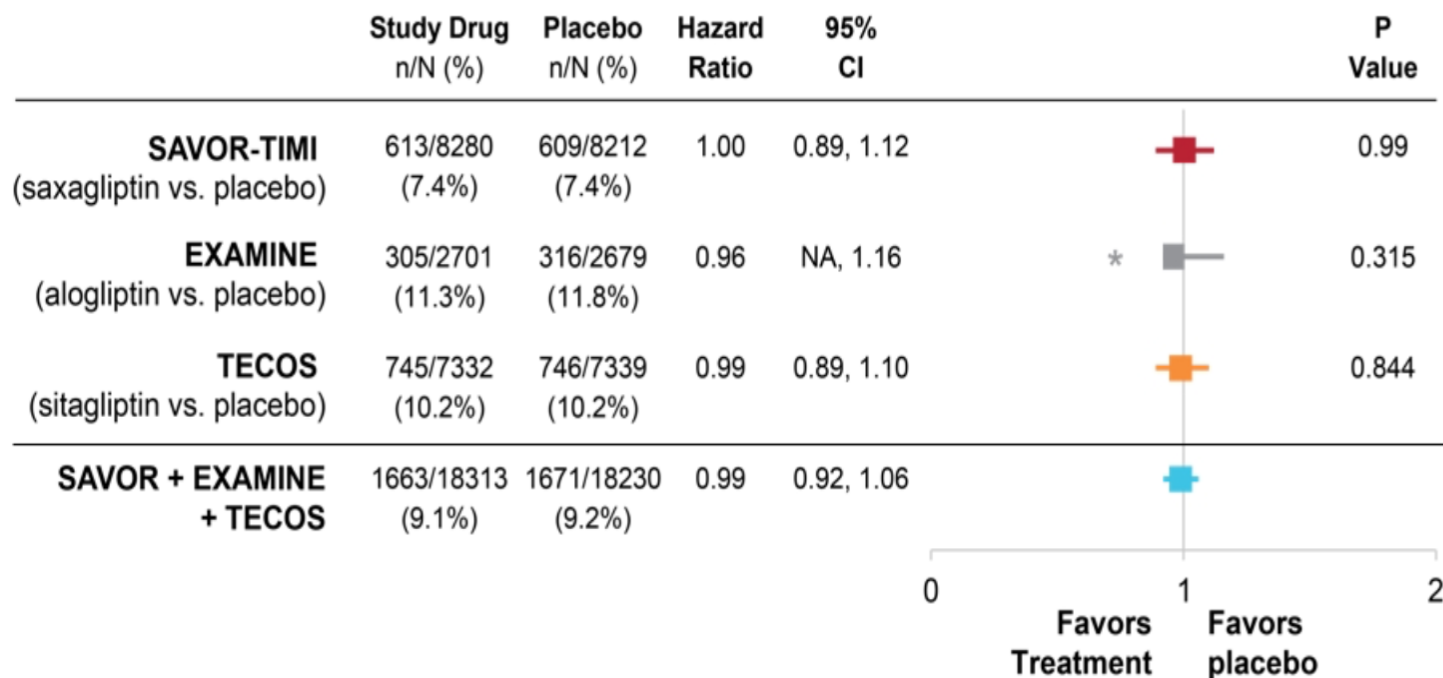
Figure 3. Kaplan-Meier curve of time to main secondary endpoint\*\*Death from any cause, non-fatal myocardial infarction (excluding silent myocardial infarction), or stroke.

John A Dormandy et al

Lancet, Volume 366, Issue 9493, 2005, 1279–1289

[http://dx.doi.org/10.1016/S0140-6736\(05\)67528-9](http://dx.doi.org/10.1016/S0140-6736(05)67528-9)

# Cardiovascular safety studies (TECOS, EXAMINE, SAVOR-TIMI)



Test for heterogeneity for 3 trials:  
 $p=0.877$ ,  $I^2=0\%$

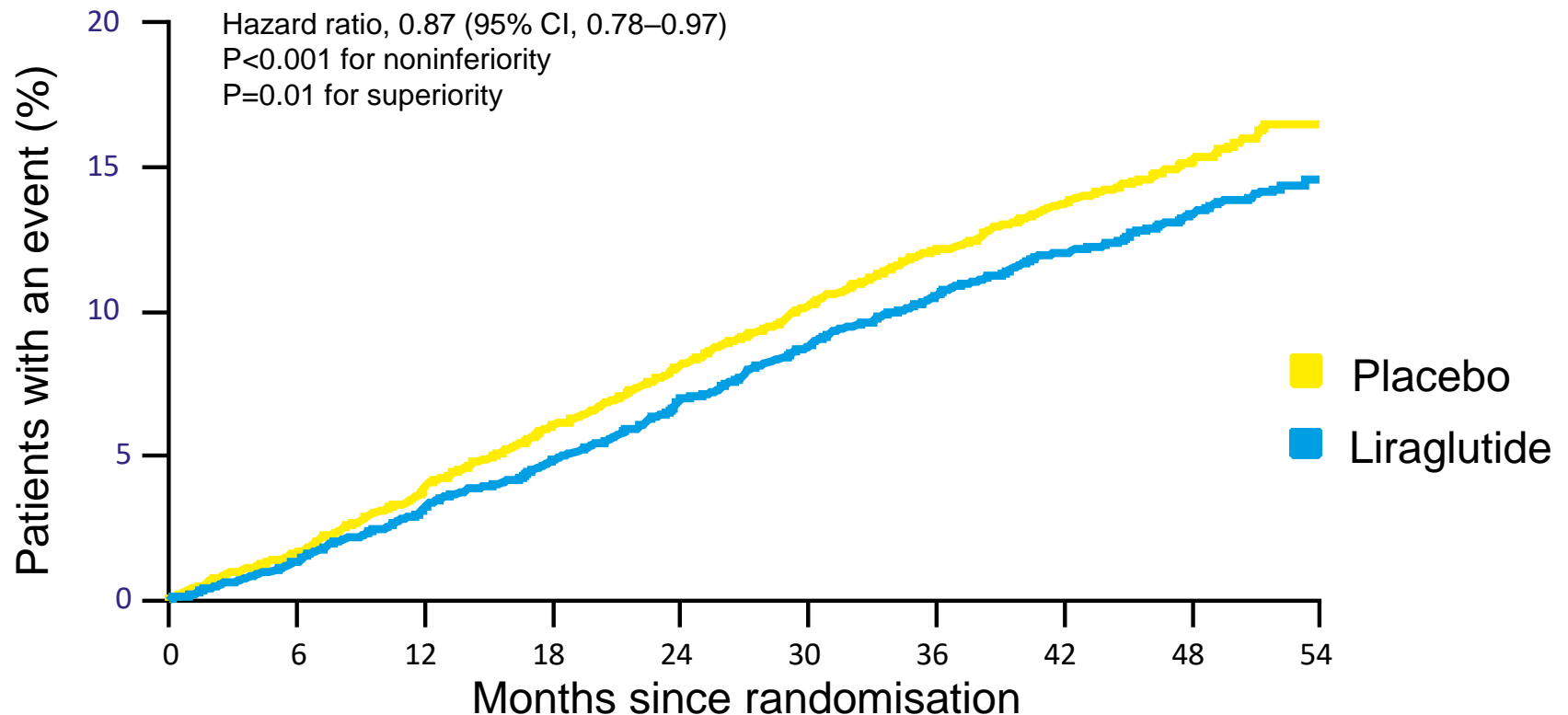
1. Scirica BM et al. N Engl J Med 2013; 369: 1317–1326
2. White WB et al. N Engl J Med 2013; 369: 1327–1335
3. Green JB et al. NEJM 2015; DOI: 10.1056/NEJMoa1501352

*\*Lower Confidence Limit not  
given for EXAMINE trial*



# LEADER trial: Primary Outcome

First occurrence of CV death, nonfatal myocardial infarction, or nonfatal stroke in the time-to-event analysis in patients with type 2 diabetes and high CV risk.

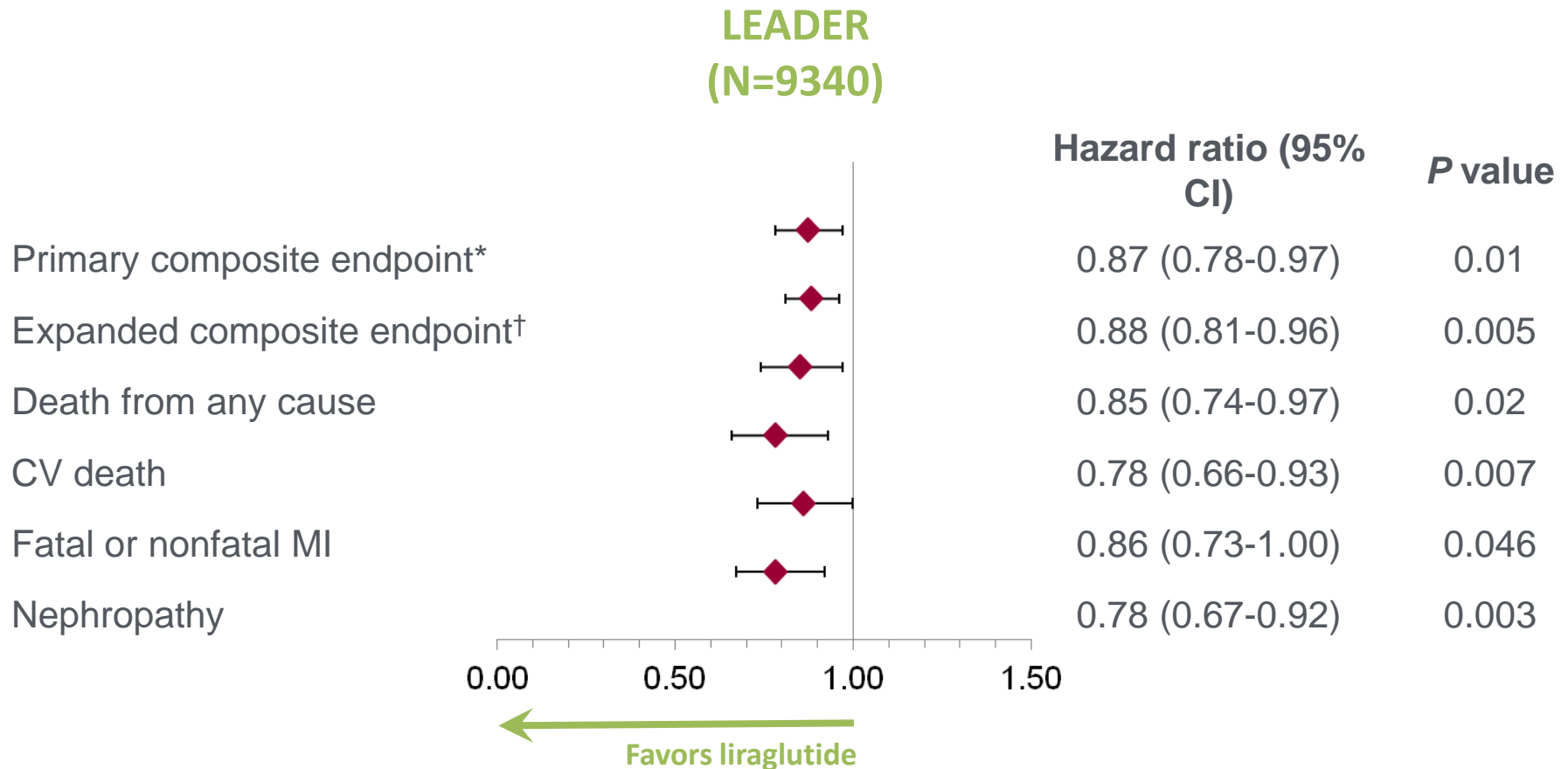


Liraglutide Effect and Action in Diabetes: Evaluation of cardiovascular outcome Results (LEADER) trial

# Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes

LEADER Trial Investigators

*N Engl J Med*, 2016

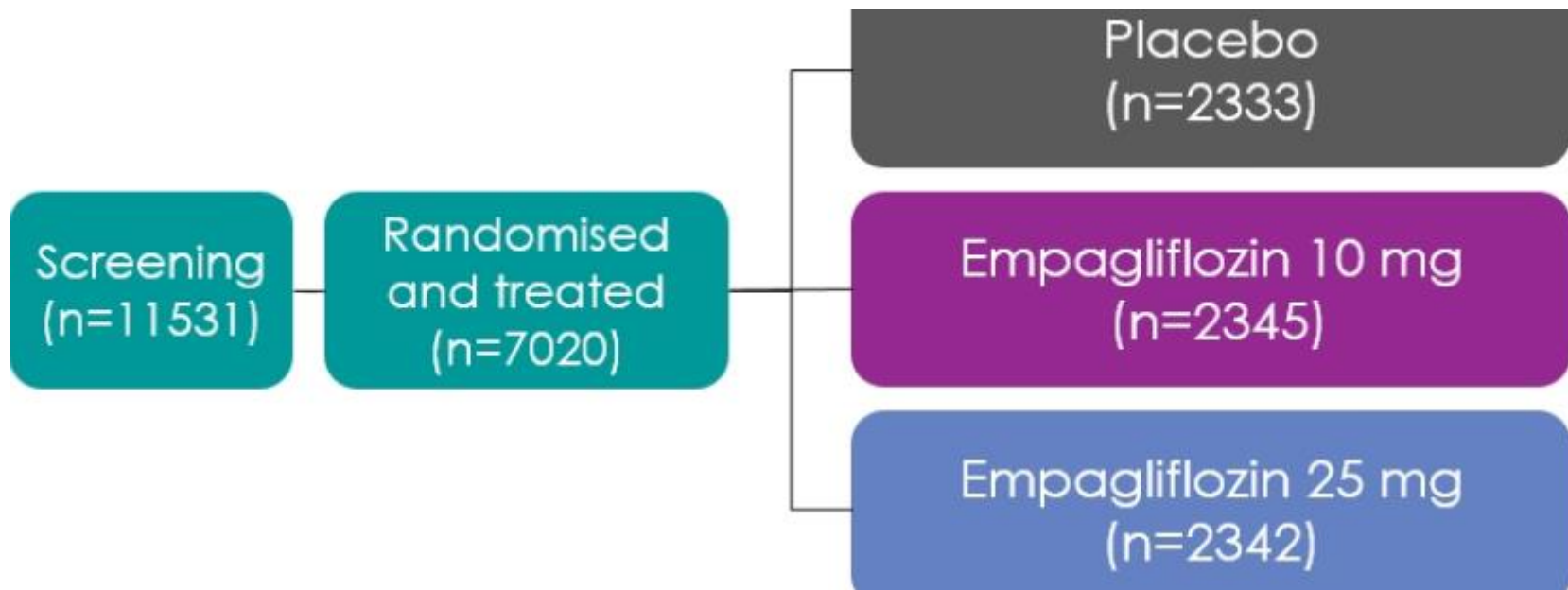


\*CV death, nonfatal MI (including silent MI), or nonfatal stroke; †CV death, nonfatal MI (including silent MI), nonfatal stroke, coronary revascularization, and hospitalization for unstable angina or HF.

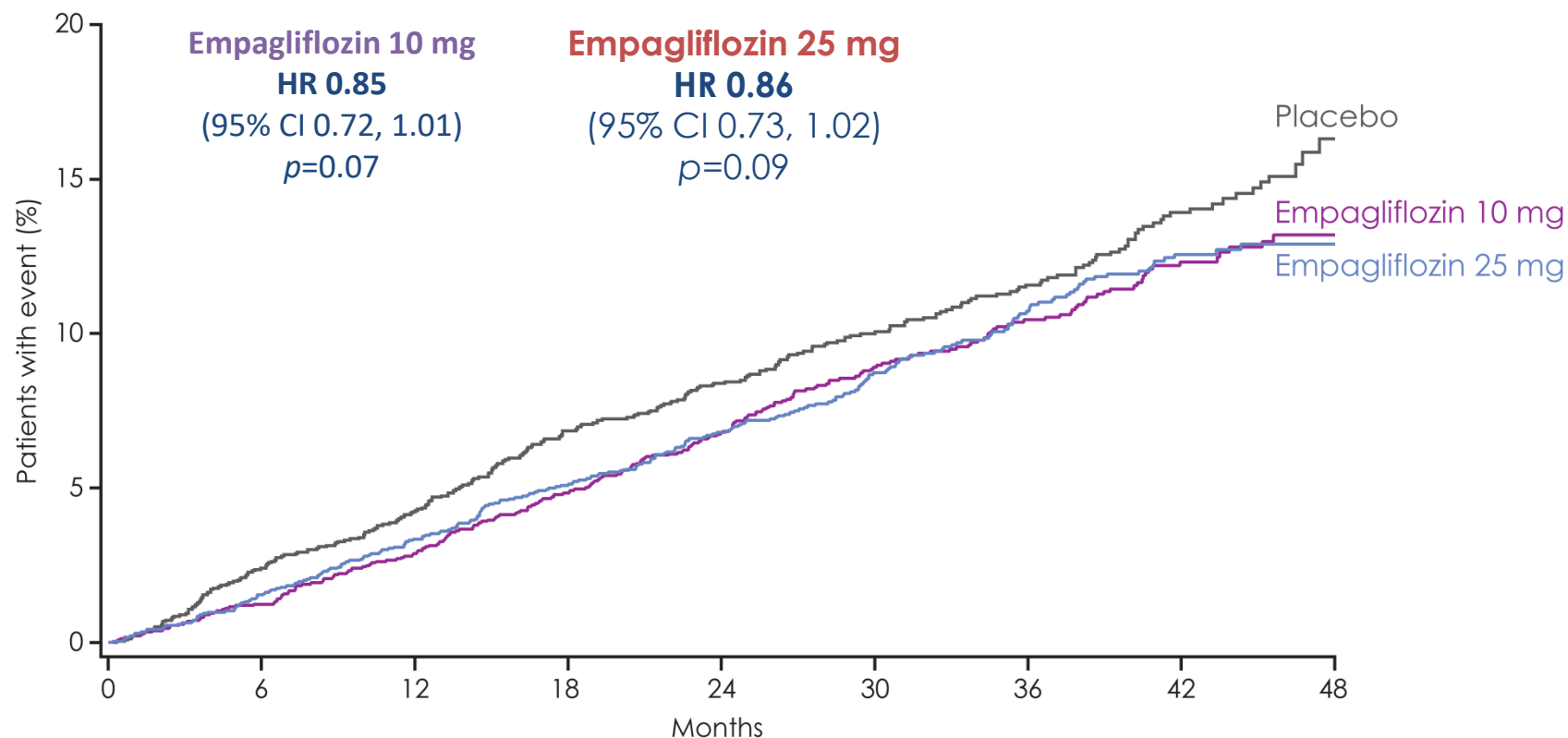
CI, confidence interval; CV, cardiovascular; MI, myocardial infarction.

# Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes

Bernard Zinman et al, NEJM, 2015



# 3-point MACE



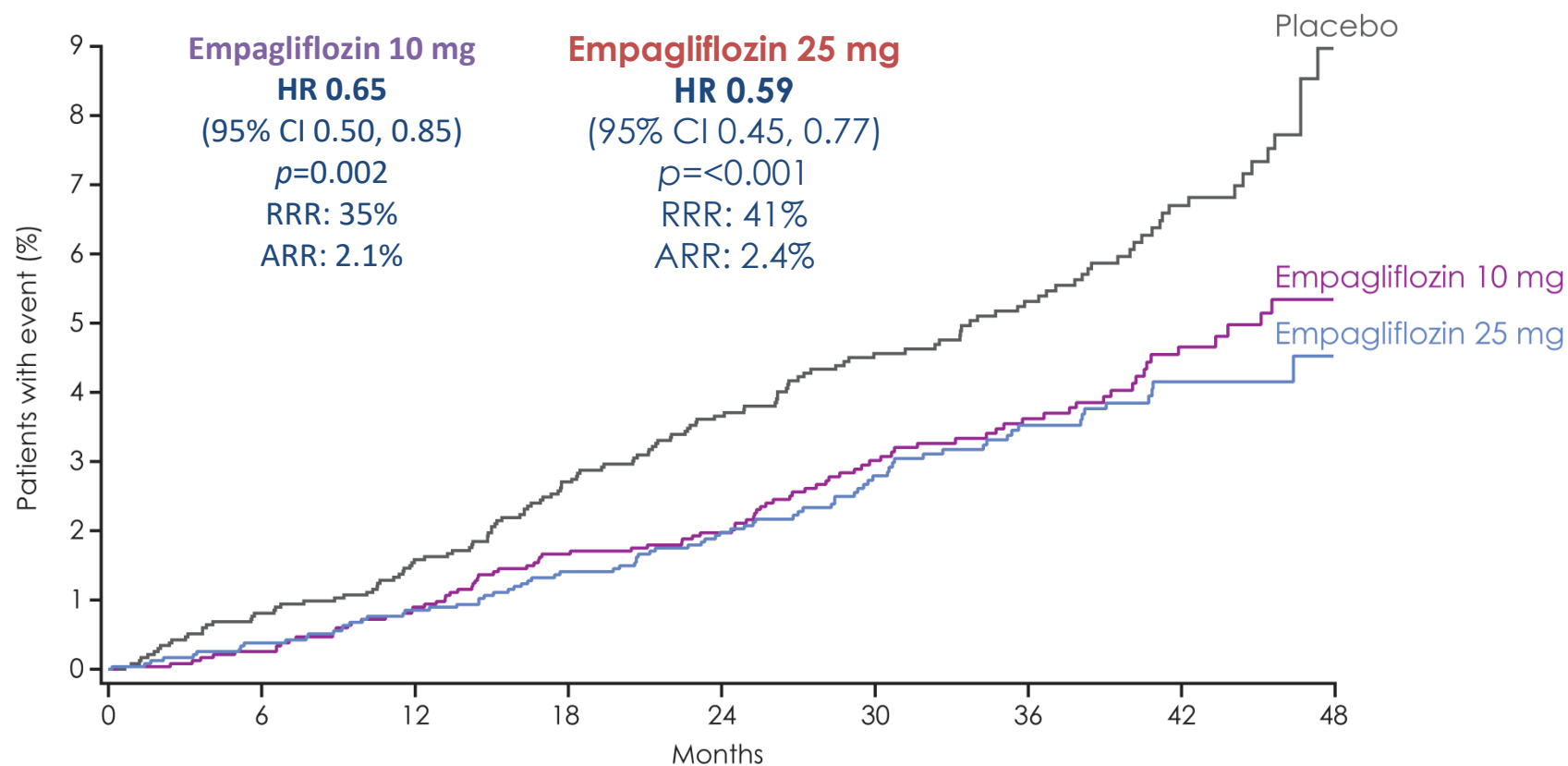
No. of patients									
Empagliflozin 10 mg	2345	2292	2233	2167	1918	1415	1177	753	178
Empagliflozin 25 mg	2342	2288	2222	2161	1933	1406	1182	781	192
Placebo	2333	2256	2194	2112	1875	1380	1161	741	166

Cumulative incidence function. MACE, Major Adverse Cardiovascular Event; HR, hazard ratio

Zinman B et al. N Engl J Med 2015 DOI: 10.1056/NEJMoa1504720 Supplementary Appendix



# CV death

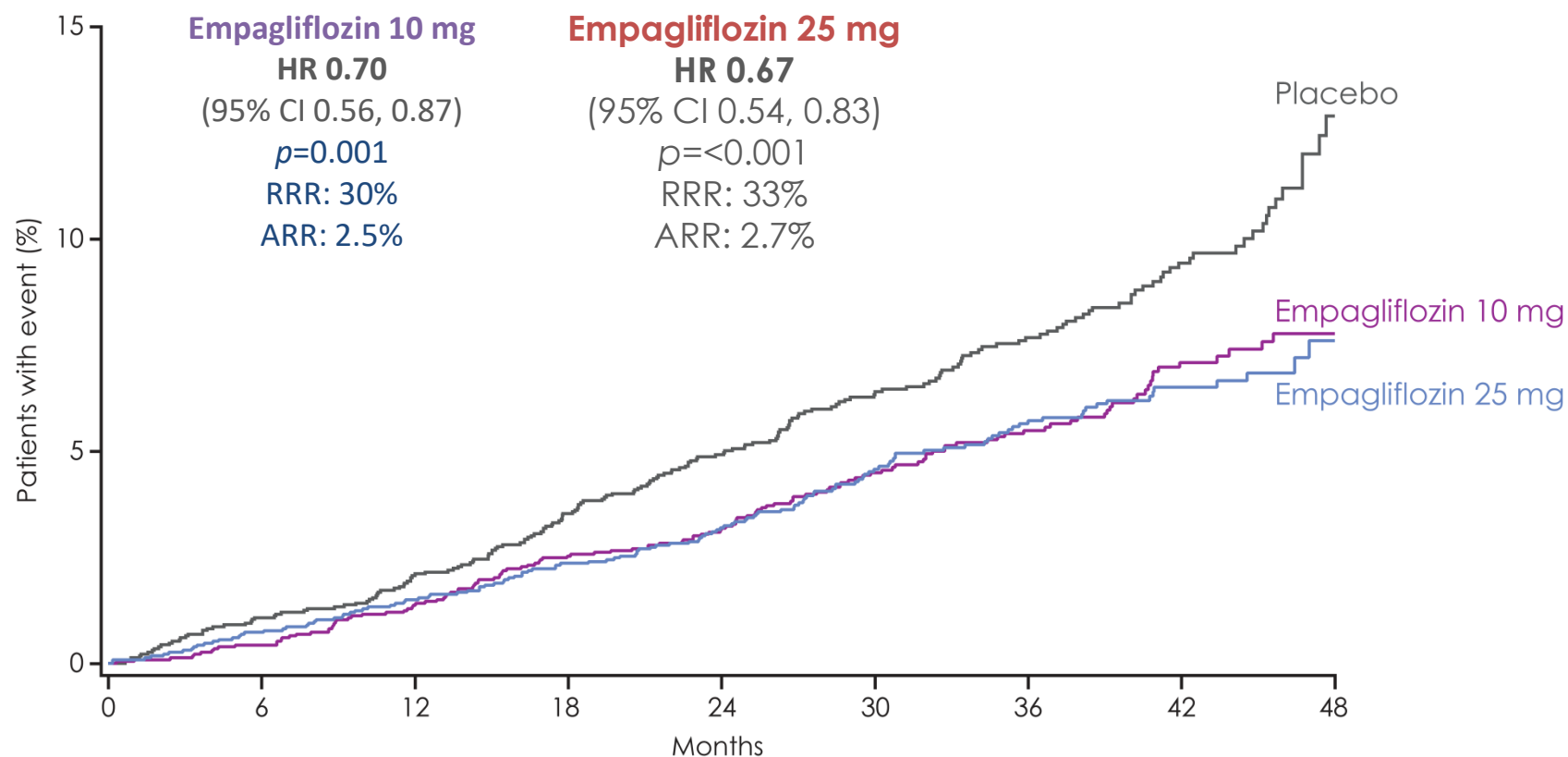


No. of patients

Empagliflozin 10 mg	2345	2327	2305	2274	2055	1542	1303	847	201
Empagliflozin 25 mg	2342	2324	2303	2282	2073	1537	1314	875	213
Placebo	2333	2303	2280	2243	2012	1503	1281	825	177

Cumulative incidence function. HR, hazard ratio; RRR: Relative risk reduction; ARR: Absolute risk reduction; CER: Control Event Rate; EER: Experimental Event rate. ARR = CER – EER. Zinman B et al. N Engl J Med 2015 DOI: 10.1056/NEJMoa1504720 Supplementary Appendix

# All-cause mortality

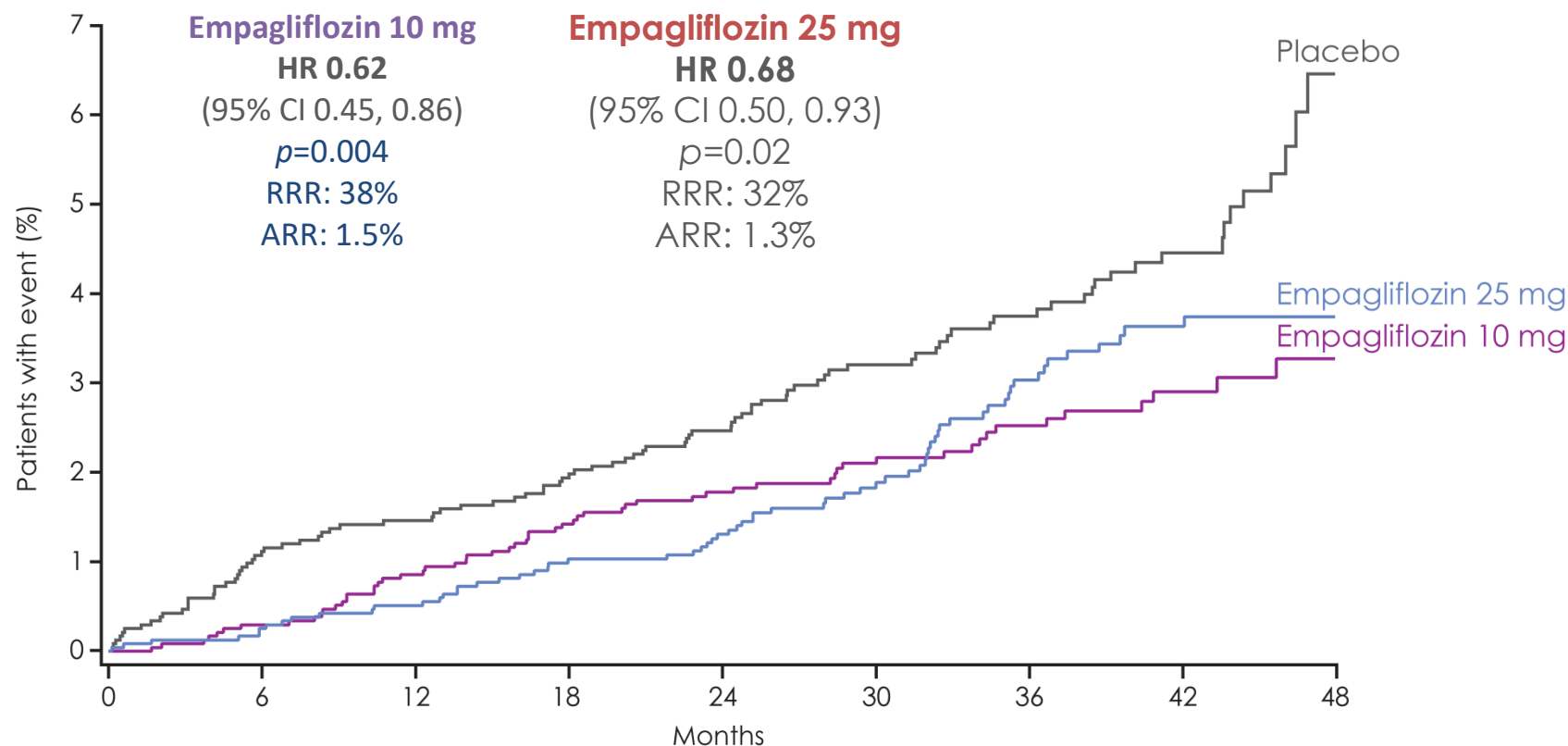


No. of patients

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Kaplan-Meier estimate. HR, hazard ratio; RRR: Relative risk reduction; ARR: Absolute risk reduction; CER: Control Event Rate; EER: Experimental Event rate. ARR = CER – EER.

# Hospitalisation for heart failure

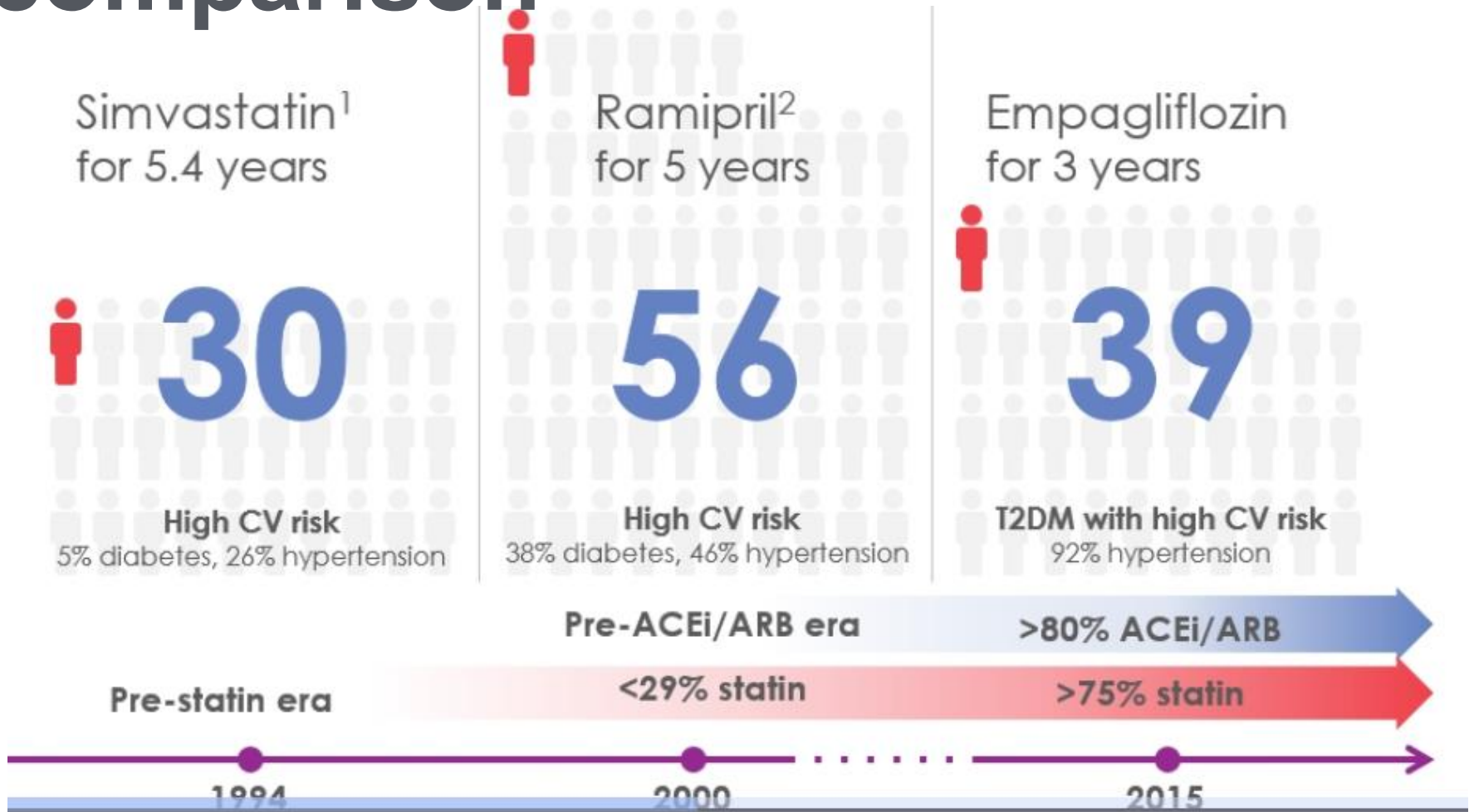


No. of patients

Empagliflozin 10 mg	2345	2306	2256	2204	1981	1473	1240	804	188
Empagliflozin 25 mg	2342	2308	2267	2223	2007	1477	1247	830	207
Placebo	2333	2271	2226	2173	1932	1424	1202	775	168

Cumulative incidence function. HR, hazard ratio; RRR: Relative risk reduction; ARR; Absolute risk reduction; CER: Control Event Rate; EER: Experimental Event rate. ARR = CER – EER

# Numbers needed to treat comparison



# Type 2 diabetes

- optimum drug sequence (in high CV risk) may be:

metformin -> empagliflozin -> liraglutide

- new evidence coming this year for other SGLT2s ?  
extending benefit into non-high CV risk patients

# Summary

- T1DM – advances are likely to come from technology / bioengineering and data science.
- T2DM – advances likely to come from optimum drug combinations based on large number of ongoing outcome trials.

