5th iHEF CARD

The 5th Indonesian Symposium on Heart Failure and Cardiometabolic Disease

ASCVD and Type 2 Diabetes : Novel Arsenal for The Deadly Duo

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Disclosure

- I have received honorarium as speaker/consultant, support for research/attendance at educational meetings from:
  - Novo Nordisk

- **Once-weekly Semaglutide 0.25 – 1 mg available in Indonesia** under the brand name of **Ozempic ®**, which is indicated for the treatment of adults with insufficiently controlled **type 2 diabetes mellitus** as an adjunct to diet and exercise in addition to metformin, metformin and sulphonylurea, metformin and basal insulin, or sodium-glucose cotransporter 2 (SGLT2) inhibitor.

- This is only for educational purpose and no off-label promotion is intended

How far can Diabetes do to Our Heart??

Meet Mr. H

Male 73 y.o with worsening exertional dyspnea

- History of PCI at Prox. LAD (2020)
- History of 3 times hHF in a year
- LVEF 35%

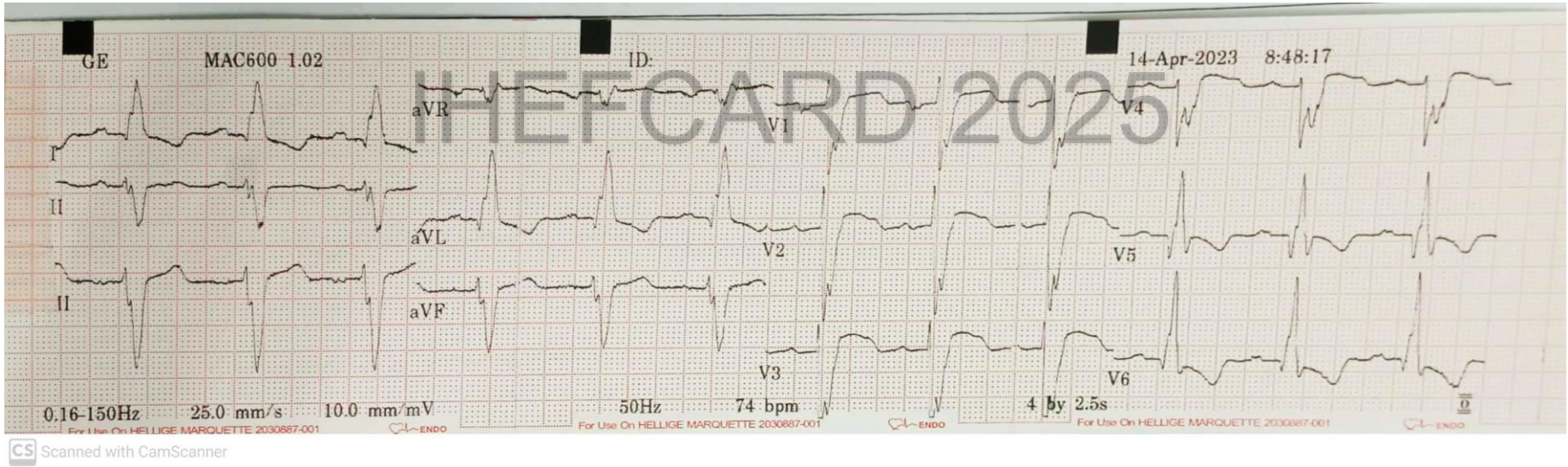
Condition(s)

- Type 2 diabetes with OAD. HbA1c 6.8%, FG : 115 mg/dL
- Dyslipidemia ; LDL-C 105 mg/dL

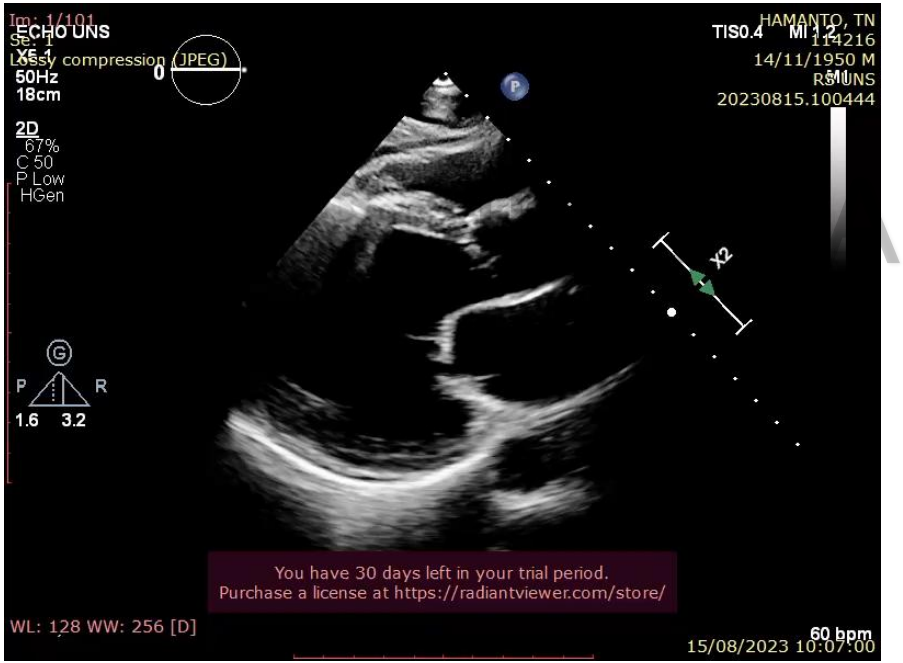
Treatments

- Candesartan 16 mg O.D
- Spironolacton 25 mg O.D
- Bisoprolol 5mg O.D
- ASA 80mg O.D
- Metformin 1000 mg BID
- Sitagliptin 100 mg OD
- Rosuvastatin 10 mg daily

ECG



Echocardiography



LVH eccentric remodelling

LVEF 32%

RWMA : akinetic at mid-apical LAD, basal-apical RCA

Moderate functional MR

Treatments

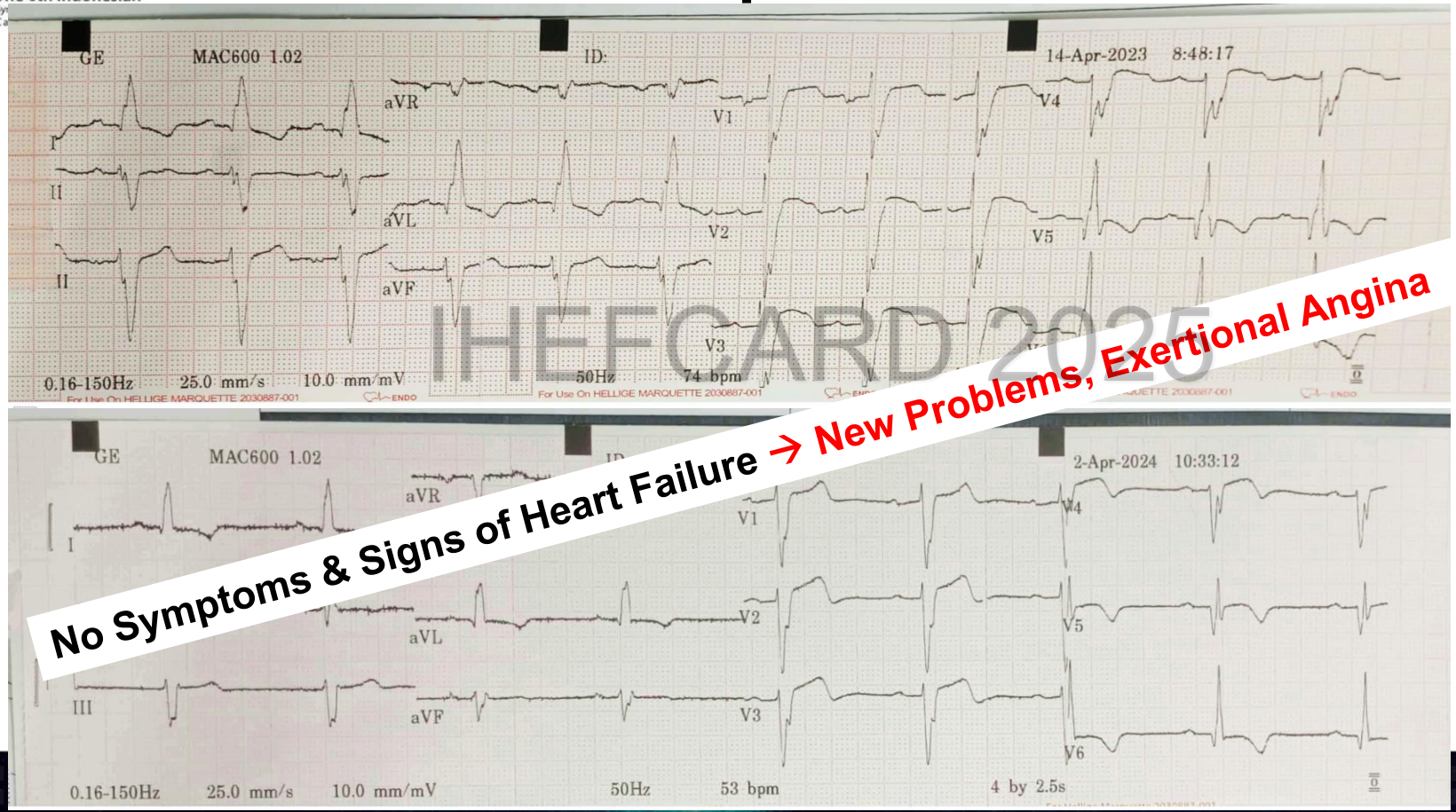
- Candesartan 16 mg O.D
- Spironolacton 25 mg O.D
- Bisoprolol 5mg O.D
- ASA 80mg O.D
- Metformin 1000 mg BID
- Sitagliptin 100 mg OD
- Rosuvastatin: 10 mg daily

New Treatments

- ARB switched to ARNI 50mg BID
- Spironolacton titrated to 50mg OD
- Bisoprolol titrated to 10 mg OD
- ASA 80mg OD
- OAD switched to Dapagliflozin/metformin 10/1000mg OD
- Statin upgraded to Rosuvastatin 40mg OD
- Furosemide 40mg OD

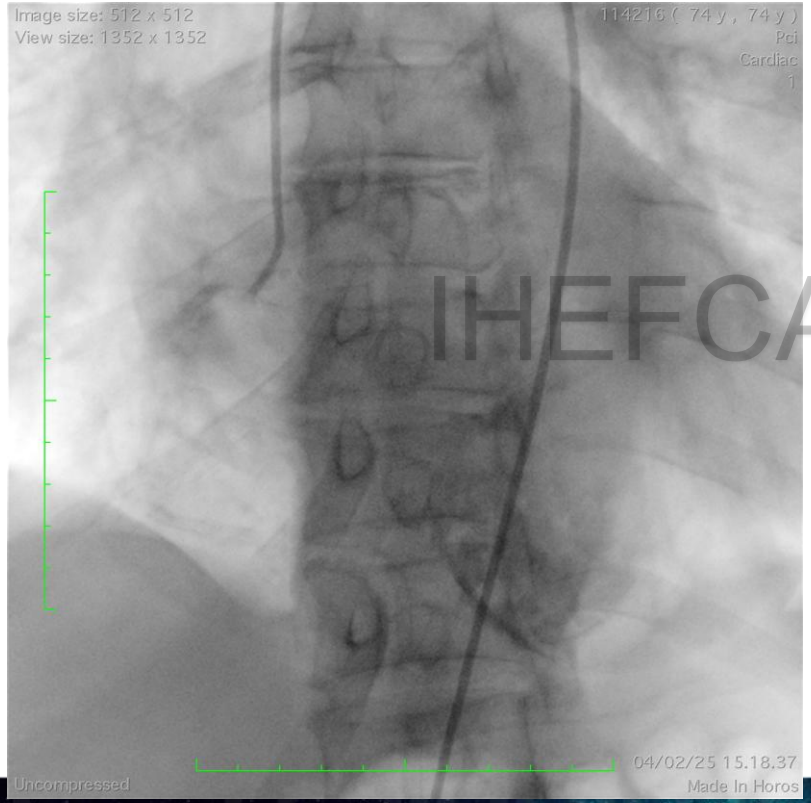
The Patient Felt much better with ZERO hospitalization in a Year

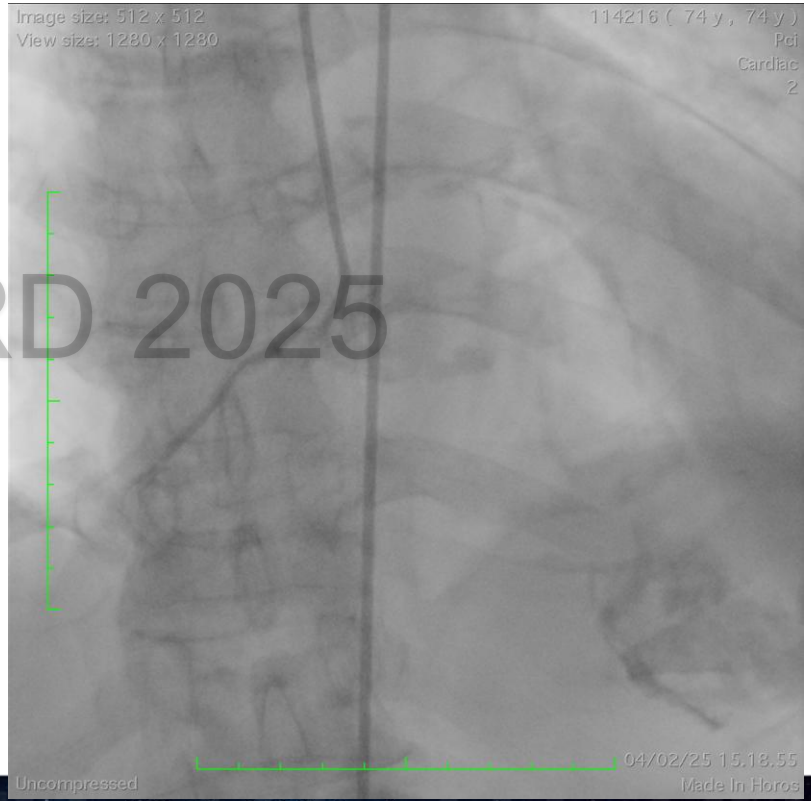
1 Years Follow Up



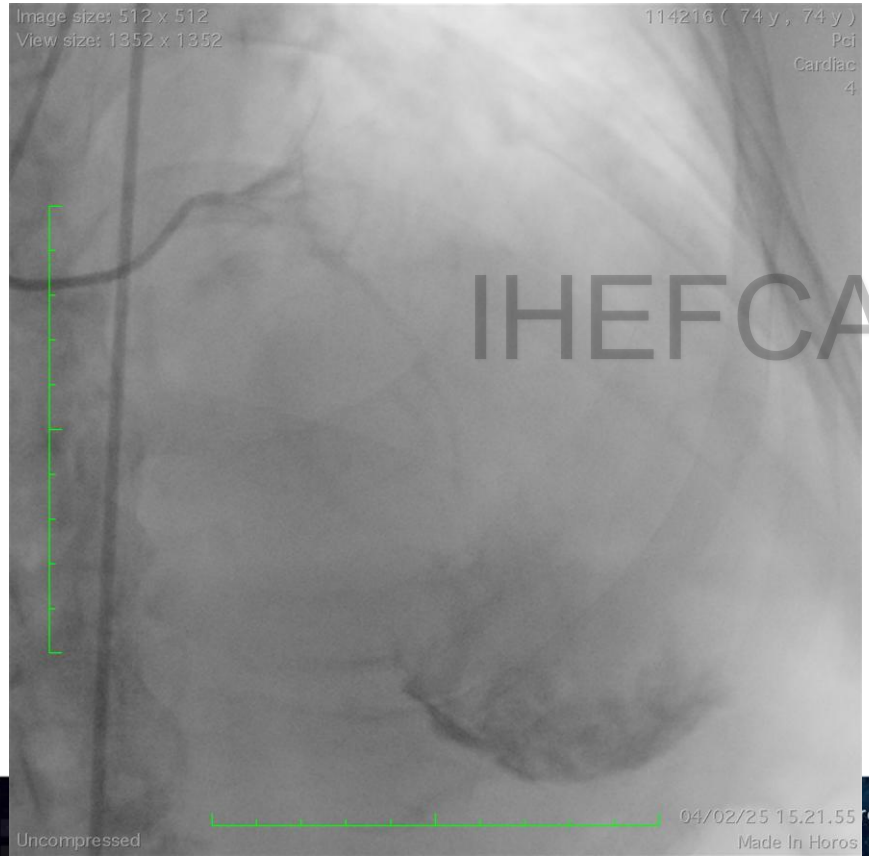
No Symptoms & Signs of Heart Failure → New Problems, Exertional Angina

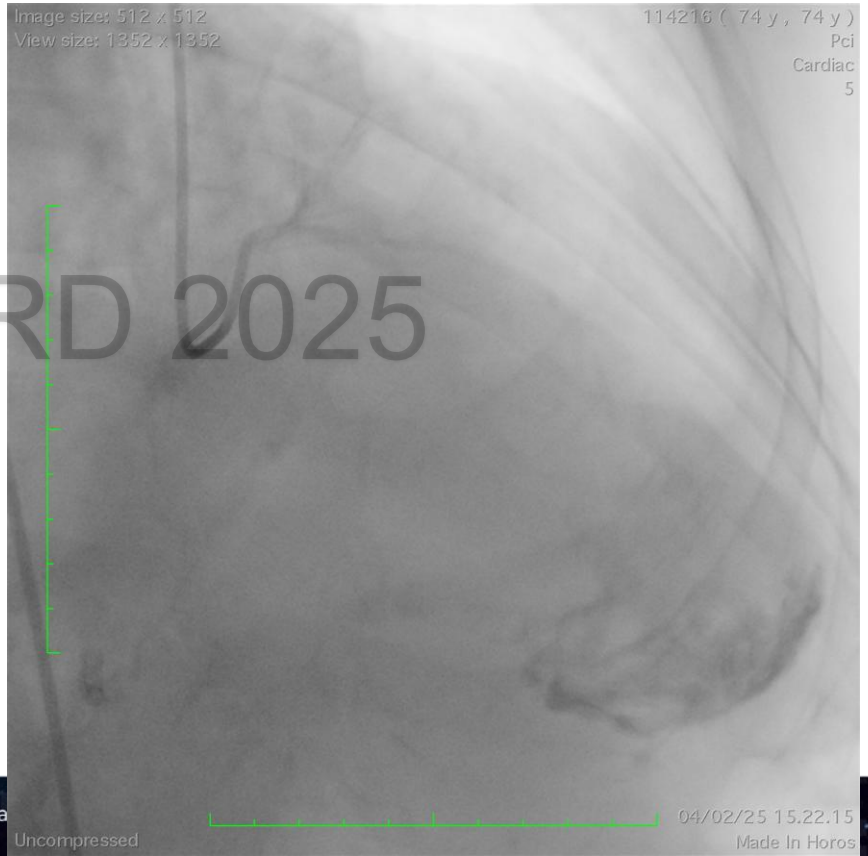
Coroangiography



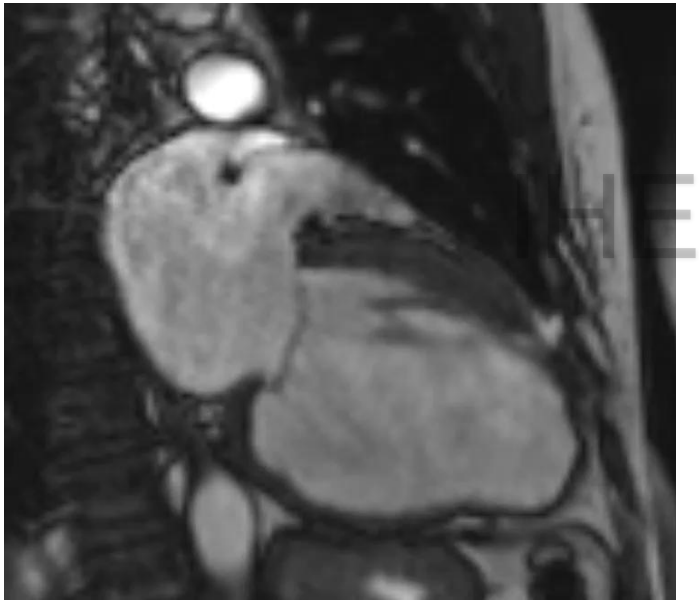


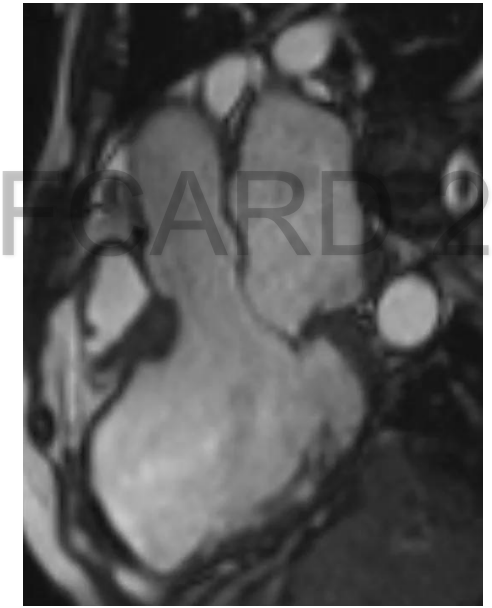
Coroangiography

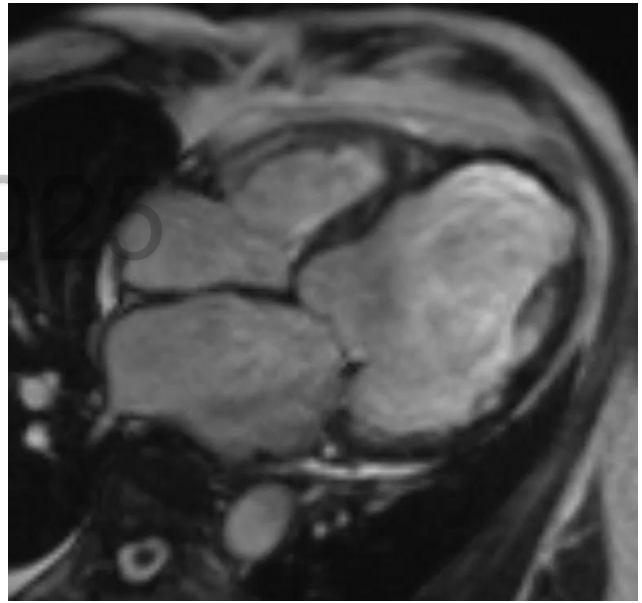




CMR-SSFP







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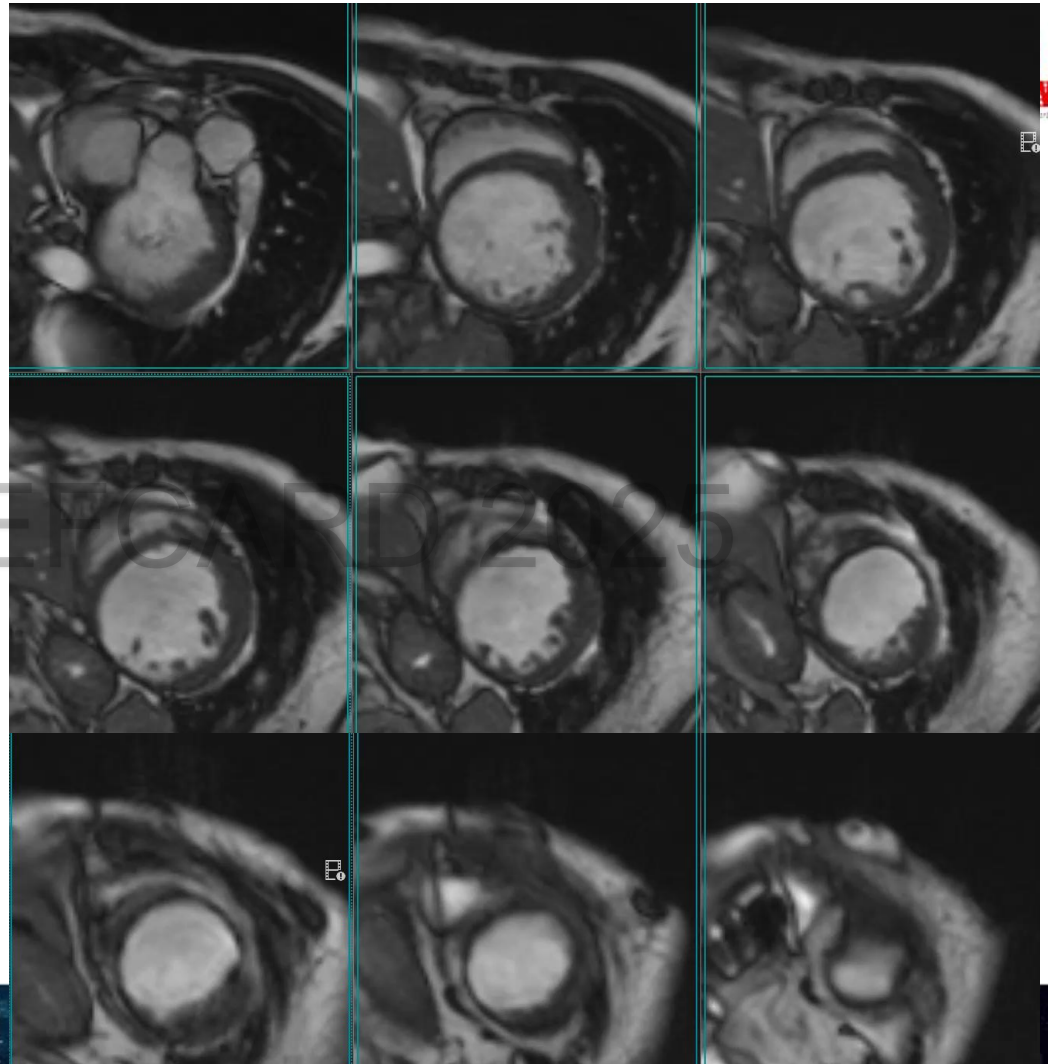
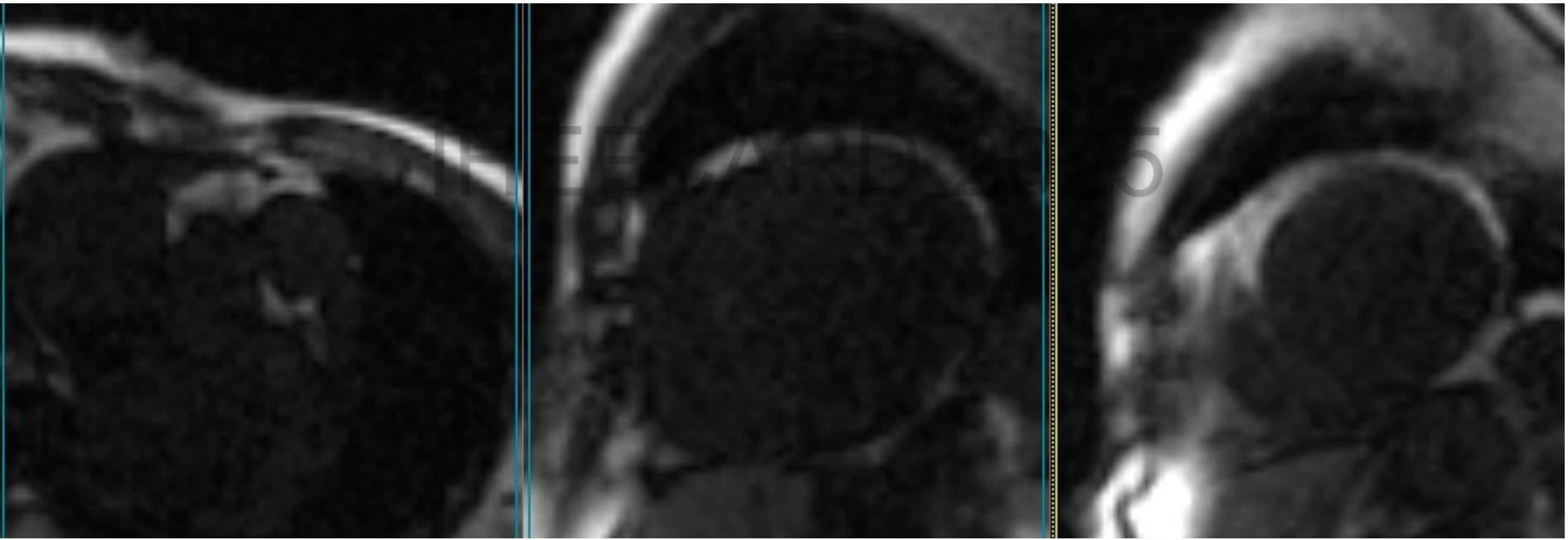
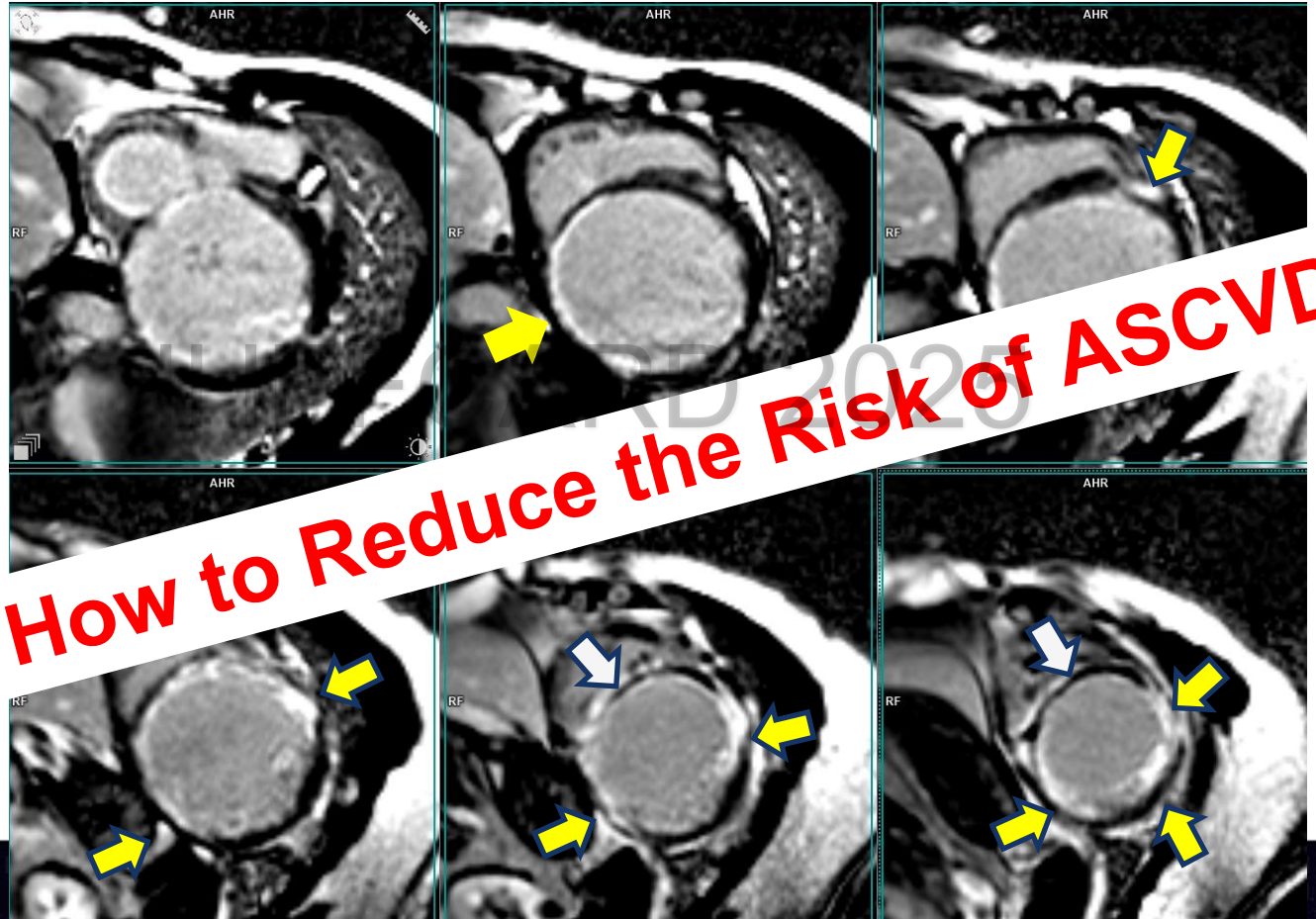
CMR-SSFP



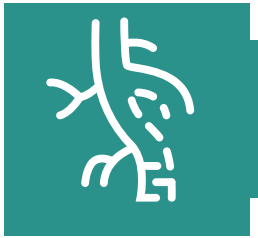
CMR-First Pass Perfusion



CMR-LGE

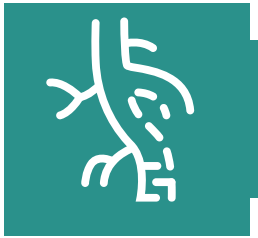


Then, How to Reduce the Risk of ASCVD?



The Link Between ASCVD & T2D

Management of People with ASCVD & T2D



The Link Between ASCVD & T2D

Management of People with ASCVD & T2D

Diabetes as a Global Emergency

At a glance	2019	2045
Total world population	7.7 billion	9.5 billion
Adult population (20–79 years)	5.0 billion	6.4 billion
Diabetes (20–79 years)		
Global Prevalence	9.3%	10.9%
Number of people with diabetes	463.0 million	700.2 million

Map 3.1 Estimated total number of adults (20–79 years) with diabetes in 2019

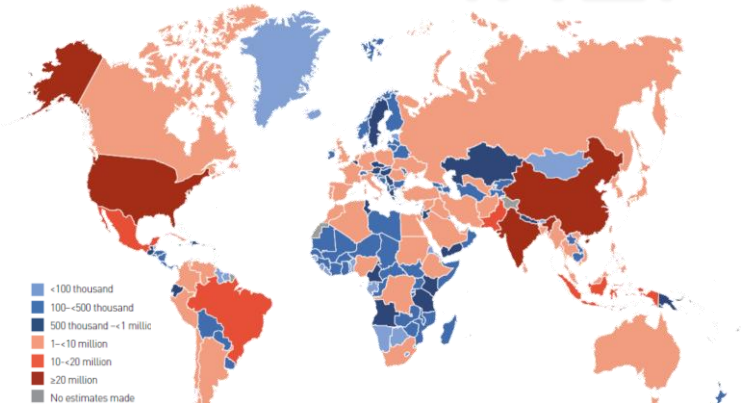


Table 3.5 Top 10 countries or territories for number of adults (20–79 years) with diabetes in 2019, 2030 and 2045

2019			2030			2045		
Rank	Country or territory	Number of people with diabetes (millions)	Rank	Country or territory	Number of people with diabetes (millions)	Rank	Country or territory	Number of people with diabetes (millions)
1	China	116.4 (108.6–145.7)[a]	1	China	140.5 (130.3–172.3)	1	China	147.2 (134.7–176.2)
2	India	77.0 (62.4–96.4)	2	India	101.0 (81.6–125.6)	2	India	134.2 (108.5–165.7)
3	United States of America	31.0 (26.7–35.8)	3	United States of America	34.4 (29.7–39.8)	3	Pakistan	37.1 (15.8–58.5)
4	Pakistan	19.4 (7.9–30.4)	4	Pakistan	26.2 (10.9–41.4)	4	United States of America	36.0 (31.0–41.6)
5	Brazil	16.8 (15.0–18.7)	5	Brazil	21.5 (19.3–24.0)	5	Brazil	26.0 (23.2–28.7)
6	Mexico	12.8 (7.2–15.4)	6	Mexico	17.2 (9.7–20.6)	6	Mexico	22.3 (12.7–26.8)
7	Indonesia	10.7 (9.2–11.5)	7	Indonesia	13.7 (11.9–14.9)	7	Egypt	16.9 (9.0–19.4)
8	Germany	9.5 (7.8–10.6)	8	Egypt	11.9 (6.4–13.5)	8	Indonesia	16.6 (14.6–18.2)
9	Egypt	8.9 (4.8–10.1)	9	Bangladesh	11.4 (9.4–14.4)	9	Bangladesh	15.0 (12.4–18.9)
10	Bangladesh	8.4 (7.0–10.7)	10	Germany	10.1 (8.4–11.3)	10	Turkey	10.4 (7.4–13.3)

[1] International Diabetes Federation. IDF Diabetes Atlas, 10th edn. Brussels, Belgium: International Diabetes Federation; 2021.

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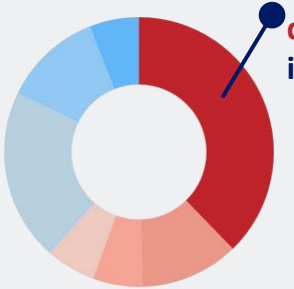
ASCVD Burden in Indonesia

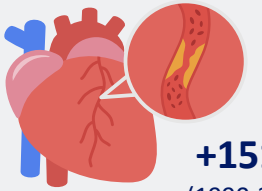
CVD prevalence in Indonesia **+120%** within 30 years



Cardiovascular diseases is responsible for

1/3 of all deaths in Indonesia

Deaths caused by ASCVD

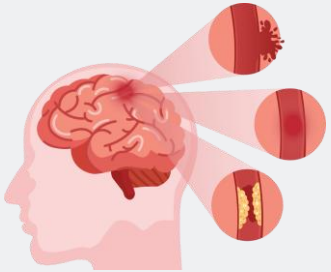


Ischemic heart disease deaths

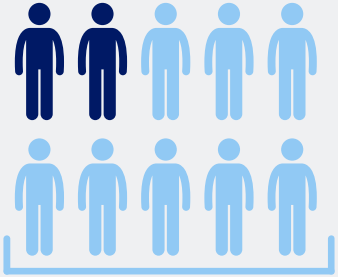
+151% (1990-2019)

Stroke deaths

+130% (1990-2019)



Only 2 in 10 people with T2D + CV risk receive proper treatment.



Treatment Gap

ESC European Society of Cardiology

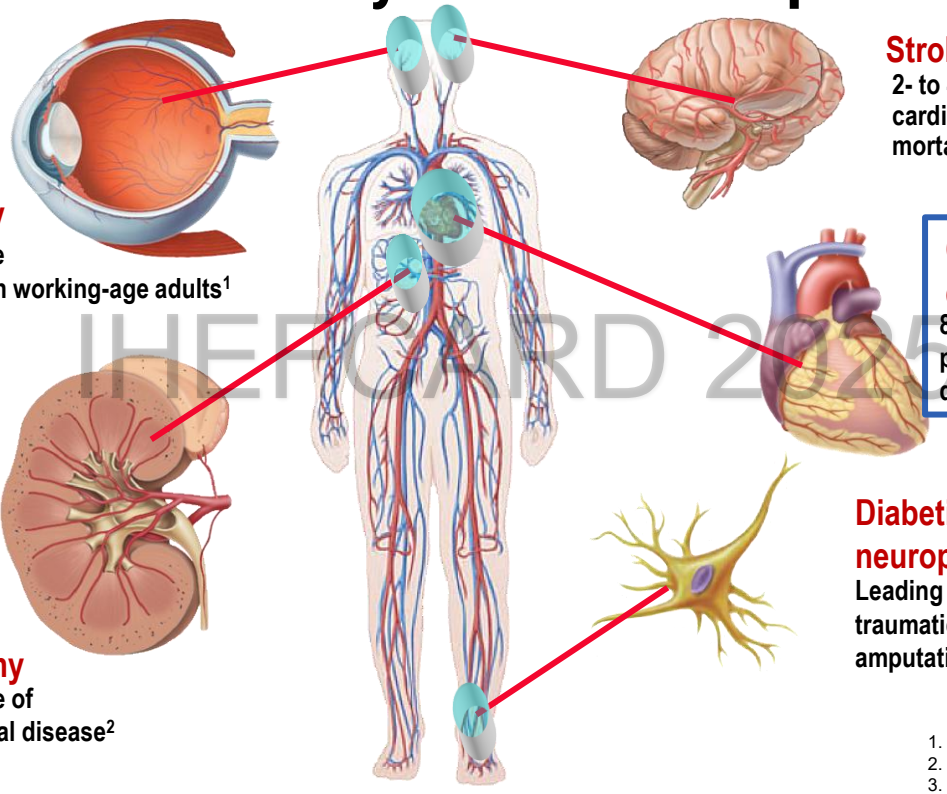
American Diabetes Association.

KDIGO

Recommended treatments **EXIST**.

Source: Muharram, F.R., Multazam, C.E.C.Z., Mustofa, A., Socha, W., Andrianto, Martini, S., Aminde, L. and Yi-Li, C. (2024), The 30 Years of Shifting in The Indonesian Cardiovascular Burden-Analysis of The Global Burden of Disease Study. Journal of Epidemiology and Global Health, 14. doi:https://doi.org/10.1007/s44197-024-00187-8.
World Heart Observatory. Indonesia. [online] Available at: https://world-heart-federation.org/world-heart-observatory/countries/indonesia/ [Accessed 9 May 2025].
Shaping the Cardiovascular Disease Access Policy Landscape Indonesia. Available at: https://www.iqvia.com/-/media/iqvia/pdfs/asia-pacific/white-papers/cvd/indonesia_shaping-cvd-access-strategy-policy-landscape-_iqvia_veng.pdf [Accessed 9 May 2025].

Diabetes and Morbidity: Overall Perspective



Diabetic retinopathy
Leading cause of blindness in working-age adults[1]

Stroke
2- to 4-fold increase in cardiovascular mortality and stroke[3]

Cardiovascular disease
8/10 diabetic patients die from CV events[4]

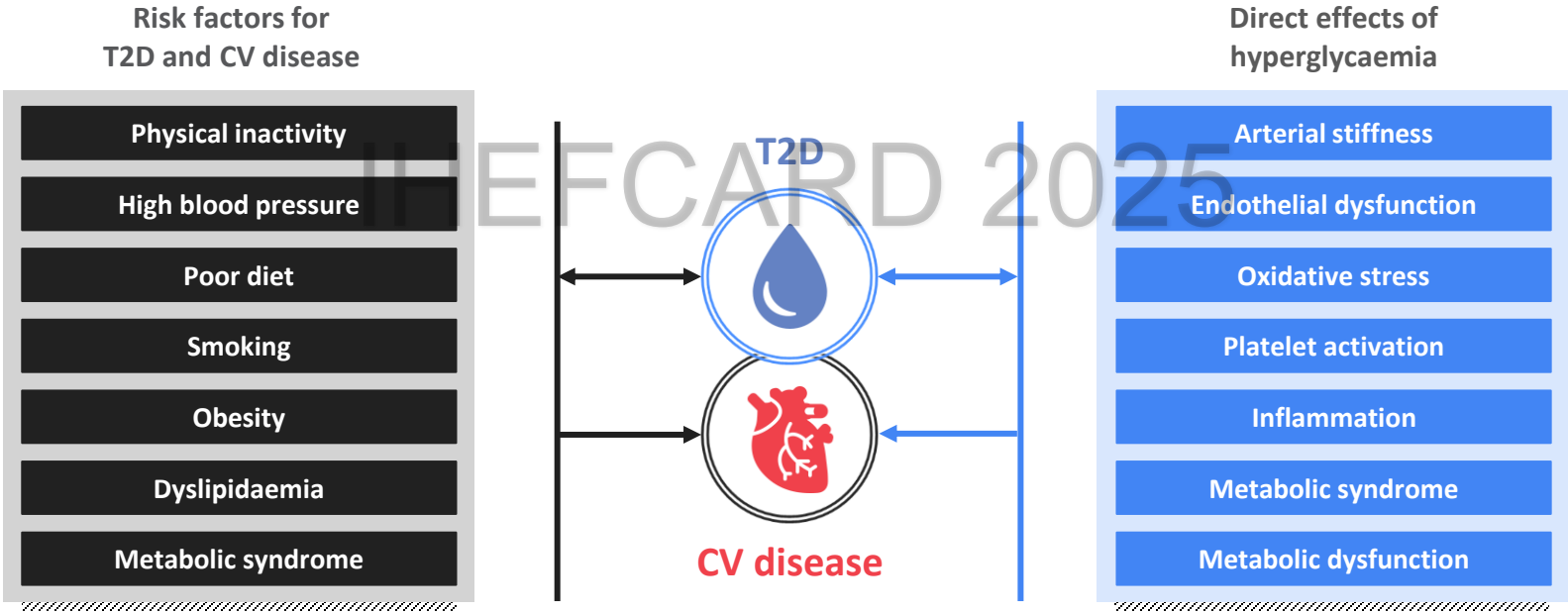
Diabetic nephropathy
Leading cause of end-stage renal disease[2]

Diabetic neuropathy
Leading cause of non-traumatic lower extremity amputations[5]

1. Kempen J, et al. Arch Ophthalmol. 2004;122(4):552-563
2. Yuan MC, et al. Clin Kidney J. 2017 Apr; 10(2): 257–262
3. Fox CS, et al. JAMA. 2004;292(20):2495-2499
4. Matheus, AS et al. Int J Hypertens. 2013; 2013: 653789.
5. Rathnayake A. World J Diabetes. 2021 Jul 15; 12(7): 875-888

The pathophysiology of CV disease in patients with T2D is complex

- T2D shares common risk factors with CV disease and contributes to vascular damage



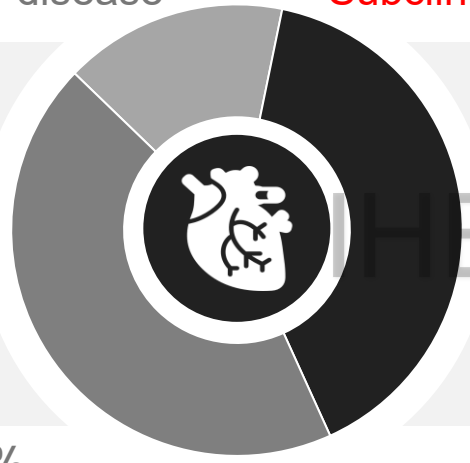
CV, cardiovascular; T2D, type 2 diabetes

Newman JD *et al. J Am Coll Cardiol* 2017;70:813

CV disease is frequently asymptomatic and unrecognized

16%
No CV disease

44%
Subclinical CV disease



40%
Clinical CV disease

Almost half of patients with diabetes have **subclinical CV disease***

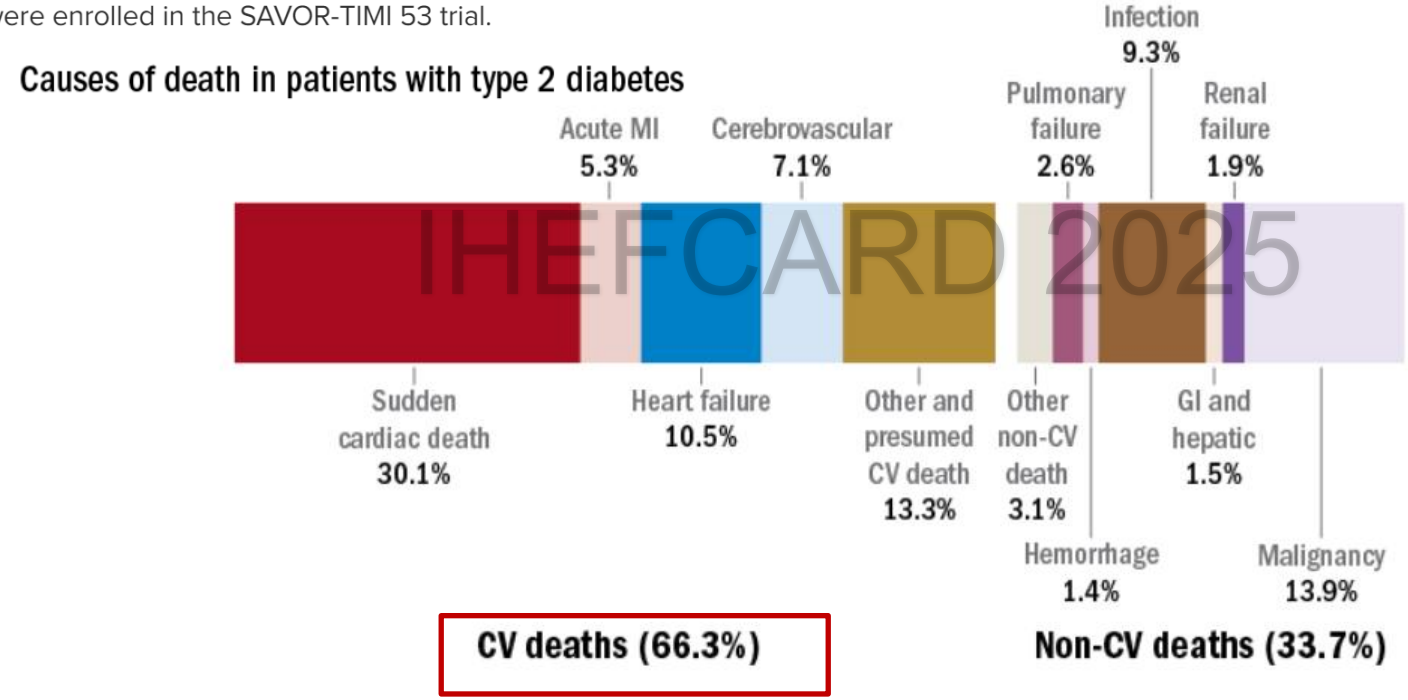
Prevalence of subclinical CV disease across 1343 patients with diabetes aged ≥65 years in the US

*Absence of prevalent clinical disease at baseline: ankle–brachial index ≤0.9, internal carotid artery wall thickness >80th percentile, common carotid artery wall thickness >80th percentile, carotid stenosis >25%, major electrocardiogram abnormalities (based on the Minnesota code), and a Rose Questionnaire positive for claudication or angina pectoris in the absence of clinical diagnosis of angina pectoris or claudication

Kuller LH *et al. Arterioscler Thromb Vasc Biol* 2000;20:823

2 out of 3 diabetes patients died from CV disease

Cardiovascular disease was the leading cause of death among the over 16,000 patients with type 2 diabetes (T2DM) who were enrolled in the SAVOR-TIMI 53 trial.



J Am Coll Cardiol. 2021 Apr 13;77[14]:1837-40

Note: There were 798 deaths in SAVOR-TIMI 53 after a median follow-up of 2.1 years.

CV disease occurs early and is the leading cause of mortality in patients with T2D

CV disease can occur

10–15 years earlier

in patients with diabetes compared with those without diabetes[1]

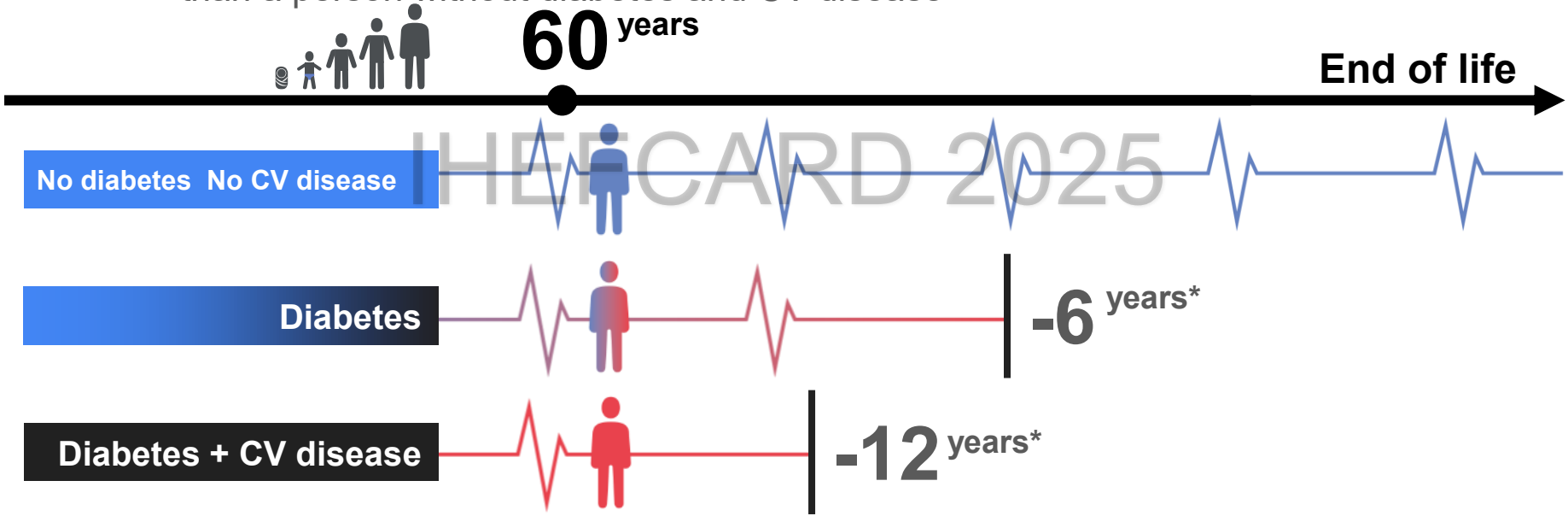
Despite advances in standard of care, most patients with T2D

die from CV disease[2]

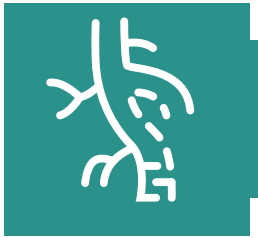
CV, cardiovascular; T2D, type 2 diabetes

Life expectancy is reduced by ~12 years in patients with diabetes and CV disease

- A 60-year-old patient with diabetes and CV disease dies, on average, 12 years earlier than a person without diabetes and CV disease



The Emerging Risk Factors Collaboration. JAMA. 2011;306(23):2579-87.



The Link Between ASCVD & T2D

Management of People with ASCVD & T2D

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Management of People with ASCVD & T2D

ESC European Society of Cardiology
European Heart Journal (2023) 44, 4043–4140
https://doi.org/10.1093/eurheartj/ehad192

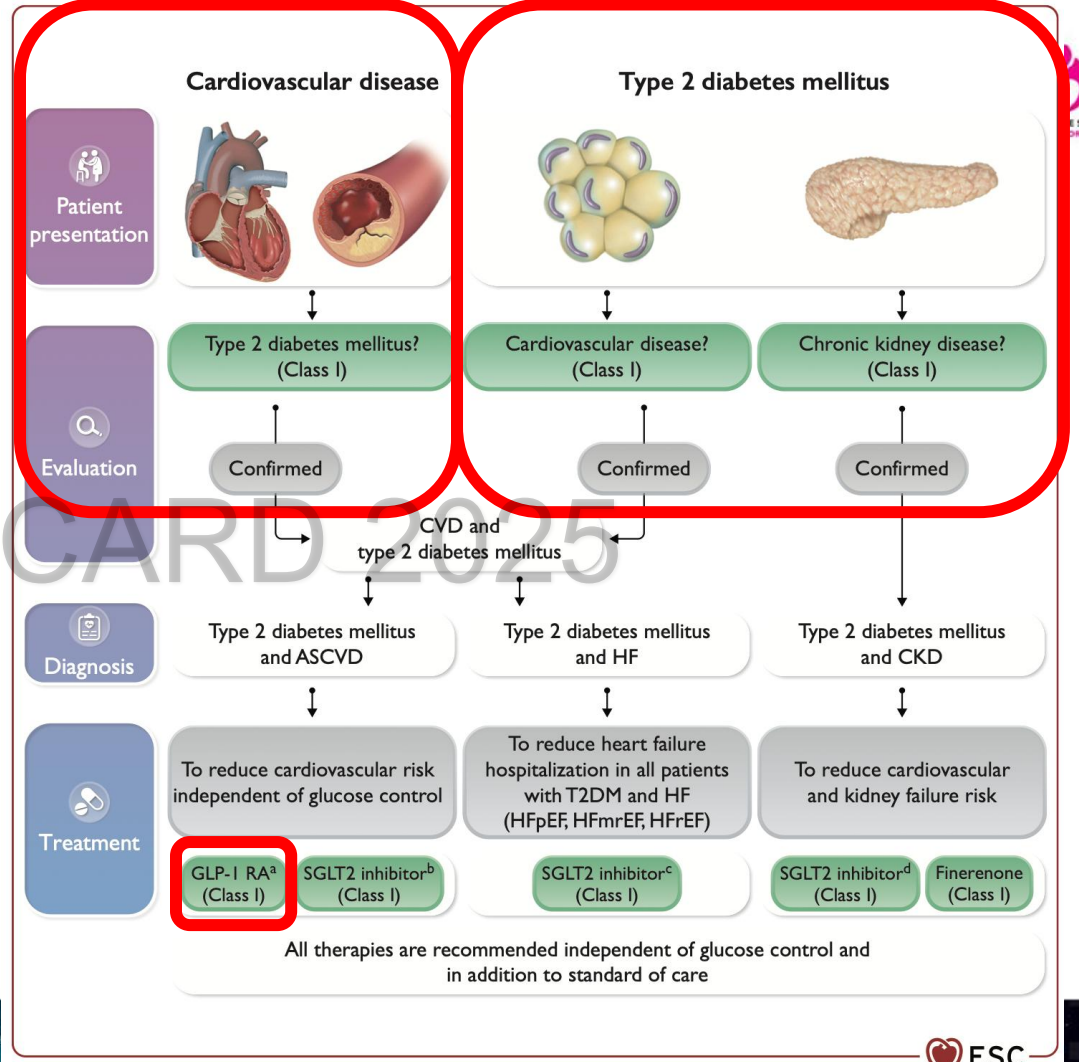
2023 ESC Guidelines for the management of cardiovascular disease in patients with diabetes

Cardiovascular Risk Categories in DM Patients

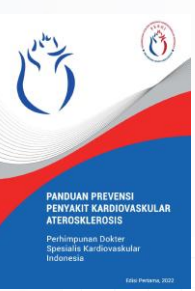
Very high CV risk	Patients with T2DM with: • Clinically established ASCVD or • Severe TOD or • 10-year CVD risk ≥20% using SCORE2-Diabetes
High CV risk	Patients with T2DM not fulfilling the very high risk criteria and a: • 10-year CVD risk 10 to <20% using SCORE2-Diabetes
Moderate CV risk	Patients with T2DM not fulfilling the very high risk criteria and a: • 10-year CVD risk 5 to <10% using SCORE2-Diabetes
Low CV risk	Patients with T2DM not fulfilling the very high risk criteria and a: • 10-year CVD risk <5% using SCORE2-Diabetes

ESC European Society of Cardiology
European Heart Journal (2023) 44, 4043–4140
https://doi.org/10.1093/eurheartj/ehad192

2023 ESC Guidelines for the management of cardiovascular disease in patients with diabetes

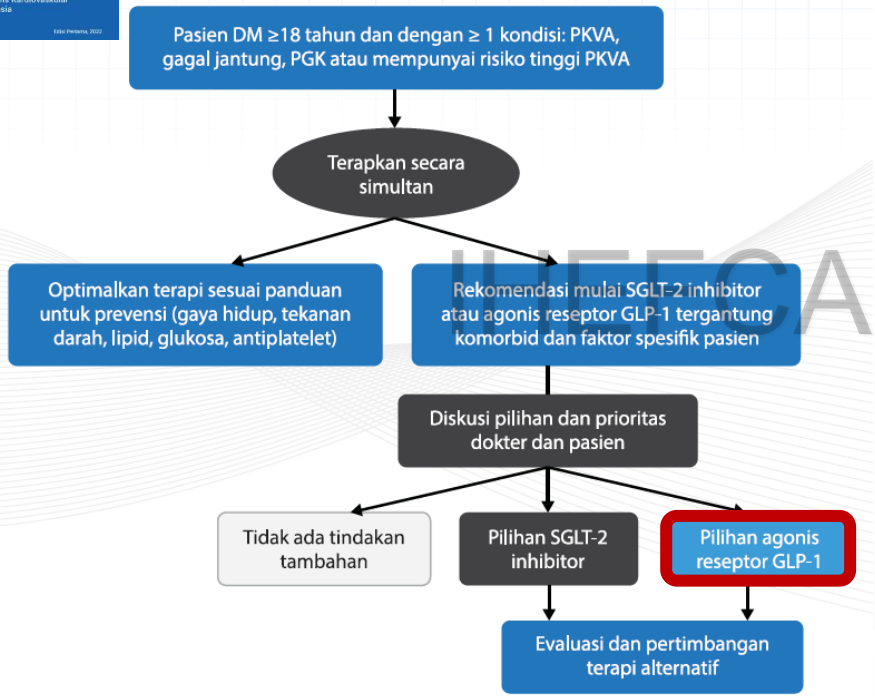


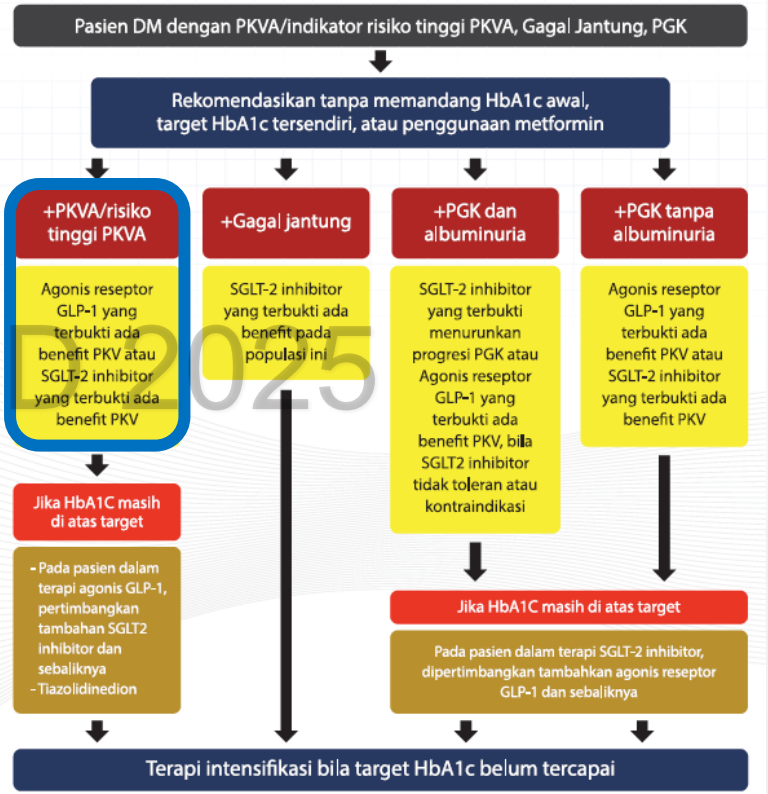
Marx N et al. European Heart Journal. 2023; 00, 1–98 https://doi.org/10.1093/eurheartj/ehad192 .



What PERKI Guideline says

Pendekatan Penurunan Risiko PKVA



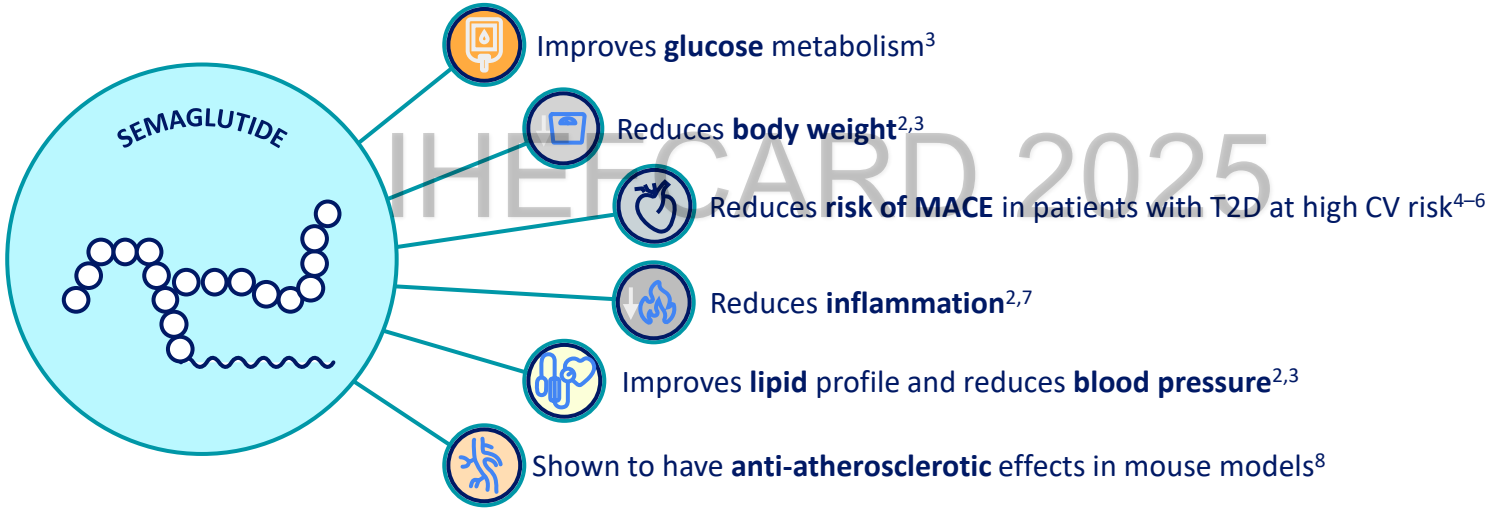


GLP-1, glucagon like peptide 1; SGLT-2, sodium-glucose co-transporter 2; PKVA, penyakit kardiovaskular aterosklerosis; PGK, penyakit ginjal kronis

1. Kelompok Kerja Prevensi dan Rehabilitasi Kardiovaskular dan Perhimpunan Dokter Spesialis Kardiovaskular Indonesia. Panduan Prevensi Penyakit Kardiovaskular Aterosklerosis. 2022

The effects of semaglutide on CV risk factors

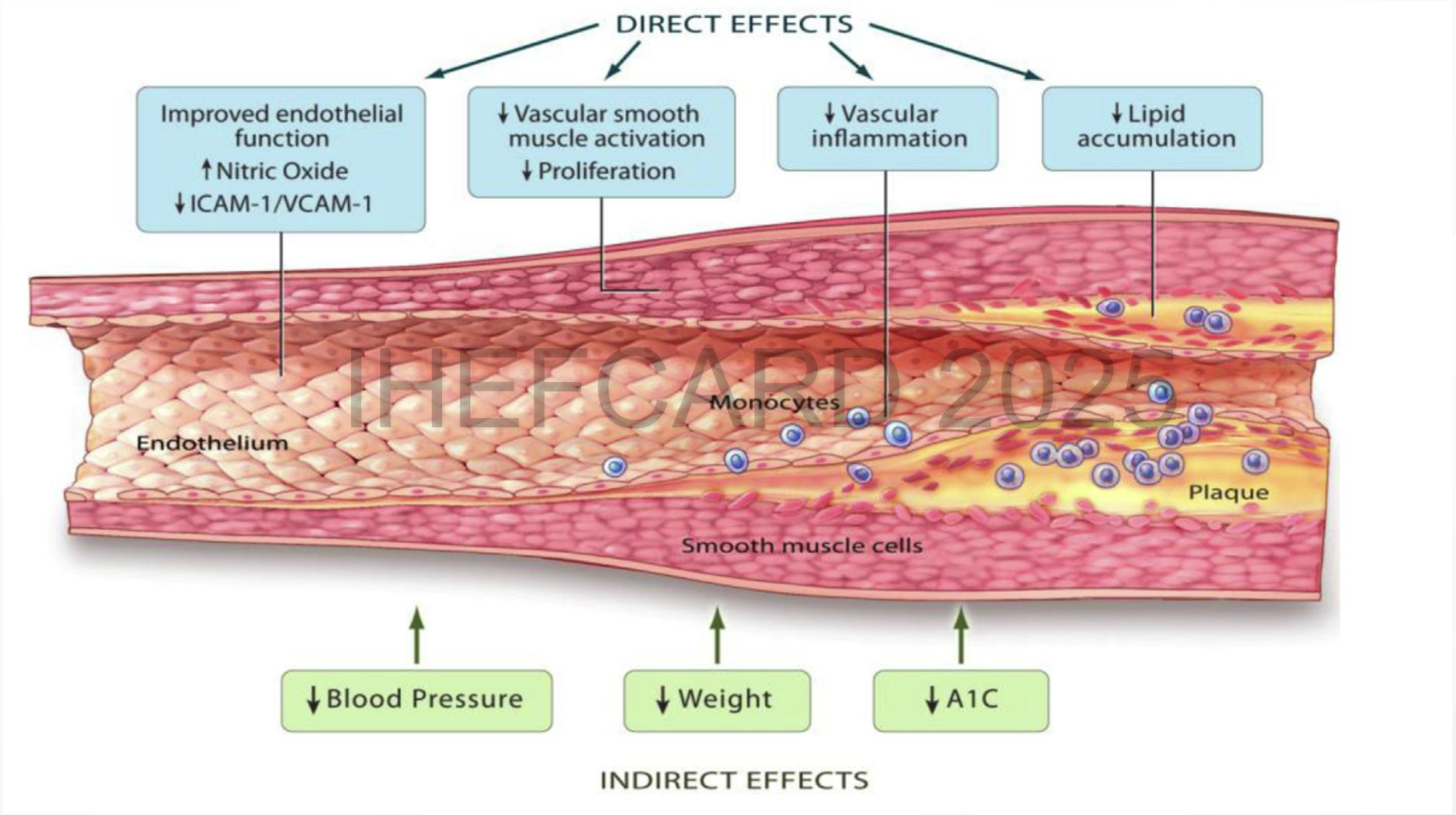
Semaglutide has pleiotropic effects on CV risk factors & reduces MACE risk in T2D[1–8]



CV, cardiovascular; GLP-1RA, GLP-1, glucagon-like peptide-1 receptor agonist; HFpEF, heart failure with preserved ejection fraction; MACE, major adverse cardiovascular events; T2D, type 2 diabetes.

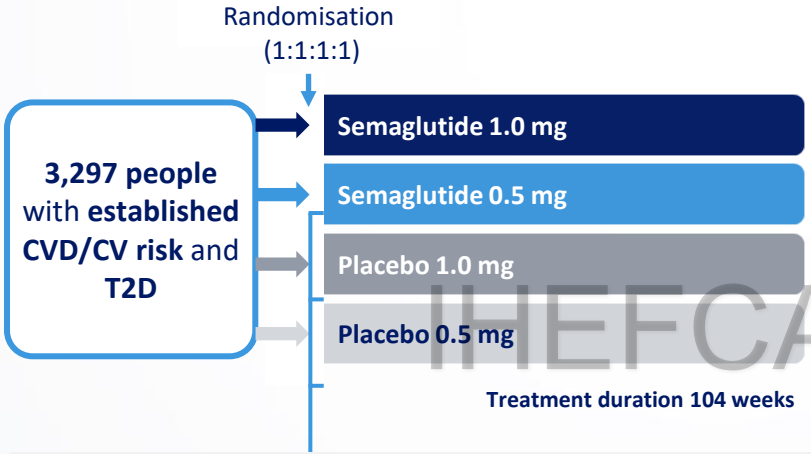
1. Arnett DK, et al. Circulation. 2019;140:e596–e646; 2. Wilding JPH, et al. N Engl J Med. 2021;384:989; 3. Aroda VR, et al. Diabetes Metab. 2019;45:409–418; 4. Marso SP, et al. N Engl J Med. 2016;375:1834–1844; 5. Husain M, et al. N Engl J Med. 2019;381:841–851; 6. Husain M, et al. Diabetes Obes Metab. 2020;22(3):442-451; 7. Knudsen LB, Lau J. Front Endocrinol (Lausanne). 2019;10:155; 8. Rakipovski G, et al. JACC Basic Transl Sci. 2018;3:844–857;.

Mechanisms of GLP-1 RA modify the risk of ASCVD



Sharma A & Verma S. Can J Diabetes 2020; 44:93 - 102

SUSTAIN 6: A 2-year CVOT for semaglutide[1,2]



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Cardiovascular and diabetes standard of care

Primary composite outcome

Time to Major Adverse Cardiovascular Events (MACE), consisting of:

- First occurrence of death from CV causes
- Non-fatal MI
- Non-fatal stroke

Patient breakdown

83%
with established CVD
(age ≥ 50 yr)

17%
with at least 1 CVD
risk factor (age ≥ 60 yr)

98%
on other anti-diabetes
medication (58% insulin)

98%
on cardiovascular
medication

94% on anti-hypertensive
77% on lipid-lowering
76% on anti-thrombotic
38% on diuretics

CVOT=cardiovascular outcomes trial; T2D=type 2 diabetes; CVD=cardiovascular disease; CV=cardiovascular; MI=myocardial infarction.

References: 1. Ozempic® [summary of product characteristics]. Bagsværd, Denmark: Novo Nordisk A/S; July 2018. 2. Marso SP et al. N Engl J Med. 2016;375(19):1834–1844

Baseline characteristics (1/2)

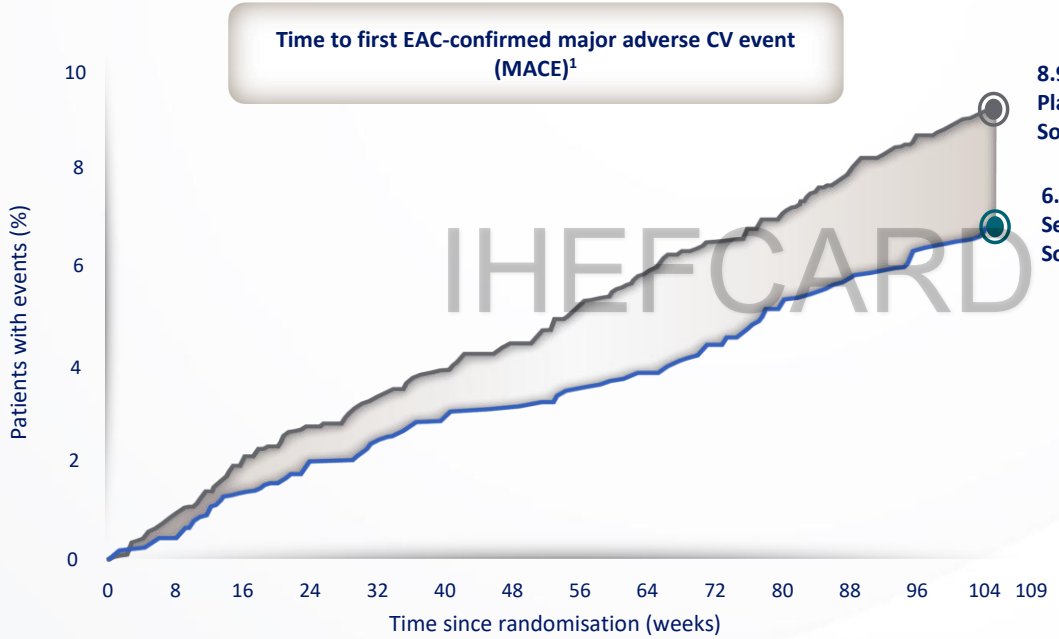
	Semaglutide 0.5 mg Mean (SD)	Semaglutide 1.0 mg Mean (SD)	Placebo 0.5 mg Mean (SD)	Placebo 1.0 mg Mean (SD)	Total Mean (SD)
Age, years	64.6 (7.3)	64.7 (7.1)	64.8 (7.6)	64.4 (7.5)	64.6 (7.4)
Sex, male, n (%)	495 (59.9)	518 (63.0)	482 (58.5)	507 (61.5)	2002 (60.7)
Body weight, kg*	91.8 (20.3)	92.9 (21.1)	91.8 (20.4)	91.9 (20.8)	92.1 (20.6)
T2D, mean (SD)					
Diabetes duration, years	14.3 (8.2)	14.1 (8.2)	14.0 (8.5)	13.2 (7.4)	13.9 (8.1)
HbA_{1c}, %	8.7 (1.4)	8.7 (1.5)	8.7 (1.5)	8.7 (1.5)	8.7 (1.5)
Cardiovascular risk factors					
Systolic blood pressure, mmHg*	136.1 (18.0)	135.8 (17.0)	135.8 (16.2)	134.8 (17.5)	135.6 (17.2)
Diastolic blood pressure, mmHg*	77.1 (9.8)	76.9 (10.2)	77.5 (9.9)	76.7 (10.2)	77.0 (10.0)
LDL cholesterol, mg/dL†	81.6 (47.1)	83.3 (41.2)	80.9 (48.1)	83.6 (45.9)	82.3 (45.6)
Never smoked‡	390 (47.2)	364 (44.3)	391 (47.5)	348 (42.2)	1493 (45.3)

*Means and standard deviations. †Geometric means and coefficients of variation. ‡Number of subjects (N) and percentage (%)
LDL, low-density lipoprotein; SD, standard deviation
Marso SP et al. *N Engl J Med* 2016;375:1834–44

Baseline characteristics (2/2)

	Semaglutide 0.5 mg N (%)	Semaglutide 1.0 mg N (%)	Placebo 0.5 mg N (%)	Placebo 1.0 mg N (%)	Total N (%)
History of cardiovascular disease					
Ischaemic heart disease	493 (59.7)	495 (60.2)	510 (61.9)	496 (60.1)	1994 (60.5)
Myocardial infarction	266 (32.2)	264 (32.1)	267 (32.4)	275 (33.3)	1072 (32.5)
Heart failure	201 (24.3)	180 (21.9)	190 (23.1)	206 (25.0)	777 (23.6)
Ischaemic stroke	89 (10.8)	89 (10.8)	96 (11.7)	109 (13.2)	383 (11.6)
Haemorrhagic stroke	28 (3.4)	24 (2.9)	27 (3.3)	29 (3.5)	108 (3.3)
Hypertension	772 (93.5)	771 (93.8)	756 (91.7)	760 (92.1)	3059 (92.8)

Semaglutide reduced CV events within 2 years



In people with established CVD /CV risk and T2D*

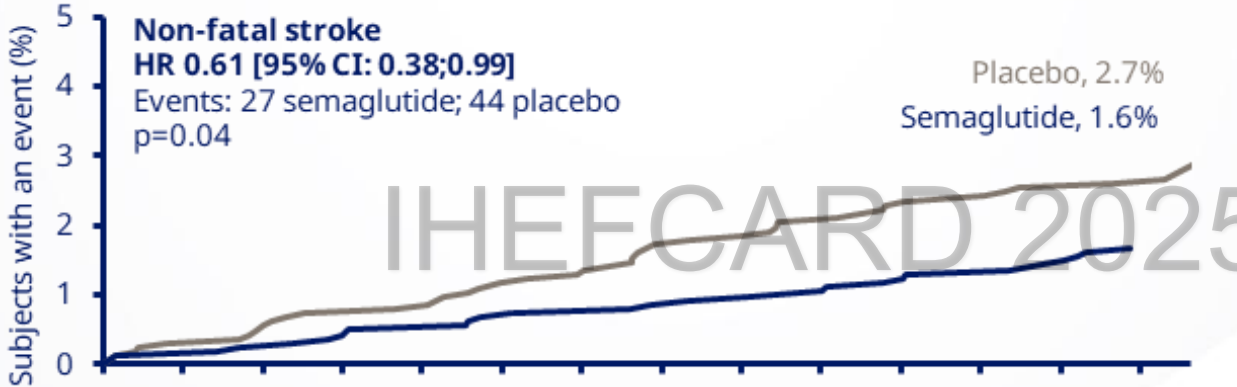
26%

CV risk reduction
(primary MACE endpoint)†

HR 0.74 [95% CI: 0.58;0.95]
p<0.001 for non-inferiority
p=0.02 for superiority*

N=3297 ; *Semaglutide reduced the risk of CV events by 26% beyond standard of care compared with placebo in **patients with T2D at high CV risk**; †MACE: Composite endpoint comprising the first occurrence of CV death, non-fatal myocardial infarction or non-fatal stroke using 'in-trial' data from subjects in the full analysis set. Hazard ratio is from a stratified proportional hazards model; ‡patients aged 55 years or older with coronary, carotid or lower extremity artery stenosis >50%, left ventricular hypertrophy, an eGFR <60 ml min^{-1} [1.73 $m]^{-2}$ or albuminuria; CI, confidence interval; CV, cardiovascular; EAC, event adjudication committee; MACE, major adverse cardiovascular event; SoC, standard of care; T2D, type 2 diabetes; 1. Marso SP et al. *N Engl J Med* 2016;375:1834–1844

Semaglutide reduces the incidence of stroke⁺



No. at risk								
Semaglutide	1,648	1,630	1,619	1,606	1,593	1,572	1,558	1,558
Placebo	1,649	1,629	1,611	1,597	1,571	1,548	1,528	1,521

In people with established CVD /CV risk and T2D*

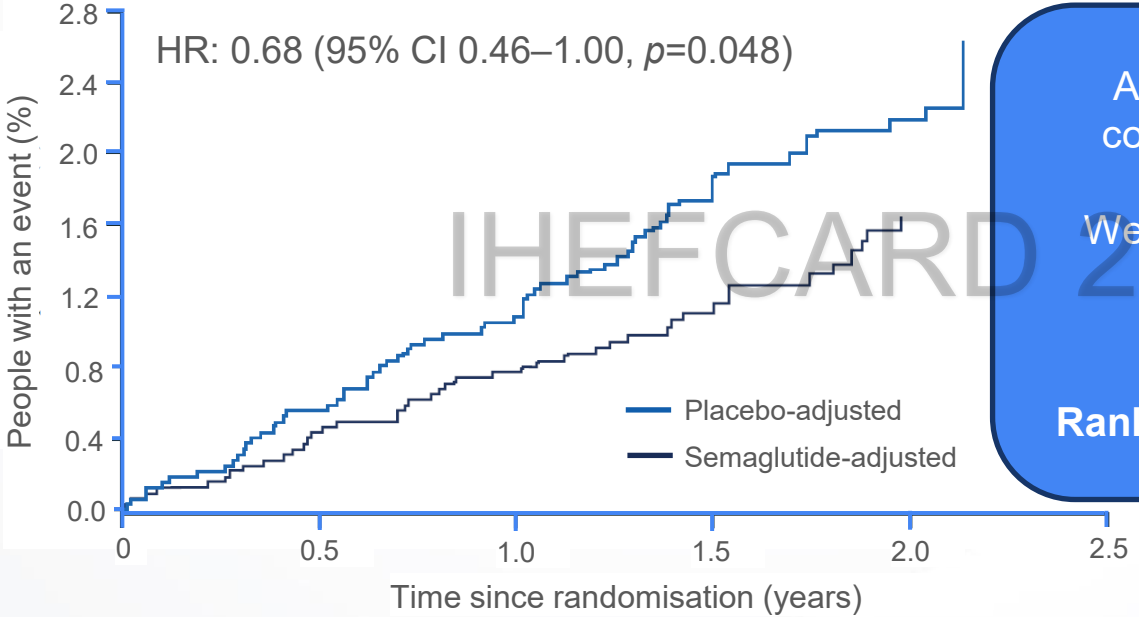
39%

reduction in stroke⁺ incidence

HR 0.61 [95% CI: 0.38;0.99]
p=0.04

N=3297 ; *Semaglutide reduced the risk of non-fatal stroke by 39% beyond standard of care compared with placebo in **patients with T2D at high CV risk**;. ⁺non-fatal stroke; Hazard ratio is from a stratified proportional hazards model; ‡patients aged 55 years or older with coronary, carotid or lower extremity artery stenosis >50%, left ventricular hypertrophy, an eGFR <60 ml min^{-1} [1.73 m]$^{-2}$ or albuminuria; CI, confidence interval; CV, cardiovascular; EAC, event adjudication committee; MACE, major adverse cardiovascular event; SoC, standard of care; T2D, type 2 diabetes; 1. Marso SP et al. *N Engl J Med* 2016;375:1834–1844

Aalen-Johansen plots for time to first occurrence of any stroke with the pooled semaglutide vs placebo



A network meta-analysis indirectly comparing GLP-1 RAs showed that

Weekly Administration of Semaglutide

had the highest probability to:

Rank First in reducing stroke and MI[2†]

Adapted from Figure 1. Semaglutide: N_{events}=43; placebo: N_{events}=63. Aalen-Johansen plots for time to first occurrence of any stroke* with the pooled semaglutide vs placebo in people with T2D at high CV risk, based on pooled data from the SUSTAIN 6 and PIONEER 6 trials. *Included fatal and nonfatal strokes. The cumulative incidence rates for time to first stroke were calculated using Aalen-Johansen method, adjusting for all-cause death as a competing risk. The hazard ratio was estimated from a Cox regression model stratified by trial with treatment (pooled semaglutide vs placebo) as a factor

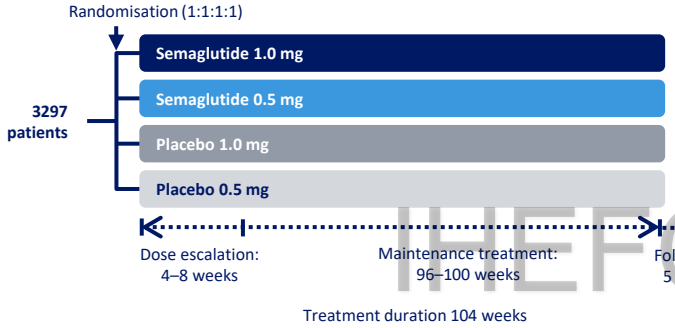
CI, confidence interval; CV, cardiovascular; HR, hazard ratio; T2D, type 2 diabetes

Strain et al. Stroke 2022; doi: 10.1161/STROKEAHA.121.037775 2. Alfayez, O.M., et al, Cardiovascular Diabetology, 2020. 19(1), pp.1-14

† Results are from a network meta-analysis that indirectly compared the CV safety and mortality effects among different GLP-1 RAs in patients with T2D. A total of 7 GLP-1 RA CVOTs were included where each compared the CV safety of a GLP-1 RA (lixisenatide, liraglutide, semaglutide s.c., exenatide, albiglutide, dulaglutide and semaglutide oral) to placebo, both as an added on therapy to the SOC (N=56004).

Semaglutide shows positive effect on a composite endpoint assessing “new or worsening nephropathy”

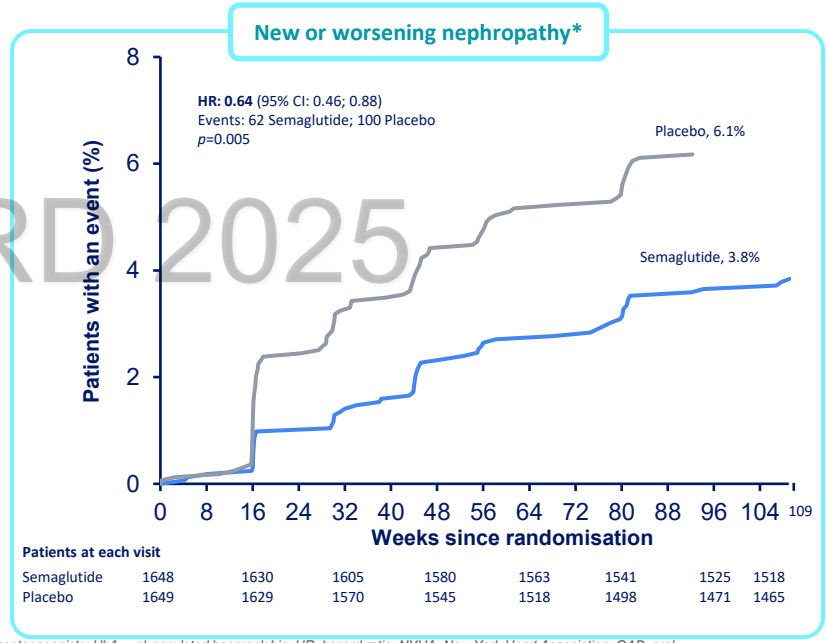
SUSTAIN 6: nephropathy composite



Trial information
- Randomised, double-blind, placebo-controlled, parallel-group
- Multi-national

Primary objective
- To evaluate CV and other long-term outcomes with semaglutide in subjects with T2D

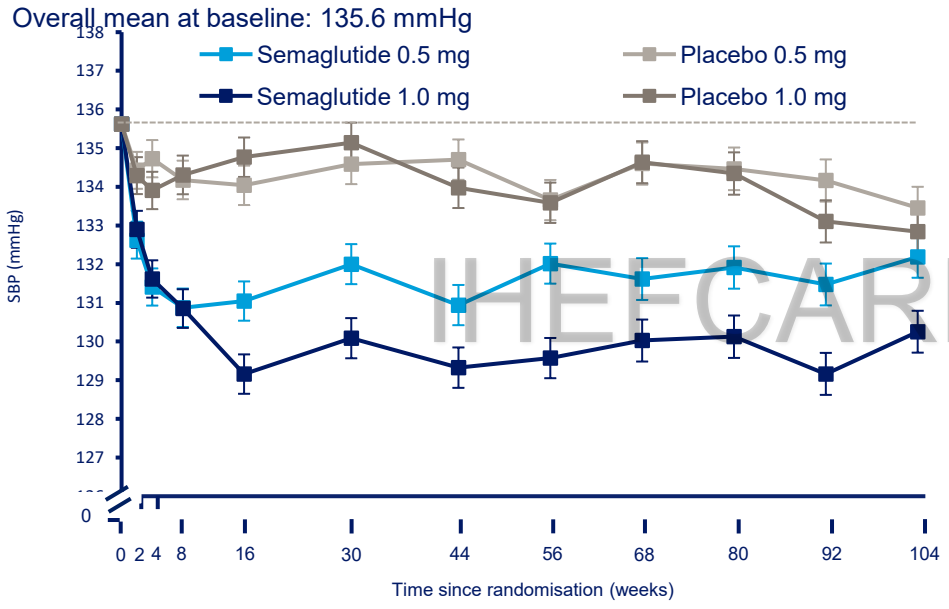
Composite renal outcome
- Persistent macroalbuminuria
- Persistent doubling of serum creatinine and creatinine clearance ≤45 mL/min/1.73 m^2
- Need for continuous renal-replacement therapy (ESRD)

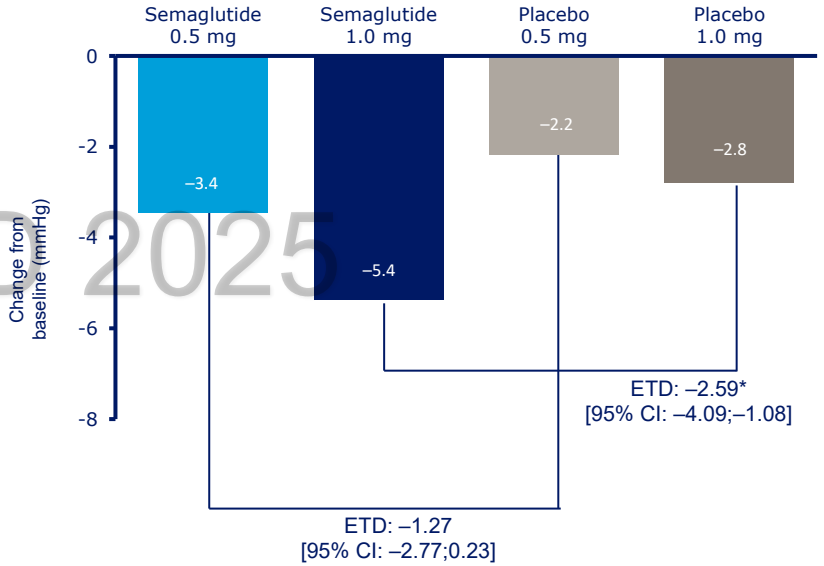


*Investigator-determined

CKD, chronic kidney disease; CV, cardiovascular; CVD, cardiovascular disease; DPP-4, dipeptidyl peptidase-4; GLP-1 RAs, glucagon-like peptide-1 receptor agonists; HbA_{1c}, glycosylated haemoglobin; HR, hazard ratio; NYHA, New York Heart Association; OAD, oral antidiabetic drug; T2D, type 2 diabetes

Marso SP et al. N Engl J Med 2016; 375(19):1834–1844



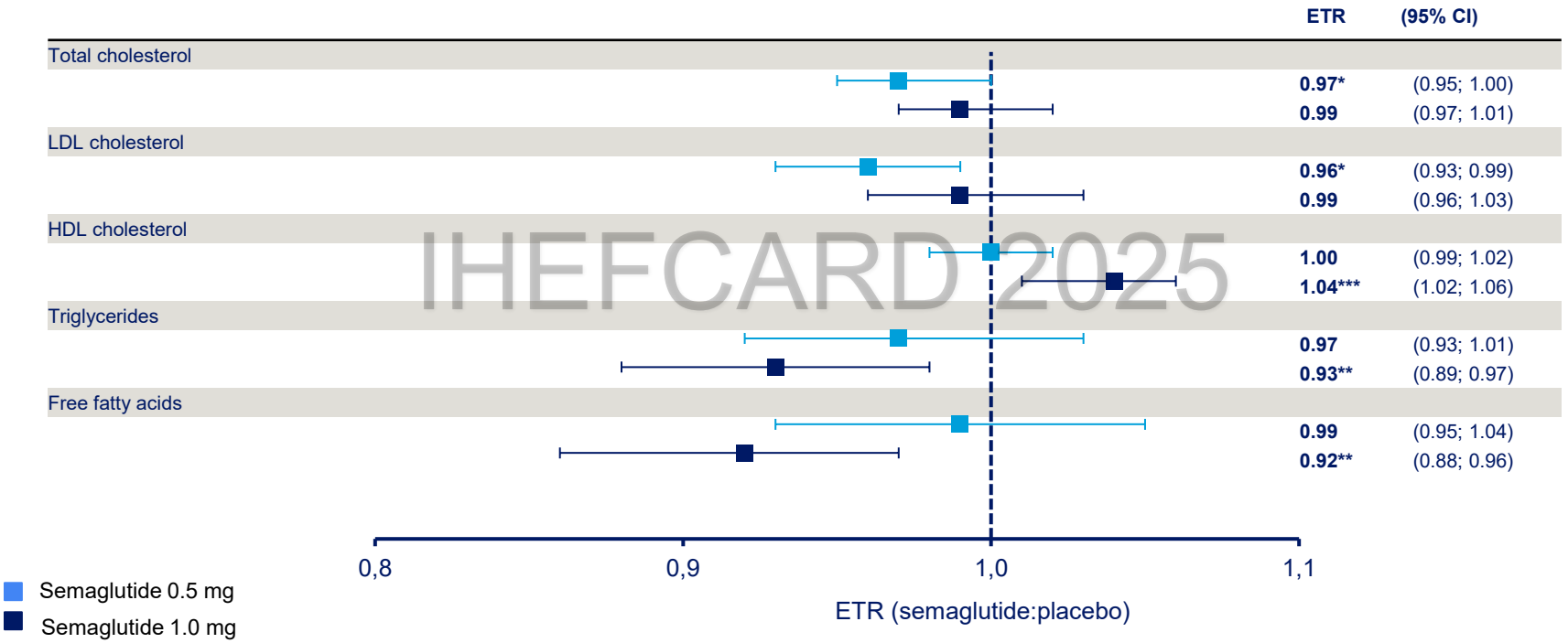


Semaglutide treated patients had a significantly lower Mean SBP compared to placebo over 2 years, this could have contributed to the observed reduction in cardiovascular risk by semaglutide.

*Data are estimated mean ± standard error of the mean. *p<0.0001.*
BP, blood pressure; CI, confidence interval; ETD, estimated treatment difference; SBP, systolic blood pressure.
Marso SP et al. N Engl J Med 2016;375:1834–44.

Lipids

RATIO TO BASELINE



Supplementary Table 10. Data are ETRs to baseline, and treatment ratios with CI, based on in-trial data for scheduled visits for the full analysis set. Each parameter was analysed by a mixed model for repeated measures with treatment group (semaglutide 0.5 and 1.0 mg and corresponding placebo doses) and stratification (9 levels) as fixed factors and the corresponding baseline value of the parameter as a covariate, all nested within visit. Lipid parameters were analysed on log-scale. CI, confidence interval; ETR, estimated treatment ratio; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol. *P<0.05; **P<0.001; ***P<0.0001.

Take Home Messages

- Cardiovascular disease still become main problem in Indonesia and another parts of the world, and diabetes responsible for more of it
- Up to 1/3 of people with established CVD have T2D & People with Type 2 Diabetes are 2-4 times more likely to experience ASCVD events (e.g. heart attack and stroke)
- Cardiovascular disease and diabetes → share the same soils of risk factor and contributes to vascular damage
- Lowering risk of CVD in diabetes patient is the most important thing to do to cut the risk of cardiovascular continuum
- In people with ASCVD and Type 2 Diabetes comorbidity, ESC 2023, ADA 2025 and PERKI Guideline 2022 recommends adding GLP-1 RA/SGLT-2i with proven CV benefits, like Semaglutide, for people with ASCVD and T2D
- The recommendation of adding GLP-1 RA/SGLT-2i with proven CV benefits is to reduce CV risk, independent of glucose control in ASCVD patients with T2D

Matur Suwun