Platelet effects of anti-diabetes drugs

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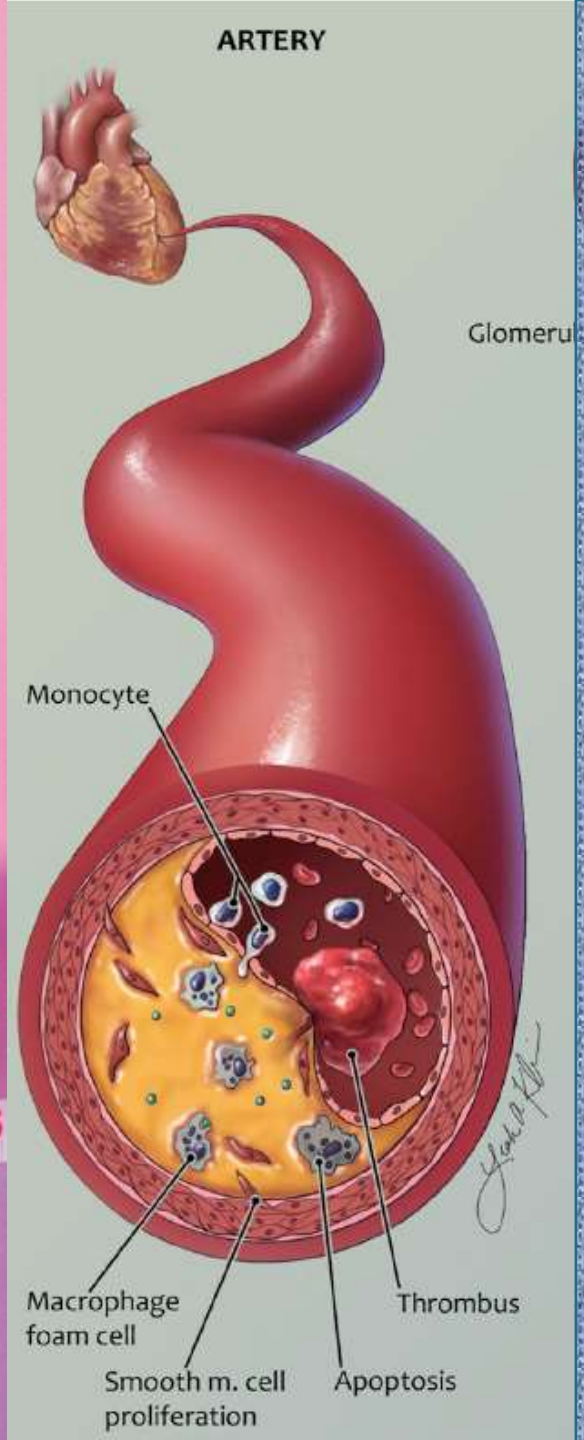
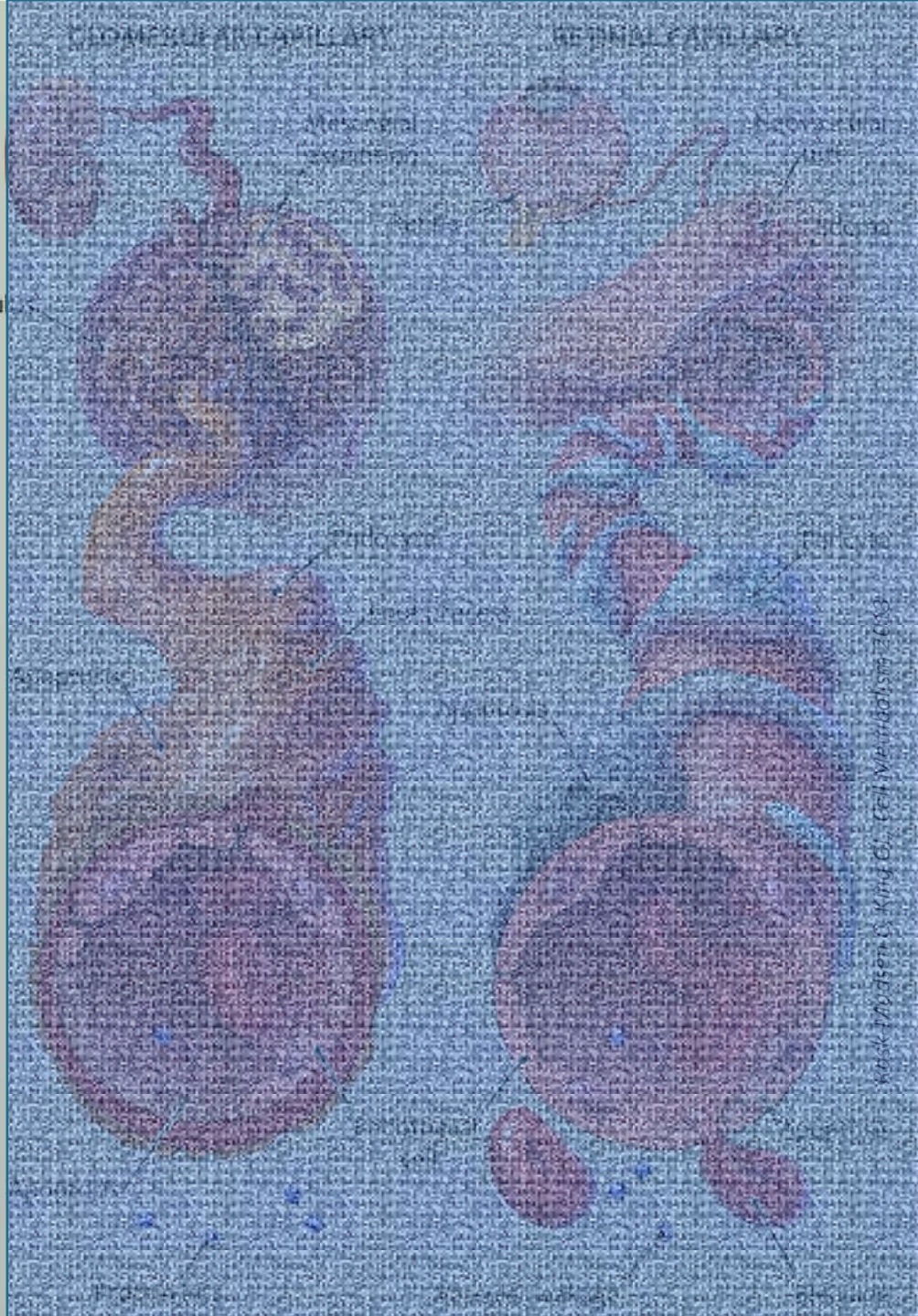
Agenda

- Thrombotic events and platelet dysfunction in diabetes
- Antidiabetes drugs and platelets

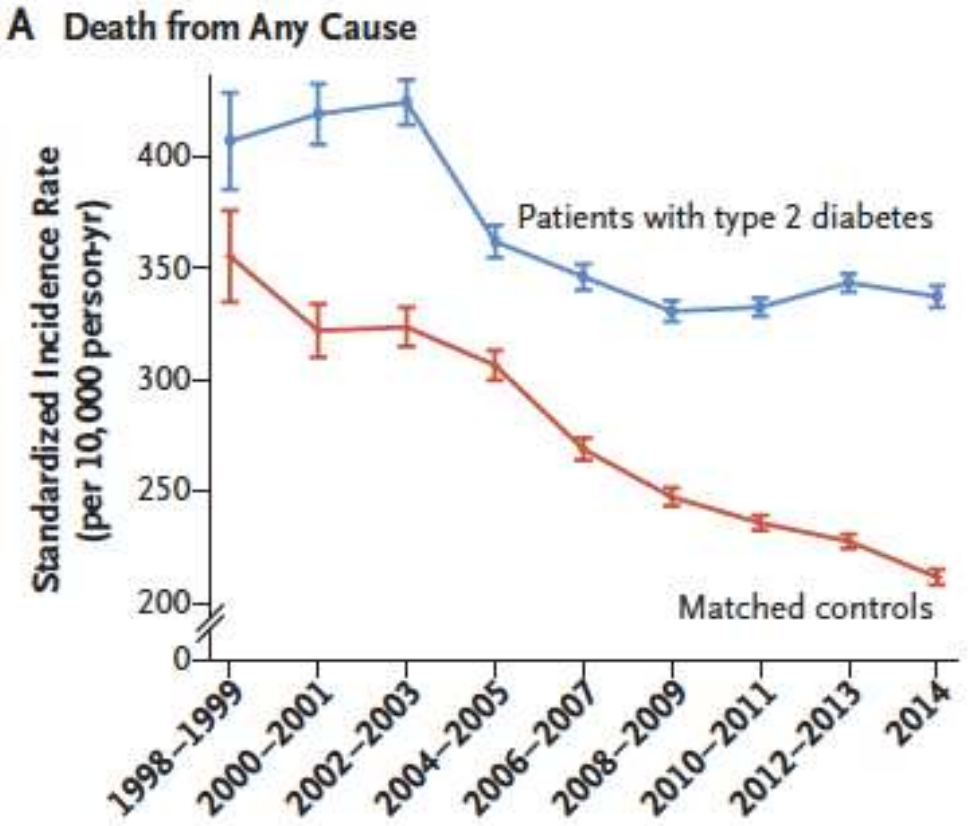
Learning objectives

- Understand the risk of thrombotic events in people with type 2 diabetes
- Learn about the effects of diabetes on platelet function
- Acquire specific knowledge about the effects of anti-diabetes drugs with CV benefits on platelet dysfunction


ARTERY
Glomeru
Monocyte
Macrophage
foam cell
Smooth m. cell
proliferation
Apoptosis
Thrombus

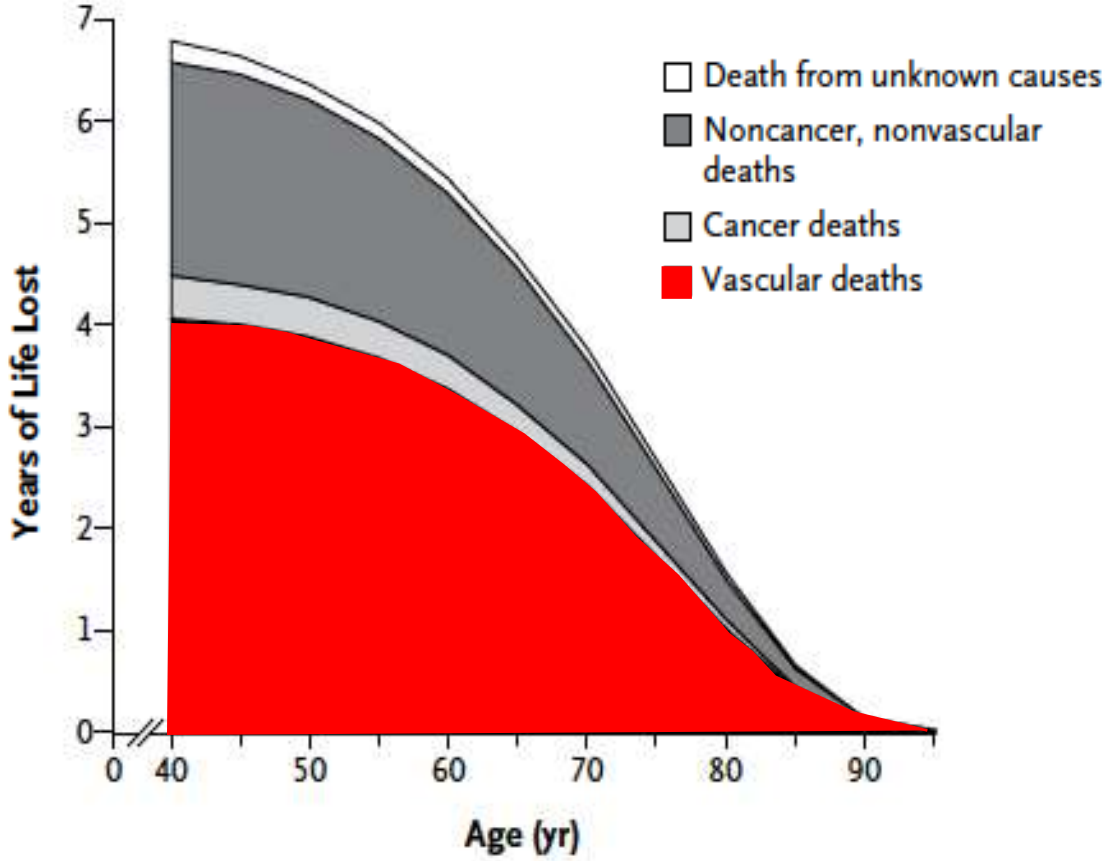


High mortality rate in diabetes



Rawshani A. et al., N Engl J Med, 2017

Causes of death in diabetes

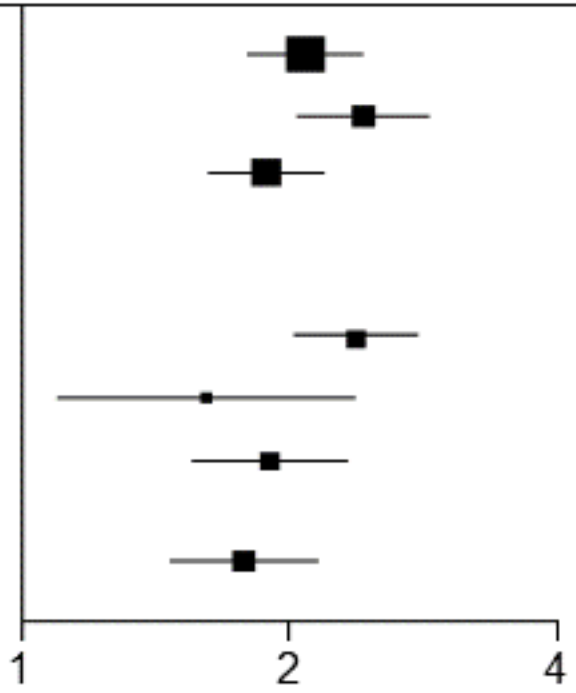


Seshasai RK et al, N Engl J Med, 2011

Hazard ratios (HRs) for vascular outcomes in people with versus without diabetes at baseline, based on analyses of 530 083 patients

ESC European Society of Cardiology

	Number of cases	HR (95% CI)	I^2 (95% CI)
Coronary heart disease*	26 505	2.00 (1.83–2.19)	64 (54–71)
Coronary death	11 556	2.31 (2.05–2.60)	41 (24–54)
Non-fatal myocardial infarction	14 741	1.82 (1.64–2.03)	37 (19–51)
Stroke subtypes*			
Ischaemic stroke	3 799	2.27 (1.95–2.65)	1 (0–20)
Haemorrhagic stroke	1 183	1.56 (1.19–2.05)	0 (0–26)
Unclassified stroke	4 973	1.84 (1.59–2.13)	33 (12–48)
Other vascular deaths	3 826	1.73 (1.51–1.98)	0 (0–26)



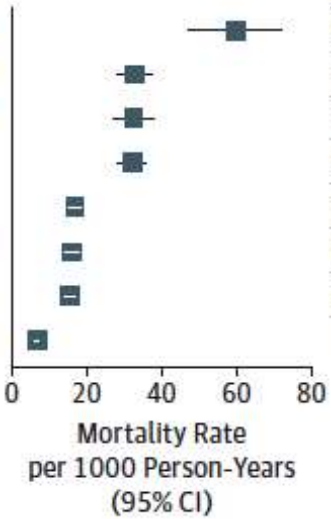
CI = confidence interval. *Includes both fatal and non-fatal events

ESC Guidelines on Diabetes, pre-diabetes and cardiovascular diseases in collaboration with EASD (European Heart Journal 2019 - doi/10.1093/eurheartj/ehz486)

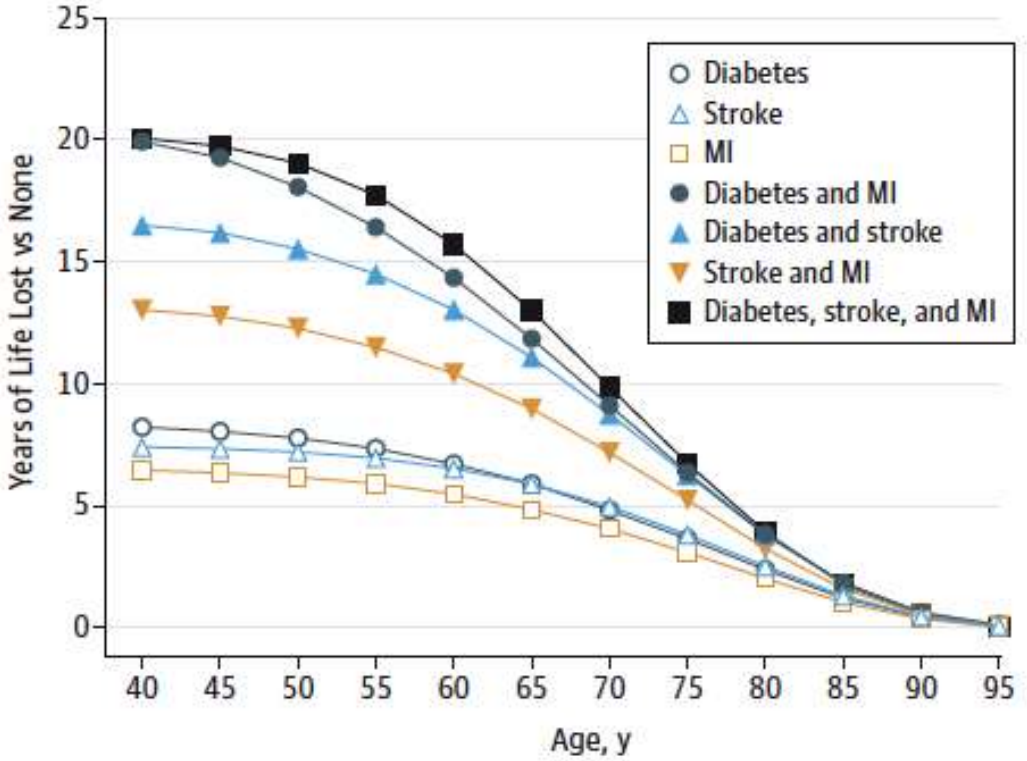
Diabetes mellitus is a cardiovascular equivalent

All-Cause Mortality by Disease Status

Disease Status at Baseline	No of. Participants	No. of Deaths	Person-Years	Mortality Rate (95% CI)[a]
Diabetes, stroke, and MI	541	379	3584	59.5 (47.0-71.9)
Stroke and MI	1836	1174	14210	32.8 (28.1-37.6)
Diabetes and stroke	1321	778	10234	32.5 (27.0-37.9)
Diabetes and MI	3233	1794	25321	32.0 (28.1-35.9)
MI	21 591	9636	216081	16.8 (15.2-18.3)
Stroke	8583	3814	82208	16.1 (14.4-17.8)
Diabetes	24677	8087	254608	15.6 (14.1-17.0)
None	627518	103181	8772977	6.8 (6.2-7.4)

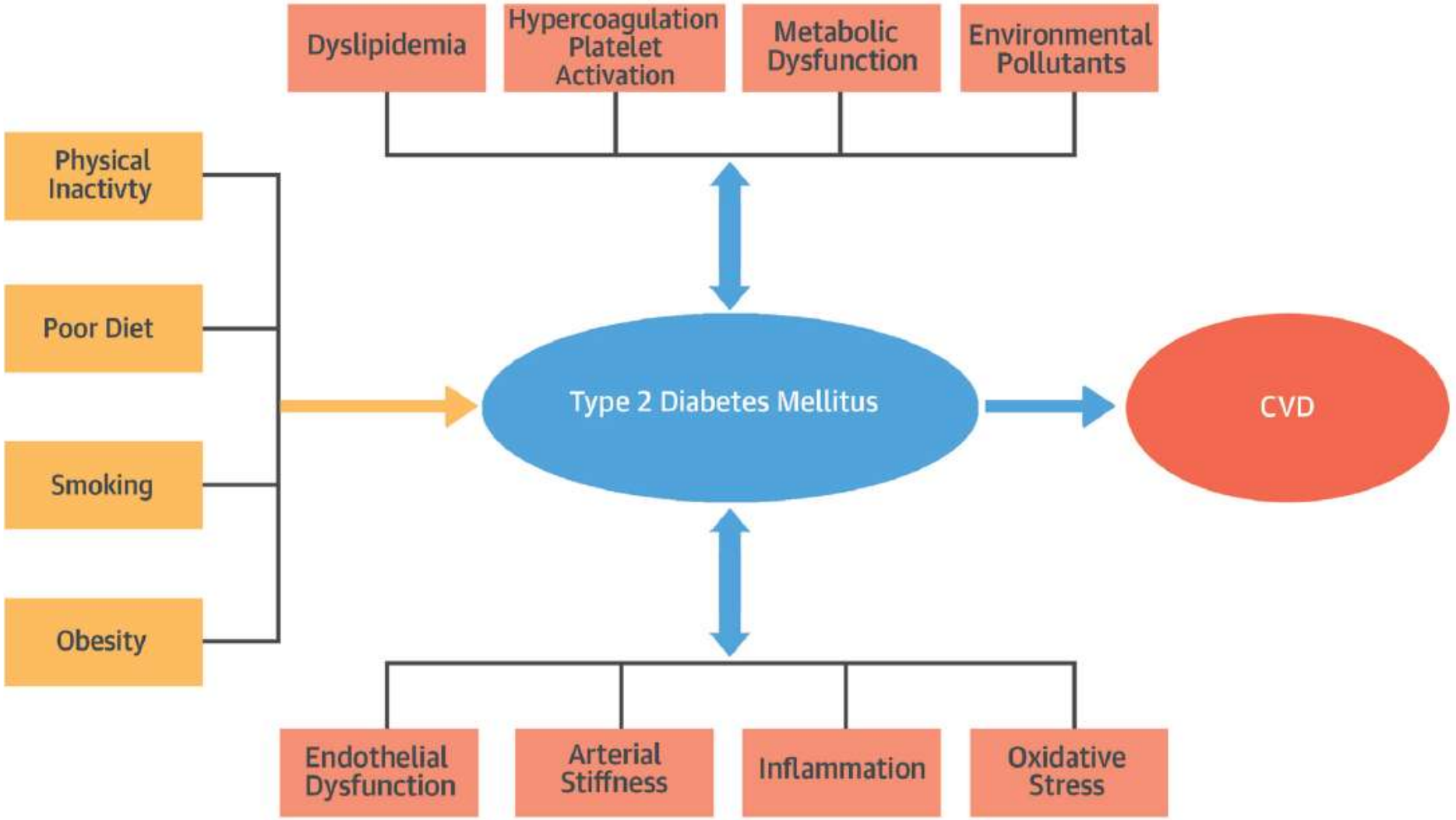


Modelling of Years of Life Lost by Disease Status

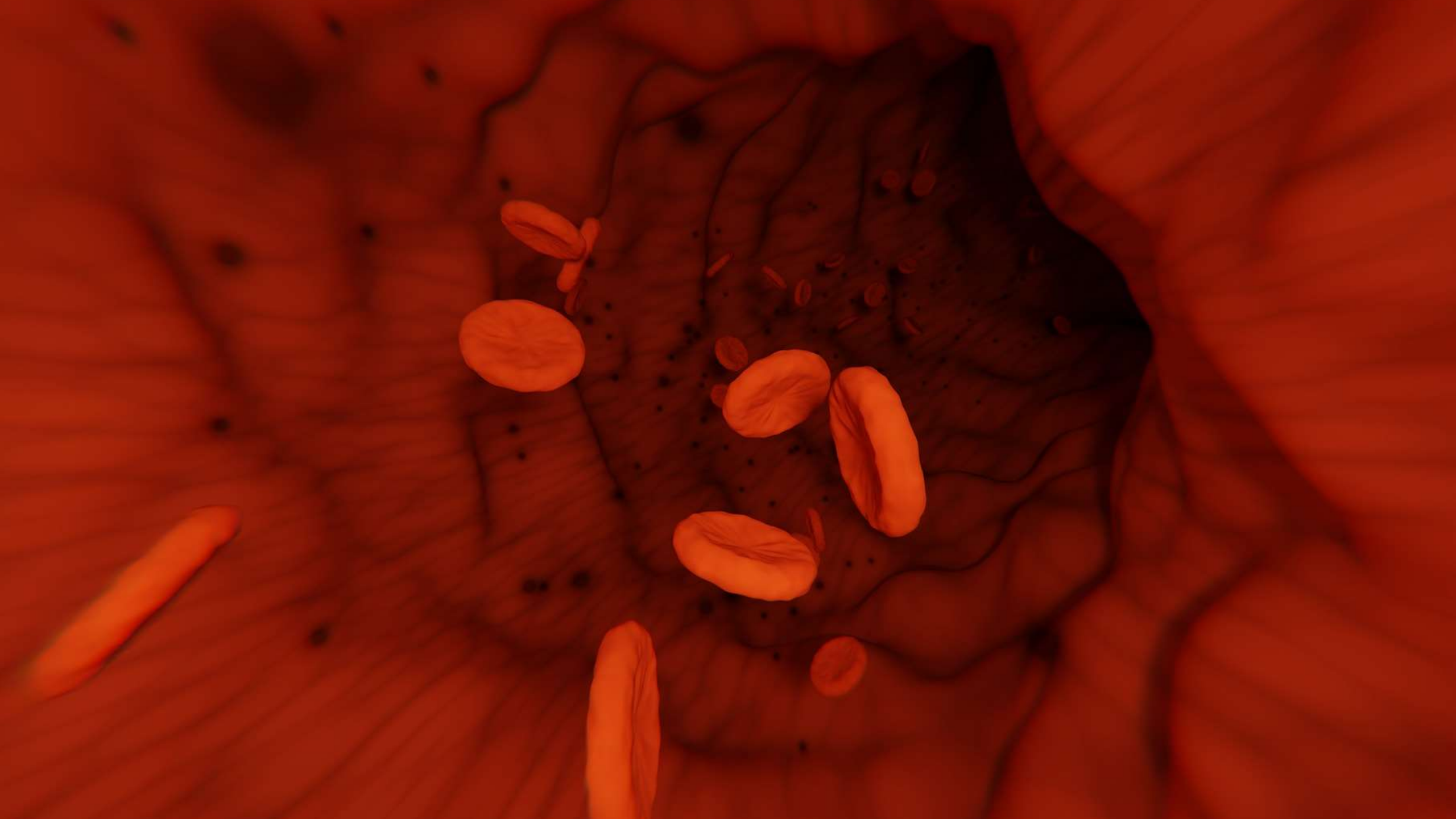


The Emerging Risk Factor Collaboration, JAMA 2015

T2D: a collector of CVD risk factors



Newman JD et al. JACC 2017



Platelet dysfunction in type 2 diabetes

People with T2D show:

- Impaired function of platelet receptors
- Impaired regulation of intracellular signal transduction
- Increased platelets' adhesion, activation and degranulation

HYPER-REACTIVE PLATELETS

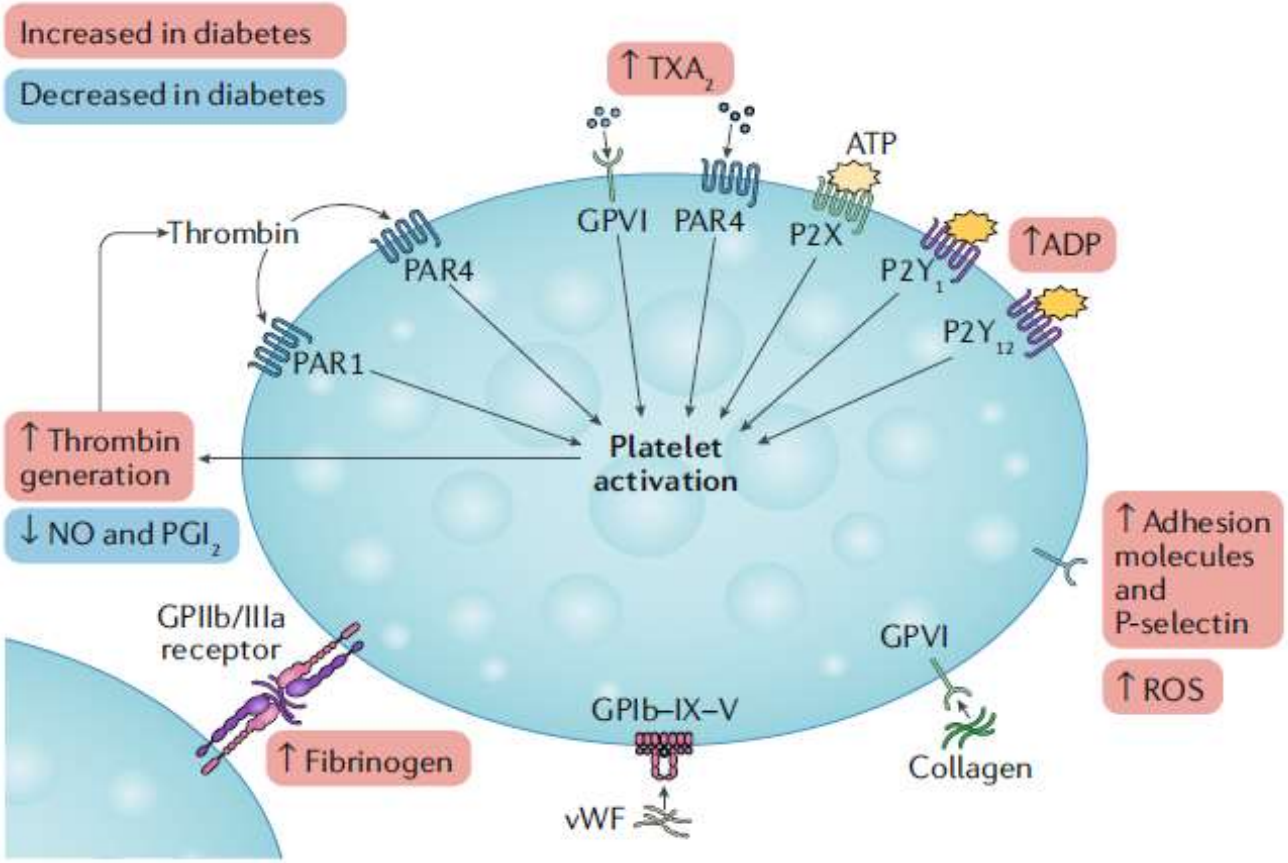
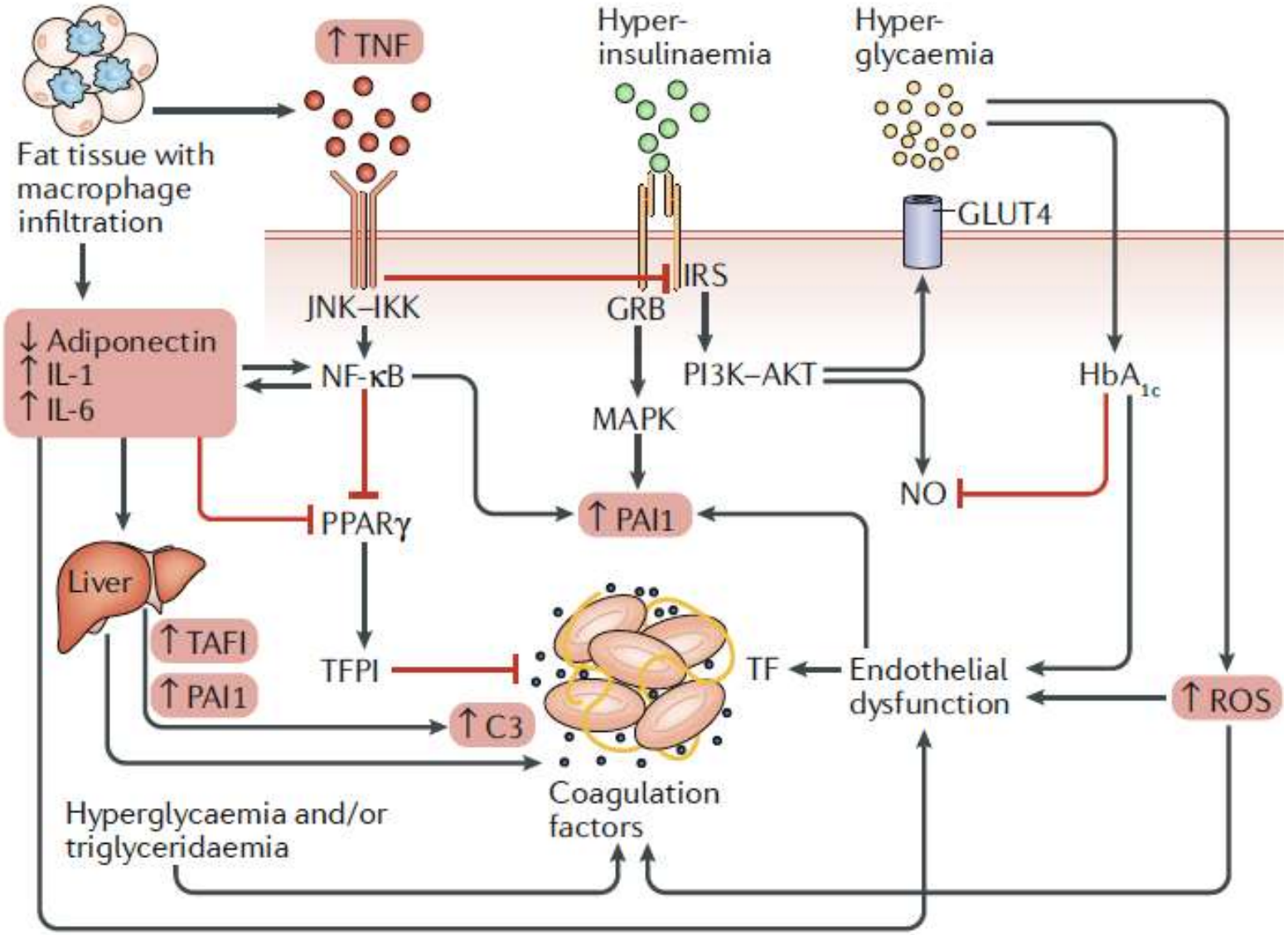


Table 2 | **Thrombotic and fibrinolytic factors in diabetes mellitus**

Factor	Function	Change in levels with diabetes	Effect
Tissue factor–coagulation factor VII	Initiates clot formation	↑	↑ Thrombosis
Fibrinogen	Forms fibrin clot	↑ (and ↑ glycation)	↑ Thrombosis and ↑ clot density
Thrombin	Converts fibrinogen to fibrin	↑	↑ Thrombosis and ↑ clot stability
Plasminogen activator inhibitor 1	Inhibits production of plasmin	↑	↓ Fibrinolysis
Plasminogen or plasmin	Breaks down fibrin clot	↓ (and ↑ glycation)	↓ Fibrinolysis and ↑ clot density
Carboxypeptidase B2	Inhibits fibrin breakdown	↑	Delayed clot lysis
Tissue-type plasminogen activator	Converts plasminogen to plasmin	↓	↓ Fibrinolysis
Complement C3	Complement system	↑	↑ Clot density
Glycated haemoglobin A_{1c}	Reflects hyperglycaemic milieu	↑	↓ Nitric oxide bioavailability
Peroxisome proliferator-activated receptor-γ	Nuclear transcription factor	↓	↓ Inhibitor of the tissue factor pathway

Patti G., Cavallari I […] Maddaloni E., et al. Nat Rev Cardiol 2019

Procoagulant patterns in type 2 diabetes



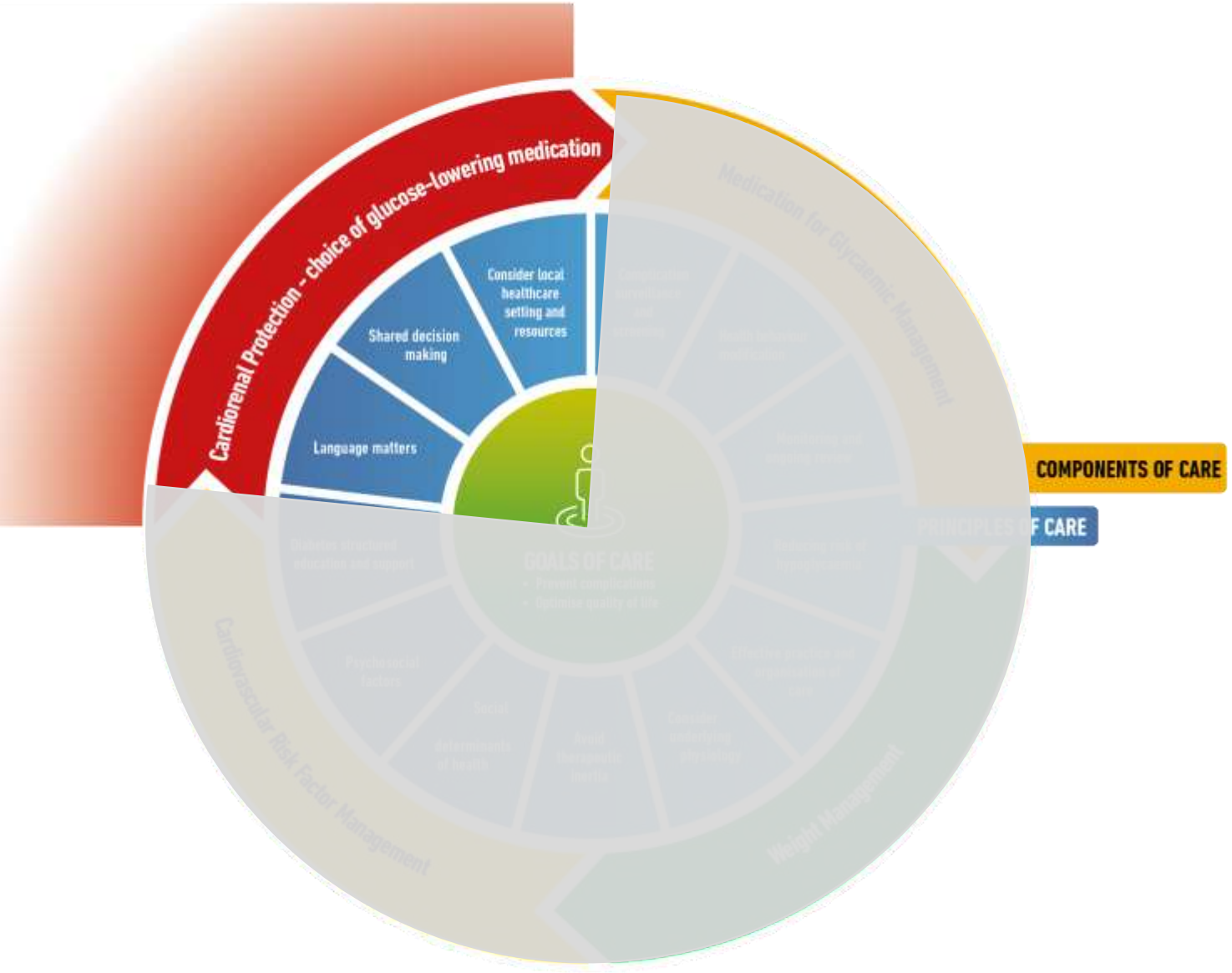
Patti G., Cavallari I […] Maddaloni E., et al. Nat Rev Cardiol 2019

Agenda

- Thrombotic events and platelet dysfunction in diabetes

- **Antidiabetes drugs and platelets**

FIGURE 4: HOLISTIC PERSON-CENTRED APPROACH TO T2DM MANAGEMENT



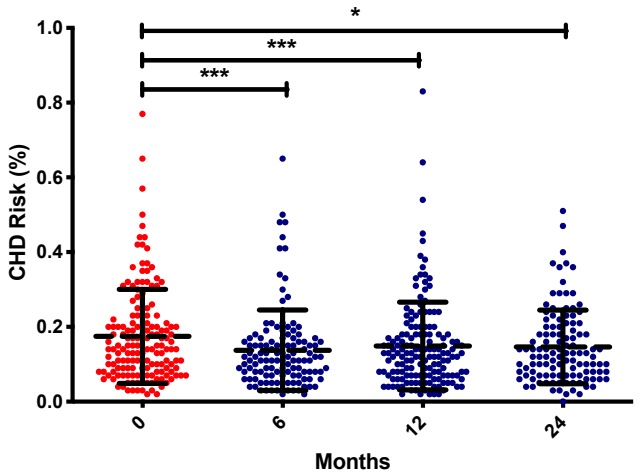
Davies MJ, Aroda VR, Collins BS, Gabbay RA, Green J, Maruthur NM, Rosas SE, Del Prato S, Mathieu C, Mingrone G, Rossing P, Tankova T, Tsapas A, Buse JB

Diabetes Care 2022; https://doi.org/10.2337/dci22-0034. *Diabetologia* 2022; https://doi.org/10.1007/s00125-022-05787-2.

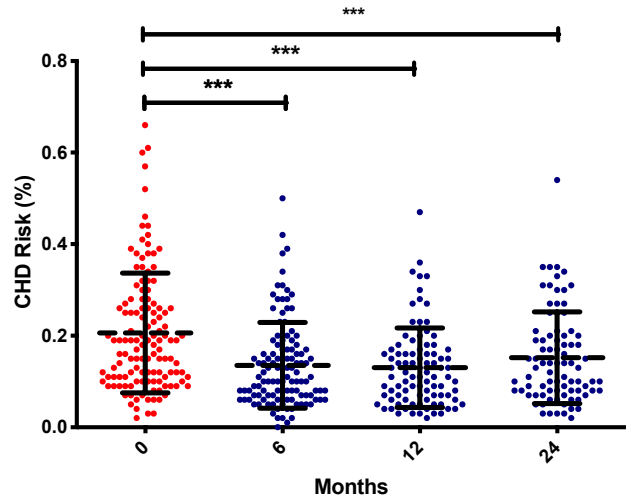
Change of coronary heart disease risk during 24 months therapy with GLP1-receptor agonists or SGLT2 inhibitors in patients in primary cardiovascular prevention

- Retrospective study
- People with T2D without previous CV events starting a GLP1-RA (n=174) or a SGLT2i (n=138)
- Primary outcome: change in CHD risk over 24 months

GLP1-RA



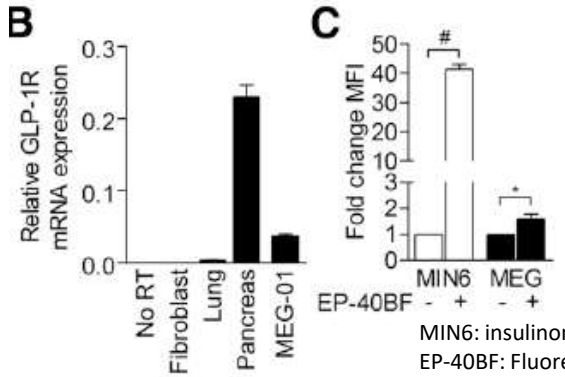
SGLT2i



D'Onofrio L […], Maddaloni E, Buzzetti R, Diabetes Research & Clinical Practice 2021

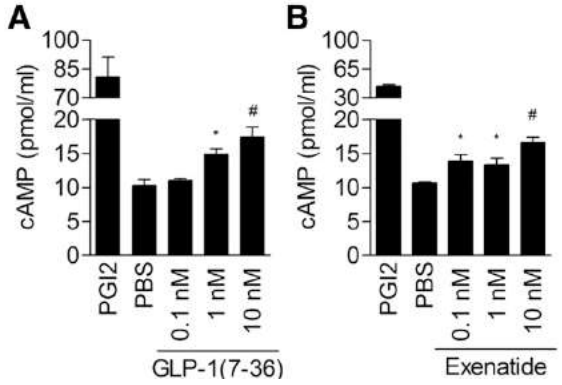
Glucagon-like peptide 1 receptor activation attenuates platelet aggregation and thrombosis

Megakaryocytes (MEG) express GLP1-Receptors

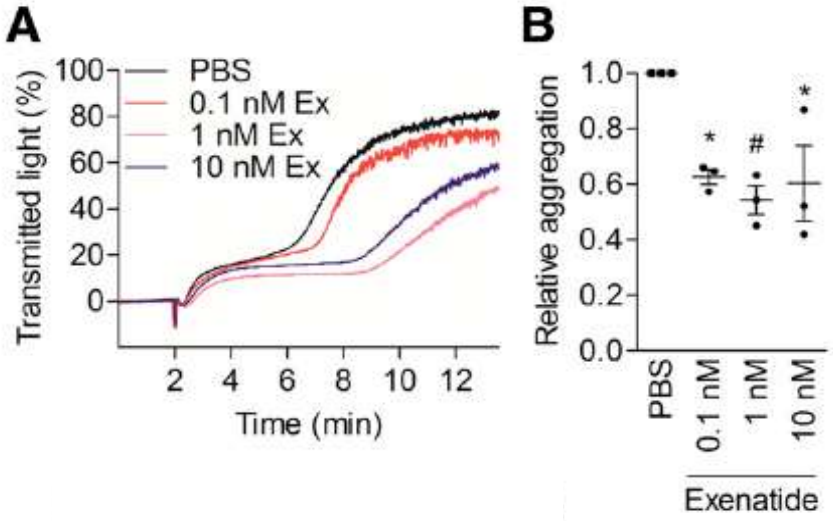


MIN6: insulinoma cell line
EP-40BF: Fluorescent exenatide peptide
MFI: mean fluorescence intensity

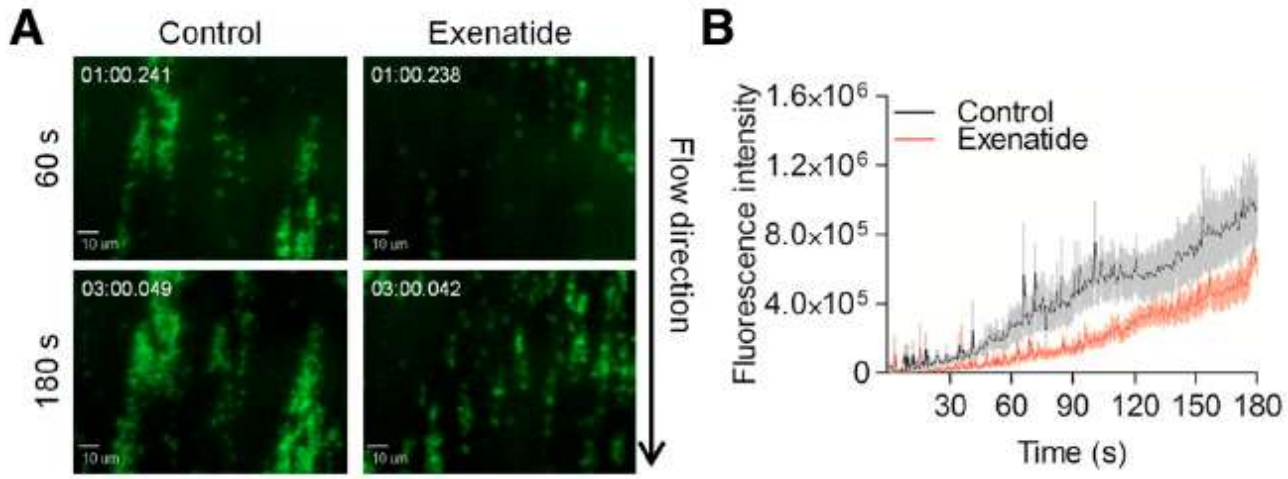
GLP1 induces intracellular signaling in megakaryocytes



GLP-1RA attenuates thrombin- induced platelet aggregation

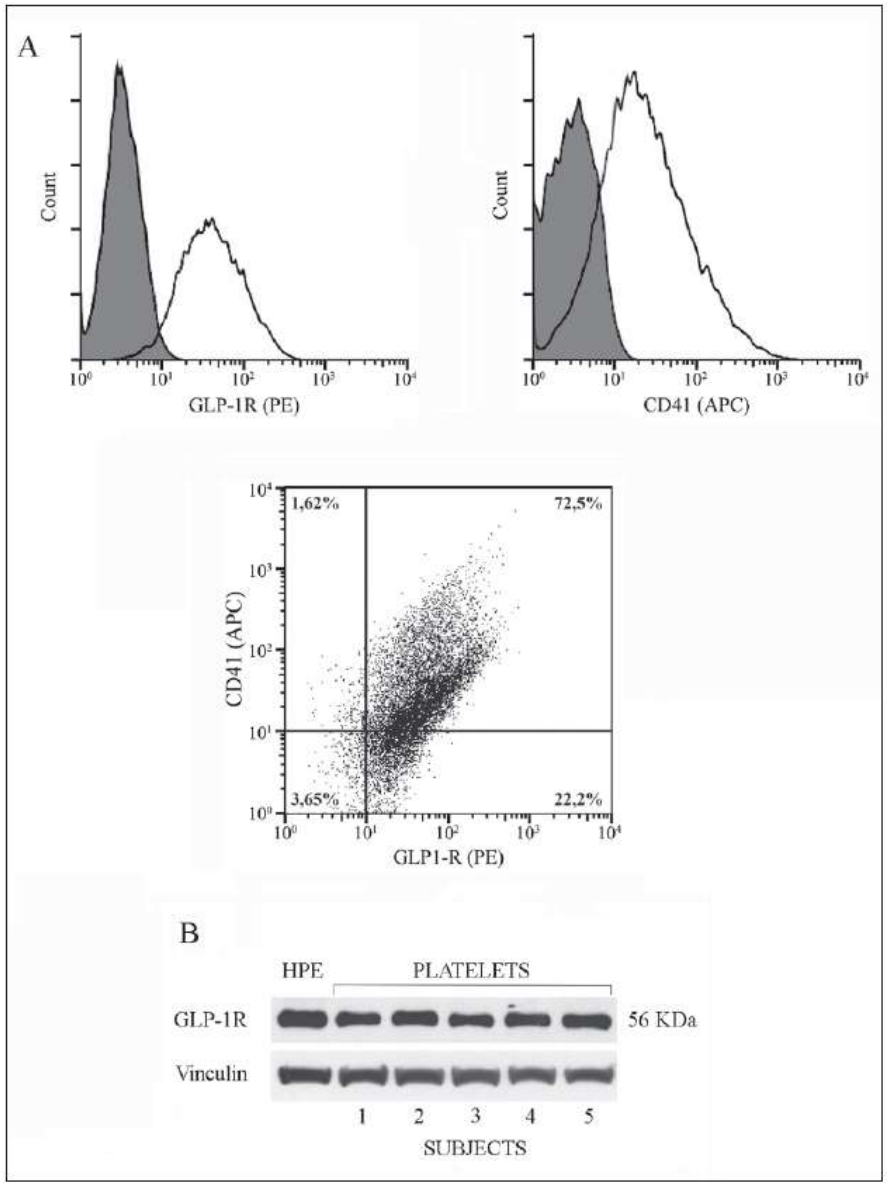


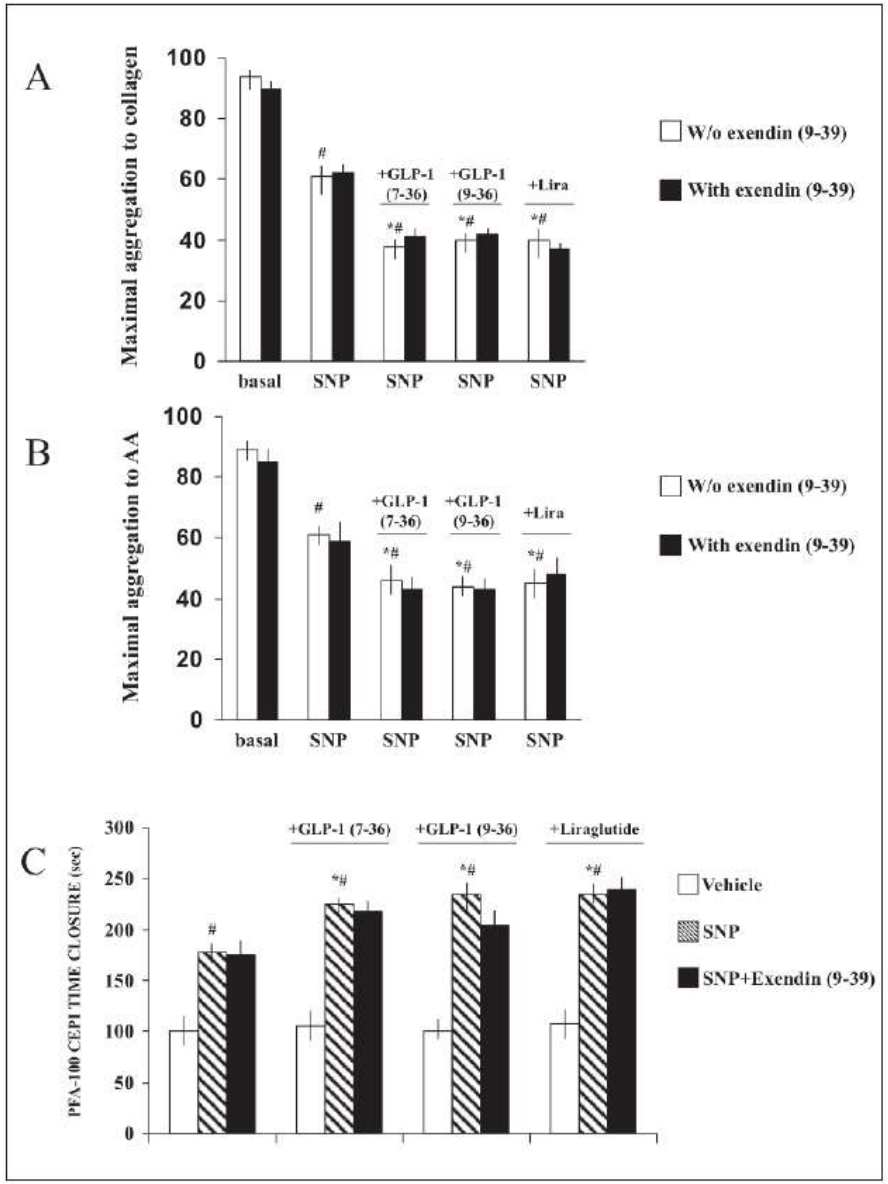
GLP-1RA inhibits collagen-induced thrombus growth



Cameron-Vendrig, A. et al. s. Diabetes 65, 1714–1723 (2016).

Glucagon-like peptide 1 reduce platelet aggregation





Barale, C. et al. Thromb. Haemost. 2017

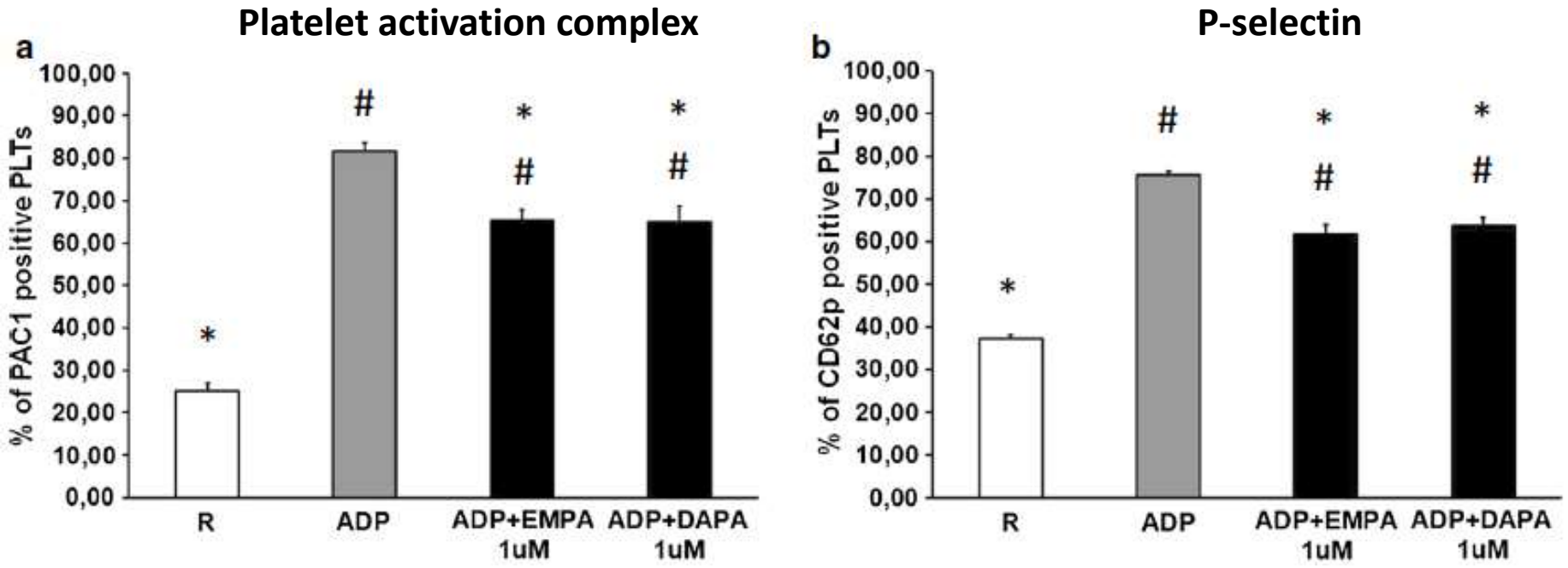
GLP1-RA / SGLT2i CVOTS

Modified from Patti G, et al. Nat Rev Cardiol 2019

Trial	Drug	N of subjects	% with overt CVD	Median FUP (years)	HR [95% CI] Primary	HR [95% CI] CV death	HR [95% CI] MI	HR [95% CI] Stroke
GLP1 Receptor Agonists								
ELIXA	Lixisenatide	6068	100%	2.1	1.02 [0.89-1.17]	0.98 [0.78-1.22]	1.03 [0.87-1.22]	1.12 [0.79-1.58]
LEADER	Liraglutide	9340	81%	3.8	**0.87 [0.78-0.97]**	**0.78 [0.66-0.93]**	**0.86 [0.73-1.00]**	0.86 [0.71-1.06]
SUSTAIN	Semaglutide (sc)	3297	83%	2.1	**0.74 [0.58-0.95]**	0.98 [0.65-1.48]	0.74# [0.51-1.08]	**0.61# [0.38-0.99]**
EXSCEL	Exenatide	14752	73%	3.2	**0.91 [0.83-1.00]**	0.88 [0.76-1.02]	0.97 [0.85-1.10]	0.85 [0.70-1.03]
HARMONY	Albiglutide	9463	100%	1.6	**0.78 [0.68-0.90]**	0.93 [0.73-1.19]	**0.75 [0.61-0.90]**	0.86 [0.66-1.14]
REWIND	Dulaglutide	9901	31%	5.4	**0.88 [0.79-0.99]**	0.91 [0.78-1.06]	0.96 [0.79-1.16]	**0.76 [0.61-0.95]**
PIONEER	Semaglutide (os)	3183	85%	1.3	0.79 [0.57-1.11]	**0.49 [0.27-0.92]**	1.18 [0.73-1.90]	0.74 [0.35-1.17]

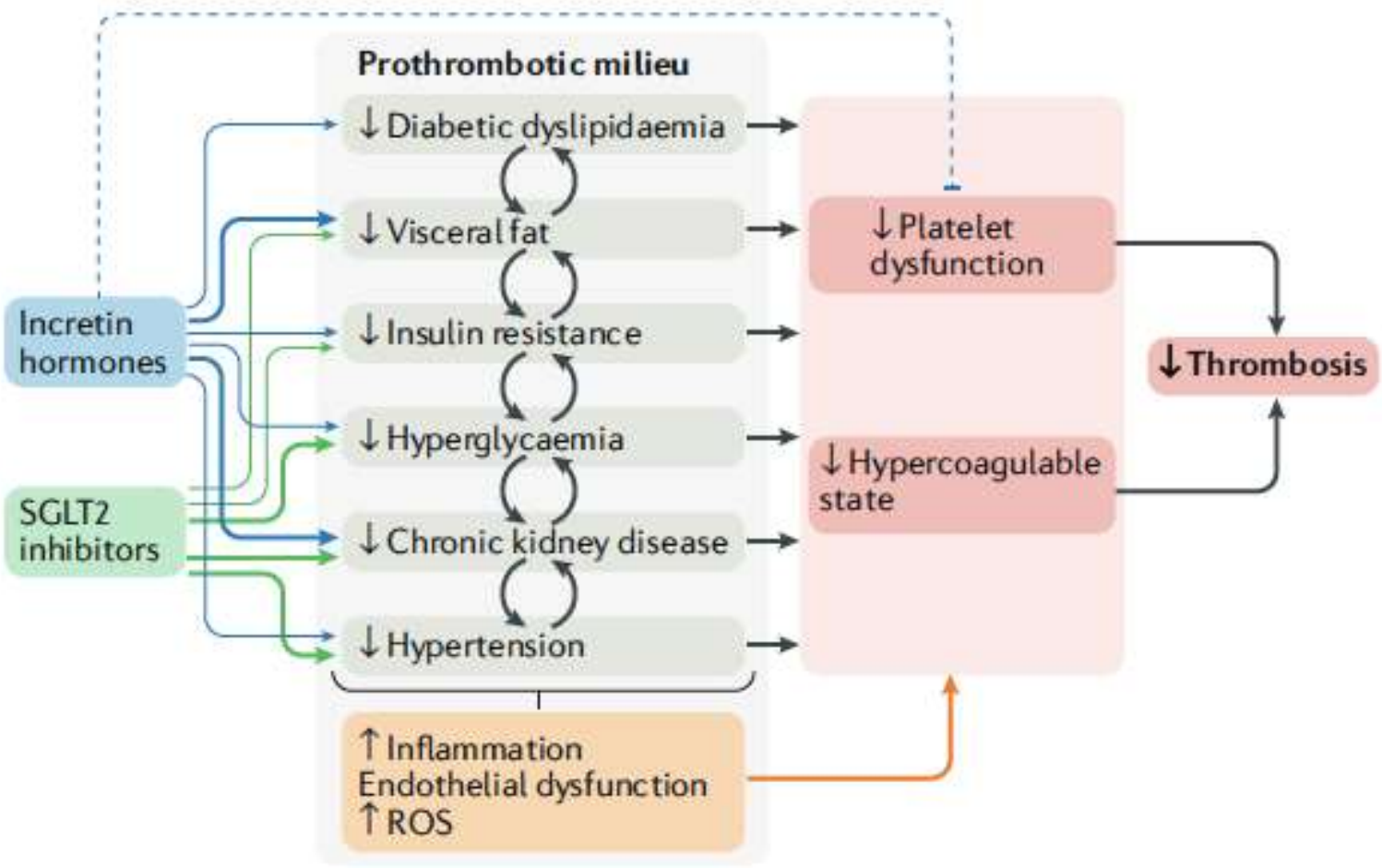
SGLT2i antagonize ADP-dependent activation in human platelets

- Platelets do not express SGLT2
- Platelets express Na/H exchanger (NHE), another potential target of SGLT2i



Spigoni V et al., Cardiovasc Diabetol 2020

Pleiotropic and synergistic effects of GLP1-RA and SGLT2i



Patti G et al., Consensus statement of the Working Group on Thrombosis of the Italian Society of Cardiology. Nat Rev Cardiol 2018

Metformin

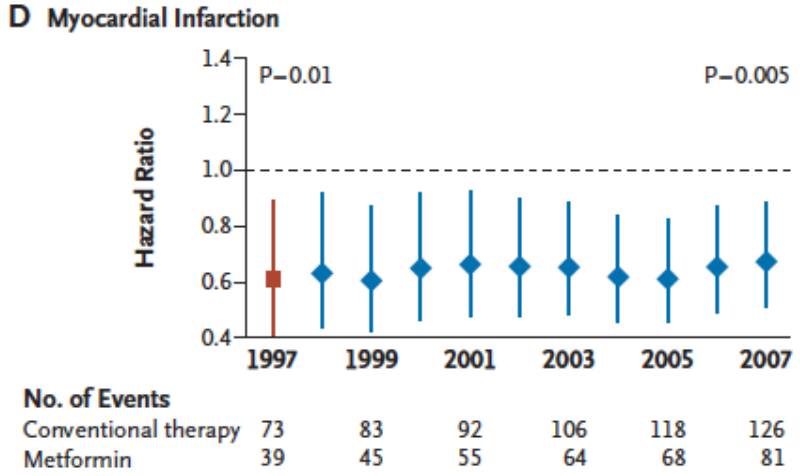
	Efficacy[1]	Hypoglycaemia	Weight change[2]	CV effects		Renal effects		Oral/SQ	Cost
				Effect on MACE	HF	Progression of DKD	Dosing/use considerations*		
Metformin	High	No	Neutral (potential for modest loss)	Potential benefit	Neutral	Neutral	• Contraindicated with eGFR <30 mL/min per 1.73 m^2	Oral	Low

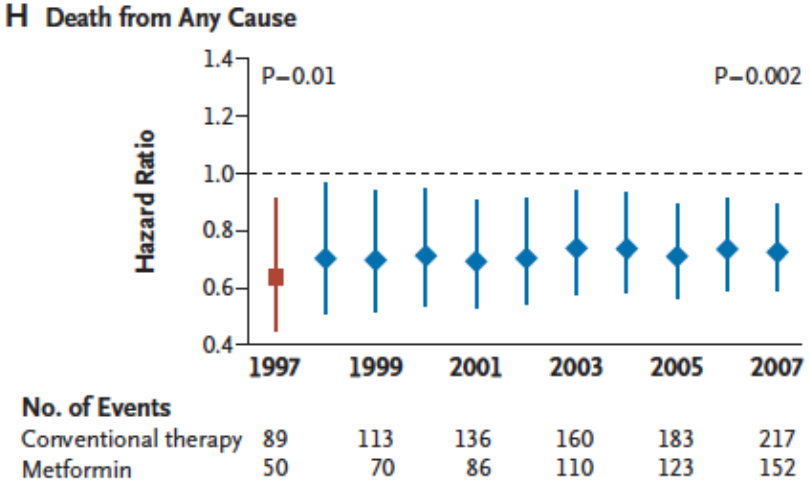
Traditionally recommended as first-line glucose-lowering therapy for type 2 diabetes, because of its high efficacy in lowering HbA_{1c}, minimal hypoglycaemia risk when used as monotherapy, potential for some modest weight loss, good safety profile, low cost

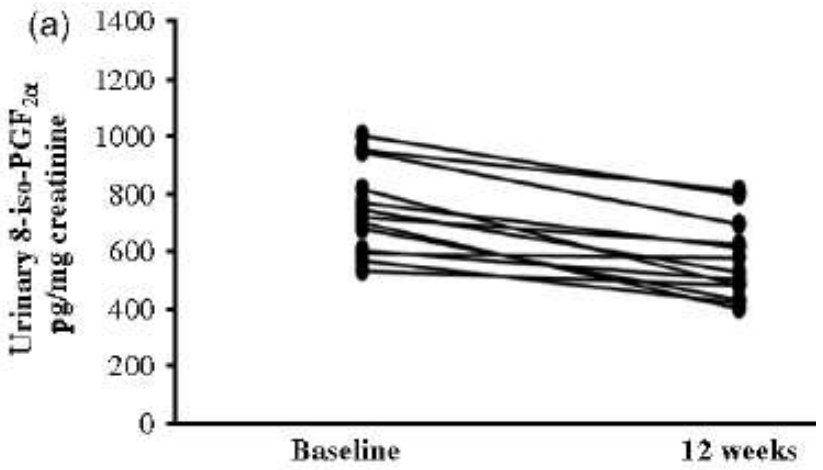
Davies MJ, Aroda VR, Collins BS, Gabbay RA, Green J, Maruthur NM, Rosas SE, Del Prato S, Mathieu C, Mingrone G, Rossing P, Tankova T, Tsapas A, Buse JB

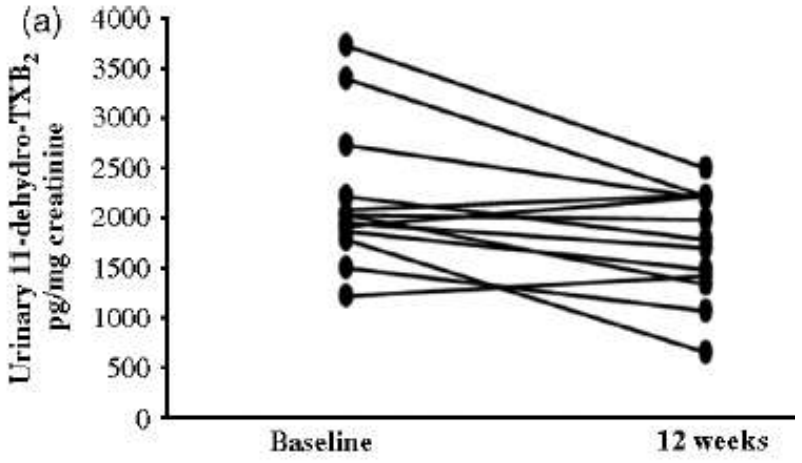
Diabetes Care 2022; https://doi.org/10.2337/dci22-0034. *Diabetologia* 2022; https://doi.org/10.1007/s00125-022-05787-2.

Metformin – CV & platelet effects









Holman RR et al., NEJM 2008

Formoso G et al., Diab Metab Res Rev 2008

Objectives learned

Understand the risk of thrombotic events in people with type 2 diabetes

- Type 2 diabetes is a CV event equivalent

Learn about the effects of diabetes on platelet function

- Platelet dysfunction is a main mechanism of CV disease in diabetes

Acquire specific knowledge about the effects of anti-diabetes drugs with CV benefits on platelet dysfunction

- Platelets express GLP1 receptors
- GLP1-RA impact on platelet function in clinical studies
- Limited evidence for platelet effects of SGLT2i
  - In vitro evidence seems to suggest that SGLT2i may affect platelets by NHE
- Metformin has CV benefits
  - Only few studies performed on platelet function

Heart failure and diabetes therapy

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Agenda

- Heart failure and diabetes
- News for HF therapy from diabetes drugs
  - SGLT2i
  - Finerenone
- Guidelines

What Is Heart Failure?

Proposed Universal Definition of HF[1]

Clinical syndrome with symptoms and/or signs caused by a structural and/or functional cardiac abnormality and corroborated by elevated natriuretic peptide levels and/or objective evidence of pulmonary or systemic congestion.

HF Categories According to LVEF[2]

HFrEF	HFmrEF	HFpEF
HF with reduced EF LVEF ≤40%	HF with mildly reduced EF LVEF 41-49%	HF with preserved EF LVEF ≥50%

EF = ejection fraction; HF = heart failure; LVEF = left ventricular ejection fraction.

1. Bozkurt B et al. *Eur J Heart Fail*. 2021;23:352-380; 2. McDonagh TA et al. *Eur Heart J*. 2021;42:3599-3726.

Heart Failure Is a Major Public Health Problem Worldwide

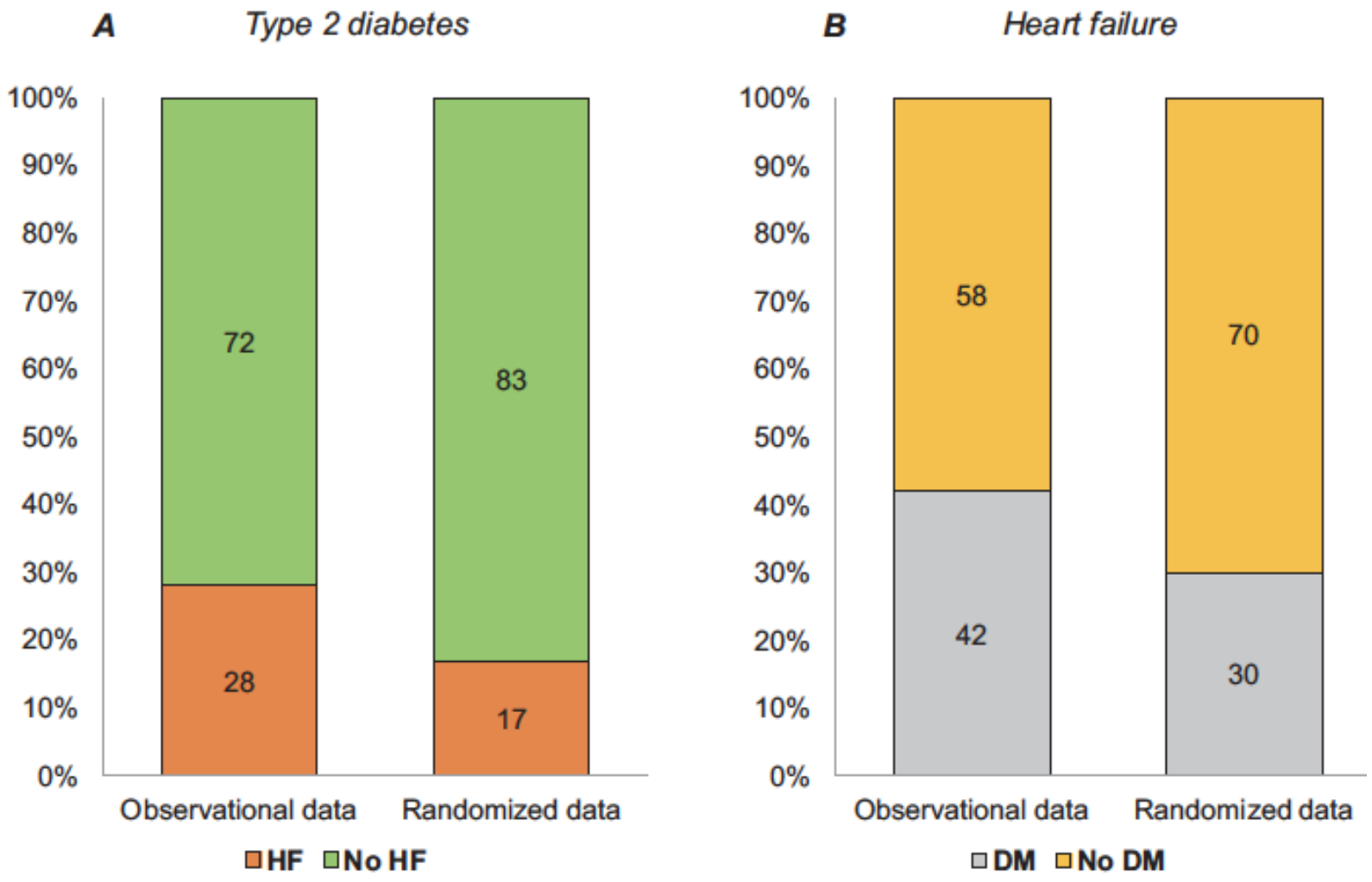
- Projected **~24% rise in cases** between 2012 and 2030[2]
- 5-year **mortality rate ~50%**[3]
- HF **mortality risk is similar** to some of the common cancers in both men and women[4]
- Economic burden **~350 billion US dollars**[2]
- **Over 50%** of patients with HF have **HFpEF**[5]

US Data

HF = heart failure; HFpEF = heart failure with preserved ejection fraction; US = United States.

1. GBD 2017 Disease and Injury Incidence and Prevalence Collaborators. *Lancet.* 2018;392:1789-1858; 2. Lippi G et al. *AME Med J.* 2020;5:15; 3. Jones NR et al. *Eur J Heart Fail*. 2019;21:1306-1325; 4. Mamas AM et al. *Eur J Heart Fail*. 2017;19:1095-1104; 5. Omote K et al. Online ahead of print. *Annu Rev Med.* 2021.

HF and diabetes



Cavallari I, Maddaloni E, et al. J Clin Endocrinol Metab 2020

T2D increases the risk of HF more than the risk of AMI

B Excess Acute Myocardial Infarction in Relation to Range of Risk-Factor Control

	Hazard Ratio (95% CI)
Control	
≥80 yr	Reference
≥65 to <80 yr	Reference
≥55 to <65 yr	Reference
<55 yr	Reference
No risk factors	
≥80 yr	0.72 (0.49–1.07)
≥65 to <80 yr	0.80 (0.69–0.93)
≥55 to <65 yr	0.93 (0.73–1.18)
<55 yr	0.91 (0.62–1.35)
1 Risk factor	
≥80 yr	1.05 (0.93–1.19)
≥65 to <80 yr	1.05 (0.97–1.14)
≥55 to <65 yr	1.14 (1.04–1.25)
<55 yr	1.46 (1.26–1.69)
2 Risk factors	
≥80 yr	1.38 (1.27–1.49)
≥65 to <80 yr	1.44 (1.39–1.50)
≥55 to <65 yr	1.54 (1.44–1.65)
<55 yr	2.08 (1.90–2.27)
3 Risk factors	
≥80 yr	1.78 (1.60–1.98)
≥65 to <80 yr	2.11 (2.02–2.20)
≥55 to <65 yr	2.16 (2.02–2.31)
<55 yr	3.02 (2.80–3.27)
4 Risk factors	
≥80 yr	2.32 (1.78–3.01)
≥65 to <80 yr	2.87 (2.62–3.14)
≥55 to <65 yr	3.32 (3.02–3.66)
<55 yr	4.56 (4.01–5.18)
5 Risk factors	
≥80 yr	3.19 (1.23–8.28)
≥65 to <80 yr	4.60 (3.37–6.29)
≥55 to <65 yr	4.84 (3.78–6.21)
<55 yr	7.69 (5.02–11.77)

1 2 3 4 6 8 10

D Excess Heart Failure in Relation to Range of Risk-Factor Control

	Hazard Ratio (95% CI)
Control	
≥80 yr	Reference
≥65 to <80 yr	Reference
≥55 to <65 yr	Reference
<55 yr	Reference
No risk factors	
≥80 yr	1.12 (0.89–1.41)
≥65 to <80 yr	1.42 (1.28–1.58)
≥55 to <65 yr	1.61 (1.31–1.97)
<55 yr	2.40 (1.63–3.54)
1 Risk factor	
≥80 yr	1.17 (1.08–1.27)
≥65 to <80 yr	1.46 (1.39–1.53)
≥55 to <65 yr	1.80 (1.63–1.98)
<55 yr	2.37 (1.99–2.82)
2 Risk factors	
≥80 yr	1.23 (1.15–1.32)
≥65 to <80 yr	1.62 (1.56–1.68)
≥55 to <65 yr	2.11 (1.98–2.26)
<55 yr	2.71 (2.40–3.05)
3 Risk factors	
≥80 yr	1.42 (1.31–1.54)
≥65 to <80 yr	2.01 (1.92–2.10)
≥55 to <65 yr	2.82 (2.63–3.02)
<55 yr	3.93 (3.50–4.42)
4 Risk factors	
≥80 yr	1.81 (1.42–2.30)
≥65 to <80 yr	2.88 (2.64–3.14)
≥55 to <65 yr	3.85 (3.47–4.26)
<55 yr	5.70 (4.84–6.71)
5 Risk factors	
≥80 yr	2.76 (0.82–9.25)
≥65 to <80 yr	3.93 (2.75–5.60)
≥55 to <65 yr	6.54 (4.85–8.81)
<55 yr	11.35 (7.16–18.01)

1 2 3 4 5 7 9

Rawshani A et al., N Eng J Med 2018

Agenda

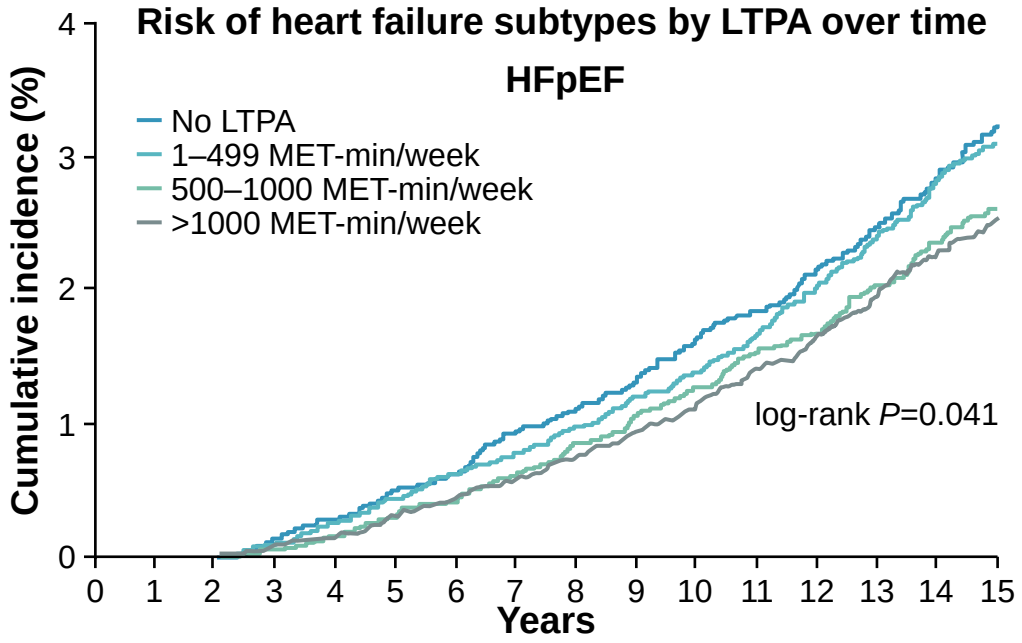
- Heart failure and diabetes

- News for HF therapy from diabetes drugs
  - SGLT2i
  - Finerenone

- Guidelines

Physical activity reduces risk of HFpEF

- Pooled results from three large prospective cohort studies[a] (N=51,451) that reported quantitative measures of LTPA and BMI at baseline and had HFrEF and HFpEF outcome adjudication on follow-up[1]
- PA quantification was derived from standardized MET values to account for intensity of PA as part of PA volume
- Dose-dependent inverse association between LTPA levels and HFpEF[b] risk was observed



LPTA: self-selected physical activity that is chosen by participants and performed in their free time

One MET is defined as the energy expenditure for sitting quietly.[2] For the average adult, this is approximately 3.5 mL of oxygen per body weight (kg) per minute

[a]Women's Health Initiative, the Multi-Ethnic Study of Atherosclerosis, and the Cardiovascular Health Study; [b]LVEF ≥45%; [c]LVEF <45%

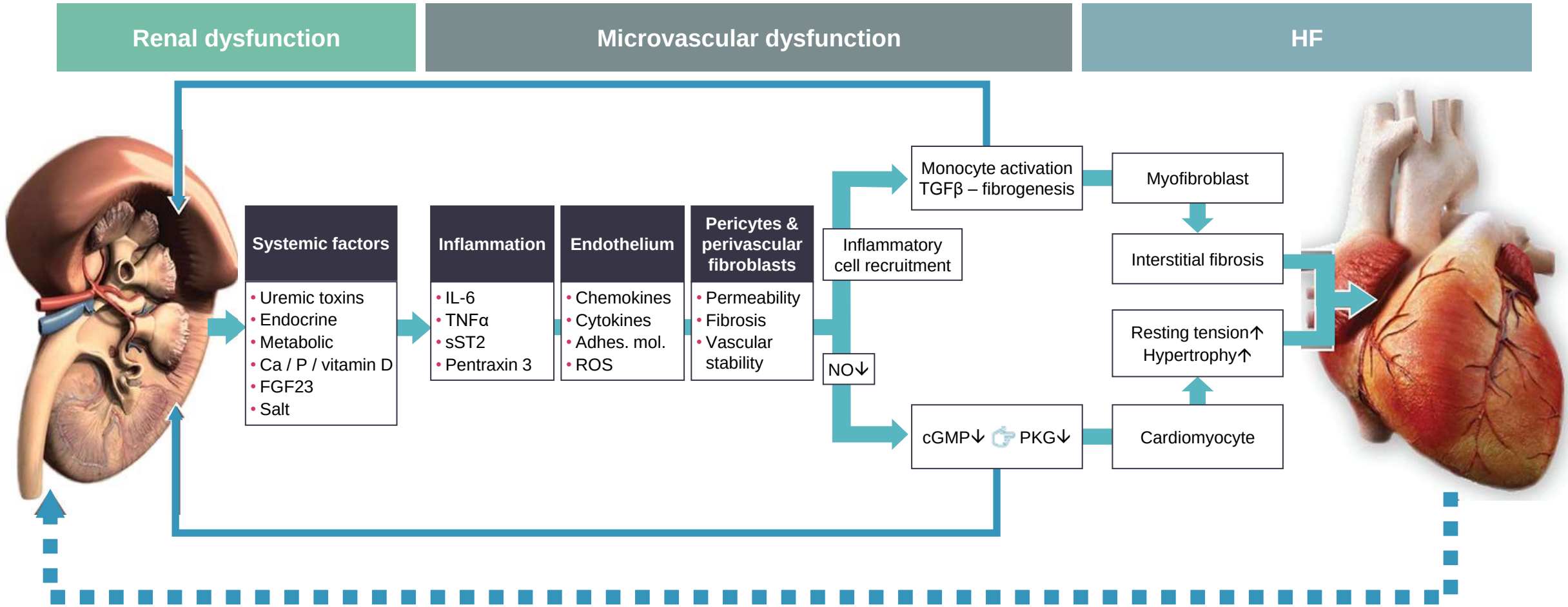
BMI, body mass index; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; MET, metabolic equivalent task; LTPA, leisure time physical activity; LVEF, left ventricular ejection fraction; PA, physical activity

1. Pandey A, et al. *Am J Coll Cardiol* 2017;69:1129–1142; 2. Ainsworth BE, et al. *Med Sci Sports Exerc* 2000;32(9 Suppl.):S498–S504

HF outcomes in CVOTs in diabetes

Cavallari I, Maddaloni E et al., J Clin Endocrinol Metab 2019

Renal dysfunction and HF share common mechanisms



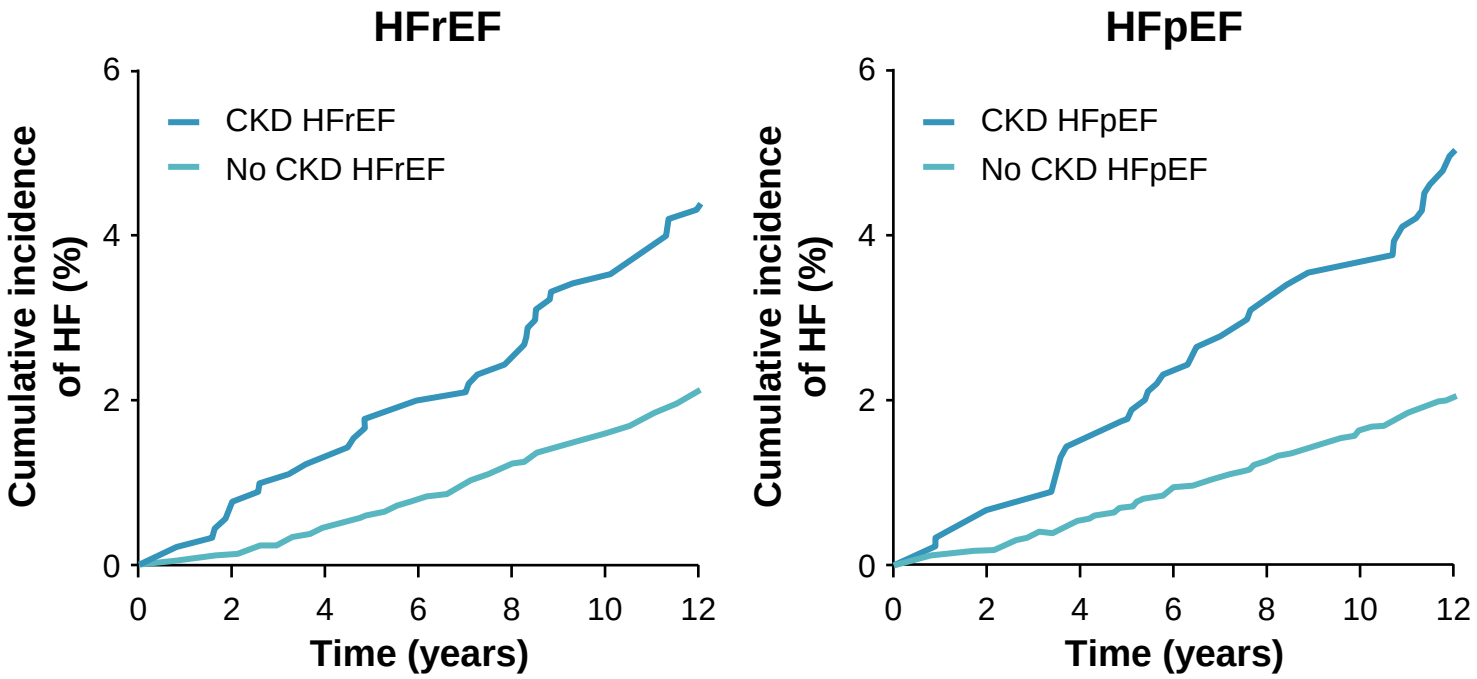
The direction of causality may prove to be in the opposite direction and most probably will be bi-directional

cGMP, cyclic guanosine monophosphate; FGF23, fibroblast growth factor 23; HFpEF, heart failure with preserved ejection fraction; IL-6, interleukin-6; PKG, protein kinase G; ROS, reactive oxygen species; sST2, soluble ST2; TNFα, tumor necrosis factor α;
TGFβ, transforming growth factor β

Ter Maaten JM, et al. *Eur J Heart Fail* 2016;18:588–598

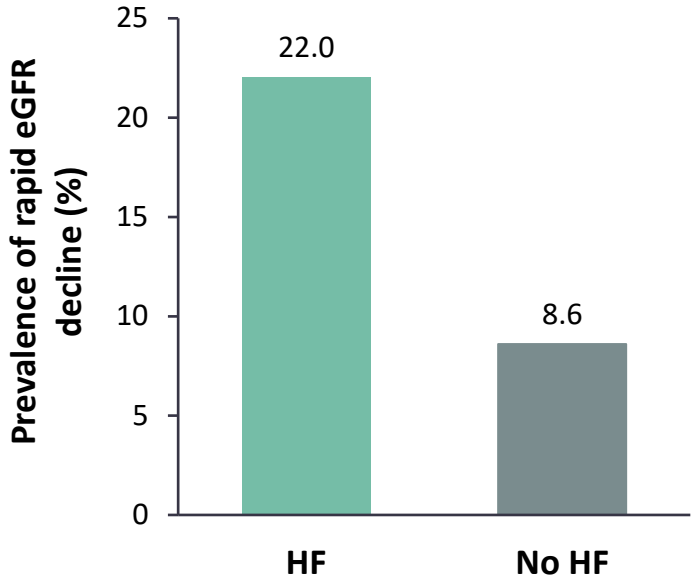
CKD and HF Are Interconnected

Incidences of HF are higher in those with CKD than those without[1]



CKD is associated with incident HF

HF is associated with rapid decline in eGFR[2,a]



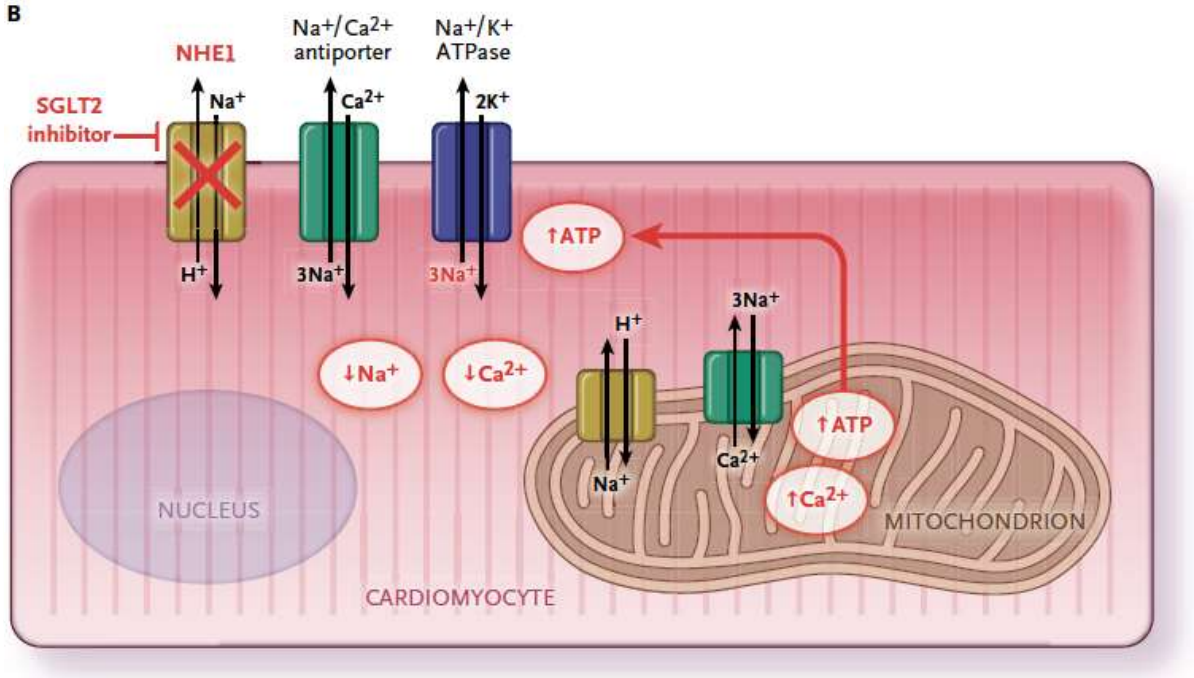
HF is associated with the risk of kidney function decline

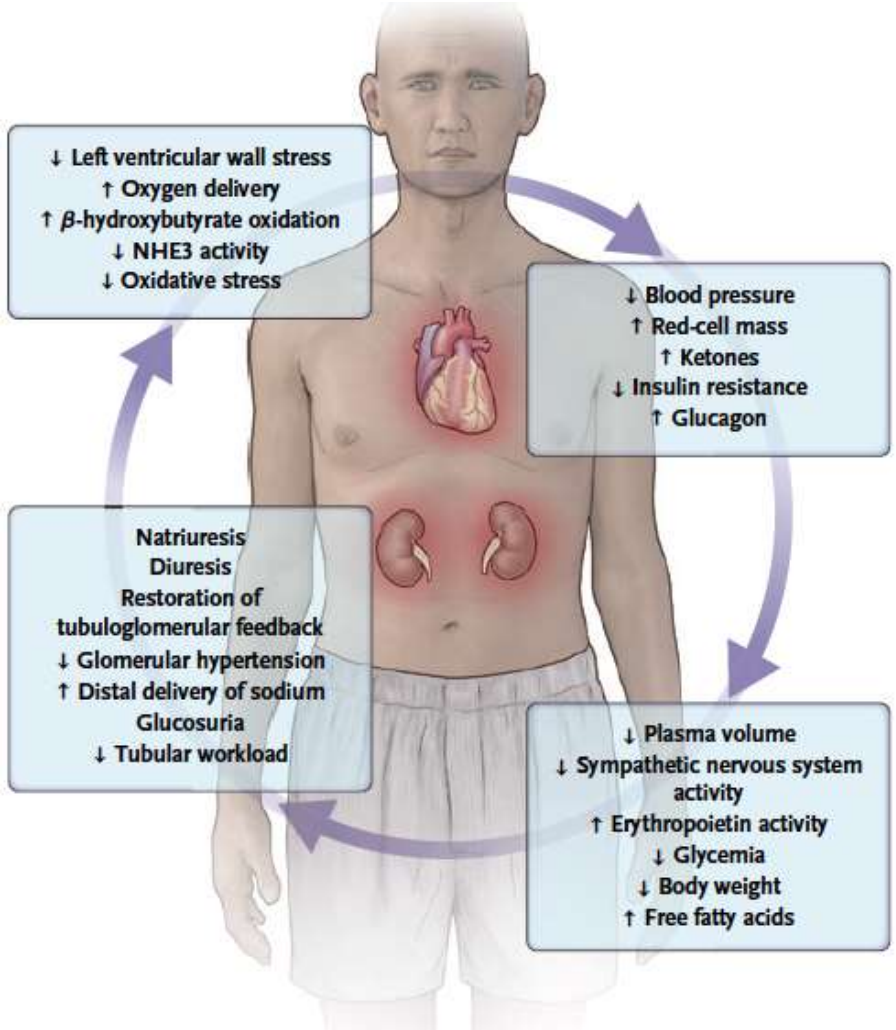
[a]Rapid rate of eGFR decline was defined as slopes steeper than −5 mL/min/1.73 m^2/year.

CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; HF = heart failure; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction.

1. Nayor M et al. *Eur J Heart Fail.* 2017;19:615-623; 2. George LK et al. *Circ Heart Fail.* 2017;10:e003825.

Direct and indirect effects of SGLT2i on HF





Braunwald E. *N Eng J Med* 2022

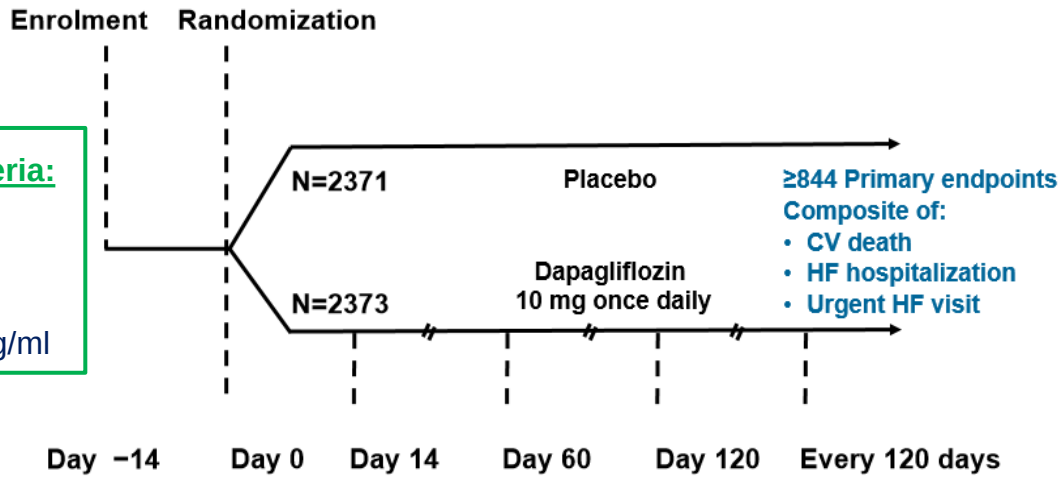
DAPA-HF

Key inclusion criteria:

Symptomatic HF

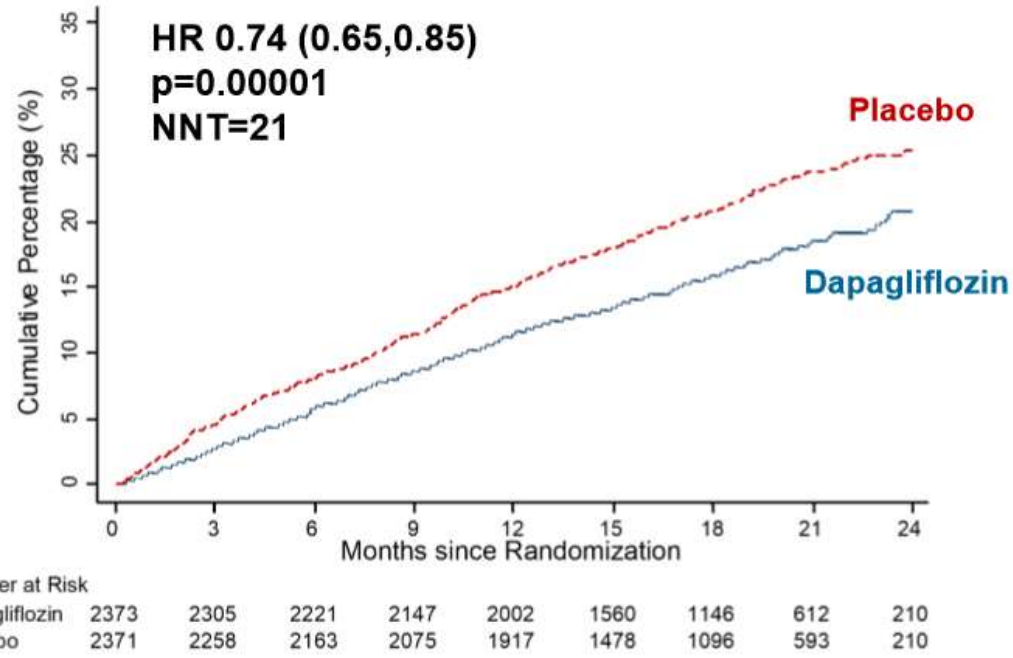
EF ≤40%

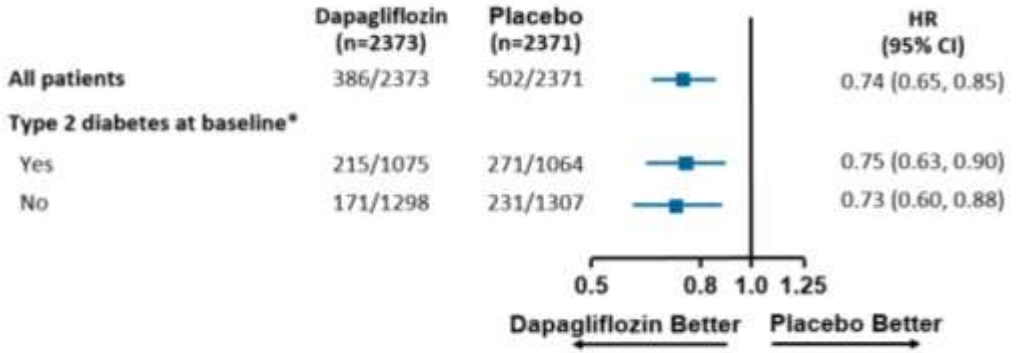
NT-proBNP ≥600 pg/ml



Characteristic	Dapagliflozin (n=2373)	Placebo (n=2371)
Mean age (yr)	66	67
Male (%)	76	77
NYHA class II/III/IV (%)	68/31/1	67/32/1
Mean LVEF (%)	31	31
Median NT pro BNP (pg/ml)	1428	1446
Mean systolic BP (mmHg)	122	122
Ischaemic aetiology (%)	55	57
Mean eGFR (ml/min/1.73m^2)	66	66
Prior diagnosis T2D (%)	42	42
Any baseline T2D (%)*	45	45

*includes 82 dapagliflozin and 74 placebo patients with previously undiagnosed diabetes i.e. two HbA1c ≥6.5% (≥48 mmol/mol)

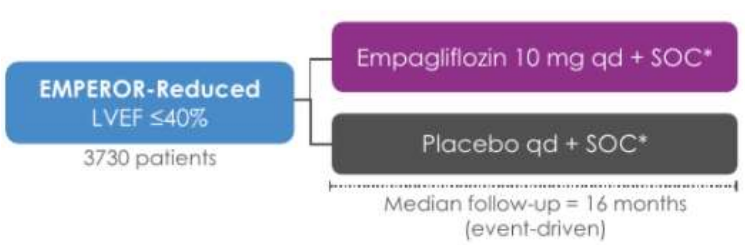




*Defined as history of type 2 diabetes or HbA1c ≥6.5% at both enrollment and randomization visits.

McMurray JJV et al. N Engl J Med 2019; McMurray JJV et al. Eur J Heart Fail 2019

EMPEROR-Reduced



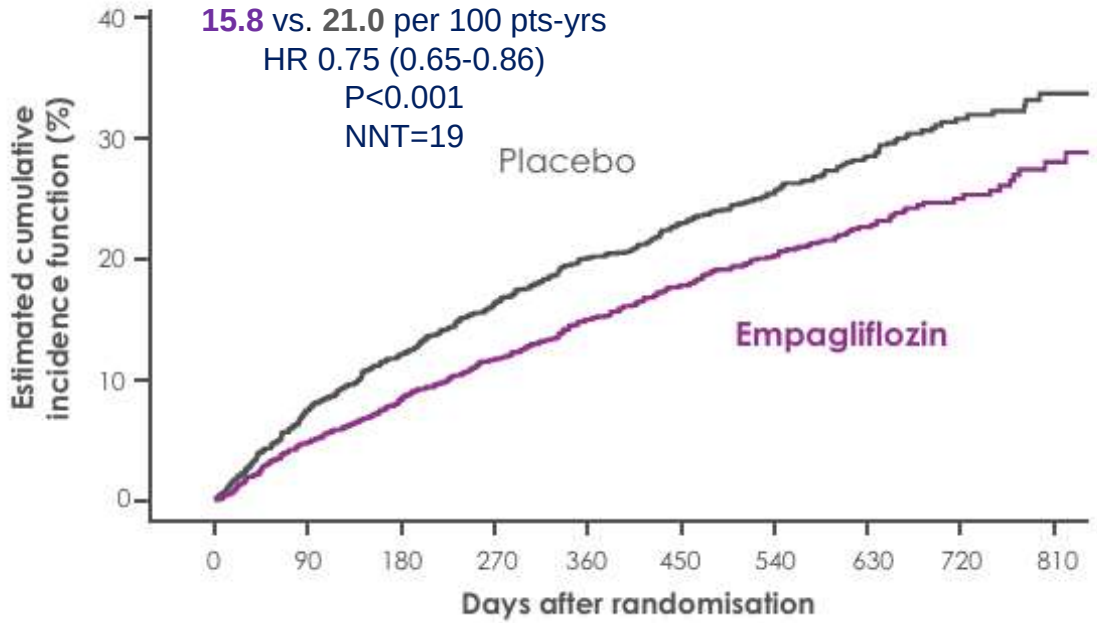
COMPOSITE PRIMARY ENDPOINT

Time to first event of adjudicated CV death or adjudicated HHF

SECONDARY ENDPOINTS

- First and recurrent adjudicated HHF events
- eGFR slope: change from baseline

Characteristic	Empagliflozin (n=1863)	Placebo (n=1867)
Body mass index (kg/m²) – mean ± SD	28.0 ± 5.5	27.8 ± 5.3
Heart rate (beats/min) – mean ± SD	71.0 ± 11.7	71.5 ± 11.8
Systolic blood pressure (mmHg) – mean ± SD	122.6 ± 15.9	121.4 ± 15.4
LV ejection fraction (%)	**27.7 ± 6.0**	**27.2 ± 6.1**
N (%) with LV ejection fraction ≤30	1337 (71.8)	1392 (74.6)
NT-proBNP (pg/ml) – median (IQR),	**1887 (1077, 3429)**	**1926 (1153, 3525)**
N (%) with NTproBNP ≥1000 pg/ml	1463/1862 (78.6)	1488/1866 (79.7)
Principal cause of heart failure – number (%)		
Ischaemic	983 (52.8)	946 (50.7)
Non-ischaemic	880 (47.2)	921 (49.3)
Cardiovascular history – N (%)		
Hospitalisation for heart failure within 12 months	577 (31.0)	574 (30.7)
Atrial fibrillation	664 (35.6)	705 (37.8)
Diabetes mellitus	**927 (49.8)**	**929 (49.8)**
Hypertension	1349 (72.4)	1349 (72.3)
eGFR (ml/min/1.73 m²) – mean ± SD	**61.8 ± 21.7**	**62.2 ± 21.5**
N (%) with eGFR <60	893/1862 (48.0)	906/1866 (48.6)

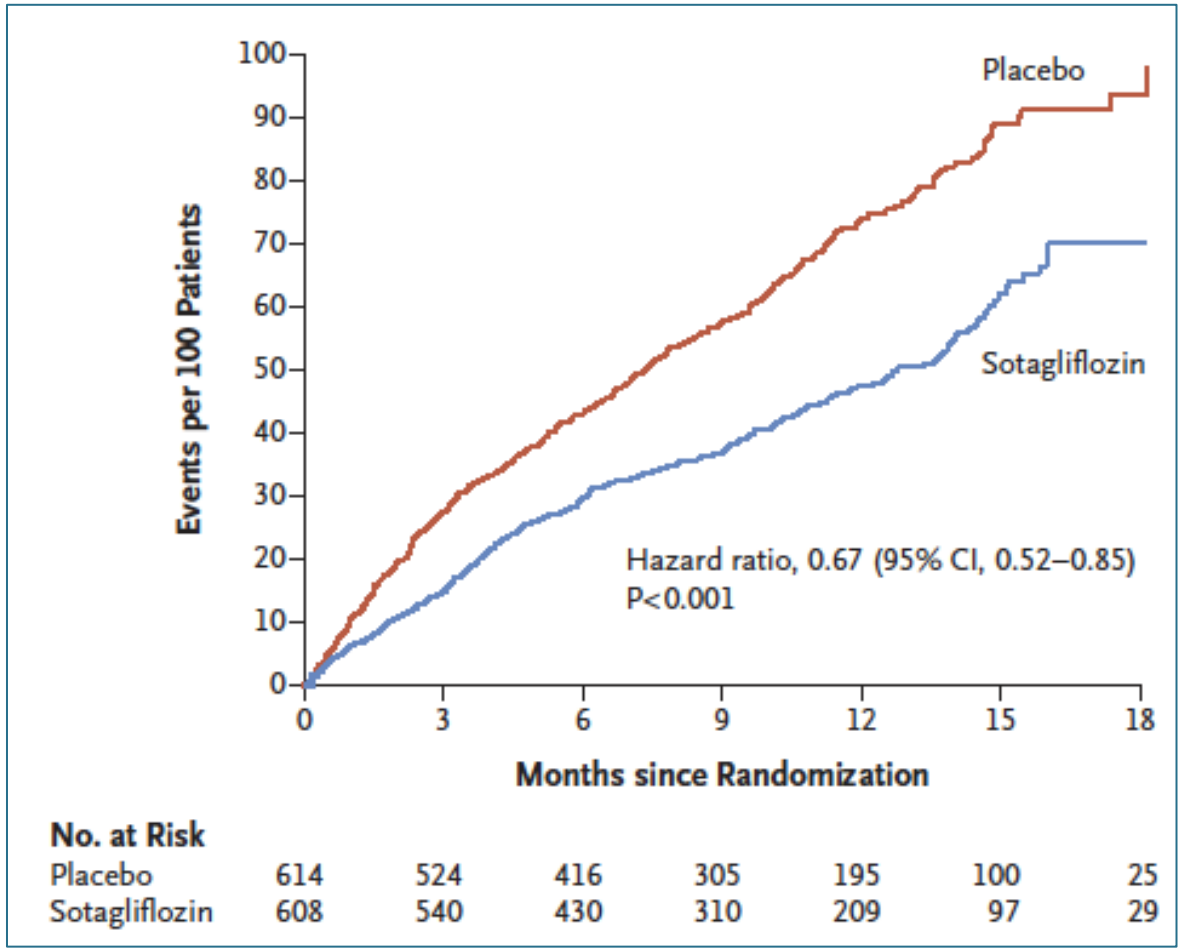


Packer M et al. N Engl J Med 2020

SOLOIST-WHF Trial: sotagliflozin immediately after HHF in T2D

- 1222 patients with type 2 diabetes mellitus who were **recently hospitalized for worsening heart failure**
- Primary end point: **CV death & hospitalizations and urgent visits for heart failure** (first and subsequent events)

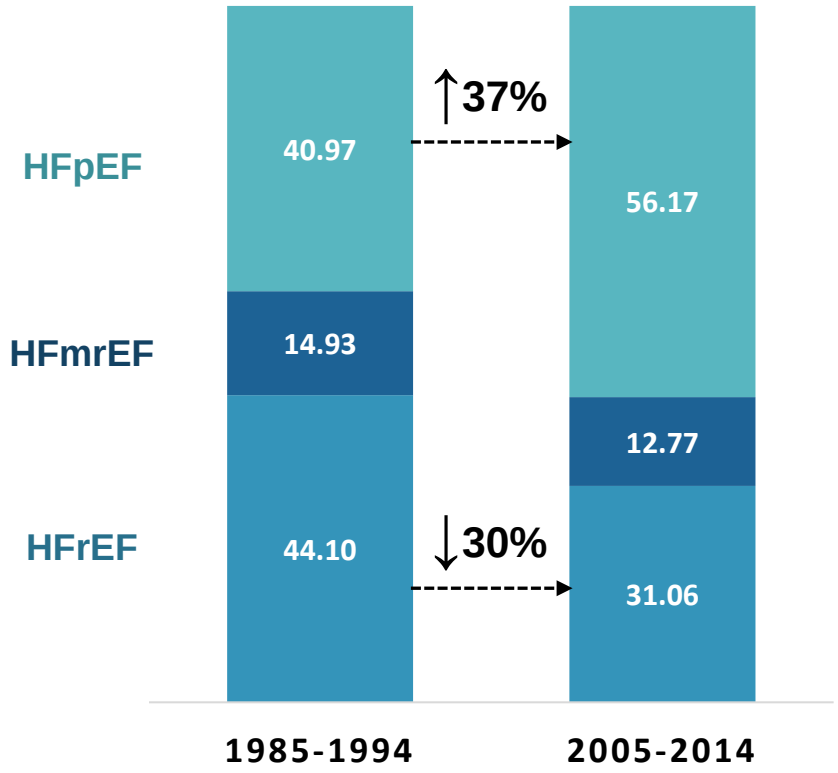
- Median follow-up: **9 months**
- Median age: **70 years**
- HFrEF: **79.1%**
- Median HbA1c: **7.1%**



Bhatt DL et al., N Engl J Med 2021

HFpEF Prevalence Rising

Percentage of Patients Within Each LVEF Category[1,a]



Reasons for Increased HFpEF Prevalence[2]

Increasing Life Expectancy and Aging of the Population

- Global population is rapidly aging
- Rate of HFpEF among patients with HF increases with age
- Increase in comorbidities associated with aging

Epidemic of Cardiac and Non-cardiac Comorbidities

- Improved survival after onset of CAD
- Rate of AF increasing due to an aging general population and increased longevity
- Increasing incidence of obesity, metabolic syndrome, and diabetes

Increased Clinical Recognition

- Improved diagnostic techniques
- Development of diagnostic guidelines

[a]HF prevalence data for 894 outpatients with new onset HF from the community based, Framingham Study over 3 decades (1985-2014). LVEF categories were defined as HFrEF (EF <40%), HF with mid-range EF (EF 40-<50%), and HFpEF (EF ≥50%).

AF = atrial fibrillation; CAD = coronary artery disease; EF = ejection fraction; HF = heart failure; HFmrEF = heart failure with mildly reduced ejection fraction; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; LVEF = left ventricular ejection fraction.

1. Vasan RS et al. *JACC Cardiovasc Imaging*. 2018;11:1-11; 2. Oktay AA et al. *Curr Heart Fail Rep*. 2013;10:401-410.

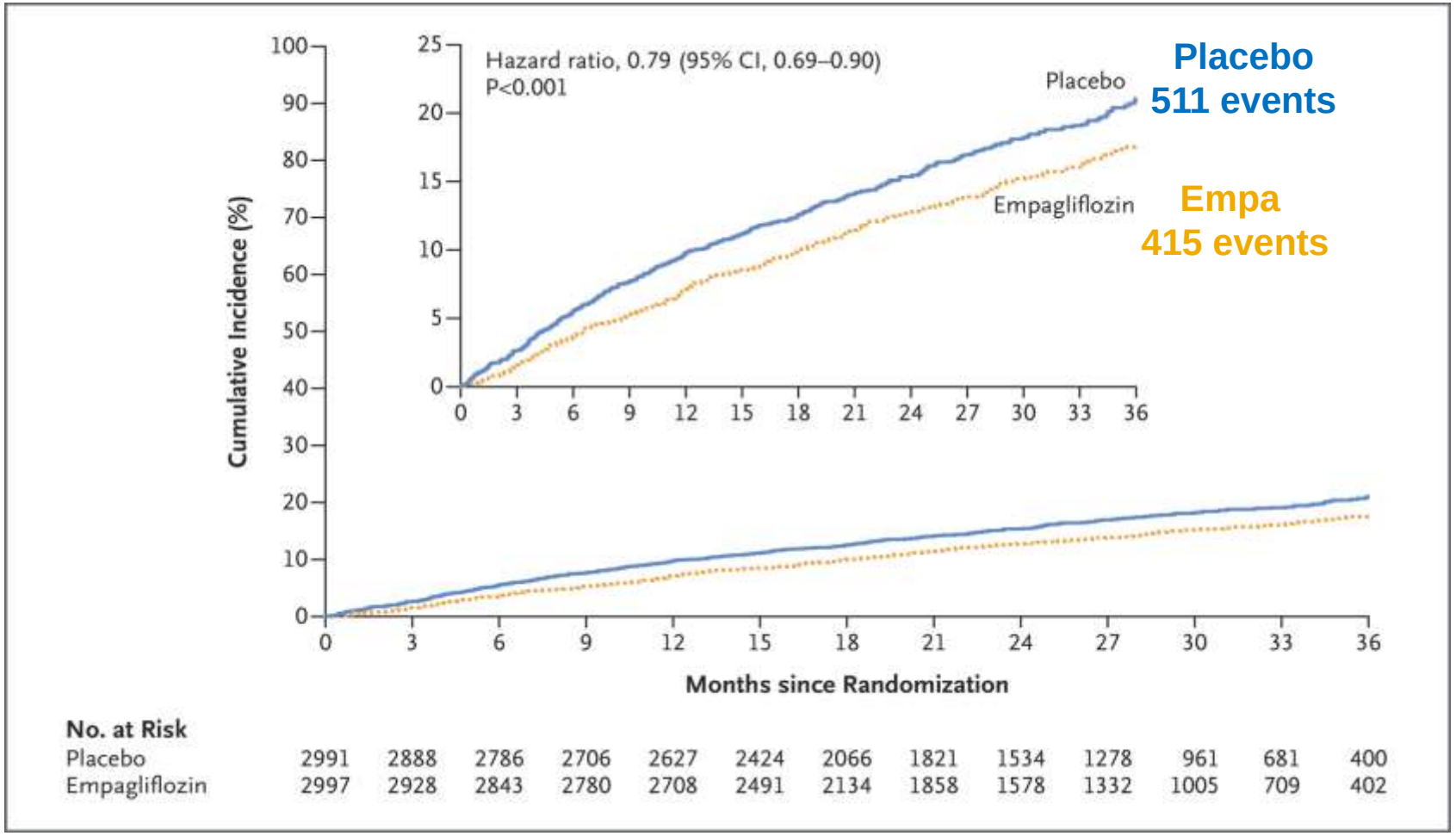
DELIVER and EMPEROR-Preserved Study Designs

	DELIVER[1,2]	EMPEROR-Preserved[3,4,5]
Interventions	Dapagliflozin 10 mg daily or placebo (1:1)	Empagliflozin 10 mg daily or placebo (1:1)
Patient population	• **≥40 years** of age with **symptomatic** NYHA Class II-IV HF at enrollment and typical signs/symptoms of HF ≥6 weeks before enrollment with **at least intermittent need for diuretic treatment** • LVEF >40% and evidence of structural heart disease[a] within 12 months • Elevated NT-proBNP levels • eGFR[b] ≥25 mL/min/1.73 m^2 • Ambulatory or hospitalized off IV HF therapy for ≥24 hours	• **≥18 years** of age (Japan: ≥20 years of age) with NYHA Class II-IV HF for ≥3 months and oral diuretic dose stable for ≥1 week, if prescribed • LVEF >40% • Structural heart disease[a] within 6 months or hHF within 12 months • Elevated NT-proBNP levels • eGFR[b] ≥20 mL/min/1.73 m^2 • No episodes of ADHF[c] within 1 week prior to or during screening
Sample size	N=6263	N=5988
Study duration	**39 months**	**26.2 months**
Primary outcome	Time to first occurrence of any component of the composite of CV death or HF events (hHF or urgent HF visit) in the full patient population and in patients with LVEF <60%	Time to first occurrence of any component of the composite of CV death or hHF
Background therapy	• SoC treatment	• SoC treatment

[a]LV hypertrophy or LA enlargement; [b]Based on the Chronic Kidney Disease-Epidemiology Collaboration Equation; [c]Requiring IV diuretics, vasodilators, inotropic agents, or mechanical support.

1. Solomon SD et al. *Eur J Heart Fail.* 2021;23;1217-1225; 2. Study NCT03619213. ClinicalTrials.gov website; 3. Study NCT03057951. ClinicalTrials.gov website; 4. Anker SD et al. *Eur J Heart Fail*. 2019;21:1279-1287; 5. Anker SD et al. *N Engl J Med*. 2021;385:1451-1461.

EMPEROR-Preserved: primary endpoint result



Placebo
511 events

Empa
415 events

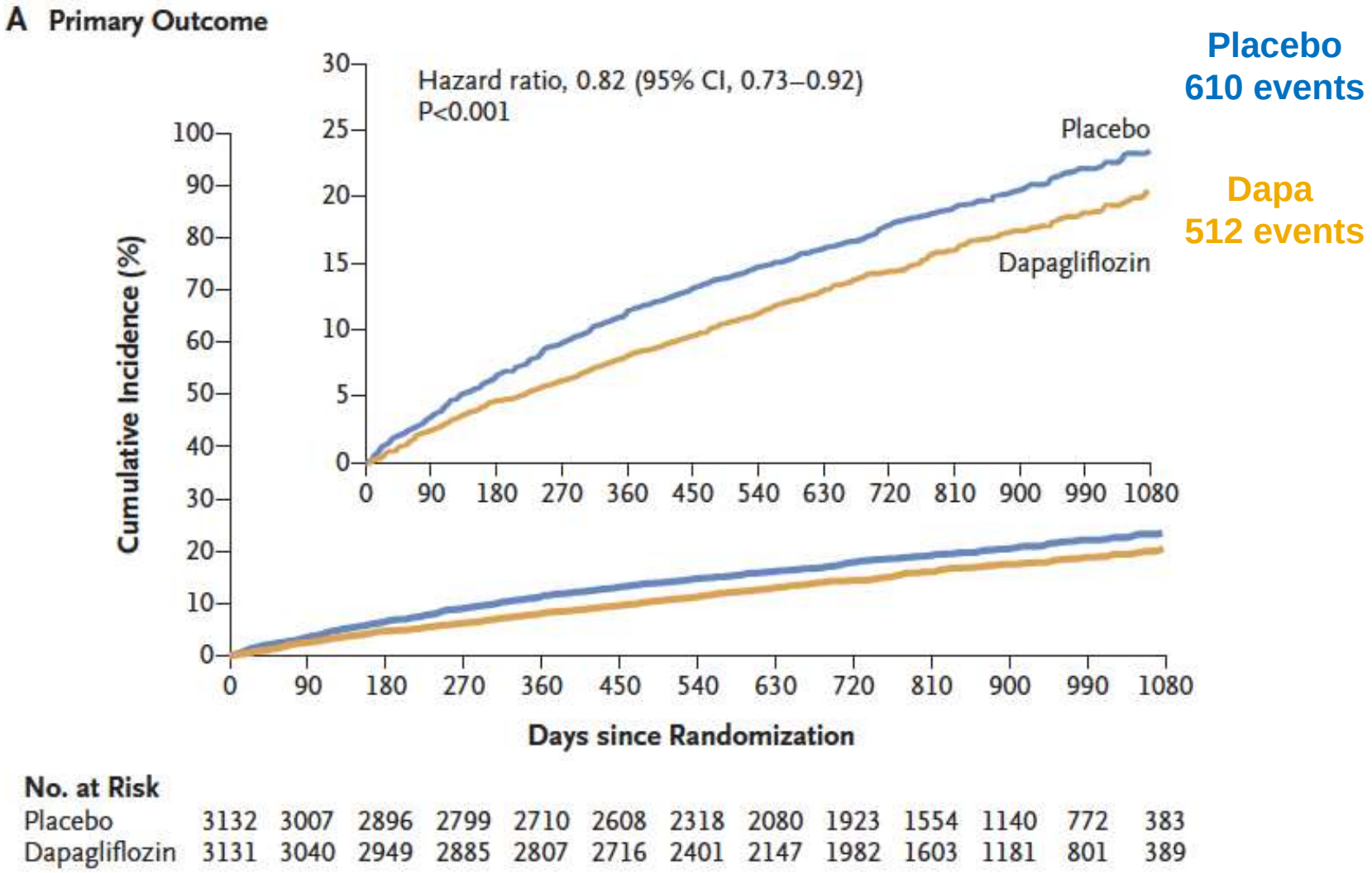
HR 0.79
(95% CI 0.69-0.90)
p<0.001

21%
RRR

NNT=30

SD Anker et. N Engl J Med 2021

DELIVER: primary endpoint result



Placebo
610 events

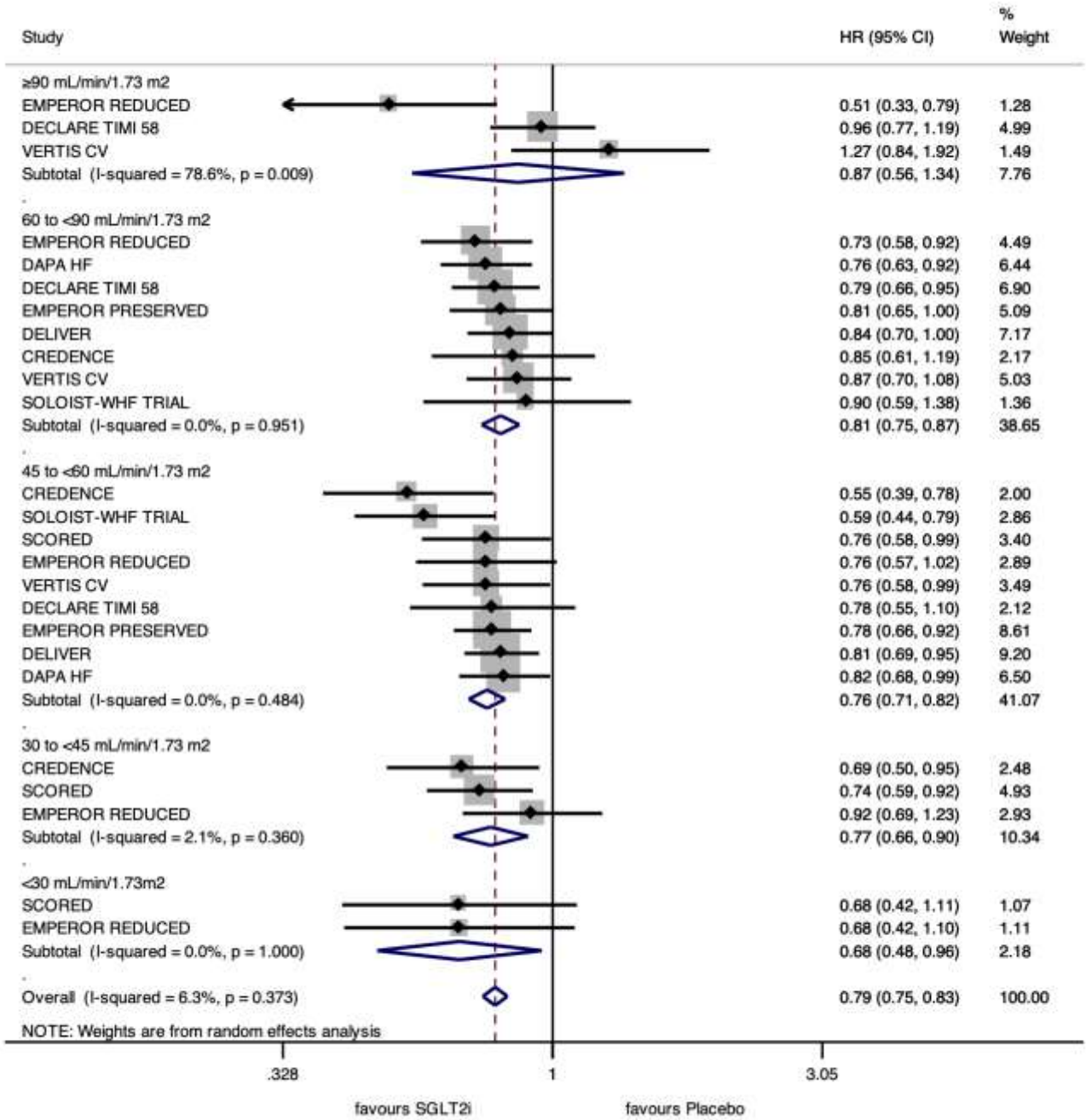
Dapa
512 events

HR 0.82
(95% CI 0.73-0.92)
p<0.001

18%
RRR

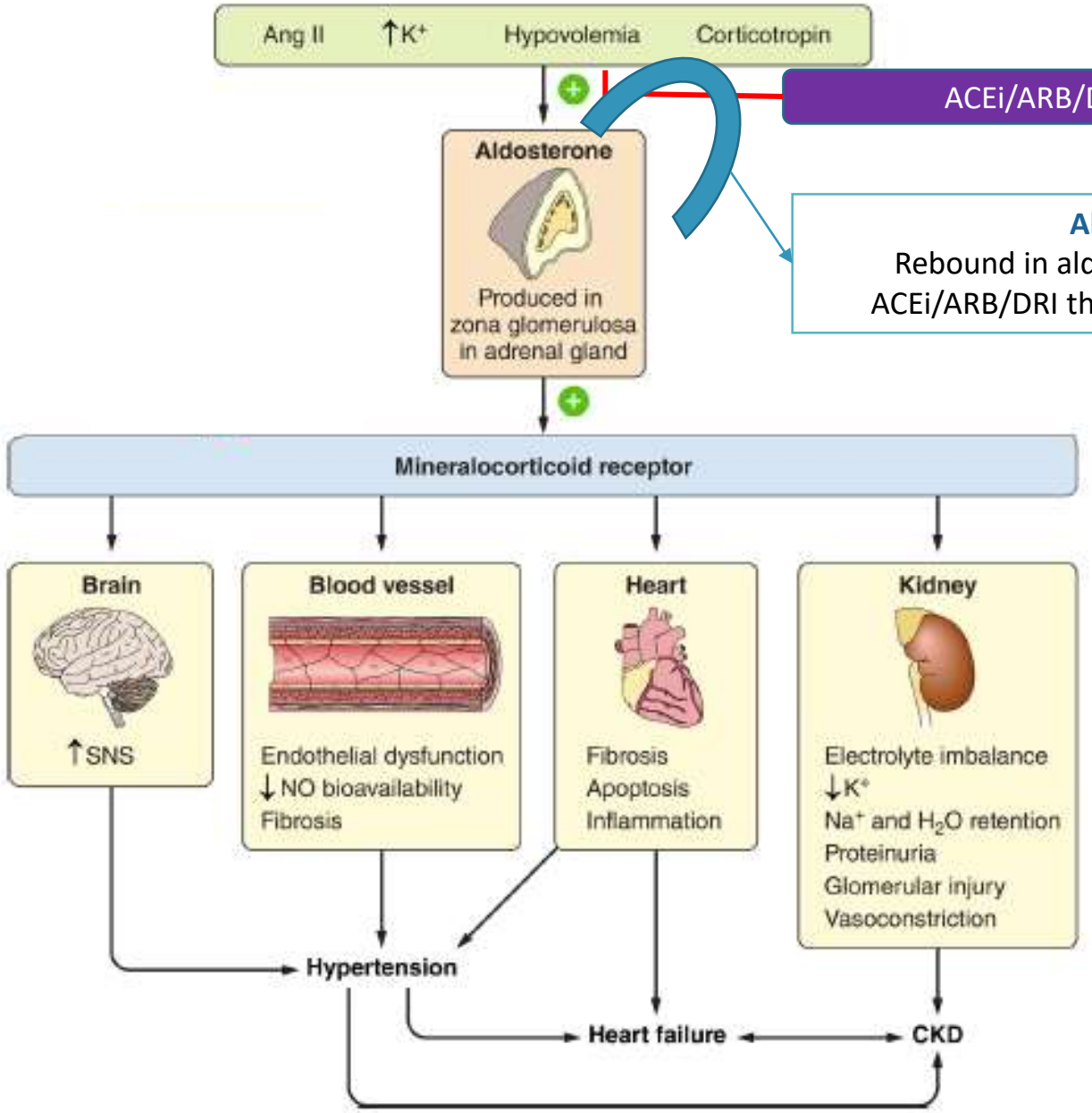
NNT=32

Solomon SD et. al N Engl J Med 2022



Maddaloni E, et al, unpublished

MR & cardio-renal complications of diabetes



Aldosterone escape

Rebound in aldosterone levels after long-term ACEi/ARB/DRI therapy **(40% of diabetes patients)**

Lytvyn Y et al., Curr Diab Rep 2019

Circulation

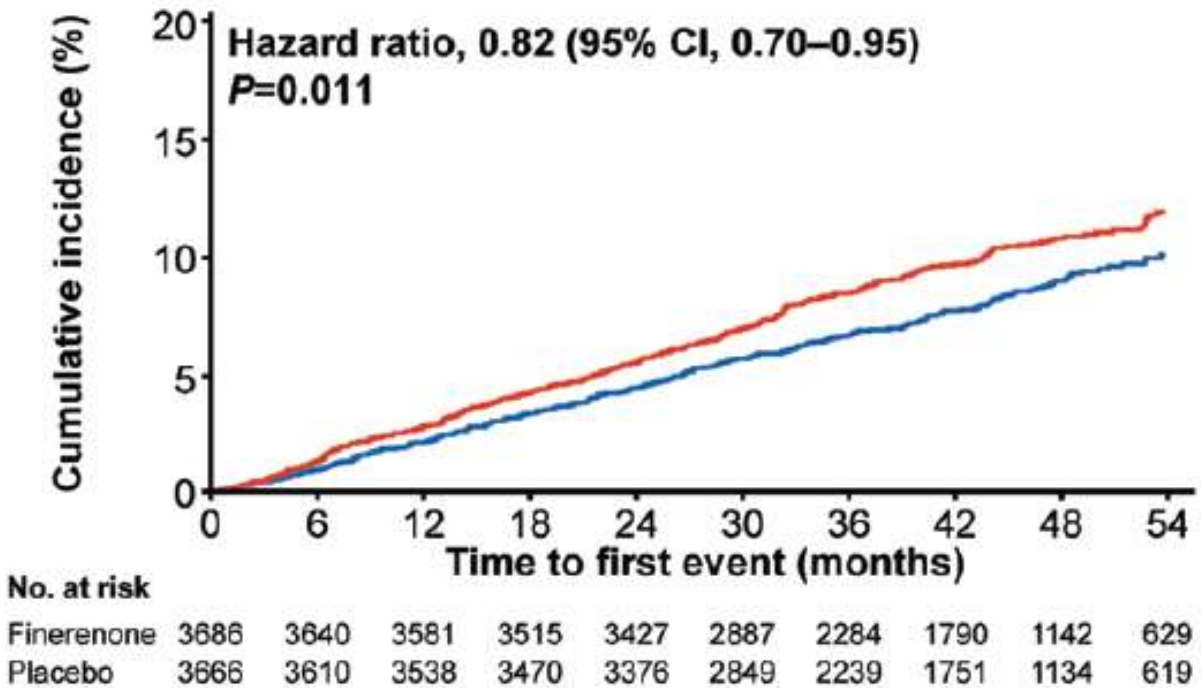
ORIGINAL RESEARCH ARTICLE

Finerenone Reduces Risk of Incident Heart Failure in Patients With Chronic Kidney Disease and Type 2 Diabetes: Analyses From the FIGARO-DKD Trial

7352 randomized patients assessed in the full analysis

Characteristic	With history of heart failure (n=571)	Without history of heart failure (n=6781)
Age, y	65.6 (8.9)	64.0 (9.9)
Male sex	350 (61.3%)	4755 (70.1%)
Systolic blood pressure, mm Hg	135.4 (13.7)	135.8 (14.0)
Diastolic blood pressure, mm Hg	76.8 (10.1)	76.8 (9.5)
Body mass index, kg/m^2	32.8 (6.2)*	31.3 (6.0)*
Duration of diabetes, y	15.1 (9.3)	14.4 (8.5)*
Glycohemoglobin, %	8.0 (1.4)*	7.7 (1.4)*
Serum potassium, mEq/L	4.4 (0.5)*	4.3 (0.4)*
estimated glomerular filtration rate, mL/min/1.73 m^2	63.4 (21.7)*	68.2 (21.7)

Kaplan-Meier estimates for time to cardiovascular death or first HHF

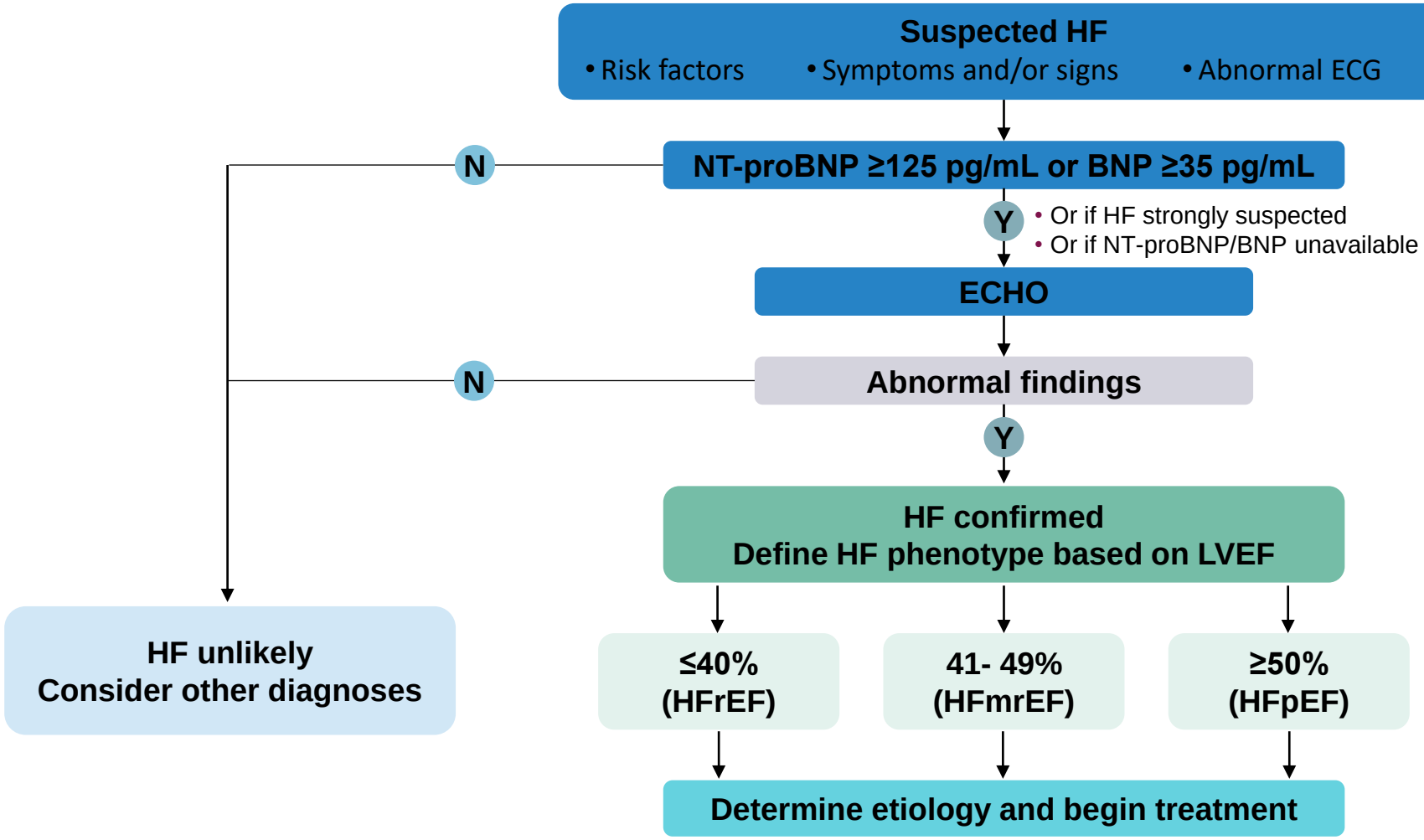


Filippatos G et al., Circulation 2022

Agenda

- Heart failure and diabetes
- News for HF therapy from diabetes drugs
  - SGLT2i
  - Finerenone
- Guidelines

ESC Diagnostic Algorithm for HF



BNP = B-type natriuretic peptide; ECG = electrocardiogram; ECHO = echocardiography; ESC = European Society of Cardiology; HF = heart failure; HFmrEF = heart failure with mildly reduced ejection fraction; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; LVEF = left ventricular ejection fraction; NT-proBNP = N-terminal pro-B-type natriuretic peptide.

McDonagh TA et al. *Eur Heart J*. 2021;42:3599-3726.

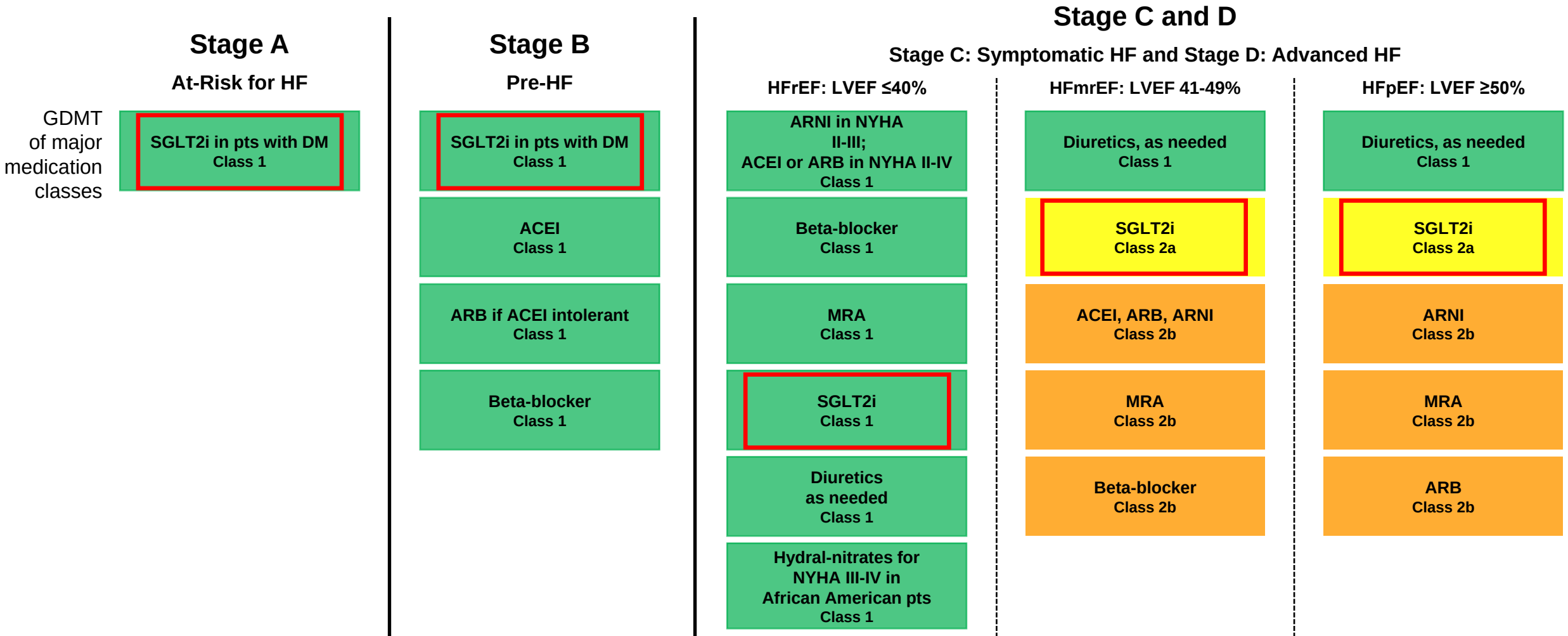
Effectiveness and cost-effectiveness of HF drugs

	ACE inhibitors	β-blockers	MRA	Ivabradine	ARNI	SGLT-2 inhibitor
Evolving background medical therapy						
Stages A-B Risk factors for HF, asymptomatic structural heart disease						
Evidence	SAVE (captopril) [10]	SAVE post hoc [9]				Meta-analysis in diabetes (note that 18% of patients included were stage C) [7]
NNT for all-cause death	20	CV death: 11				24
NNT hHF	33	Severe HF: 16				21
QALY	0.52 [40]	–				0.80–1.29 [37]
ICER per QALY in different countries[a]	UK (6687); USA 5600 [40, 41]	USA 4500 [42]				UK (5530); USA 76,167; Greece (5372); China 1539 [37]
Stages C–D Structural heart disease with current or prior symptoms, refractory HF						
Evidence	CONSENSUS (enalapril) [55]	CIBIS-II (bisoprolol) [19]	RALES (spironolactone) [21]	Intended use population in SHIFT [26]	PARADIGM-HF [27]	DAPA-HF (dapagliflozin) EMPEROR-Reduced (empagliflozin) [28, 30, 31]
NNT for all-cause death	6	18	9	50	36	64
NNT hHF	–	17	15	17	36	23
QALY	0.21 [52]	–	0.07 [54]	0.24–0.28 [50, 51]	0.42–0.52 [46, 47]	0.48–0.50 [43]
ICER per QALY[a]	USA 3419 [52]	Sweden per year of life gained (18,643) [53]	USA 20,579 [54]	UK (18,643); USA 24,920 [50, 51]	UK (23,162); USA 45,017; Germany (30,466) [46, 47]	UK (7886); Germany (6236); Spain (10,905); Australia (9320); China 3828 [43–45]

Cavallari I, Maddaloni E, Grigioni F, *Am J Cardiovasc Drugs* 2022

2022 AHA/ACC/HFSA HF Guidelines: SGLT2i are now recommended in all HF subtypes

GDMT Across HF Stages



ACC = American College of Cardiology; ACEI = angiotensin-converting enzyme inhibitor; AHA = American Heart Association; ARB = angiotensin-receptor blocker; ARNI = angiotensin-receptor neprilysin inhibitor; DM = diabetes mellitus; GDMT = guideline-directed medical therapy; HF = heart failure; HFmrEF = heart failure with mildly reduced ejection fraction; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; HFSA = Heart Failure Society of America; Hydral-nitrates: hydralazine and isosorbide dinitrate; LVEF = left ventricular ejection fraction; MRA = mineralocorticoid receptor antagonist; NYHA = New York Heart Association; SGLT2i = sodium-glucose cotransporter 2 inhibitor.

Adapted from Heidenreich PA et al. Central Illustration. Online ahead of print. *J Am Coll Cardiol.* 2022.

Conclusions

- Heart failure is a prevalent and deadly condition, often associated with T2D
- SGLT2i ameliorates heart failure outcomes in both people with and without T2D through both direct and indirect effects
- Among heart failure therapies, SGLT2i have the strongest evidence in HFpEF
- SGLT2i is a cost-effective option for the treatment of heart failure
- Finerenone improves HF outcomes in people with CKD and T2D