Prioritizing Choices for Glycemic Management in Type 2 Diabetes

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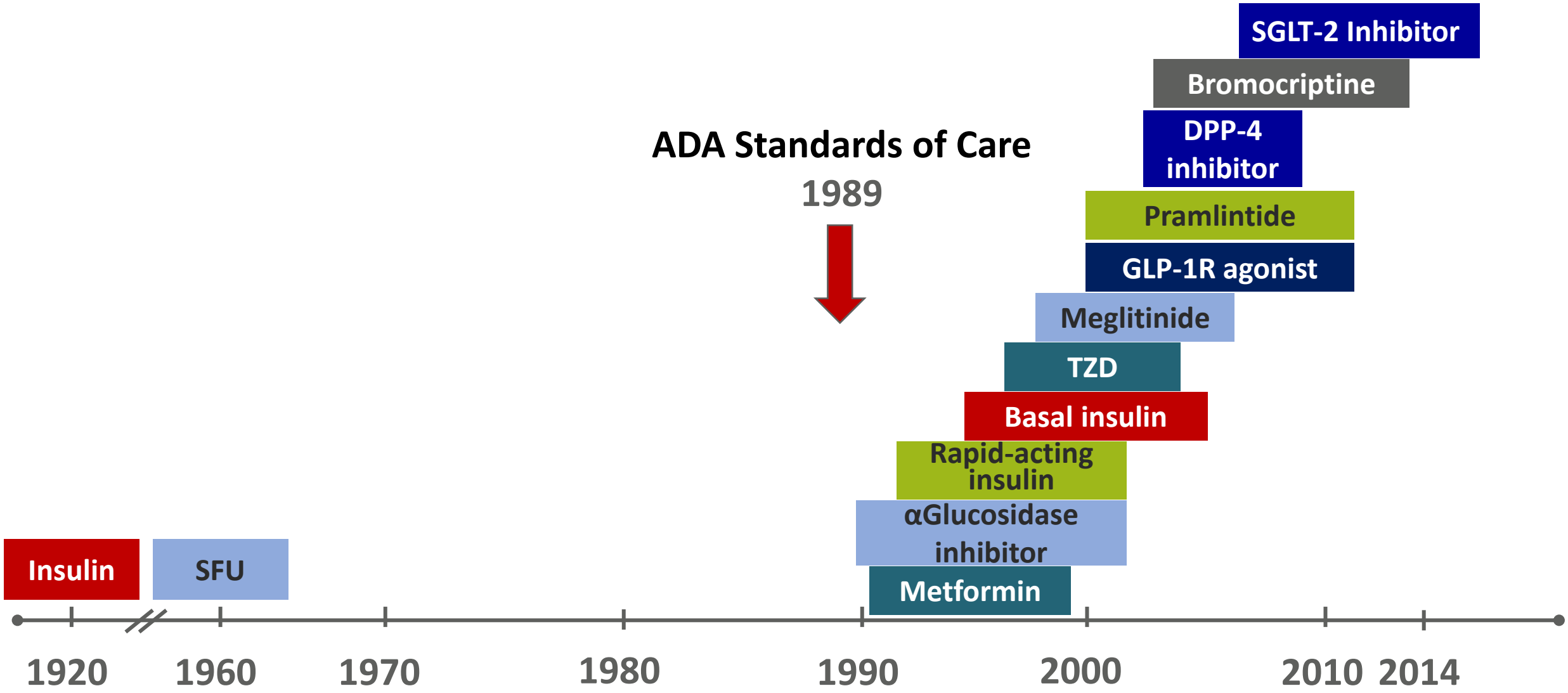
  Regeneron

- Consultant/ Honoraria:
  Clinical Overview (Elsevier)

- Editorial Board
  Dynamed Plus

No Stocks or Options in any Pharma/Biotech

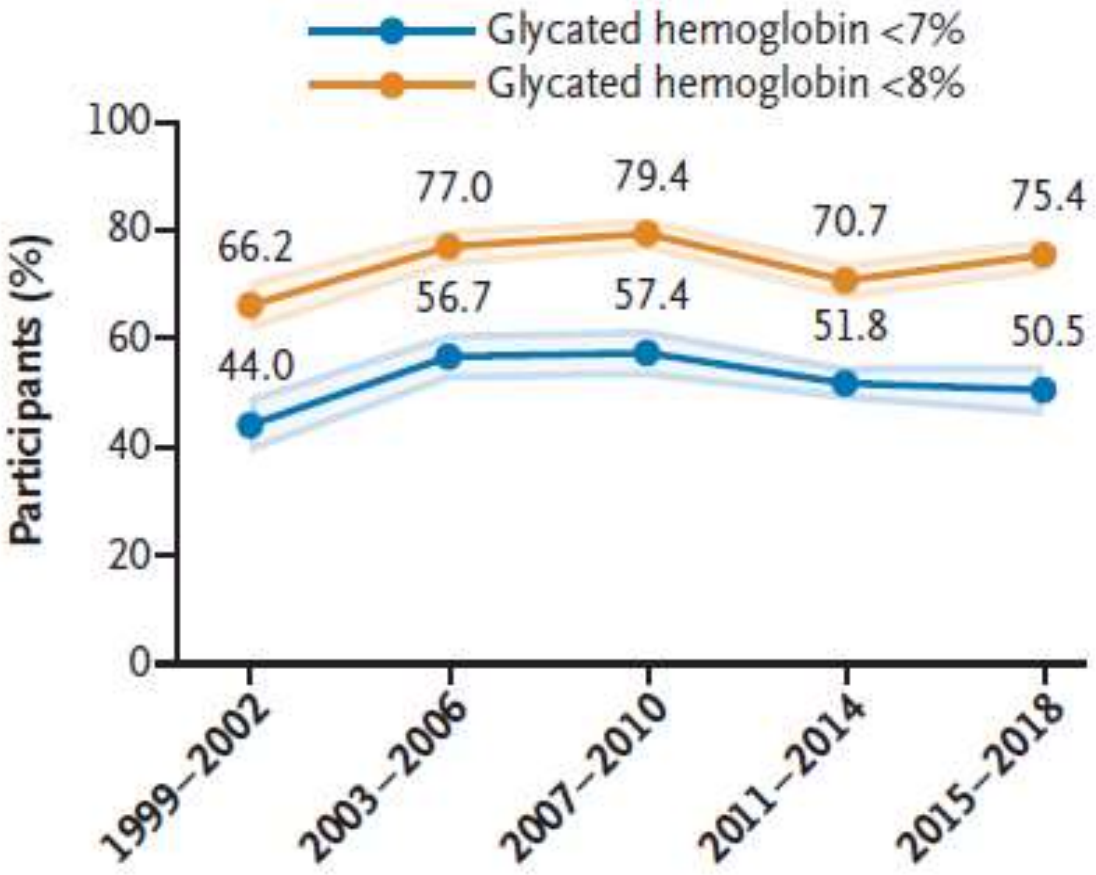
Recent Therapeutic Advances

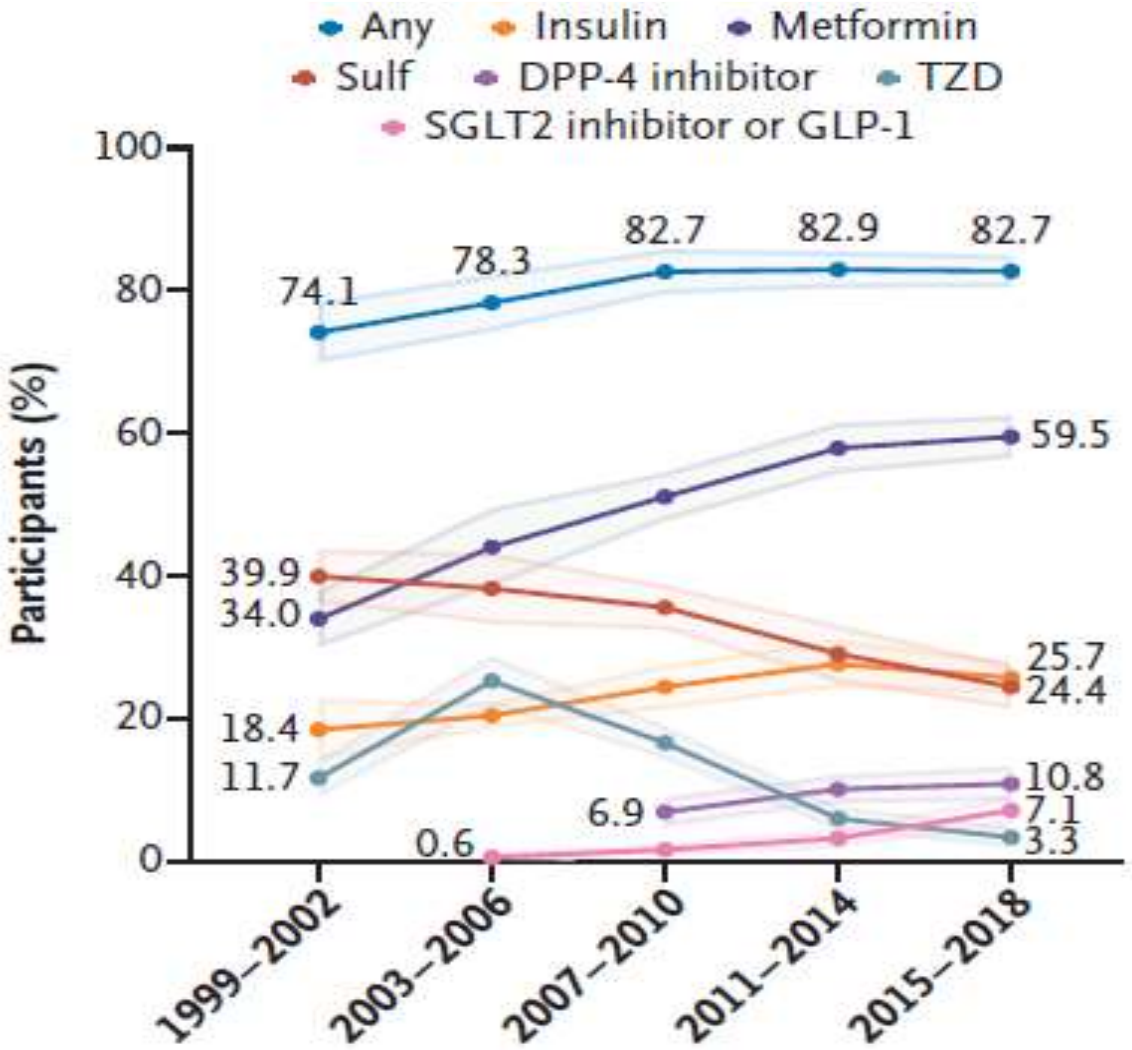


The availability of GLP-1 receptor agonists and SGLT2 inhibitors has ushered in a dramatic advance in the management of type 2 DM, beyond glycemic control.

<u>This is mainly facilitated by their multi-factorial effects on cardiovascular and renal systems</u>

US-NHANES Data: 20-year Trends in Glucose Control and Use of Medications





Fang, M et al NEJM 2021

Problems Unique to India and other regions

- **Lack of adequate Resources**
- **PCPs: Too many patients; too little time**
- **Lack of Health Literacy: very limited diabetes educator availability**
- **Lifestyle Concerns; including high carb intake, physical inactivity**
- **Lack of Adherence to treatment regimen**
- **Affordability of medications (Cost…)**

USE OF GLUCOSE-LOWERING MEDICATIONS IN THE MANAGEMENT OF TYPE 2 DIABETES

HEALTHY LIFESTYLE BEHAVIORS; DIABETES SELF-MANAGEMENT EDUCATION AND SUPPORT (DSMES); SOCIAL DETERMINANTS OF HEALTH (SDOH)

TO AVOID THERAPEUTIC INERTIA REASSESS AND MODIFY TREATMENT REGULARLY (3–6 MONTHS)

Goal: Cardiorenal Risk Reduction in High-Risk Patients with Type 2 Diabetes (in addition to comprehensive CV risk management)*

+ASCVD†

Defined differently across CVOTs but all included individuals with established CVD (e.g., MI, stroke, any revascularization procedure). Variably included: conditions such as transient ischemic attack, unstable angina, amputation, symptomatic or asymptomatic coronary artery disease.

+Indicators of high risk

While definitions vary, most comprise ≥55 years of age with two or more additional risk factors (including obesity, hypertension, smoking, dyslipidemia, or albuminuria)

+ASCVD/Indicators of High Risk

GLP-1 RA# with proven CVD benefit

EITHER/ OR

SGLT2i§ with proven CVD benefit

If HbA_{1c} above target

- For patients on a GLP-1 RA consider adding SGLT2i with proven CVD benefit or vice versa
- TZD^

+HF

Current or prior symptoms of HF with documented HFrEF or HFpEF

+HF

SGLT2i§ with proven HF benefit in this population

+CKD

eGFR <60 mL/min per 1.73 m^2 OR albuminuria (ACR ≥3.0 mg/mmol [30mg/g]). These measurements may vary over time; thus, a repeat measure is required to document CKD.

+CKD (on maximally tolerated dose of ACEi/ARB)

PREFERABLY

SGLT2i§ with primary evidence of reducing CKD progression

Use SGLT2i in people with an eGFR ≥20 mL/min per 1.73 m^2; once initiated should be continued until initiation of dialysis or transplantation

OR

GLP-1 RA with proven CVD benefit if SGLT2i not tolerated or contraindicated

If HbA_{1c} above target, for patients on SGLT2i, consider incorporating a GLP-1 RA or vice versa

If additional cardiorenal risk reduction or glycemic lowering needed

Goal: Achievement and Maintenance of Glycemic and Weight Management Goals

Glycemic Management: Choose approaches that provide the efficacy to achieve goals:

Metformin OR Agent(s) including COMBINATION therapy that provide adequate EFFICACY to achieve and maintain treatment goals

Consider avoidance of hypoglycemia a priority in high-risk individuals

In general, higher efficacy approaches have greater likelihood of achieving glycemic goals

Efficacy for glucose lowering

Very High:
Dulaglutide (high dose), Semaglutide, Tirzepatide

Insulin

Combination Oral, Combination Injectable (GLP-1 RA/Insulin)

High:
GLP-1 RA (not listed above), Metformin, SGLT2i, Sulfonylurea, TZD

Intermediate:
DPP-4i

Achievement and Maintenance of Weight Management Goals:

Set individualized weight management goals

General lifestyle advice: medical nutrition therapy/eating patterns/ physical activity

Intensive evidence-based structured weight management program

Consider medication for weight loss

Consider metabolic surgery

When choosing glucose-lowering therapies:

Consider regimen with high-to-very-high dual glucose and weight efficacy

Efficacy for weight loss

Very High:
Semaglutide, Tirzepatide

High:
Dulaglutide, Liraglutide

Intermediate:
GLP-1RA (not listed above), SGLT2i

Neutral:
DPP-4i, Metformin

If HbA_{1c} above target

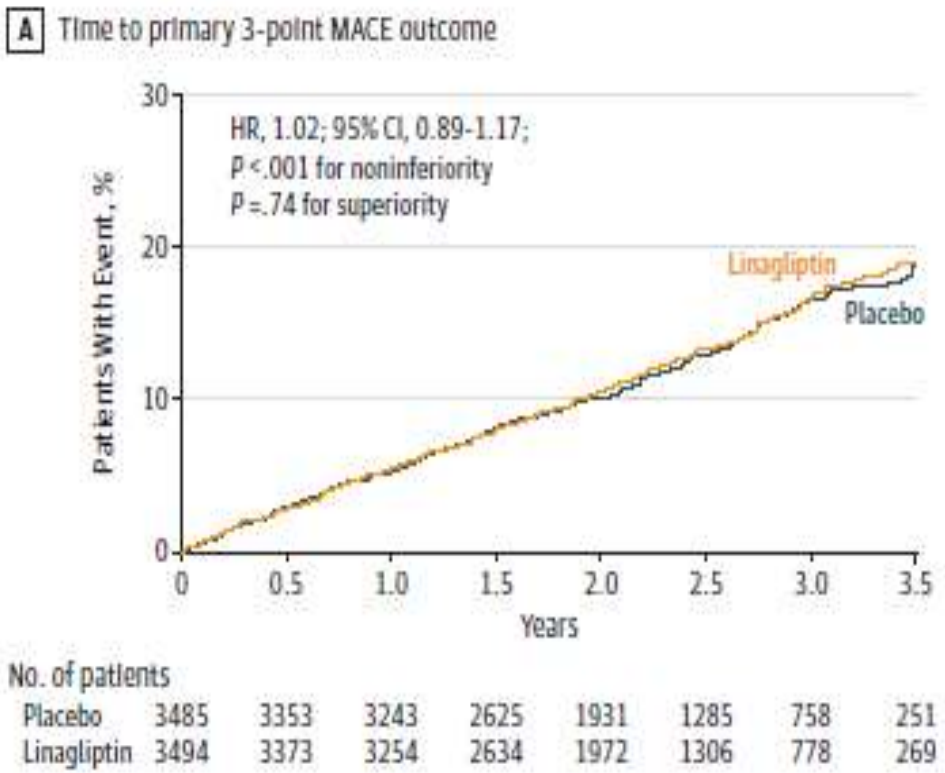
Cardiovascular Outcomes with DPP-4 Inhibitors vs placebo

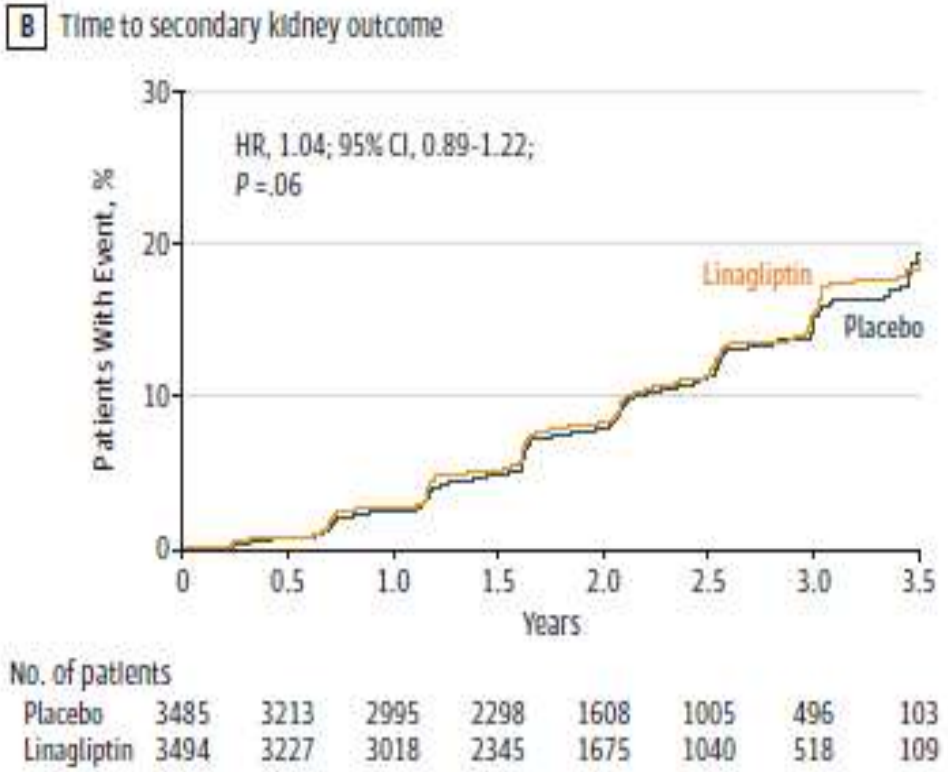
All 4 Major CVOTs with Saxagliptin, Alogliptin, Sitagliptin, and Linagliptin, showed non- inferiority, but also no superiority, over standard of care treatments.

CARMELINA: CV and Renal Outcomes

Linagliptin 5 mg vs placebo

n= 6,979, Mean age, 66yr, eGFR 55, 80 % with u- alb > 30 mg/g





Hospitalization for HF; HR 0.90 (95% CI, 0.74-1.08)

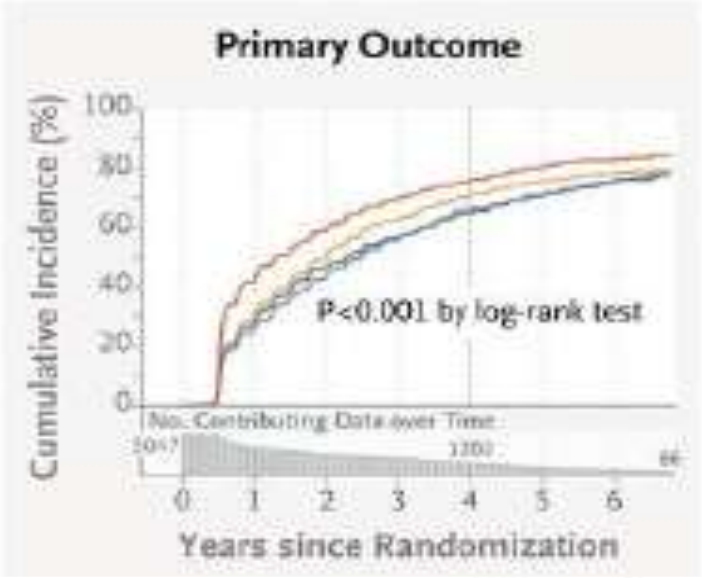
Rosenstock, J et al JAMA 2019; 321: 69-79

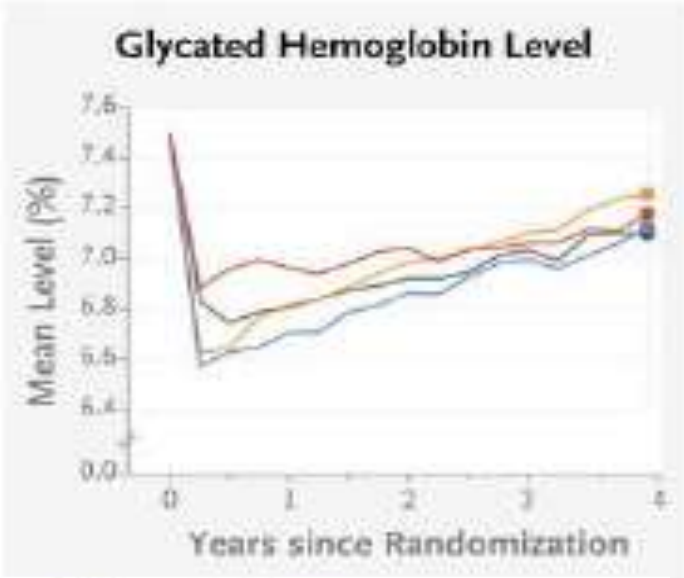
Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness Study (GRADE)

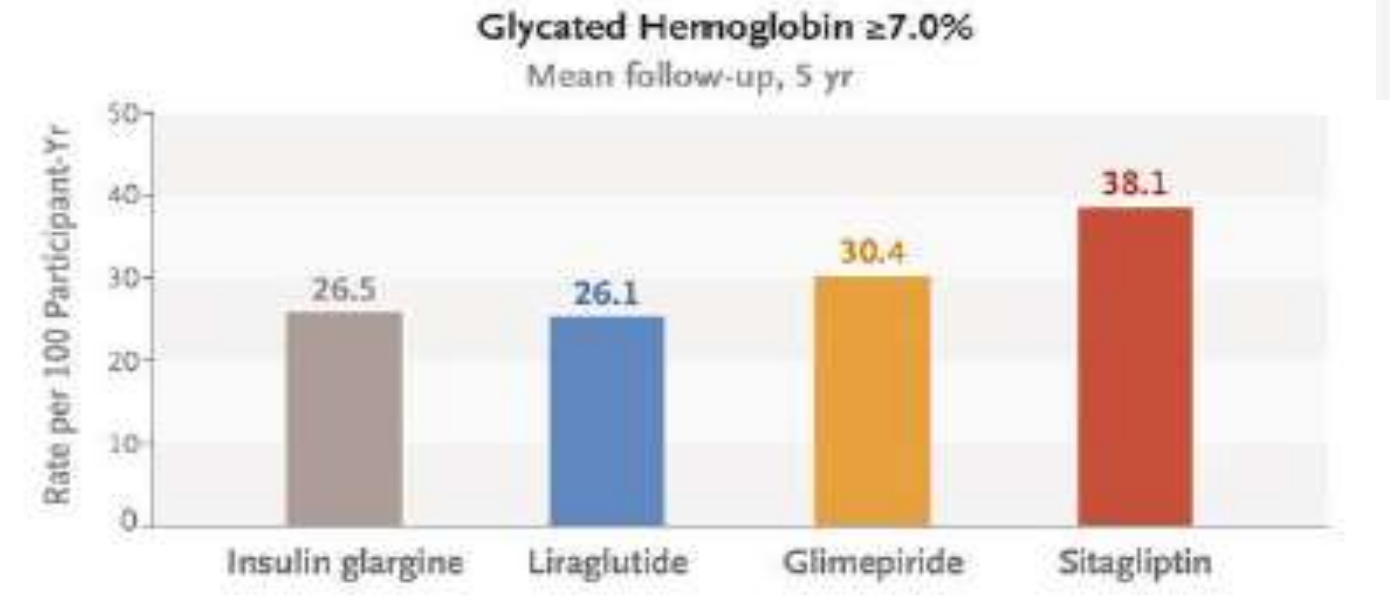
Sponsored by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)

GRADE: Design and Primary Outcome

N=5,047, mean age 57 ± 10.0 yr; mean duration of DM 4.2 ± 2.7 yr; f/u 5.0 yr







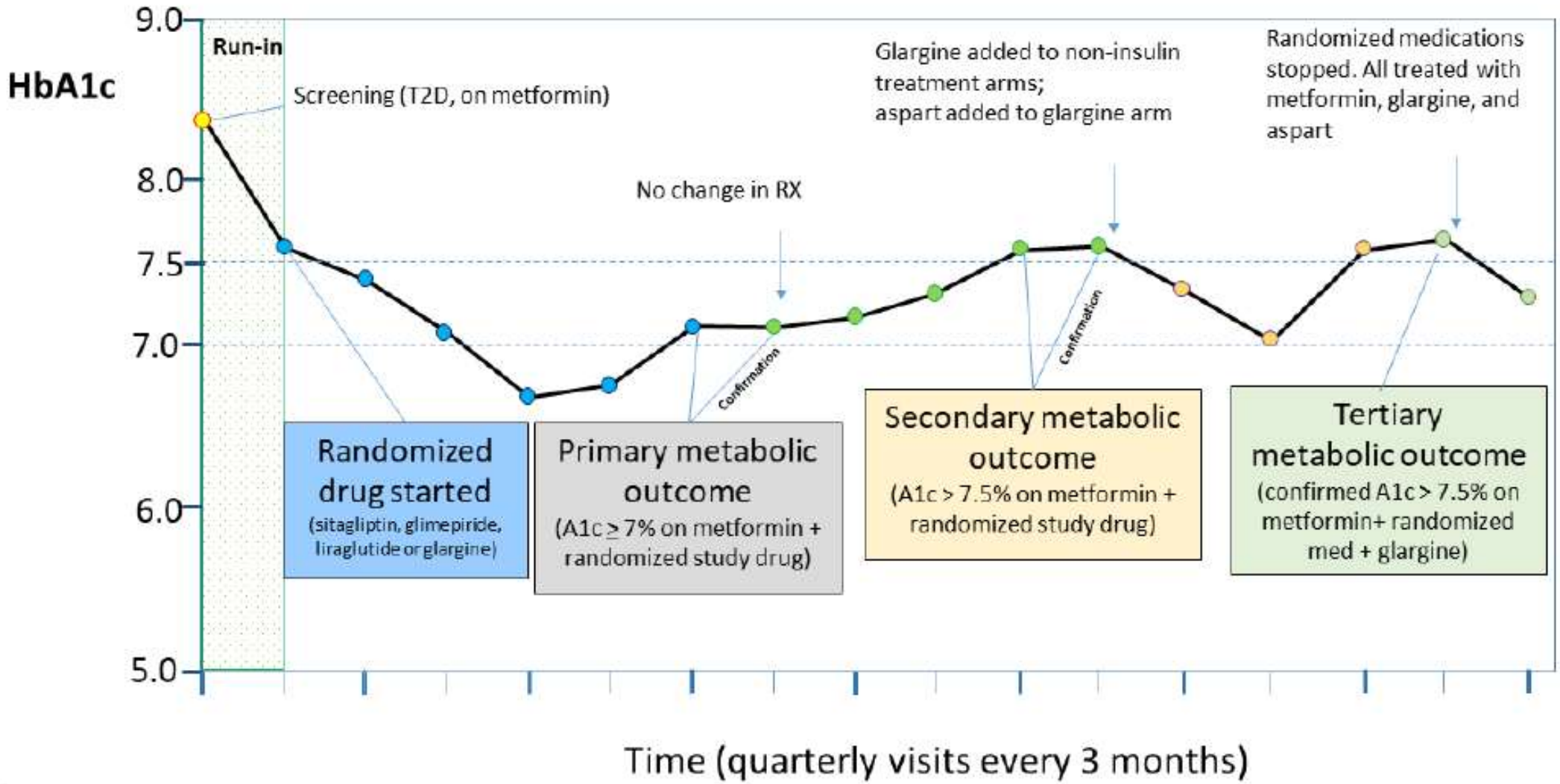
The Grade Study Group
NEJM 2022; 187: 1063-74

Mean and Median Medication Doses across Years 1 and 4 of Follow-up

	Insulin Glargine U-100	Glimepiride	Liraglutide	Sitagliptin
Mean dose				
1 year post-randomization	34.7 units/day	3.7 mg/day	1.6 mg/day	99.5 mg/day
4 years post-randomization	43.7 units/day	4.6 mg/day	1.7 mg/day	98.3 mg/day
Median dose				
1 year post-randomization	28 units/day	3 mg/day	1.8 mg/day	100 mg/day
4 years post-randomization	36 units/day	4 mg/day	1.8 mg/day	100 mg/day

The Grade Study Group NEJM 2022; 187: 1063-74

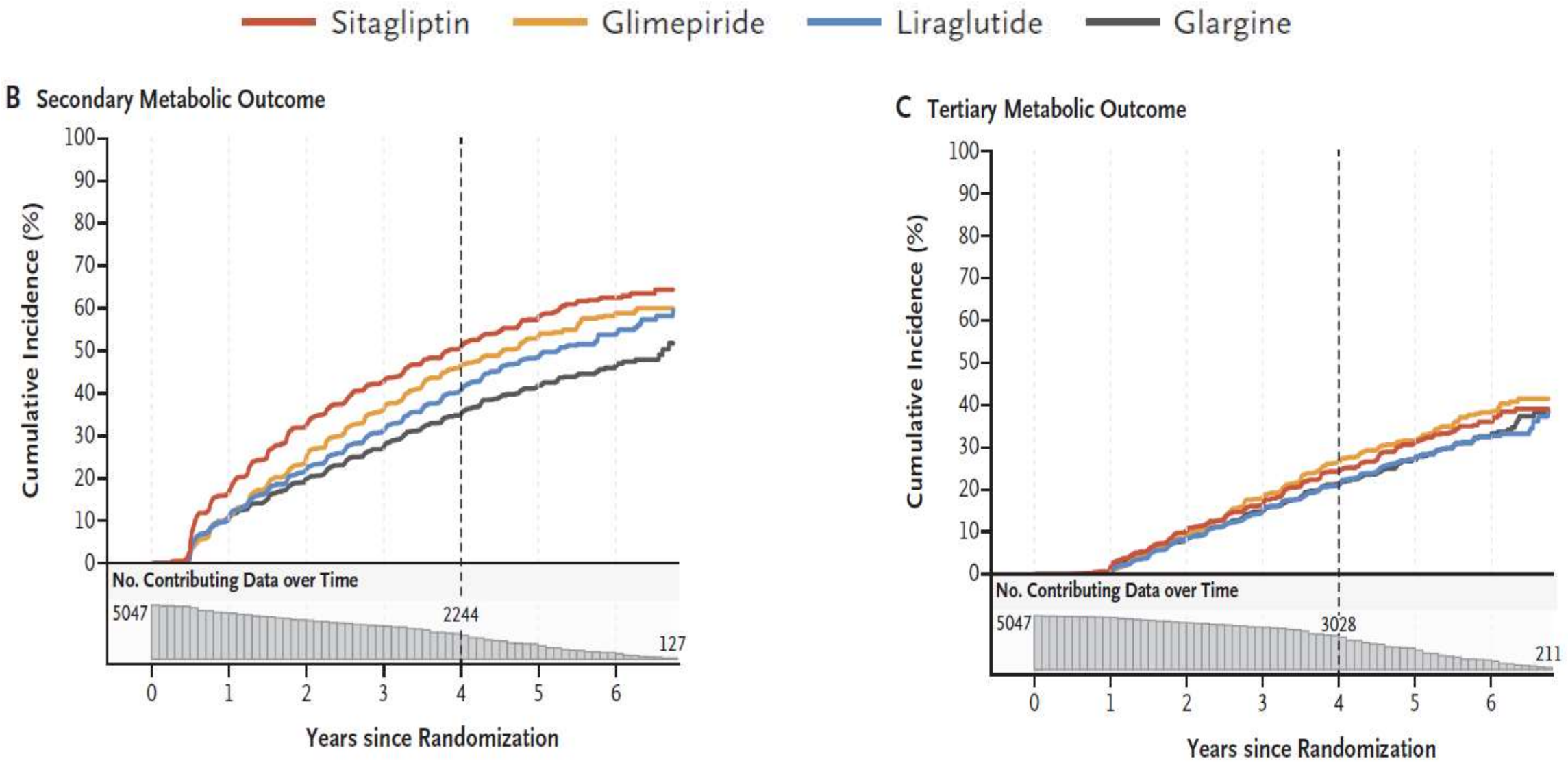
Progression to Secondary or Tertiary Outcomes



GRADE

The Grade Study Group NEJM 2022; 187: 1063-74

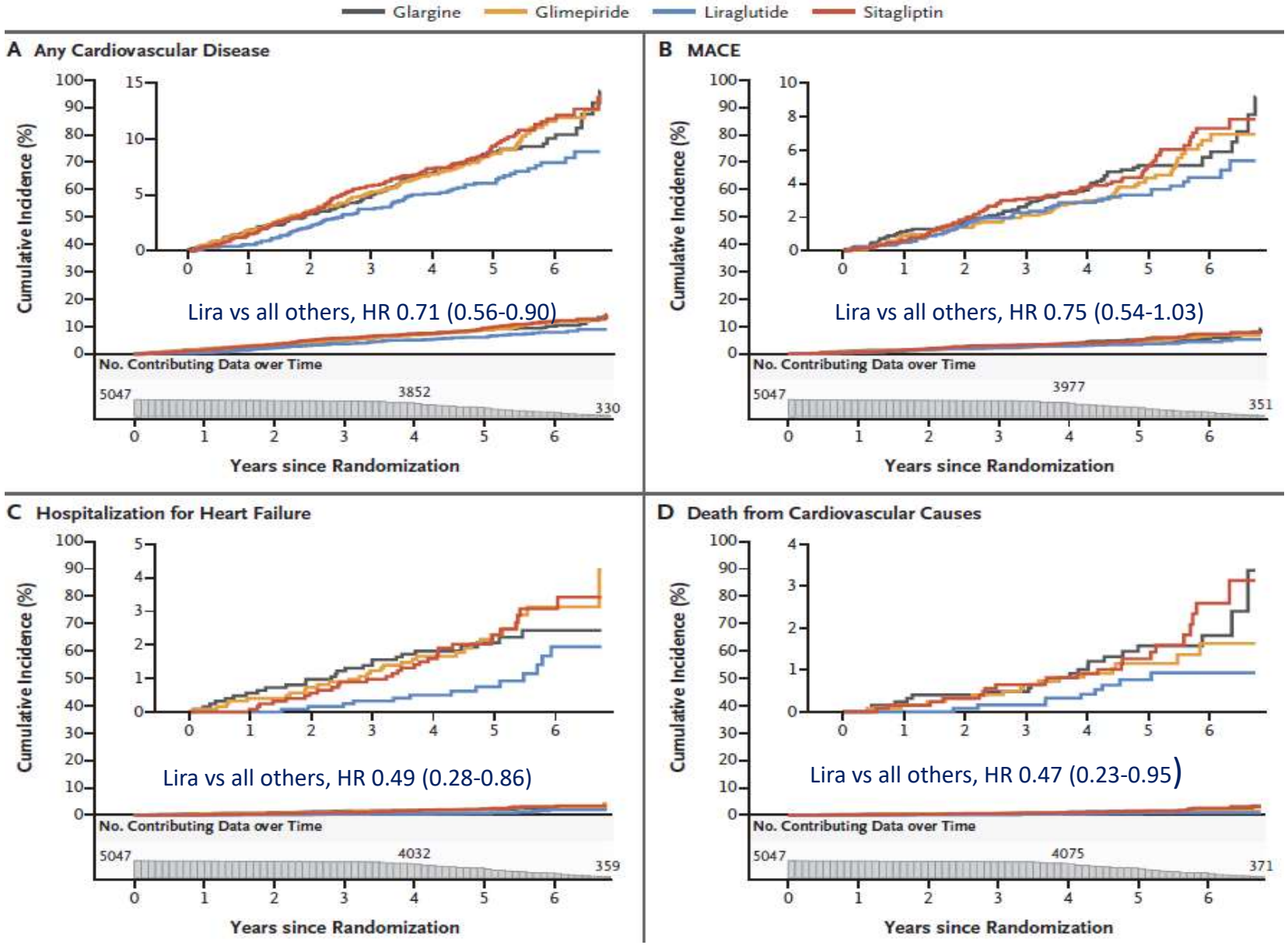
GRADE: Secondary and Tertiary Outcomes



The Grade Study Group NEJM 2022; 187: 1063-74

GRADE: Cumulative CV Events

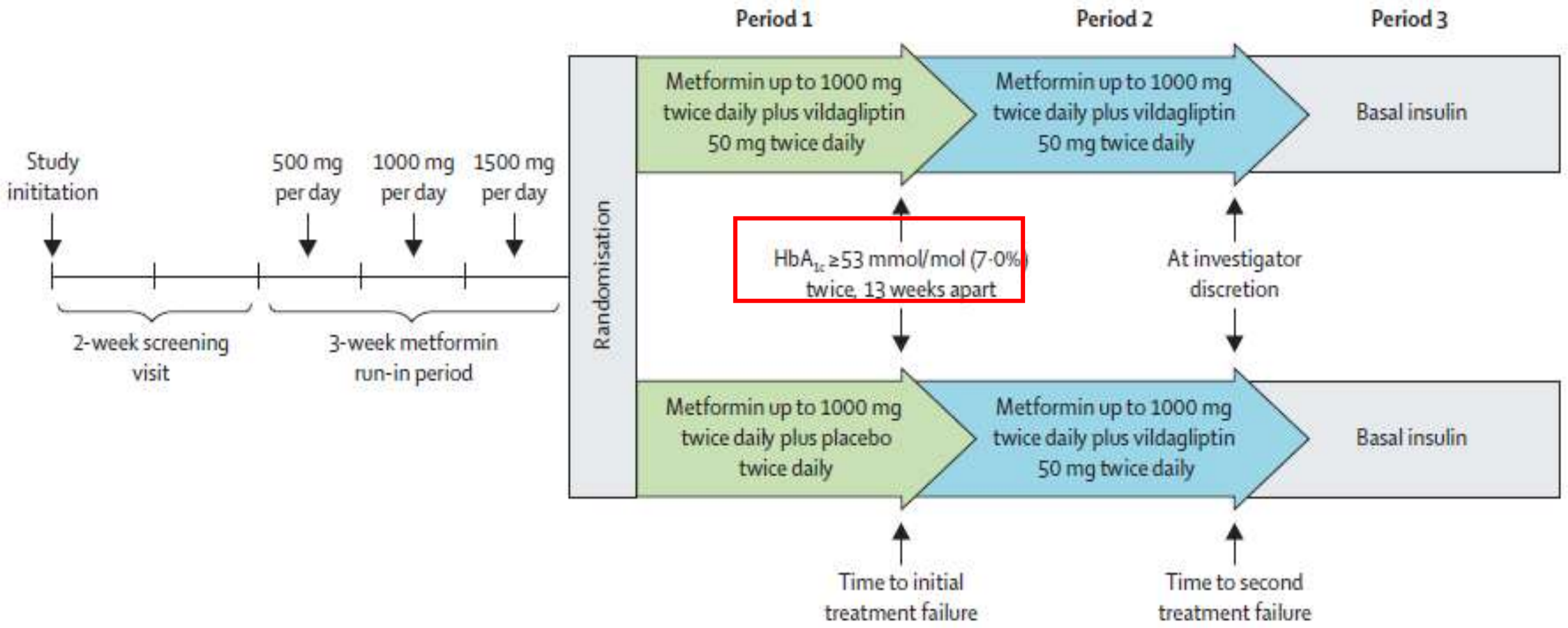
Clinical ASCVD at baseline: 6.6 %



The Grade Study Group NEJM 2022; 187: 1075-88

VERIFY: Early Combination vs Monotherapy

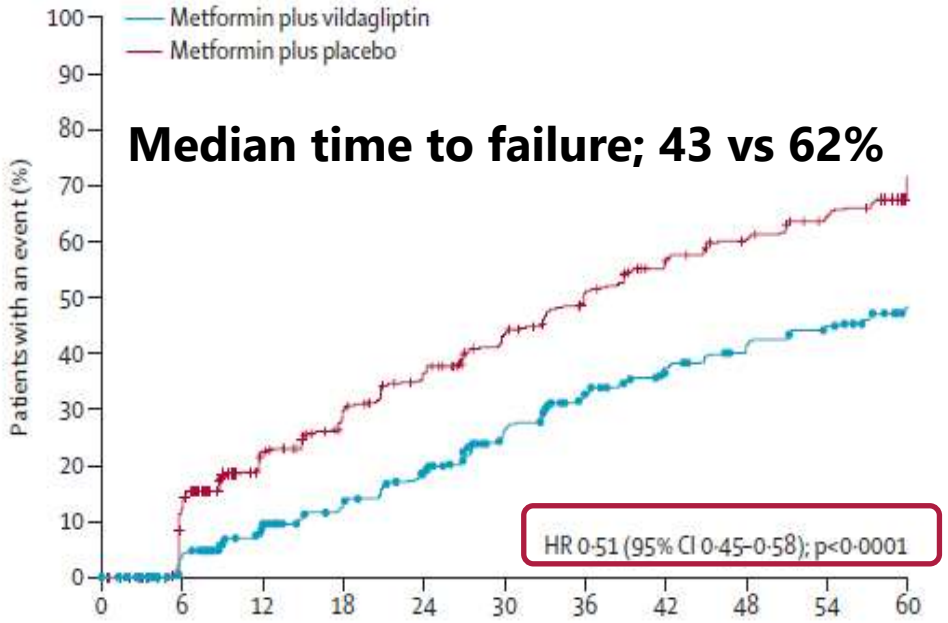
A multinational 5-year, RCT, comparing Early Combo with Met + Vildagliptin vs Metformin alone, n=2001



Matthews DR et al Lancet , 2019

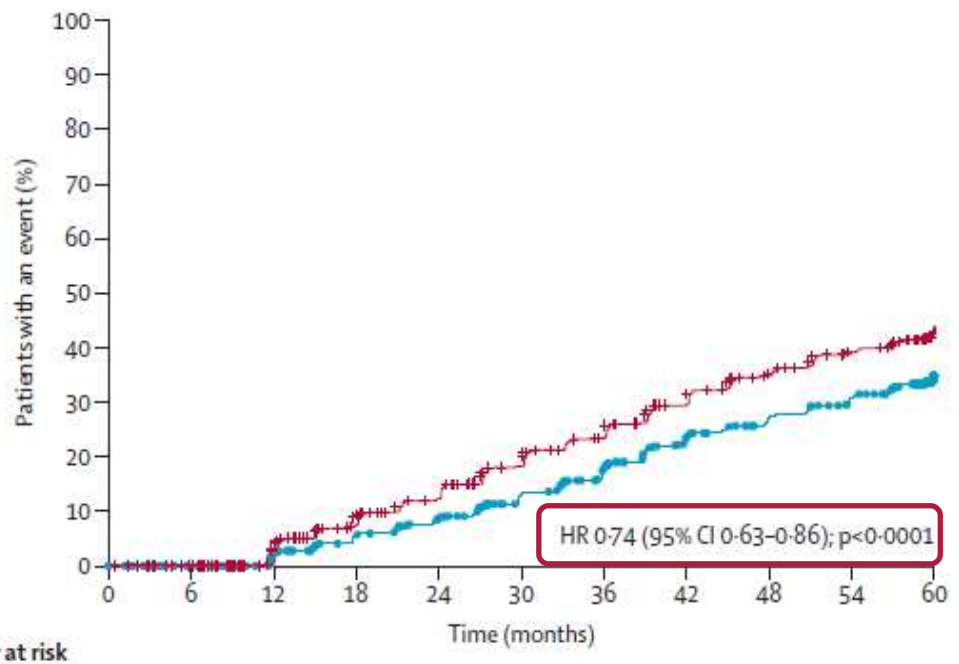
VERIFY: Early Combination vs Monotherapy

First Treatment Failure



Number at risk (number censored)											
Metformin plus vildagliptin	983	960	862	815	752	671	597	551	509	478	187
Metformin plus placebo	989	937	733	661	576	503	434	377	337	299	108

Second Treatment Failure



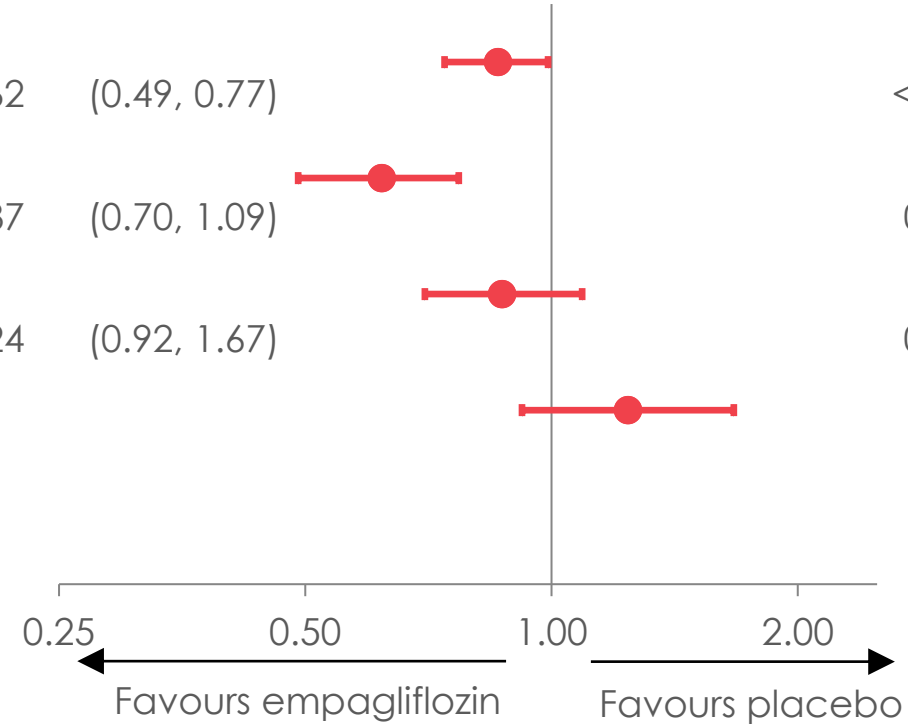
Number at risk (number censored)											
Metformin plus vildagliptin	983	966	918	870	830	768	715	644	602	565	221
Metformin plus placebo	989	968	897	821	761	698	643	575	531	490	179

Matthews DR et al Lancet , 2019

GLP1-RA: Preferred Agents for Prevention of Stroke ?

Empa- Reg: CV death, MI and stroke

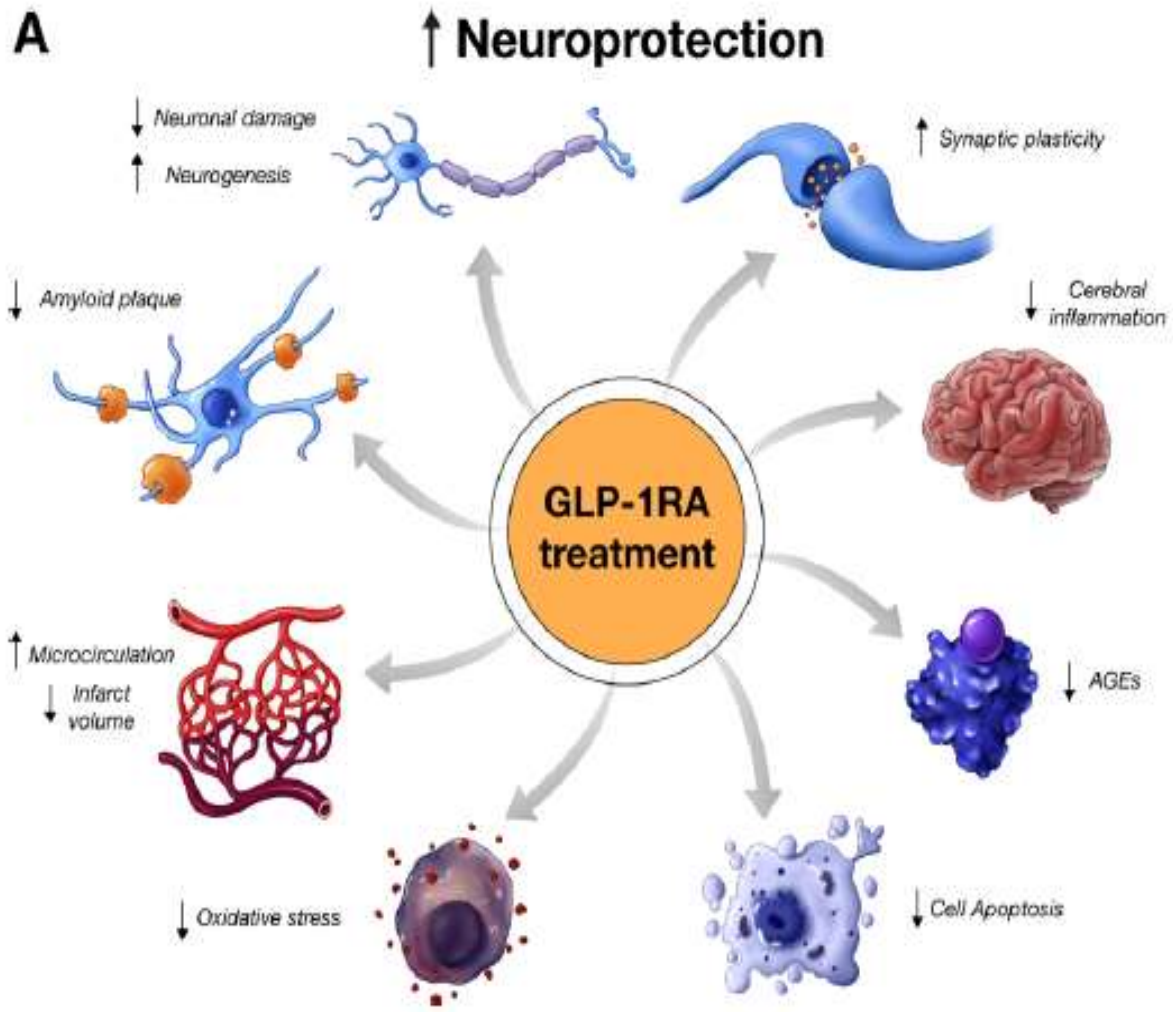
	Patients with event/analysed Empagliflozin	Placebo	HR	(95% CI)	*p*-value
3-point MACE	490/4687	282/2333	0.86	(0.74, 0.99)*	0.0382
CV death	172/4687	137/2333	0.62	(0.49, 0.77)	<0.0001
Non-fatal MI	213/4687	121/2333	0.87	(0.70, 1.09)	0.2189
Non-fatal stroke	150/4687	60/2333	1.24	(0.92, 1.67)	0.1638

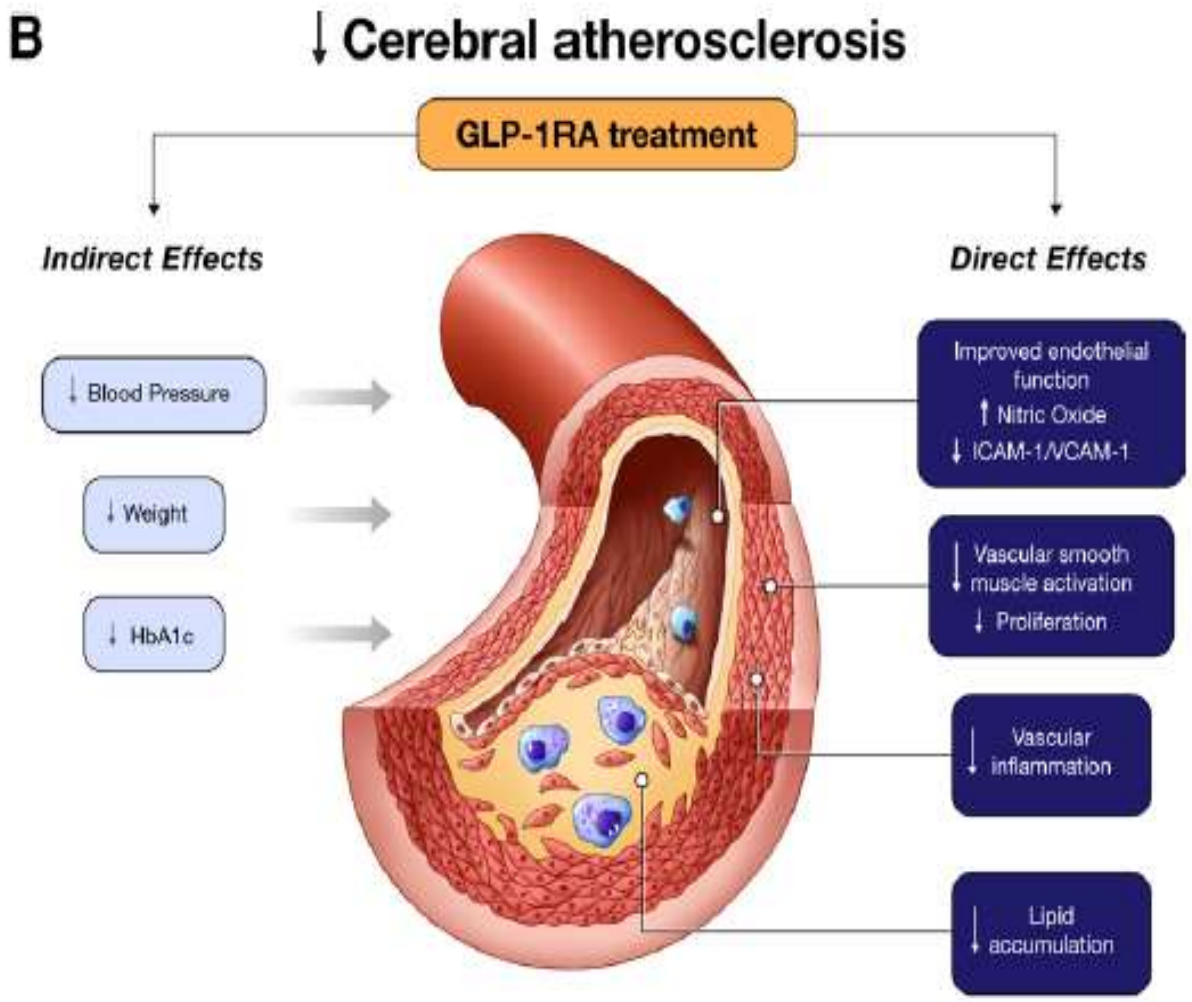


Cox regression analysis. MACE, Major Adverse Cardiovascular Event; HR, hazard ratio; CV, cardiovascular; MI, myocardial infarction
*95.02% CI

EMPA-REG OUTCOME®

GLP-1RAs: Postulated Mechanisms for Stroke Prevention

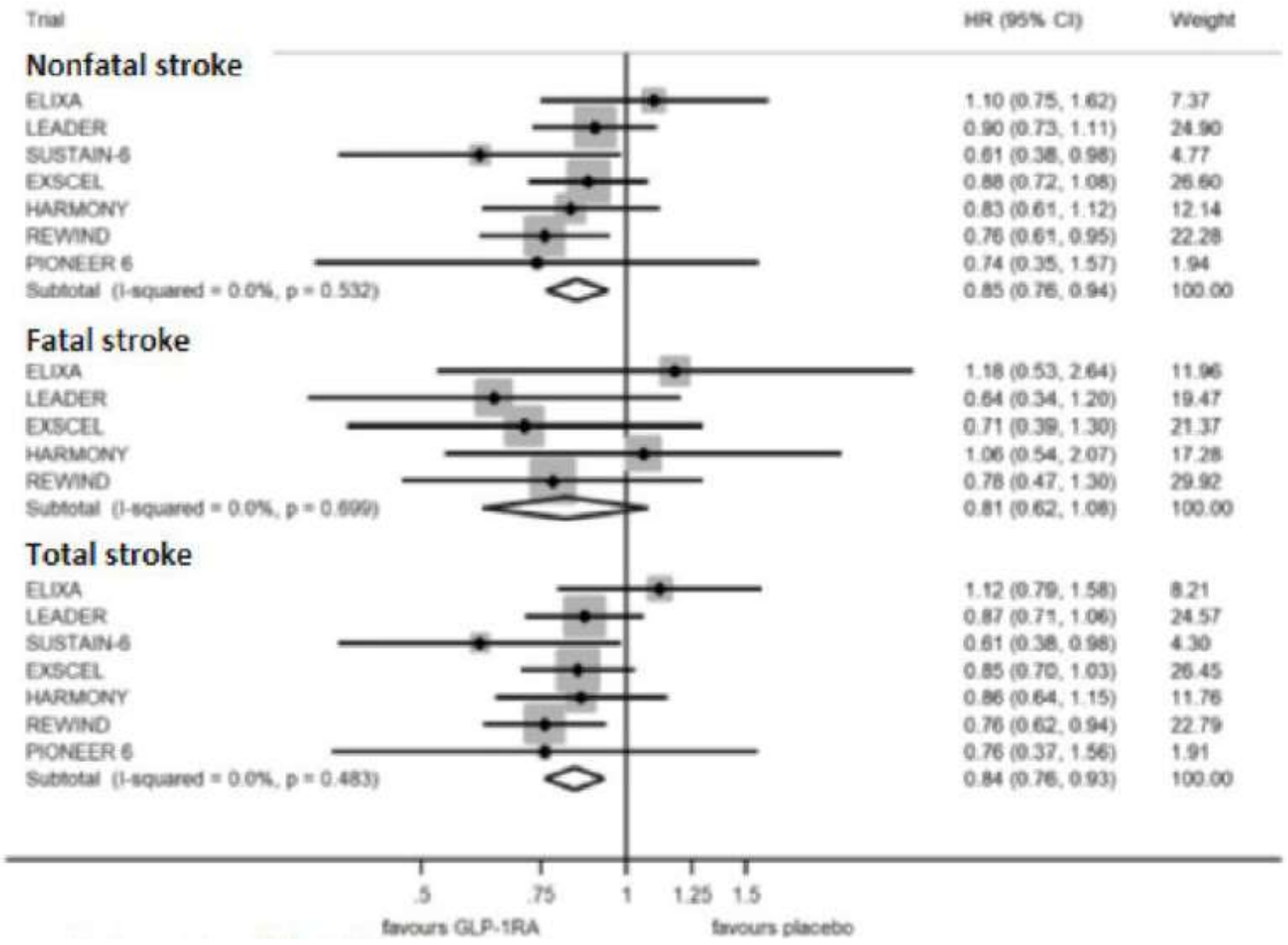




Goldenberg RM et al Stroke 2022

GLP1-RAs and Stroke Prevention: Meta-analysis

N=56,004; Seven RCTs



↓ 15%

↓ 19%

↓ 16%

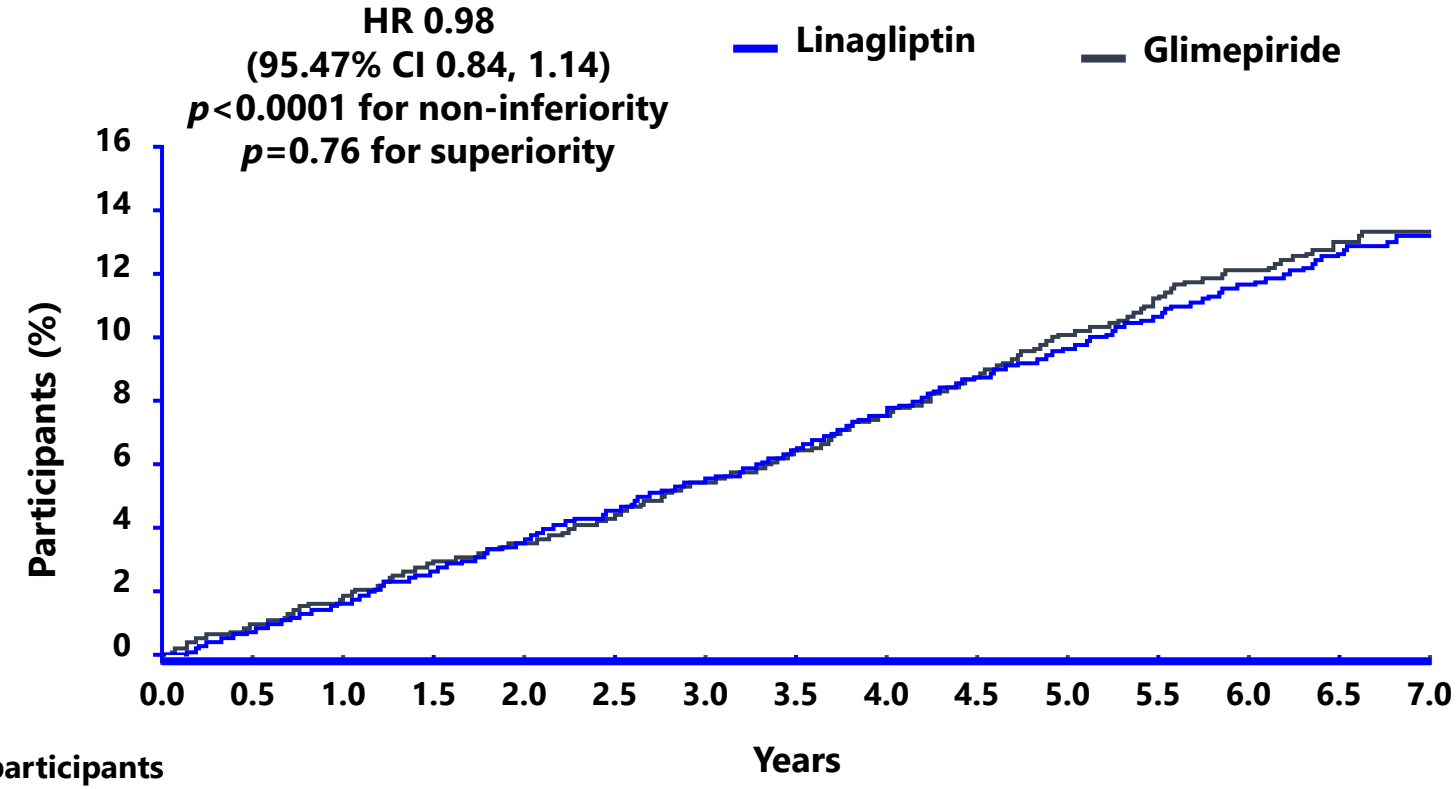
Bellastella, G et al
Stroke 2020; 51: 666-669

Several older drugs are still effective and safe in reducing glycemic burden, particularly in combination!

Are Sufonylureas associated with CV Injury?

CAROLINA: Primary Outcome

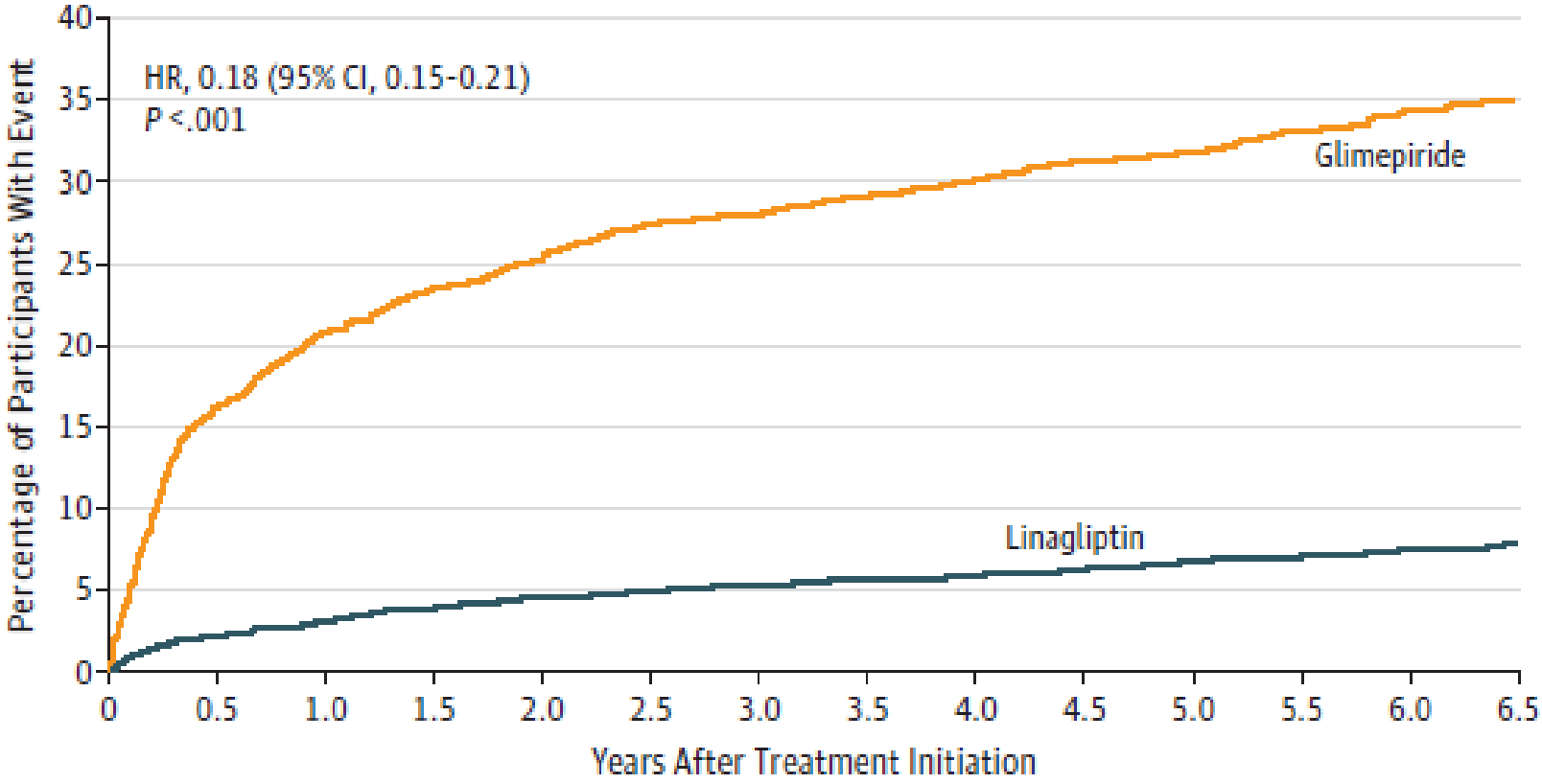
CV death, non-fatal myocardial infarction, or non-fatal stroke



No. of participants															
Linagliptin (n)	3023	2957	2901	2846	2803	2762	2725	2679	2627	2582	2534	2451	1830	1040	213
Glimepiride (n)	3010	2940	2890	2833	2797	2757	2710	2662	2618	2569	2509	2414	1865	1020	207

Rosenstock, J et al
JAMA 2019, Sept 19

CAROLINA: Moderate or severe Hypoglycemia



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

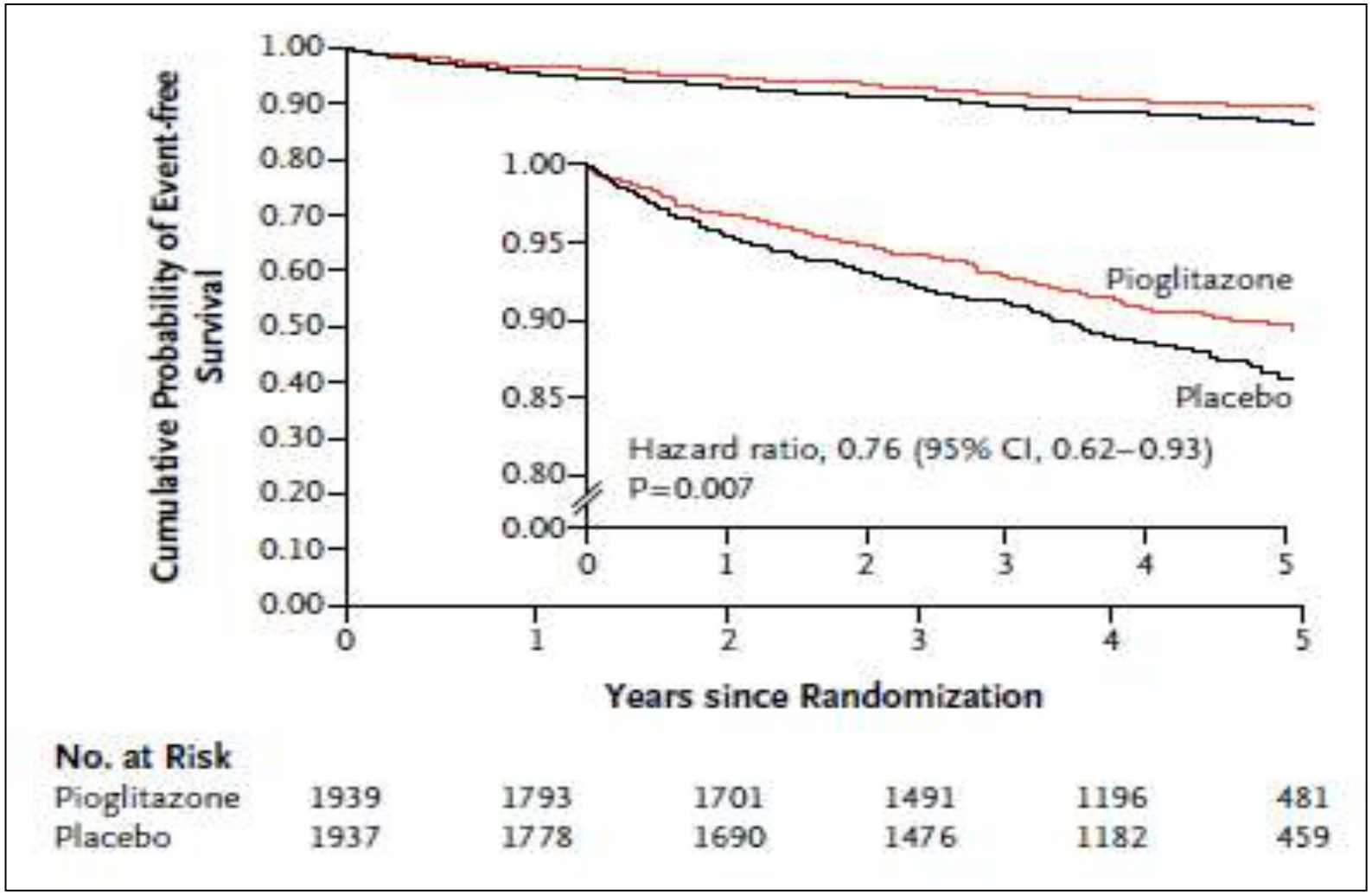
Rosenstock, J et al
JAMA 2019, Sept 19

Where do we stand now with TZDs: Still a Role in Patients with Insulin Resistance?

IRIS: Primary Outcomes: Fatal or non- fatal Stroke or MI

n= 3,876 patients with Insulin resistance (HOMA- IR > 3.0) and recent stroke or TIA

Cumulative Event-Free Survival Probability



Cumulative event rates:

Pio: 9.3 %
Placebo: 11.8 %

Kernan WN *et al. N Engl J Med*, published on-line Feb 17, 2016 DOI: 10.1056/NEJMoa1506930

PLACE OF INSULIN[1]

Consider immediate start of insulin

- Severe hyperglycaemia
- Acute glycaemic dysregulation
- When T1D is suspected

If not already on GLP-1 RA, consider use of GLP-1 RA

When not familiar with insulin use or when targets not reached, consider shared care with specialist team

Consider adding insulin when personalised HbA_{1c} targets are not met with strategies described in Fig. 4

- Maintain cardiorenal protective agents
- Maintain metformin, SGLT2i and GLP-1 RA to avoid weight gain and limit insulin dose and hypoglycaemia risk
- Consider using combination products of basal insulin/GLP-1 RA

Start using basal insulin* (10 U or 0.1–0.2 U/kg per day) at bedtime or more flexibility with timing for longer-acting analogues

Titrate to FPG target but avoid overbasalisation of insulin (consider introduction of CGM)

When FPG is on target but HbA1c or TIR is not

If not already on GLP-1 RA, consider use of GLP-1 RA

Intensify along the way and preferentially at each step

- Healthy behaviour
- Nutritional therapy
- DSMES: with additional focus on injection technique, hypoglycaemia, weight

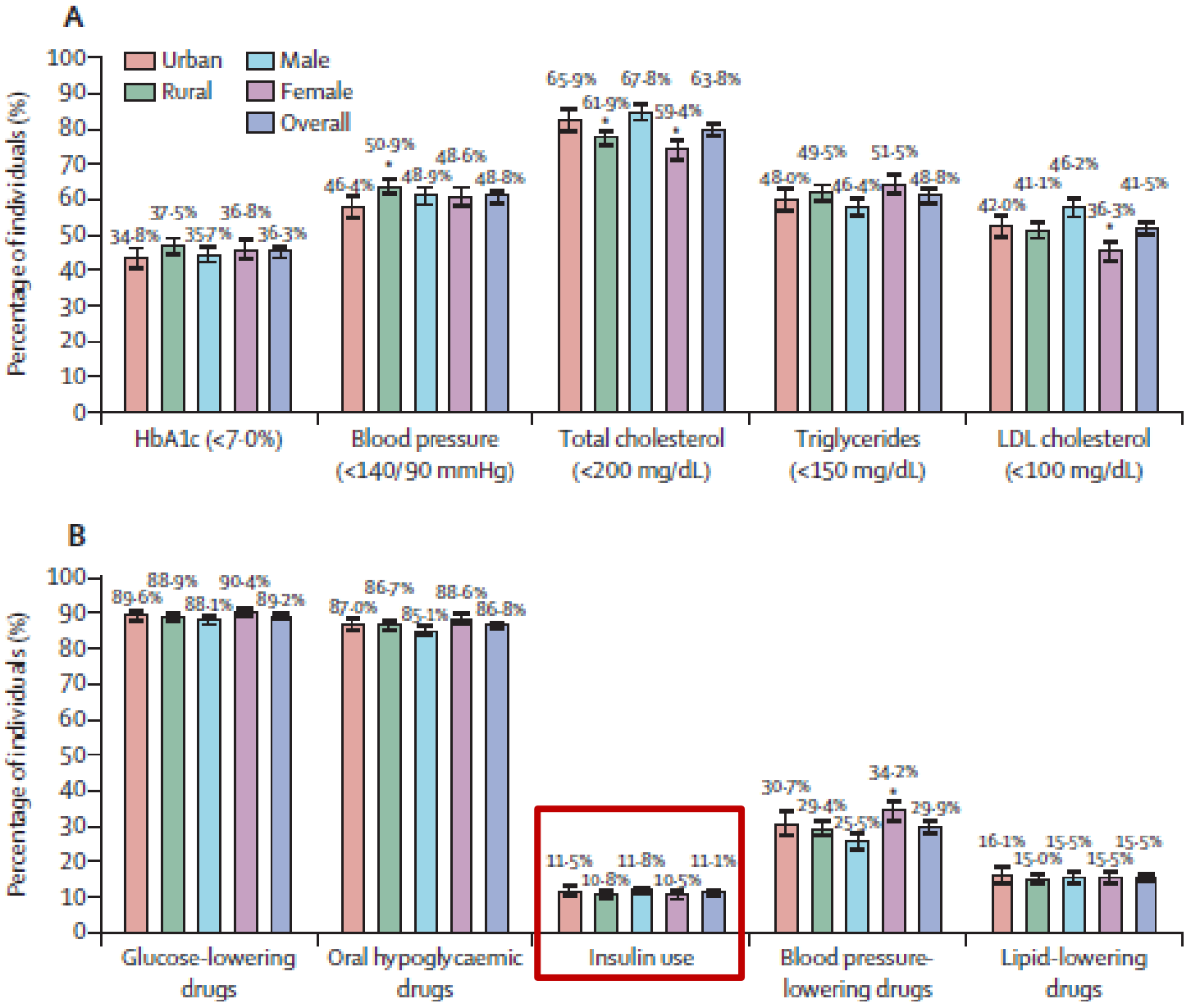
ADD MEALTIME INSULIN UNDER FORM OF:

- Basal plus (progressive addition of boluses)
- Premixed insulins
- MDI (multiple daily injections)

Data from India: ICMR-INDIAB

2008-2020
N=5,789,
self- reported DM
Urban and Rural
Mean age 56.1 Yr,
Duration 4.9 yr

ABC targets achieved
7.7%



Anjana RM et al Lancet D/E , April 2022

Conclusions

- Type 2 DM is a heterogenous disorder, requiring personalized approach
- For secondary intervention to reduce ASCVD and CKD burden, the recent trials have established a novel paradigm
- For primary prevention, Metformin, SU, and TZDs are useful options, but early glycemic control with combination therapy is the key
- The “traditional” Anti-hyperglycemic drugs are here to stay!