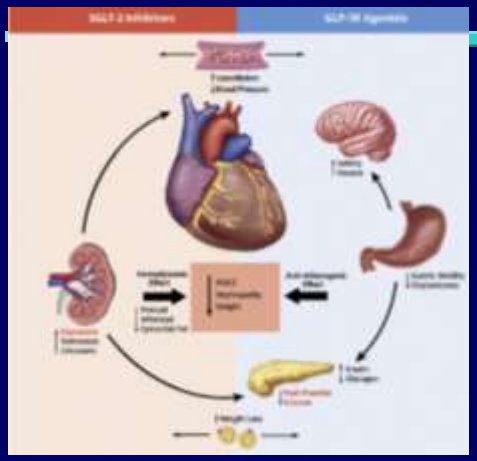
KARVA - Voorjaarsymposium



Diabetes: What's new ?

Luc Van Gaal, MD, PhD
Dept Endocrinol-Diabetology & Metabolism
Antwerp University Hospital
Antwerp, Belgium

The unmet needs in diabetes

Progression of T2D and obesity

β-cell function declines[1]

Glycaemic targets harder to reach[1]

Weight gain & hypoglycaemia

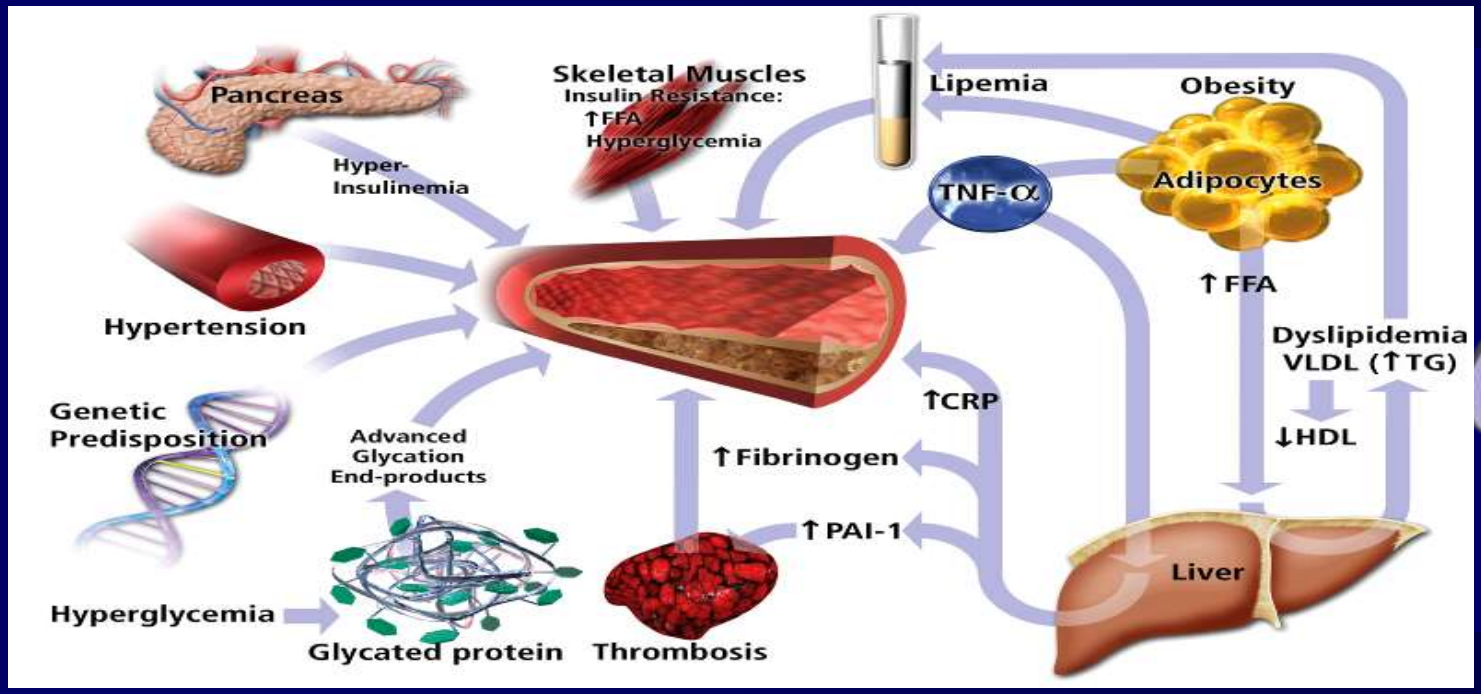
Microvascular comorbidities[3]
Nephropathy
Neuropathy
Retinopathy

Macrovascular comorbidities[3]
Cardiac ischaemia
Heart failure

Can new medications help to prevent complications ?

1. Scheen AJ *& Van Gaal LF, Lancet Diabetes Endocrinol* 2014;2:911–22;
2. Van Gaal L *et al. Diabetes Care* 2015;38:1161–7;
3. Phillips LS *et al. Diabetes Care* 2014;37:2668–76

T2DM patients have high CV risk and increased CV mortality



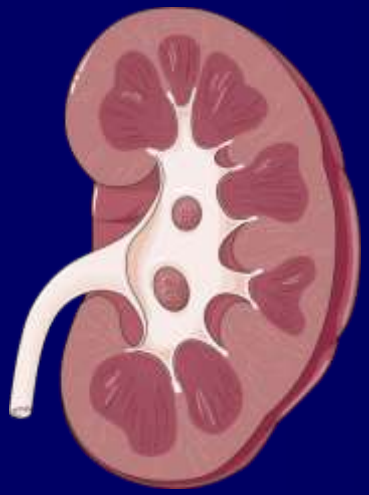
79% of T2DM patients are overweight or obese
63% of T2DM patients have arterial hypertension
70% of T2DM patients have dyslipidemia

Libby et al. *Circulation* 2002;106:2760–2763;
Jacobs et al. *Diabetes Res Clin Pract* 2005;70:263–269

There is a close relationship between cardiac and renal pathophysiology in type 2 diabetes

Concomitant cardiorenal dysfunction in type 2 diabetes[1]

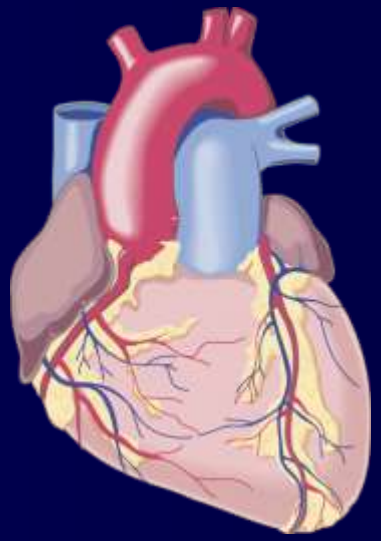
CKD Stage 1-2
Glomerular/Interstitial damage



Cardiorenal Risk factors

Type 2 diabetes
Smoking
Obesity
Hypertension
Dyslipidemia
Genetic risk factors
Acquired risk factors

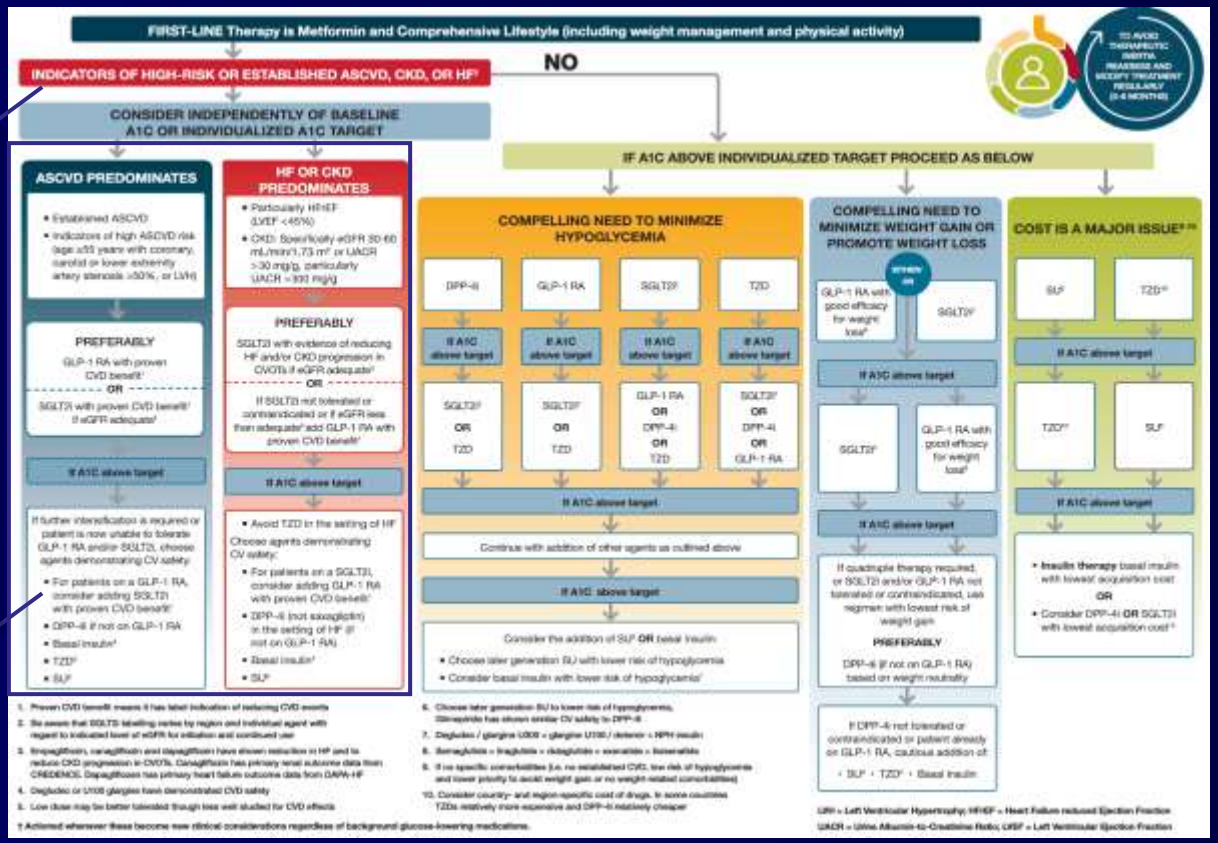
Heart Disease
Increased ischaemic risk
Left ventricular hypertrophy



1. Ronco C, et al. *J Am Col Cardiol*. 2008;52(19):1527–1539; 2. AACE. *Endocr Pract*. 2007;13 Suppl 1:1-683;
3. Afghahi H et al. *Nephrol Dial Transplant*. 2011;26(4):1236-43;
4. Radbill B et al. *Mayo Clin Proc*. 2008;83(12):1373-1381; 5. UKPDS Group. *BMJ*. 2000;321:405-412

Recommendations in the ADA Standards of Medical Care in Diabetes 2020 represent a major paradigm treatment shift

"In appropriate **high-risk individuals with established T2D**, the decision to treat with a **GLP-1 RA or SGLT2 inhibitor** to reduce MACE, HHF, CV death or CKD progression should be considered **independently** of baseline HbA_{1c} or individualised HbA_{1c} target"

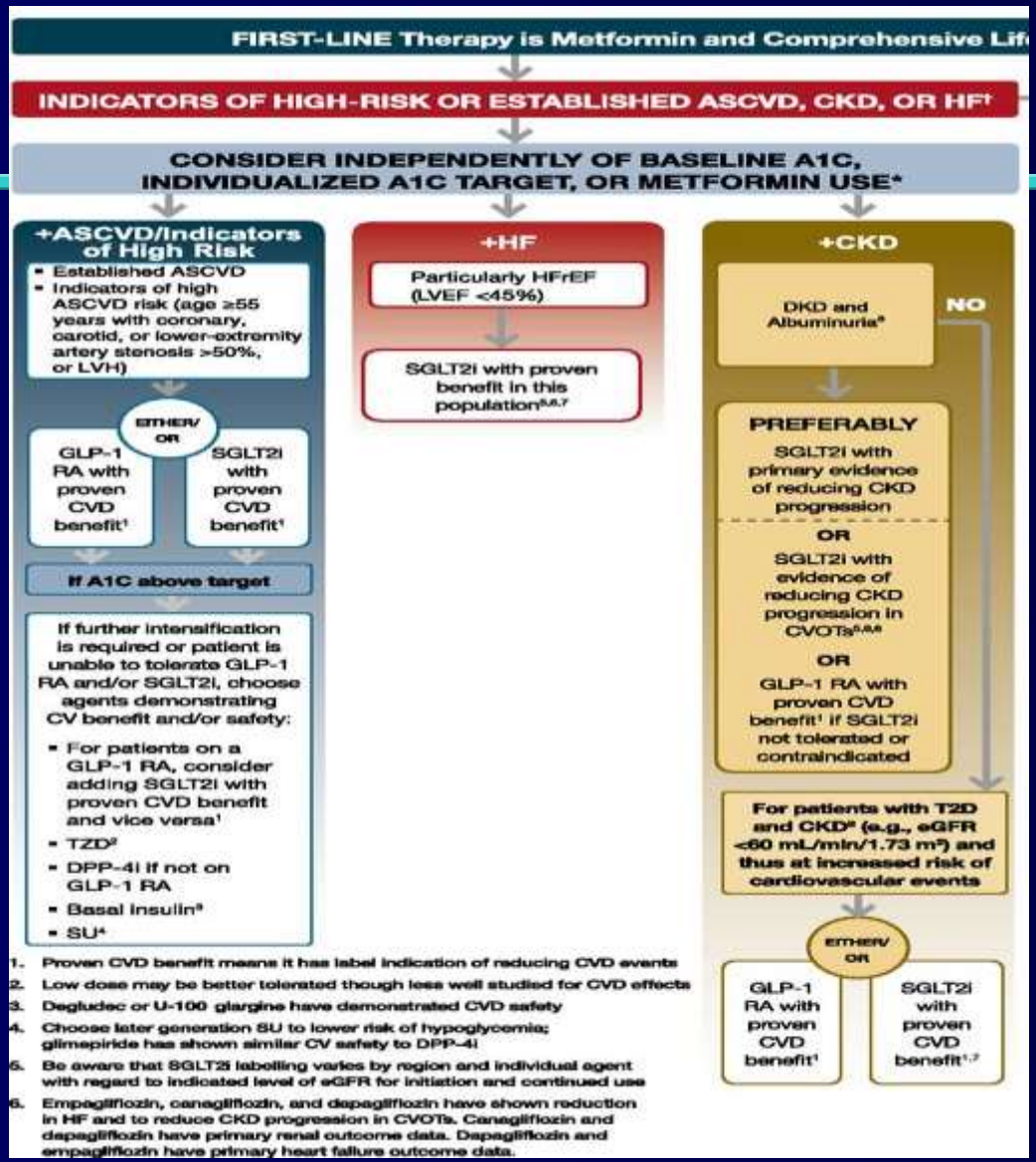


ADA, American Diabetes Association; ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; CV, cardiovascular; CVD, cardiovascular disease; CVOT, cardiovascular outcomes trial; DPP4i, dipeptidyl peptidase-4 inhibitor; eGFR, estimated glomerular filtration rate; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HbA_{1c}, glycated haemoglobin; HF, heart failure; SGLT2i, sodium-glucose co-transporter-2 inhibitor; SU, Sulphonylurea; T2D, type 2 diabetes

American Diabetes Association. *Diabetes Care* 2020;43:S1

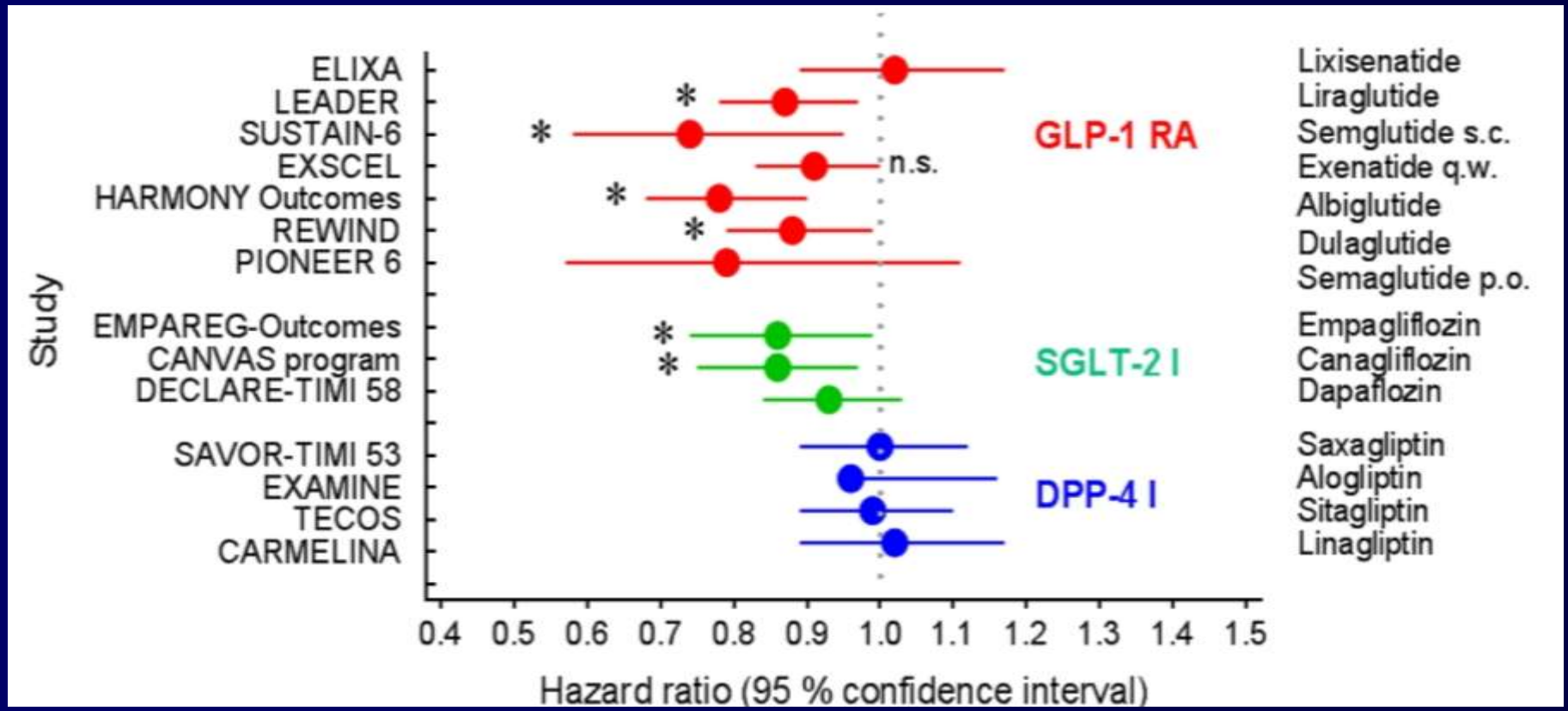
2021Recommendations

"In appropriate **high-risk individuals with established T2D**, the decision to treat with a **GLP-1 RA or SGLT2 inhibitor** to reduce MACE, HHF, CV death or CKD progression should be considered **independently** of baseline HbA_{1c} or individualised HbA_{1c} target"



American Diabetes Association, Diab Care 2021;44:S111-S124

Meta-analysis
Cardiovascular MACE outcomes in CVOT studies MACE

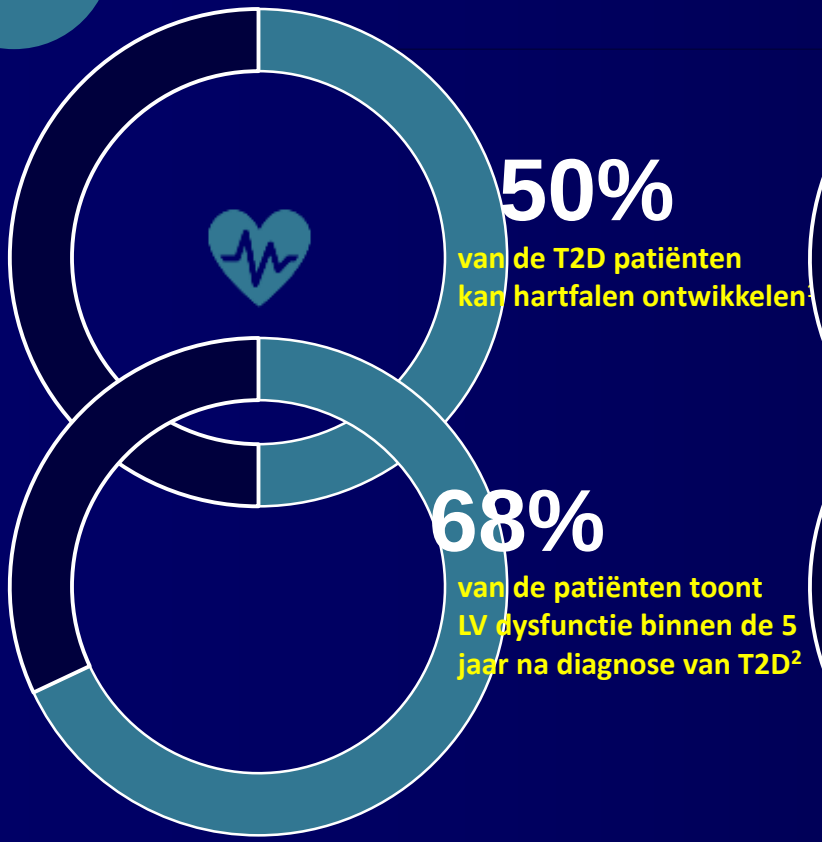


Nauck M, Meier J. *Eur J Endocrinol* 2019 Oct 1. pii: EJE-19-0566.R1. doi:10.1530/EJE-19-0566

The 4F of heart failure in Diabetes

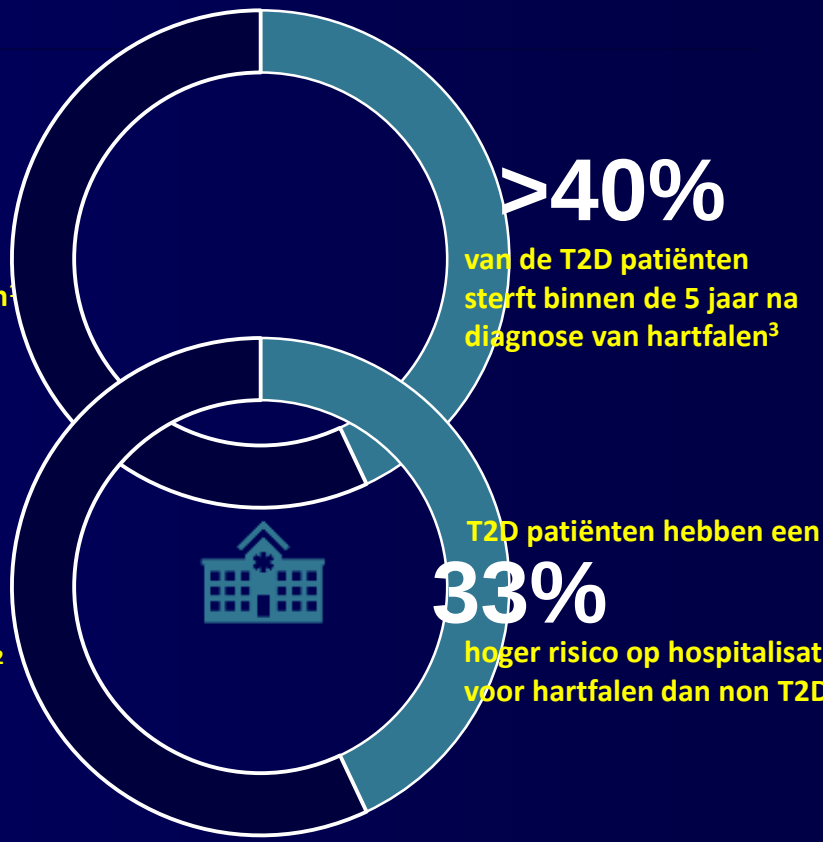
"FIRST, FREQUENT, FATAL & FORGOTTEN"

4F



50%
van de T2D patiënten kan hartfalen ontwikkelen[1]

68%
van de patiënten toont LV dysfunctie binnen de 5 jaar na diagnose van T2D[2]

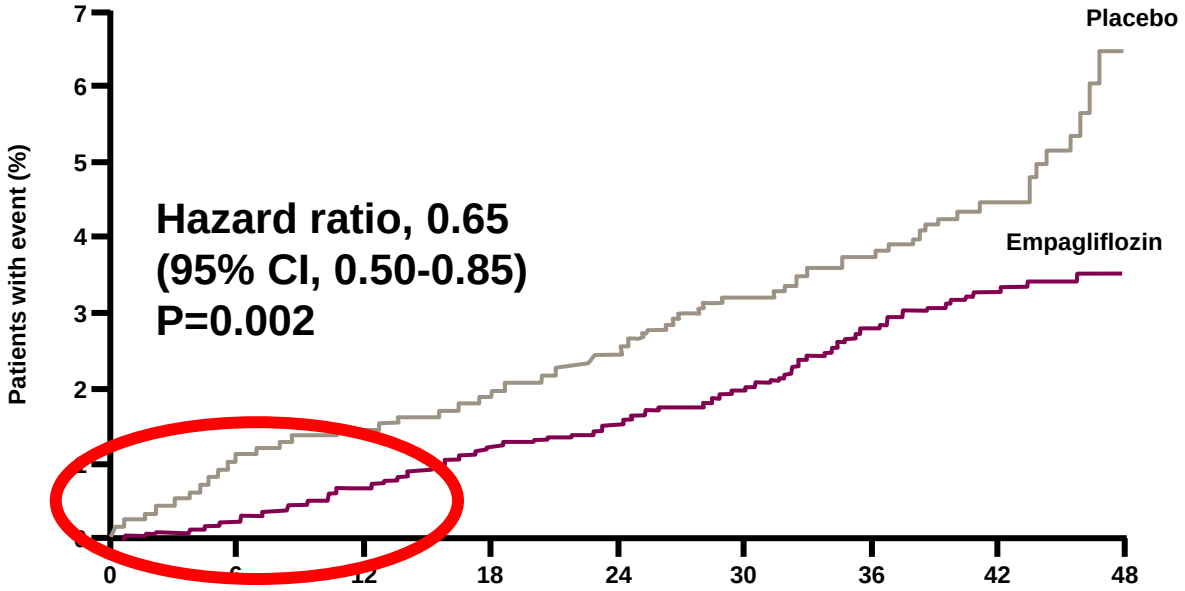


>40%
van de T2D patiënten sterft binnen de 5 jaar na diagnose van hartfalen[3]

T2D patiënten hebben een
33%
hoger risico op hospitalisatie voor hartfalen dan non T2D[4]

1. American Diabetes Association. Diabetes Care 2019; 42(suppl1):S103-S112
2. Faden G et al. Diabetes Res Clin Pract. 2013;101(3):309–316
3. Bertoni AG et al. Diabetes Care 2004; 27(3):699-703
4. Cavender MA et al. Circulation. 2015;132:923-931

EMPA-REG: Type 2 diabetes with established CVD Hospitalisation for heart failure

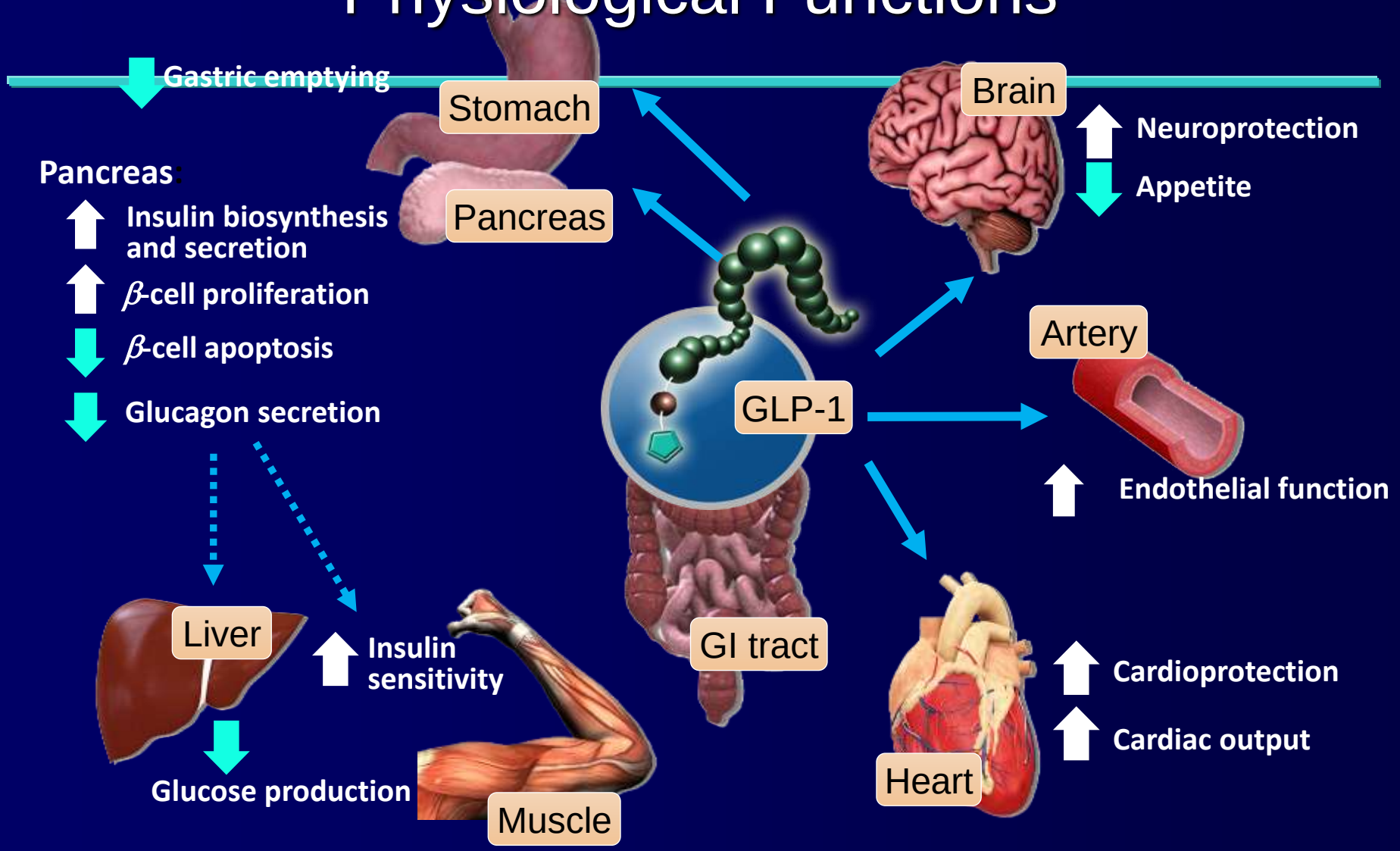


No. of patients									
Empagliflozin	4687	4614	4523	4427	3988	2950	2487	1634	395
Placebo	2333	2271	2226	2173	1932	1424	1202	775	168

Cumulative incidence function
CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio

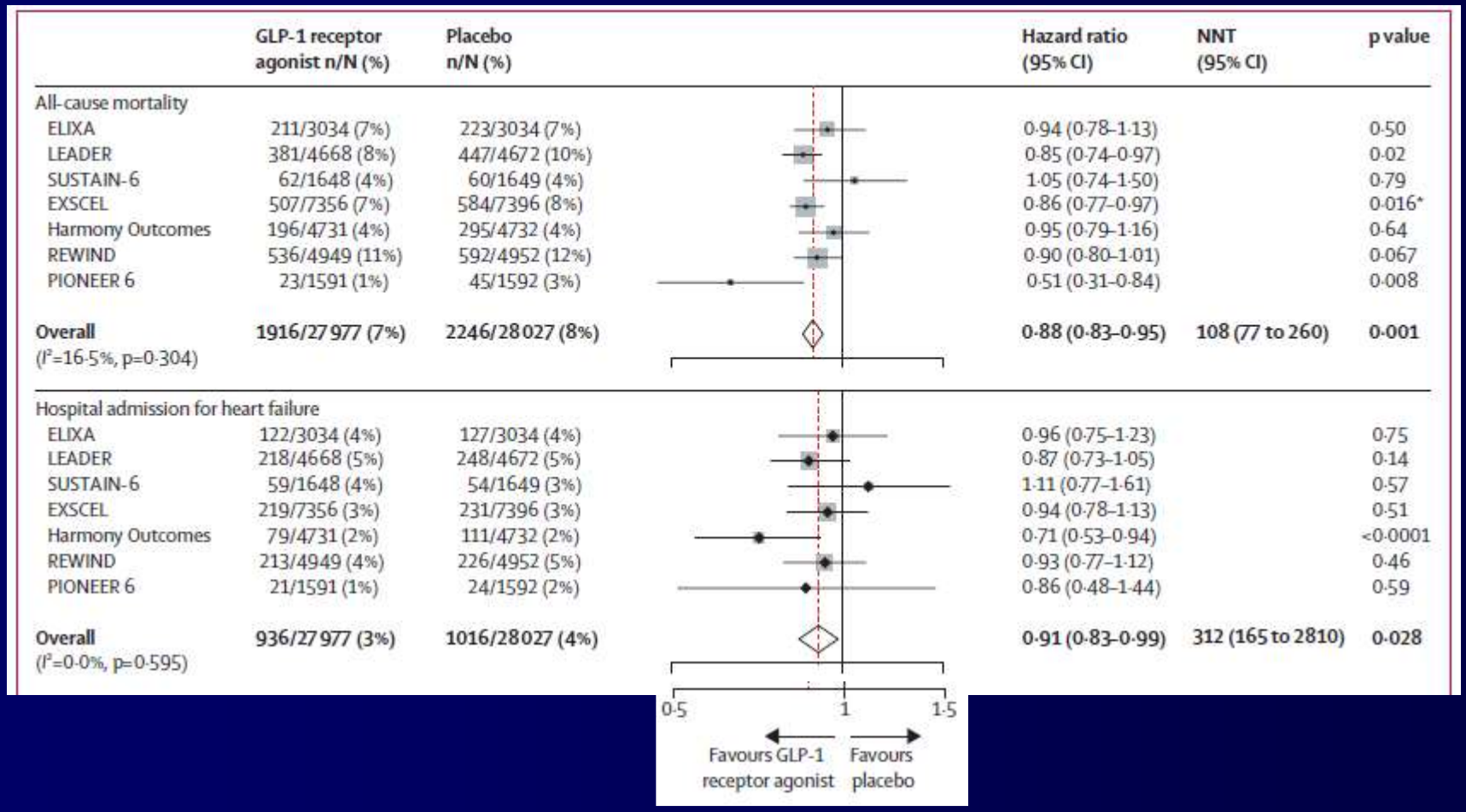
Zinman B, et al. *N Engl J Med* 2015;373:2117–2128

GLP-1 Modulates Numerous Physiological Functions



Modified from Drucker DJ. *Cell Metab* 2006;3:153-65.

Effects of all GLP-1 RA's on mortality and heart failure



	GLP-1 receptor agonist n/N (%)	Placebo n/N (%)	Hazard ratio (95% CI)	NNT (95% CI)	p value
All-cause mortality					
ELIXA	211/3034 (7%)	223/3034 (7%)	0·94 (0·78–1·13)		0·50
LEADER	381/4668 (8%)	447/4672 (10%)	0·85 (0·74–0·97)		0·02
SUSTAIN-6	62/1648 (4%)	60/1649 (4%)	1·05 (0·74–1·50)		0·79
EXSCEL	507/7356 (7%)	584/7396 (8%)	0·86 (0·77–0·97)		0·016*
Harmony Outcomes	196/4731 (4%)	295/4732 (4%)	0·95 (0·79–1·16)		0·64
REWIND	536/4949 (11%)	592/4952 (12%)	0·90 (0·80–1·01)		0·067
PIONEER 6	23/1591 (1%)	45/1592 (3%)	0·51 (0·31–0·84)		0·008
Overall (I^2=16·5%, p=0·304)	**1916/27 977 (7%)**	**2246/28 027 (8%)**	**0·88 (0·83–0·95)**	**108 (77 to 260)**	**0·001**
Hospital admission for heart failure					
ELIXA	122/3034 (4%)	127/3034 (4%)	0·96 (0·75–1·23)		0·75
LEADER	218/4668 (5%)	248/4672 (5%)	0·87 (0·73–1·05)		0·14
SUSTAIN-6	59/1648 (4%)	54/1649 (3%)	1·11 (0·77–1·61)		0·57
EXSCEL	219/7356 (3%)	231/7396 (3%)	0·94 (0·78–1·13)		0·51
Harmony Outcomes	79/4731 (2%)	111/4732 (2%)	0·71 (0·53–0·94)		<0·0001
REWIND	213/4949 (4%)	226/4952 (5%)	0·93 (0·77–1·12)		0·46
PIONEER 6	21/1591 (1%)	24/1592 (2%)	0·86 (0·48–1·44)		0·59
Overall (I^2=0·0%, p=0·595)	**936/27 977 (3%)**	**1016/28 027 (4%)**	**0·91 (0·83–0·99)**	**312 (165 to 2810)**	**0·028**

Kristensen SL et al, Lancet Diab Endocrinol 2019

SGLT2i CVOTs: MACE & kidney outcome

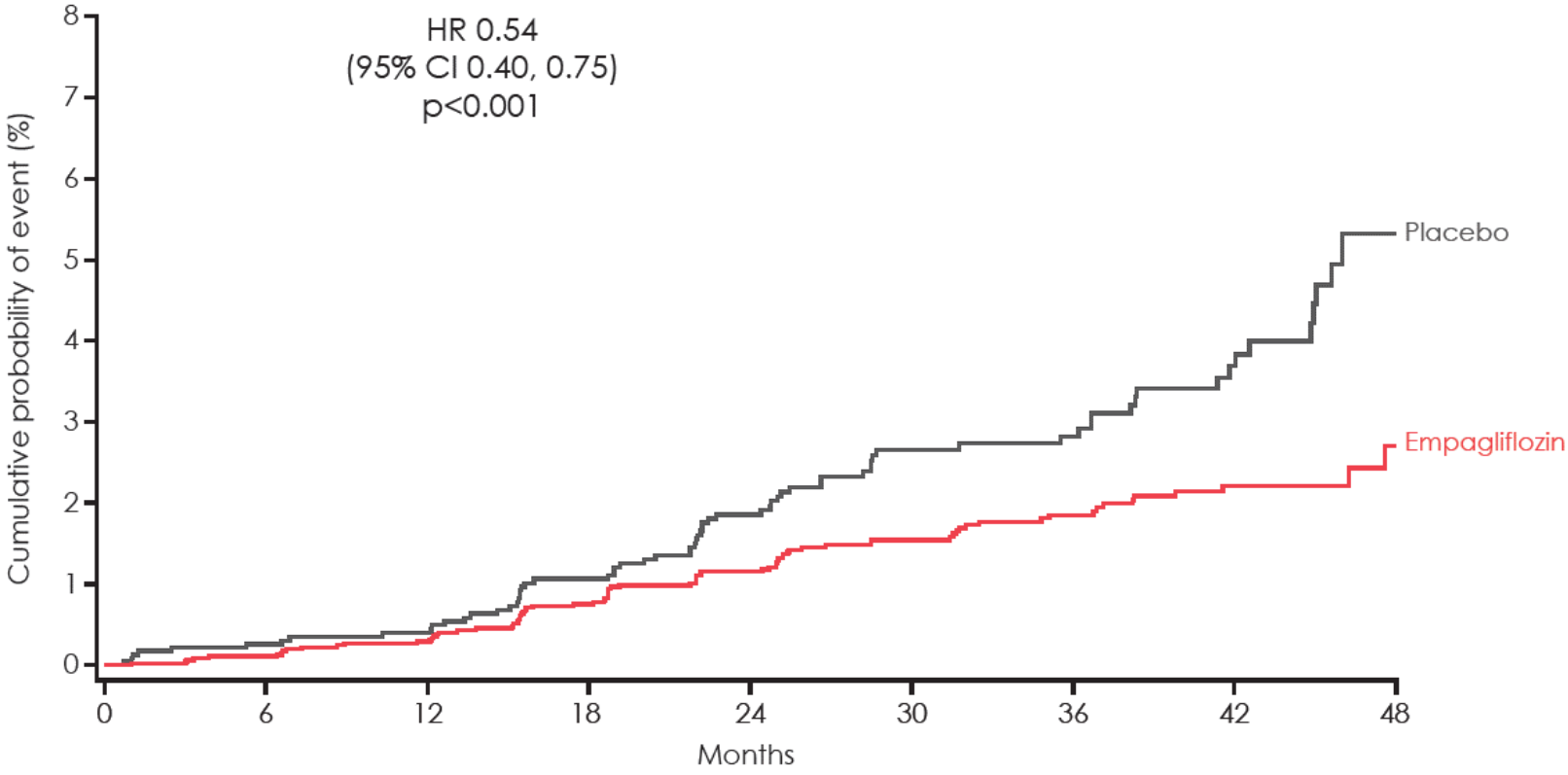
TABLE 1 SGLT2i Cardiovascular Outcome Trials

	EMPA-REG Empagliflozin (n = 7,020)	CANVAS Program Canagliflozin (n = 10,142)	DECLARE Dapagliflozin (n = 17,160)	CREDENCE Canagliflozin (n = 4,401)	DAPA-HF Dapagliflozin (n = 4744)	VERTIS CV (Ertugliflozin) (n=8246)NS
Median follow-up, yrs	3.1	2.4	4.2	2.6	1.5	3.0
Mean age, yrs	63	63	64	63	66	64
Female, %	29	36	37	34	23	30
Mean BMI, kg/m^2	30.6	32.0	32.1	31.3	28.2	32.0
HbA1c, %	8.1	8.3	8.3	8.3	NR	8.2
Baseline metformin, %*	73	77	82	**66**	73	76
Baseline eGFR†	74	77	85	56	65	76
eGFR† <60 ml/min/1.73 m^2, %	26	20	7	59	40	22
Prior CVD, %	99	66	41	50		100
Prior HF, %	10	14	10	15		**24**
3P-MACE	0.86 (0.74-0.99)	0.86 (0.67-0.91)	0.93 (0.84-1.03)	0.80 (0.67-0.95)	0.74 (0.65-0.85)	0.97 (0.85-1.11)
CV death	0.62 (0.49-0.77)	0.87 (0.72-1.06)	0.98 (0.82-1.17)	0.78 (0.61-1.00)	0.75 (0.65-0.85)	0.92 (0.77-1.11)
Nonfatal MI	0.87 (0.70-1.09)	0.89 (0.73-1.09)	0.89 (0.77-1.01)	NR	0.82 (0.69-0.98)	1.0 (0.86-1.27)
Nonfatal stroke	1.18 (0.89-1.56)	0.87 (0.69-1.09)	1.01 (0.84-1.21)	NR	0.83 (0.71-0.97)	1.0 (0.76-1.32)
CV death or HHF	0.66 (0.55-0.79)	0.78 (0.67-0.91)	0.83 (0.73-0.95)	0.69 (0.57-0.83)		0.88 (0.75-1.03)
All-cause mortality	0.68 (0.57-0.82)	0.87 (0.74-1.01)	0.93 (0.82-1.04)	0.83 (0.68-1.02)		
HHF	0.65 (0.50-0.85)	0.67 (0.52-0.87)	0.73 (0.61-0.88)	0.61 (0.47-0.80)	0.70 (0.59-0.83)	0.70 (0.54-0.90)
Renal events‡	0.61 (0.53-0.70)	0.60 (0.47-0.77)	0.53 (0.43-0.66)	0.70 (0.59-0.82)	0.83 (0.44-1.16)	0.81 (0.63-1.04)

Wilcox T, De Block C, et al. JACC 2020

EMPA-REG OUTCOME®: renal outcomes

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



No. of patients									
Empagliflozin	4645	4500	4377	4241	3729	2715	2280	1496	360
Placebo	2323	2229	2146	2047	1771	1289	1079	680	144

*Accompanied by eGFR [MDRD] ≤45 ml/min/1.73m^2.

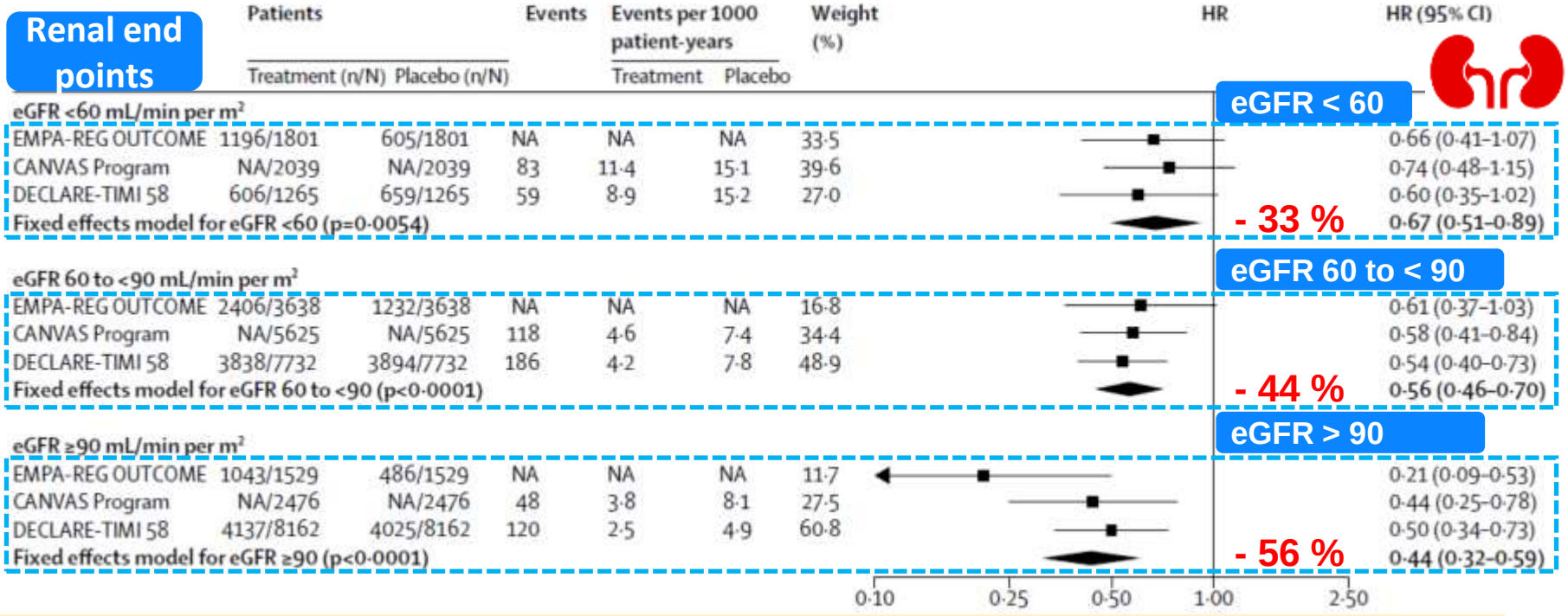
C. Wanner et al, New Engl J Med, 2016

ACROSS T2D

Meta-analysis of SGLT2i CVOT trials on Renal End Points

composite of worsening of renal function, end-stage renal disease, or renal death

Renal end points



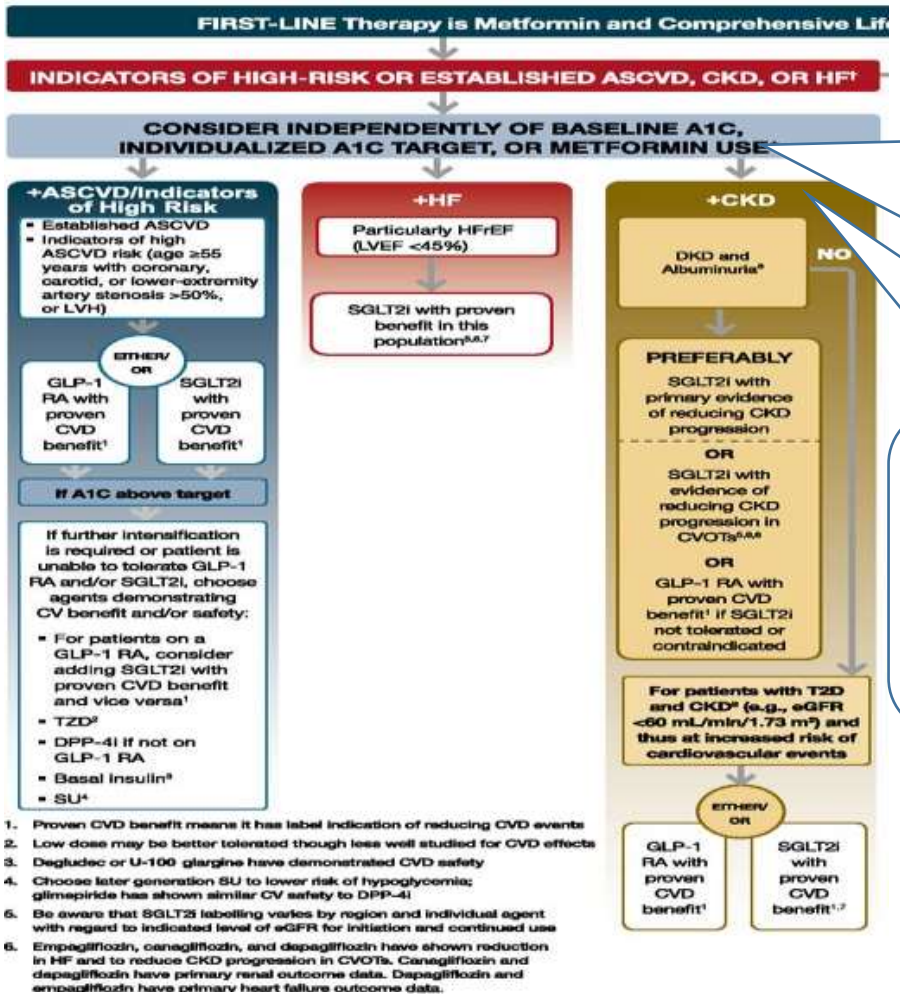
Renal benefit has been showed at all eGFR categories and seems greater effect with better eGFR

Renal composite endpoint without CV death defined as sustained confirmed eGFR decrease ≥ 40% to eGFR < 60 ml/min/1.73m² using CKD-EPI equation and/or ESRD (dialysis ≥ 90 days or kidney transplantation, sustained confirmed eGFR < 15 ml/min/1.73m²) and/or renal death (pre-specified additional renal composite outcome) CV, cardiovascular; CKD, chronic kidney disease; Dapa, dapagliflozin; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease

Zelniker TA 2018. Lancet; Published online November 10, 2018 http://dx.doi.org/10.1016/S0140-6736(18)32590-X 3

Terugbetaling in België

"In appropriate **high-risk individuals with established T2D**, the decision to treat with a **GLP-1 RA or SGLT2 inhibitor** to reduce MACE, HHF, CV death or CKD progression should be considered **independently** of baseline HbA_{1c} or individualised HbA_{1c} target"



GLP-1 : HbA1c > 7.5% en BMI ≥ 30
SGLT2i: HbA1c 7% - 9%

GLP-1 RA: no limit
SGLT2i: eGFR>60 ml/min

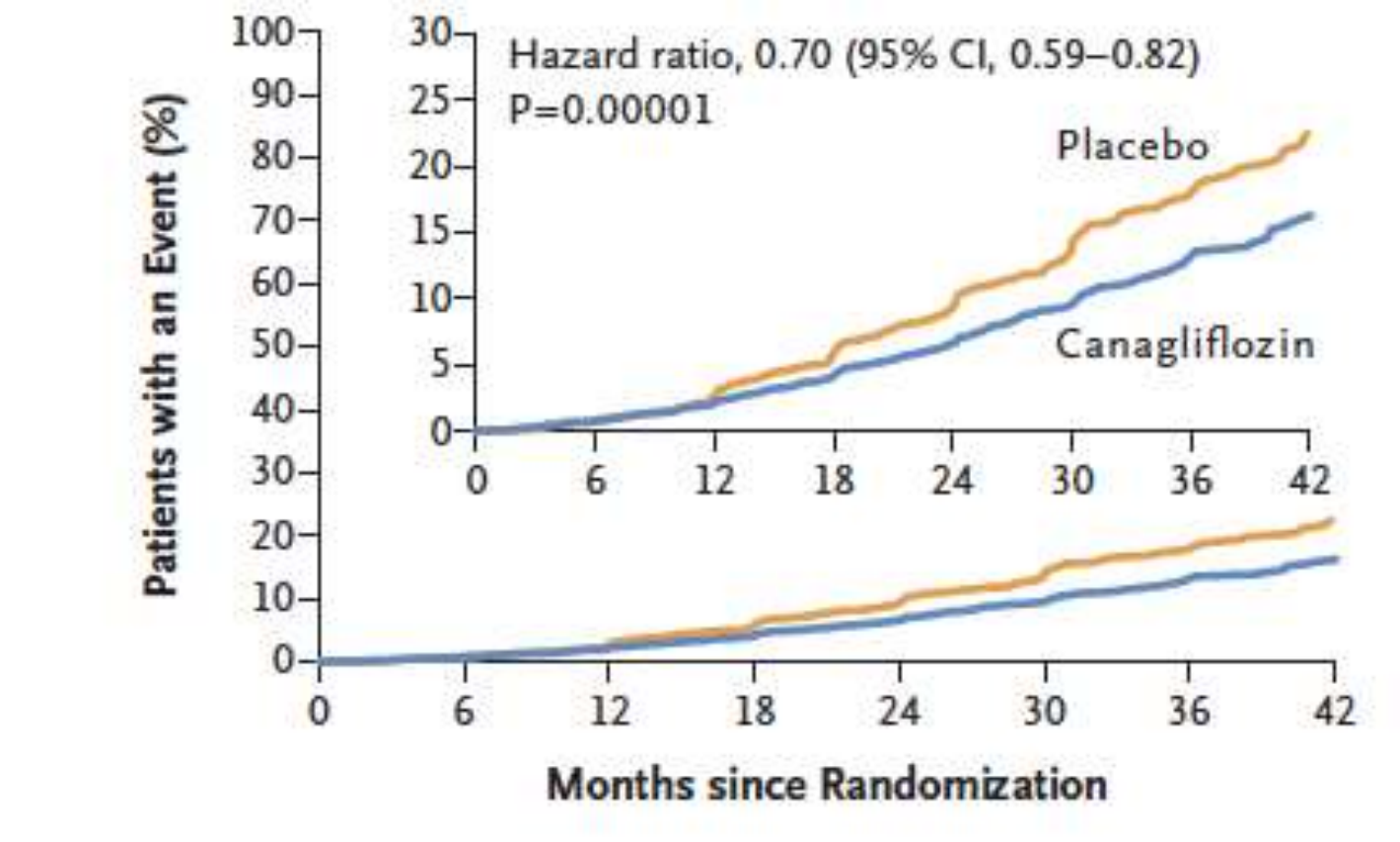
American Diabetes Association Dia Care 2021;44:S111-S124

CREDENCE: Baseline Renal Characteristics

	Canagliflozin (n = 2202)	Placebo (n = 2199)	Total (N = 4401)
Mean eGFR, mL/min/1.73 m²	**56**	**56**	**56**
eGFR ≥90, %	5	5	5
eGFR ≥60 to <90, %	36	35	35
eGFR ≥45 to <60, %	29	29	29
eGFR ≥30 to <45, %	27	27	27
eGFR <30, %	4	4	4
Median UACR (IQR), mg/g	**923 (459-1794)**	**931 (473-1868)**	**927 (463-1833)**
UACR <30, %	<1	<1	<1
UACR 30-300, %	11	11	11
UACR >300-≤3000, %	77	76	77
UACR >3000, %	11	12	11

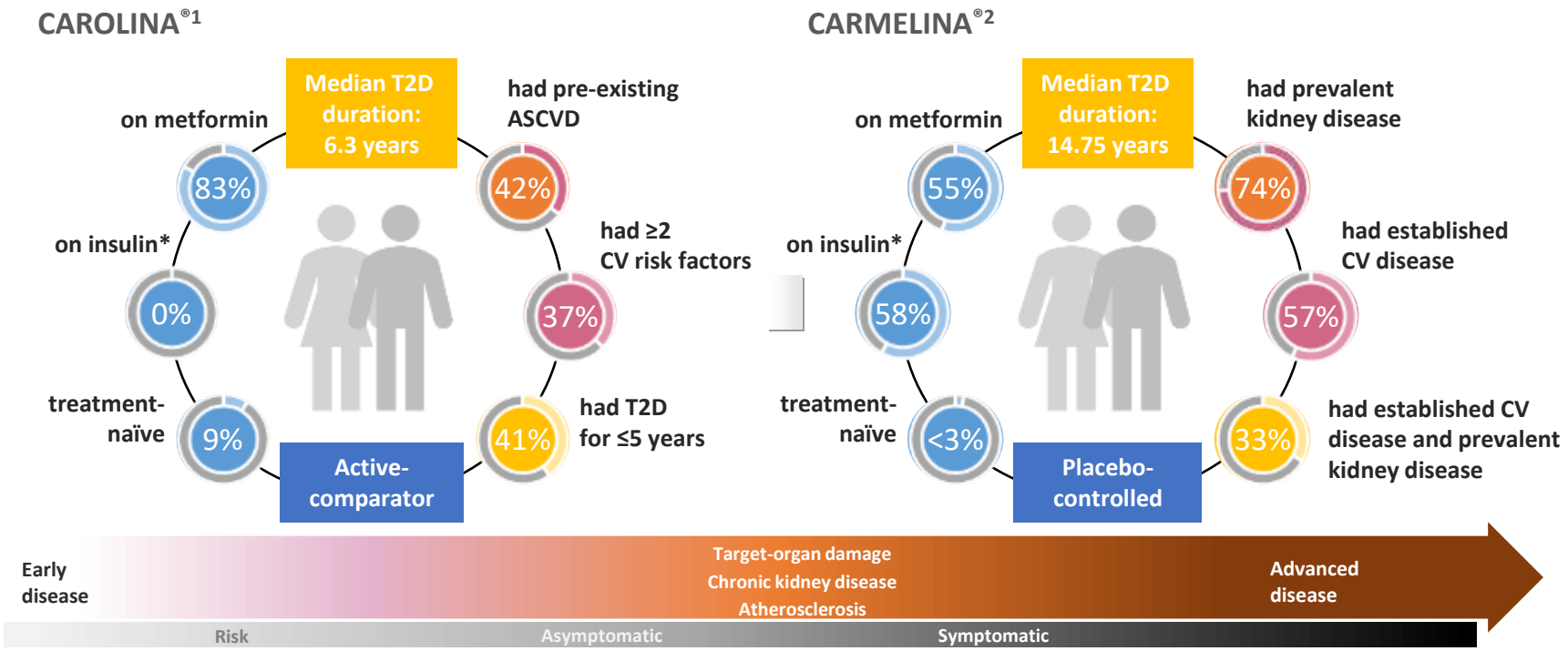
Perkovic V et al, NEJM 2019

Credence outcome with cana



Perkovic V et al, NEJM 2019

CAROLINA and CARMELINA provide evidence across a broad spectrum of T2D duration, CV and kidney risk



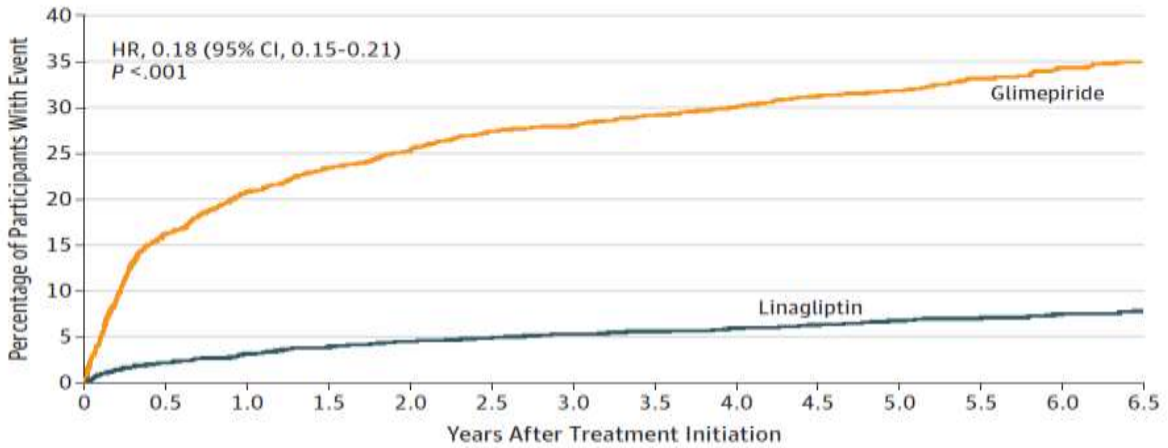
*Exclusion criteria

ASCVD, atherosclerotic cardiovascular disease; CV, cardiovascular

1. Rosenstock J *et al. JAMA* 2019;321:69; 2. Rosenstock J *et al. JAMA* 2019; doi:10.10 01/jama.2019.13772

Moderate or severe Hypoglycemia in Carolina

Figure 4. Moderate or Severe Hypoglycemia Over Time by Treatment Groups



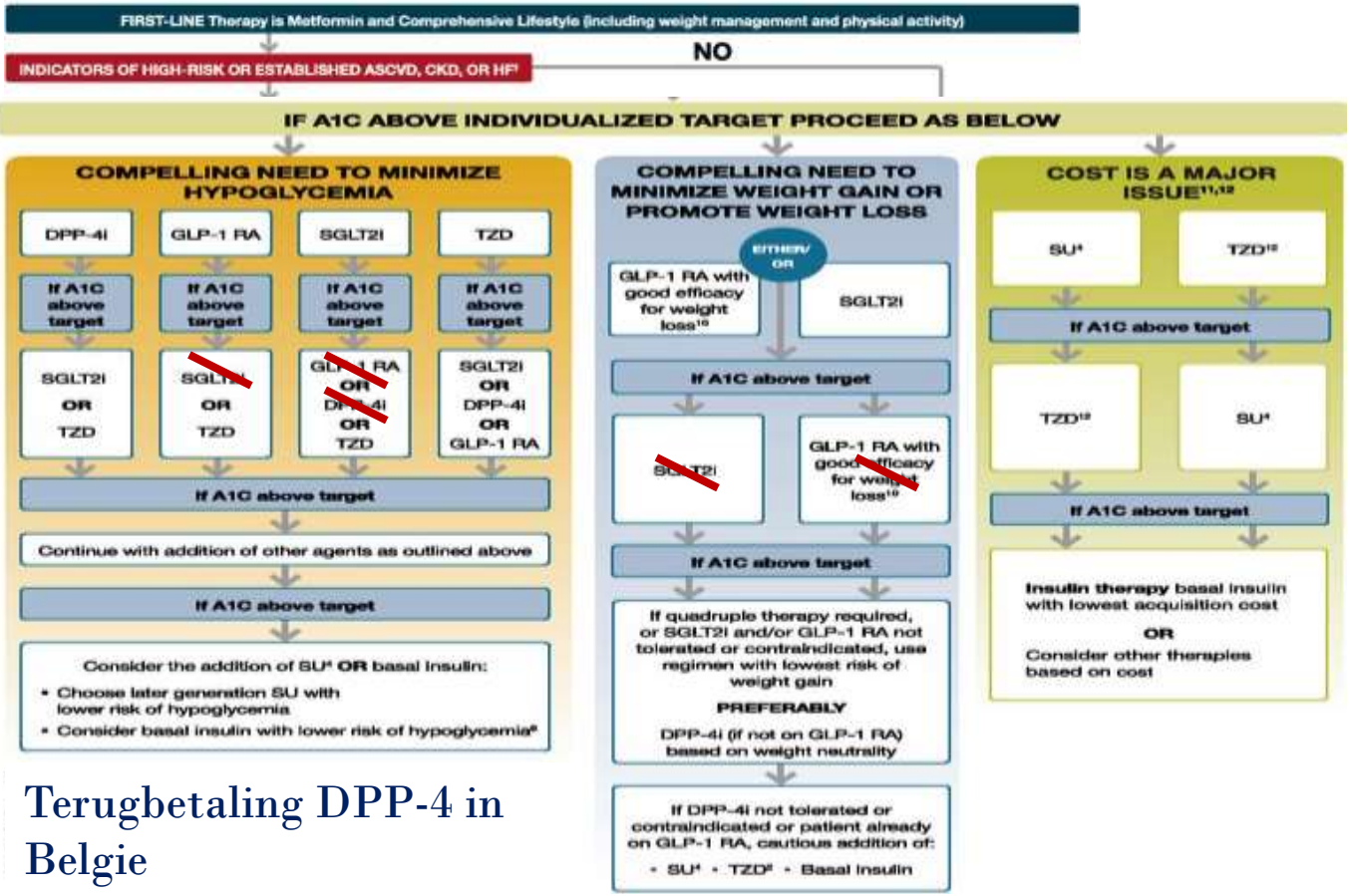
No. of participants

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

Hypoglycemic adverse events[b]				
≥1 Investigator-reported episode of hypoglycemia	320 (10.6)	2.3	1132 (37.7)	11.1
≥1 Investigator-reported episode of symptomatic hypoglycemia with plasma glucose ≤70 mg/dL or severe hypoglycemia	195 (6.5)	1.4	927 (30.9)	8.4
≥1 Investigator-reported episode of severe hypoglycemia[f]	10 (0.3)	0.1	65 (2.2)	0.5
≥1 Episode of hospitalized hypoglycemia	2 (0.1)	<0.1	27 (0.9)	0.2

Rosenstock et al. JAMA, 2019

Terugbetaling in België

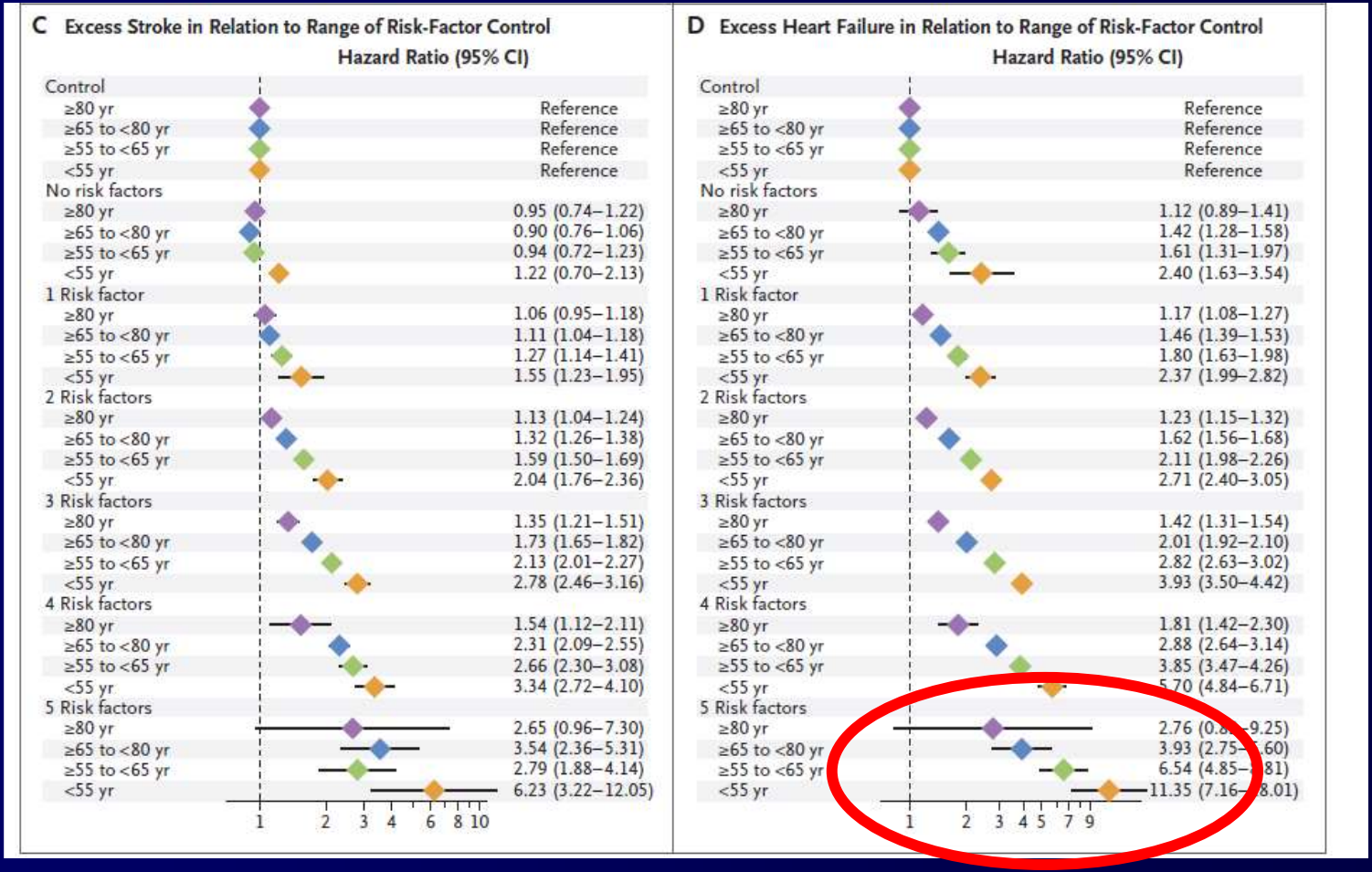


Terugbetaling DPP-4 in Belgie
HbA1c 7-9 %

How to detect early heart failure ?

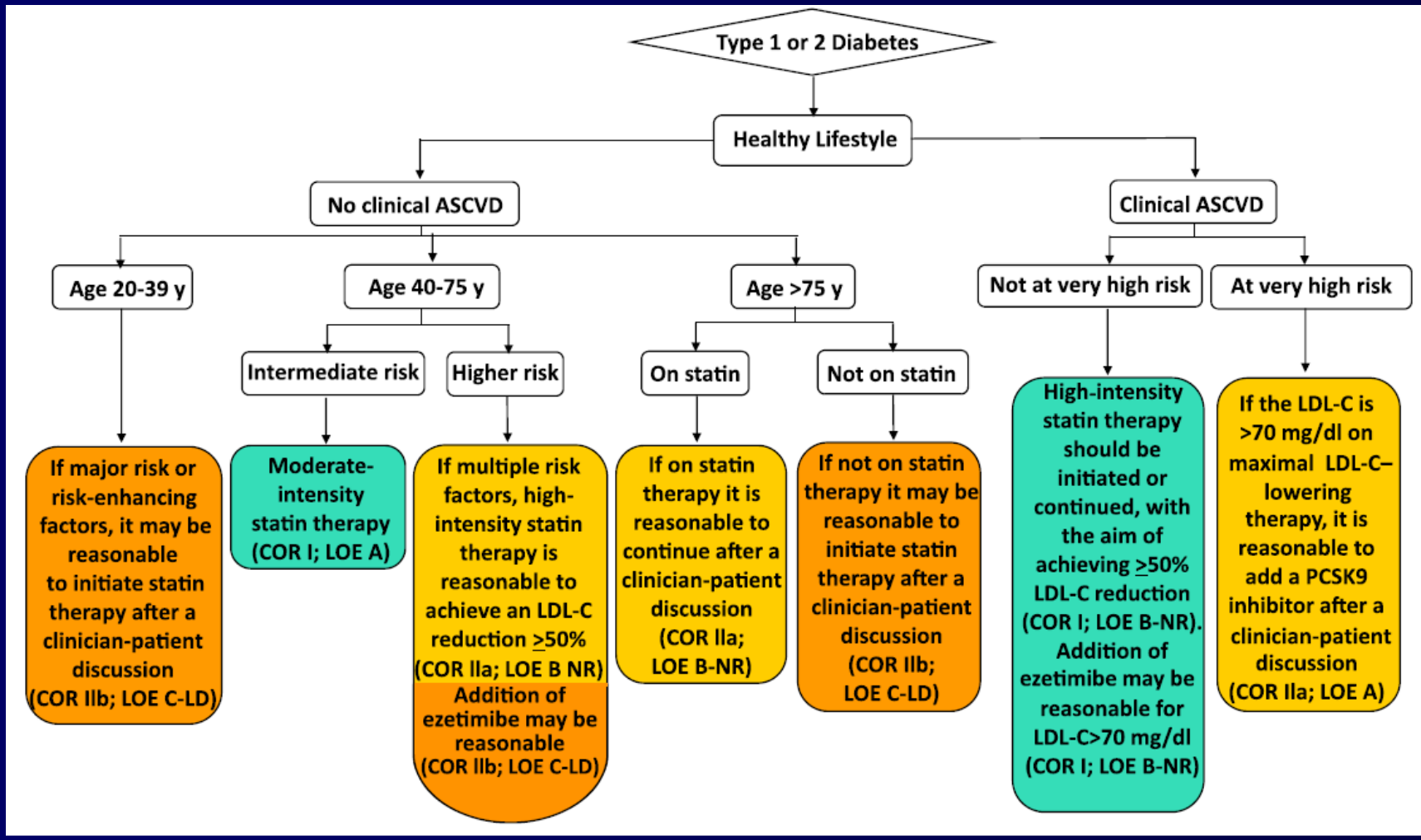
- **Symptom detection**
- **Analysis of natriuretic peptides (pro-BNP)**
- **Echocardiography**
- **Risk profiling of patient (Rawshani RF)**

Contributors to heart failure: ways to screen



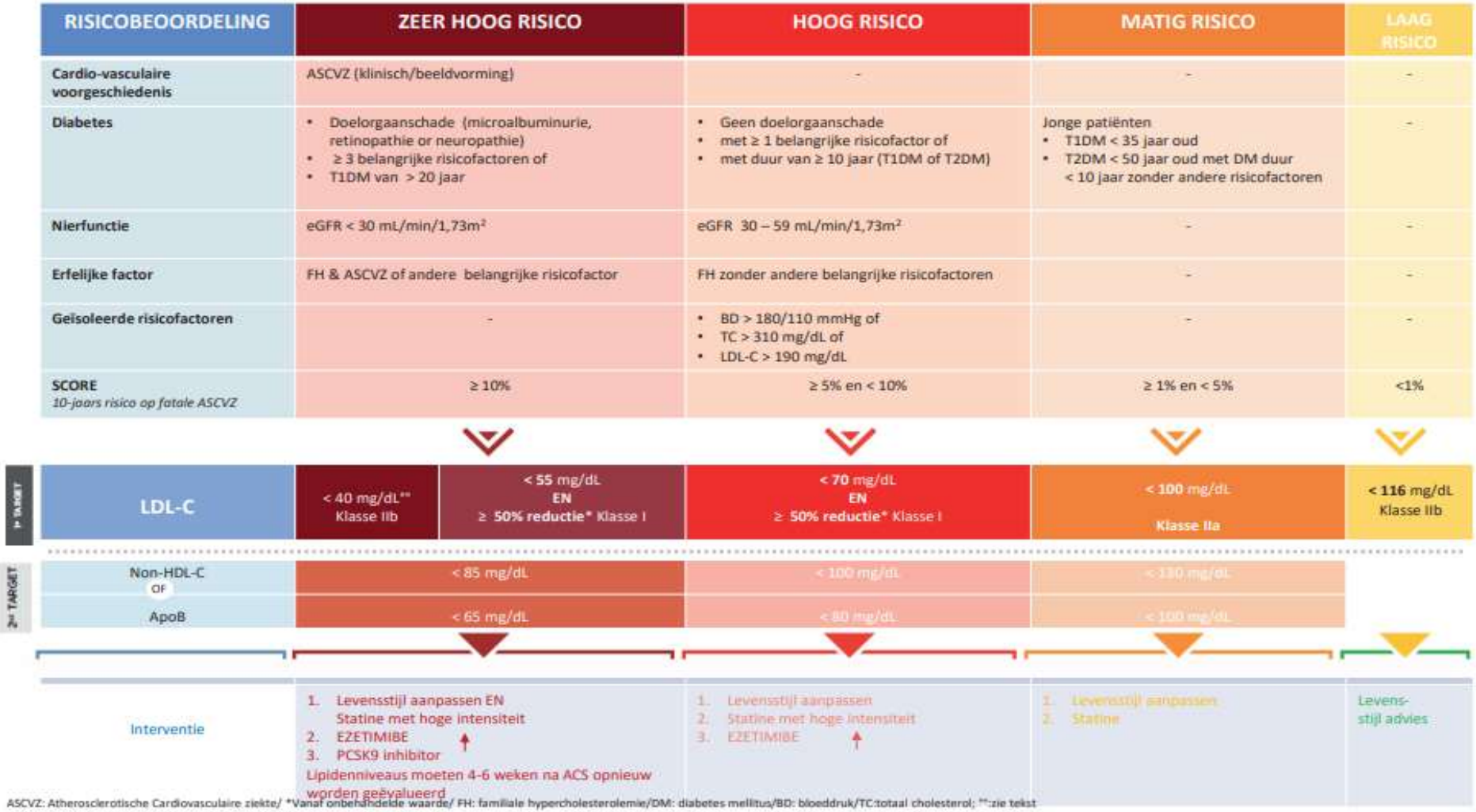
Rawshani A et al, New Eng J Med 2018

What about lipids in diabetes ?



Goldberg et al. Diabetes Care, 2020

What about lipids in diabetes ?



RISICOBEOORDELING	ZEER HOOG RISICO	HOOG RISICO	MATIG RISICO	LAAG RISICO
Cardio-vasculaire voorgeschiedenis	ASCVZ (klinisch/beeldvorming)	-	-	-
Diabetes	• Doelorgaanschade (microalbuminurie, retinopathie or neuropathie) • ≥ 3 belangrijke risicofactoren of • T1DM van > 20 jaar	• Geen doelorgaanschade • met ≥ 1 belangrijke risicofactor of • met duur van ≥ 10 jaar (T1DM of T2DM)	Jonge patiënten • T1DM < 35 jaar oud • T2DM < 50 jaar oud met DM duur < 10 jaar zonder andere risicofactoren	-
Nierfunctie	eGFR < 30 mL/min/1,73m²	eGFR 30 – 59 mL/min/1,73m²	-	-
Erfelijke factor	FH & ASCVZ of andere belangrijke risicofactor	FH zonder andere belangrijke risicofactoren	-	-
Geïsoleerde risicofactoren	-	• BD > 180/110 mmHg of • TC > 310 mg/dL of • LDL-C > 190 mg/dL	-	-
SCORE *10-jaars risico op fatale ASCVZ*	≥ 10%	≥ 5% en < 10%	≥ 1% en < 5%	<1%
1e TARGET LDL-C	< 40 mg/dL** Klasse IIb	< 55 mg/dL EN ≥ 50% reductie* Klasse I	< 70 mg/dL EN ≥ 50% reductie* Klasse I	< 100 mg/dL Klasse IIa	< 116 mg/dL Klasse IIb
2e TARGET Non-HDL-C OF ApoB	< 85 mg/dL < 65 mg/dL	< 100 mg/dL < 80 mg/dL	< 130 mg/dL < 100 mg/dL	
Interventie	1. Levensstijl aanpassen EN Statine met hoge intensiteit 2. EZETIMIBE 3. PCSK9 inhibitor Lipidenniveaus moeten 4-6 weken na ACS opnieuw worden geëvalueerd	1. Levensstijl aanpassen 2. Statine met hoge intensiteit 3. EZETIMIBE	1. Levensstijl aanpassen 2. Statine	Levens-stijl advies

ASCVZ: Atherosclerotische Cardiovasculaire ziekte/ *Vanaf onbehandelde waarde/ FH: familiale hypercholesterolemie/DM: diabetes mellitus/BD: bloeddruk/TC:totaal cholesterol; **:zie tekst

Waarom Technologie?

RESCUE trial

Belgische data (515 T1DM)

Change in HbA_{1c} from baseline

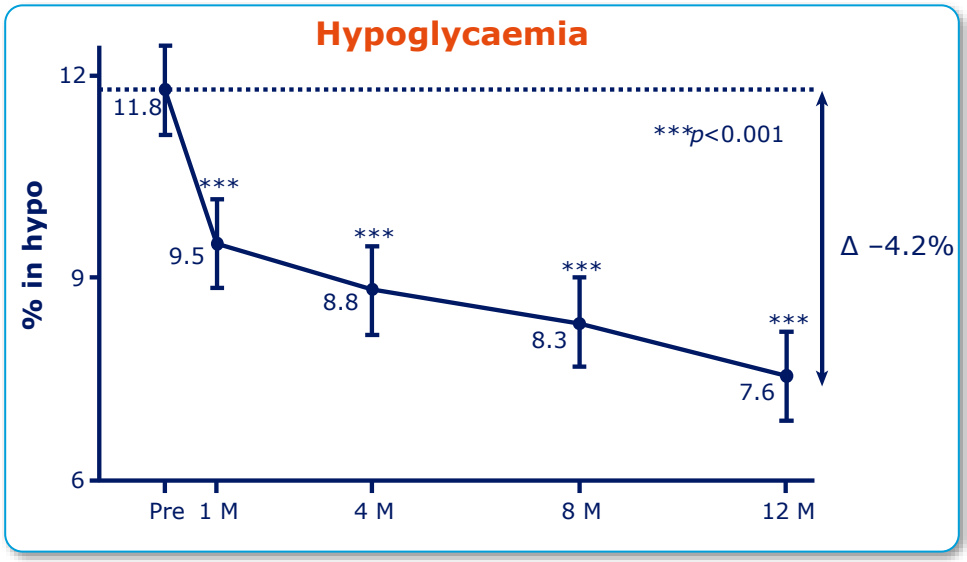
Baseline: **7.7 ± 0.9%** → 12 months: **7.4 ± 0.8%**

p<0.0001

Effect of Continuous Glucose Monitoring on Glycemic Control, Acute Admissions, and Quality of Life: A Real-World Study

Sara Charleer,[1,2] Chantal Mathieu,[1] Frank Nobels,[3] Christophe De Block,[4] Regis P. Radermecker,[5] Michel P. Hermans,[6] Youri Taes,[7] Chris Vercammen,[8] Guy T'Sjoen,[9] Laurent Crenier,[10] Steffen Fieuws,[11] Bart Keymeulen,[12] and Pieter Gillard,[1] for the RESCUE Trial Investigators

Hypoglycaemia



Admission to the hospital for severe hypoglycaemic or ketoacidosis episodes

Year before reimbursement **16%**

p<0.0005

Year after reimbursement **4%**

Reduction in hospitalisation days from 53.5 to 17.8 days per 100 patient-years

Quality of life improved significantly, with a strong decline in fear of hypoglycaemia

QoL 1ST

Charleer et al. *J Clin Endocrinol Metab* 2018, 103:1224–32.

Current development in Artificial Pancreas

User input and interaction

Insulin pump

Combination insulin pump and CGM system

Low glucose suspension

Predictive low glucose suspension

Hybrid closed-loop system

System integration and automation

Current development in Artificial Pancreas

User input and interaction

Insulin pump ✓

Combination insulin pump and CGM system ✓

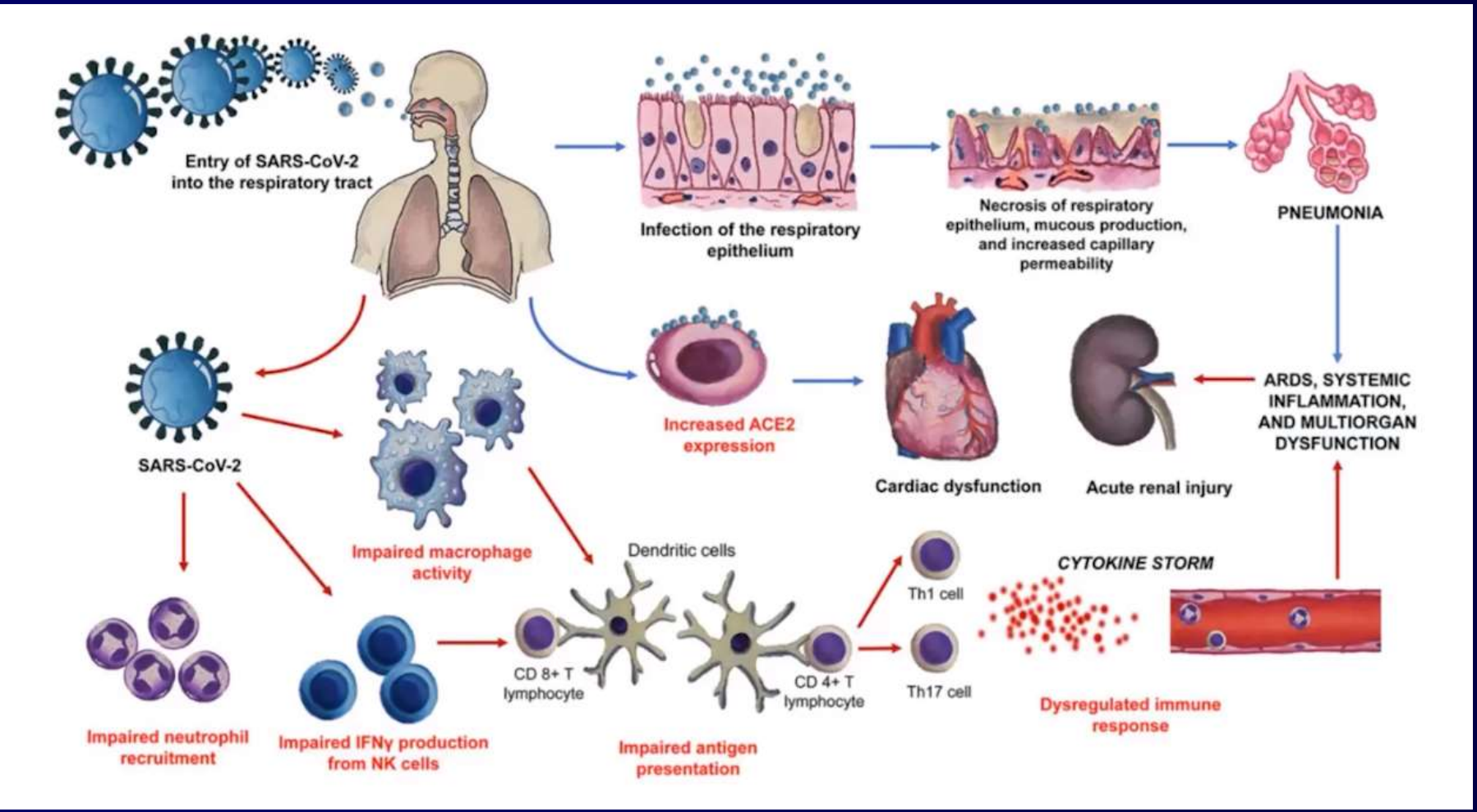
Low glucose suspension ✓

Predictive low glucose suspension ✓

Hybrid closed-loop system ✓

System integration and automation

Covid-19 pathophysiology



Practical recommendations for the management of diabetes in patients with COVID-19

Stefan R Bornstein, Francesco Rubino, Kamlesh Khunti, Geltrude Mingrone, David Hopkins, Andreas L Birkenfeld, Bernhard Boehm, Stephanie Amiel , Richard IG Holt, Jay S Skyler, J Hans DeVries, Eric Renard, Robert H Eckel, Paul Zimmet, Kurt George Alberti, Josep Vidal, Bruno Geloneze, Juliana C Chan, Linong Ji, Barbara Ludwig

Panel: **Consideration of potential metabolically interfering effects of drugs in suspected or COVID-19 positive patients with type 2 diabetes**

Metformin

- Dehydration and lactic acidosis will probably occur if patients are dehydrated, so patients should stop taking the drug and follow sick day rules
- During illness, renal function should be carefully monitored because of the high risk of chronic kidney disease or acute kidney injury

Sodium-glucose-co-transporter 2 inhibitors

- These include canagliflozin, dapagliflozin, and empagliflozin
- Risk of dehydration and diabetic ketoacidosis during illness, so patients should stop taking the drugs and follow sick day rules
- Patients should avoid initiating therapy during respiratory illness
- Renal function should be carefully monitored for acute kidney injury

Glucagon-like peptide-1 receptor agonists

- These include albiglutide, dulaglutide, exenatide-extended release, liraglutide, lixisenatide, and semaglutide
- Dehydration is likely to lead to a serious illness so patients should be closely monitored
- Adequate fluid intake and regular meals should be encouraged

Dipeptidyl peptidase-4 inhibitors

- These include alogliptin, linagliptin, saxagliptin, and sitagliptin
- These drugs are generally well tolerated and can be continued

Insulin

- Insulin therapy should not be stopped
- Regular self-monitoring of blood-glucose every 2–4 hours should be encouraged, or continuous glucose monitoring
- Carefully adjust regular therapy if appropriate to reach therapeutic goals according to diabetes type, comorbidities, and health status

Connected Health models and Telemedicine should be used to continue regular reviews and self-management education programmes virtually and ensure patients are adherent to therapy.

www.thelancet.com/diabetes-endocrinology **Published online April 23, 2020**

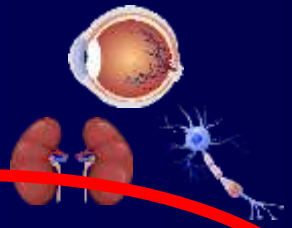
The unmet needs in diabetes

Progression of T2 Diabetes

β-cell function declines[1]

Glycaemic targets harder to reach[1]

Weight gain & hypoglycaemia



Microvascular comorbidities[3]
Nephropathy
Neuropathy
Retinopathy

Macrovascular comorbidities[3]
Cardiac ischaemia
Heart failure

Can oral combination therapy help in unmet needs?

1. Scheen AJ *& Van Gaal LF, Lancet Diabetes Endocrinol* 2014;2:911–22;
2. Van Gaal L *et al. Diabetes Care* 2015;38:1161–7;
3. Phillips LS *et al. Diabetes Care* 2014;37:2668–76

Thank you very much !