Nuove opportunità terapeutiche nel Diabete Mellito

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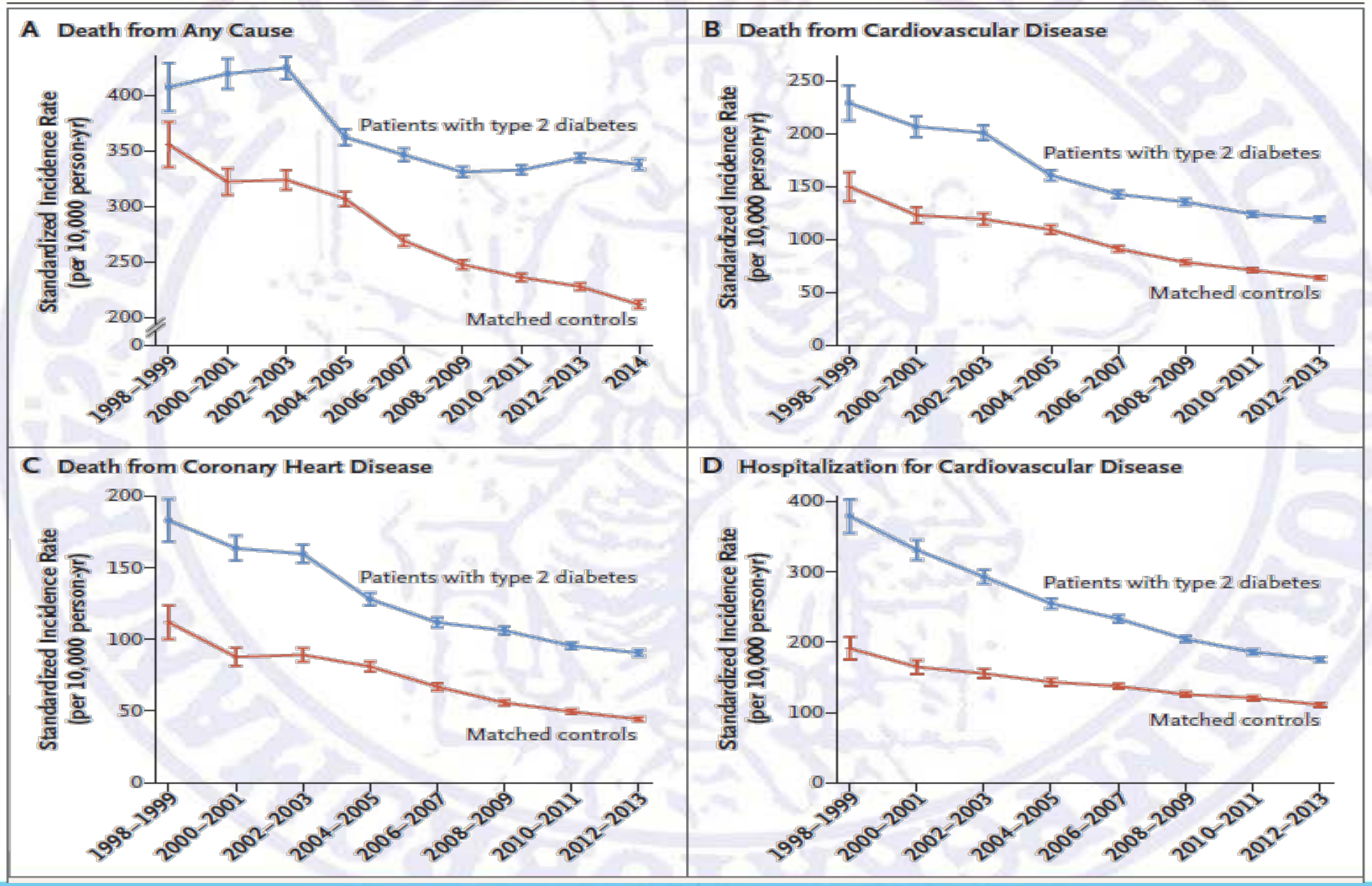
Potenziali conflitti d'interessi

Il prof. Raffaele Napoli dichiara di aver ricevuto negli ultimi due anni compensi o finanziamenti dalle seguenti aziende:

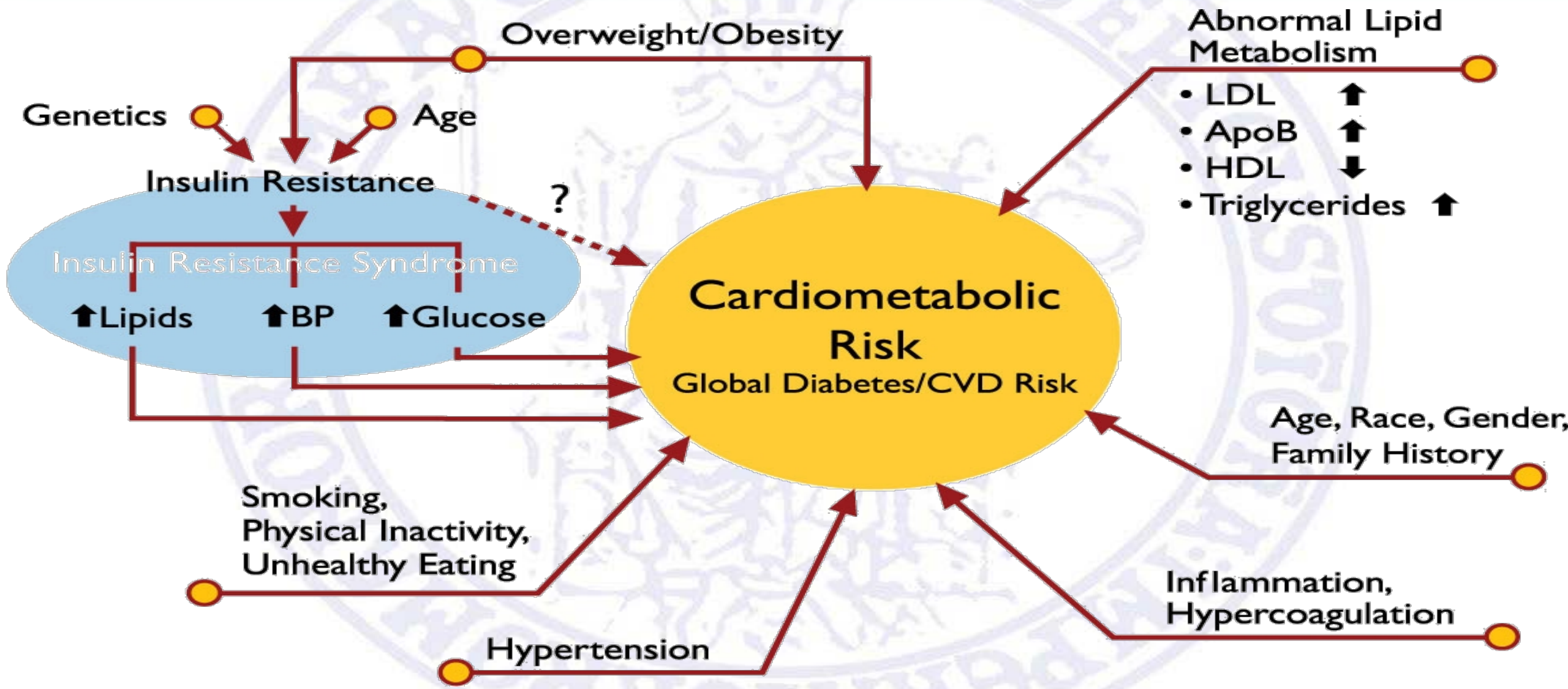
- Astra Zeneca
- Boehringer Ingelheim
- Eli Lilly
- MSD
- Novo Nordisk
- Sanofi
- Alpha Sigma
- Takeda

Diabetes-related deaths in the Swedish NDR, 1998-2014



Rawshani A, et al. *N Engl J Med* 2017;376:1407-1418.

Cardiometabolic Risk



Impact of Intensive Therapy for Diabetes

Study	Microvasc		CVD		Mortality	
UKPDS	↓	↓	↔	↓	↔	↓
DCCT / EDIC*	↓	↓	↔	↓	↔	↔
ACCORD	↓		↔		↑	
ADVANCE	↓		↔		↔	
VADT	↓		↔		↔	

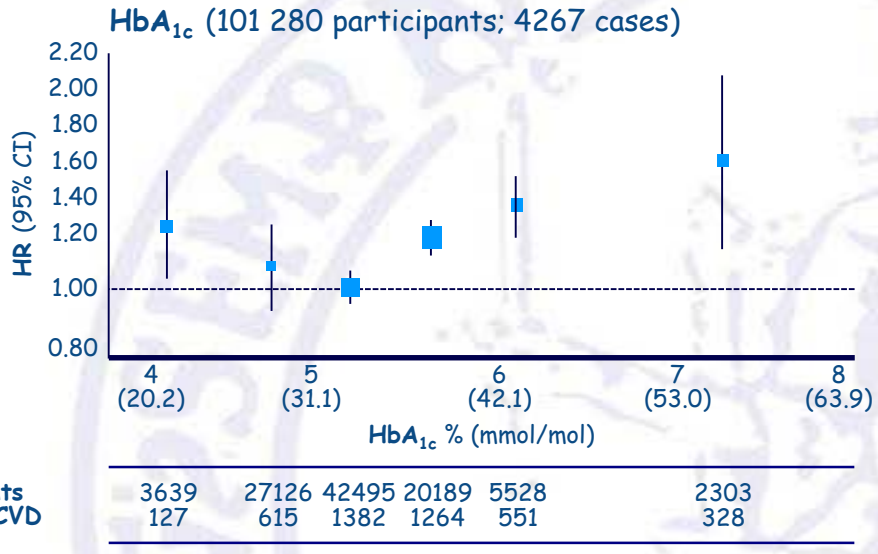
* in T1DM

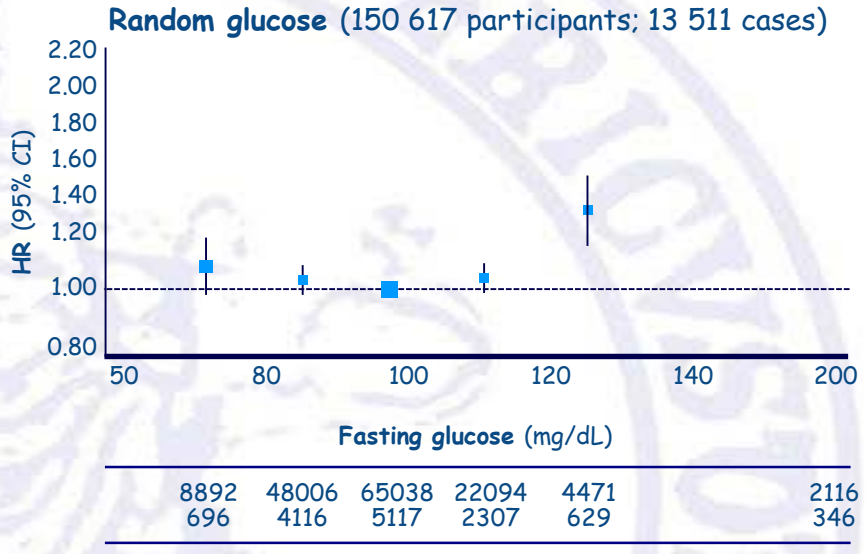
Initial Trial

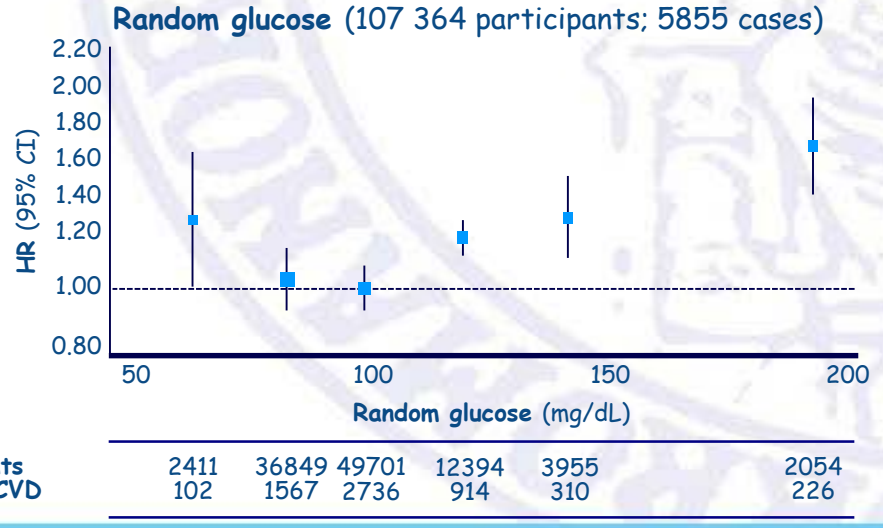
Long Term Follow-up

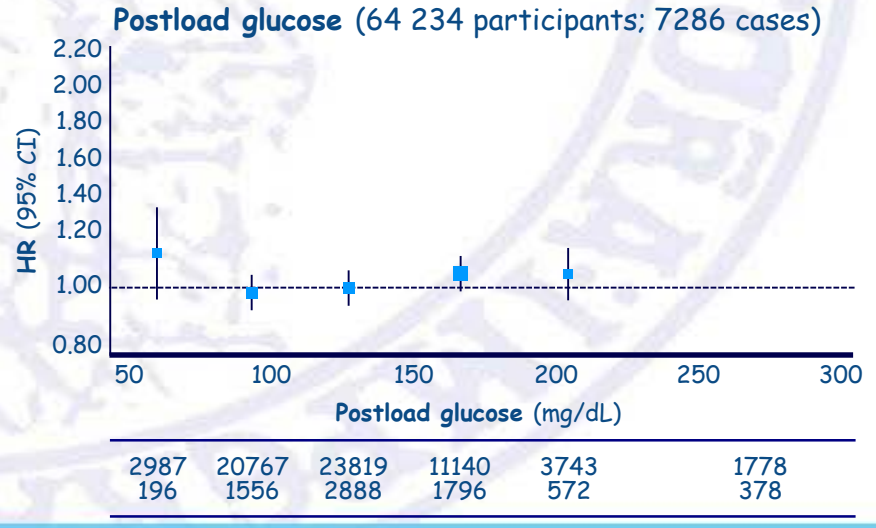
UKPDS *Lancet* 1998; Holman RR et al. *NEJM* 2008; DCCT Research Group. NEJM 1993; Gerstein HC et al. *NEJM* 2008; Patel A et al. NEJM 2008; Duckworth W et al. NEJM 2009.

HbA1c Measurement and Prediction of CVD

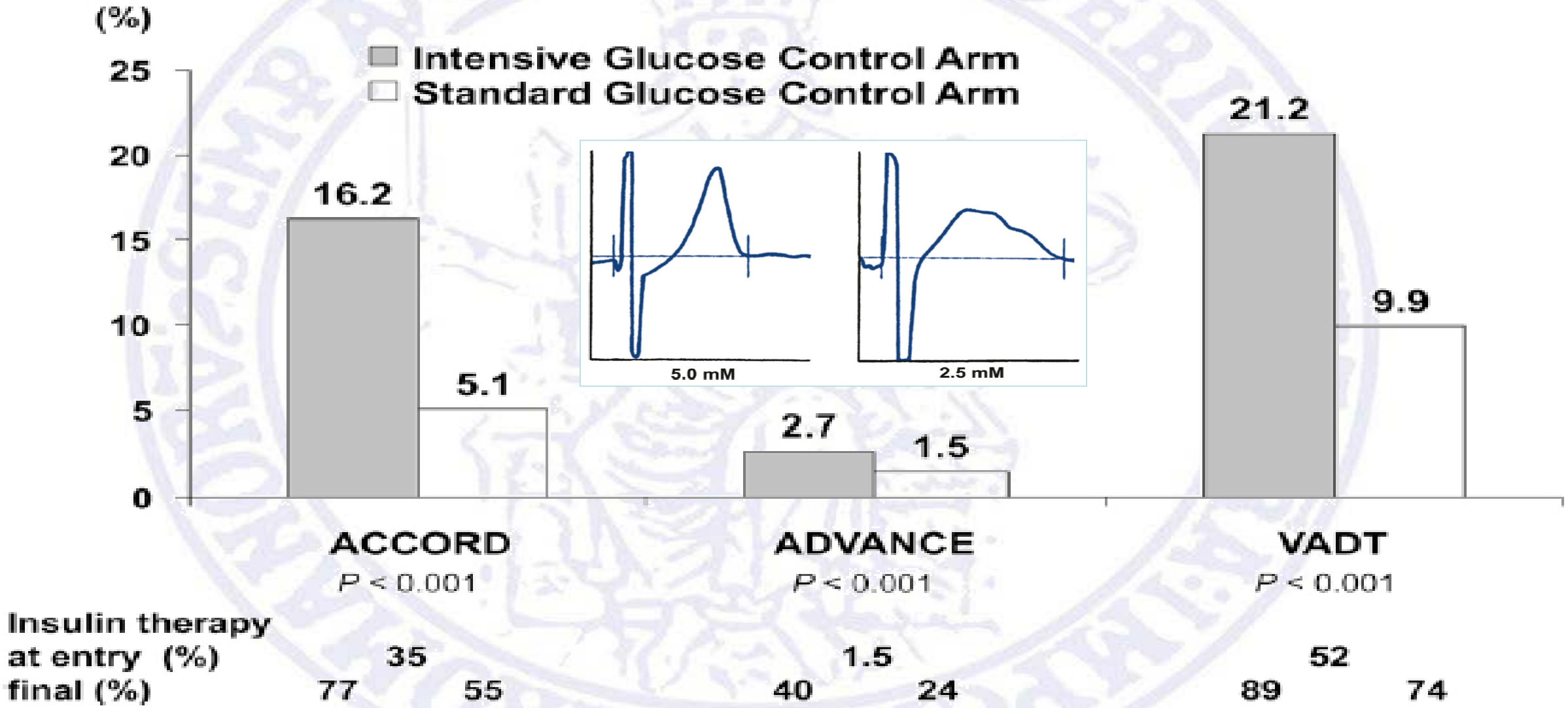




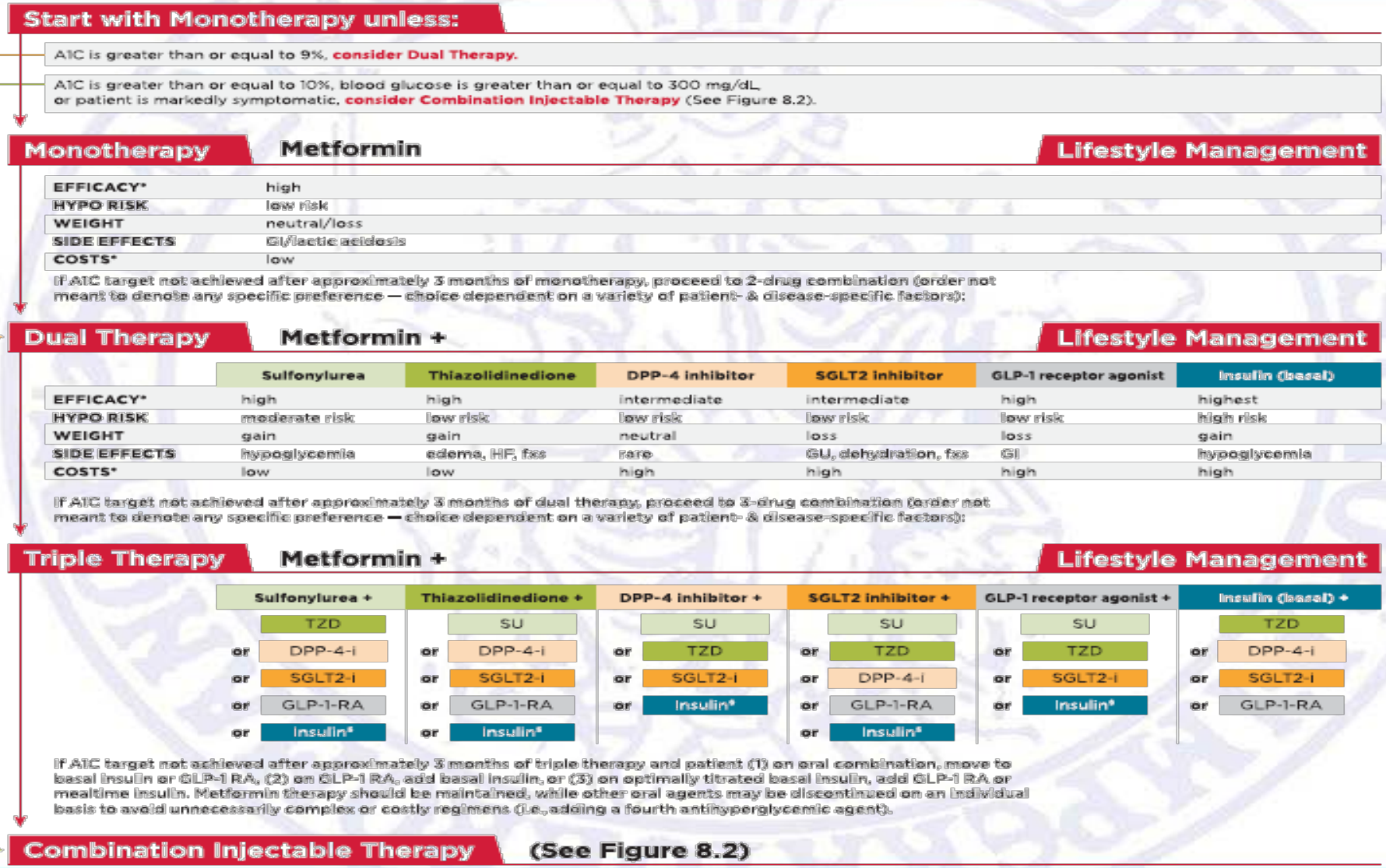




Severe Hypoglycemic Events

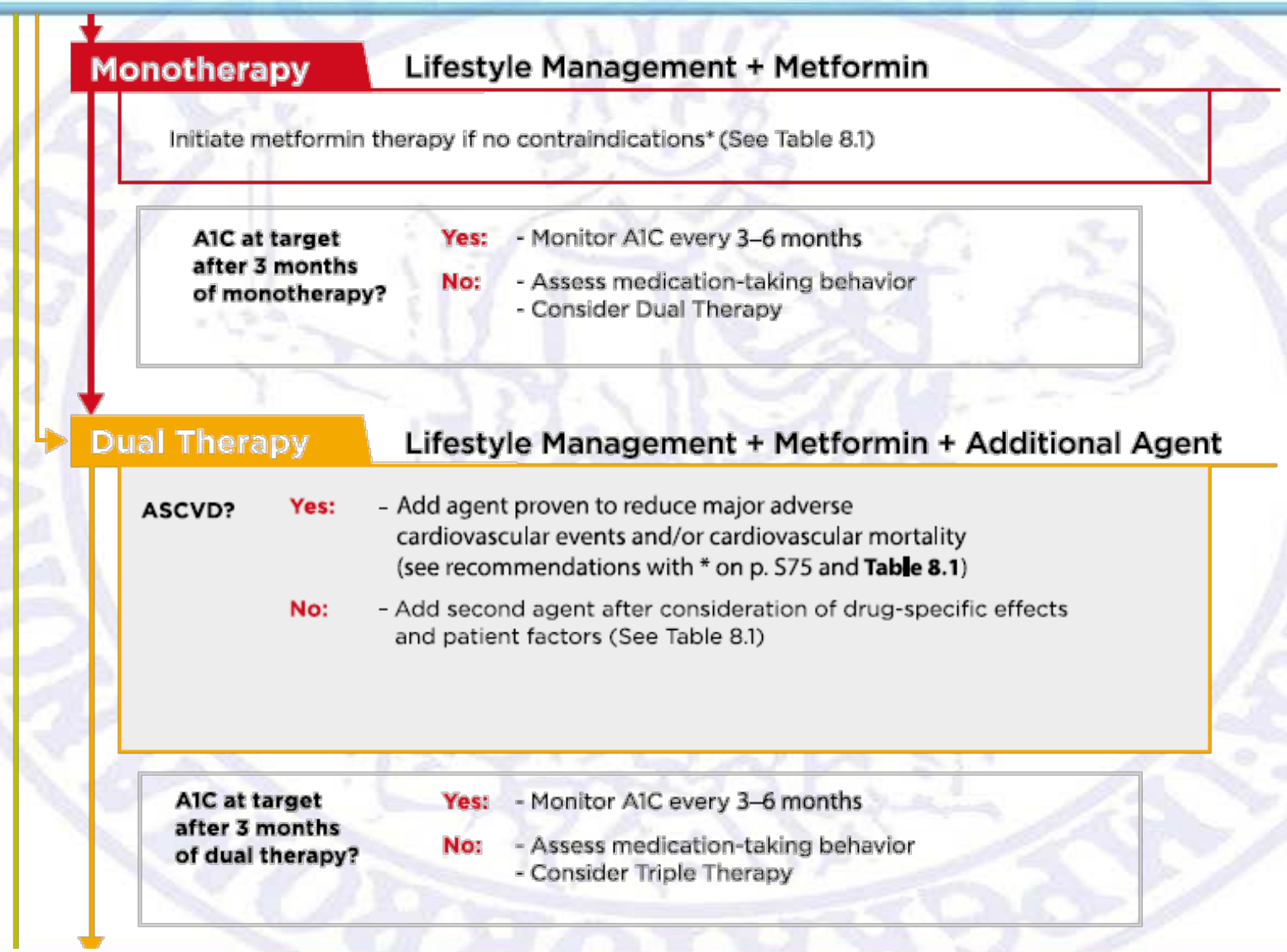


Standards of Medical Care in Diabetes-ADA

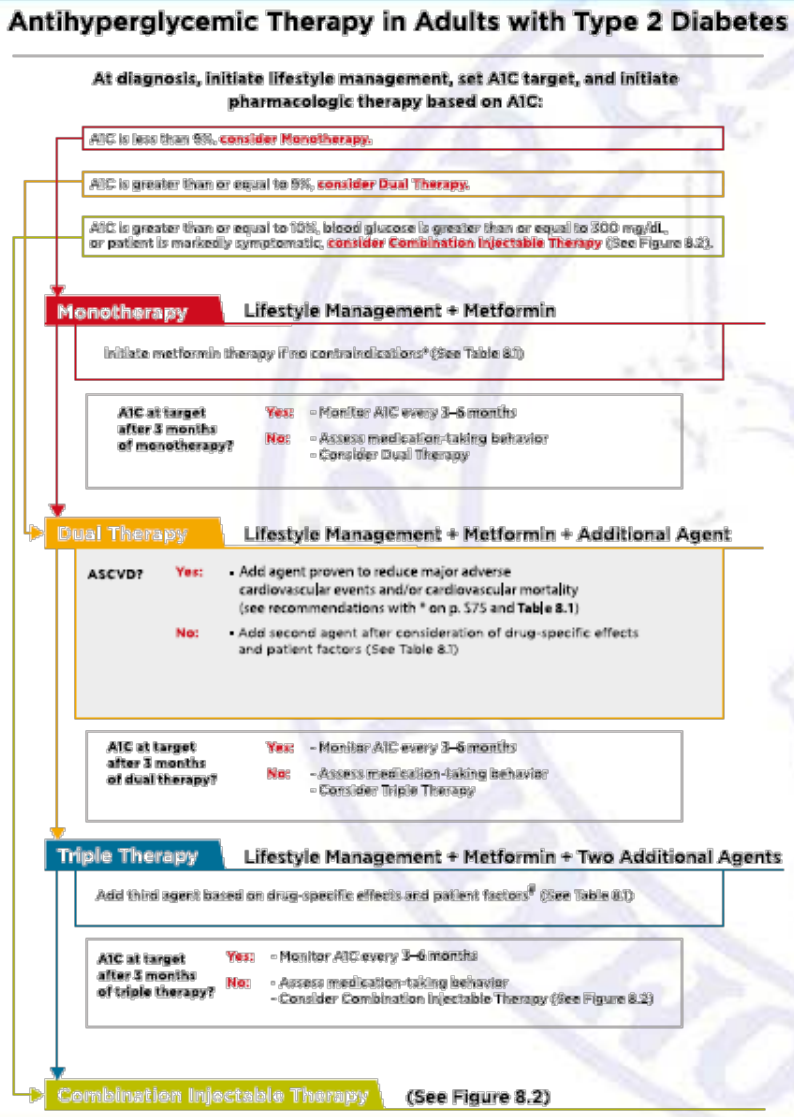


American Diabetes Association Standards of Medical Care in Diabetes, 2017

Standards of Medical Care in Diabetes-ADA



Drug-specific and patient factors to consider in treatment of T2D adults



	Efficacy*	Hypoglycemia	Weight Change	CV Effects		Cost	Oral/SQ	Renal Effects		Additional Considerations
				ASCVD	CHF			Progression of DKD	Dosing/Use considerations	
Metformin	High	No	Neutral (Potential for Modest Loss)	Potential Benefit	Neutral	Low	Oral	Neutral	▪ Contraindicated with eGFR <30	▪ Gastrointestinal side effects cor (diarrhea, nausea) ▪ Potential for B12 deficiency
SGLT-2 Inhibitors	Intermediate	No	Loss	Benefit: canagliflozin, empagliflozin†	Benefit: canagliflozin, empagliflozin	High	Oral	Benefit: canagliflozin, empagliflozin	▪ Canagliflozin: not recommended with eGFR <45 ▪ Dapagliflozin: not recommended with eGFR <60; contraindicated with eGFR <30 ▪ Empagliflozin: contraindicated with eGFR <30	▪ **FDA Black Box:** Risk of amputation (**canagliflozin**) ▪ Risk of bone fractures (canagliflozin) ▪ DKA risk (all agents, rare in T2DM) ▪ Genitourinary infections ▪ Risk of volume depletion, hypotension ▪ ↑LDL cholesterol
GLP-1 RAs	High	No	Loss	Neutral: lixisenatide, exenatide extended release Benefit: liraglutide†	Neutral	High	SQ	Benefit: liraglutide	▪ Exenatide: not indicated with eGFR <30 ▪ Lixisenatide: caution with eGFR <30 ▪ Increased risk of side effects in patients with renal impairment	▪ **FDA Black Box:** Risk of thyroid C-cell tumors (**liraglutide, albiglutide, dulaglutide, exenatide extended release**) ▪ Gastrointestinal side effects common (nausea, vomiting, diarrhea) ▪ Injection site reactions ▪ ?Acute pancreatitis risk
DPP-4 Inhibitors	Intermediate	No	Neutral	Neutral	Potential Risk: saxagliptin, alogliptin	High	Oral	Neutral	▪ Renal dose adjustment required; can be used in renal impairment	▪ Potential risk of acute pancreatitis ▪ Joint pain
Thiazolidinediones	High	No	Gain	Potential Benefit: pioglitazone	Increased Risk	Low	Oral	Neutral	▪ No dose adjustment required ▪ Generally not recommended in renal impairment due to potential for fluid retention	▪ **FDA Black Box:** Congestive heart failure [**pioglitazone, rosiglitazone**] ▪ Fluid retention (edema; heart failure) ▪ Benefit in NASH ▪ Risk of bone fractures ▪ Bladder cancer (pioglitazone) ▪ ↑LDL cholesterol (rosiglitazone)
Sulfonylureas (2nd Generation)	High	Yes	Gain	Neutral	Neutral	Low	Oral	Neutral	▪ Glyburide: not recommended ▪ Glipizide & glimepiride: initiate conservatively to avoid hypoglycemia	▪ FDA Special Warning on increased risk of cardiovascular mortality based on studies of an older sulfonylurea (tolbutamide)
Insulin Human Insulin	Highest	Yes	Gain	Neutral	Neutral	Low	SQ	Neutral	▪ Lower insulin doses required with a decrease in eGFR; titrate per clinical response	▪ Injection site reactions ▪ Higher risk of hypoglycemia with human insulin (NPH or premixed formulations) vs. analogs
Insulin Analogs						High	SQ			

*See ref. 31 for description of efficacy. †FDA approved for CVD benefit. CVD, cardiovascular disease; DKA, diabetic ketoacidosis; DKD, diabetic kidney disease; NASH, nonalcoholic steatohepatit RAs, receptor agonists; SQ, subcutaneous; T2DM, type 2 diabetes.

STANDARDS OF MEDICAL CARE IN DIABETES—2018, Diabetes Care, January 2018

Drug-specific and patient factors to consider in treatment of T2D adults

	Efficacy*	Hypoglycemia	Weight Change	CV Effects		Cost	Oral/SQ	Renal Effects		Additional Considerations
				ASCVD	CHF			Progression of DKD	Dosing/Use considerations	
SGLT-2 inhibitors	Intermediate	No	Loss	Benefit: canagliflozin, empagliflozin†	Benefit: canagliflozin, empagliflozin	High	Oral	Benefit: canagliflozin, empagliflozin	▪ Canagliflozin: not recommended with eGFR <45 ▪ Dapagliflozin: not recommended with eGFR <60; contraindicated with eGFR <30 ▪ Empagliflozin: contraindicated with eGFR <30	▪ **FDA Black Box:** Risk of amputation (**canagliflozin**) ▪ Risk of bone fractures (canagliflozin) ▪ DKA risk (all agents, rare in T2DM) ▪ Genitourinary infections ▪ Risk of volume depletion, hypotension ▪ ↑LDL cholesterol
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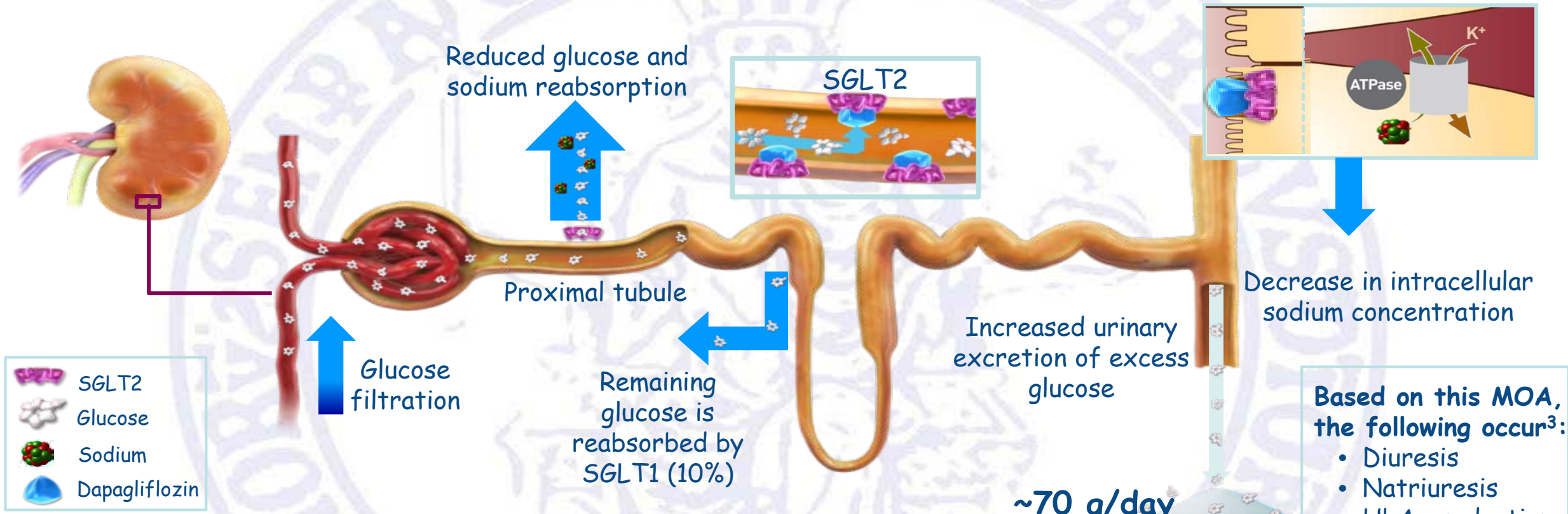
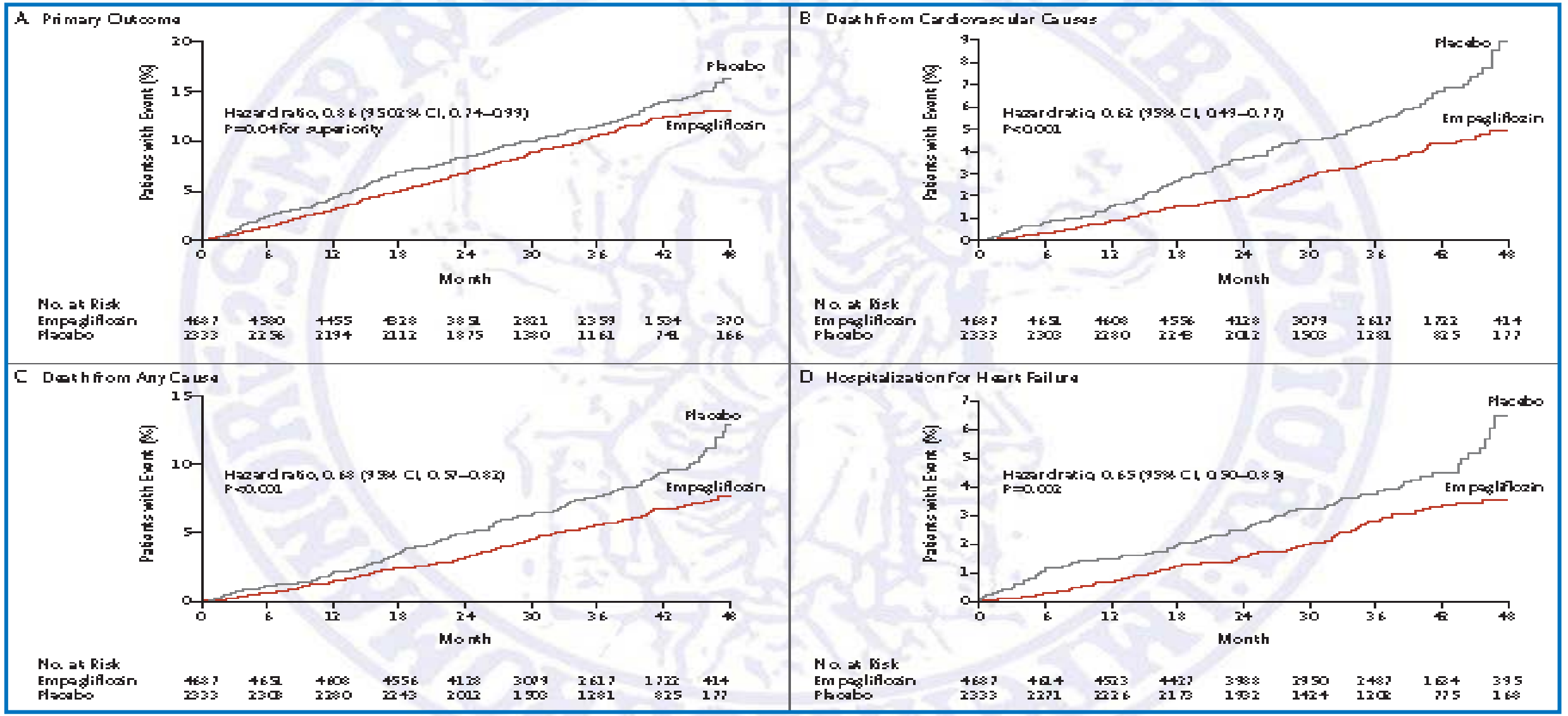
Gliflozins Block SGLT2 and Reduces Glucose and Na^+ Reabsorbtion



[a]Increases urinary volume by only ~1 additional void/day (~375 mL/day) in a 12-week study of healthy patients and patients with Type 2 diabetes[1]

HbA_{1c}, glycated hemoglobin; SBP, systolic blood pressure; SGLT, sodium-glucose co-transporter

EMPA-REG Outcome Trial



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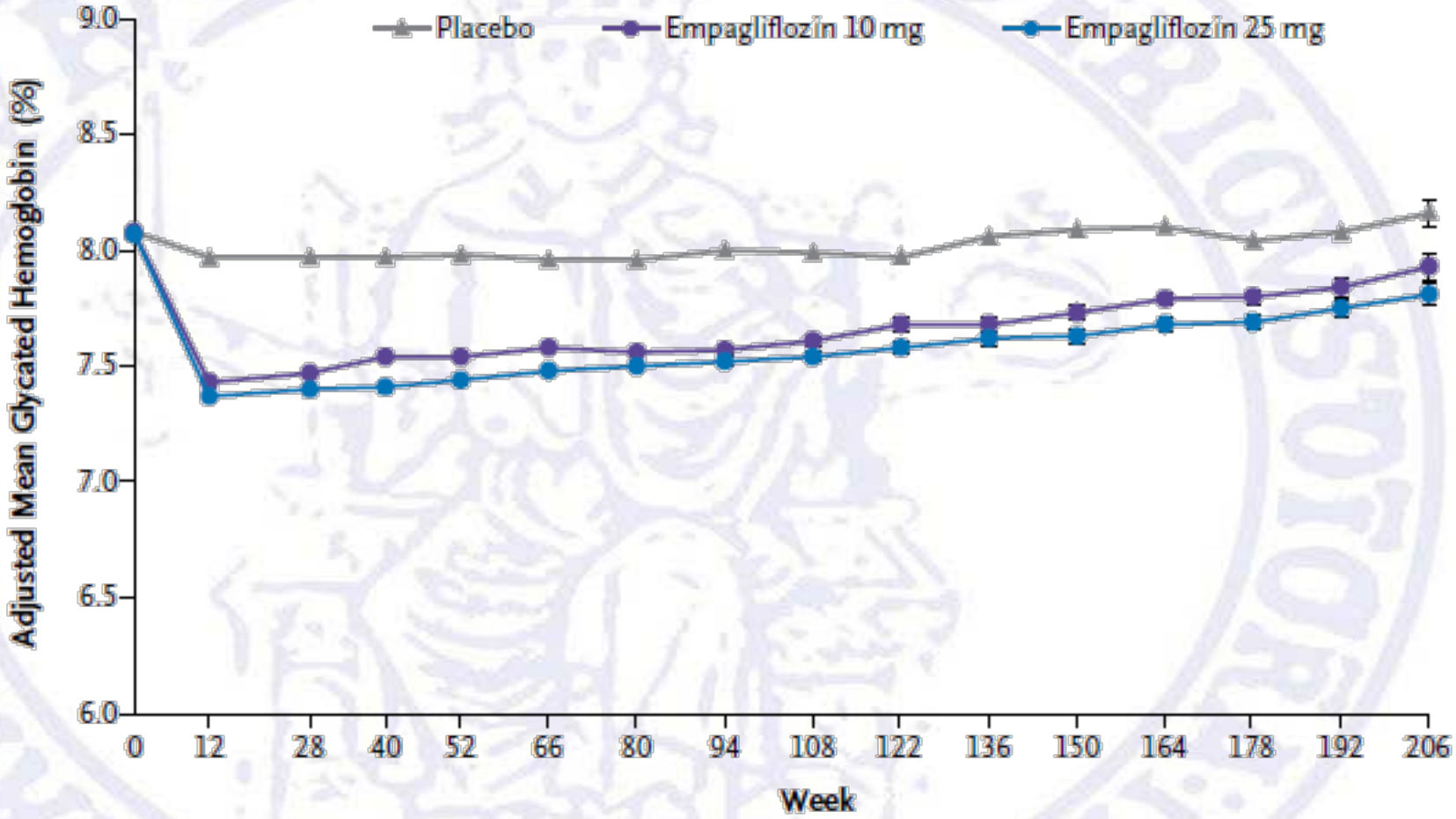
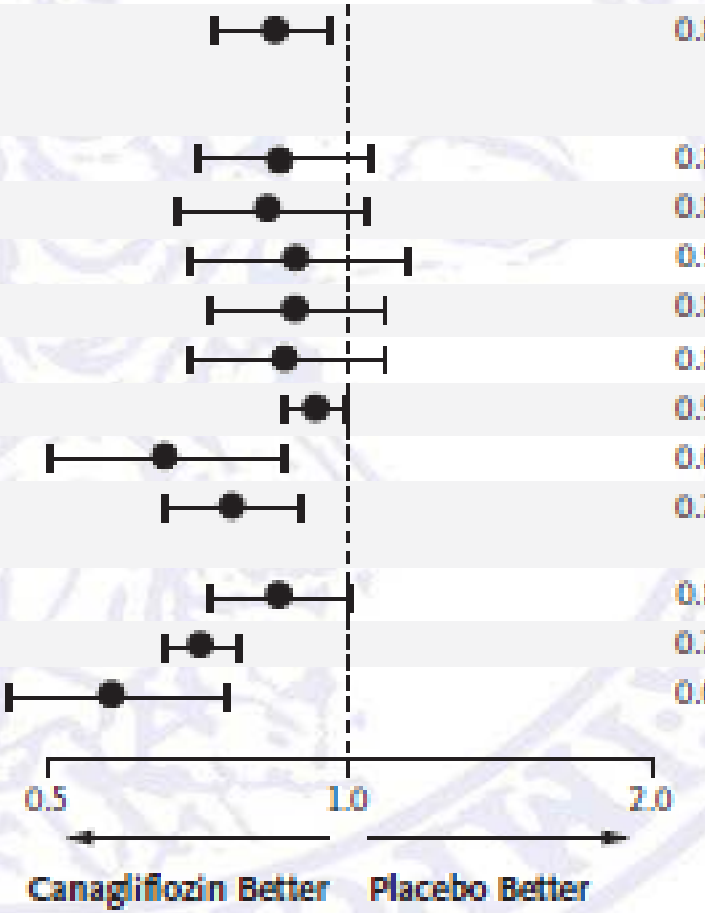


No. at Risk																
Placebo	2294	2272	2188	2133	2113	2063	2008	1967	1741	1456	1241	1109	962	705	420	151
Empagliflozin 10 mg	2296	2272	2218	2150	2155	2108	2072	2058	1805	1520	1297	1164	1006	749	488	170
Empagliflozin 25 mg	2296	2280	2212	2152	2150	2115	2080	2044	1842	1540	1327	1190	1043	795	498	195

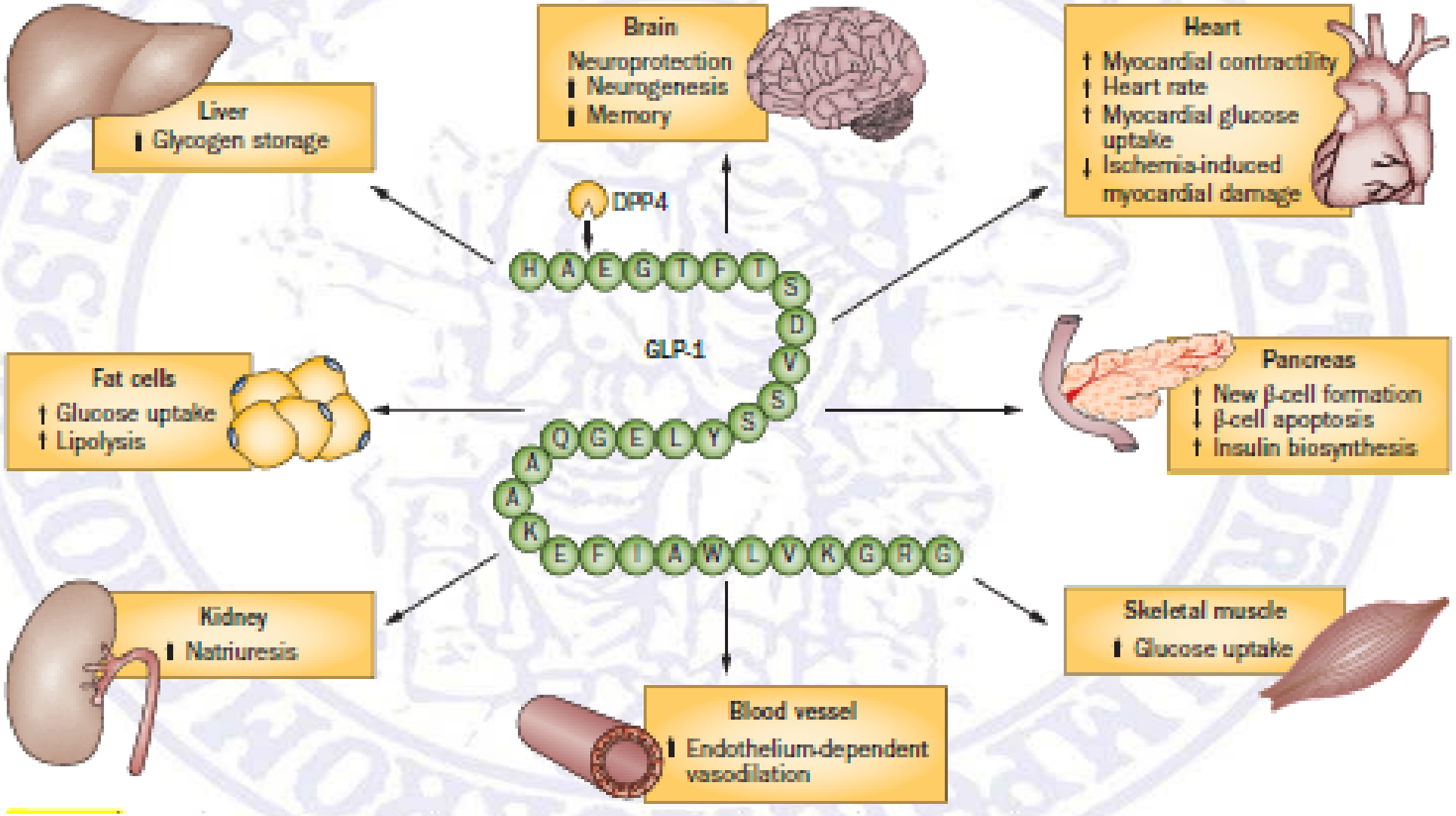
Zinman B et al., N Engl J Med 2015;373:2117-28.

CANVAS Trial

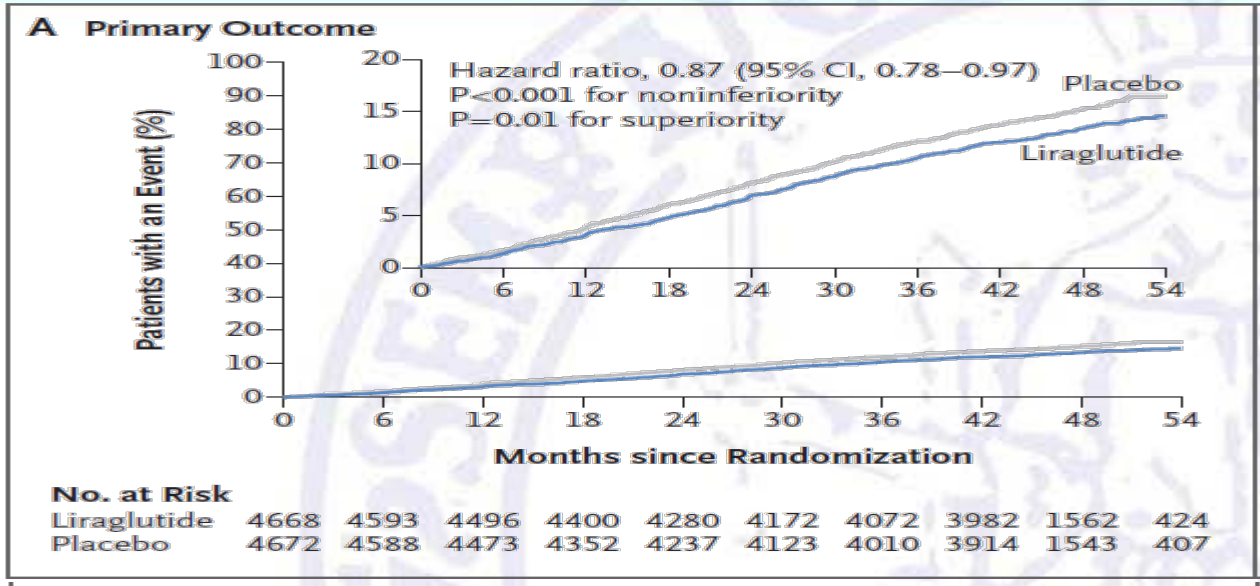
Outcome	Canagliflozin (N=5795)	Placebo (N=4347)	Hazard Ratio (95% CI)
	no. of participants per 1000 patient-yr		
Death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke	26.9	31.5	0.86 (0.75–0.97)
Death from cardiovascular causes	11.6	12.8	0.87 (0.72–1.06)
Nonfatal myocardial infarction	9.7	11.6	0.85 (0.69–1.05)
Nonfatal stroke	7.1	8.4	0.90 (0.71–1.15)
Fatal or nonfatal myocardial infarction	11.2	12.6	0.89 (0.73–1.09)
Fatal or nonfatal stroke	7.9	9.6	0.87 (0.69–1.09)
Hospitalization for any cause	118.7	131.1	0.94 (0.88–1.00)
Hospitalization for heart failure	5.5	8.7	0.67 (0.52–0.87)
Death from cardiovascular causes or hospitalization for heart failure	16.3	20.8	0.78 (0.67–0.91)
Death from any cause	17.3	19.5	0.87 (0.74–1.01)
Progression of albuminuria	89.4	128.7	0.73 (0.67–0.79)
40% reduction in eGFR, renal-replacement therapy, or renal death	5.5	9.0	0.60 (0.47–0.77)

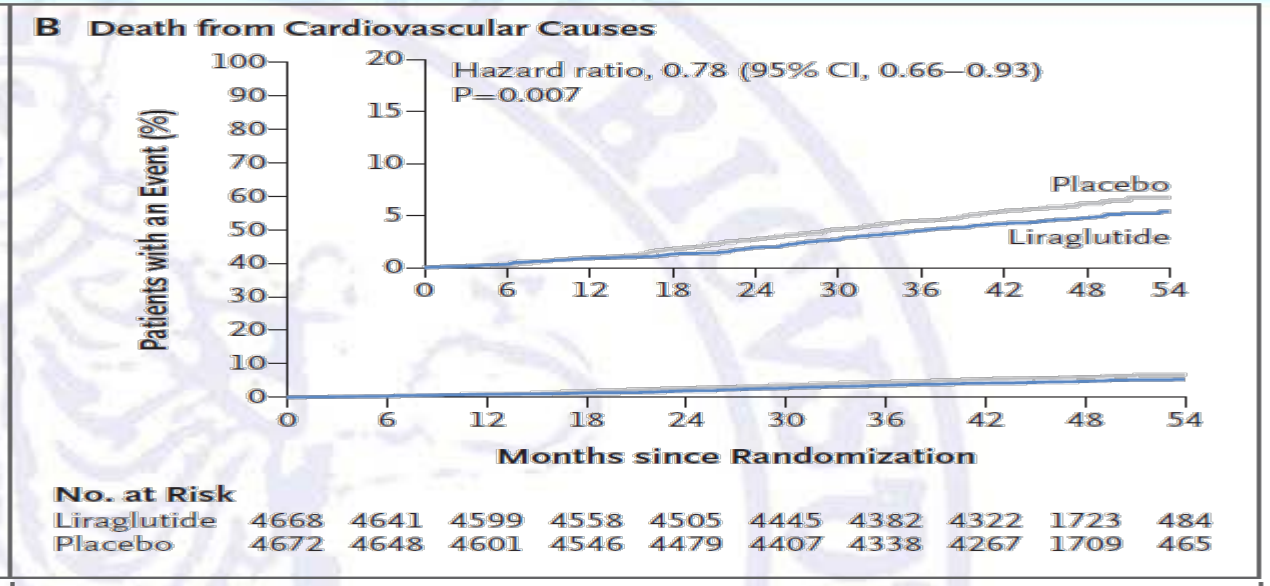


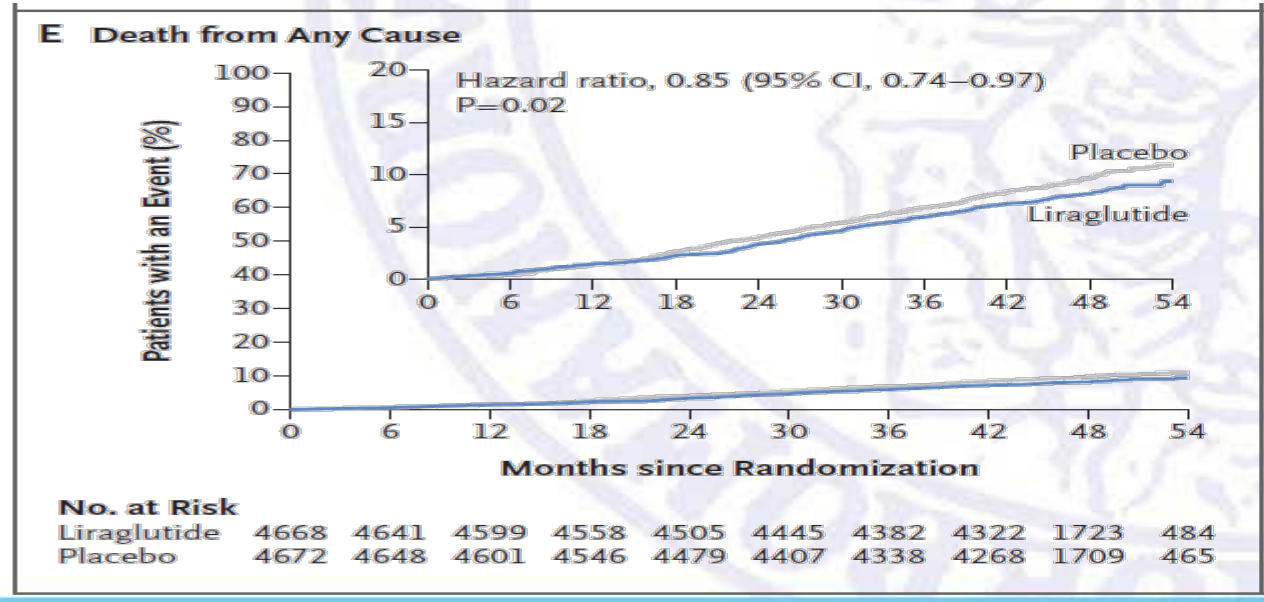
Pleiotropic effects of Glp-1 or Glp-1R agonists

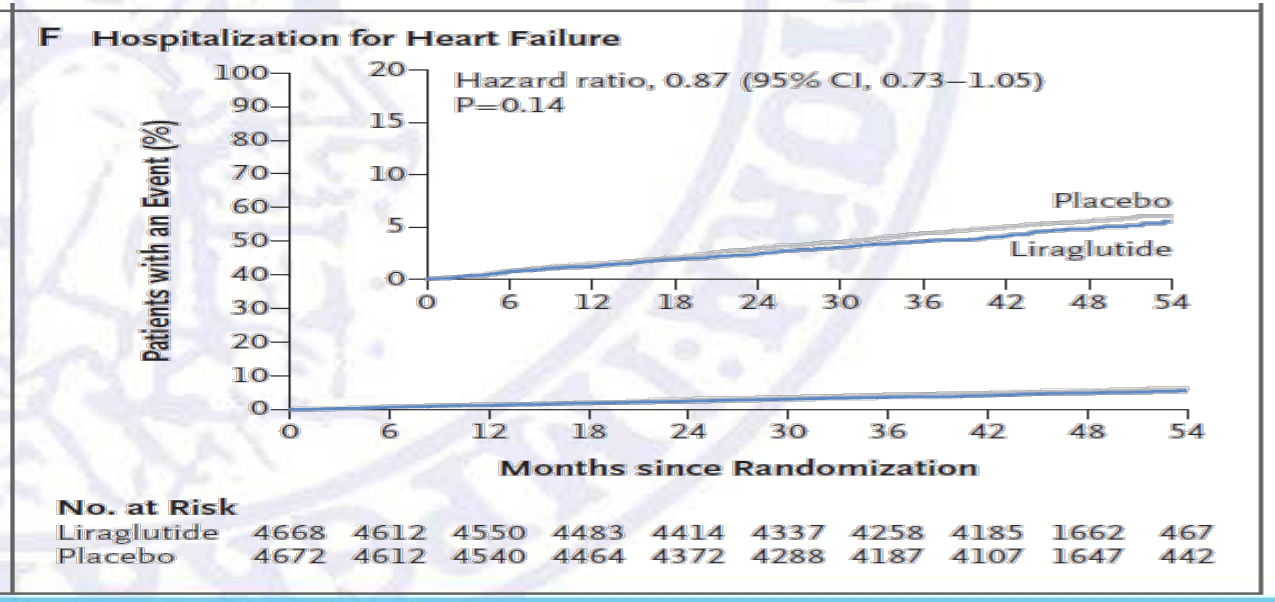


LEADER Trial









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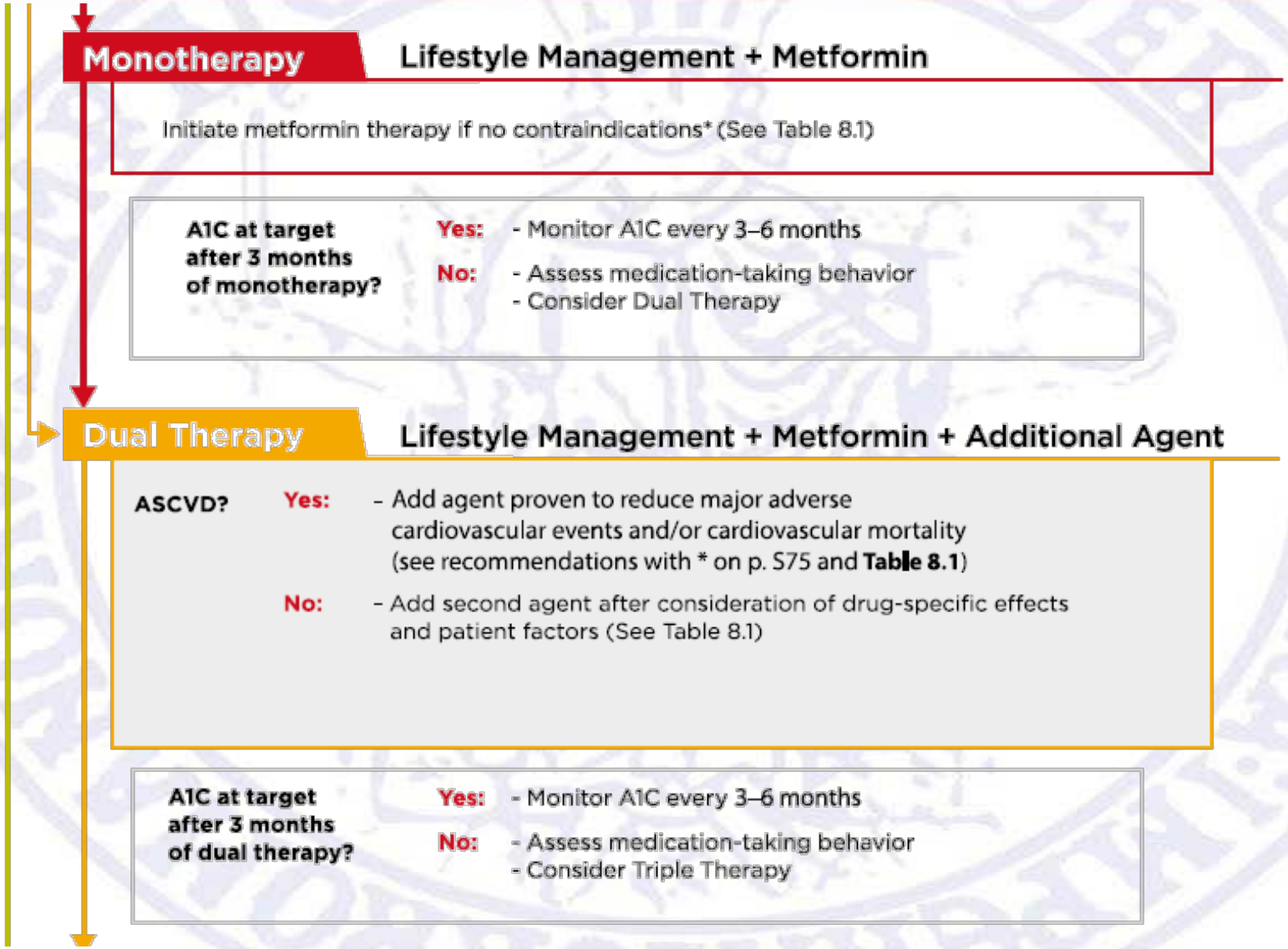
Diagnosi principali di ricovero ordinario

Rank	Dia-gnosi	Diagnosi principale	N. totale ricoveri	% su totale ricoveri (N=180.671)	Δ % Casi vs Controlli	N. pazienti ricove-rati	Ricoverati per 1000 diabetici (N=640.846)	N. medio ricoveri per paziente ricoverato	% spesa	Spesa media per ricovero	N. medio gg di degenza
1	428	Insufficienza cardiaca (scompenso cardiaco)	12.301	6,8	62,0%	7344	11,5	1,7	6,1	4.015	12
2	250	Diabete mellito	11.222	6,2	-	5604	8,7	2	5,4	3.905	9
3	518	Insufficienza respiratoria e/o edema polmonare acuto	6.802	3,8	28,0%	4147	6,5	1,6	4,1	4.820	14
4	410	Infarto miocardico acuto	4.736	2,6	22,0%	2987	4,7	1,6	3,9	6.680	10
5	427	Aritmie cardiache	4.189	2,3	49,0%	2556	4	1,6	3,3	6.406	9

Standards of Medical Care in Diabetes-ADA

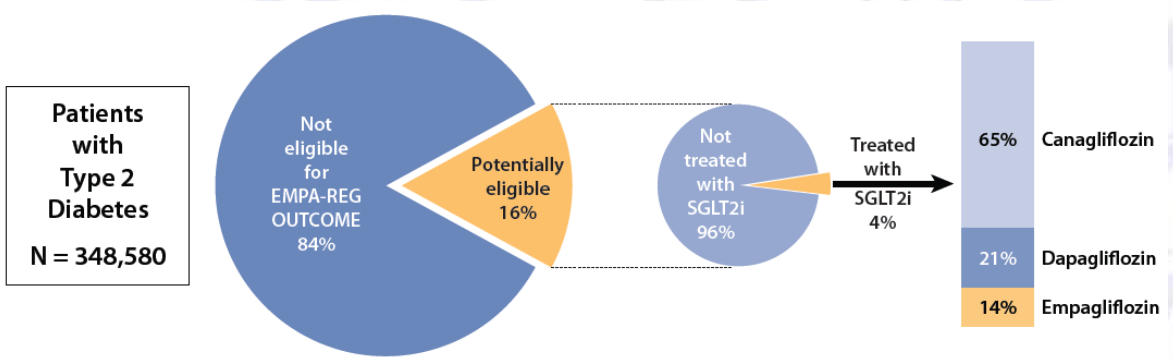


Eligibility for EMPA-REG OUTCOME

Slide kindly provided by Peter Fenici

Diabetes Collaborative Registry:

- In a large US-based outpatient registry, ~1 in 6 patients with T2DM met the main eligibility criteria for EMPA-REG OUTCOME



	RCGP-RSC total type II diabetes group (n = 60,327)
	Risk factor present % (95% CI)[1]
Myocardial infarction	4.9 (4.8 to 5.1)
Coronary artery disease	5.9 (5.7 to 6.0)
Unstable angina	0.9 (0.8 to 0.9)
Stroke	4.3 (4.2 to 4.5)
Peripheral artery disease	4.4 (4.3 to 4.6)
Any major CV risk factor	15.7 (15.5 to 16.0)

Royal College of General Practitioners (RCGP) Research and Surveillance Centre database

- 16% of T2D patients from the UK-eMR database met the inclusion criteria

CVD-REAL

Slide kindly provided by Peter Fenici

CardioVascular events in Diabetes- Reduction of Events According to real Life data

- **Comparative Effectiveness** study comparing the **risk of all-cause death, hospitalization for HF, myocardial infarction and stroke** in patients with Type 2 diabetes **newly initiated on SGLT2 inhibitors** vs other glucose-lowering drugs

CVDREAL CVDREAL^2

Truven MarketScan Claims & Encounters and **linked Medicare**

CVDREAL NORDIC

- **National full-population registries**
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- **National full-population registries**

Clinical Practice Research Datalink (CPRD) and **The Health Improvement Network (THIN)**

Diabetes Patienten Verlaufsdokumentation (DPV) initiative

Australia – National Diabetes Services Scheme (NDSS)*

Canada – Manitoba Population Health Research Data Repository

Israel – The Maccabi Health Management Organization

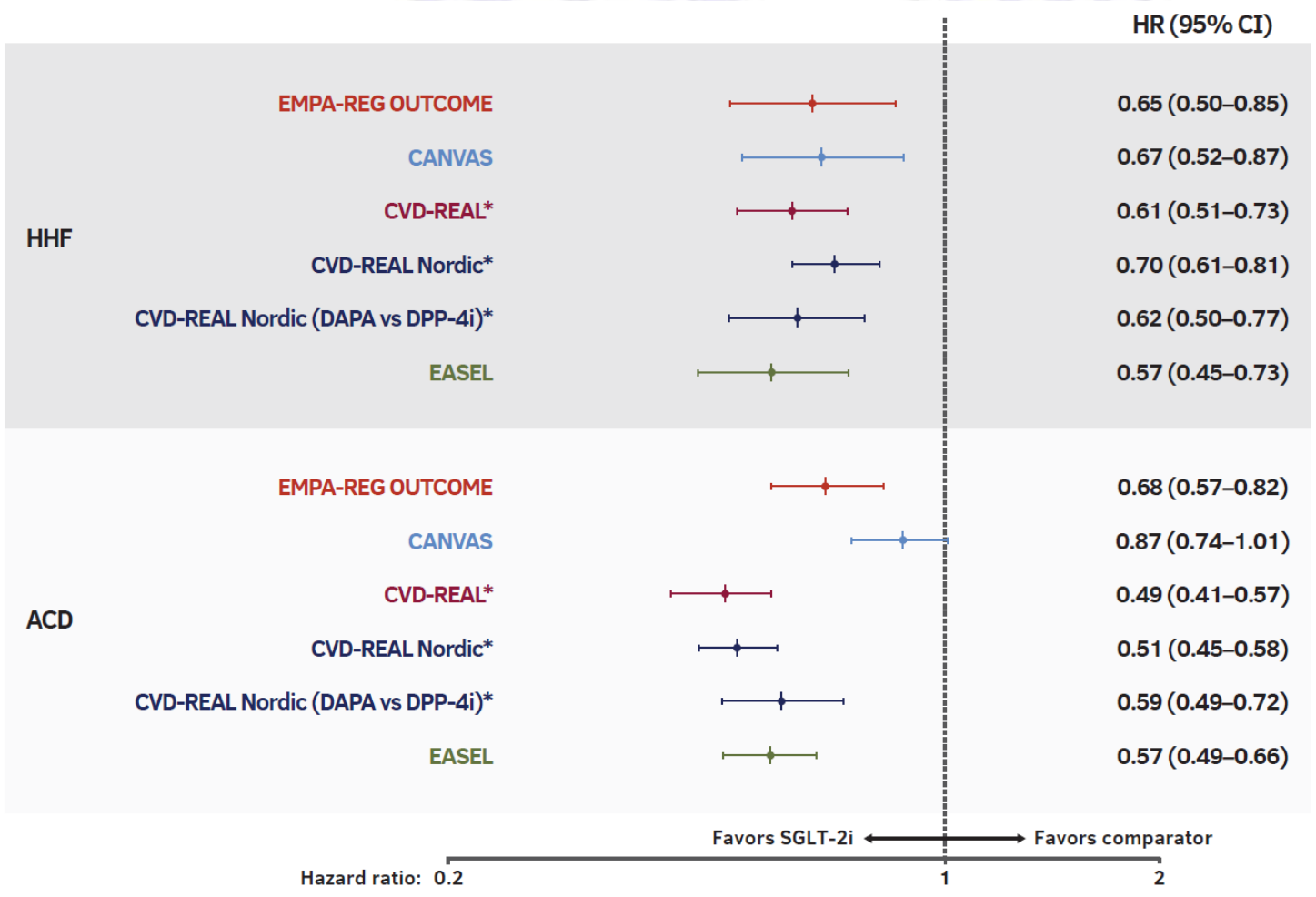
Japan – Medical Data Vision

Singapore – SingHealth Diabetes Registry

South Korea – National Health Insurance Service (NHIS)

Kosiborod M et al.,Circulation 2017; Kosiborod M, et al. *J Am Coll Cardiol 2018*

What we know today: Side-by-side plot of the CVOTs and RWEs results



Hospitalization for Heart Failure

P-value for SGLT2i vs. oGLD: p=0.001

Database	N	# of events	HR (95% CI)
Korea	336,644	5149	0.87 (0.82, 0.92)
Japan	67,780	565	0.75 (0.63, 0.89)
Singapore	2726	67	0.62 (0.38, 1.02)
Israel	19,472	128	0.53 (0.37, 0.75)
Canada	16,064	88	0.36 (0.24, 0.56)
Total	442,686	5997	0.64 (0.50, 0.82)

Heterogeneity p-value: p<0.001
ITT, unadjusted analysis

Favor SGLT2i ← → Favor oGLD
Hazard Ratio: 0.25 0.50 1.00 2.00

CVDREAL 2

All-Cause Death

P-value for SGLT2i vs. oGLD: p<0.001

Database	N	# of events	HR (95% CI)
Korea	336,644	3445	0.72 (0.67, 0.77)
Japan	67,780	557	0.56 (0.47, 0.67)
Singapore	2726	36	0.75 (0.38, 1.47)
Israel	19,472	199	0.41 (0.30, 0.55)
Canada	16,064	261	0.51 (0.41, 0.65)
Australia	27,442	718	0.32 (0.27, 0.38)
Total	470,128	5216	0.51 (0.37, 0.70)

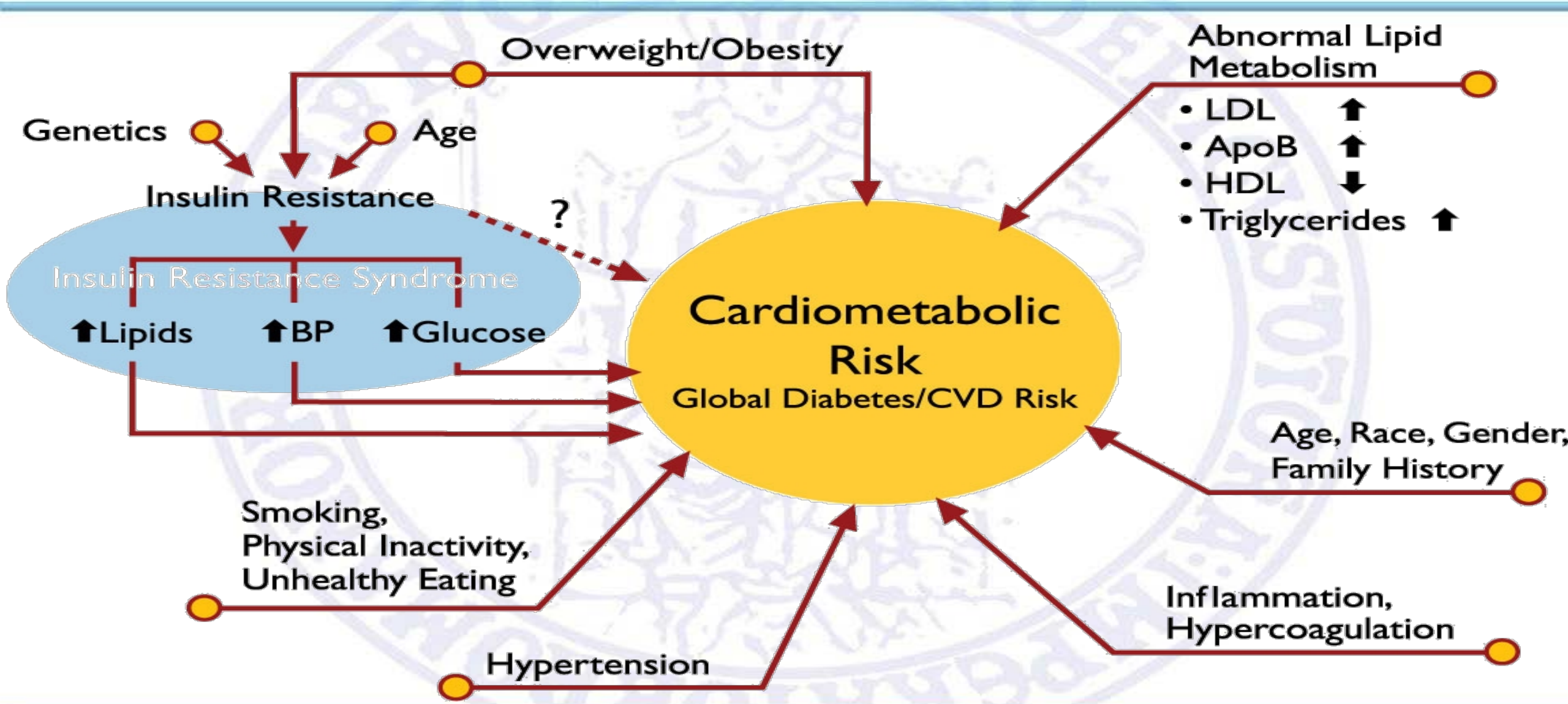
Heterogeneity p-value: p<0.001
ITT, unadjusted analysis

Favor SGLT2i ← → Favor oGLD
Hazard Ratio: 0.25 0.50 1.00 2.00

These studies differ in design, patient population, comparator and follow-up period. The graph does not represent a direct H2H comparison between studies. *On-treatment population. ACD, all-cause death; HR, hazard ratio; HHF, hospitalization for heart failure

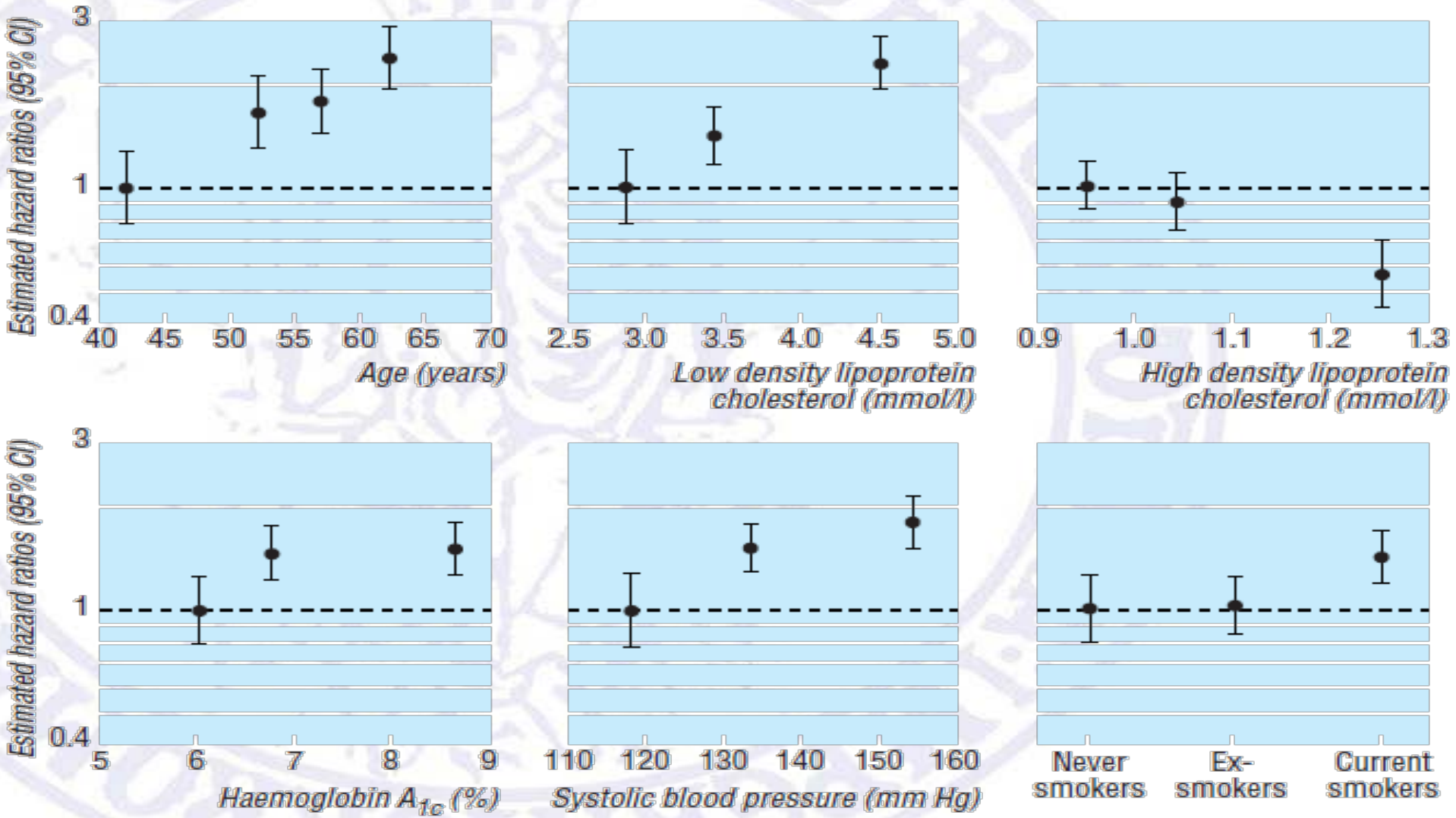
1. Zinman B, et al. N Engl J Med 2015;373(22):2117-28
2. Neal B, et al. N Engl J Med 2017;376:644-57
3. Kosiborod M, et al. Circulation. 2017;136(3):249-59
4. Birkeland KI, et al. Lancet Diabetes Endocrinol. 2017; 5(9):709-717
5. Persson F, et al. Diabetes Obes Metab. 2017;1–8
6. Udell JA, et al. Circulation. 2017; Nov 13 [Epub ahead of print]
7. Kosiborod M, et al.. J Am Coll Cardiol (in press). DOI: 10.1016/j.jacc.2018.03.009

Cardiometabolic Risk



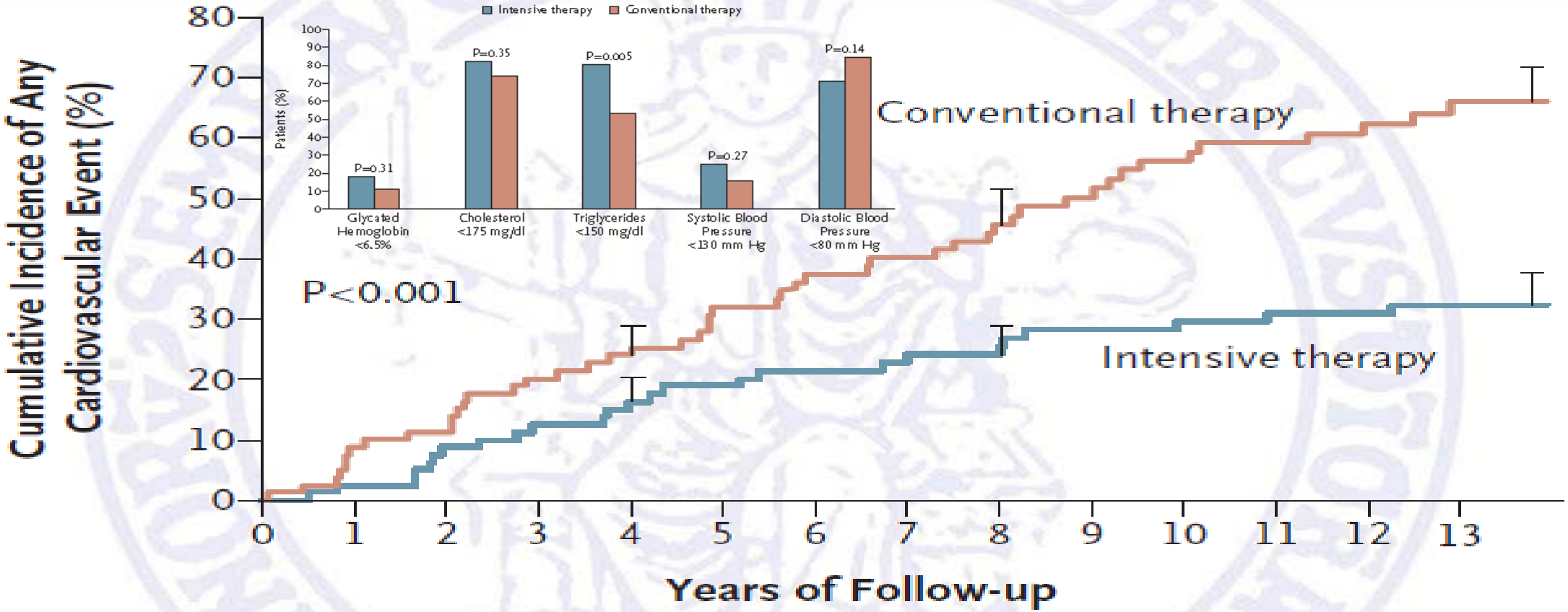
Risk factors for coronary artery disease in noninsulin dependent diabetes mellitus: United Kingdom prospective diabetes study (UKPDS: 23)

Estimated hazard ratios for significant risk factors for coronary artery disease occurring in 335 out of 3055 diabetic patients (expressed as floating absolute risks)



R C Turner, *BMJ 1998;316:823-8*

Multifactorial Intervention and CDV in T2D

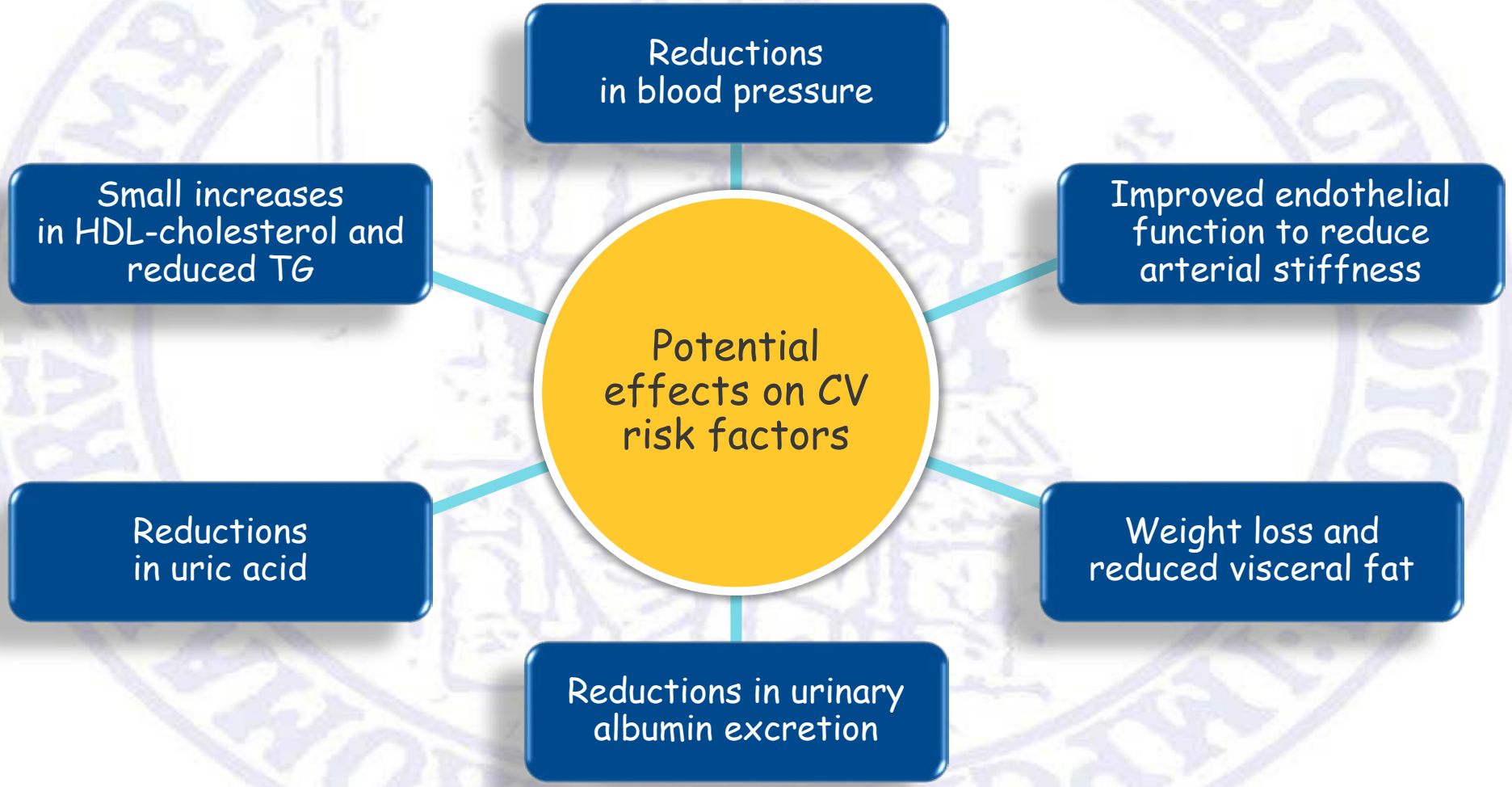


No. at Risk

Intensive therapy	80	72	65	61	56	50	47	31
Conventional therapy	80	70	60	46	38	29	25	14

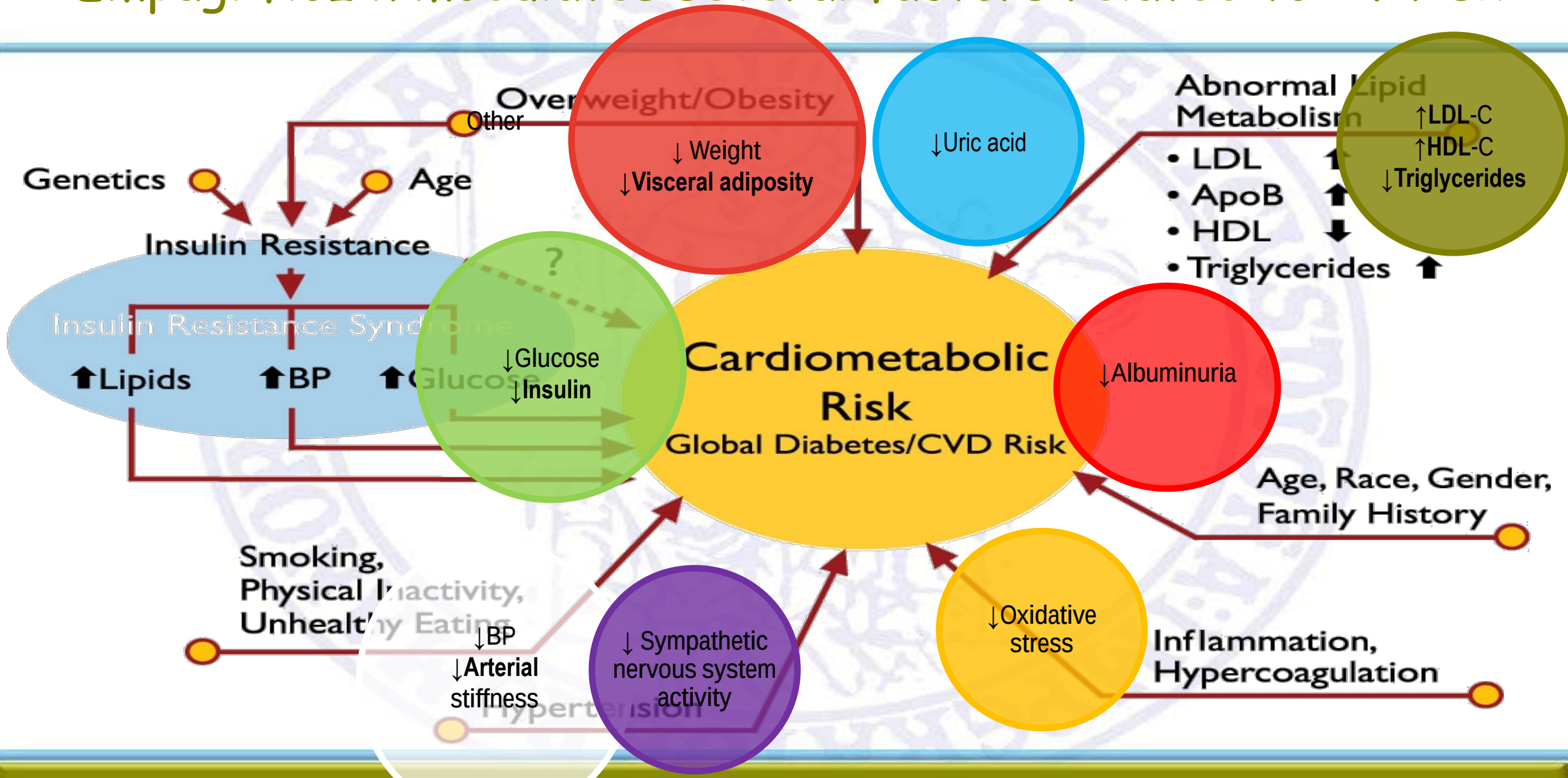
Gaede P et al., NEJM 2008

SGLT2i & GLP1RA Effects and Potential CV Impact



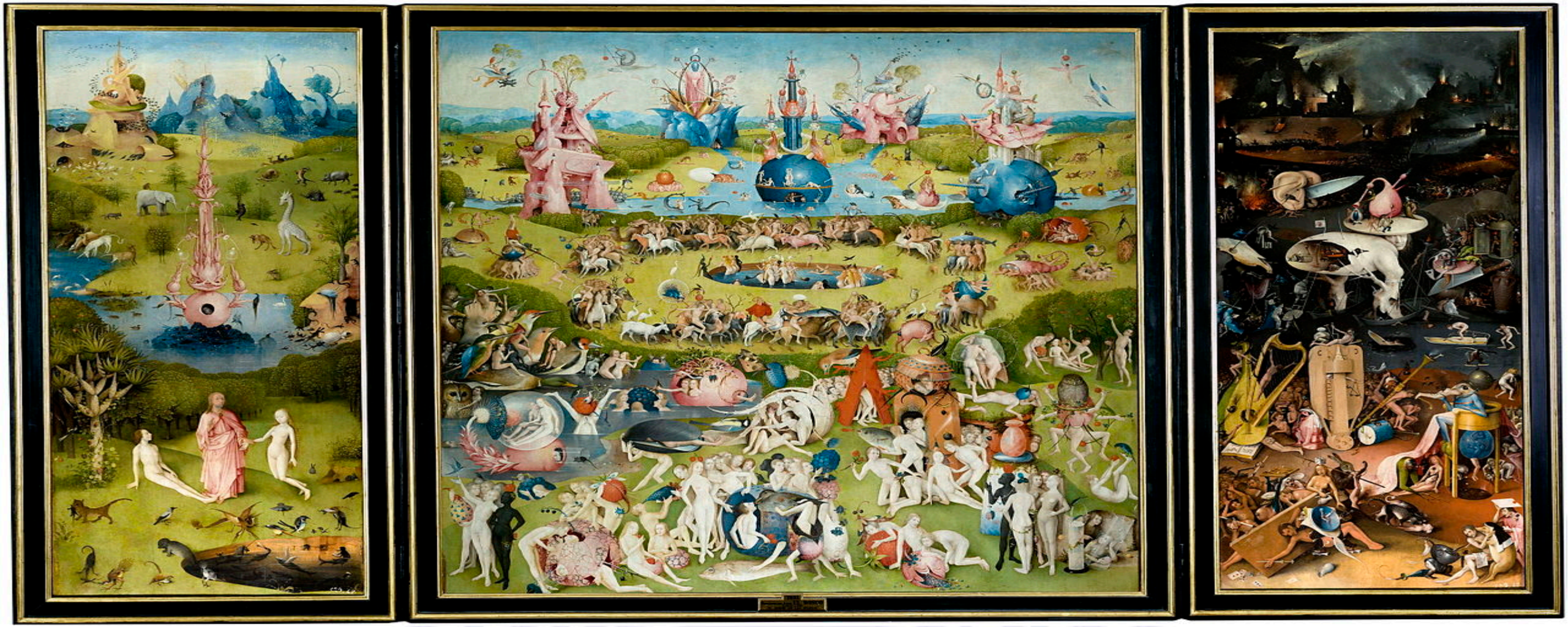
Modified from Inzucchi SE, et al. Diab Vasc Dis Res 2015;12:90–100

Empagliflozin modulates several factors related to CV risk



Adapted from Inzucchi SE, Zinman, B, Wanner, C et al. Diab Vasc Dis Res 2015;12:90-100

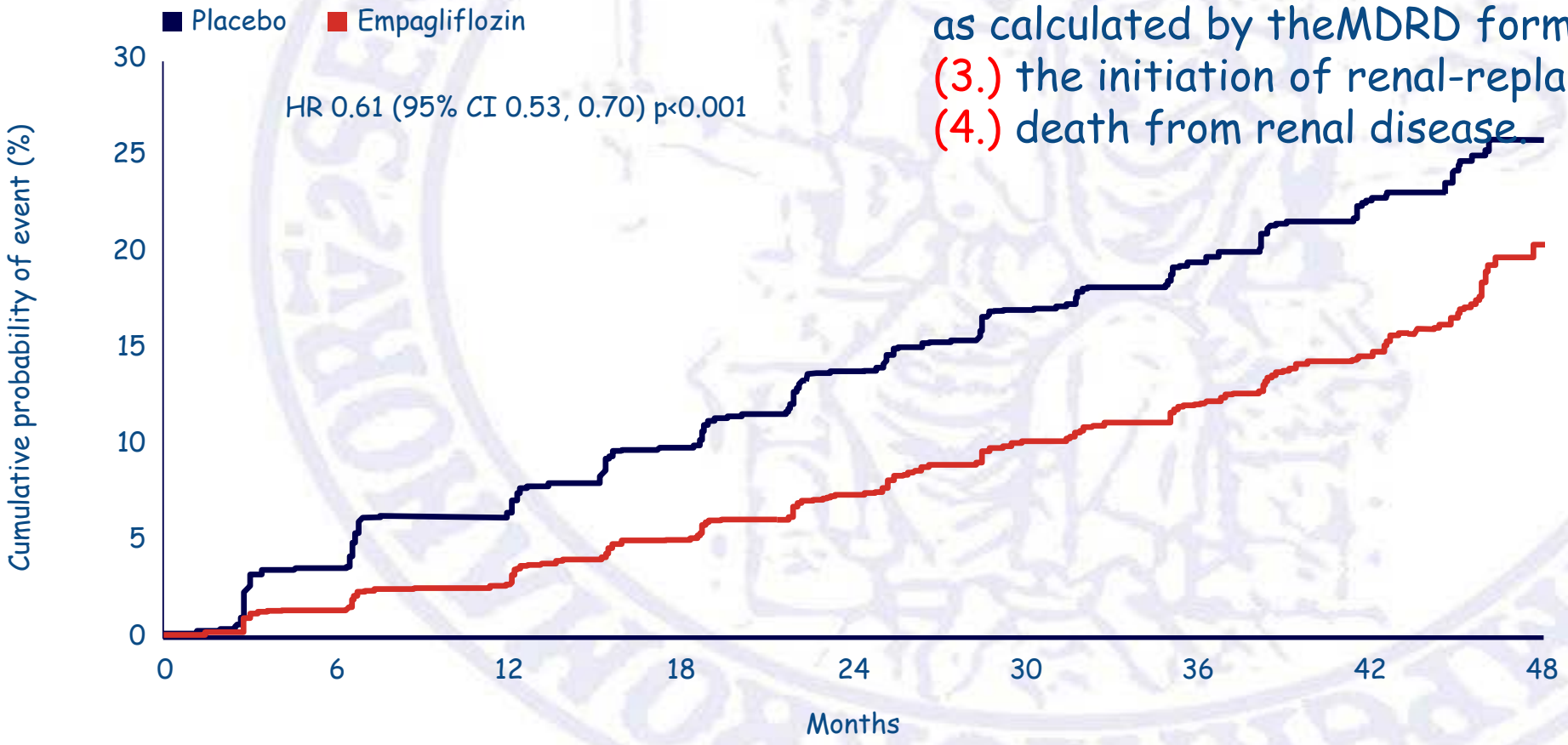
New Perspectives in T2D Treatment



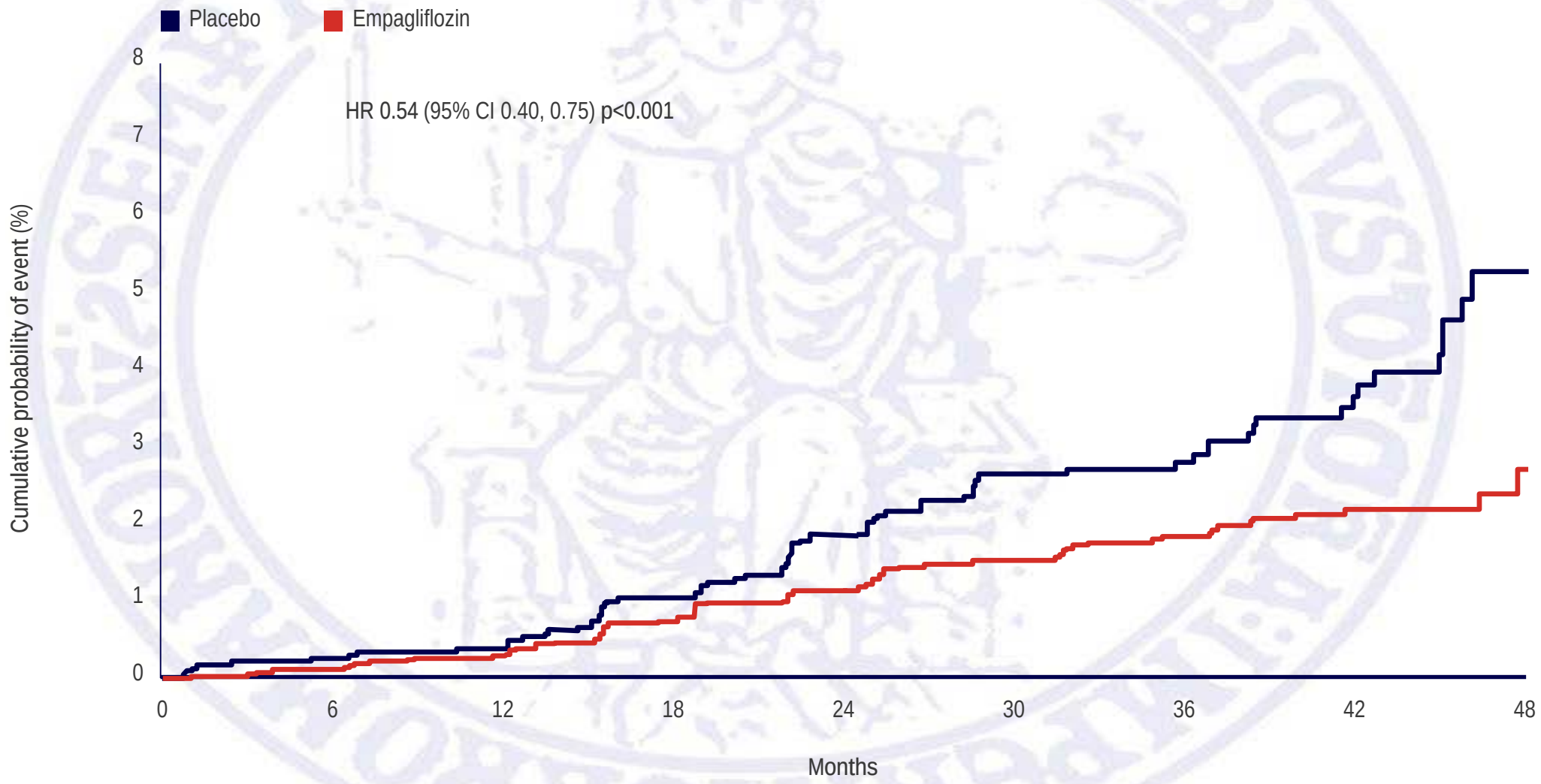
Hieronymus Bosh, The Garden of Earthly Delights, 1490

Incident or worsening nephropathy*

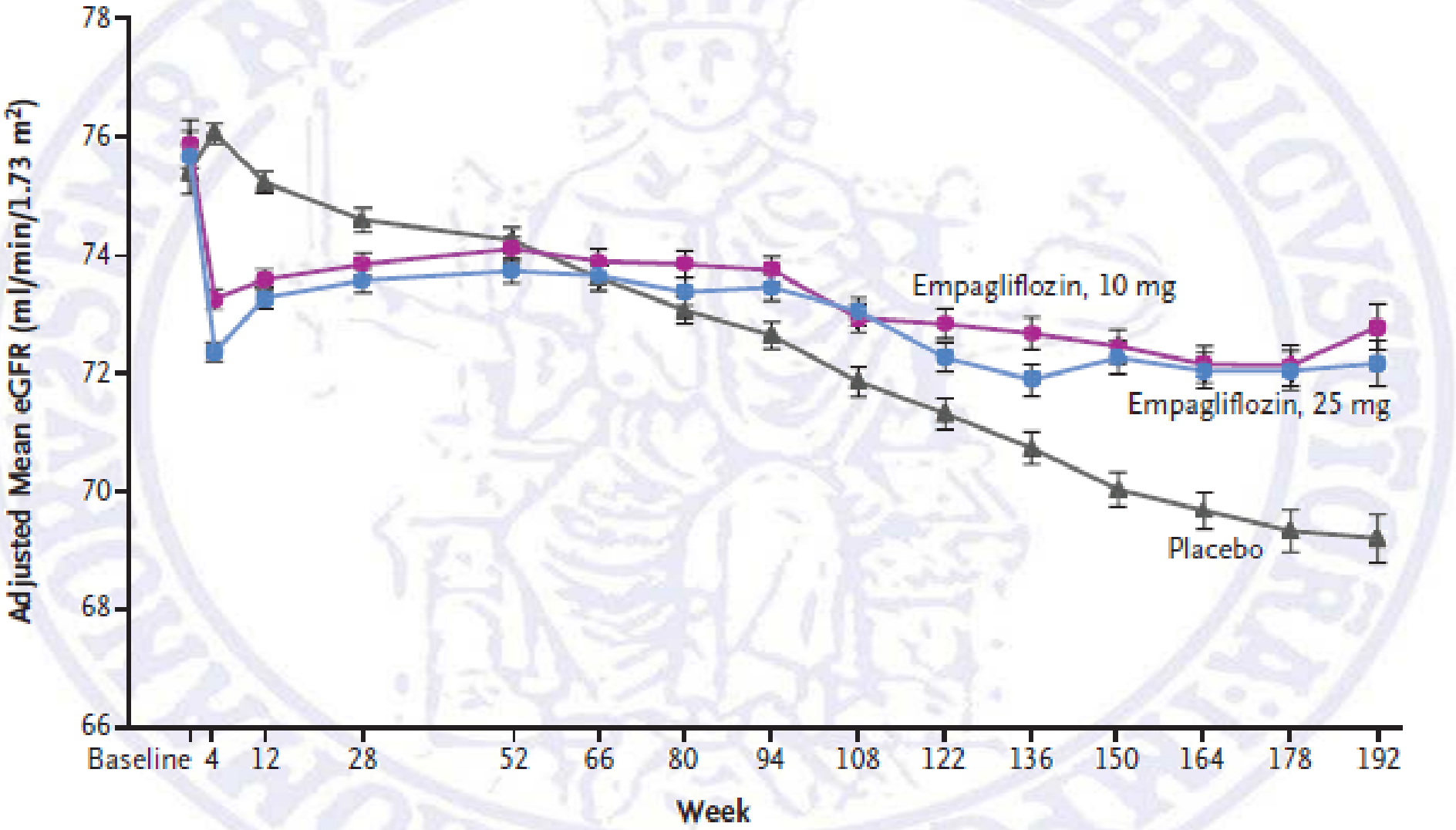
* (1.) Progression to macroalbuminuria (urinary albuminto-creatinine ratio, >300 mg of albumin per gram of creatinine); (2.) a doubling of the serum creatinine level, accompanied by an eGFR of ≤45 ml per minute per 1.73 m2, as calculated by theMDRD formula;
(3.) the initiation of renal-replacement therapy; or
(4.) death from renal disease



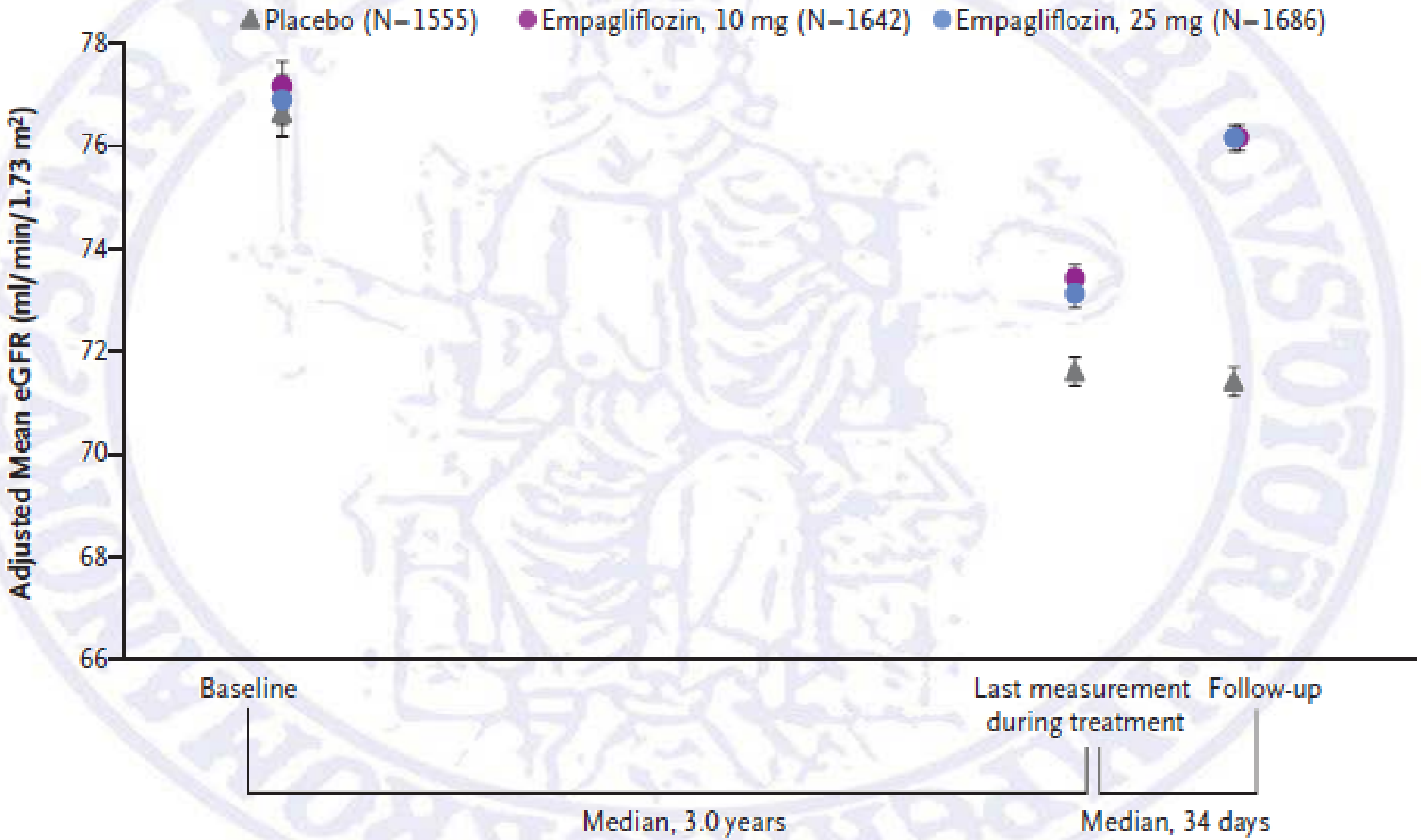
Doubling of serum creatinine, initiation of renal replacement therapy, or death due to renal disease



eGFR (CKD-EPI) over 192 weeks

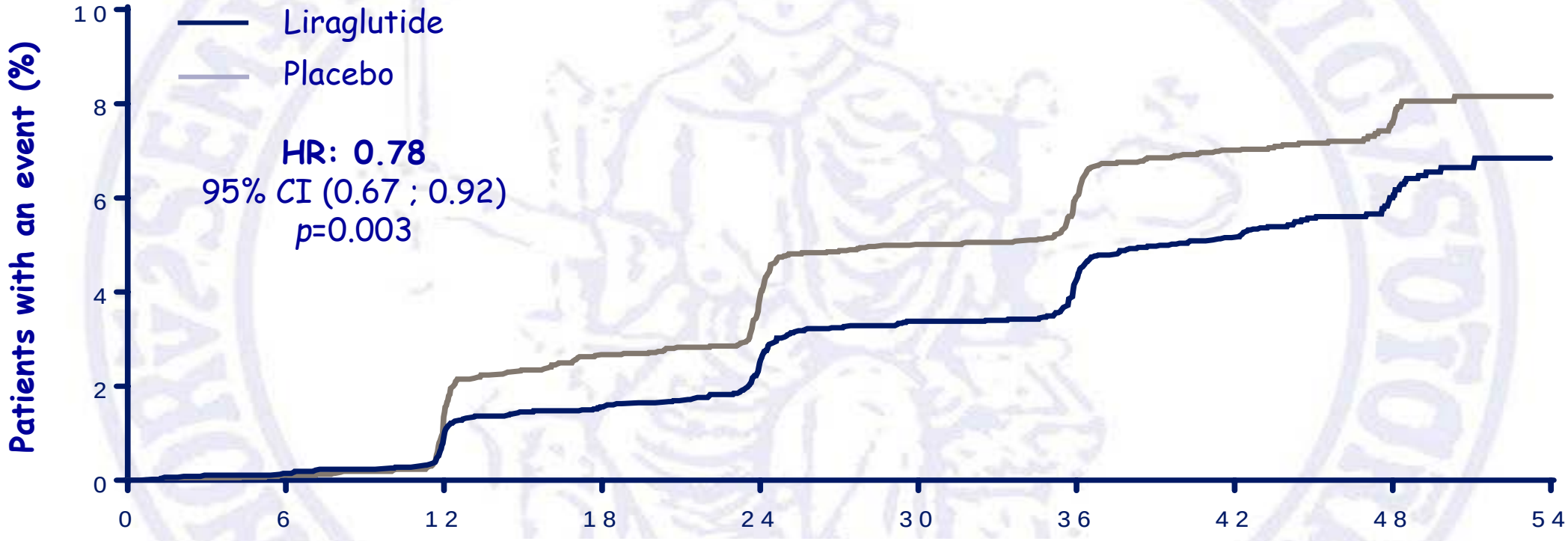


Change in eGFR from baseline



Composite renal outcome

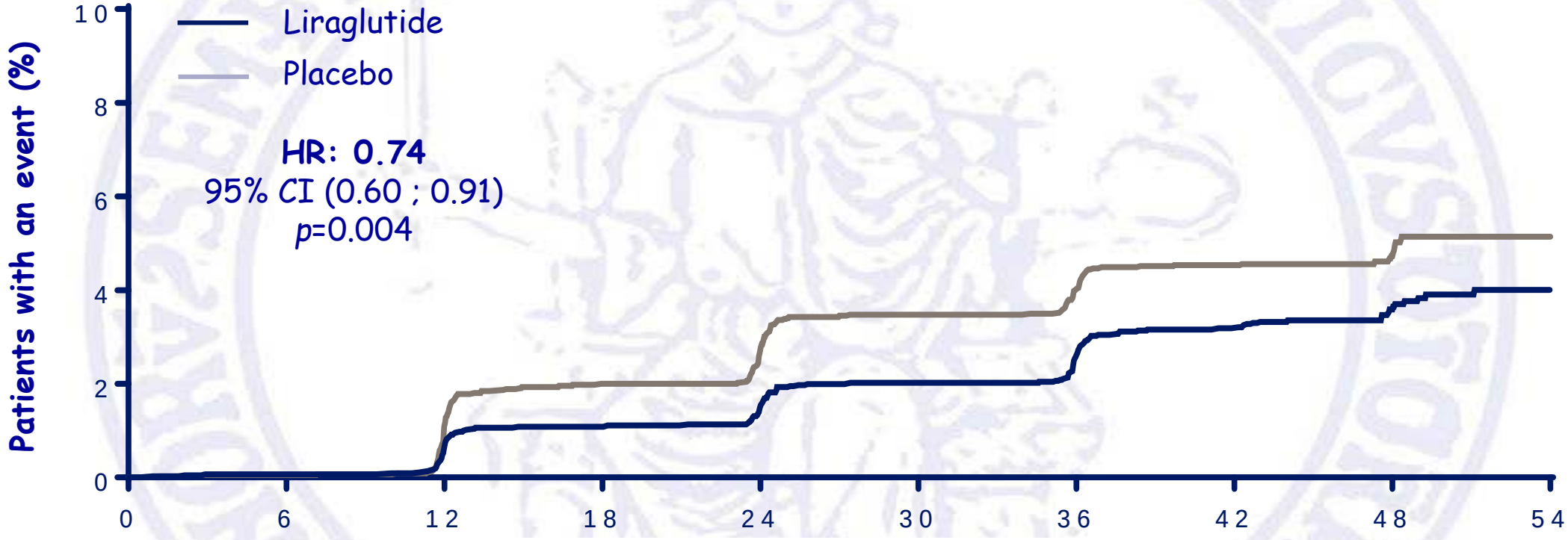
Macroalbuminuria, doubling of serum creatinine,* ESRD, renal death (N=605)



No. at risk										
Liraglutide	4668	4635	4561	4492	4400	4304	4210	4114	1632	454
Placebo	4672	4643	4540	4428	4316	4196	4094	3990	1613	433

*And eGFR ≤45 mL/min/1.73 m^2 per MDRD. The cumulative incidences were estimated with the use of the Kaplan–Meier method and the hazard ratios with the use of the Cox proportional-hazard regression model. The data analyses are truncated at 54 months because less than 10% of the patients had an observation time beyond 54 months. CI, confidence interval; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; HR, hazard ratio; MDRD, modification of diet in renal disease

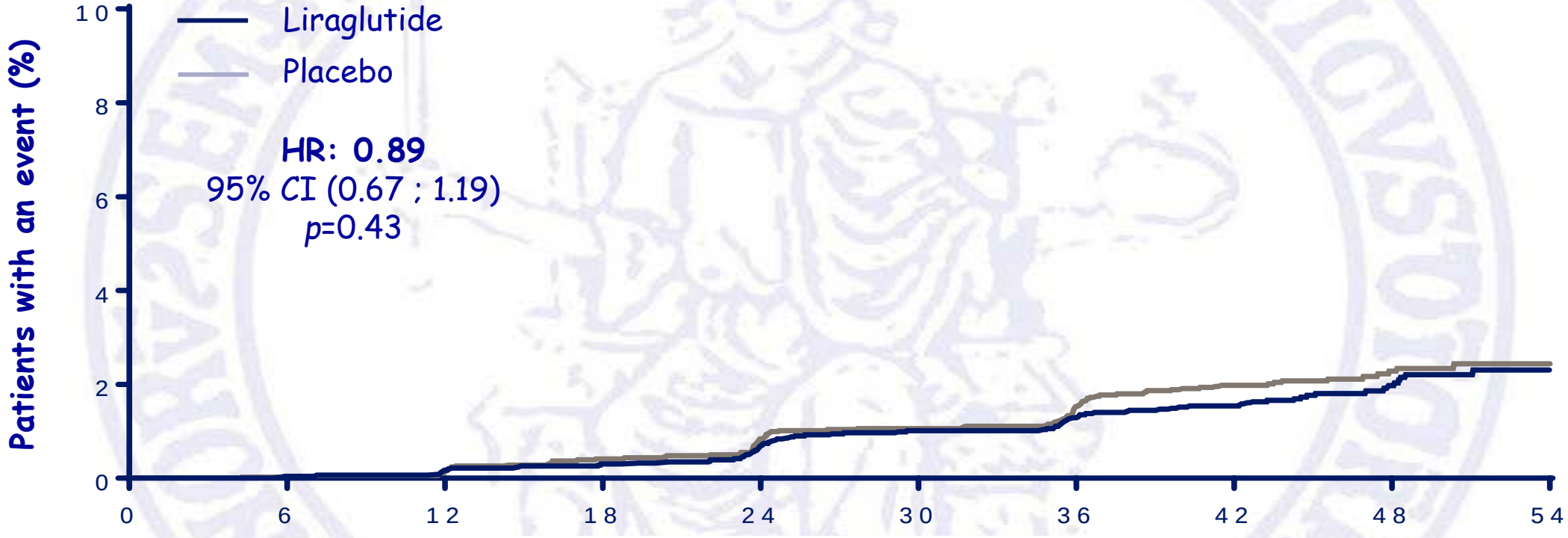
New onset of persistent macroalbuminuria



No. at risk										
Liraglutide	4668	4638	4570	4508	4437	4353	4268	4182	1662	461
Placebo	4672	4646	4551	4455	4359	4252	4162	4073	1642	442

Full analysis set. EAC-confirmed index events from randomisation to follow-up. The cumulative incidences were estimated with the use of the Kaplan–Meier method, and the hazard ratios with the use of the Cox proportional-hazard regression model. The data analyses are truncated at 54 months because less than 10% of the patients had an observation time beyond 54 months. Macroalbuminuria was defined as urine albumin >300 mg/g creatinine.
CI, confidence interval; EAC, event adjudication committee; HR, hazard ratio

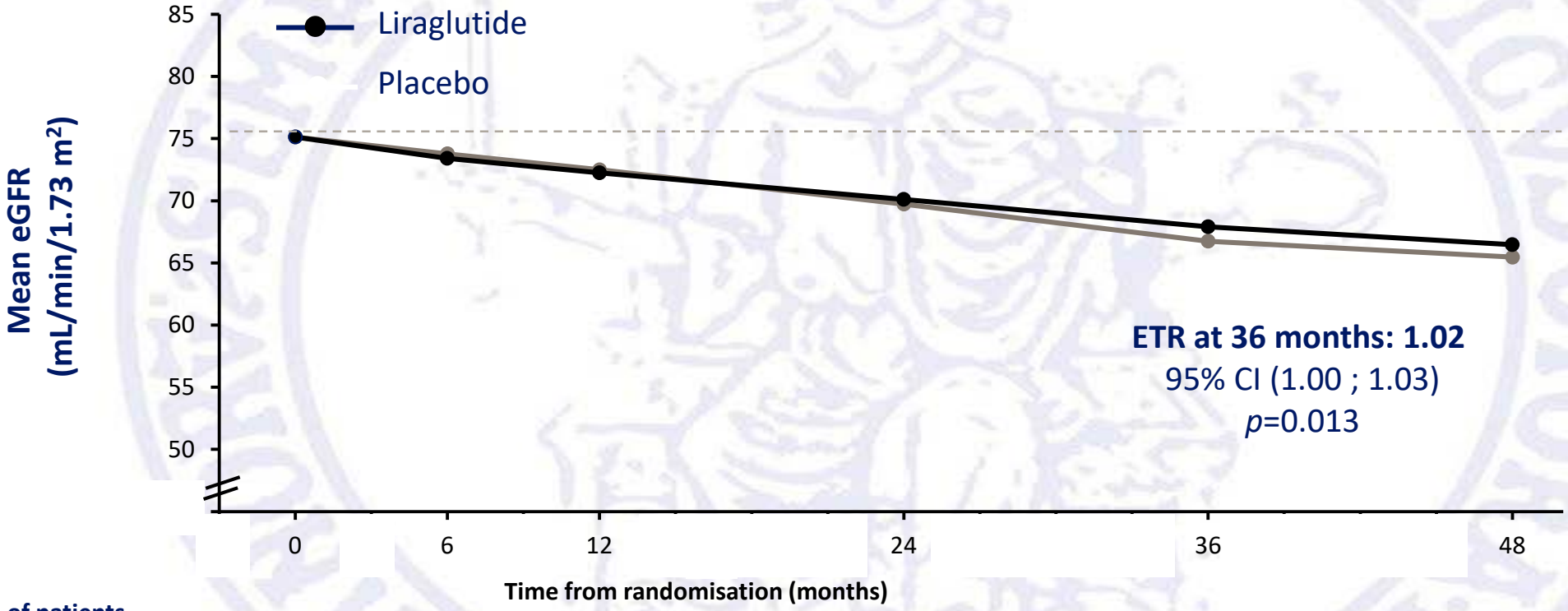
Persistent doubling of serum creatinine*



No. at risk										
Liraglutide	4668	4639	4591	4544	4476	4403	4332	4264	1692	475
Placebo	4672	4647	4596	4529	4447	4367	4282	4196	1682	456

*And eGFR per MDRD ≤45 mL/min/1.73 m^2; Full analysis set. EAC-confirmed index events from randomisation to follow-up. The cumulative incidences were estimated with the use of the Kaplan–Meier method, and the hazard ratios with the use of the Cox proportional-hazard regression model. The data analyses are truncated at 54 months because less than 10% of the patients had an observation time beyond 54 months. CI, confidence interval; EAC, event adjudication committee; eGFR, estimated glomerular filtration rate; HR, hazard ratio; MDRD, modification of diet in renal disease

Changes in estimated glomerular filtration rate

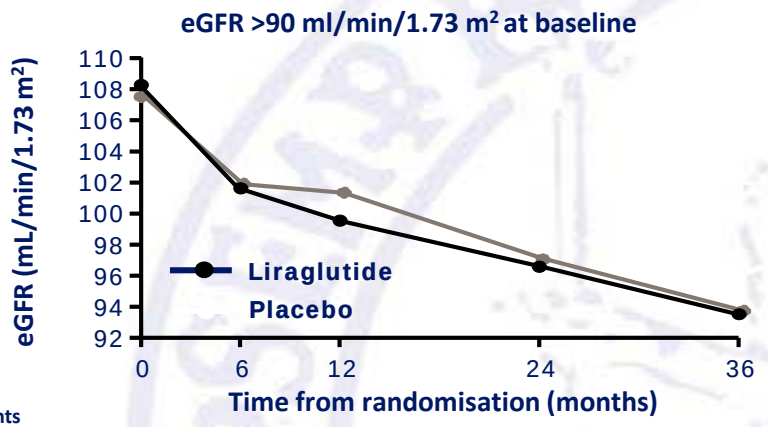


No. of patients						
Liraglutide	4668	4349	4288	4031	3806	812
Placebo	4672	4356	4237	3911	3634	755

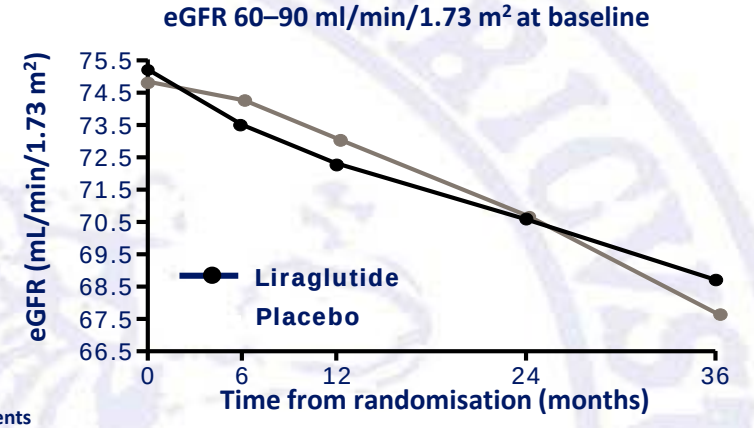
Full analysis set. Estimated means ± standard error. Change from baseline to last assessment analysed using a linear mixed model for log-transformed assessment accounting for repeated measures. Analyses truncated at 48 months as <10% of patients had an observation time beyond 48 months.
Similar results obtained when the CKD-EPI creatinine equation was used.
CI, confidence interval; eGFR, estimated glomerular filtration rate; ETR, estimated trial-group ratio; MDRD, modification of diet in renal disease

Mann JFE et al. *N Engl J Med* 2017;377:839–848. doi:10.1056/NEJMoa1616011

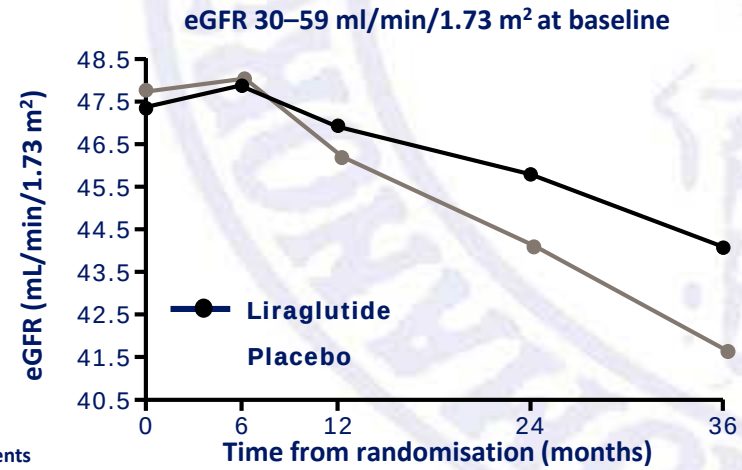
eGFR during the trial, according to eGFR at baseline



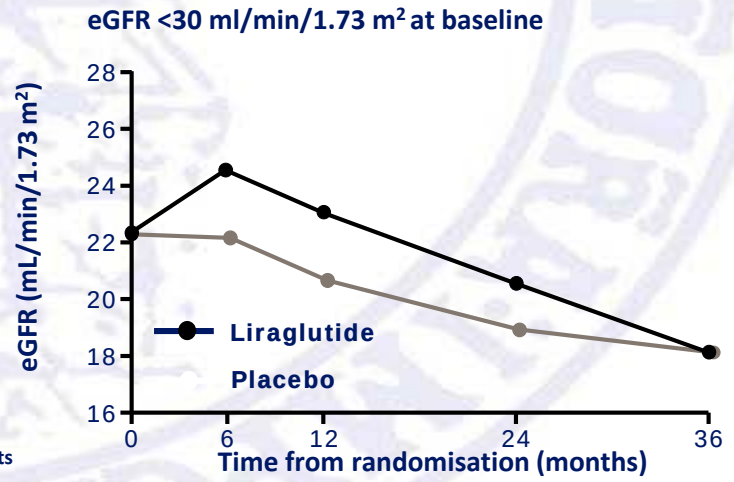
No. of patients					
Liraglutide	1589	1509	1500	1428	1364
Placebo	1616	1542	1514	1415	1332



No. of patients					
Liraglutide	1907	1825	1795	1689	1607
Placebo	1947	1856	1817	1696	1574



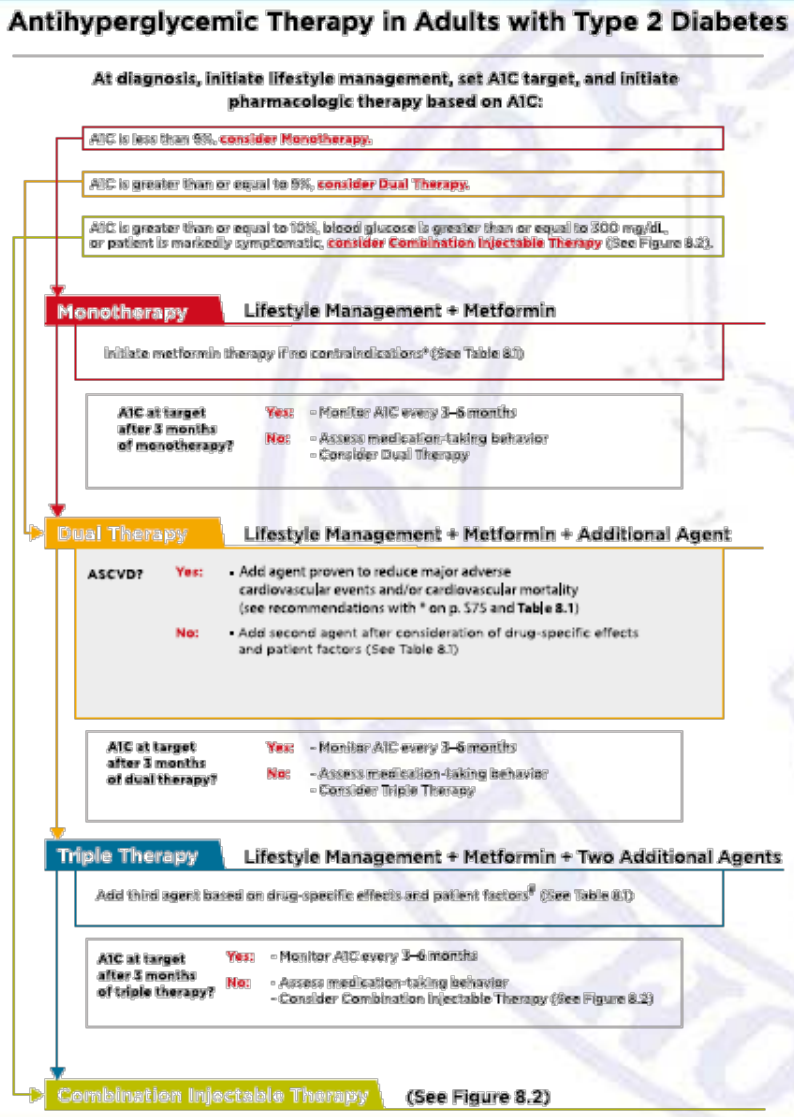
No. of patients					
Liraglutide	986	912	896	826	754
Placebo	919	865	821	725	663



No. of patients					
Liraglutide	115	103	97	88	81
Placebo	104	93	85	75	64

Mann JFE et al. *N Engl J Med* 2017;377:839–848. doi:10.1056/NEJMoa1616011

Drug-specific and patient factors to consider in treatment of T2D adults

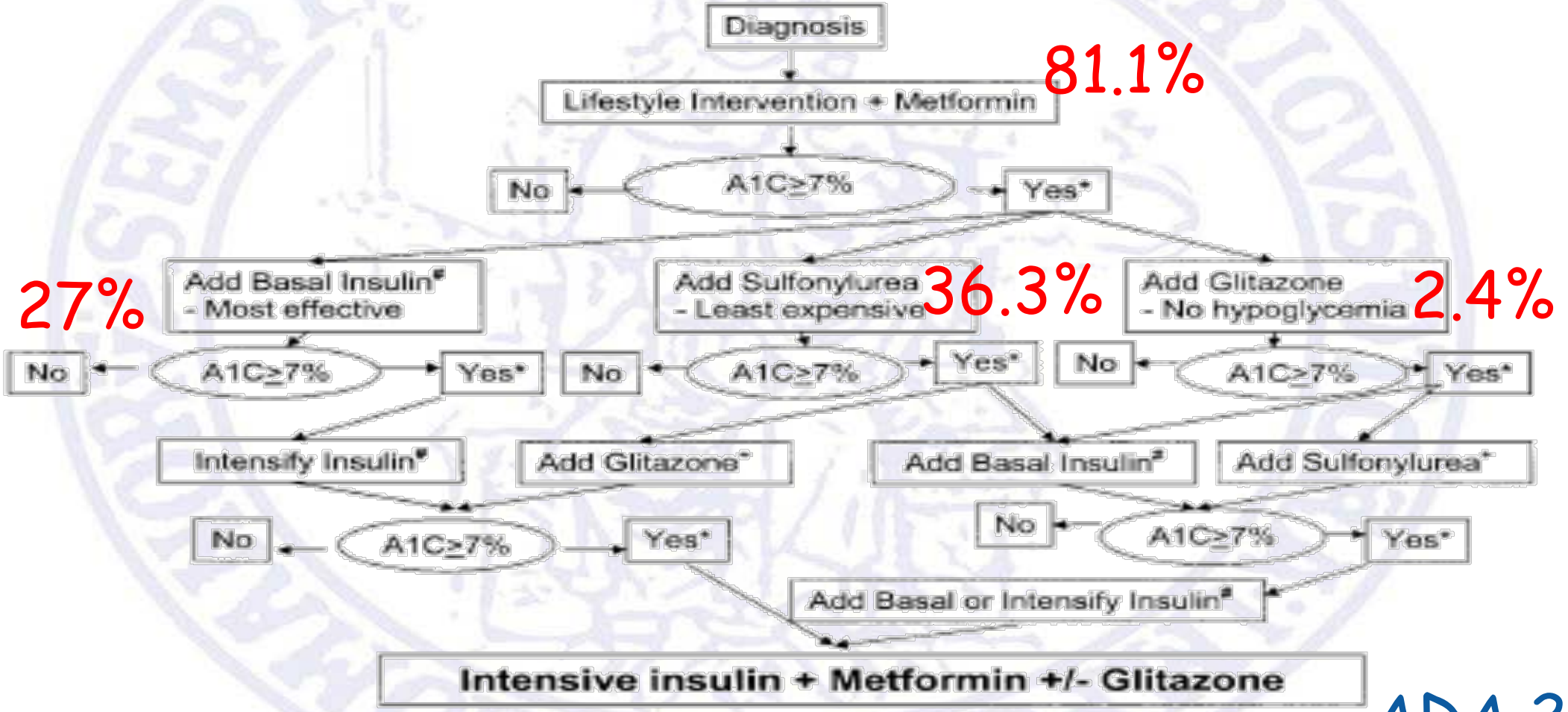


	Efficacy*	Hypoglycemia	Weight Change	CV Effects		Cost	Oral/SQ	Renal Effects		Additional Considerations
				ASCVD	CHF			Progression of DKD	Dosing/Use considerations	
Metformin	High	No	Neutral (Potential for Modest Loss)	Potential Benefit	Neutral	Low	Oral	Neutral	▪ Contraindicated with eGFR <30	▪ Gastrointestinal side effects cor (diarrhea, nausea) ▪ Potential for B12 deficiency
SGLT-2 Inhibitors	Intermediate	No	Loss	Benefit: canagliflozin, empagliflozin†	Benefit: canagliflozin, empagliflozin	High	Oral	Benefit: canagliflozin, empagliflozin	▪ Canagliflozin: not recommended with eGFR <45 ▪ Dapagliflozin: not recommended with eGFR <60; contraindicated with eGFR <30 ▪ Empagliflozin: contraindicated with eGFR <30	▪ **FDA Black Box:** Risk of amputation (**canagliflozin**) ▪ Risk of bone fractures (canagliflozin) ▪ DKA risk (all agents, rare in T2DM) ▪ Genitourinary infections ▪ Risk of volume depletion, hypotension ▪ ↑LDL cholesterol
GLP-1 RAs	High	No	Loss	Neutral: lixisenatide, exenatide extended release Benefit: liraglutide†	Neutral	High	SQ	Benefit: liraglutide	▪ Exenatide: not indicated with eGFR <30 ▪ Lixisenatide: caution with eGFR <30 ▪ Increased risk of side effects in patients with renal impairment	▪ **FDA Black Box:** Risk of thyroid C-cell tumors (**liraglutide, albiglutide, dulaglutide, exenatide extended release**) ▪ Gastrointestinal side effects common (nausea, vomiting, diarrhea) ▪ Injection site reactions ▪ ?Acute pancreatitis risk
DPP-4 Inhibitors	Intermediate	No	Neutral	Neutral	Potential Risk: saxagliptin, alogliptin	High	Oral	Neutral	▪ Renal dose adjustment required; can be used in renal impairment	▪ Potential risk of acute pancreatitis ▪ Joint pain
Thiazolidinediones	High	No	Gain	Potential Benefit: pioglitazone	Increased Risk	Low	Oral	Neutral	▪ No dose adjustment required ▪ Generally not recommended in renal impairment due to potential for fluid retention	▪ **FDA Black Box:** Congestive heart failure [**pioglitazone, rosiglitazone**] ▪ Fluid retention (edema; heart failure) ▪ Benefit in NASH ▪ Risk of bone fractures ▪ Bladder cancer (pioglitazone) ▪ ↑LDL cholesterol (rosiglitazone)
Sulfonylureas (2nd Generation)	High	Yes	Gain	Neutral	Neutral	Low	Oral	Neutral	▪ Glyburide: not recommended ▪ Glipizide & glimepiride: initiate conservatively to avoid hypoglycemia	▪ FDA Special Warning on increased risk of cardiovascular mortality based on studies of an older sulfonylurea (tolbutamide)
Insulin Human Insulin	Highest	Yes	Gain	Neutral	Neutral	Low	SQ	Neutral	▪ Lower insulin doses required with a decrease in eGFR; titrate per clinical response	▪ Injection site reactions ▪ Higher risk of hypoglycemia with human insulin (NPH or premixed formulations) vs. analogs
Insulin Analogs						High	SQ			

*See ref. 31 for description of efficacy. †FDA approved for CVD benefit. CVD, cardiovascular disease; DKA, diabetic ketoacidosis; DKD, diabetic kidney disease; NASH, nonalcoholic steatohepatit RAs, receptor agonists; SQ, subcutaneous; T2DM, type 2 diabetes.

STANDARDS OF MEDICAL CARE IN DIABETES—2018, Diabetes Care, January 2018

The Algorithm of Therapy



ADA 2007

Osservatorio ARNO Diabete
Il profilo assistenziale della popolazione con diabete

Descrizione	Trattati (n=516.073)	% Trattati*	% spesa sul totale	Spesa media per trattato €	Spesa media pro capite € (n=640.846)
Iperglicemici orali o iniettabili	446.320	86,5	50	150	104,5
Metformina	321.009	62,2	9,4	39,3	19,7
Sulfoniluree	99.127	19,2	3,8	51,8	8
Glinidi (Repaglinide)	45.942	8,9	2,8	80,6	5,8
Metformina e sulfoniluree	42.527	8,2	1,9	59,2	3,9
Metformina e Inibitori DPP-4	35.942	7	10	371,5	20,8
Inibitori DDP-4	25.991	5	7	358,2	14,5
Inibitori alfa-glicosidasi (Acarbosio)	19.210	3,7	1,2	84,6	2,5
Metformina e pioglitazone	14.245	2,8	3	285,6	6,3
Analoghi GLP-1	12.447	2,4	7,2	778,5	15,1
Glitazoni (Pioglitazone)	9.582	1,9	1	141,9	2,1
Inibitori SGLT-2	7.236	1,4	1,4	257,1	2,9
Metformina e inibitori SGLT-2	4.425	0,9	0,8	230,8	1,6
Glimepiride e pioglitazone	1.361	0,3	0,3	310,2	0,7
Pioglitazone e alogliptin	1.009	0,2	0,2	270,9	0,4

La *Parabola dei ciechi* (1568), Pieter Bruegel il Vecchio, Museo Nazionale di Capodimonte, Napoli