Treatment Options in Diabetes and Hyperlipidemia and CV Risk Reduction

St. Dominic’s NeuroCardio CME

Ben W. Seale, MD - April 27, 2024

Disclosures

I currently speak on behalf of:

Abbvie

Eli-Lilly

NovoNordisk

Objectives

1. To Improve awareness of up-to-date guidelines in the management of diabetes and hyperlipidemia

2. To ensure emphasis on treatment options that provide specific demonstrable benefit with regards to reduction in cardiovascular risk

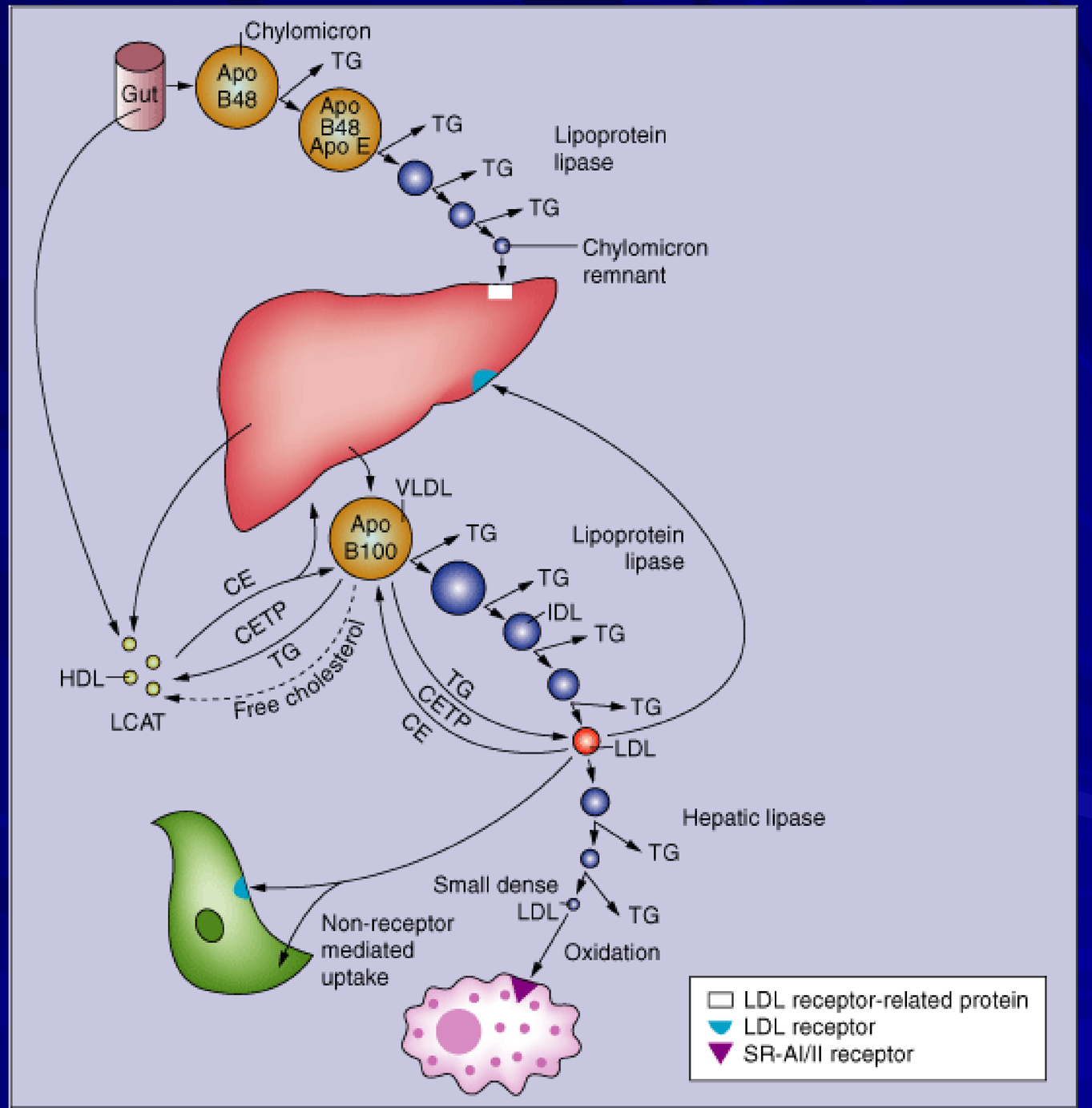
3. To improve the percentage of patients who have modifiable cardiovascular risk factors at recommended targets

The Holy Trinity

The Holy Trinity

The Holy Trinity

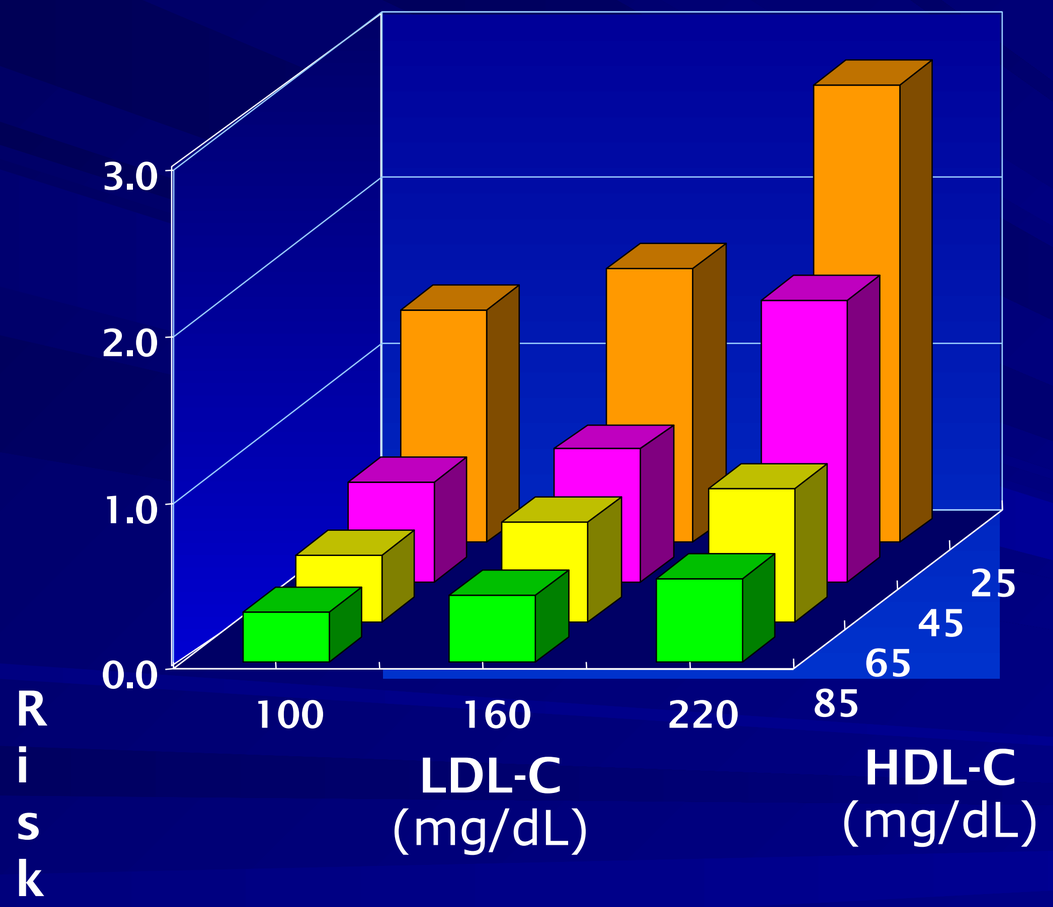
Metabolism of chylomicrons, VLDL, IDL and LDL



LDL

CV Risk: LDL-C and HDL-C

Data From Framingham Study



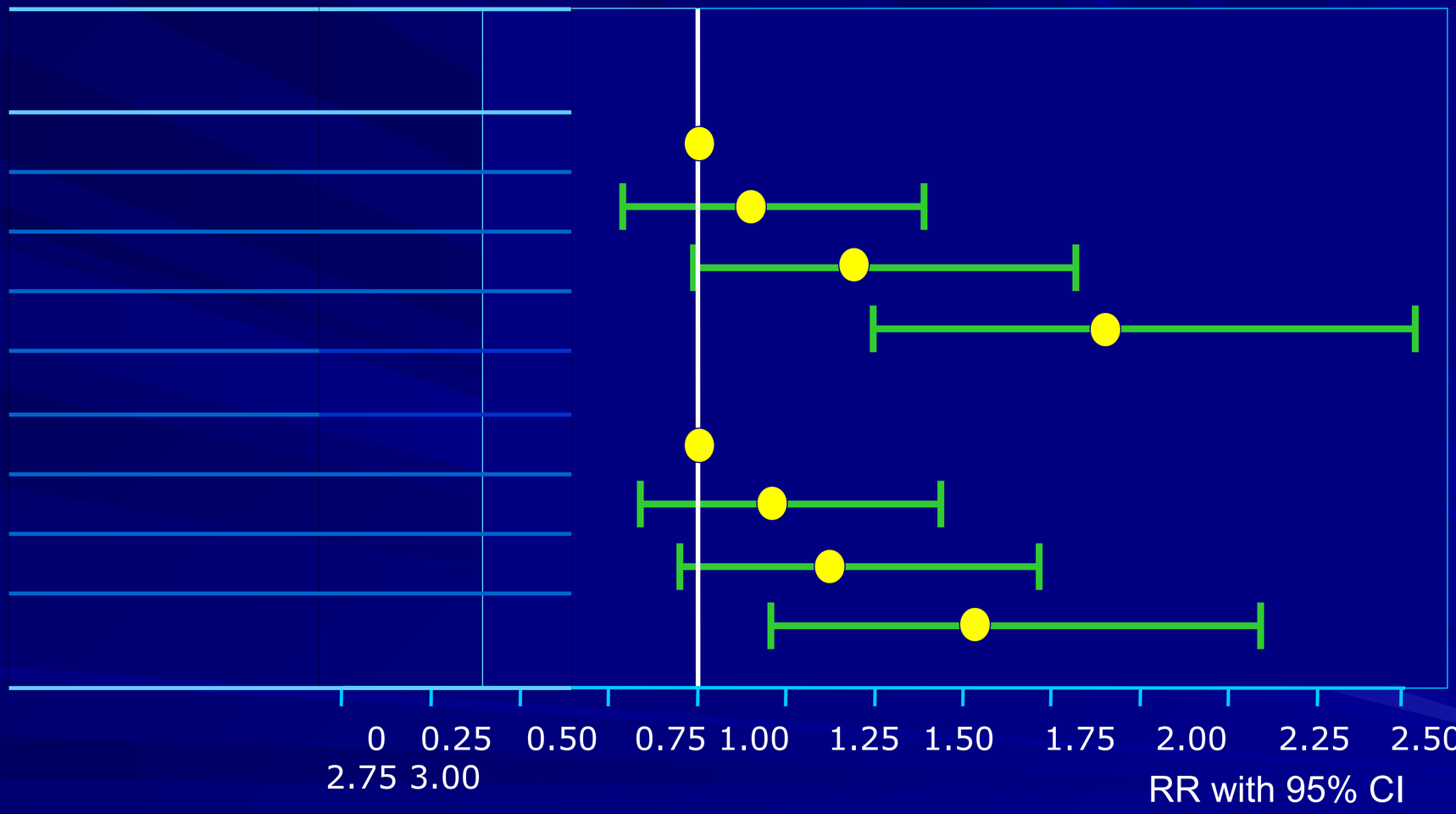
For any level of LDL-C, HDL-C is inversely related to CHD risk

Rule of 1's

For every 1% shift in HDL-C or LDL-C, event rates are ~1% lower

Gordon T et al. *Am J Med* 1977;62:707-714.

LRC Follow-up Study: *CVD Mortality by Non-HDL-C and LDL-C in Men*



LRC = Lipid Research Clinics; RR = Relative risk; CI = confidence interval.

Cui Y et al. *Arch Intern Med* 2001;161:1413-1419.

LDL – Lowering Drugs

Bile Acid Sequestrants: ↓ 15-30%

Fibrates: ↓ 5-20%

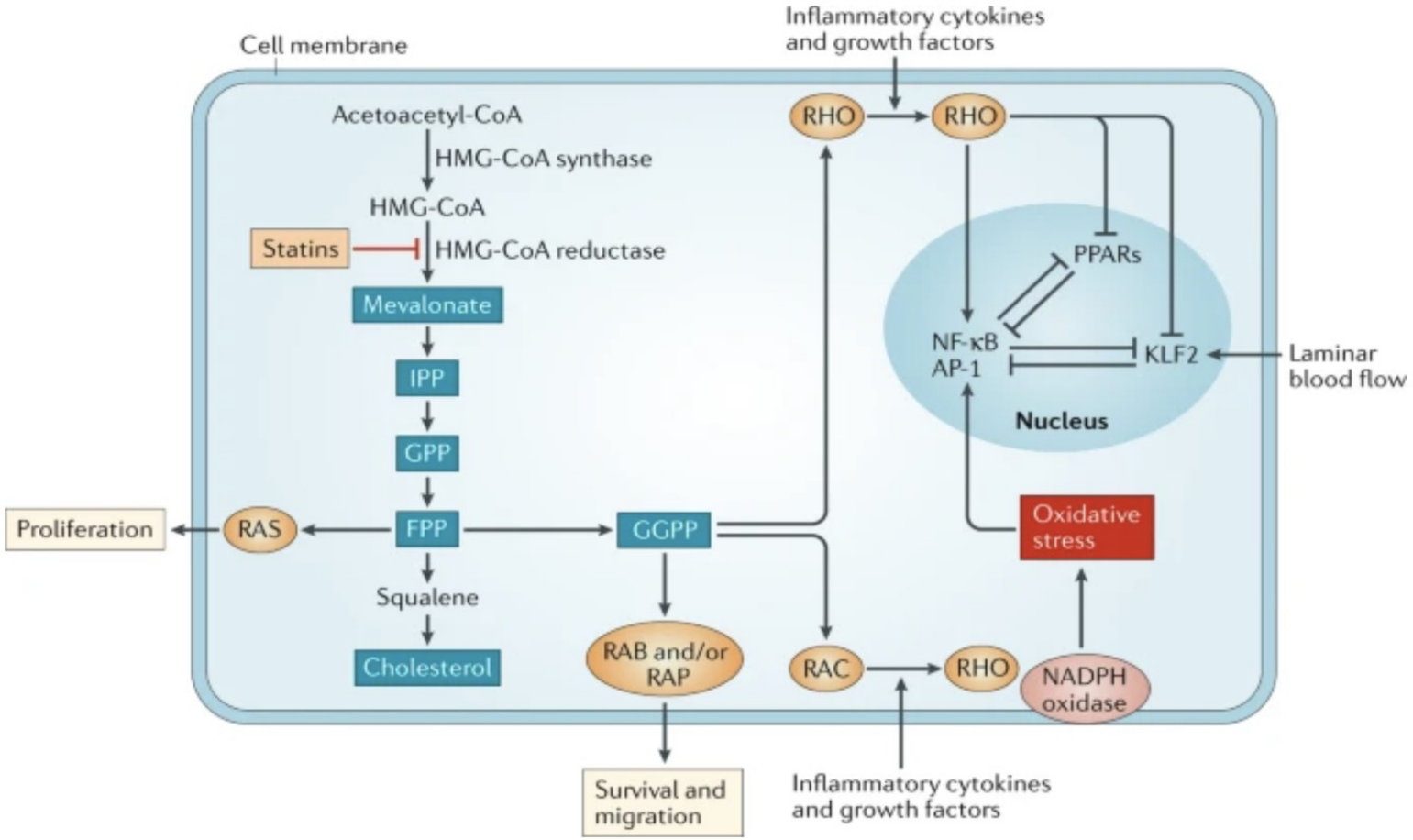
Nicotinic Acid: ↓ 5-25% (≥ 1,000 mg/day)

HMG CoA reductase inhibitors: (Statins)
↓ 18-55%
Rosuvastatin > Atorvastatin > Simvastatin >
Lovastatin, Pravastatin, Fluvastatin

Ezetimibi: Up to 30%

STATINS

Fig. 1: The effect of statins on cellular processes.

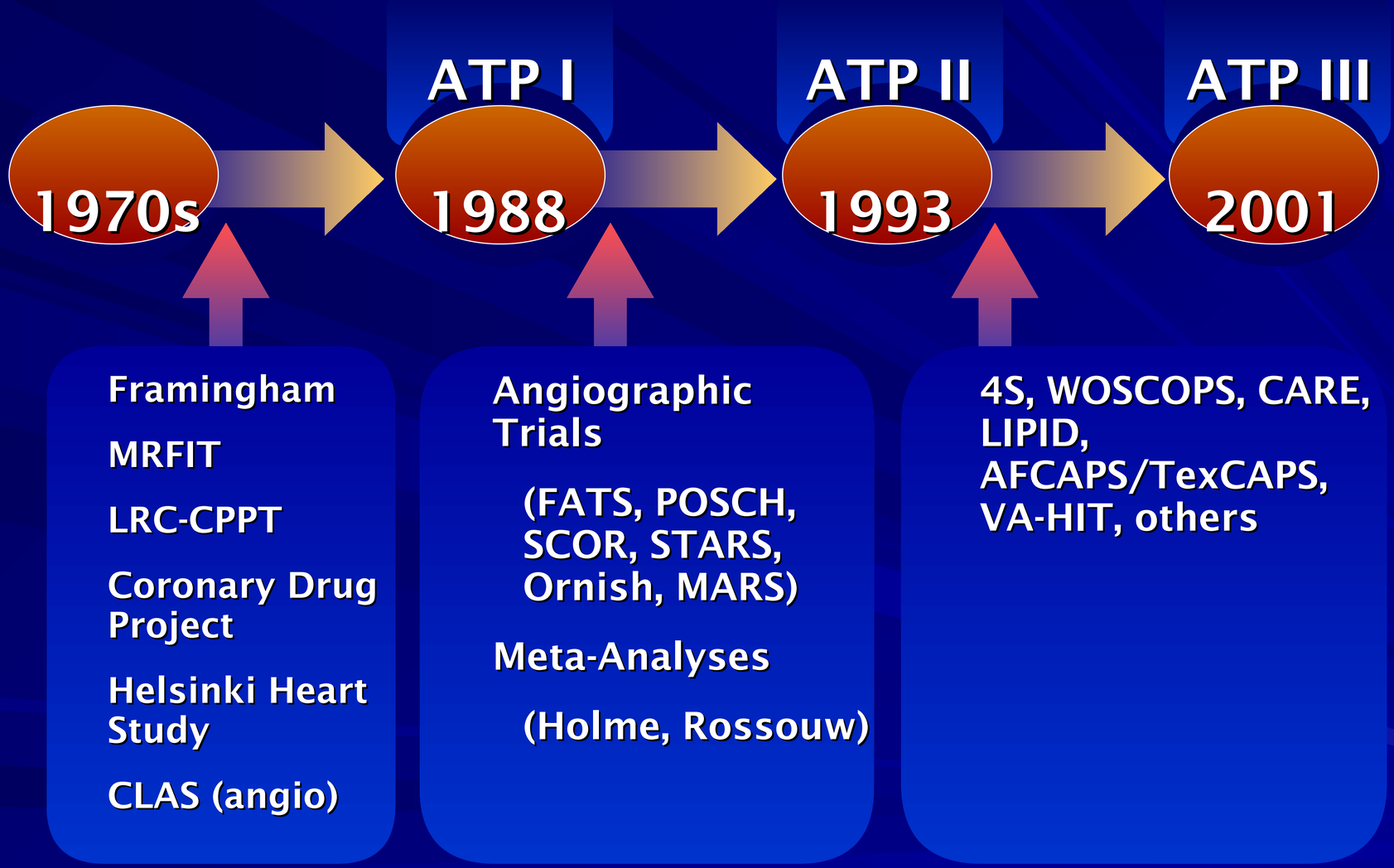


Major Initial Statin Trials

Updated ATP III LDL-C Goals and Cutpoints for Therapy

Grundy SM et al. *Circulation*

Evolution of the NCEP Guidelines



Post–ATP III Clinical Trials

HPS (simvastatin 40)

PROSPER (pravastatin 40)

ALLHAT-LLT (pravastatin 40)

ASCOT-LLA (atorvastatin 10)

PROVE IT (pravastatin 40 vs. atorvastatin 80)

HEART PROTECTION STUDY

The Lancet, July 6, 2002 and June 14, 2003

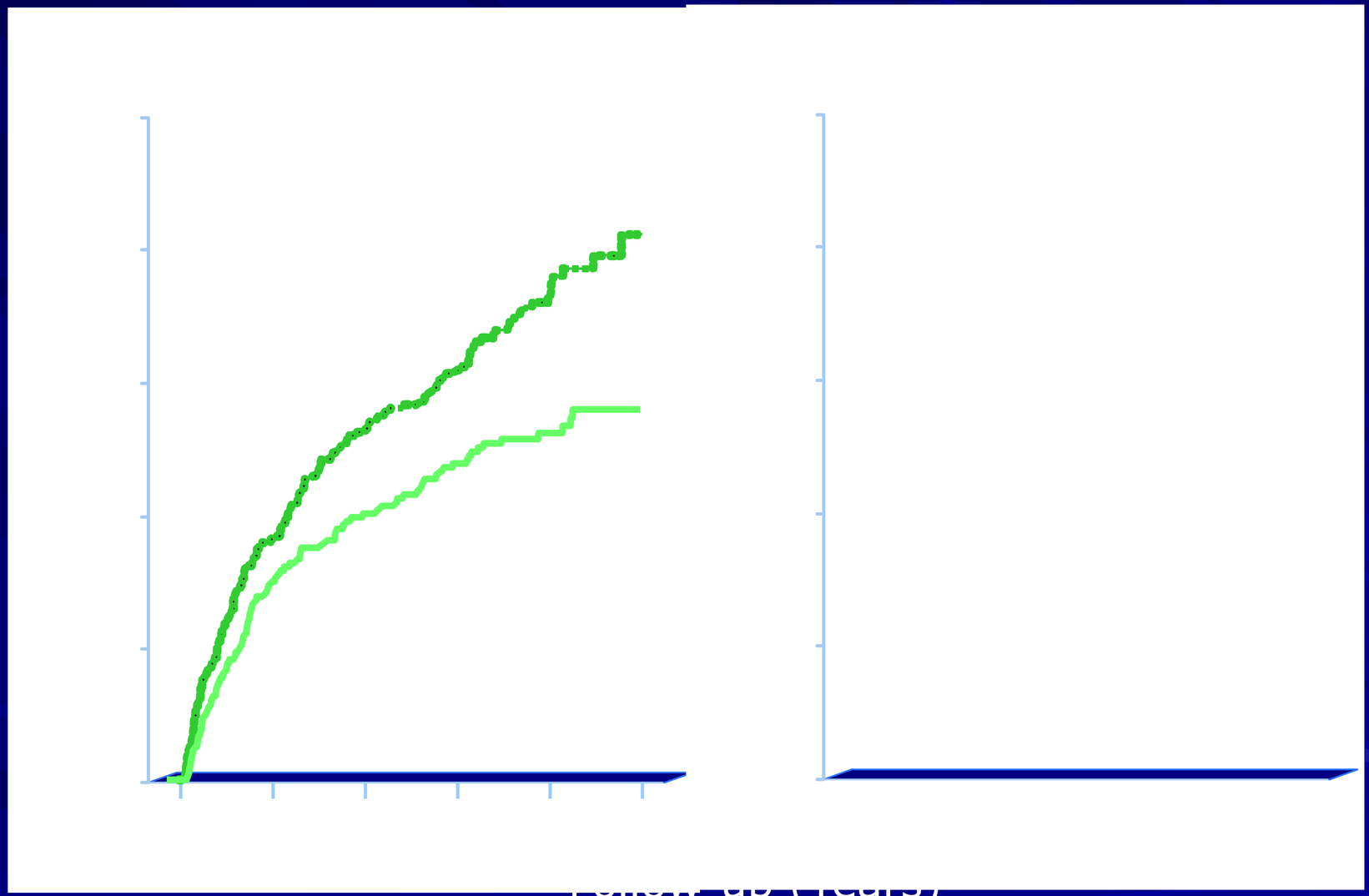
14, 573 patients with CAD (5,963 with DM)

Looked at those whose LDL started <116

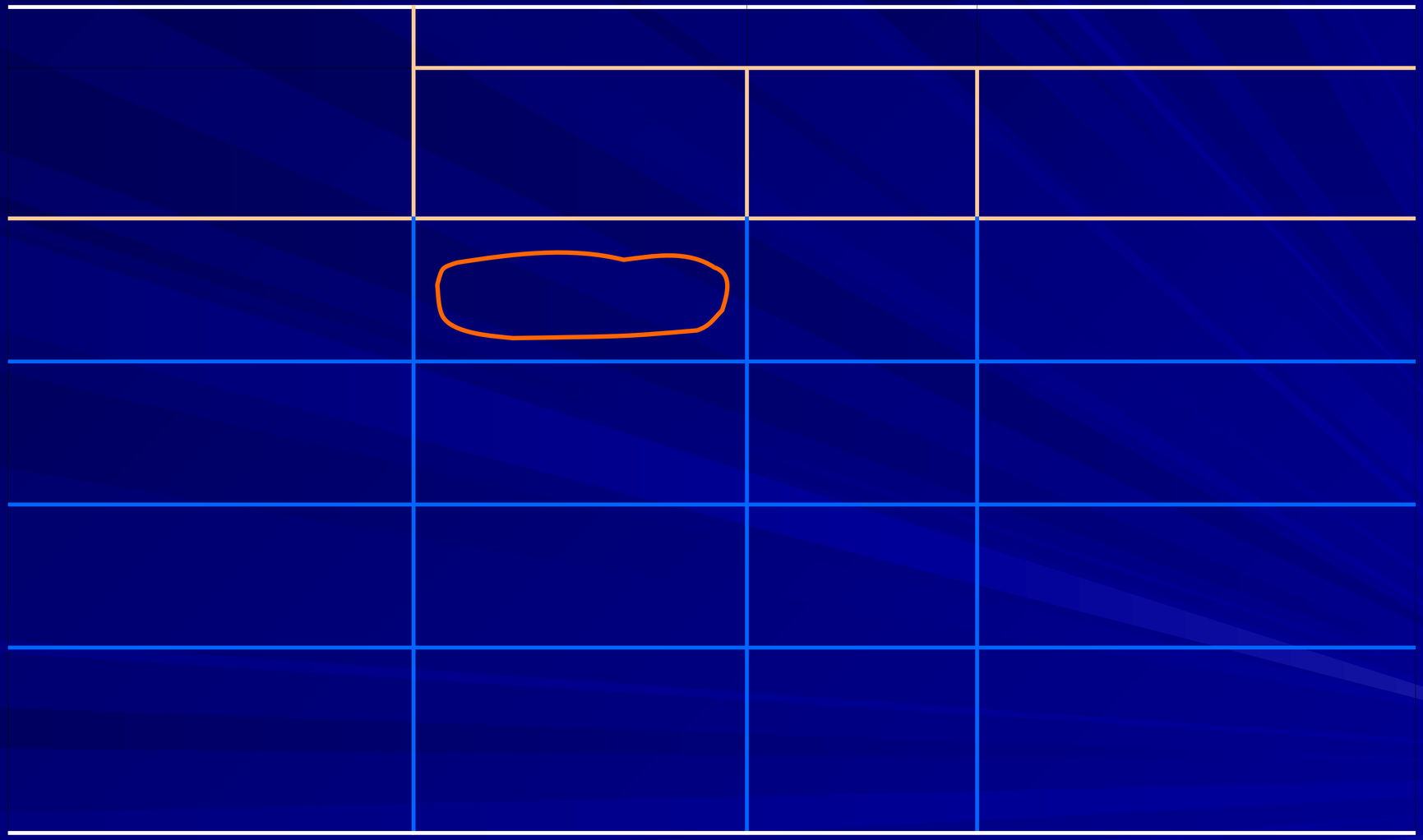
- LDL < 77 mg/dL showed ~25% RR red. in CV death
- Subsequent paper looked at DM vs. non-DM pts.
  - Diabetics had major risk reduction with LDL < 77
  - Non-diabetics had RR red. that was borderline with LDL < 77
- Lower range of those who benefited was 70 mg/dL

So, diabetics with CAD benefited clearly from LDL reduction to at least < 77, perhaps < 70

Incidence of Recurrent MI or CHD Death according to Achieved LDL-C or CRP Levels: PROVE IT–TIMI 22



Updated ATP III LDL-C Goals and Cutpoints for Therapy

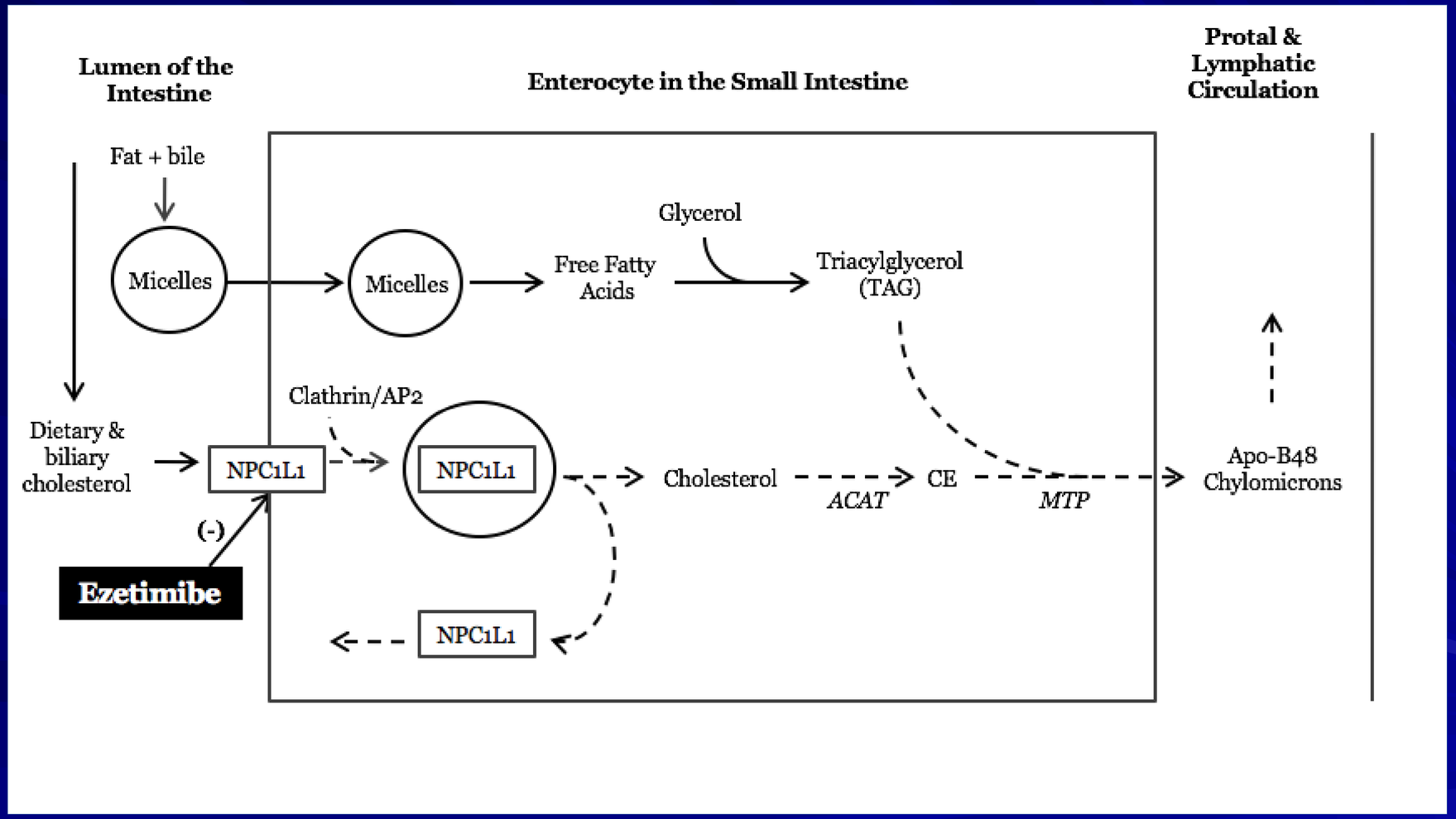


Grundy SM et al. *Circulation*

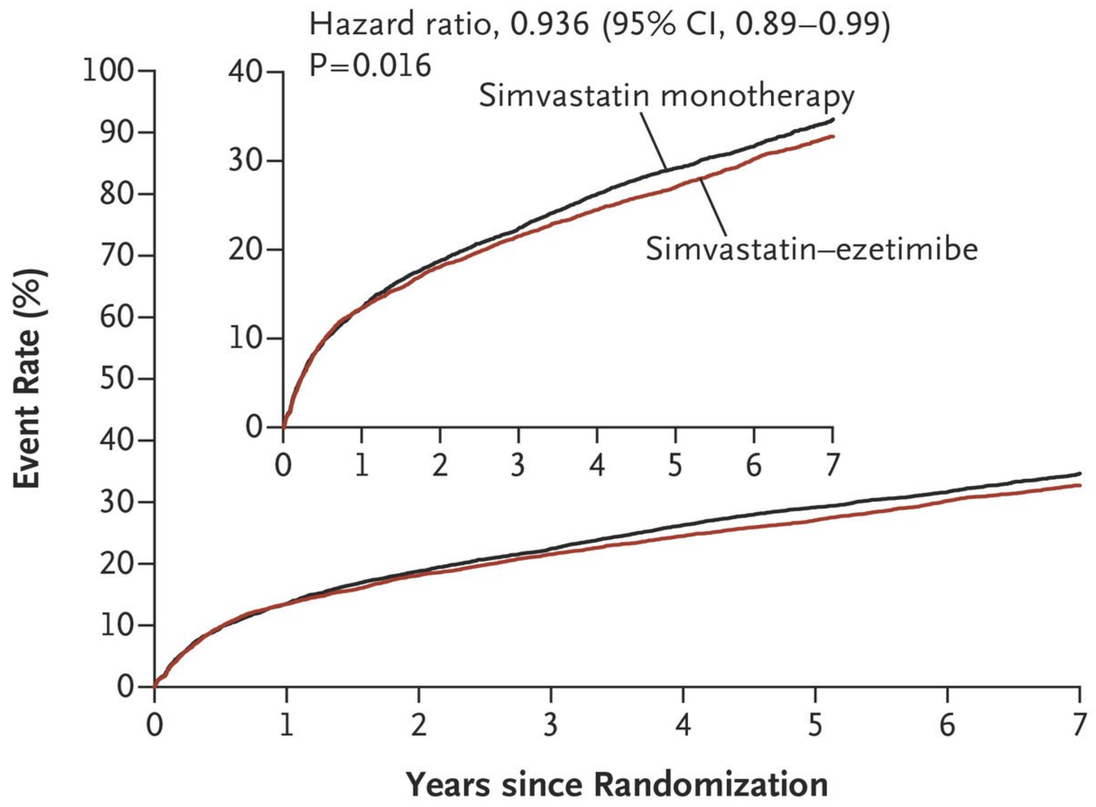
STATINS

Statin equivalent dosages						
% LDL reduction (approx.)	Atorvastatin	Fluvastatin	Lovastatin	Pravastatin	Rosuvastatin	Simvastatin
10–20%	–	20 mg	10 mg	10 mg	–	5 mg
20–30%	–	40 mg	20 mg	20 mg	–	10 mg
30–40%	10 mg	80 mg	40 mg	40 mg	5 mg	20 mg
40–45%	20 mg	–	80 mg	80 mg	5–10 mg	40 mg
46–50%	40 mg	–	–	–	10–20 mg	80 mg*
50–55%	80 mg	–	–	–	20 mg	–
56–60%	–	–	–	–	40 mg	–
* 80 mg dose no longer recommended due to increased risk of rhabdomyolysis						

Ezetimibe

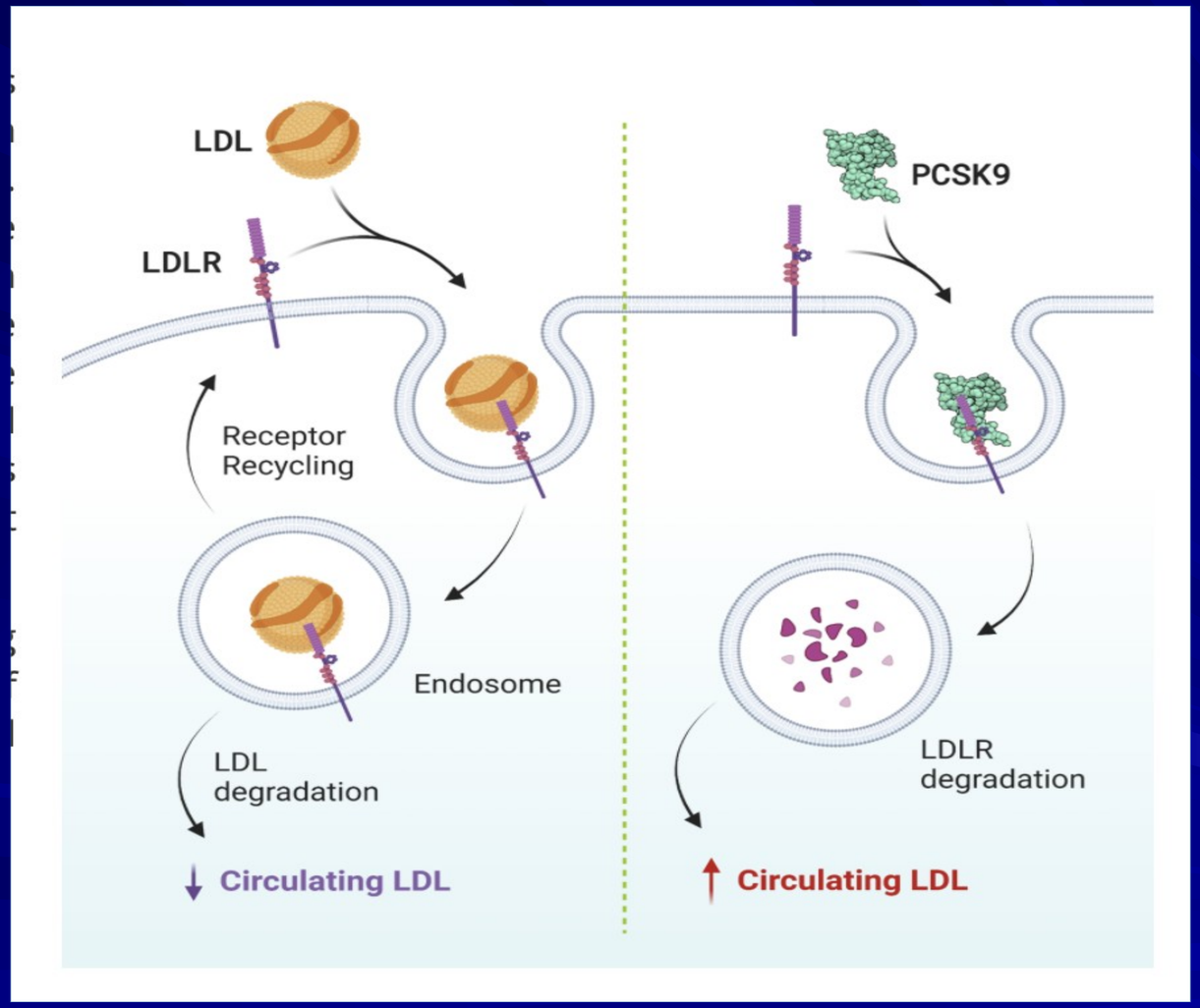

Lumen of the Intestine
Enterocyte in the Small Intestine
Protal & Lymphatic Circulation
Fat + bile
Micelles
Micelles
Free Fatty Acids
Glycerol
Triacylglycerol (TAG)
Clathrin/AP2
Dietary & biliary cholesterol
NPC1L1
NPC1L1
Cholesterol
ACAT
CE
MTP
Apo-B48 Chylomicrons
(-)
Ezetimibe
NPC1L1

IMPROVE-IT



No. at Risk								
Simvastatin–ezetimibe	9067	7371	6801	6375	5839	4284	3301	1906
Simvastatin	9077	7455	6799	6327	5729	4206	3284	1857

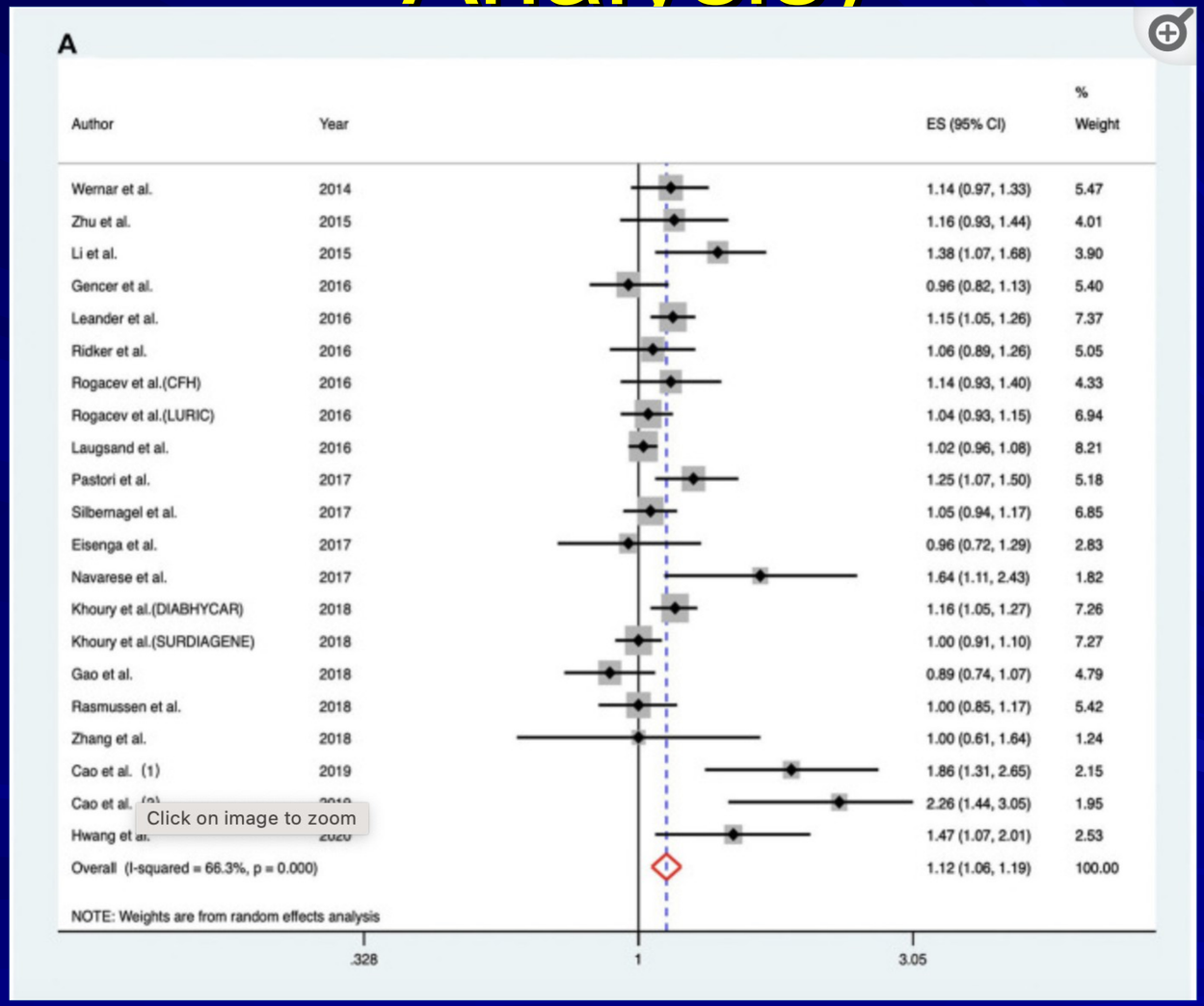
PCSK-9


LDL
LDLR
Receptor
Recycling
Endosome
LDL
degradation
Circulating LDL
PCSK9
LDLR
degradation
Circulating LDL

PCSK-9

- Discovered in 2003
- Montreal Clinical Research Institute (Canada)
- Chromosome 1
- Expressed primarily in liver, kidney, and intestine
- GOF mutation in French family with FH
  - Very high cholesterol
  - High incidence of CVD
- Dallas Heart Study, LOF mutation in AA family
  - Very low cholesterol
  - Markedly reduced incidence of CVD

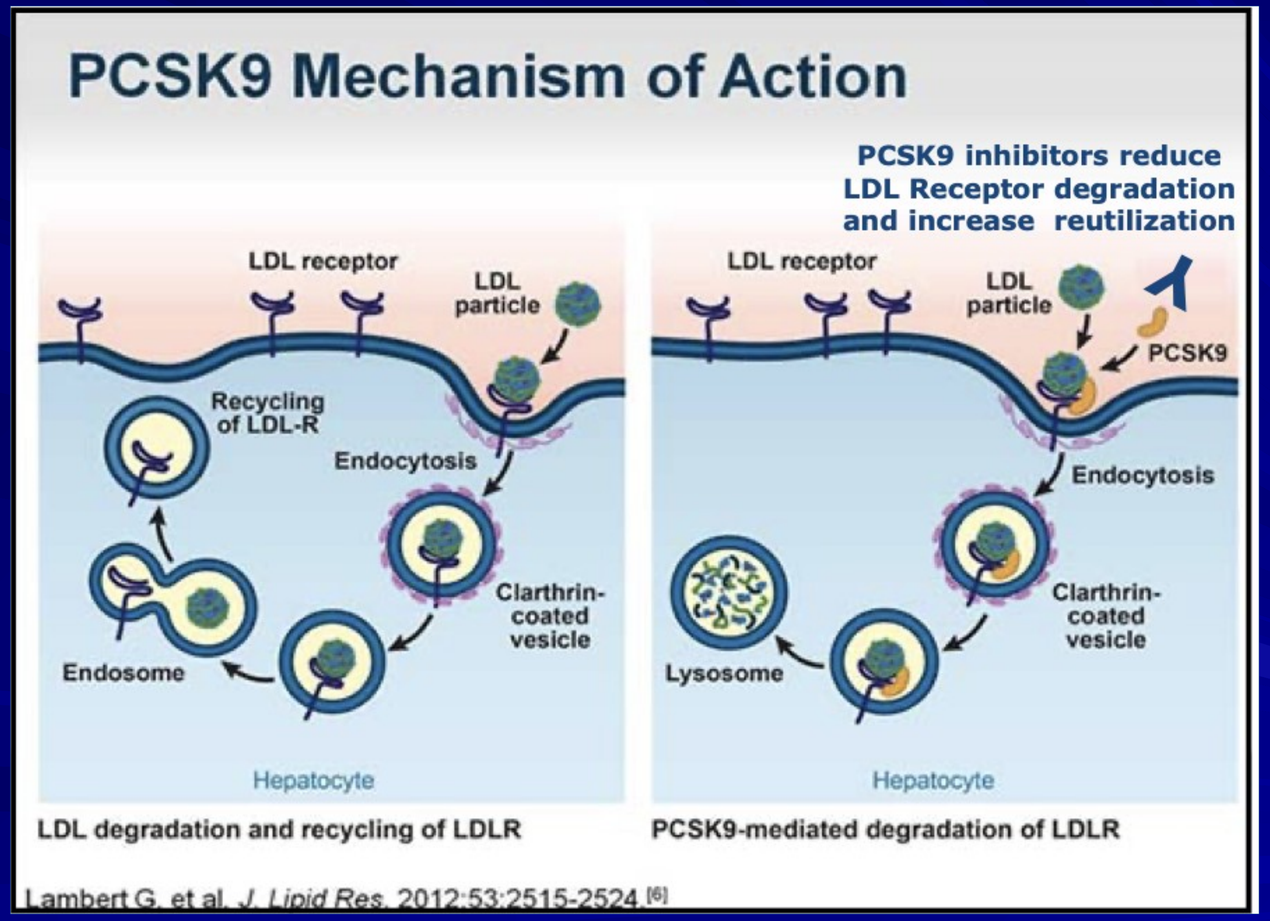
Yimo Zhou, et. al (Meta Analysis)



PCSK-9 Inhibition

- First available in 2015
- Monoclonal Antibodies
  - Alirocumab (Praluent)
  - Evolocumab (Repatha)
- Nucleic Acid Drugs
  - Antisense Oligonucleotides (ASO's)
  - Inclisiran (Leqvio)

PCSK-9 Inhibitors



Praluent (alirocumab)

- **Indication**: Adjunct to diet and maximally-tolerated statin therapy in:
  - HeFH
  - ASCVD
  - Reduction in risk of MI, CVA, UA requiring hospitalization
- **Dosage**: 75mg SQ every 14 days (may be increased to 150mg)
- **Dosage forms**: 75 mg/mL or 150 mg/mL
  - Auto-injector
  - Pre-filled syringe

Alirocumab Clinical Trials

Study	Patient Population (Maximally tolerated statin ± lipid-lowering therapy, LDL not at goal)	Intervention	Mean LDL Change from Baseline at Week 24
FH I & FH II (n=735)	HeFH (45% ASCVD) Mean baseline LDL: 141 mg/dL	• Alirocumab 75 mg every 14 days vs. placebo	-51% versus +3% with placebo (p<0.0001)
COMBO I (n=316)	Hyperlipidemia (84% ASCVD) Mean baseline LDL: 102 mg/dL	• Alirocumab 75 mg every 14 days vs. placebo	-48% versus -2% with placebo (p<0.0001)
ODYSSEY LONG TERM (n=2,341)	HeFH and/or ASCVD (69% ASCVD only and 18% HeFH only) Mean baseline LDL: 122 mg/dL	• Alirocumab 150 mg every 14 days vs. placebo	-62% versus +1% with placebo (p<0.0001)

ODYSSEY LONG TERM
Post Hoc Analysis

Cardiovascular Event	Placebo (%)	Alirocumab (%)	P-value
Death from CHD, including unknown cause	0.9	0.3	0.26
Non-fatal MI	2.3	0.9	**0.01**
Fatal or nonfatal ischemic stroke	0.3	0.6	0.35
Unstable angina requiring hospitalization	0.1	0	0.34
Composite CV events	**3.3**	**1.7**	**0.02**

Repatha (evolocumab)

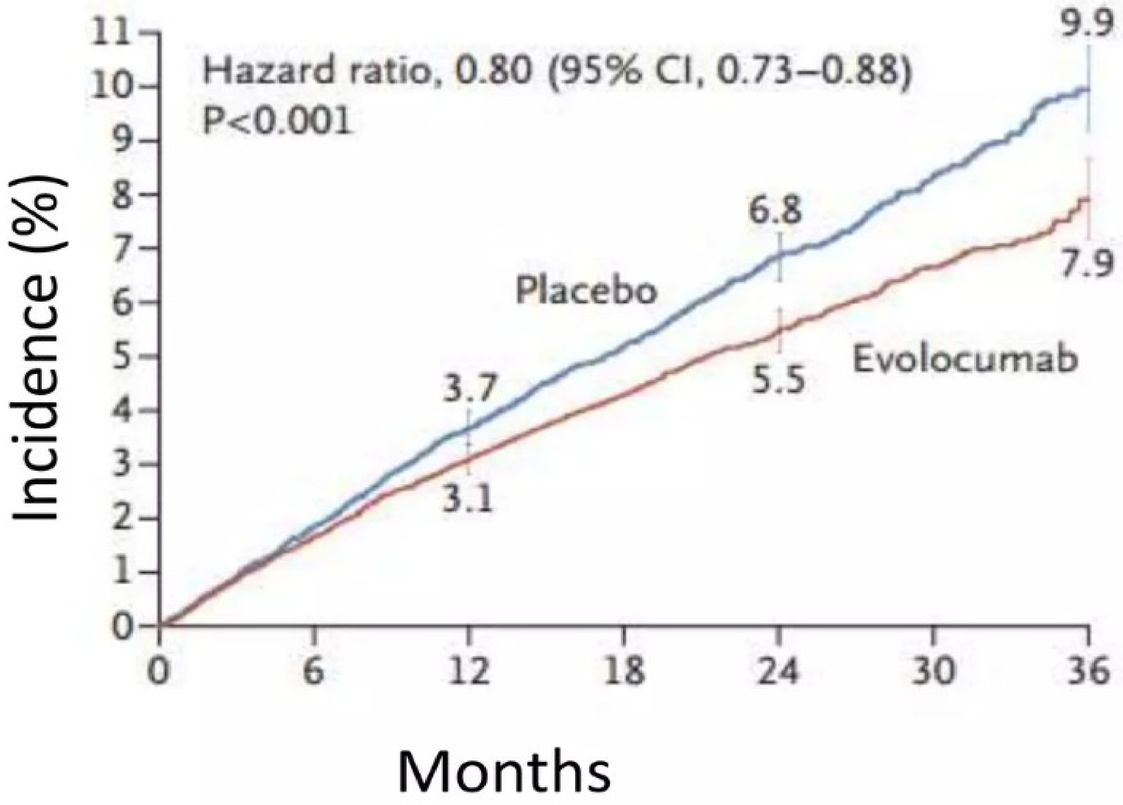
- **Indication**: Adjunct to diet and maximally-tolerated statin therapy in:
  - HeFH
  - ASCVD
  - HoFH
  - Reduction in risk of MI, CVA, and coronary revascularization
- **Dosage**:
  - **HeFH** or **ASCVD**: 140mg SQ every 14 days or 420mg SQ monthly
  - **HoFH**: 420mg SQ once monthly
- **Dosage forms**: 140 mg/mL SureClick Pens or pre-filled syringes

Evolocumab Clinical Trials

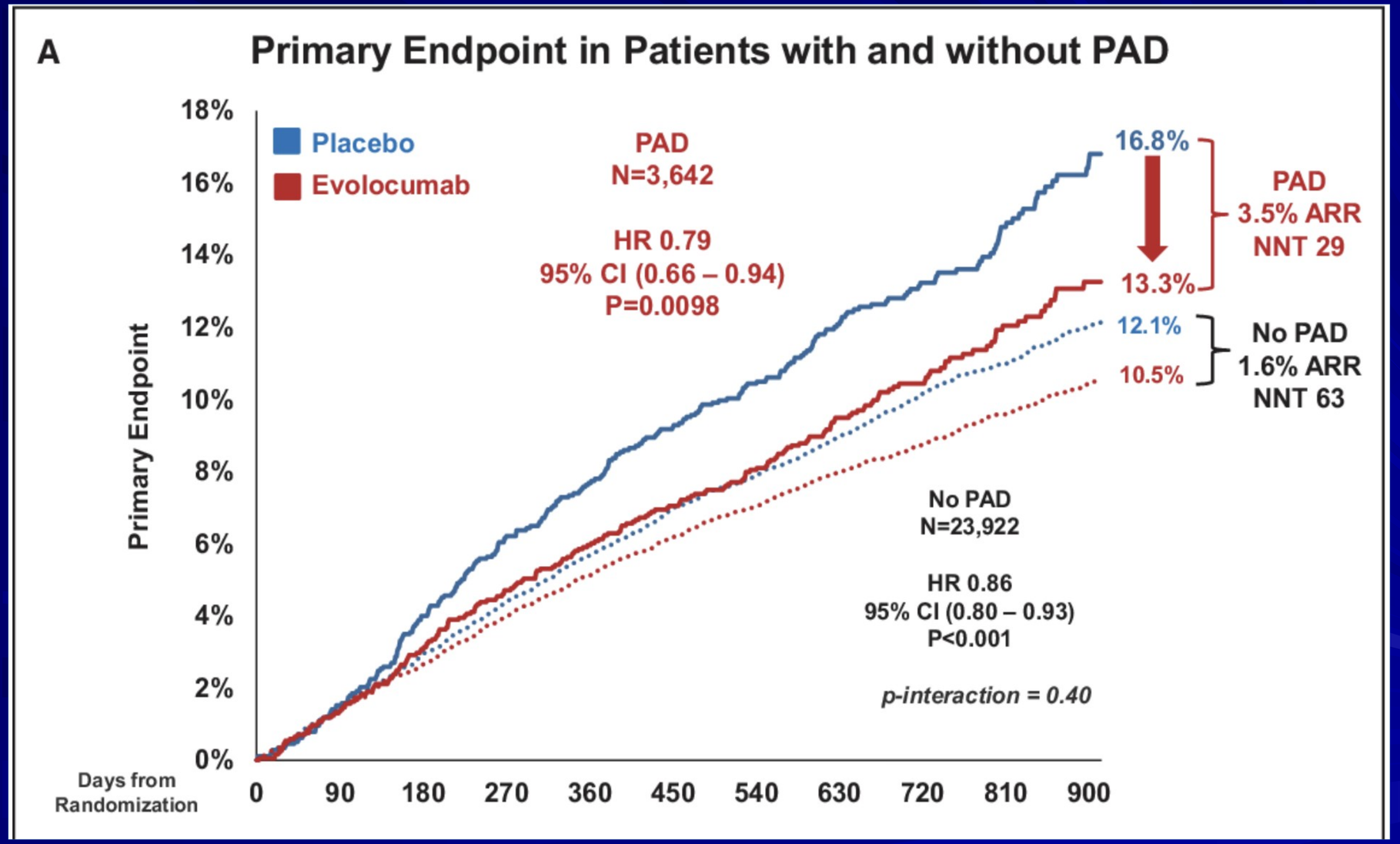
Study	Patient Population (Maximally tolerated statin ± lipid-lowering therapy, LDL not at goal)	Interventions	Mean LDL Change from Baseline at Week 12
LAPLACE-2 (n=2067)	Hyperlipidemia (30% ASCVD) Mean baseline LDL: 108 mg/dL	Evolocumab 140 mg every 2 weeks or 420 mg monthly vs. placebo	-64% versus -1% with placebo (p<0.0001) with background atorvastatin 80 mg
RUTHERFORD-2 (n=331)	HeFH (38% ASCVD) Mean baseline LDL: 156 mg/dL	Evolocumab 140 mg every 2 weeks or 420 mg monthly vs. placebo	-62% versus -1% with placebo (p<0.0001)
TESLA Part B (n=49)	HoFH (43% ASCVD) Mean baseline LDL: 162 mg/dL	Evolocumab 420 mg monthly	-23% versus +8% with placebo (P<0.0001)

FOURIER Trial

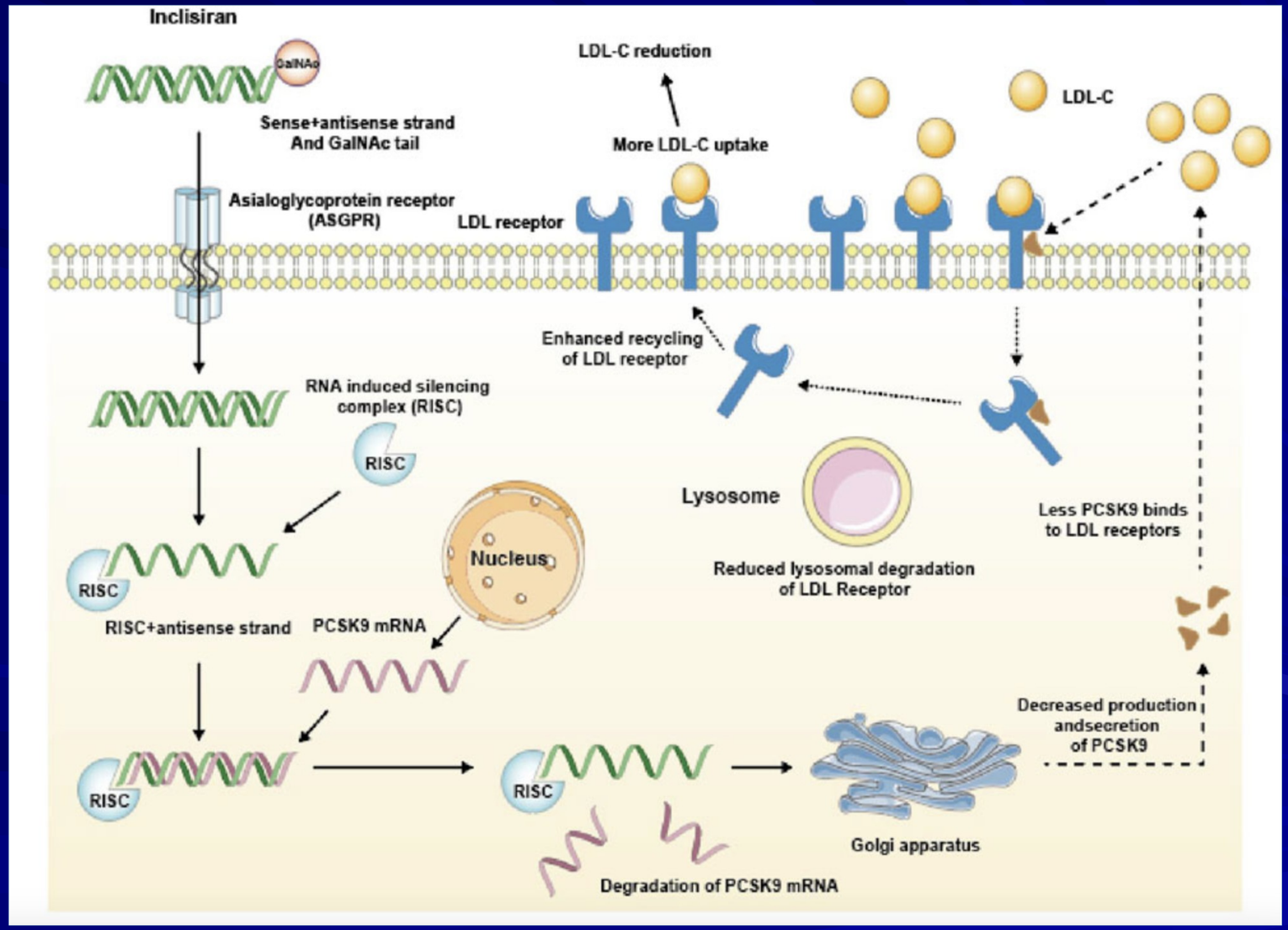
- **Primary outcome of MCE**
  - ↓nonfatal MI, stroke, coronary revascularization by 20%
  - NNT=75 over 2 yrs
  - Mean LDL:0.78*
- **Secondary Outcomes**
  - No ↓ overall or CV mortality
  - CV death low (< 2%) in both grps
  - **SE:** injection-site reactions (2%)



FOURIER Trial



Leqvio (inclisiran)



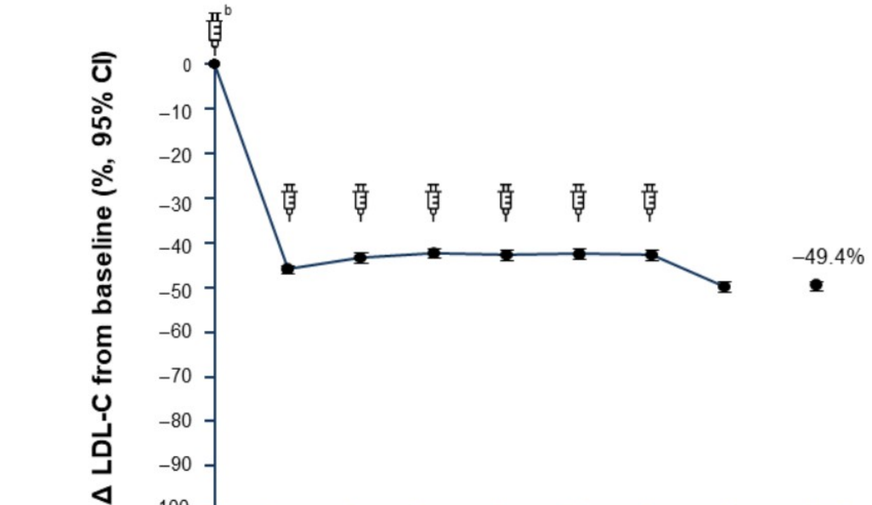
Leqvio (inclisiran)

- **Indication**: Adjunct to diet and maximally-tolerated statin therapy in:
  - HeFH
  - Primary hypercholesterolemia or mixed dyslipidemia
- **Dosage**:
  - 284mg SQ initial dose and at 3 months
  - 284mg SQ every 6 months thereafter
- **Dosage forms**: 284mg/1.5mL pre-filled syringe

Leqvio (inclisiran)

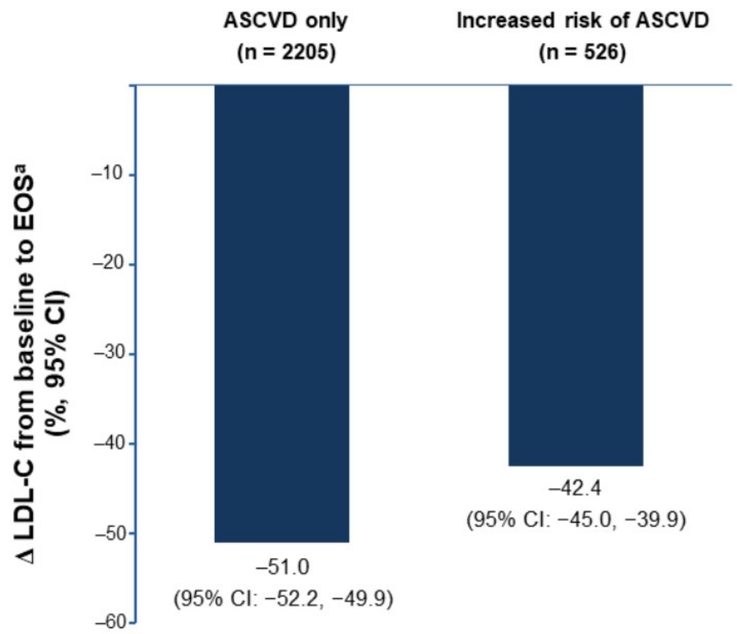
ORION-8: Open-Label Extension Study

Secondary End Point: Percentage Changes in LDL-C From Baseline to EOS[a]



Patient numbers at each visit	BL	D90	D270	D450	D630	D810	D990	D1080	EOS[a]
	3274	3224	3012	2887	2661	2550	2431	2377	2731

Overall safety population



Δ, change; ASCVD, atherosclerotic cardiovascular disease; BL, baseline; D, day; EOS, end of study; LDL-C, low-density lipoprotein cholesterol.
[a]EOS was defined as D1080 after the last LEQVIO dose. [b]Baseline value of LDL-C is taken from the baseline of feeder trials.
Wright R et al. Presented at: European Society of Cardiology; Aug 25-28; 2023; Amsterdam, Netherlands.

Leqvio (inclisiran)

Trial-specific inclusion criteria

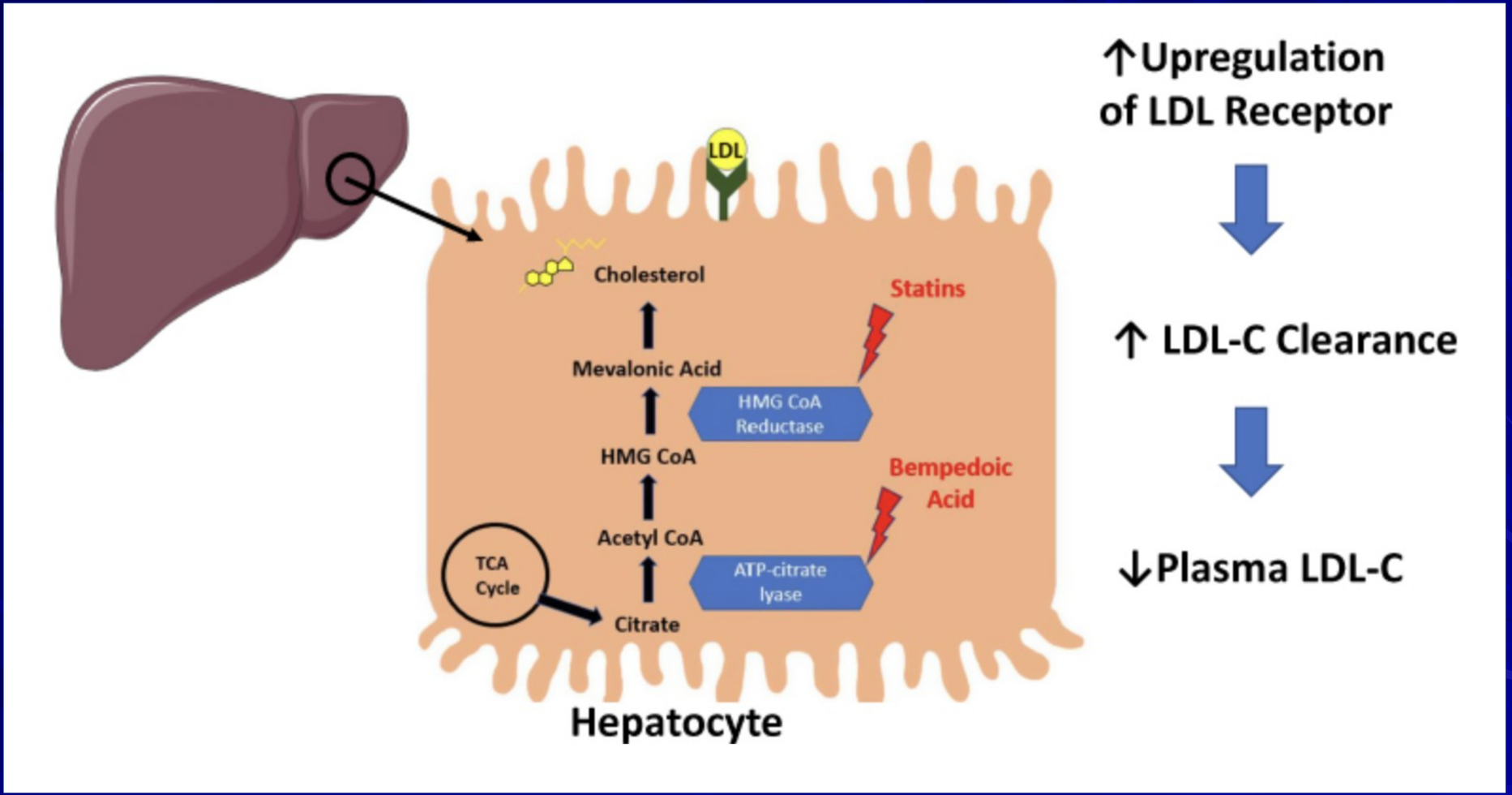
ORION[1,2,4] 9	ORION[1,3,5] 10	ORION[1,3,5] 11
HeFH	**ASCVD**	**ASCVD and increased risk of ASCVD**
FH established either genetically or phenotypically[a]	CHD, CVD, PAD	ASCVD: CHD, CVD, PAD **Increased risk of ASCVD:** Includes FH, T2DM, or 10-year risk of ≥20%
LDL-C ≥100 mg/dL	**LDL-C ≥70 mg/dL**	**ASCVD: LDL-C ≥70 mg/dL** **Increased risk of ASCVD: LDL-C ≥100 mg/dL**
8 countries[b]	US	Europe and South Africa

Similar efficacy and safety of inclisiran in lowering low-density lipoprotein cholesterol (LDL-C) demonstrated across the 3 studies when added to statin therapy.[1]

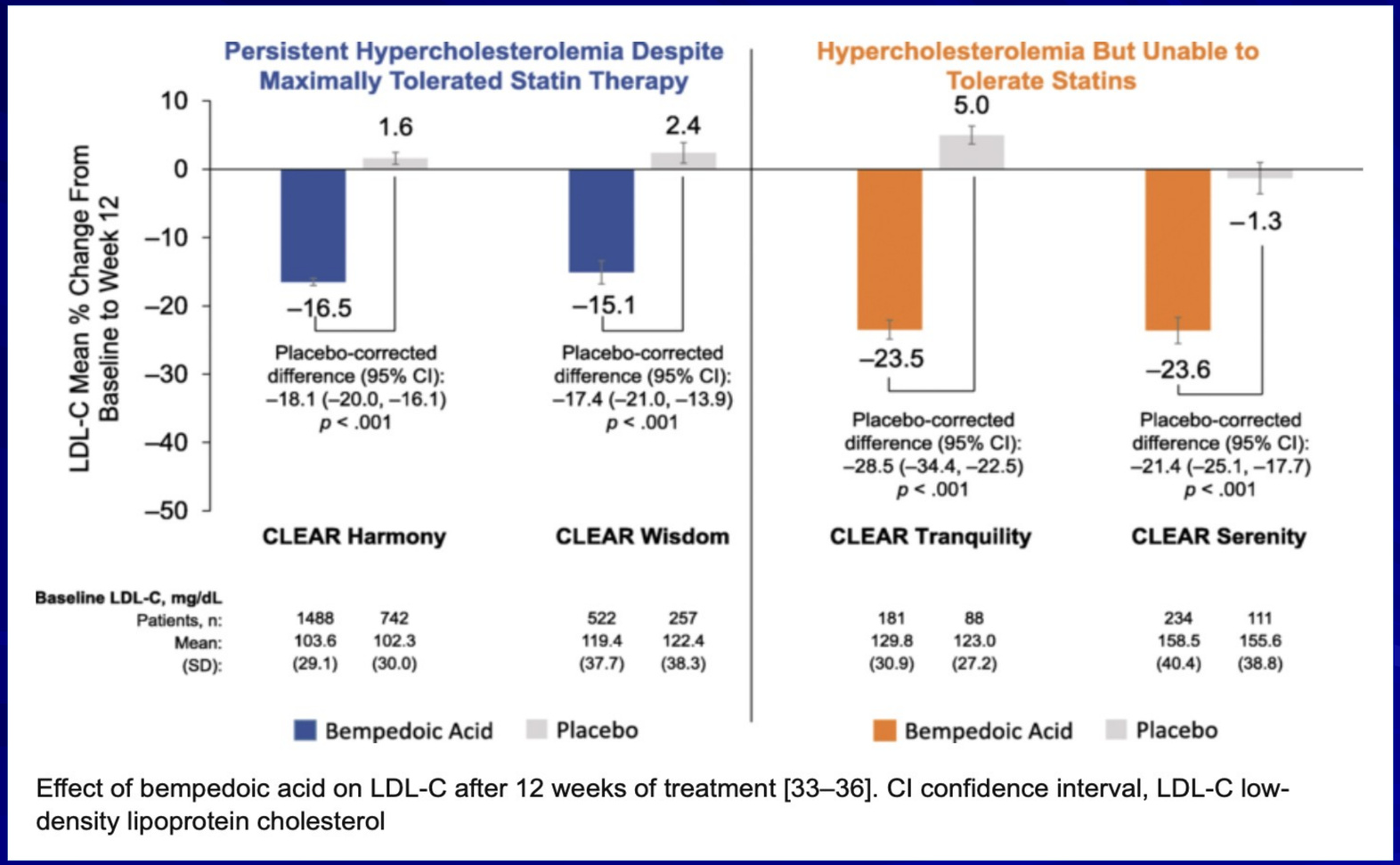
ASCVD, atherosclerotic cardiovascular disease; CHD, coronary heart disease; CVD, cerebrovascular disease; FH, familial hypercholesterolemia; HeFH, heterozygous FH; PAD, peripheral artery disease; T2DM, type 2 diabetes mellitus.
[a]Using the Simon Broome criteria. [b]8 countries, including Canada, Czech Republic, Denmark, Netherlands, South Africa, Spain, Sweden, and the United States.

1. Leqvio. Prescribing information. Novartis Pharmaceuticals Corp. **2.** Raal FJ et al. *N Engl J Med.* 2020;382(16):1520-1530. **3.** Ray KK et al. *N Engl J Med.* 2020;382(16):1507-1519. **4.** Raal FJ et al. *N Engl J Med.* 2020;382(suppl):1520-1530. **5.** Ray KK et al. *N Engl J Med.* 2020;382(suppl):1507-1519.

Nexletol (bempedoic acid)



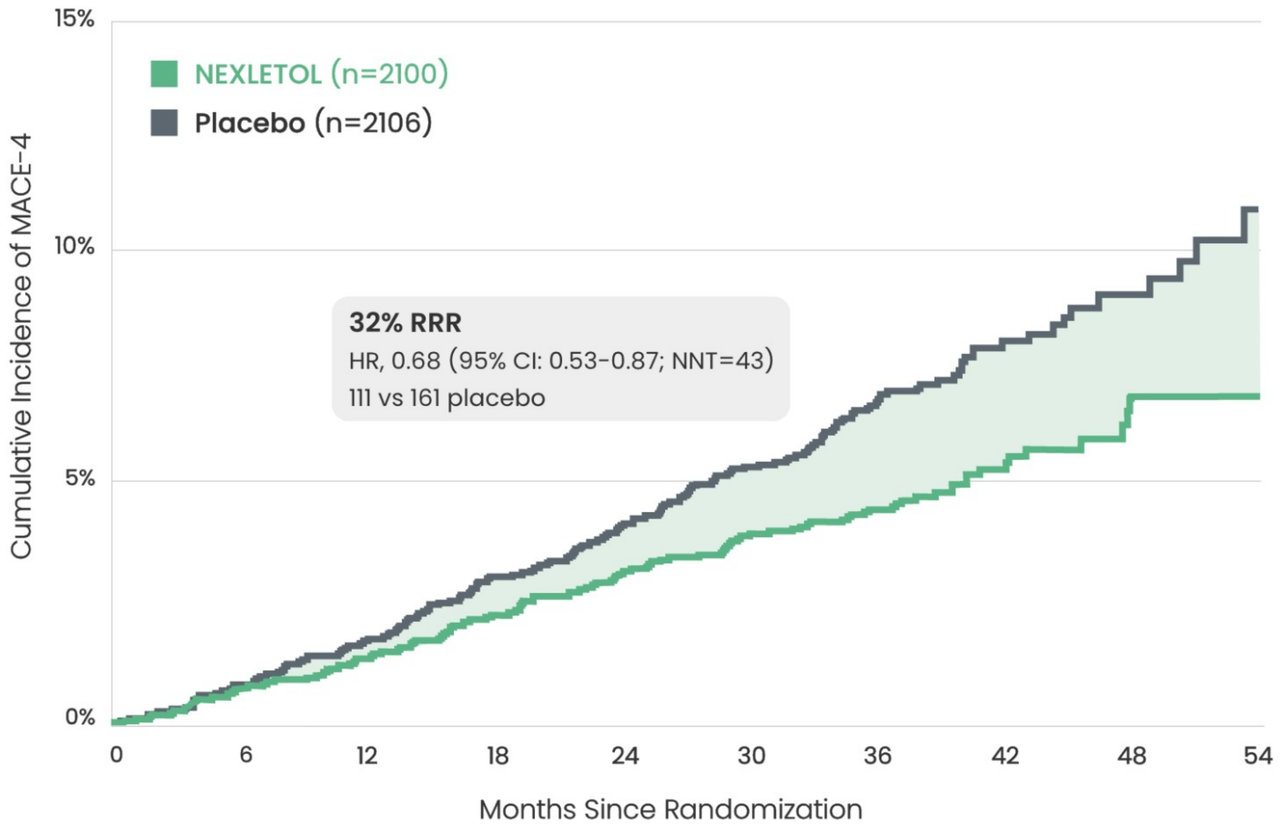
Nexletol (bempedoic acid)



Effect of bempedoic acid on LDL-C after 12 weeks of treatment [33–36]. CI confidence interval, LDL-C low-density lipoprotein cholesterol

CLEAR Trial

Time to First Occurrence of MACE-4 in Primary Prevention Patients[2,3]
(nonfatal MI, coronary revascularization, nonfatal stroke, or CV death)



Nexletol (bempedoic acid)

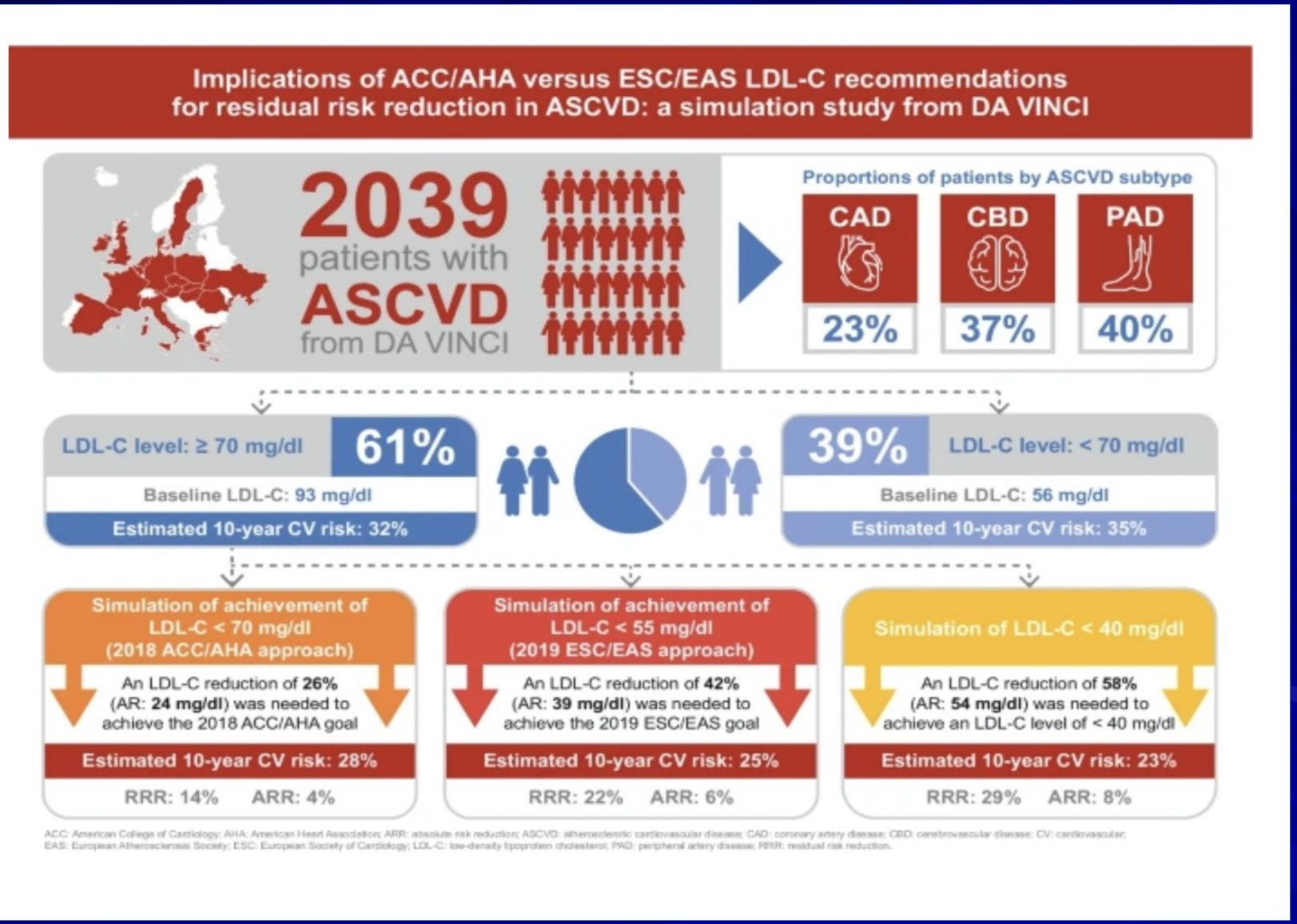
- **Indication**: Adjunct to diet:
  - With other LDL-lowering therapy
  - Alone when concomitant LDL-lowering therapy is not possible
  - Primary hyperlipidemia
  - HeFH
  - Reduction in risk of MI and coronary revascularization

    Adults unable to take recommended statin therapy

    Established CVD or high-risk for CV event (without known CVD)

- **Dosage**:
  - **Nexletol**: 180mg tablets
  - **Nexlizet**: 180/10mg tablets (bempedoic acid + ezetimibe)

How low should we go ?



Newer Diabetic Treatment Options

Treatment of Diabetes Mellitus

Orals:

- Biguanides
  - Metformin (Liver releases less sugar, insulin works better)
- Sulfonylureas
  - Glipizide, glyburide, glimepiride (↑ insulin release)
- Thiazolidinediones
  - Actos, Avandia (Insulin works better)
- DPP—4 Inhibitors
  - Januvia, Onglyza, Tradjenta, Nesina
    (helps pancreas at meal-time)
- Alpha-glucosidase inhibitors
  - Acarbose (blocks gucose absorption in gut)
- SGLT-2 Inhibitors
  - Invokana, Farxiga, Jardiance, Stegalatro
    (pass more glucose in urine, weight loss)

Injectable Incretin Therapy

Byetta, Victoza, Bydureon, Trulicity, Ozempic, Mounjaro
(helps pancreas, weight loss)

Treatment of Diabetes Mellitus

INSULIN

Basal:

Long-acting: Lantus, Levemir, Toujeo, Tresiba
Intermediate: NPH (N)

Prandial:

Fast-acting: Regular (R)
Rapid-acting: Novolog, Humalog, Apidra
Ultra-rapid-acting: Fiasp, Lyumjuev

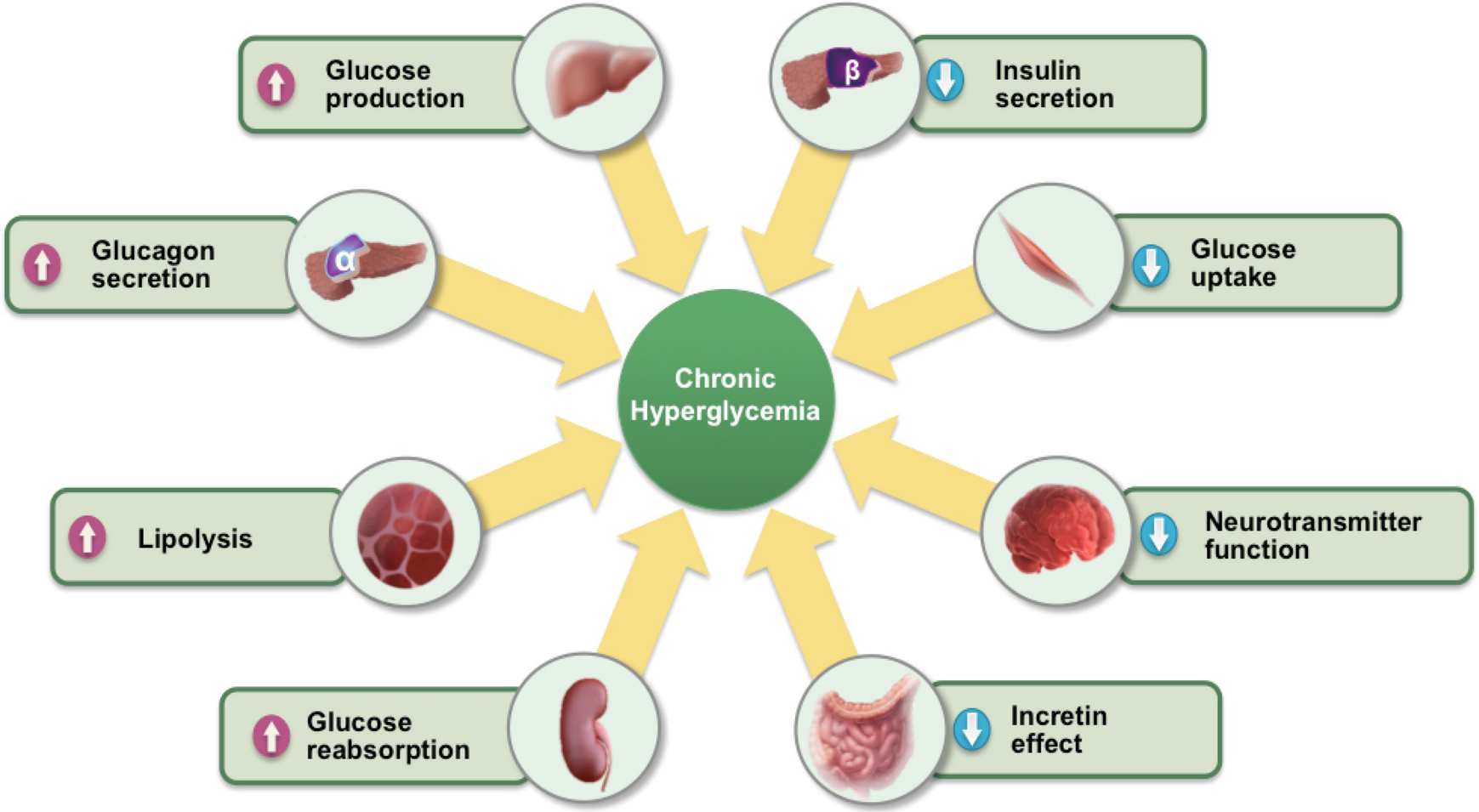
Mixed:

70/30 (NPH + R) (NPH + log)
75/25 (NPH + R) (NPH + log)
50/50 (NPH + R) (NPH + log)

Humulin R U500 (500u/mL), for those requiring >200 units per day

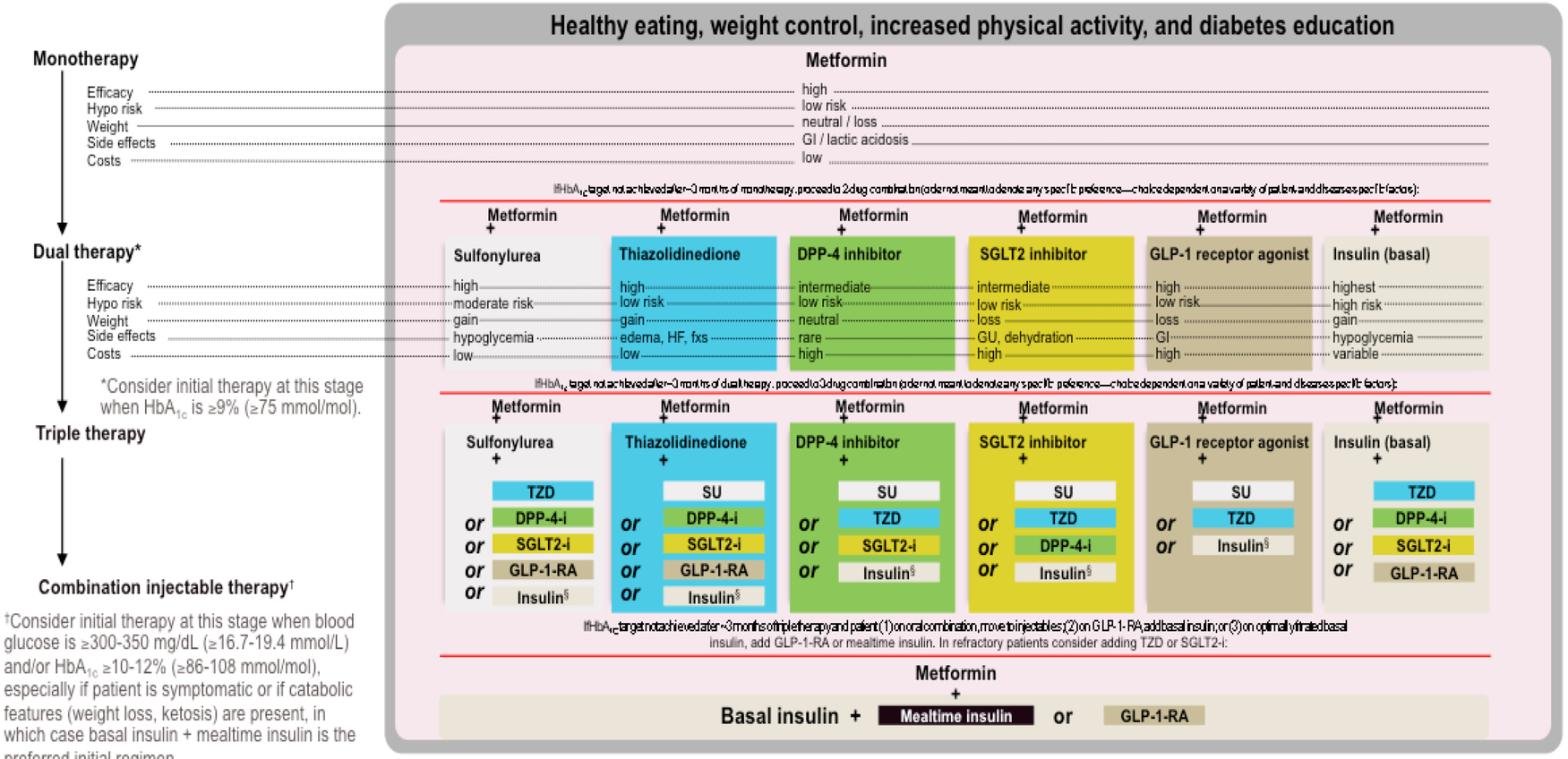
Basal/GLP-1:
Xultify, Soliqua

The Multifactorial Pathophysiology of Type 2 Diabetes Is a Key Factor for Optimizing Individualization of Therapy[1-2]



1. DeFronzo RA. *Diabetes*. 2009;58:773-795.
2. Inzucchi SE et al. *Diabetes Care*. 2012;35:1364-1379.

American Diabetes Association/EASD general therapy recommendations in type 2 diabetes[1]



†Consider initial therapy at this stage when blood glucose is ≥300-350 mg/dL (≥16.7-19.4 mmol/L) and/or HbA_{1c} ≥10-12% (≥86-108 mmol/mol), especially if patient is symptomatic or if catabolic features (weight loss, ketosis) are present, in which case basal insulin + mealtime insulin is the preferred initial regimen.

Trulicity® has not been studied in combination with basal insulin.

§Usually a basal insulin (eg, NPH, glargine, detemir, degludec).

HbA_{1c}=glycated hemoglobin; DPP-4-i=dipeptidyl peptidase-4 inhibitor; EASD=European Association for the Study of Diabetes; fxs=fractures; GU=genitourinary infections; HF=heart failure; SU=sulfonylurea; TD=thiazolidinedione.

1. Inzucchi SE, et al. *Diabetes Care*. 2015;38(1):140-149.

Glycemic Control Algorithm

INDIVIDUALIZE GOALS

A1C ≤ 6.5% For patients without concurrent serious illness and at low hypoglycemic risk

A1C > 6.5% For patients with concurrent serious illness and at risk for hypoglycemia

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

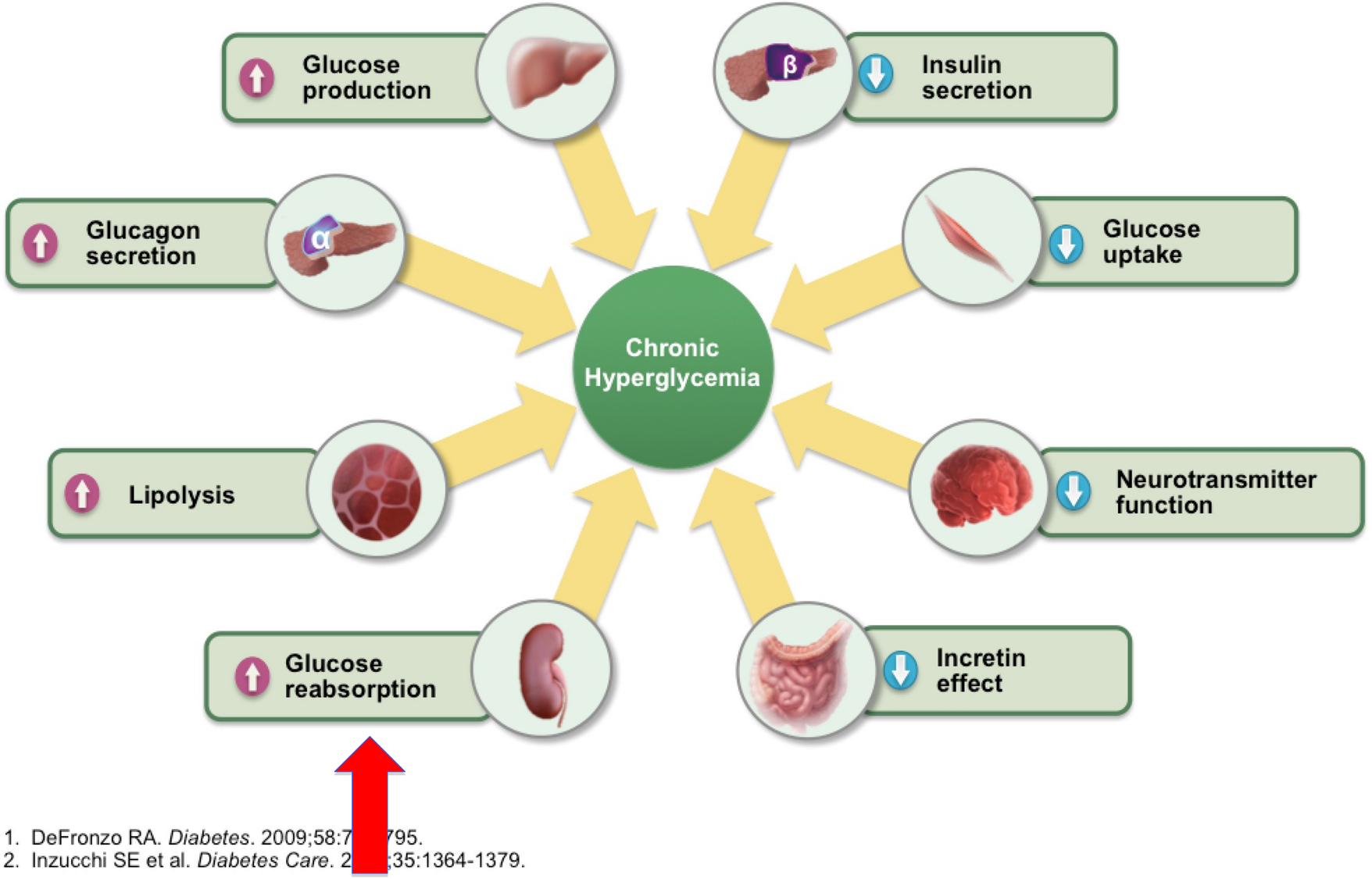
- ✓ Few adverse events and/or possible benefits
- ⚠ Use with caution

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

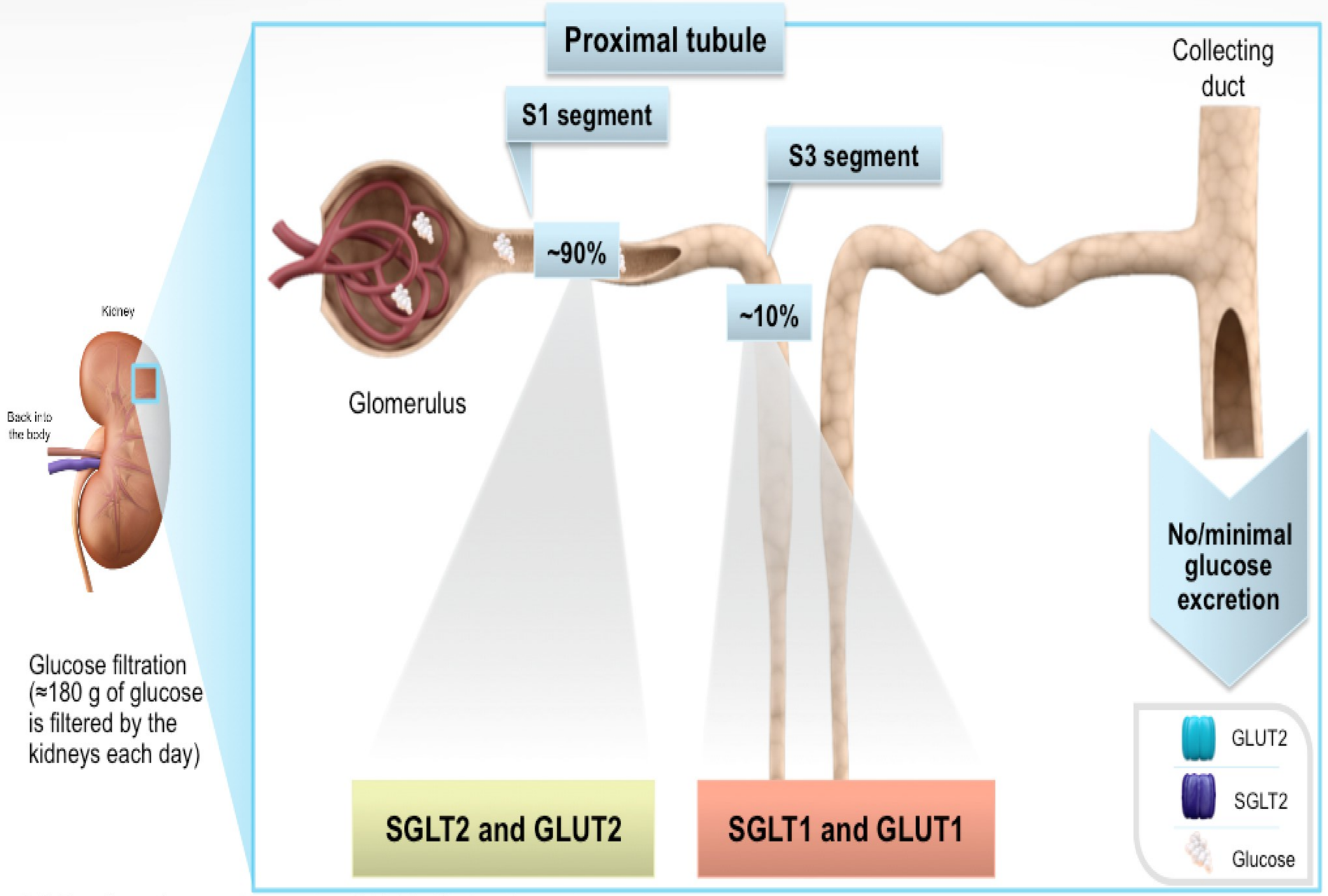
PROGRESSION OF DISEASE

 DOI 10.4158/CS-2017-0153

The Multifactorial Pathophysiology of Type 2 Diabetes Is a Key Factor for Optimizing Individualization of Therapy[1-2]

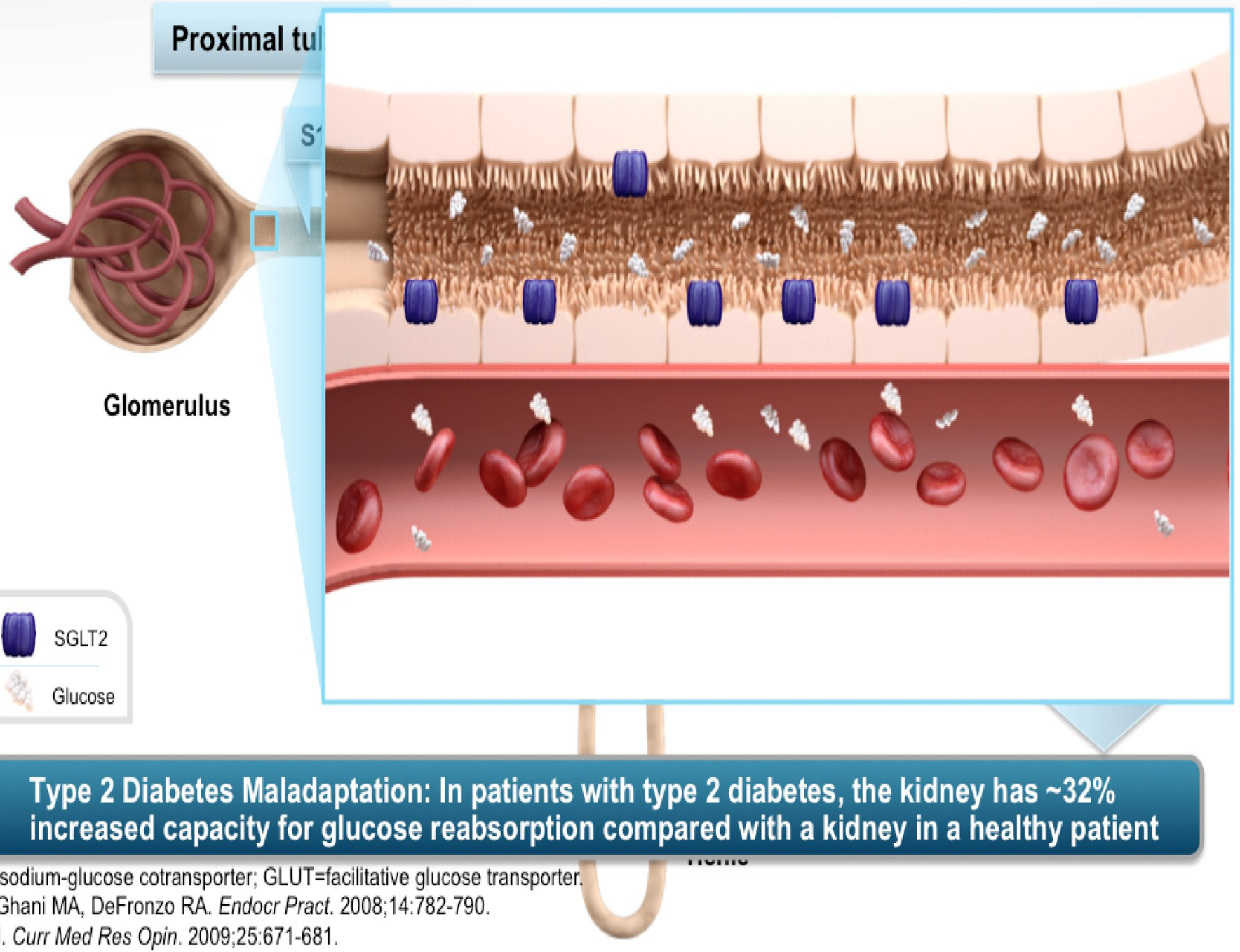


1. DeFronzo RA. *Diabetes*. 2009;58:7 795.
2. Inzucchi SE et al. *Diabetes Care*. 2 ;35:1364-1379.



SGLT=sodium-glucose cotransporter; GLUT=facilitative glucose transporter.

1. Abdul-Ghani MA, DeFronzo RA. *Endocr Pract*. 2008;14:782-790.
2. Bays H. *Curr Med Res Opin*. 2009;25:671-681.



Type 2 Diabetes Maladaptation: In patients with type 2 diabetes, the kidney has ~32% increased capacity for glucose reabsorption compared with a kidney in a healthy patient

SGLT=sodium-glucose cotransporter; GLUT=facilitative glucose transporter.

1. Abdul-Ghani MA, DeFronzo RA. *Endocr Pract*. 2008;14:782-790.
2. Bays H. *Curr Med Res Opin*. 2009;25:671-681.
3. DeFronzo RA. *Diabetes Care*. 2013;36:3169-3176.

SGLT2 Inhibitors

FDA-Approved Agents

- Canagliflozin
- Dapagliflozin
- Empagliflozin
- Ertugliflozin

Key Features

- Oral administration
- Inhibit reabsorption of glucose into the bloodstream from renal fluid

Safety Considerations with SGLT2 Inhibitors

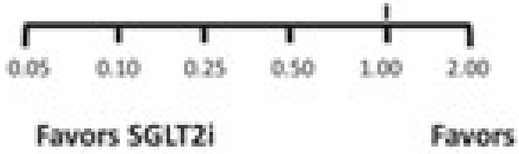
Lower rates of hospitalization for heart failure and all-cause death in new users of SGLT-2 inhibitors:

The CVD-REAL Study

Highlights from findings presented March 19, 2017
American College of Cardiology 66th Annual Scientific Session
Washington DC

CVD-REAL Study
HHF Primary Analysis

Database	N	No. of events	HR (95% CI)
USA	233,798	298	0.55 (0.44, 0.69)
Norway	25,050	278	0.62 (0.49, 0.79)
Denmark	18,468	167	0.77 (0.59, 1.01)
Sweden	18,378	191	0.61 (0.45, 0.82)
UK	10,462	16	0.36 (0.12, 1.13)
Germany	2900	11	0.14 (0.03, 0.68)
Total	309,056	961	0.61 (0.51, 0.73)



***P* value for SGLT2i vs oGLD: <.001**

Reproduced with permission from Kosiborod M, et al. ACC 2017. Abstract 415-14.

CVDREAL

All-Cause Death

ACC.17

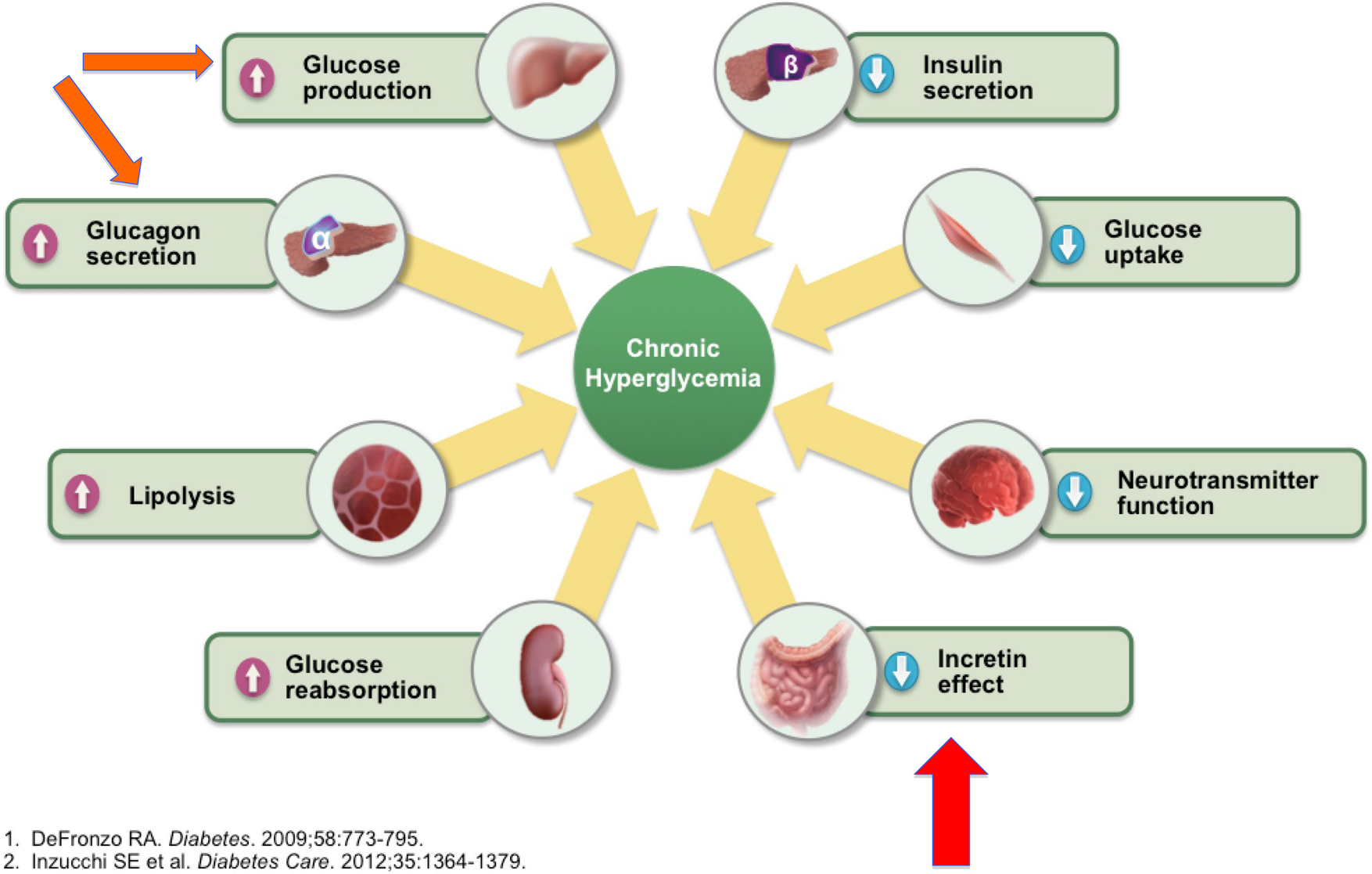
Database	N	# of events	HR (95% CI)
US	143,264	250	0.38 (0.29, 0.50)
Norway	25,050	364	0.55 (0.44, 0.68)
Denmark	18,468	323	0.46 (0.37, 0.57)
Sweden	18,378	317	0.47 (0.37, 0.60)
UK	10,462	80	0.73 (0.47, 1.15)
Total	215,622	1334	0.49 (0.41, 0.57)

P-value for SGLT2i vs oGLD: <0.001

Heterogeneity p-value: 0.09

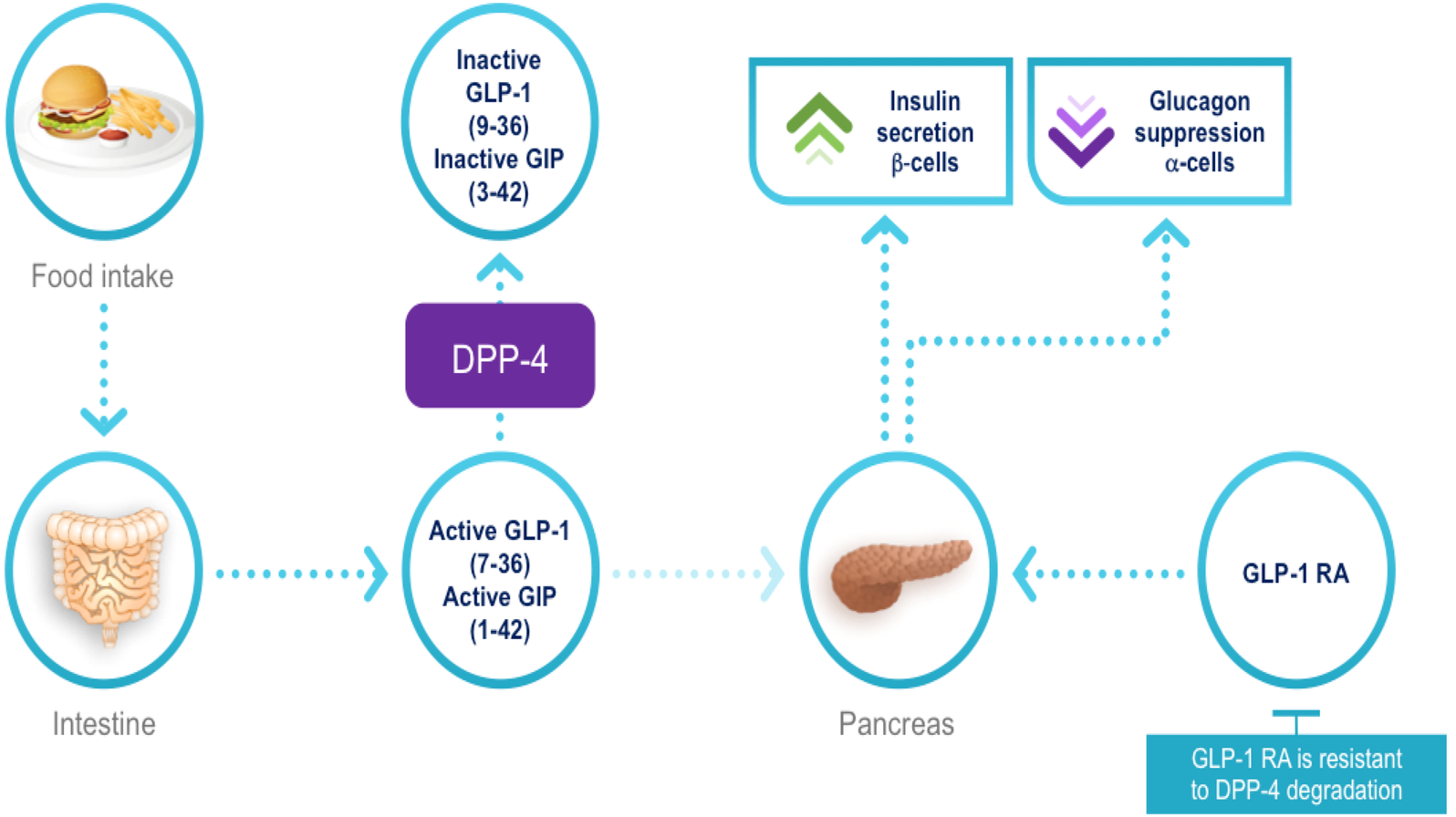
Data are on treatment, unadjusted; oGLD=other glucose-lowering drug; HR=hazard ratio

The Multifactorial Pathophysiology of Type 2 Diabetes Is a Key Factor for Optimizing Individualization of Therapy[1-2]



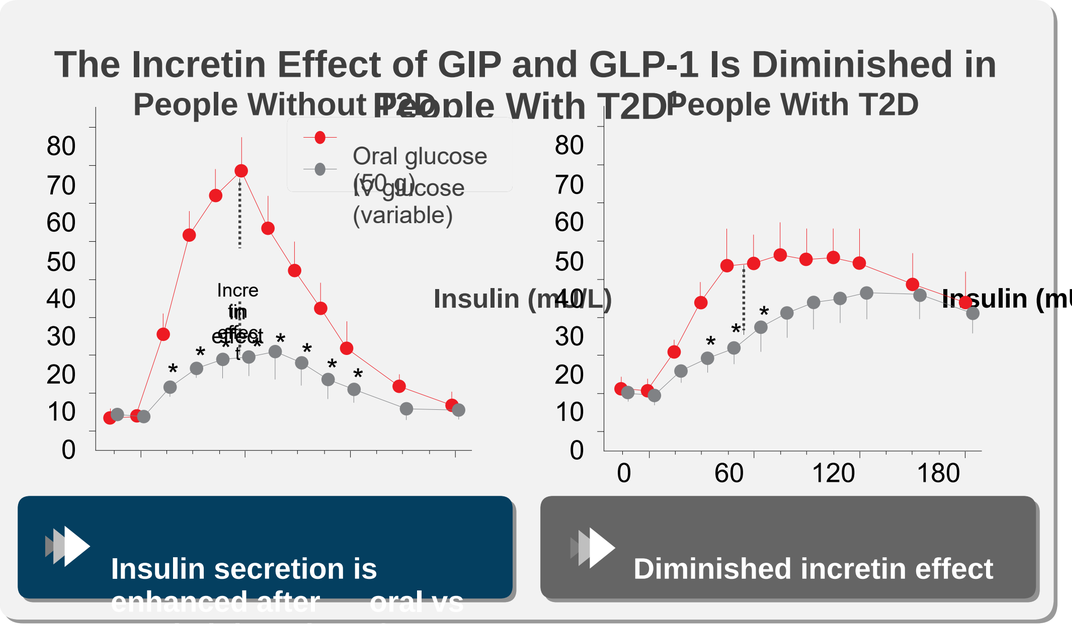
1. DeFronzo RA. *Diabetes*. 2009;58:773-795.
2. Inzucchi SE et al. *Diabetes Care*. 2012;35:1364-1379.

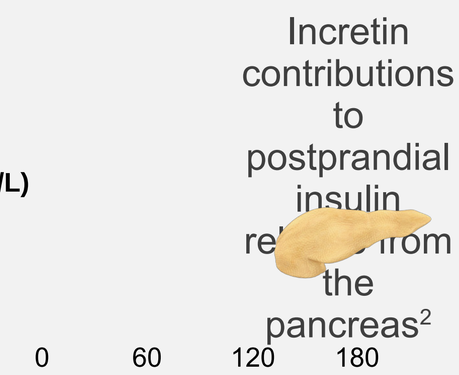
GLP-1 mediates glucose-stimulated insulin production and suppresses glucagon release[1]



1. Baggio LL, et al. *Gastroenterology*. 2007;132(6):2131-2157.

GIP IS A POTENT INSULIN SECRETAGOGUE AND THE PRIMARY MEDIATOR OF THE INCRETIN EFFECT[1,2]





GIP is responsible for nearly **two-thirds** of the incretin effect in people without T2D, contributing more to insulin secretion than GLP-1.[2]

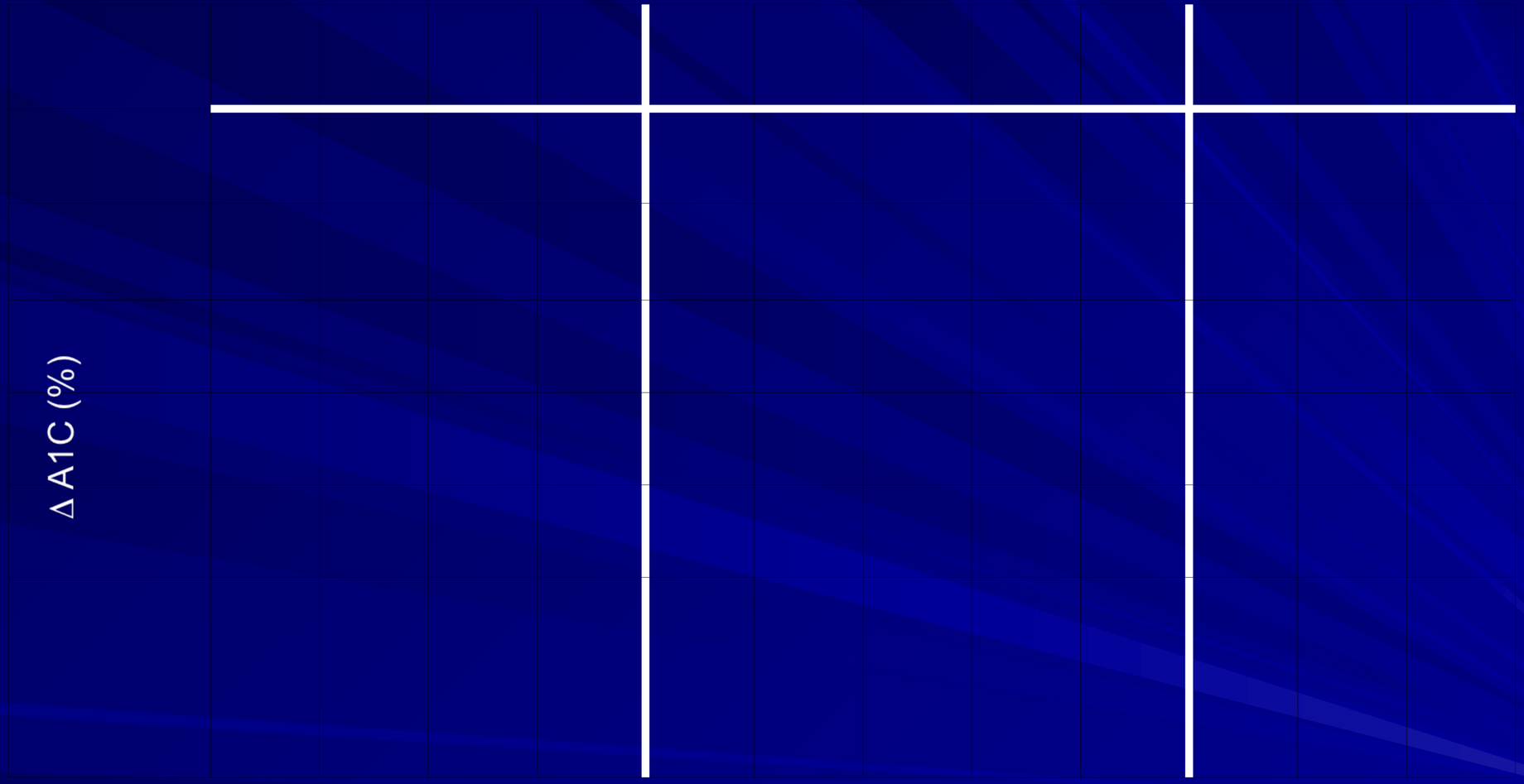
Please see Important Safety Information, including Boxed Warning about possible thyroid tumors, including thyroid cancer, throughout this deck, the Full Prescribing Information, and Medication Guide in the participant guide.

1. Nauck MA, et al. *Diabetes Obes Metab*. 2018;20(suppl 1):5-21. 2. Nauck MA, et al. *Diabetes*. 2019;68(5):897-909.

Incretin Therapy

Safety Considerations with GLP-1 RA’s

Glucose Reduction



Treatment of Diabetes Mellitus

GOALS OF TREATMENT:

Diabetic Goals:

	ADA	ACE
A1c:	< 7%	< 6.5%
Preprandial:	70-130	< 110
Postprandial:	< 180	< 140

How aggressive should we be?

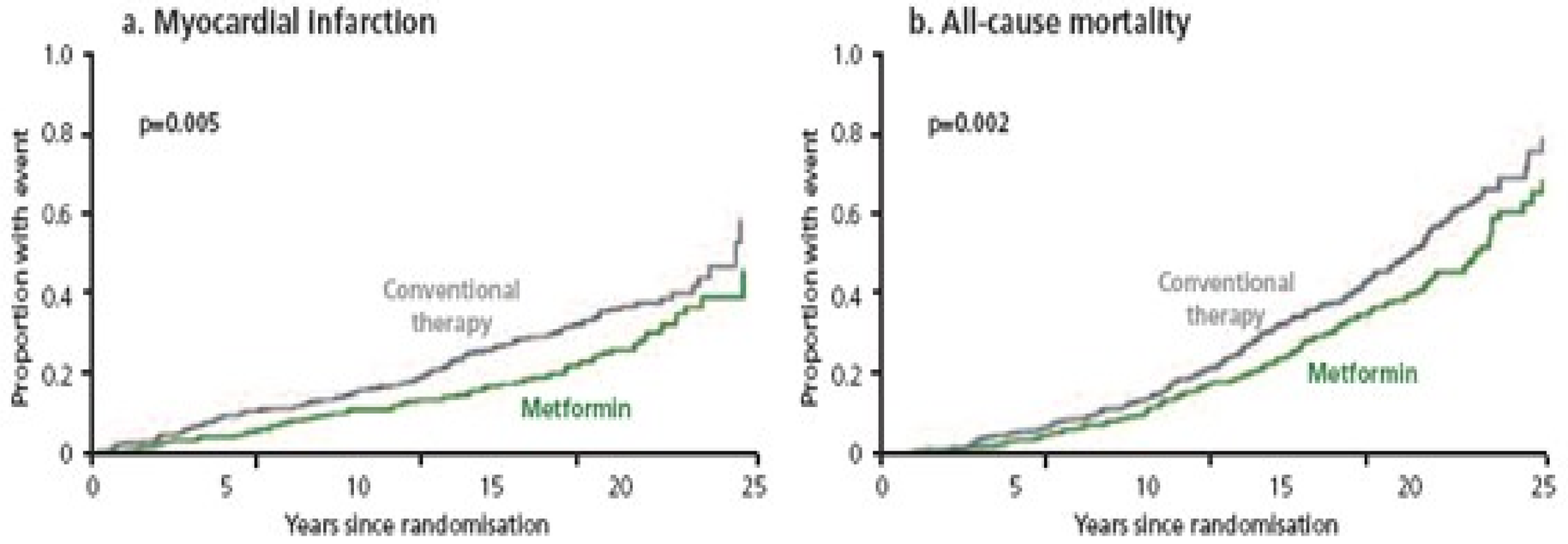
- Age
- Risk of hypoglycemia
- Pre-existing cardiovascular disease burden
- Does the drug impact CV risk ?

Diabetes Mellitus and CVD

Macrovascular Outcomes: There have been xxx clinical studies establishing conclusive evidence of macrovascular risk reduction with Trulicity or any other antidiabetic drug.

UKPDS 34(metformin)

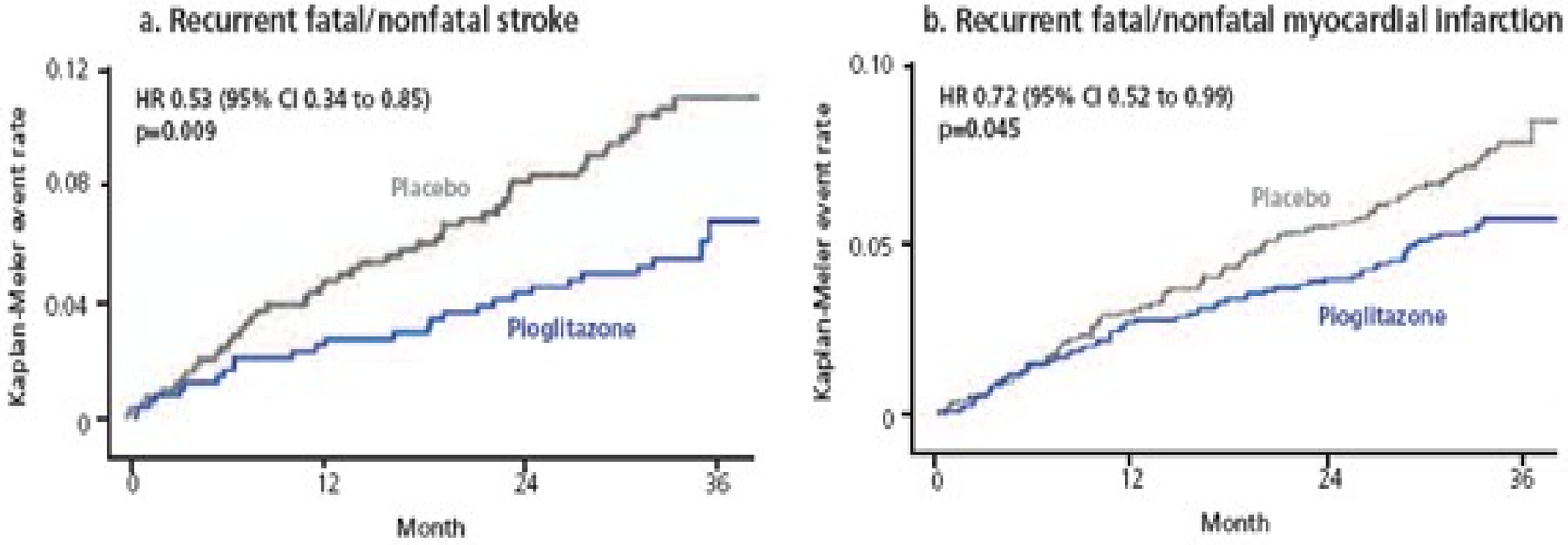
Figure 2. The proportions of patients in the United Kingdom Prospective Diabetes Study who had myocardial infarction (Figure 2a) and death from any cause (Figure 2b) for the metformin group versus the conventional therapy group



Kaplan-Meier plots show cumulative incidence and log-rank P values are shown at 5-year intervals during a 25 year period from the start of the interventional trial (including randomised treatment followed by observational post-trial follow-up). Reproduced with permission from ref 3.

PROactive Study(pioglitazone)

Figure 4. Kaplan-Meier curve of the time to fatal stroke/non-fatal stroke in the patients in the PROactive study who had had a previous stroke (Figure 4a) and of time to fatal/non-fatal myocardial infarction (excluding silent myocardial infarction) in patients in the PROactive study who had had a previous myocardial infarction (Figure 4b)



HR: hazard ratio. Reproduced with permission from refs 9 and 10.

CV Outcome Trials: DPP-4 Inhibitors

Trial	Therapies	#	Population	Primary endpoint	End Date
EXAMINE	Alogliptin/ Placebo	5400	ACS 15-90 days before	Non-inferiority: time to occurrence of MACE	PUBLISHED
SAVOR	Saxagliptin/ Placebo	16,500	CVD or ≥ 2 RF	Superiority efficacy, non-inferiority safety: composite CV death, NF MI, NF stroke	PUBLISHED
CARMELINA	Linagliptin/ Placebo	8,300	High risk of CV events	Time to first occurrence of composite CV outcome	Jan 2018
CAROLINA	Linagliptin/ Glimepiride	6000	CVD or ≥ 2 RF	Non-inferiority: time to first occurrence of any component of MACE composite outcome	Sept 2018
TECOS	Sitagliptin/ Placebo	14,000	Established CVD	Non-inferiority: time to first occurrence of composite CV outcome	PUBLISHED

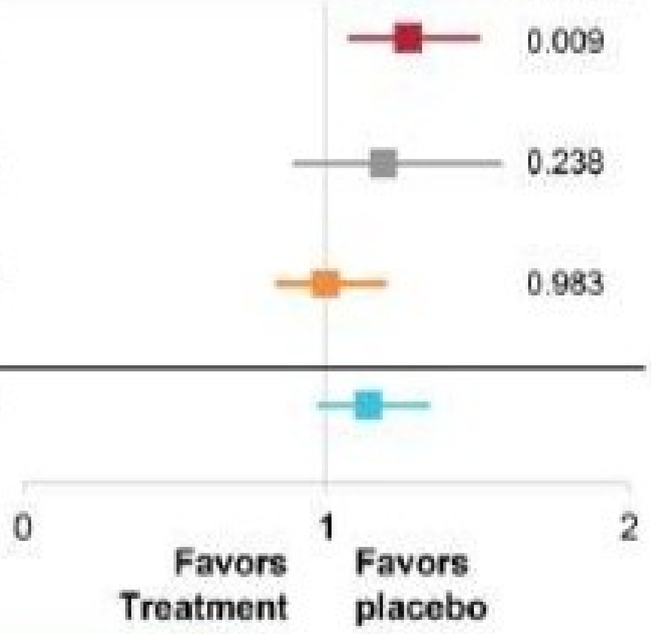
ACS: Acute coronary syndrome; CVD: Cardiovascular disease; RF: Risk factor

Golden SH. *Am J Cardiol* 2011; 108(Suppl):59B-67B; Fonseca V. *Am J Cardiol* 2011; 108(Supp):52B–58B; www.clinicaltrials.gov

SAVOR-TIMI 53, EXAMINE, and TECOS:

Hospitalization for Heart Failure

	Study Drug n/N (%)	Placebo n/N (%)	Hazard Ratio	95% CI	P Value
SAVOR-TIMI (saxagliptin vs. placebo)	289/8280 (3.5%)	228/8212 (2.6%)	1.27	1.07, 1.51	0.009
EXAMINE (alogliptin vs. placebo)	106/2701 (3.9%)	89/2679 (3.3%)	1.19	0.89, 1.58	0.238
TECOS (sitagliptin vs. placebo)	228/7332 (3.1%)	229/7339 (3.1%)	1.00	0.83, 1.20	0.983
SAVOR + EXAMINE + TECOS	623/18313 (3.4%)	546/18230 (3.0%)	1.14	0.97, 1.34	



Test for heterogeneity for 3 trials: p=0.178, I^2=42%

1. Sorica 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

EMPA-REG

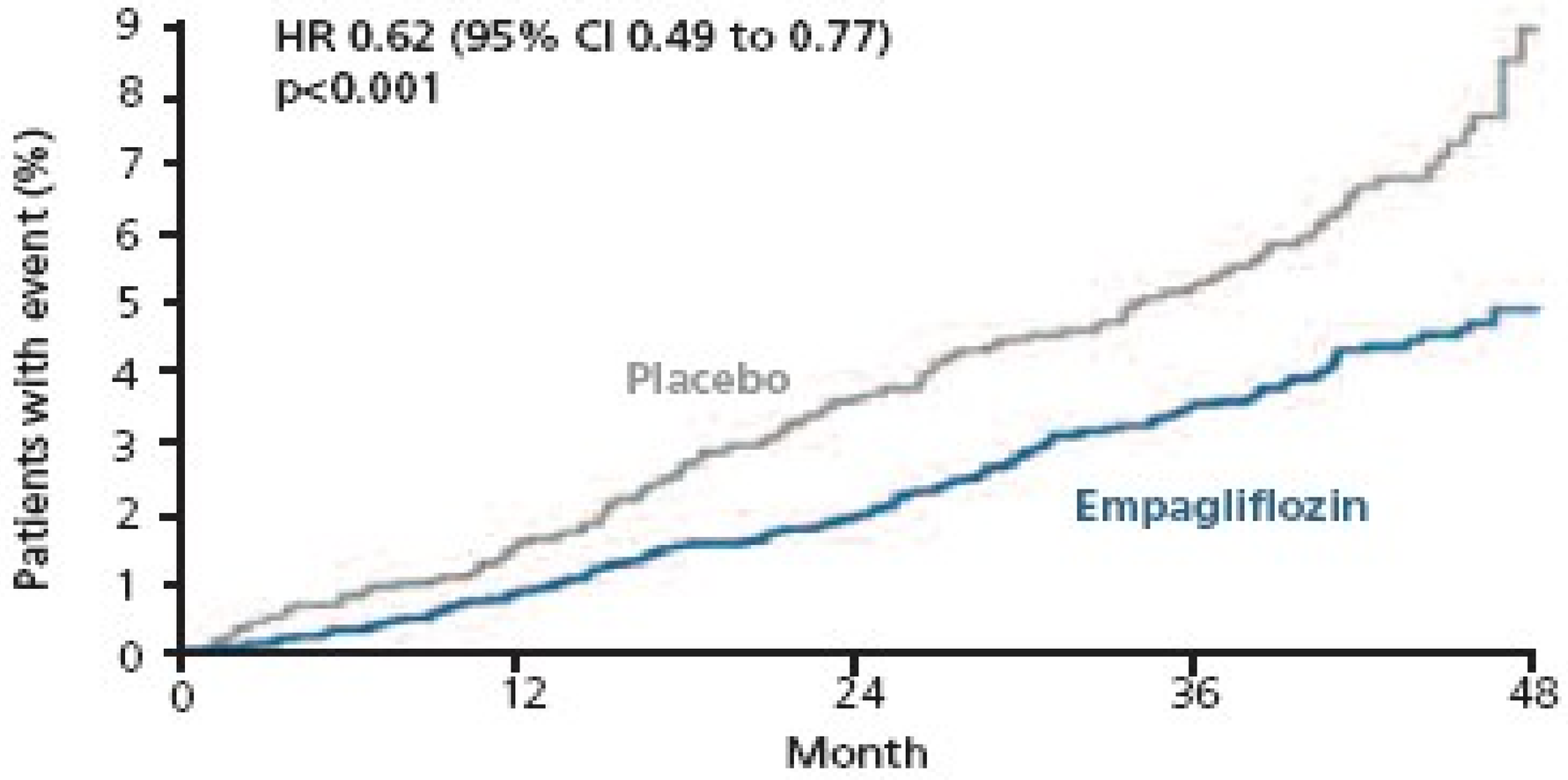
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes

Bernard Zinman, M.D., Christoph Wanner, M.D., John M. Lachin, Sc.D., David Fitchett, M.D., Erich Bluhmki, Ph.D., Stefan Hantel, Ph.D., Michaela Mattheus, Dipl. Biomath., Theresa Devins, Dr.P.H., Odd Erik Johansen, M.D., Ph.D., Hans J. Woerle, M.D., Uli C. Broedl, M.D., and Silvio E. Inzucchi, M.D., for the EMPA-REG OUTCOME Investigators

Figure 1. The cumulative incidence of death from cardiovascular causes in the empagliflozin group versus placebo group in the EMPA-REG OUTCOME



Hazard ratios (HR) are based on Cox regression analysis. Reproduced with permission from ref 2.

INDICATIONS AND LIMITATIONS OF USE

JARDIANCE is indicated to reduce the risk of cardiovascular (CV) death in adults with type 2 diabetes mellitus and established CV disease.

LEADER Trial

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes

Steven P. Marso, M.D., Gilbert H. Daniels, M.D., Kirstine Brown-Frandsen, M.D., Peter Kristensen, M.D., E.M.B.A., Johannes F.E. Mann, M.D., Michael A. Nauck, M.D., Steven E. Nissen, M.D., Stuart Pocock, Ph.D., Neil R. Poulter, F.Med.Sci., Lasse S. Ravn, M.D., Ph.D., William M. Steinberg, M.D., Mette Stockner, M.D., Bernard Zinman, M.D., Richard M. Bergenstal, M.D., and John B. Buse, M.D., Ph.D., for the LEADER Steering Committee on behalf of the LEADER Trial Investigators*

ABSTRACT

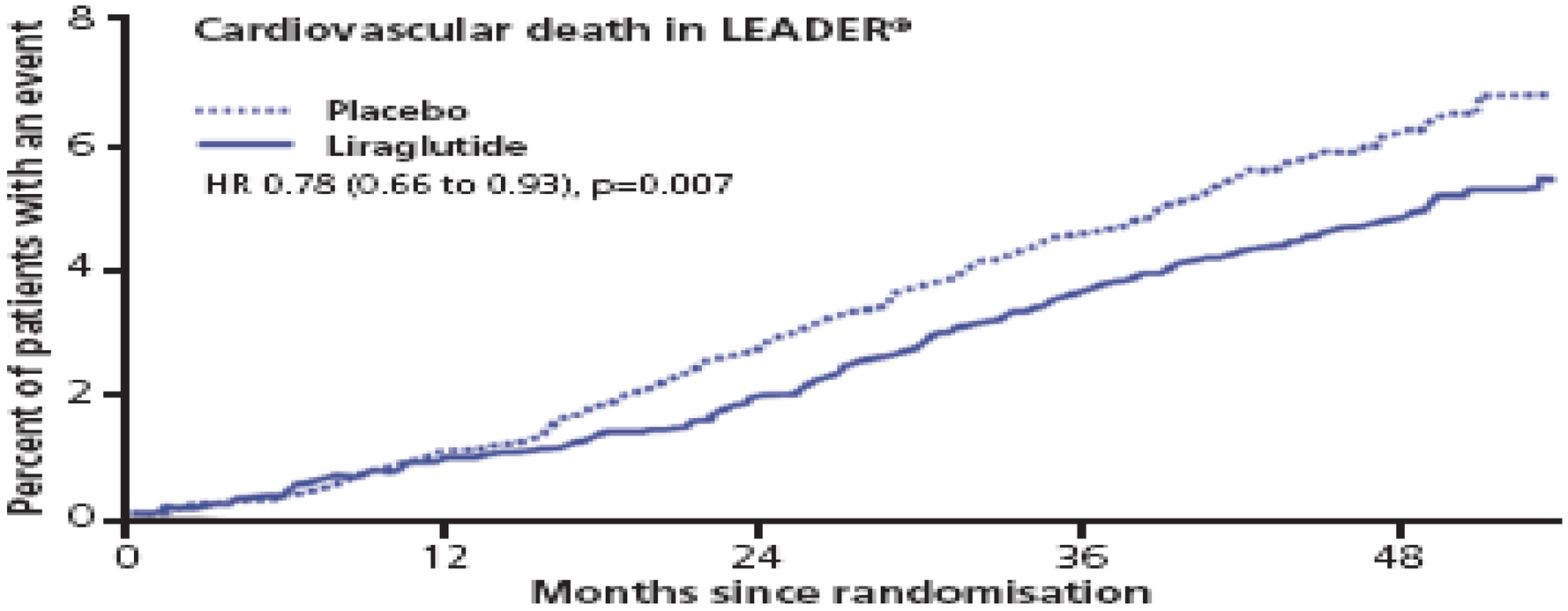
BACKGROUND

The cardiovascular effect of liraglutide, a glucagon-like peptide-1 analogue, when

LEADER Trial

Primary Outcome

Figure 1. Cumulative incidence of death from cardiovascular causes in the liraglutide group versus placebo group in the LEADER study



Hazard ratios [HR (95%CI)] based on Cox regression analysis
Adapted from reference 6

'Victoza® is indicated:

- as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.
- **as an adjunct to standard treatment of cardiovascular risk factors to reduce the risk of major adverse cardiovascular events (cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke) in adults with type 2 diabetes mellitus and high cardiovascular risk.'**

SUSTAIN-6

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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*

SUSTAIN-6

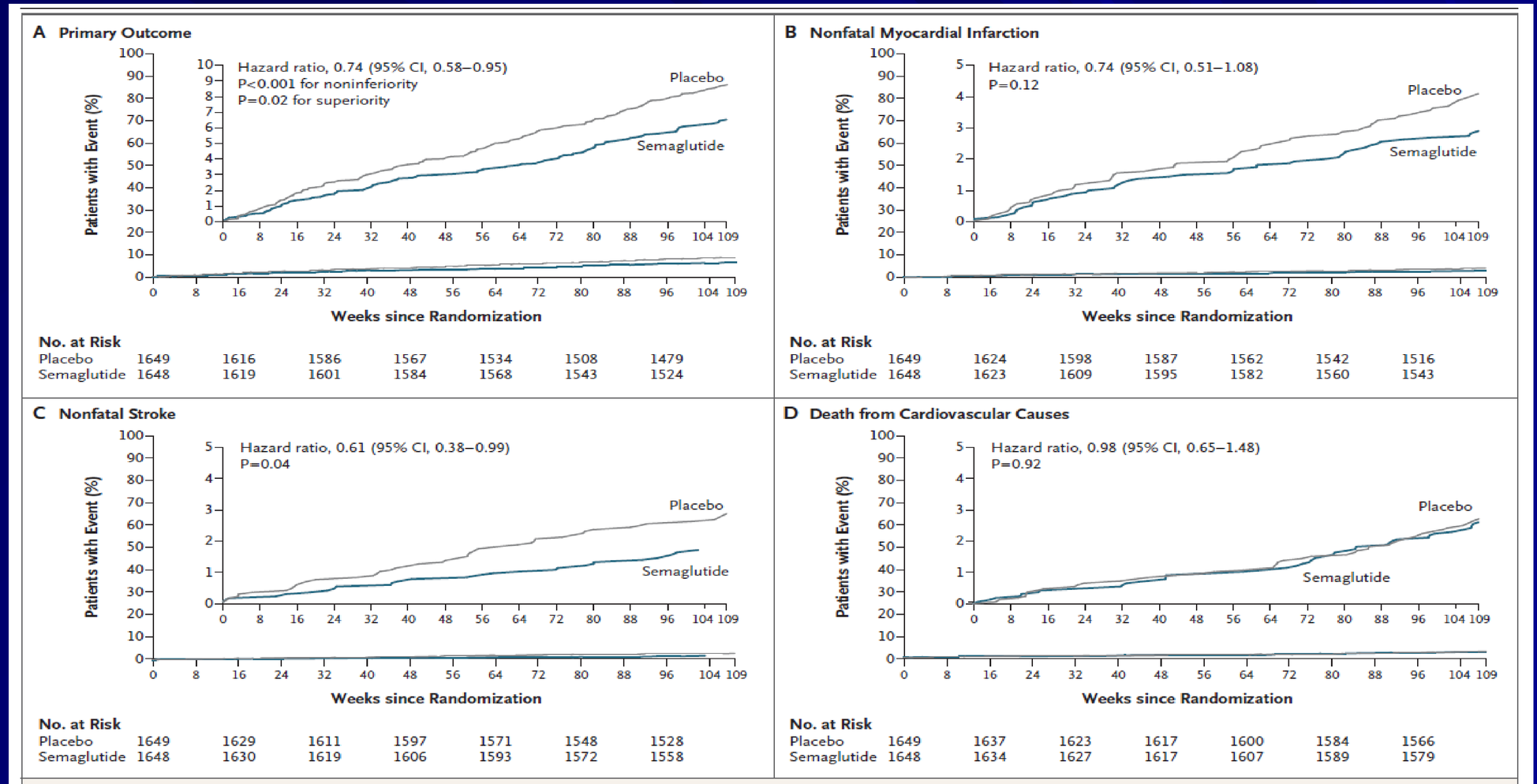
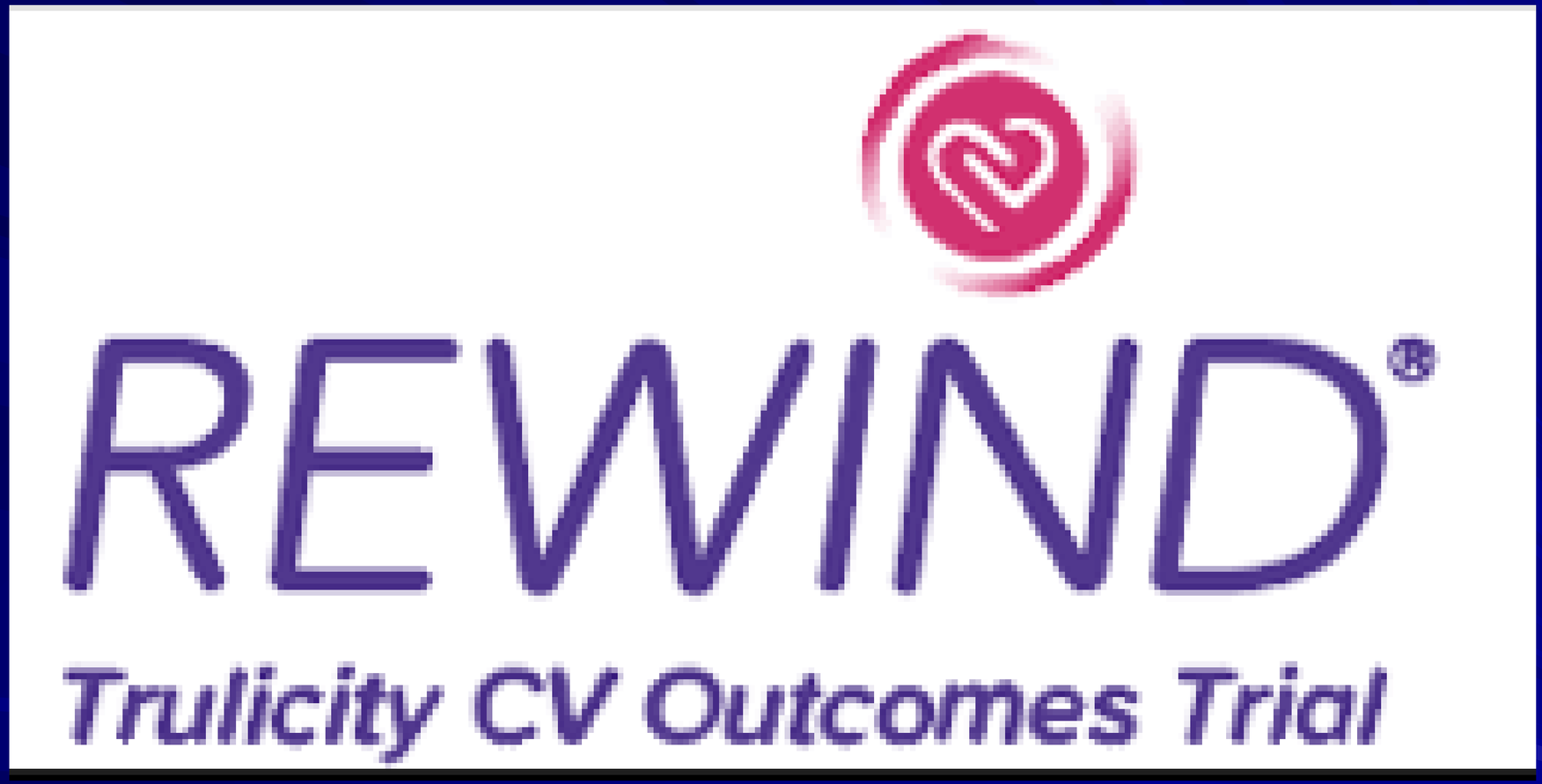


Figure 1. Cardiovascular Outcomes.

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.

REWIND



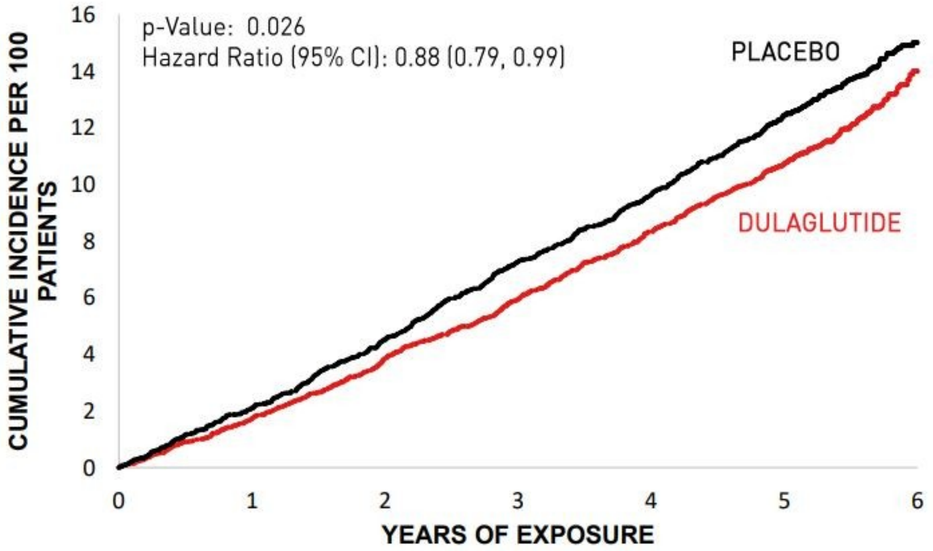
REWIND

TRULICITY CV OUTCOME TRIAL

Lilly

PRIMARY MACE 3 RESULT

Dulaglutide significantly reduced the risk of Major Adverse Cardiovascular Events (MACE 3: CV death, non-fatal MI or non-fatal stroke) **by 12% vs. placebo**

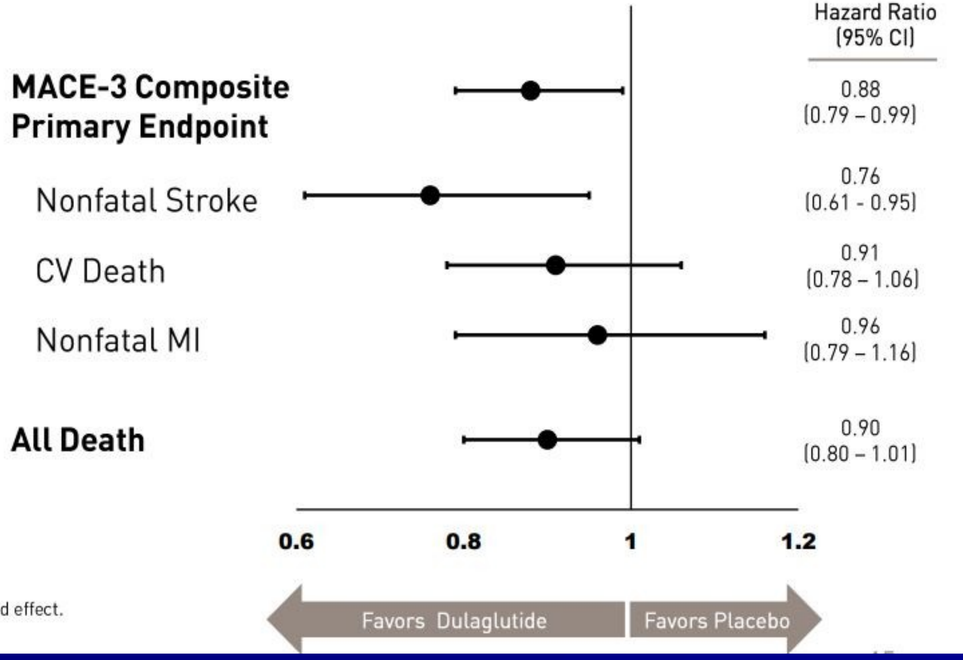


Note: Hazard Ratio and its CI and p-value obtained from Cox Proportional Hazards Regression Model with treatment as a fixed effect.

Gerstein et al. Lancet 2019.

CV OUTCOMES

Consistent effect across three components of MACE, greatest difference observed in Nonfatal Stroke



Medications Showing CV Benefit:

Metformin – (obese, newly-dx) - ★CV event and (AC)death

Pioglitazone – (recent CV event) - ★CV event and (AC) death

SGLT-2's - ★ hospitalization for HF and (AC) death

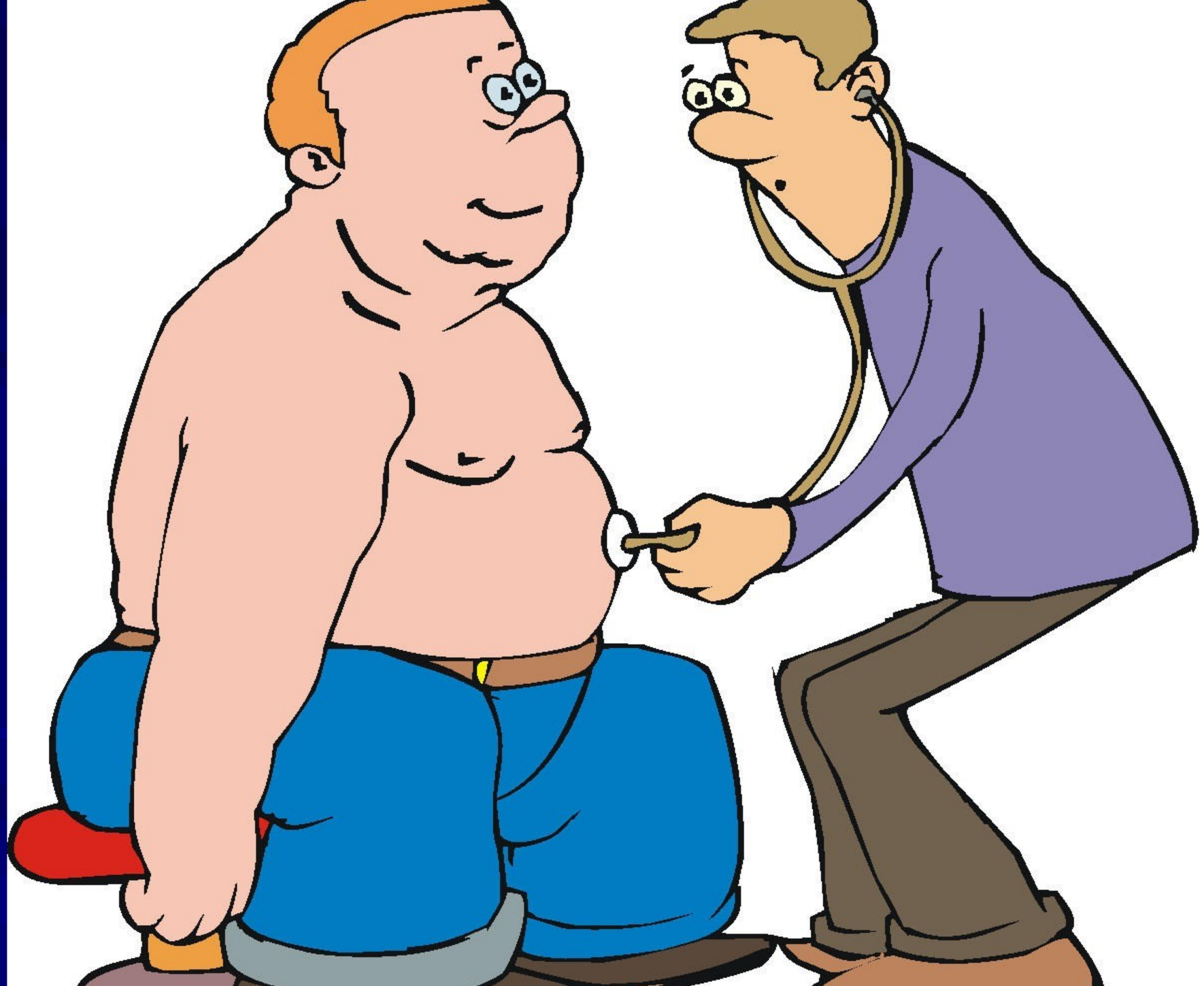
Empagliflozin – ★MACE and (CV) death

Canagliflozin - ★MACE

Liraglutide – ★MACE and (CV) death (DM w/ CVD)

Semaglutide – ★MACE and non-fatal stroke (DM w/ CVD)

Dulaglutide – ★MACE and non-fatal stroke (DM w/wo CVD)



MOC Assessment Question:

Which of the following medications have demonstrable reduction in cardiovascular risk?

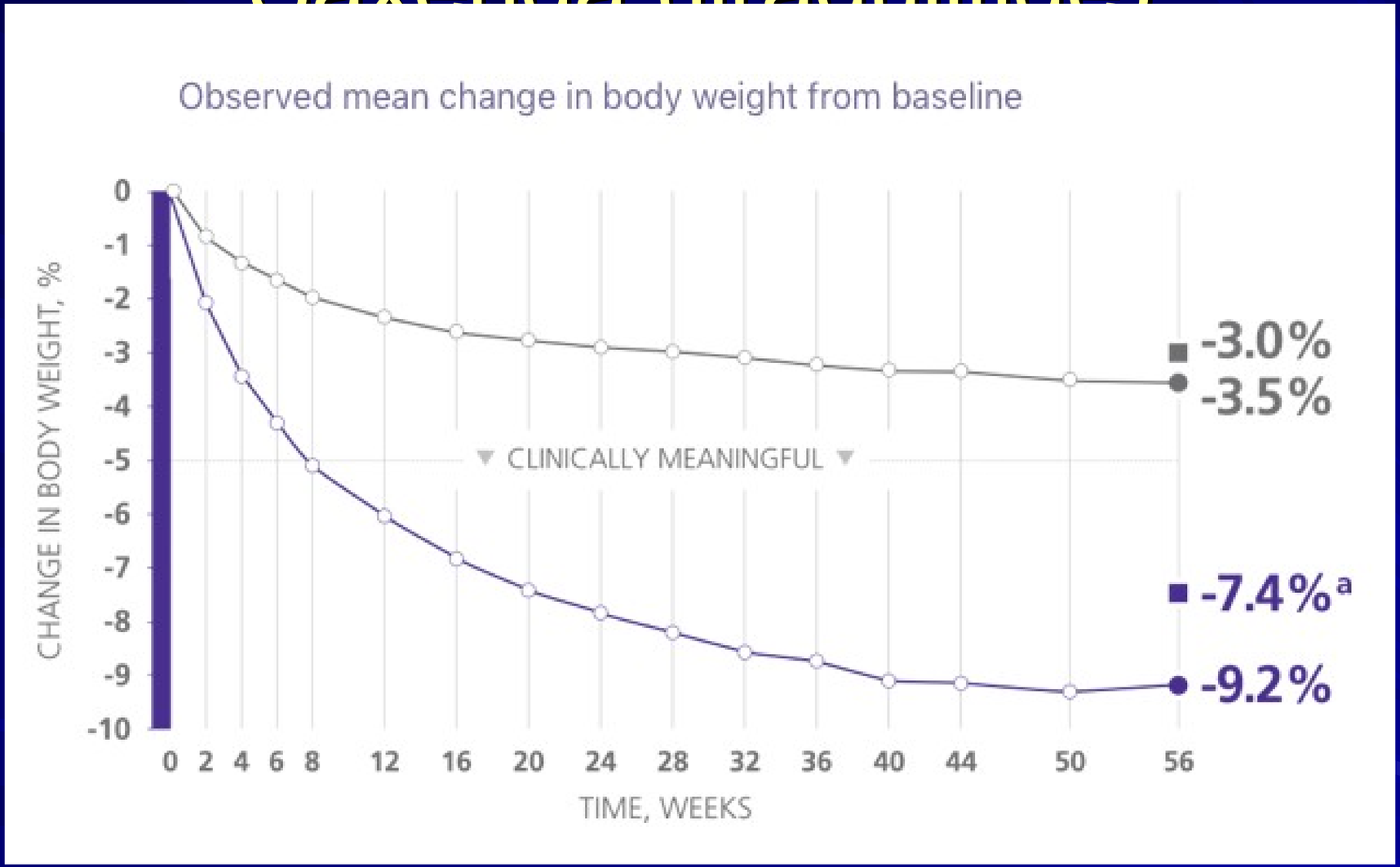
A. Liraglutide
B. Semaglutide
C. Dulaglutide
D. Empaglaflozin
E. All of the above

QUESTIONS

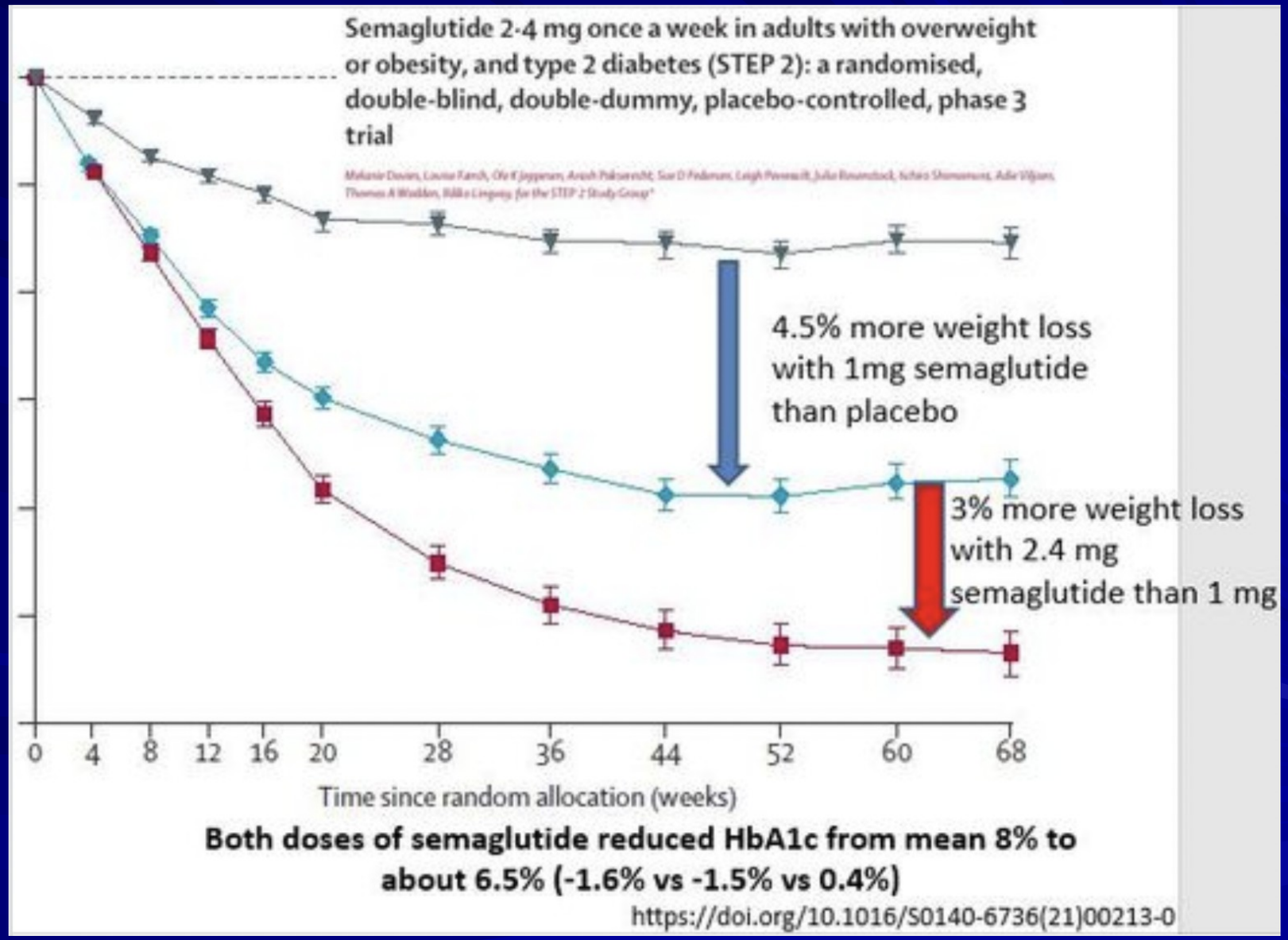
benseale@yahoo.com

Incretins for Weight Loss ?

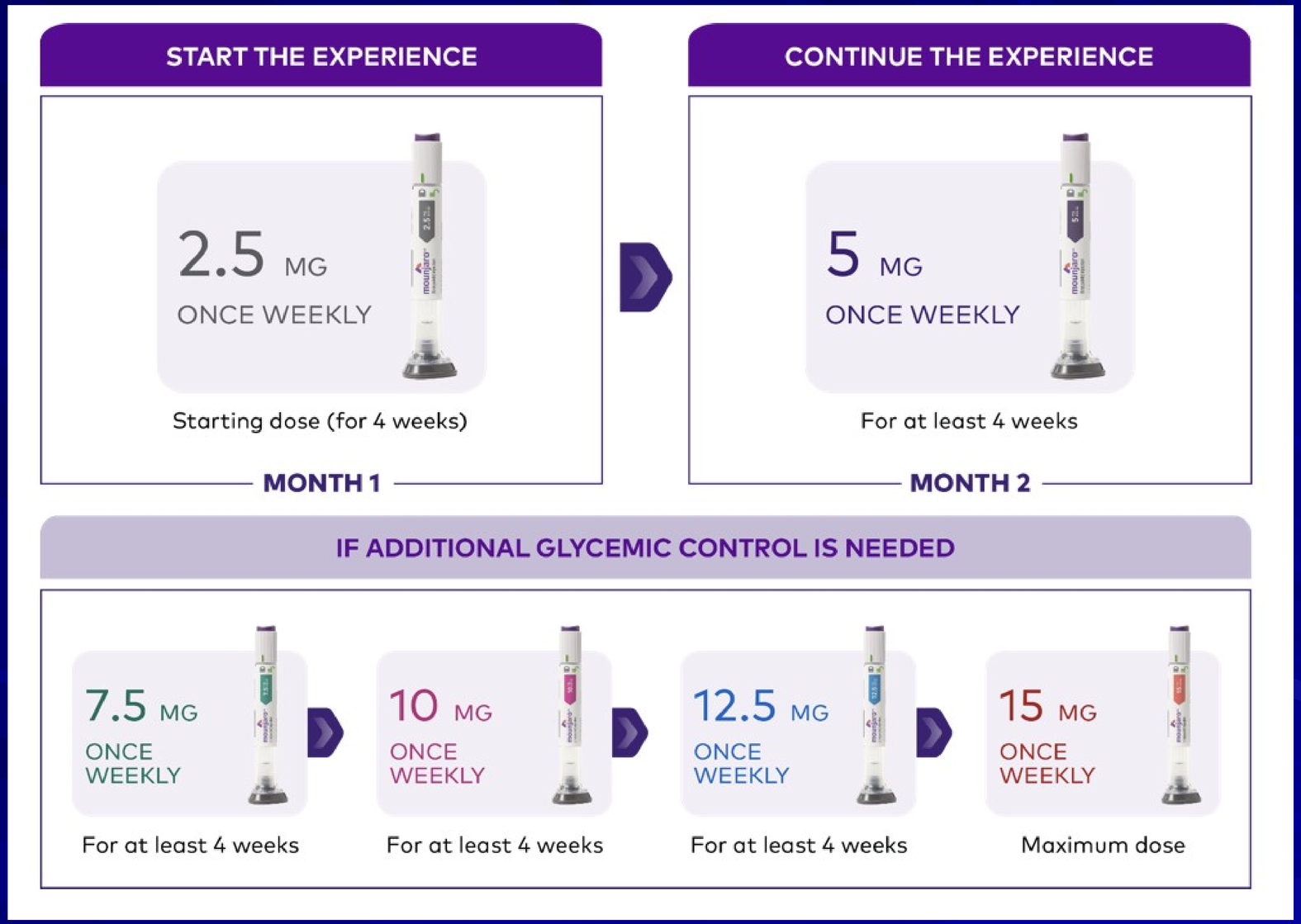
Saxenda (liraglutide)



Wegovy (semaglutide)



Mounjaro (tirzepatide)

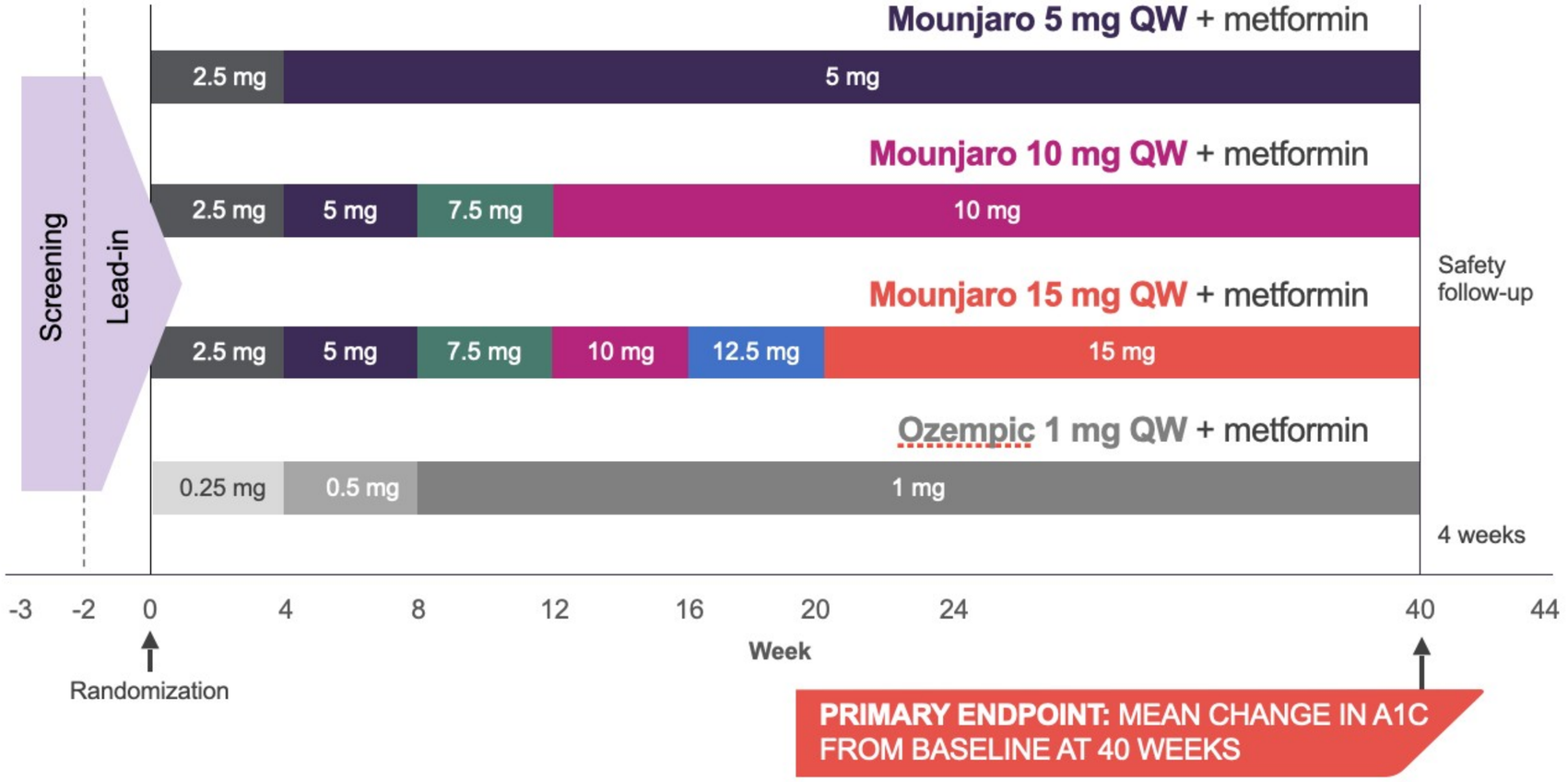


MOUNJARO IS THE FIRST AND ONLY APPROVEDGIP AND GLP-1 RECEPTOR AGONIST[1]

Mounjaro is a single molecule that activates GIP and GLP-1 receptors in the body

Structure	Based on the backbone of native GIP[1,2]
Mean half-life	Approximately 5 days, enabling once-weekly dosing[1,2]
Dose adjustment	No dose adjustment of Mounjaro is recommended for patients with renal or hepatic impairment[1]

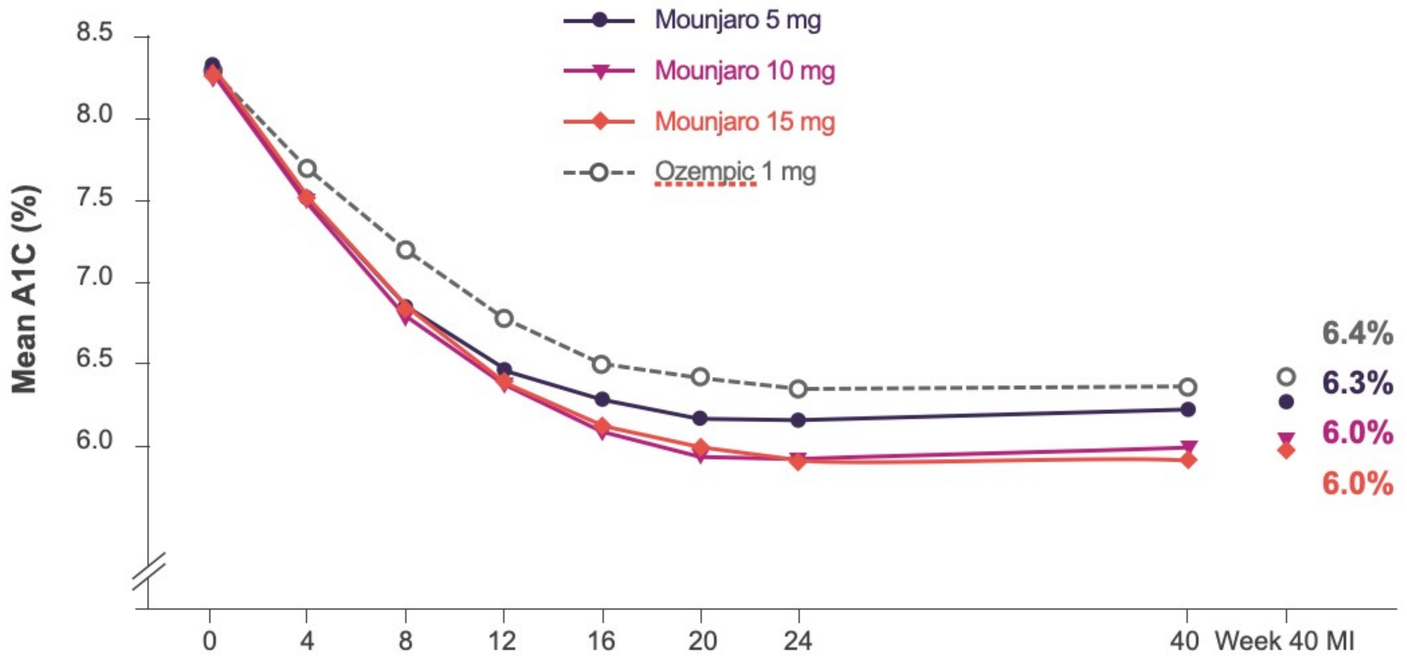
MOUNJARO 5 MG, 10 MG, AND 15 MG VS OZEMPIC 1 MG AS THE ONLY ADD-ON TO METFORMIN[1,2]



MOUNJARO DELIVERED SUSTAINED A1C REDUCTIONS AT EVERY DOSE THROUGH WEEK 40

Observed mean A1C over time from baseline to 40 weeks†

Mean baseline A1C for all treatment groups: 8.3%

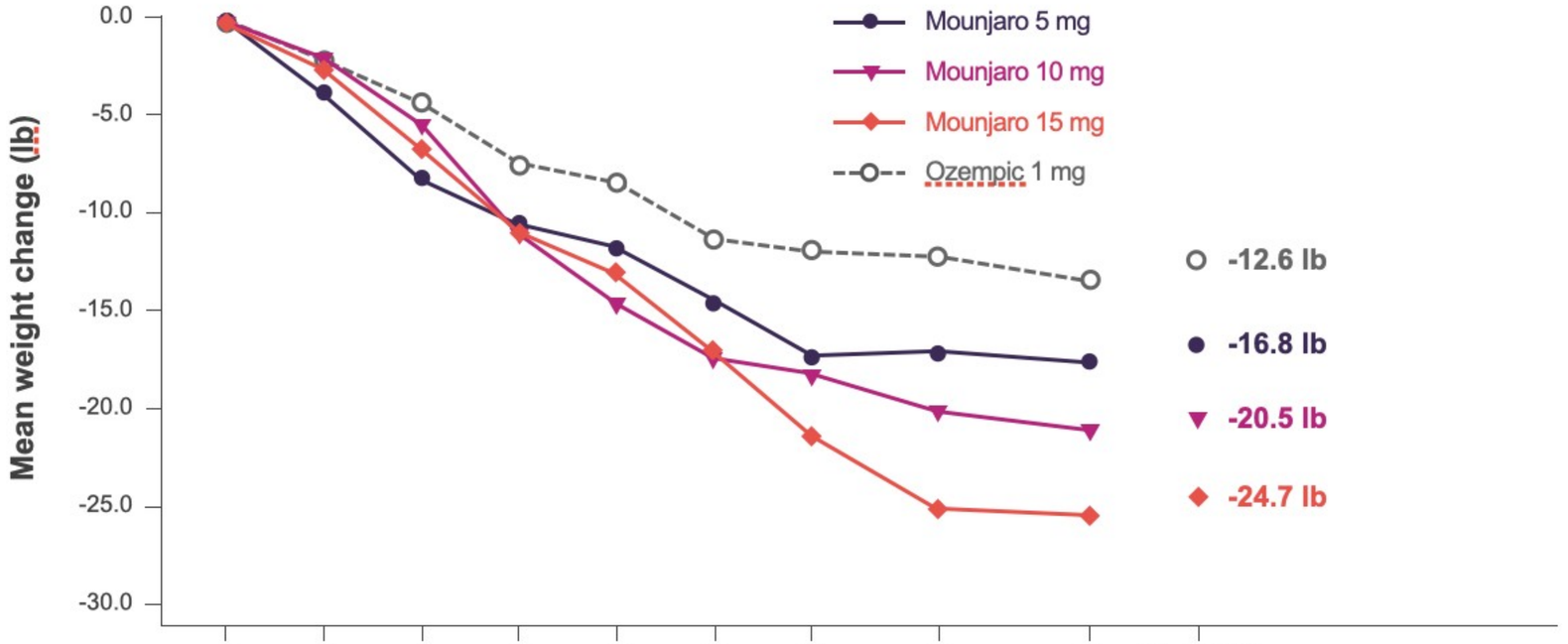


Number of patients									
Mounjaro 5 mg	470							451	470
Mounjaro 10 mg	469							445	469
Mounjaro 15 mg	469							447	469
Ozempic 1 mg	468							443	468

PATIENTS TAKING MOUNJARO HAD WEIGHT REDUCTIONS THAT CONTINUED THROUGH 40 WEEKS[1-3,*,†]

Observed mean weight change over time from baseline to 40 weeks[1-3,†]

Mean baseline weight: Mounjaro 5 mg, 203.9 lb; Mounjaro 10 mg, 209.1 lb; Mounjaro 15 mg, 206.8 lb; Ozempic 1 mg, 206.6 lb



Number of patients	0	40	Week 40 MI
Mounjaro 5 mg	470	450	470
Mounjaro 10 mg	469	443	469
Mounjaro 15 mg	469	448	469
Ozempic 1 mg	468	444	468

How did we get here?

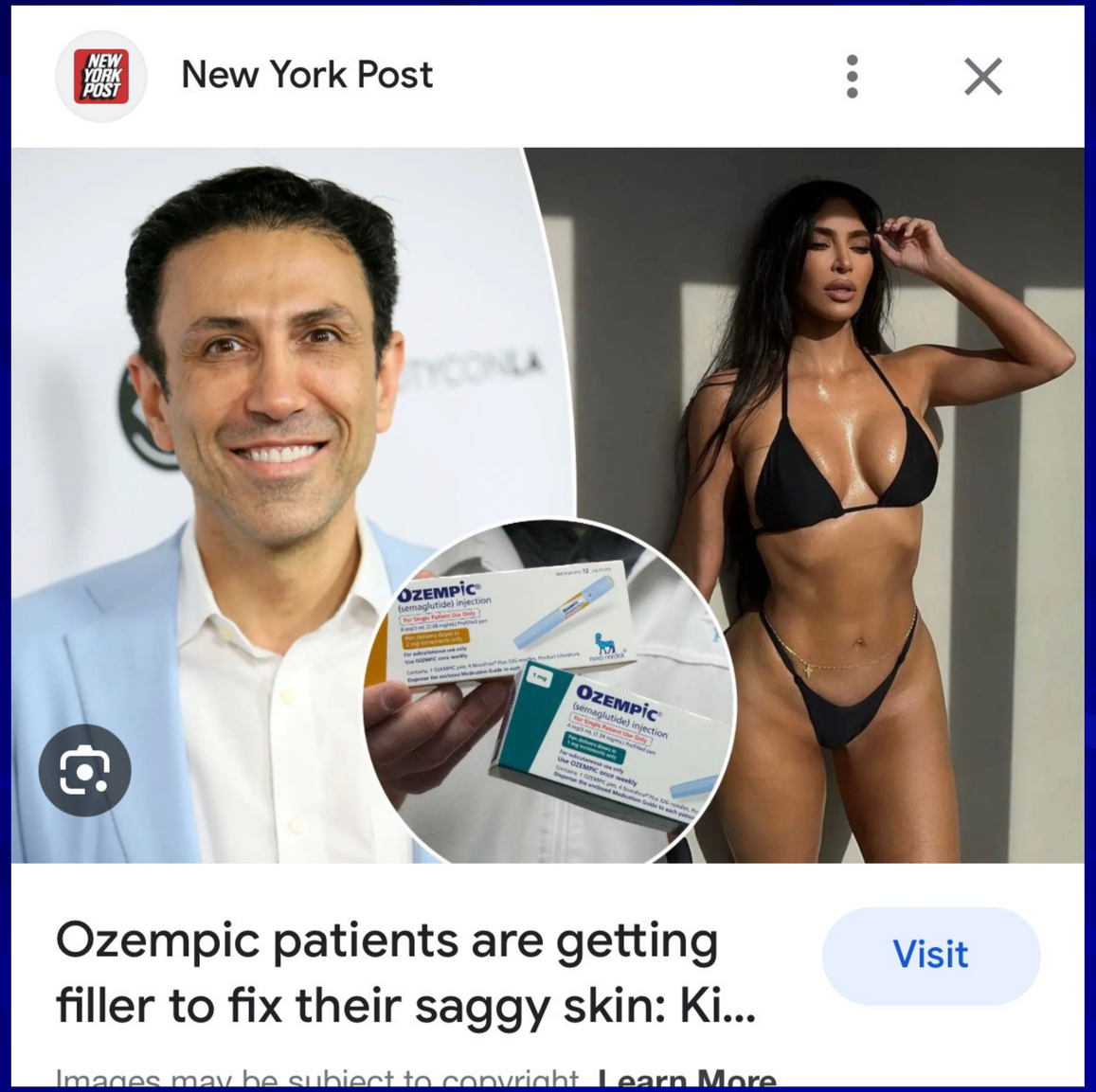
How did we get here?

From your Watch later playlist

Semaglutide, Kardashians, and Female Body Image

PowerfulJRE · 2M views · 7 months ago

How did we get here?



How did we get here?

In Summary

Treat to goal
Be aggressive early
Avoid hypoglycemia
Choose agents that improve outcomes
  CVD, stroke
  CHF
  Renal loss

Blame Kim Kardashian