Management of Type 2 DM

(Role of DPP4 inhibitor)

Case scenario

Prof Moe Wint Aung

Case scenario 1

- 55 year salesman , DM & HT for 15 years
- Social drinker and occasional smoker
- Family history of Diabetes in father and siblings
- Maximal therapy with Glimiperide 2 mg BD + Janu-Met 50/500 mg BD
- Amlodipine 10 mg OD + valsartan 80 mg OD
- Atorvastation 20 mg HS + Aspirin 80 mg OD
- Pregabalin 50 mg HS

- Has been suffering from polyuria at night and daytime fatigue and tiredness,
- Sensory peripheral neuropathy at feet
- BMI 32.5 kg/m2
- BP 140/80 , HR 98 /min, Heart & lungs NAD
- HbA1c – 9.2 % (80 mmol/mol)
- LDL – 120 mg/dl, TG – 150mg/dl , HDL 35 mg/dl
- Creatinine 115 mg % , Urine microalbumin 218 mcg/min

Case scenario 1

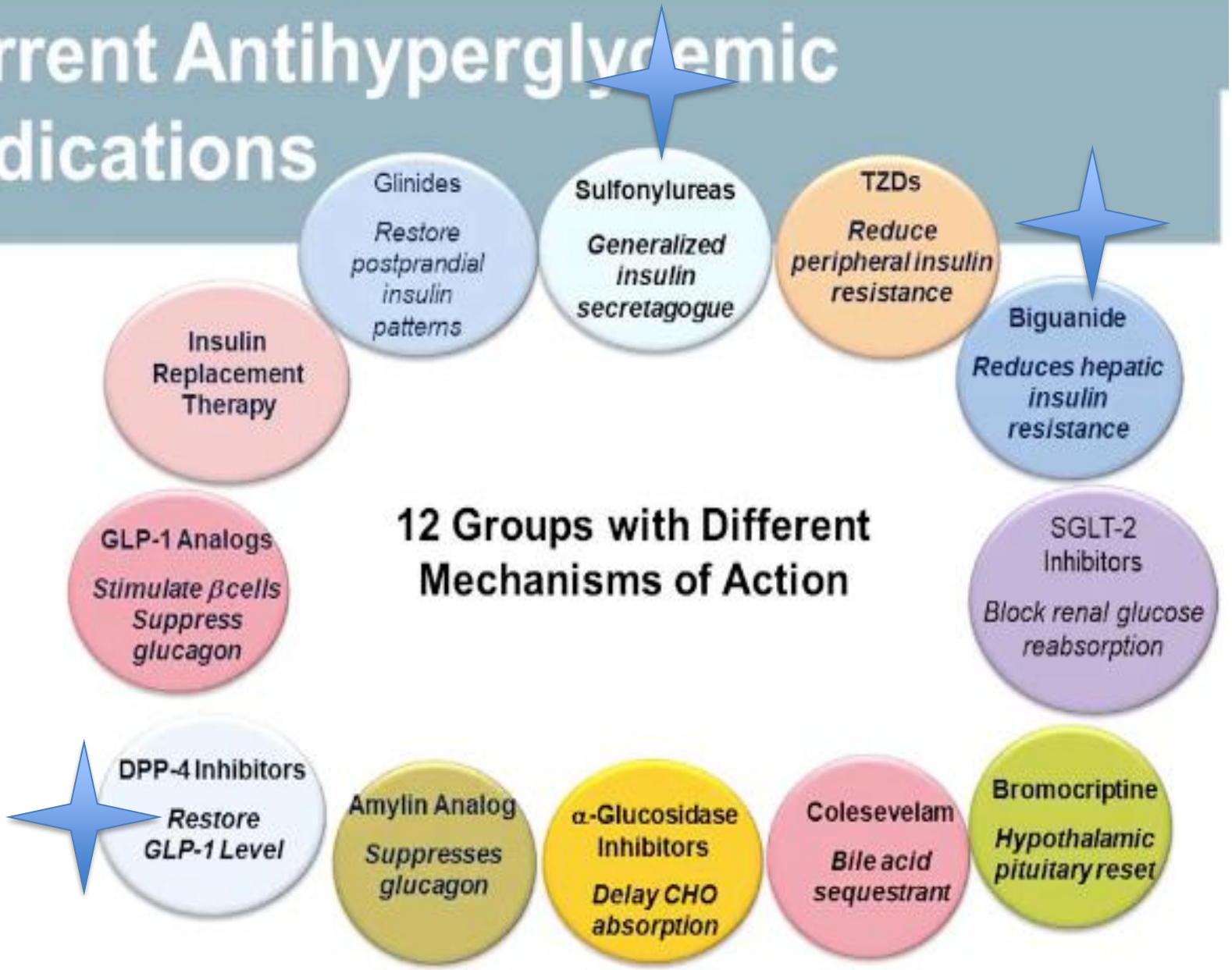
- Poorly controlled Type 2DM (long duration)
- Hyperlipidaemia
- Microalbuminuria
- Peripheral neuropathy
- CVD risk

WHAT IS THE NEXT LINE OF MANAGEMENT ?

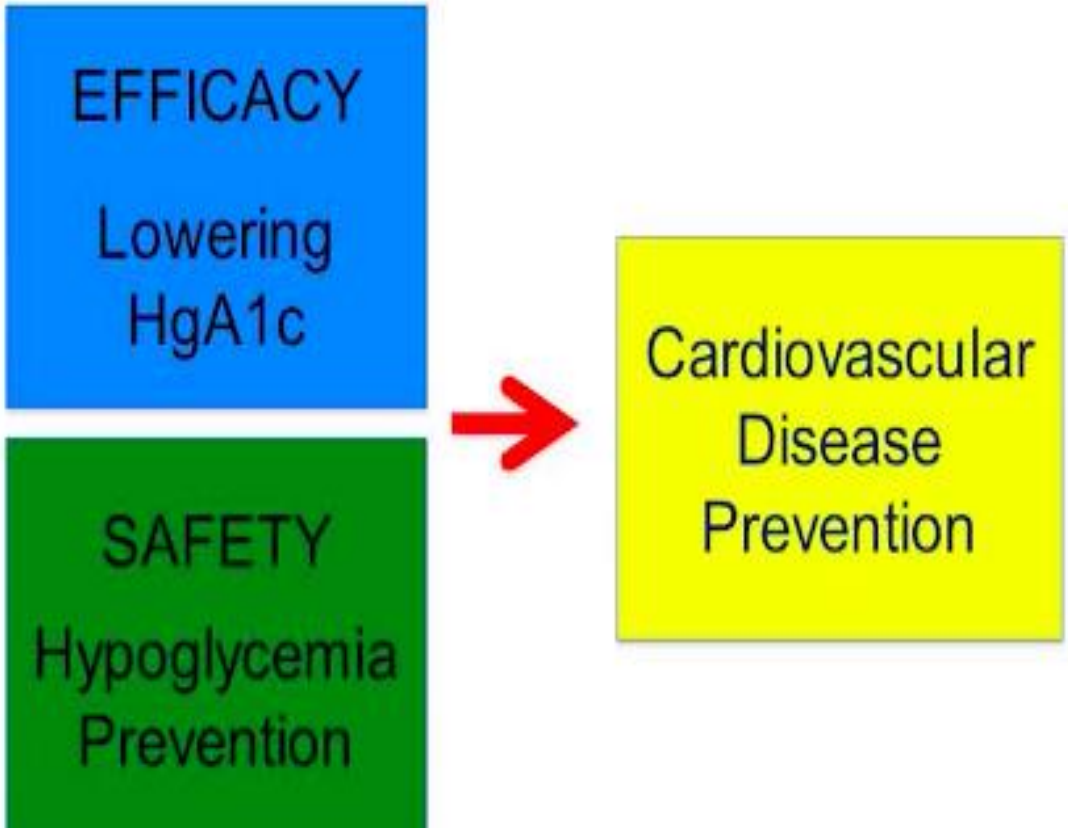
OHA Failure

- **Primary OHA failure** : initial resistance
- **Secondary OHA failure** : gradual resistance
- What is the underlying cause: beta cell failure
- What to do next ---- eventually needing insulin

Current Antihyperglycemic Medications



Management of Type 2 Diabetes: 2017



ADA 2017

Initial Management and Monotherapy

- Lifestyle modification
- Metformin
- consider Sulphonylurea (SU) if symptomatic or Metformin contraindicated or not tolerated

Dual Therapy

HbA1c target (individualised) or >48mmol/mol (6.5%) after ~3months

- Metformin + SU
- Metformin + Pioglitazone
- Metformin + DPP-IV Inhibitor
- Metformin + GLP-1 Receptor Agonist
- Metformin + SGLT-2 Inhibitor
- Metformin + Basal Insulin

Triple Therapy

HbA1c target (individualised) or >58mmol/mol (7.5%) after ~3-6months

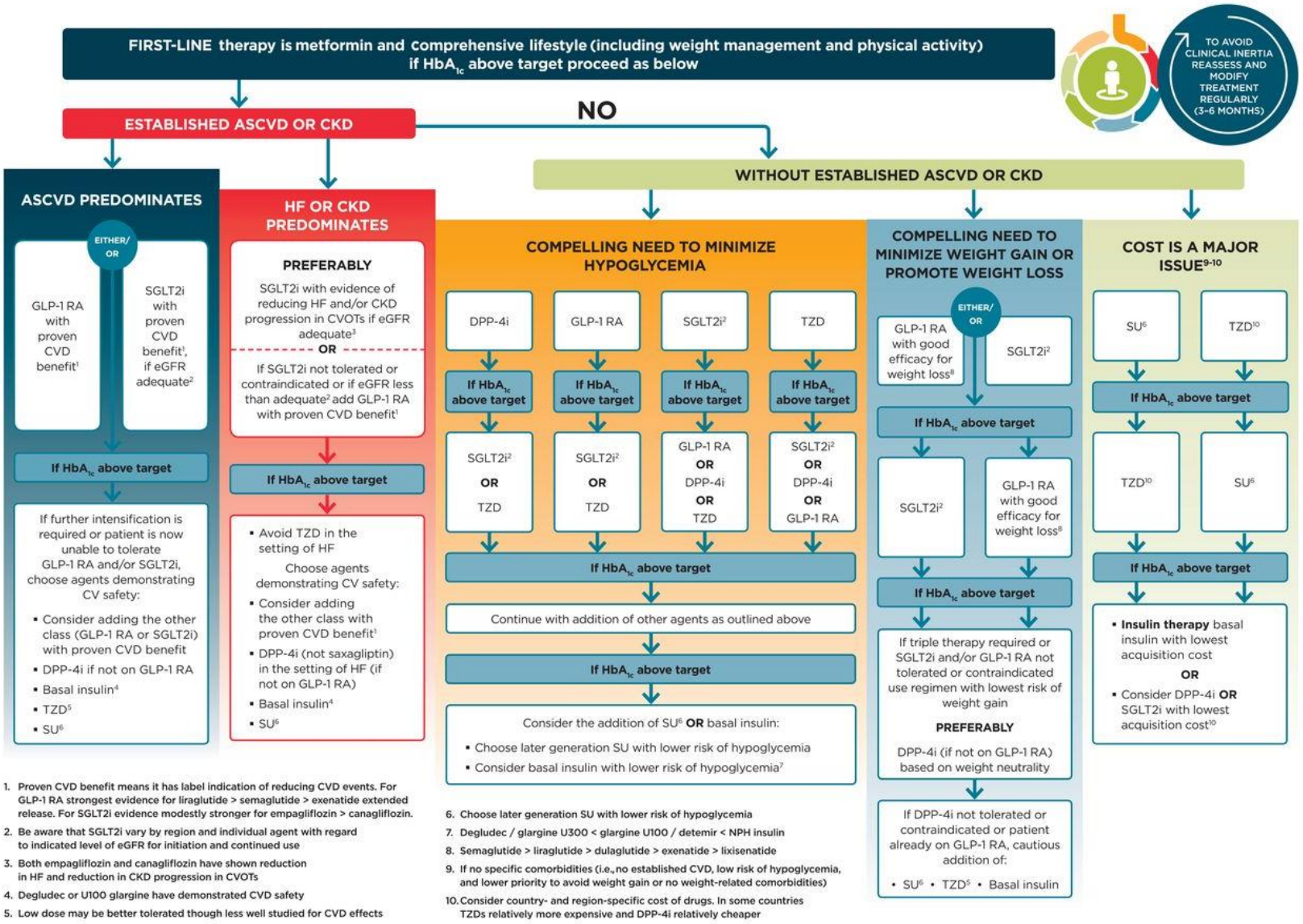
- Metformin + SU + Pioglitazone
- Metformin + Pioglitazone + SU
- Metformin + DPP-IV Inhibitor + SU
- Metformin + SU + SGLT-2 Inhibitor
- Metformin + SU + GLP-1 Receptor Agonist
- Metformin + SU + Basal Insulin

More complex insulin strategies

If combination therapy including basal insulin does not achieve HbA1c target after 3-6 months in combination with 1-2 non-insulin agents, more complex insulin strategies are required

Complex insulin strategies may be combined with:-
Metformin
DPP-IV Inhibitors
SGLT-2 Inhibitors
GLP-1 Receptor Agonists

ADA 2020



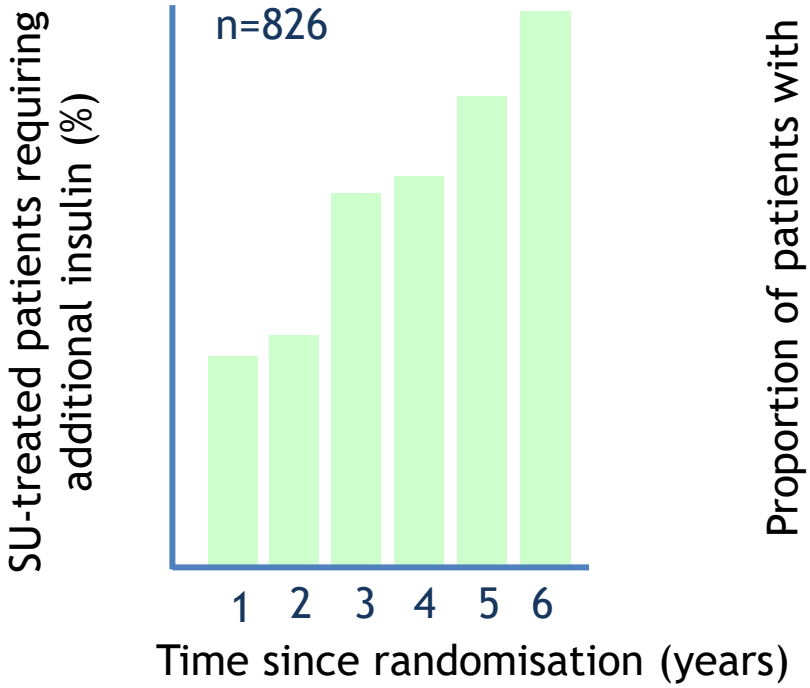
1. Proven CVD benefit means it has label indication of reducing CVD events. For GLP-1 RA strongest evidence for liraglutide > semaglutide > exenatide extended release. For SGLT2i evidence modestly stronger for empagliflozin > canagliflozin.
2. Be aware that SGLT2i vary by region and individual agent 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 hypoglycemia
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 hypoglycemia, 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

Summary of guidelines

	ADA			AACE	NICE		WHO
	Metformin tolerated		**Metformin not-tolerated**	**In order of priority**	**Metformin tolerated**	**Metformin not-tolerated**	
First line	**Metformin**		Individualized choice	▪ Metformin ▪ GLP – 1 RA ▪ SGLT-2i ▪ DPP-4i ▪ TZD ▪ AGi ▪ SU/ GLN	Metformin	• **DPP-4i** • **Pioglitazone** • **SU** • **SGLT-2i instead of DPP-4i if SU or Pio is not appropriate**	Metformin
Second line	**ASCVD (+)** Metformin + ▪ SGLT-2i ▪ GLP-1 RA	**No ASCVD** ▪ Hypoglycaemic concern ▪ Weight oncern ▪ Cost concecrn	Individualized choice	**Metformin/ other first line agent +** second line agent + ▪ GLP – 1 RA ▪ SGLT-2i ▪ TZD ▪ Basal insulin ▪ DPP-4i ▪ Colesevelam ▪ Bromocriptine QR ▪ AGi ▪ SU/ GLN	**Metformin +** ▪ **DPP-4i** ▪ **Pioglitazone** ▪ **SU** ▪ **SGLT-2i**	❑**Dual therapy** • **DPP-4i + Pioglitazone** • **DPP-4i + SU** • **Pioglitazone + SU**	**Metformin + SU (public Healthh approach)**

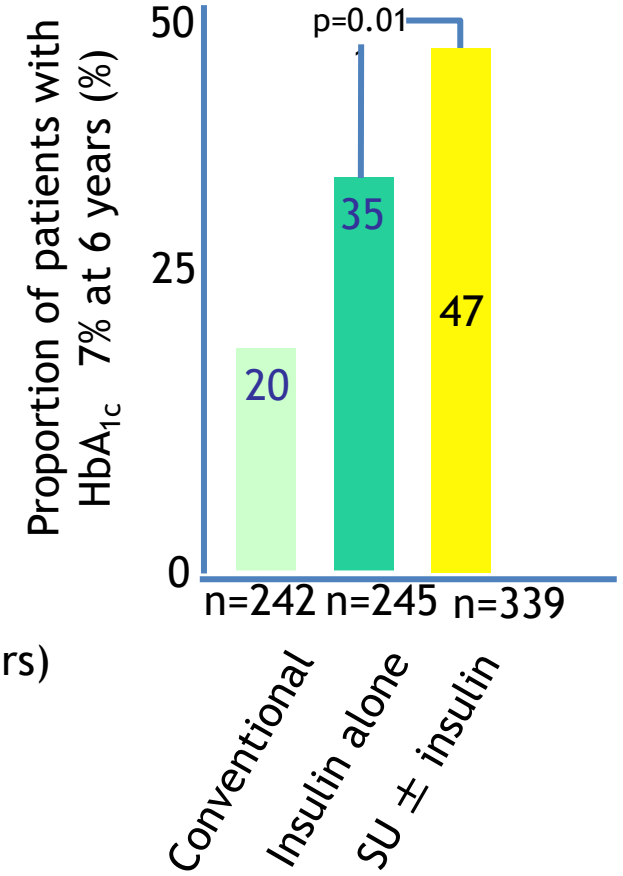
When OHAs fail, early addition of insulin optimises glycaemic control

OHAs fail over time



Add-on insulin therapy gives best glycaemic control

Insulin added when FBG >6 mmol/l (>108 mg/dl)



sulphonylurea

UKPDS 57: Adapted from Wright A, et al. Diabetes Care 2002;25

UKPDS 57 STUDY

- **Early insulin use, prior to β cell failure**

  helped in

  – preserving and sustaining β cell secretory capacity
  – achieving smoother, better glycemic control
  – lowering incidence of hypoglycemia
  – Causing less weight gain

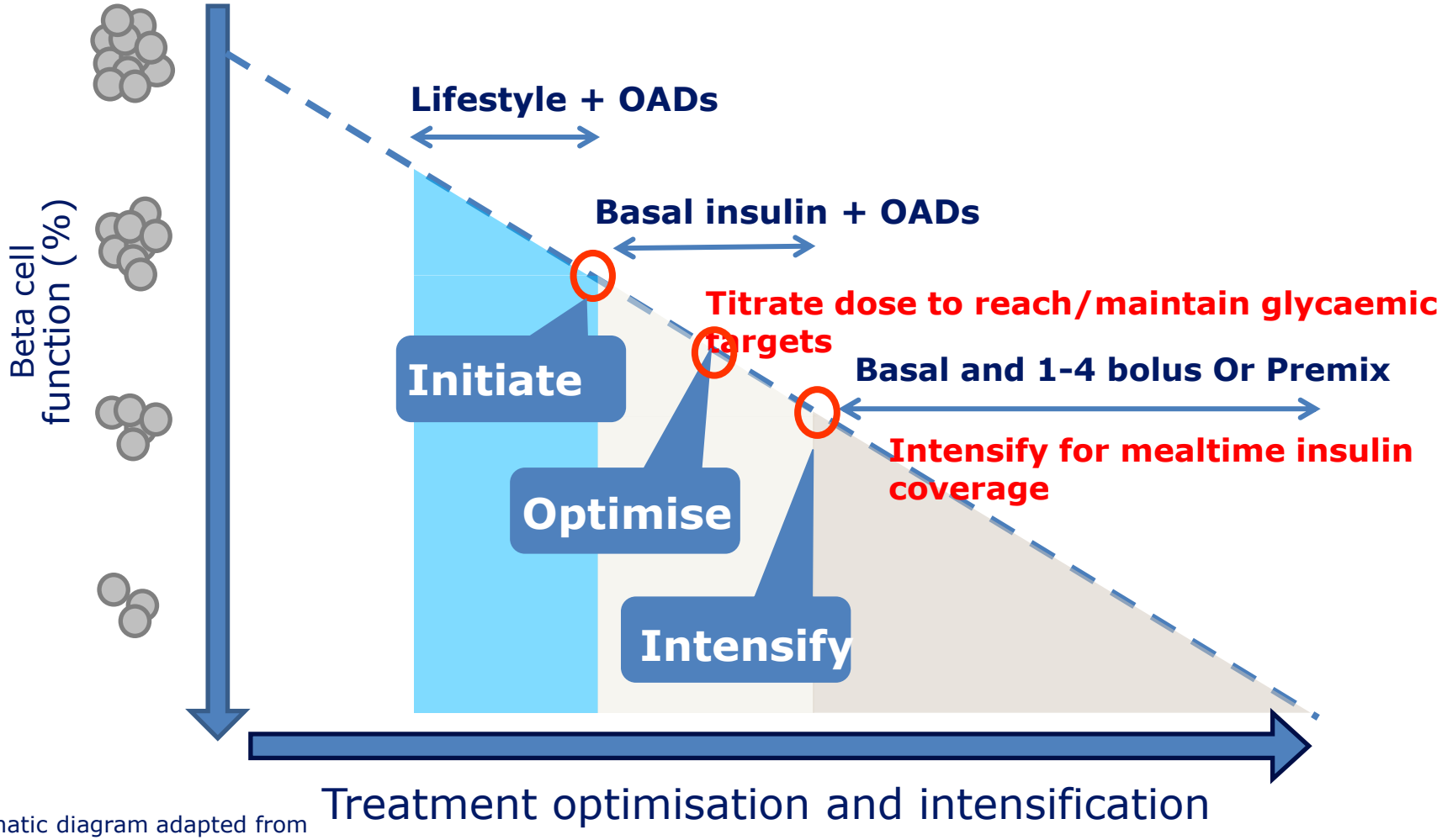
Insulin therapy is not the Last Resort

By the time insulin is initiated (or considered) patients often have had the disease for more than 10 to 15 years and have already developed complications

Greater glycemic control achieved by the early initiation of insulin therapy may reduce morbidity and mortality, limit healthcare costs and improve quality of life (QOL)

INITIATE INSULIN THERAPY EARLIER

Insulin optimisation and intensification should follow disease progression



Schematic diagram adapted from Kahn. Diabetologia 2003; 46:3–19
Inzucchi et al. Diabetologia 2012;55(6):1577-96.

Insulin is the most potent to achieve glycemic control

	Intervention	Expected Decrease in A1C With Monotherapy (%)	Advantages	Disadvantages
Step 1: initial therapy	Lifestyle to decrease weight and increase activity	1.0-2.0	Broad benefits	Insufficient for most within first year
	Metformin	1.0-2.0	Weight neutral	GI side effects, contraindicated with renal insufficiency
Step 2: additional therapy	Insulin	1.5-3.5	No dose limit, rapidly effective, improved lipid profile	1-4 injections daily, monitoring, weight gain, hyperglycemia, analogues are expensive
	Sulfonylurea	1.0-2.0	Rapidly effective	Weight gain, hyperglycemia (especially with glibenclamide or chlorpropamide)

GI=gastrointestinal.

Nathan DM et al. *Diabetes Care*. 2008;31. Epub ahead of publication.

Benefits of Insulin

- Most Clinical Experience, Best Understood Physiological actions
- Recombinant Human DNA Insulin – Easy to use
- No Drug Interactions
- Easily Titratable
- Unlimited potential for glucose lowering
- Reverses "Glucotoxicity
- Anabolic Effects – ↓glucosuria[1], ↓protein[2] breakdown, ↓lipolysis[3], ↑weight gain

Case Scenario 2

- 45 year middle school teacher, known Diabetes for 10 years , had inferior AMI last year, admitted recently with post infarct angina with CCF

- She was under cardiologists consultation taking many heart medications : antiplatelet, beta blocker, Valsartan, antimetabolic agents

- metformin 500 mg TDS + Diamicron MR 60 mg Od + Insulin glargine 14 units HS

- BMI 26 kg/m2, poor compliance to lifestyle

- FBS 145 mg/dl, PPBS > 220 mg /dl , HbA1c 8.9%
- Direct LDL 160, TG 120 , CRP 16 , Pro BNP 265 pg/ml
- Creatinine 112 mg /dl, UACR 48mg/g
- Echocardiogram revealed reduced LVEF 35%, mild MR, moderate TR ,right ventricular dysfunction,
- She was referred for optimization of glycemic control;
- She refused for intensification of insulin as afraid of weight gain & hypoglycemia

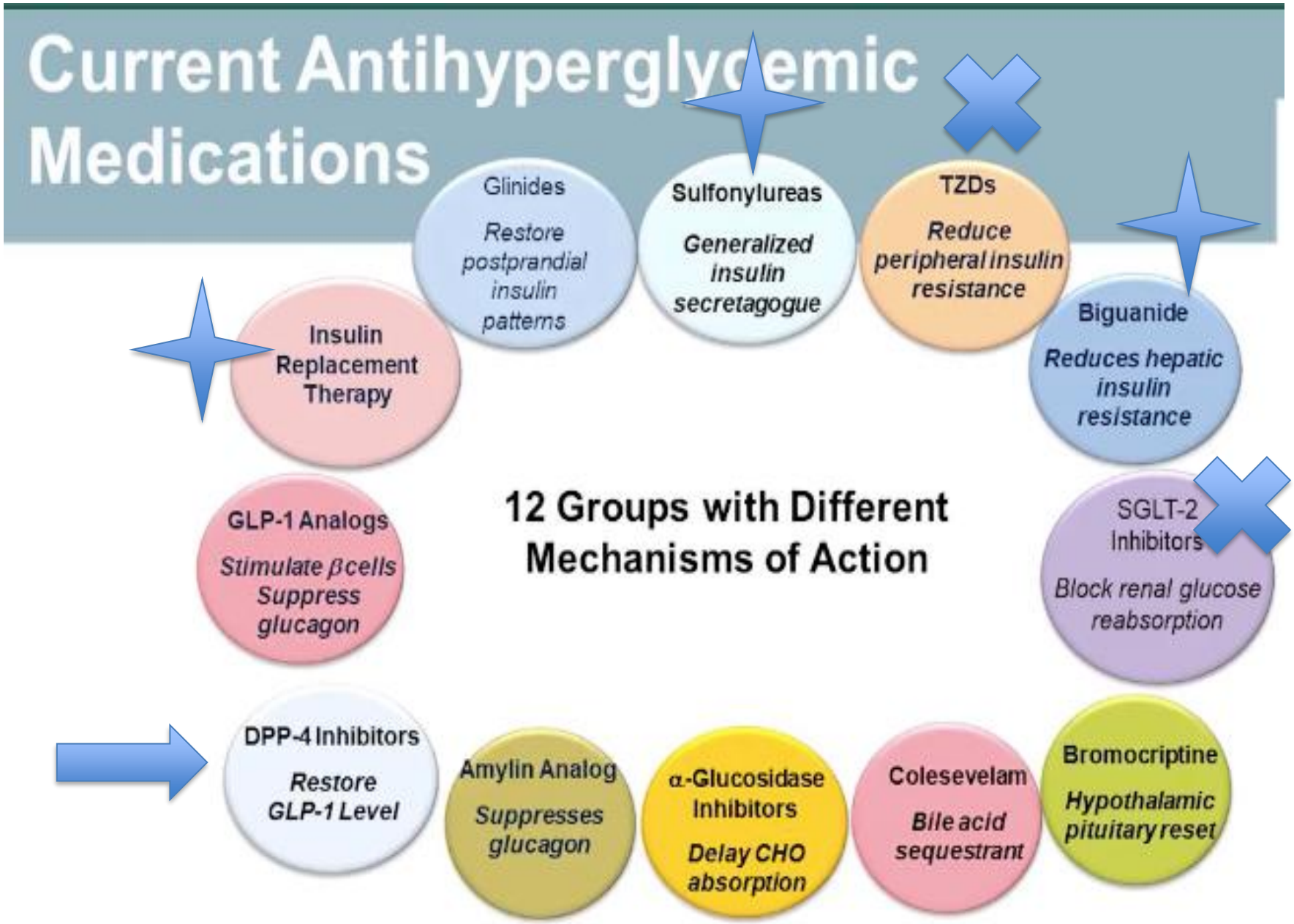
- Finally Dapagliflozin was added and follow up appointment to see endocrinologist in 2 months time

- She appeared with early appointment with problems of recurrent UTI, no good response to antibiotics, symptoms affecting her daily life

- Her SMBG appears better controlled but she doesn’t want to continue DAPA

- What would be the alternative medication for
- Uncontrolled T2DM, overweight lady , high CVD risk with CCF, Early Nephropathy , recurrent UTI
- Any drug that we miss out??

Current Antihyperglycemic Medications



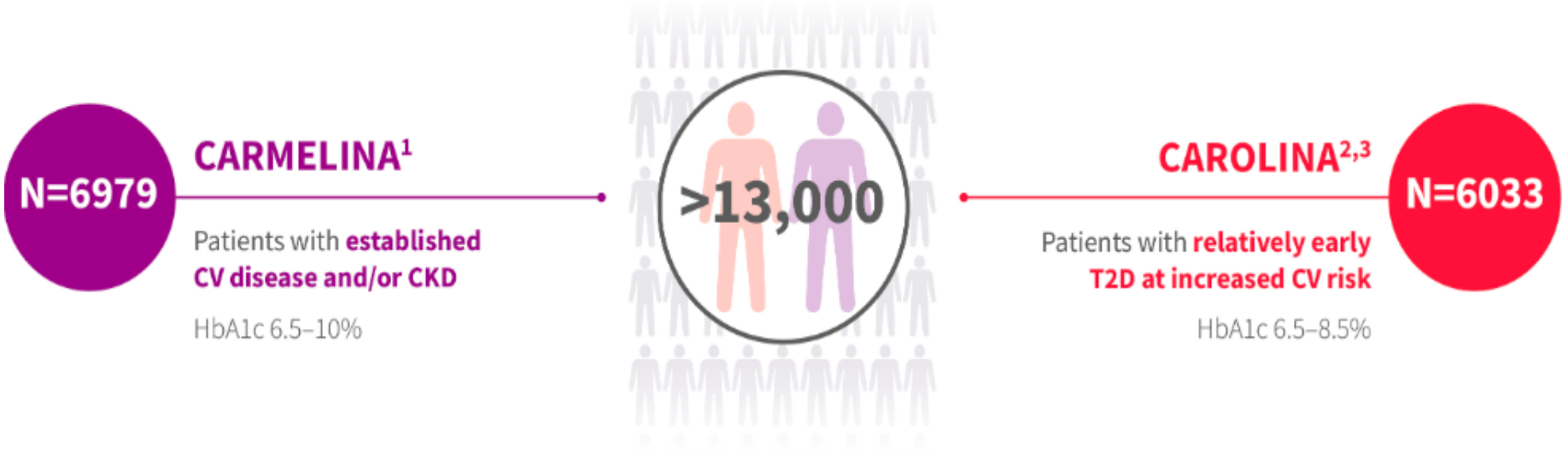
DPP-4 inhibitor

- Weight neutral
- No serious hypoglycemia
- No dose adjustment for renal dysfunction
- Can combine with insulin + OHA
- No liver toxicity
- Renal safe
- Cardiologically safe??

CVOT (DPP4- inhibitors)

DPP-4 inhibitor	CAROLINA	TECOS	SAVOR-TIMI53	EXAMINE
	Linagliptan	Sitagliptan	Saxagliptan	Alogliptan
comparator	sulphonylurea	placebo	placebo	placebo
No of patients	6,000	14,000	16,500	5,400
Trial initiation	Oct 2010	Nov 2008	May 2010	Sept 2009
Diabetes stage focus	Early	Advanced	Advanced	All but limited to acute event
Diabetes background Tx	Predominantly on metformin	Any	Any	Any
Results	HR 0.98 (95.47%CI 0.84-1.14)	HR 0.98(95% CI 0.88 – 1.09)	HR 1.0(95% CI 0.89 -1.12)	HR 0.96 (95% CI <1.16)

Together, CARMELINA and CAROLINA constitute a comprehensive CV outcomes trial programme



CARMELINA and CAROLINA constitute a comprehensive CVOT programme demonstrating the long-term safety profile of linagliptin in a broad range of patients with T2D

CAROLINA

- CARdiovascular Outcome Trial of LINAgliptan vs Glimeperide in Type 2DM) is the randomized double blind longest term active control CVOT

- Testing the Safety of DPP-4inhibitor vs Sulphonylurea added to Metformin on usual care

- **Cardiovascular outcome**
- Primary : time to 1st occurrence of any of 3P-MACE
- - CV death(fatal MI & fatal stroke)
- - Non fata MI (excluding silent MI)
- - Non fatal stroke
- Secondary: time to first occurrence of 4P-MACE(occurrence of hospitalization for unstable angina)

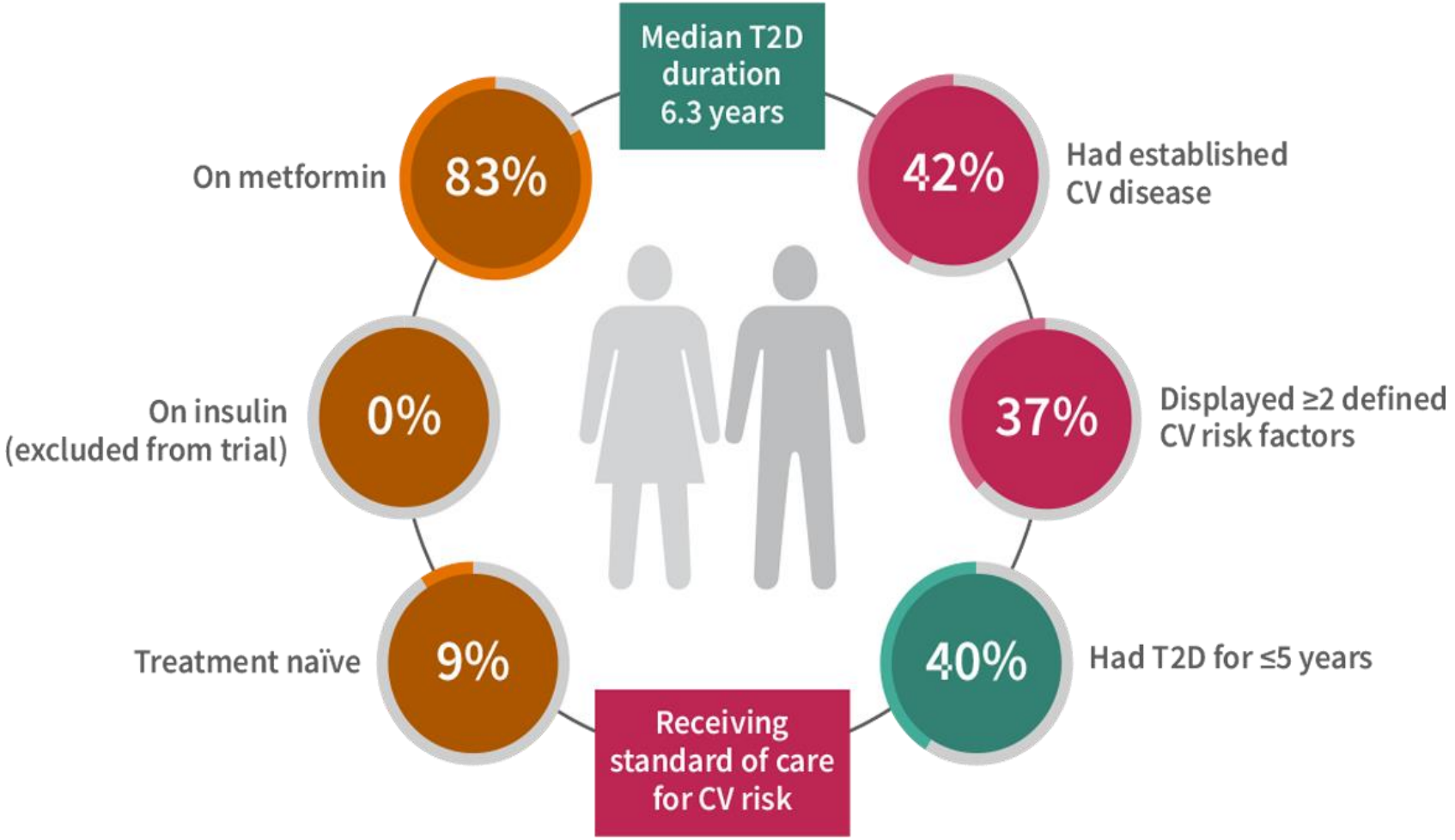
- **Metabolic outcome**
- secondary metabolic efficacy outcome
- maintain HbA1c <5.7% between end of titration & final visit

  - without needing rescue medication

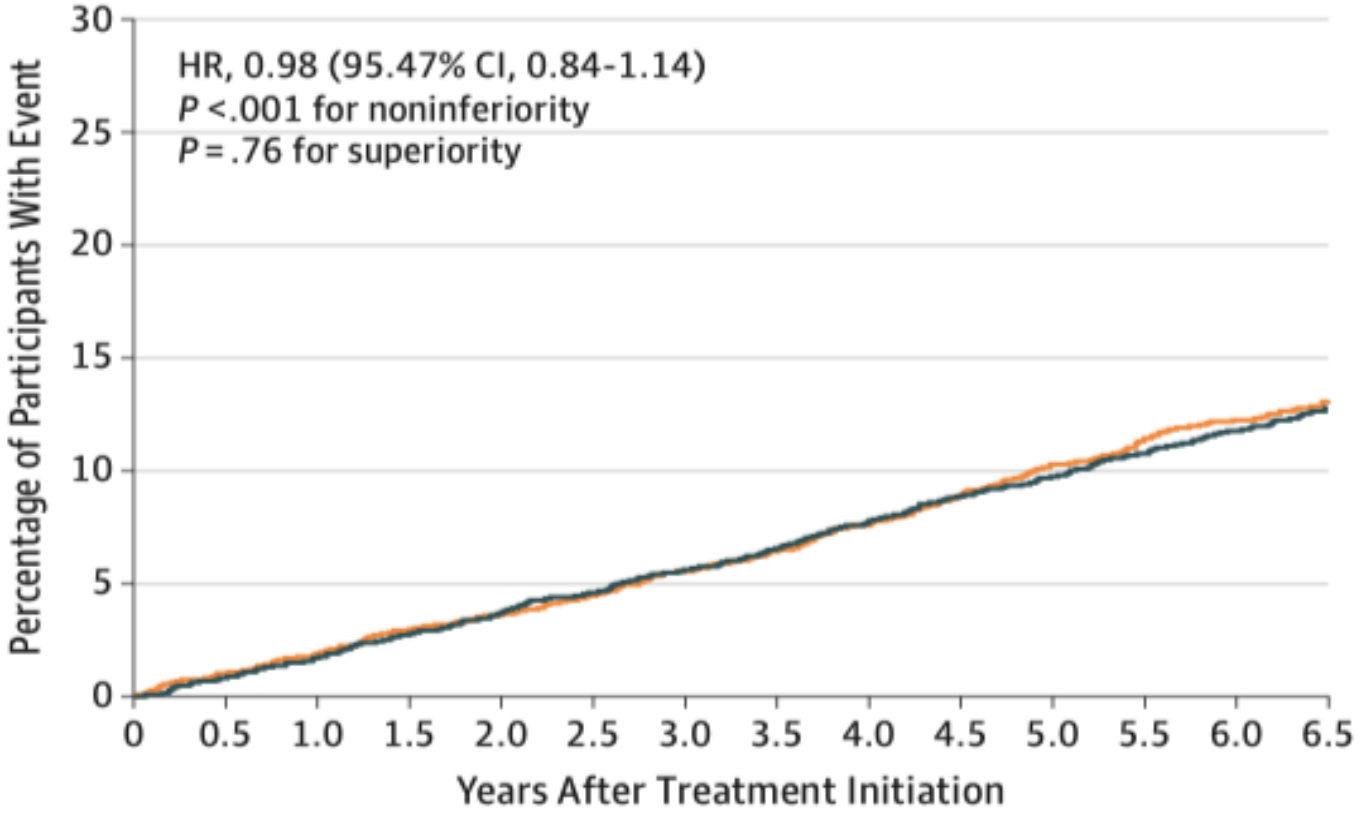
  - with weightgain <2%

  - without moderate or severe hypoglycemia

CAROLINA included participants with relatively early T2D at increased CV risk



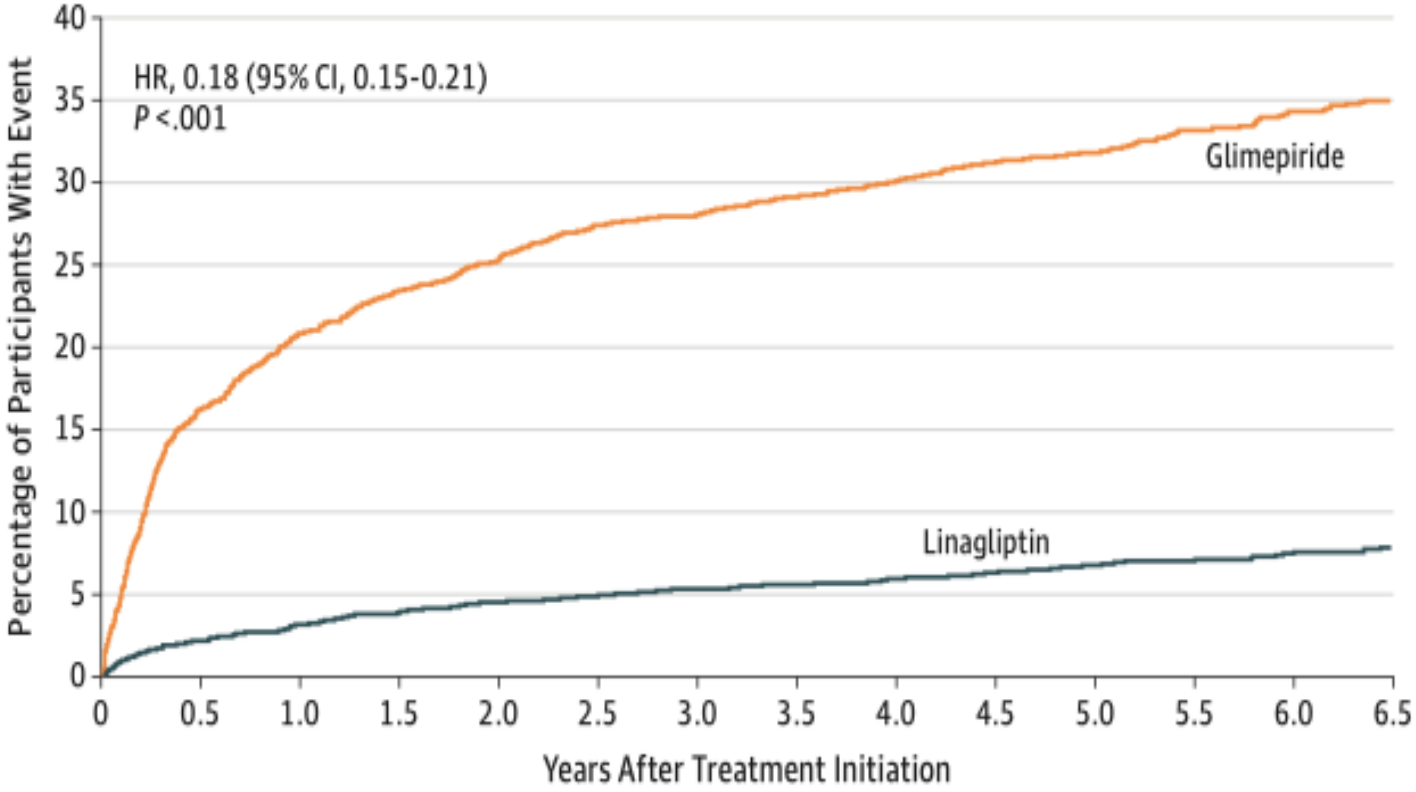
Linagliptin was non-inferior to Glimepride for 3P MACE



No. of participants

Glimepiride	3010	2890	2797	2710	2618	2509	1865
Linagliptin	3023	2901	2803	2725	2627	2534	1830

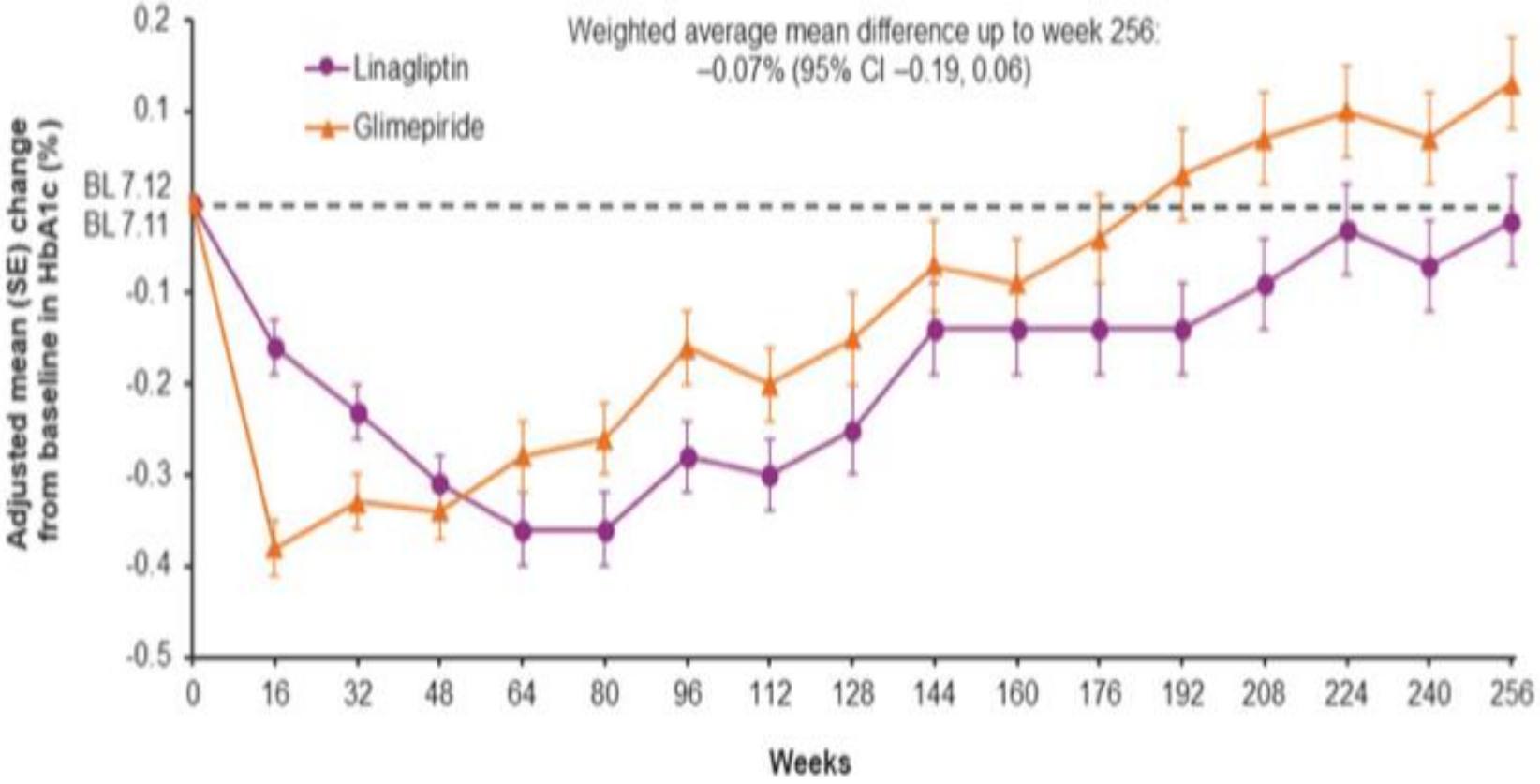
Occurence of any hypoglycaemic AE was lower with Linagliptin versus Glimepride



No. of participants

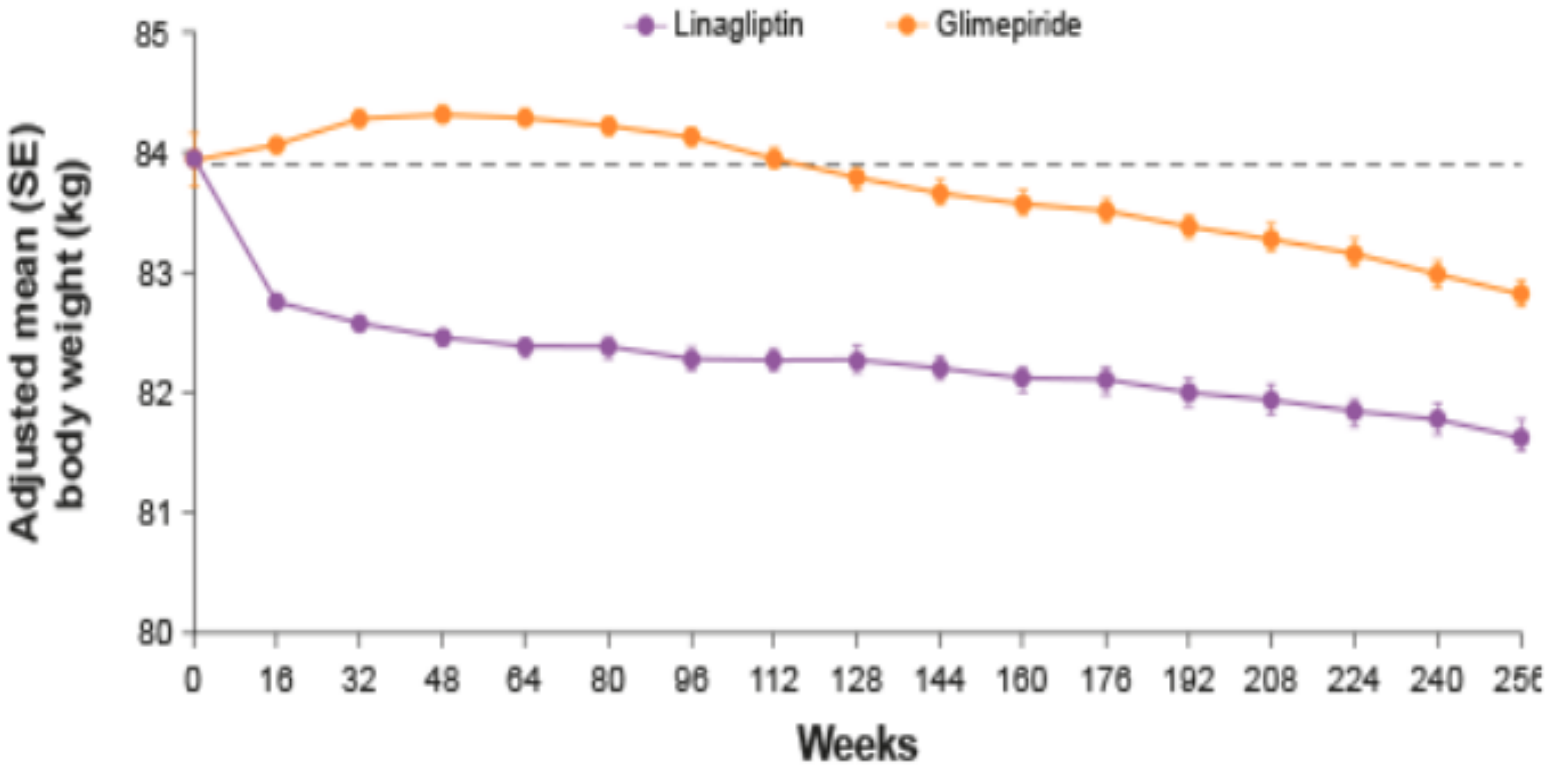
Glimepiride	3000	2382	2145	1999	1882	1779	1691	1607	1539	1473	1411	1325	957	344
Linagliptin	3014	2763	2596	2499	2386	2298	2234	2140	2072	2001	1932	1850	1333	526

No differences in HbA1c levels in both arms

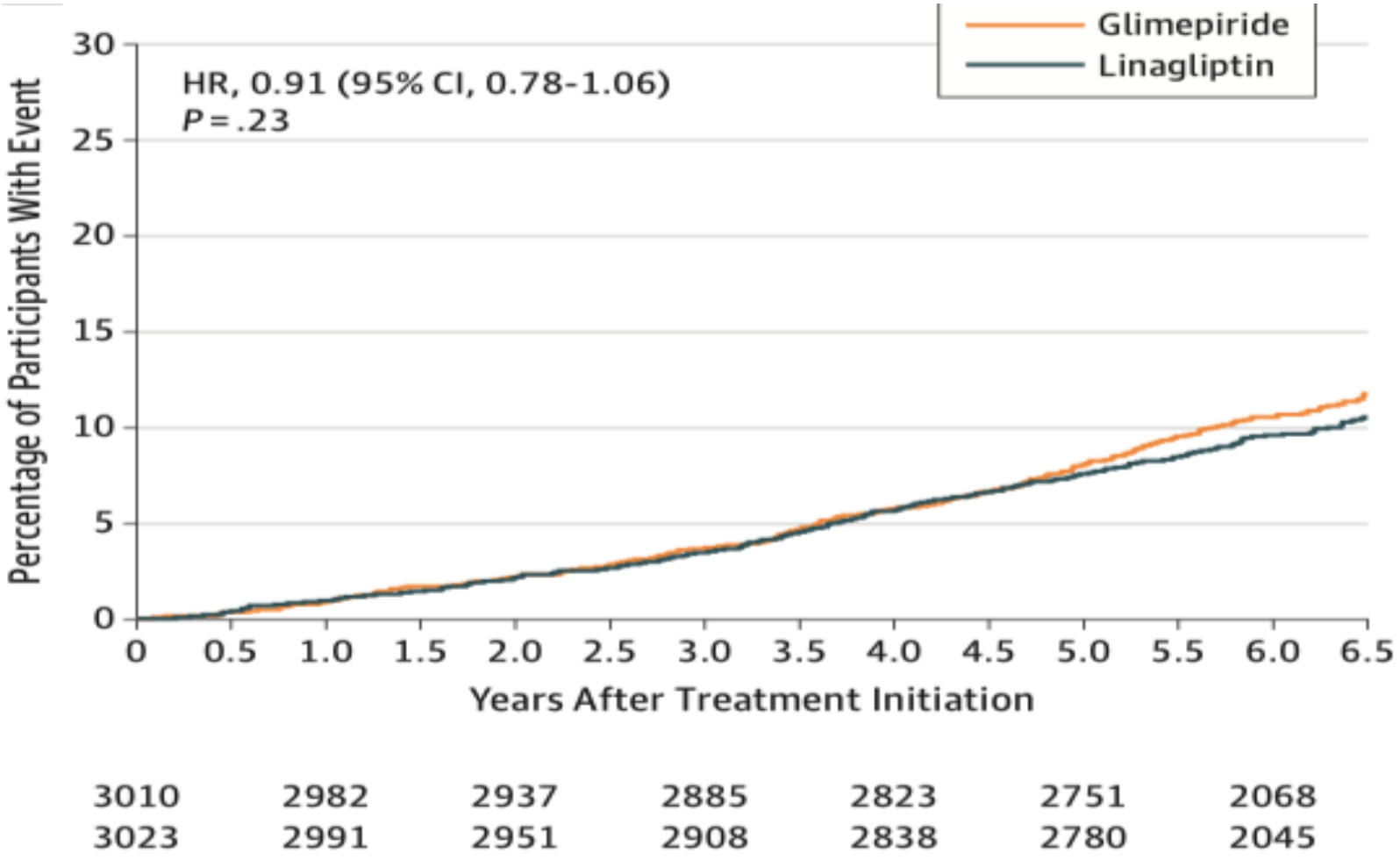


Linagliptin (*n*)	465	458	440	432	428	423	408	397	396	400	402	394	392	389	393	386	386
Glimepiride (*n*)	468	459	447	441	435	427	420	407	405	404	401	397	389	389	384	383	376

Linagliptin was associated with reduced weight compared with Glimepride

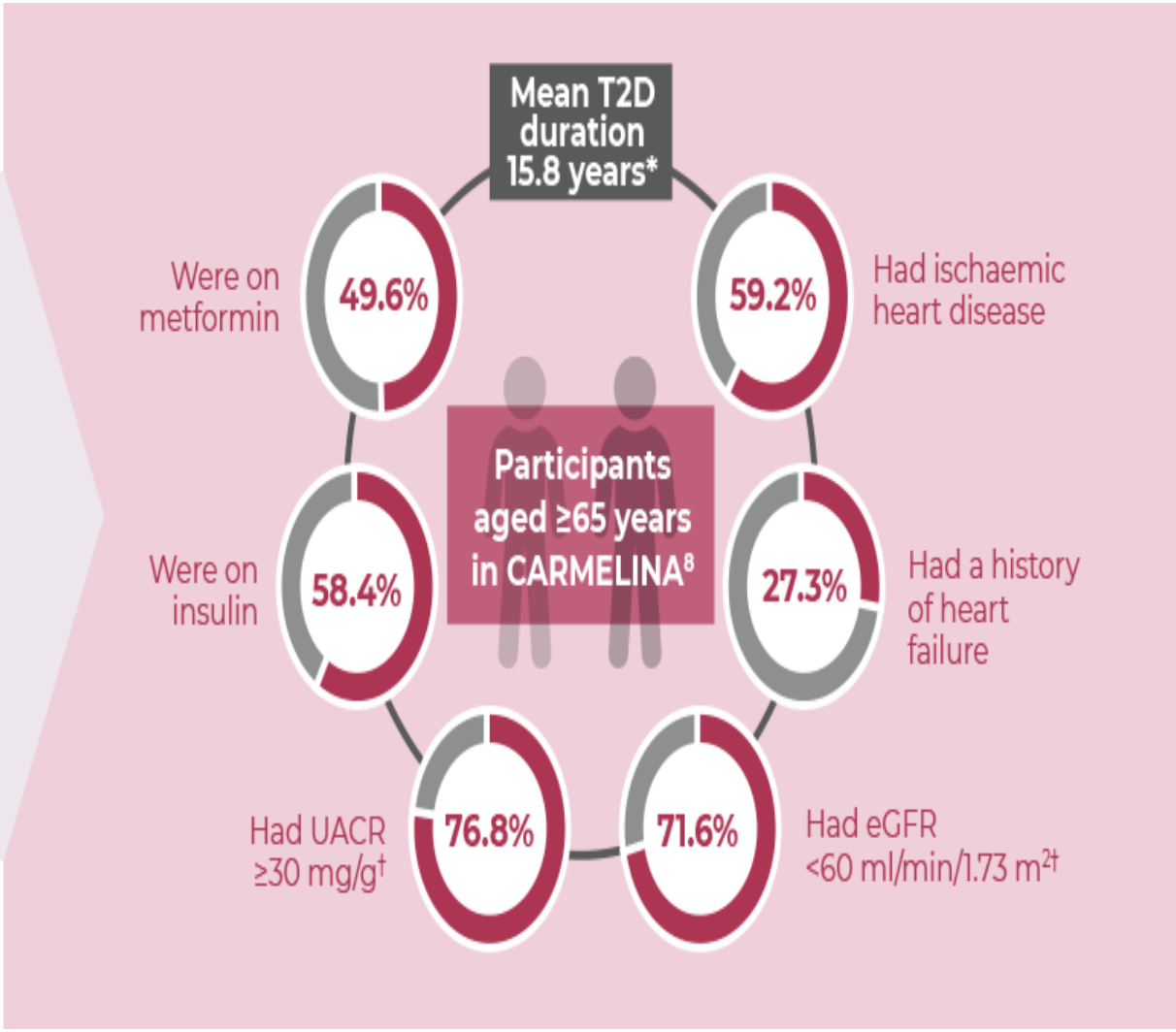


Linagliptin did not increase the risk for all cause mortality compared with Glimepride, although the curves separated at 5 years

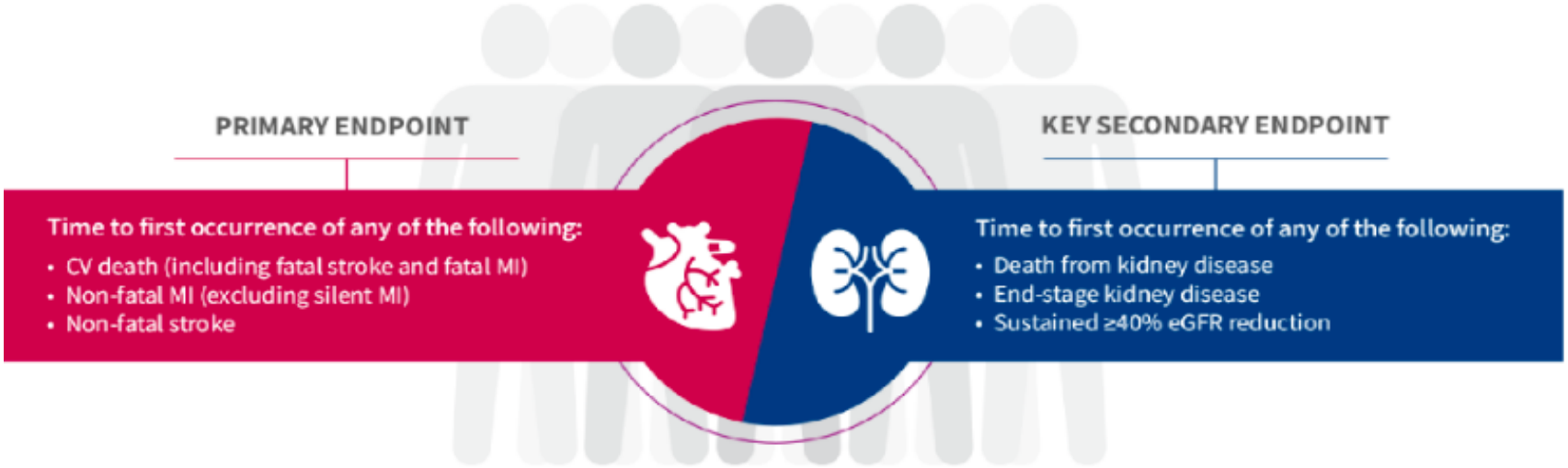


CARMILENA trial

...of the trial population were aged ≥65 years old (n=4011)[8]

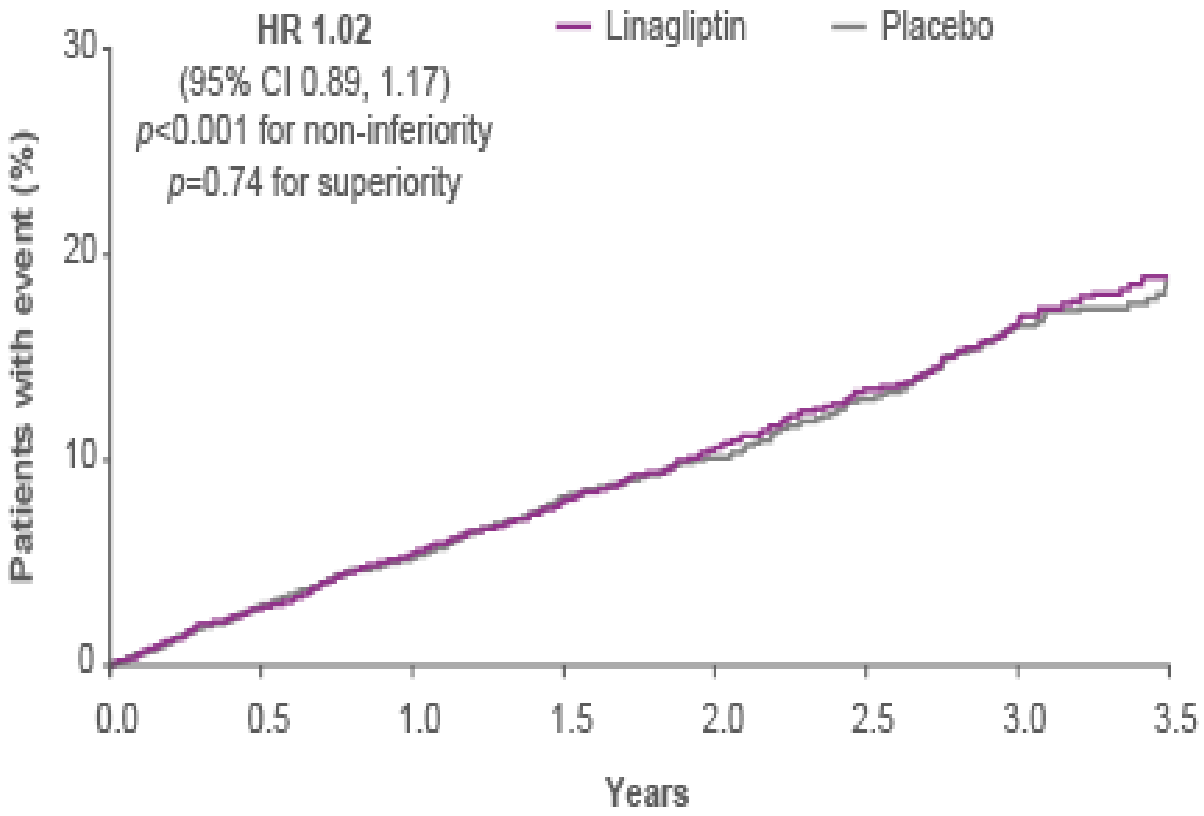


Effect of Linagliptan vs placebo in adverse cardiovascular outcomes in patients with T2DM with high Cardiovascular and renal risk



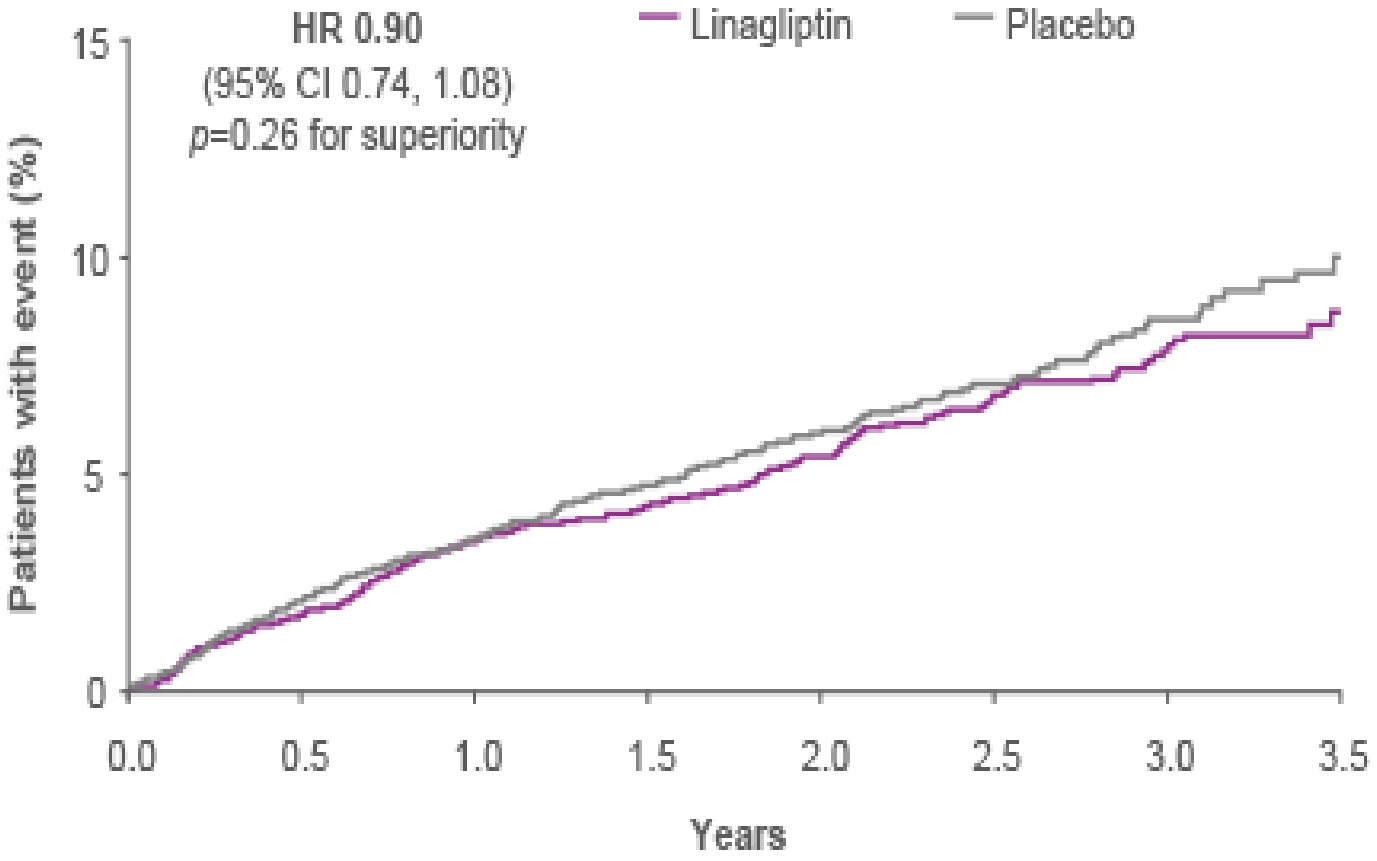
Long term CV safety profile of linagliptin was confirmed

Time to first occurence of 3P MACE



The 3P-MACE‡ primary outcome occurred in 434/3494 (12.4%) and 420/3485 (12.1%) patients in the linagliptin and placebo groups, respectively

Hospitalisation for heart failure

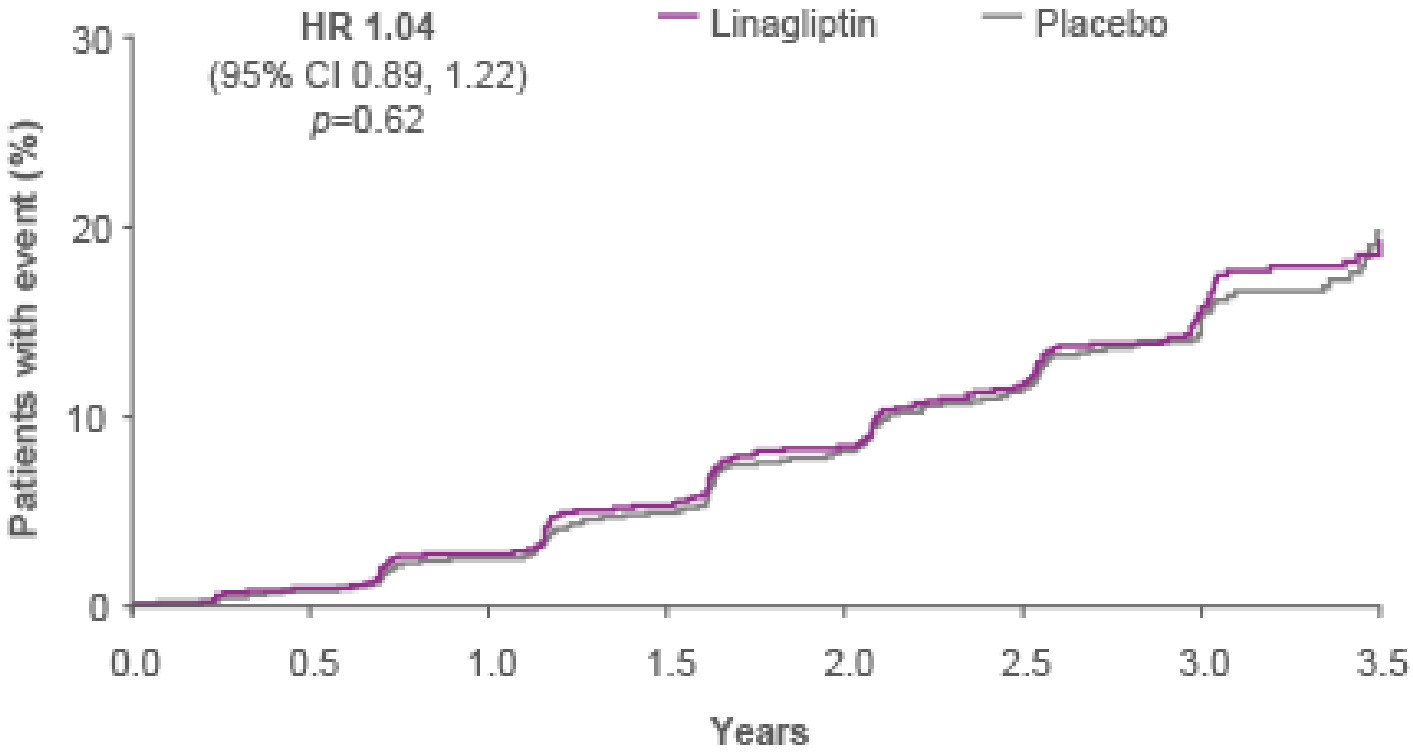


No increased risk of hospitalisation for heart failure‡

Rates of hospitalisation for heart failure did not differ between treatment groups: 209/3494 (6.0%) and 226/3485 (6.5%) in the linagliptin and placebo groups

The long-term renal safety profile of linagliptin was confirmed

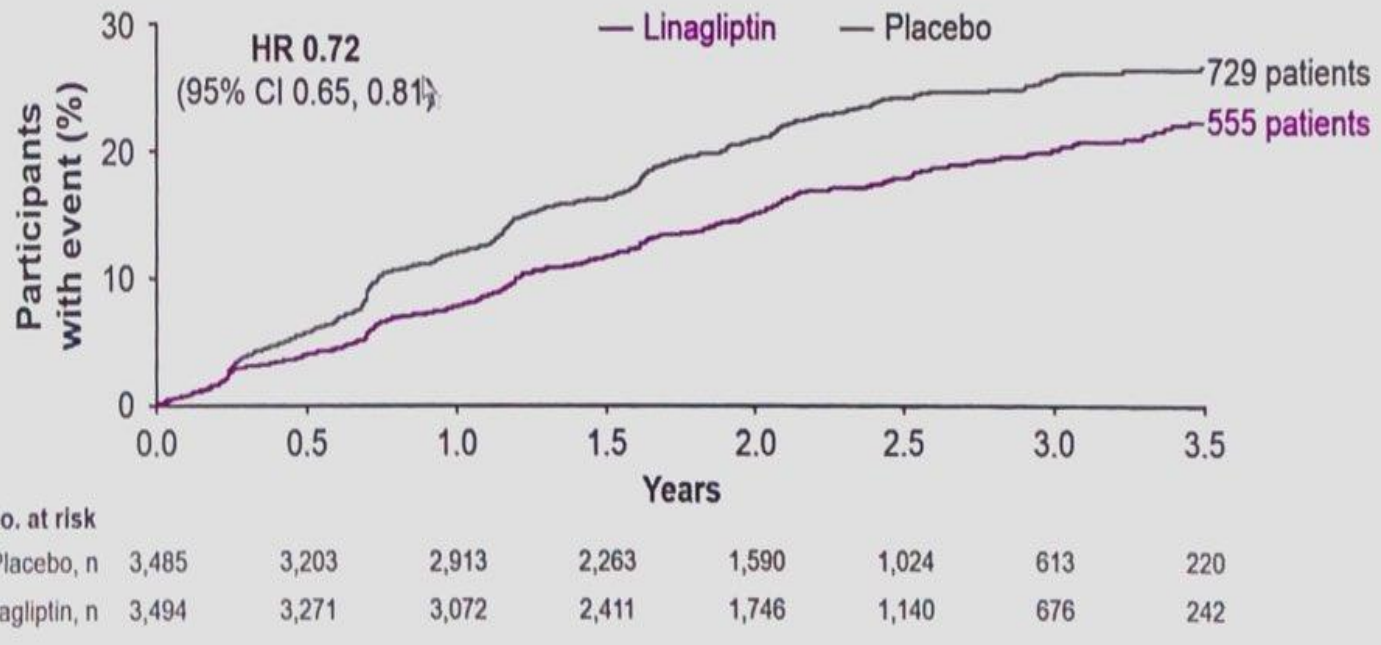
Time to death to kidney disease, progression to ESKD or sustained eGFR decrease of ≥ 40%



The key kidney outcome occurred in 327/3494 (9.4%) and 306/3485 (8.8%) patients in the linagliptin and placebo groups, respectively

Linagliptin, fewer patients initiated or increased insulin dose

Initiation or dose increase of insulin



No. at risk								
Placebo, n	3,485	3,203	2,913	2,263	1,590	1,024	613	220
Linagliptin, n	3,494	3,271	3,072	2,411	1,746	1,140	676	242

Treated set. Post-hoc analysis: Kaplan-Meier estimate. Hazard ratio and 95% CI based on Cox regression model

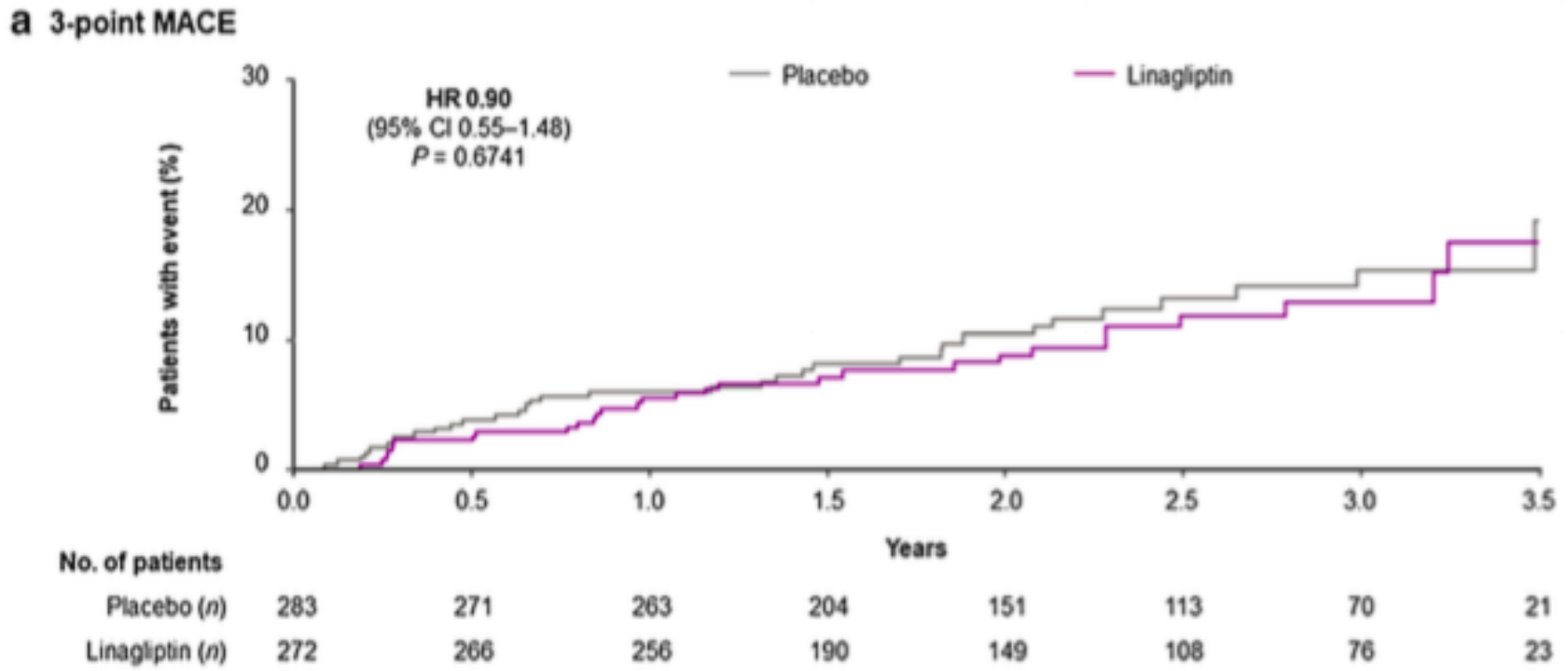
CARMELINA

CARMELINA study ASIAN subsets

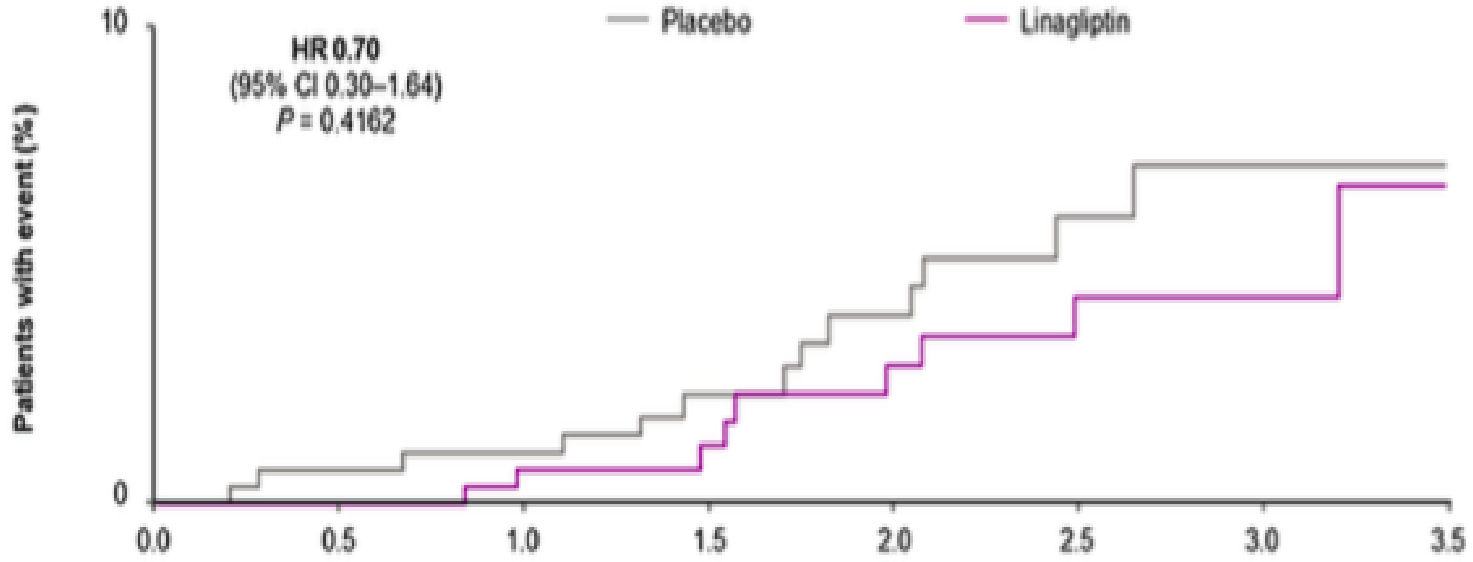
- **Linagliptin and cardiorenal outcomes in Asians with type 2 diabetes mellitus and established cardiovascular and/or kidney disease: subgroup analysis of the randomized CARMELINA® trial**
- **The Japan Diabetes Society 2019**
- **Diabetology International https://doi.org/10.1007/s13340-019-00412-x**

- **555 participants from Asian countries**

Time to first cardiovascular events and hospitalisation for heart failure in Asian patients

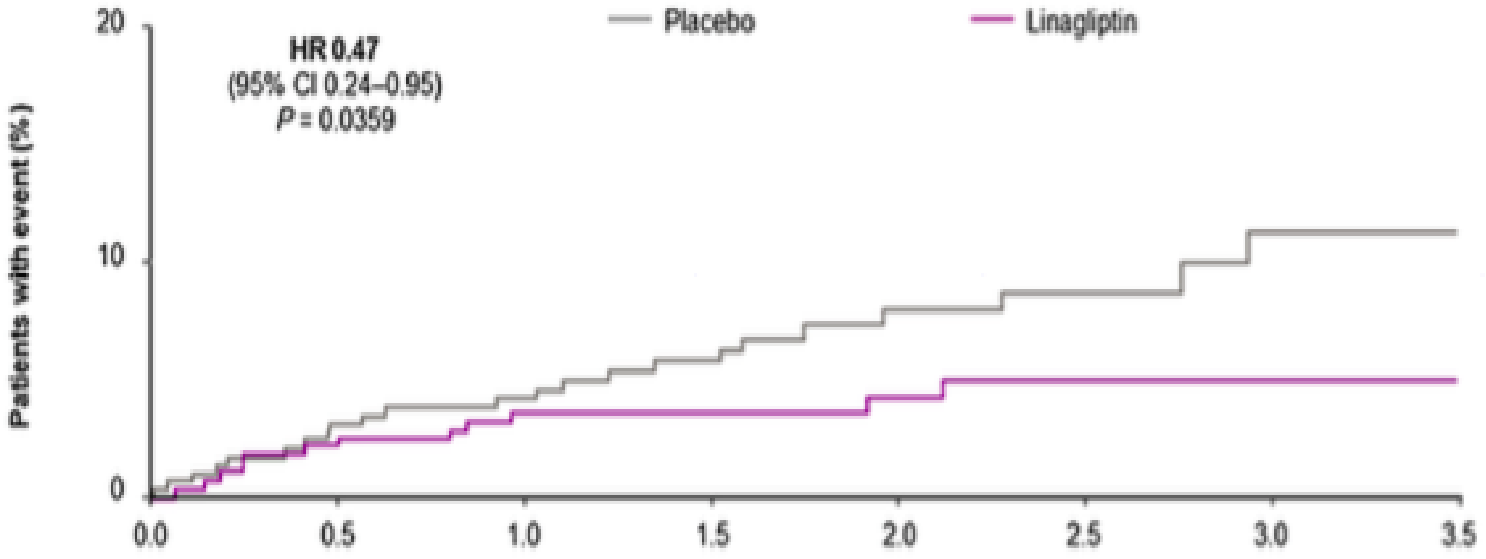


b Cardiovascular death



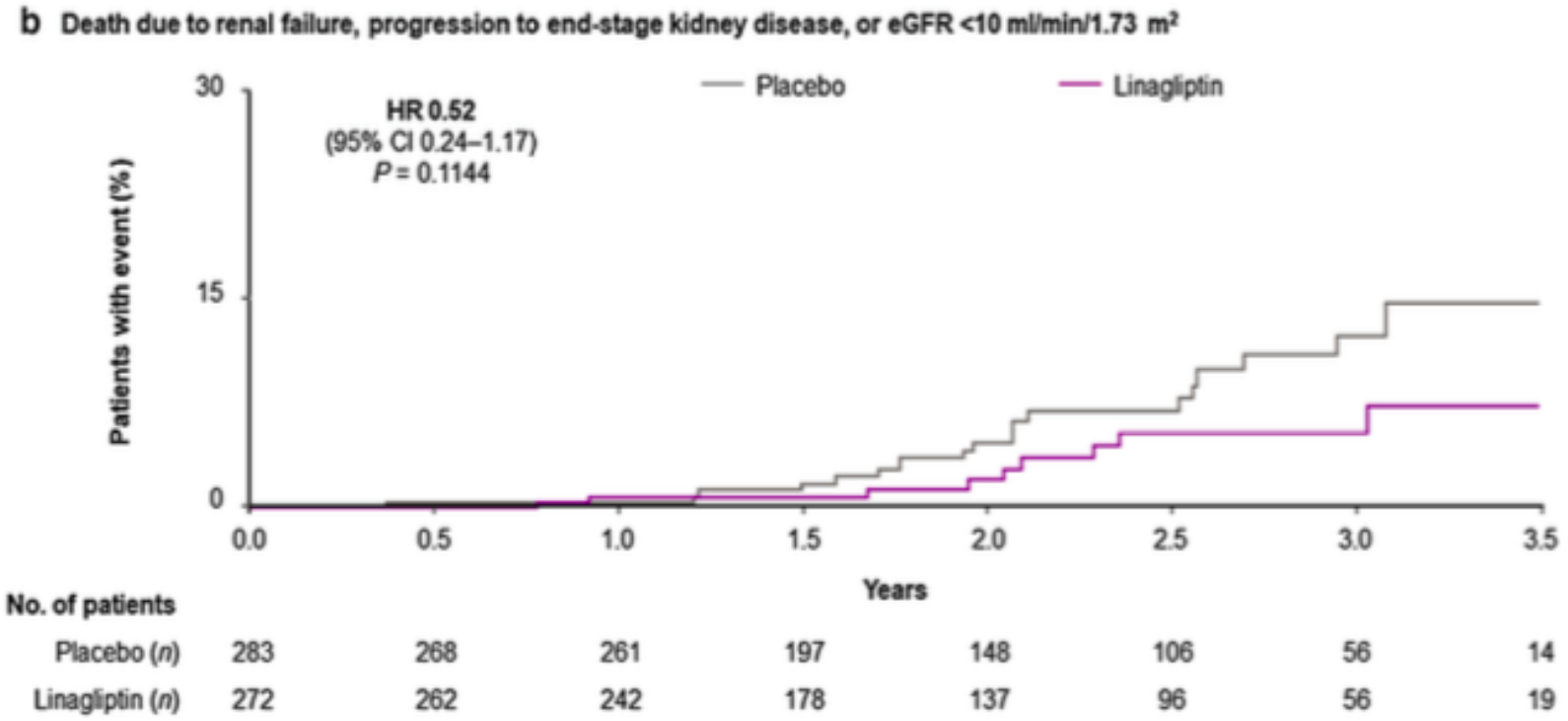
No. of patients								
Placebo (*n*)	283	279	275	211	159	117	72	23
Linagliptin (*n*)	272	272	268	198	155	115	82	26

C Hospitalization for heart failure



No. of patients								
Placebo (*n*)	283	270	264	201	149	110	66	23
Linagliptin (*n*)	272	266	260	192	150	109	77	25

Time to first kidney events in Asian patients



- After 12 weeks of treatment of Asian patients, the adjusted mean difference in HbA1c level with linagliptin compared with placebo was 0.60% (95% CI – 0.73 to – 0.47)

- There was no difference in change over time in body weight, cholesterol levels, or blood pressure with linagliptin compared with placebo

- Fewer linagliptin-treated Asian patients (77.9%) had an adverse event compared with placebo-treated Asian patients (84.8%)

- The incidence of hypoglycemia was also slightly lower with linagliptin than placebo, including severe episodes

Final recommendation

- subgroup analysis of the multinational CARMELINA® trial indicates that **linagliptin did not increase the risk of MACE in Asian T2DM patients with established CVD with albuminuria and/or kidney disease**.
- Furthermore, ***linagliptin did not increase the risk of clinically relevant kidney complications or heart failure.***

The best choice for this scenario is

- **DPP-4 inhibitor which is Cardiovascular safe as well as Renal safe is**

- **LINAGLIPTAN**

THANK YOU