The 3rd Indonesia Symposium on Heart Failure and Cardiometabolic Disease 2023

How to Apply the Latest Recommendations: Advancing Management of Type 2 Diabetes in Heart Failure

Ketut Suastika

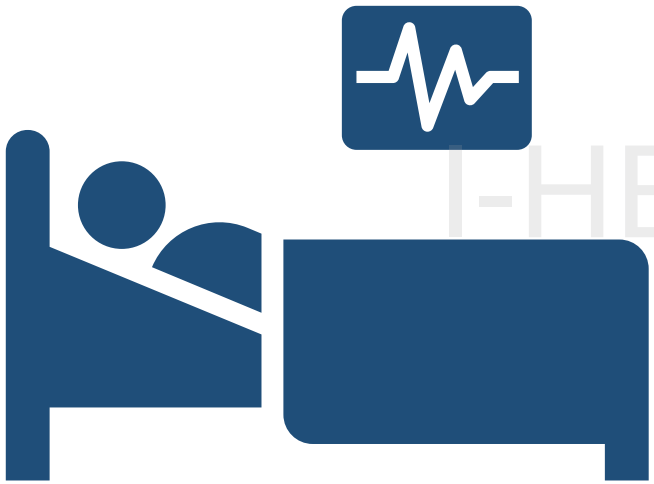
FK Unud-RSUP Prof. IGNG Ngoerah, Denpasar

Disclosures

I have received honorarium as speaker at educational meetings from:

- PT Kalventis Sinergi Farma

Case



- Men, 56 y.
- ICCU due to HFrEF (LVEF Biplane 30%)
- T2DM for 9 y.
- BP: 110/70 mmHg
- Random PG: 290 mg/dL
- HbA1c: 8.9%
- eGFR 50
- Last medications:
  - Metformin 2x500 and Glimepiride 4 mg per day
  - Ramipril 1x5 mg, bisoprolol 1x5 mg, spironolactone 1x50 mg

Polling

1. What is your suggestion to this patient diabetes therapy?
   A. Increased the dose of existing oral anti-diabetics
   B. Stop glimepiride, continued metformin + insulin basal-bolus
   C. Stop glimepiride and metformin, replaced by insulin iv drip
   D. Stop glimepiride and metformin, replaced by SGLT2i + insulin basal-bolus
   E. Continued oral anti-diabetics+ SGLT2 + insulin iv drip
2. To your knowledge, what drug is contraindicated for patient with HF?
   A. SUs
   B. Metformin
   C. TZD
   D. DPP4i
   E. SGLT2i
3. To your knowledge, what drug is chosen for patient with both HFpEF and HFrEF?
   A. SUs
   B. Metformin
   C. DPP4i
   D. SGLT2i
   E. GPL1 RA

Diabetes and Heart Failure

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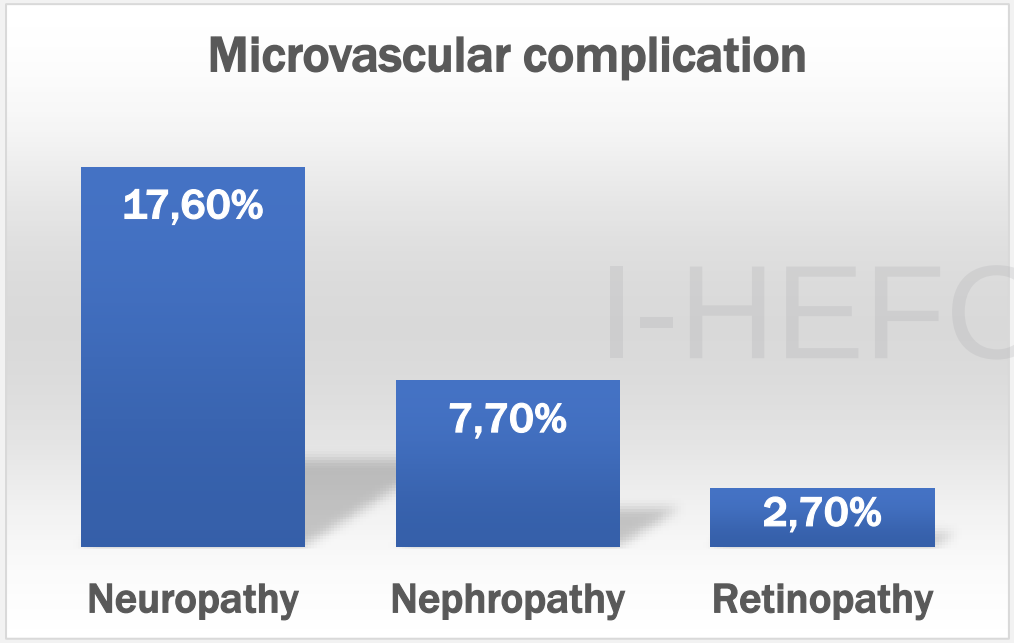
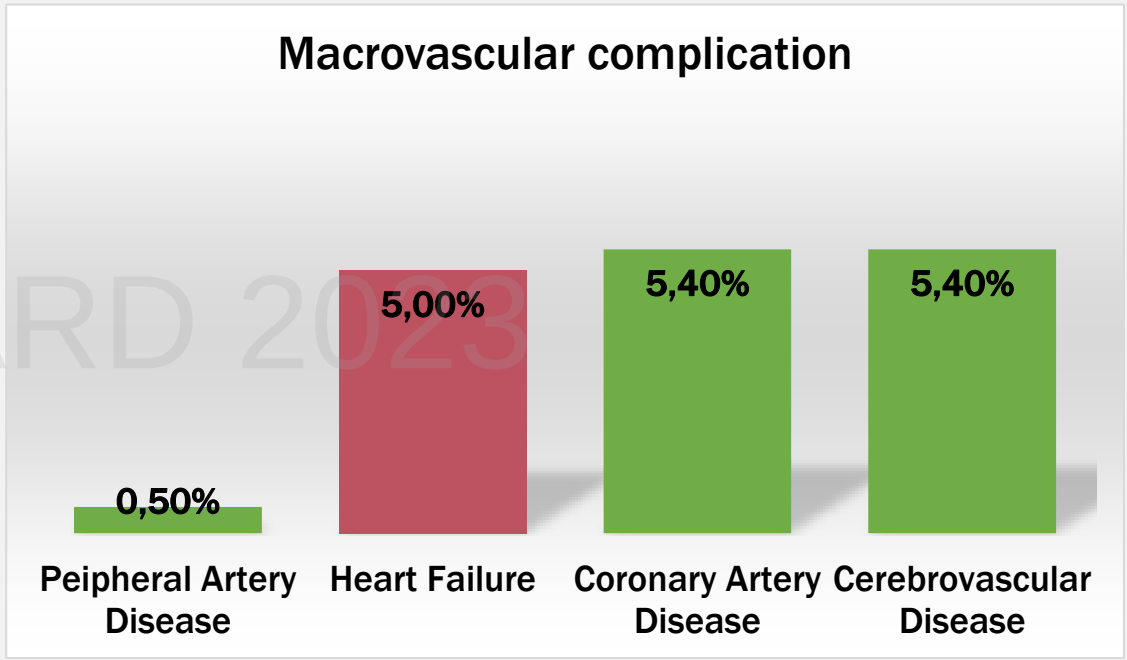
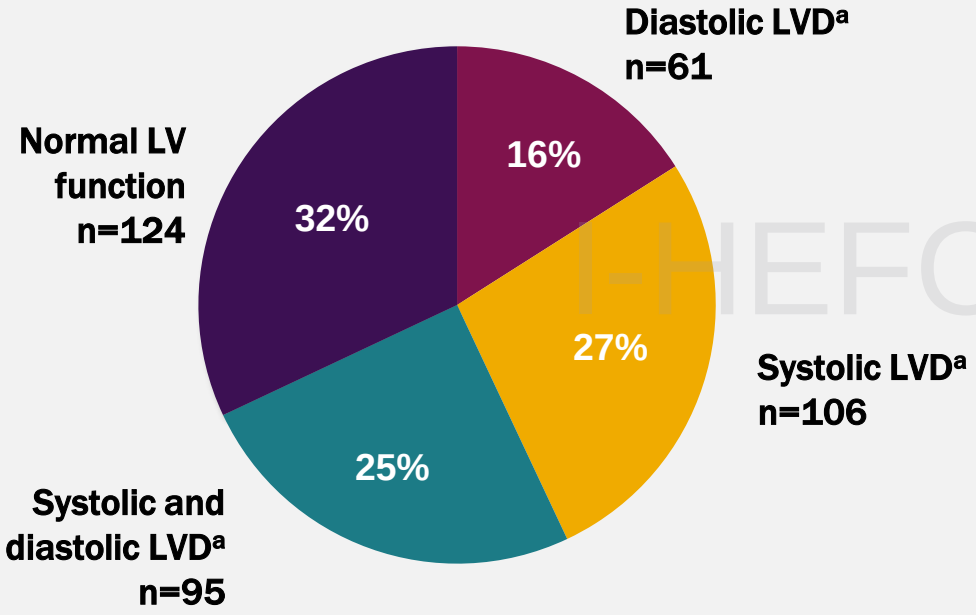
Micro and macrovascular complication remains high in T2D Indonesia patients (IDF 2019)





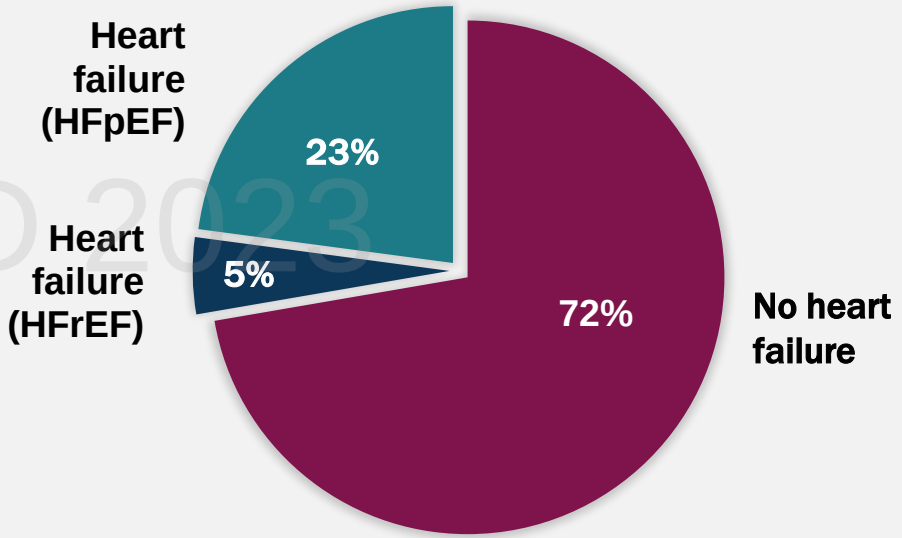
International Diabetes Federation, *IDF Diabetes Atlas*, 9th ed. 2019.

HF and LV dysfunction are early and often undetected complications of T2D



Patients had no evidence of inducible ischemia

Undiagnosed HF was detected in 28% of patients[b] with diabetes (N=581) during cardiac screening[2]

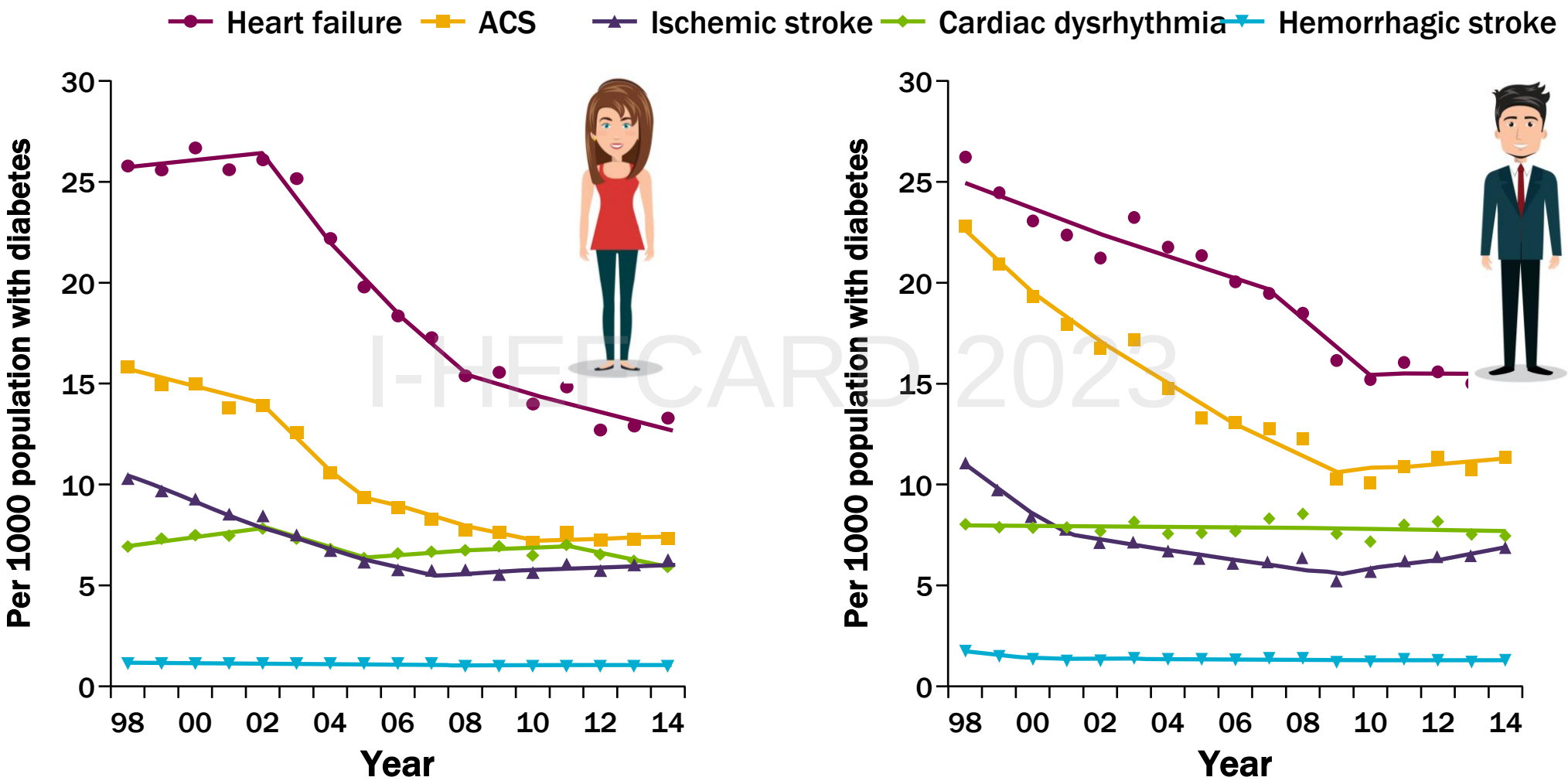


HF is an early and forgotten complication in T2D patients[1,2]

[a] Asymptomatic; [b]Western European cohort ≥60 years of age.
HF = heart failure; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; LV = left ventricular; LVD = left ventricular dysfunction; T2D = type 2 diabetes.
1. Faden G et al. *Diabetes Res Clin Pract*. 2013;101:309-316; 2. Boonman-de Winter LJ et al. *Diabetologia*. 2012;55:2154-2162.

Name

HF is the most common cause of hospitalization in T2D



ACS, acute coronary syndrome; hHF, hospitalized heart failure; T2D, Type 2 diabetes
Burrows NR, et al. *Diabetes Care* 2018;41:293–302

Diabetes and Heart Failure

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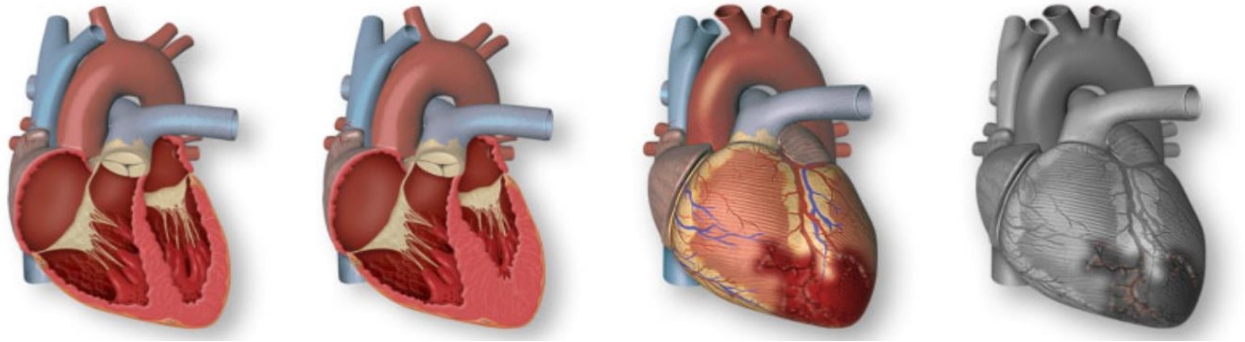
The different stages of diabetic cardiomyopathy

- Mitochondrial dysfunction
- Insulin resistance
- Impaired insulin signaling
- Hyperglycemia
- ROS generation
- Inflammation
- Fibrosis
- Hypertrophy
- Dyslipidemia
- Pertrbed Ca^{2+} handling
- Contractile protein dysfunction
- Autophagy
- Lipotoxicity
- Glucotoxicity
- Cell death
- O-GlcNAcylation
- AGEs
- Neurohormonal mechanisms
- Ischemia
- Hypertension
- Renal failure
- Microangiopathy
- Coronary artery disease
- Macroangiopathy



HFpEF | HFrEF | Severe HF | Death

Progression of diabetes

Early stage | Mild stage | Late stage | Final stage

Karwi QG et al. Cardiovascular Research (2022) 118, 686–715

Diabetes and Heart Failure

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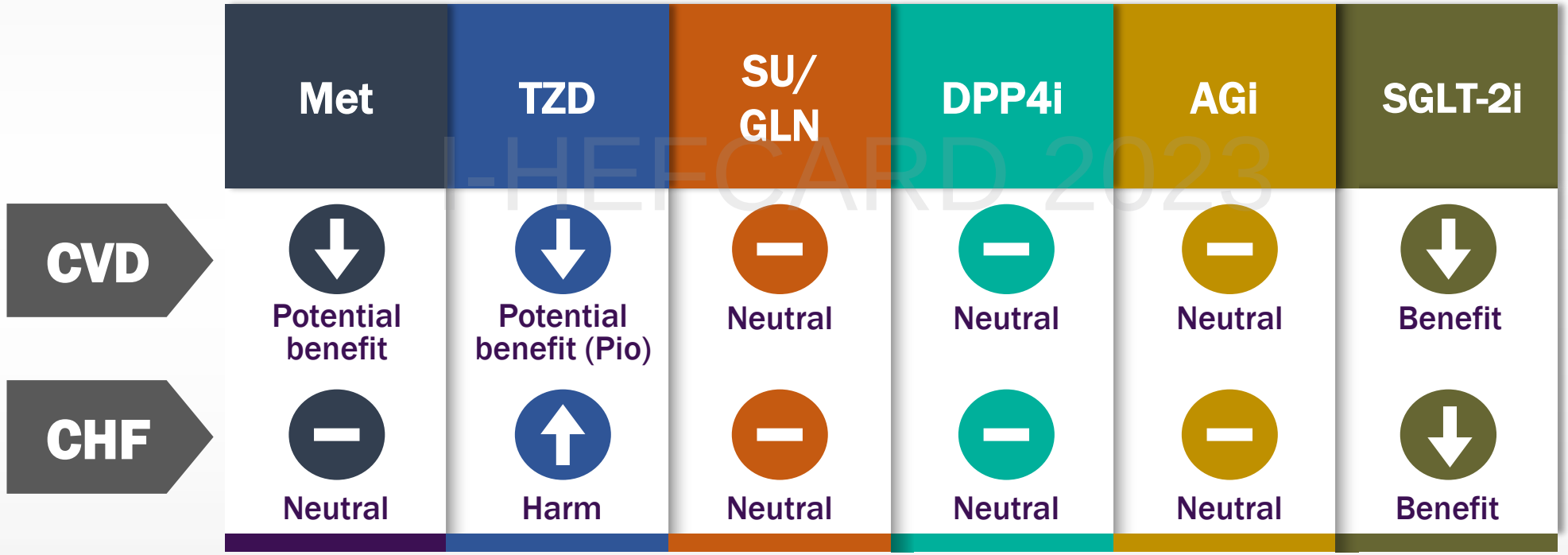
SGLT-2 inhibitors are the only oral GLDs that have demonstrated CVD risk reduction in patients with T2DM

Effect of oral GLDs on CV risk in patients with T2DM



AGi, alpha-glucosidase inhibitor; CVD, cardiovascular disease; CHF, congestive heart failure; DPP4i, dipeptidyl peptidase 4 inhibitor; Met, metformin; GLN, glinides; SGLT-2i, sodium glucose cotransporter-2 inhibitor; SU, sulfonylurea; TZD, thiazolidinedione; GLP-RA, Glucagon-like peptide 1 receptor agonists

1. Garvey WT et al. Endocr Pract 2016;22 Suppl 3:1–203; 2. American Diabetes Association. Diabetes care. 2017;40(Suppl 1):S1–S135

CV Outcomes in SGLT-2 Inhibitors CVOTs

	3P-MACE	CV Death	HHF	All-cause mortality	Renal Endpoints
EMPA-REG Outcome (Empagliflozin)	14% HR 0.86 (0.74-0.99)	38% HR 0.62 (0.49-0.77)	35% HR 0.65 (0.50-0.85)	32% HR 0.68 (0.57-0.82)	39% HR 0.61 (0.53-0.70)
CANVAS Program (Canagliflozin)	14% HR 0.86 (0.75-0.97)	13% HR 0.87 (0.72-1.06)	33% HR 0.67 (0.52-0.87)	13% HR 0.87 (0.74-1.01)	40% HR 0.60 (0.47-0.77)
DECLARE-TIMI 58 (Dapagliflozin)	7% HR 0.93 (0.84-1.03)	2% HR 0.98 (0.82-1.17)	27% HR 0.73 (0.61-0.88)	7% HR 0.93 (0.82-1.04)	47% HR 0.53 (0.43-0.66)
VERTIS CV (Ertugliflozin)	3% HR 0.97 (0.85-1.11)	8% HR 0.92 (0.77-1.11)	30% HR 0.70 (0.54-0.90)	7% HR 0.93 (0.80-1.08)	19% HR 0.81 (0.63-1.04)

Superior Non-inferior

Empagliflozin is indicated in adult patients with type 2 diabetes mellitus to improve glycemic control, when metformin used alone does not provide adequate glycemic control, in combination with: Metformin, Metformin and a sulfonylurea, Metformin and pioglitazone. When the existing therapy, along with diet and exercise, does not provide adequate glycemic control. For study results with respect to combination, effects on glycemic control and cardiovascular events, and the populations studied, see sections Special warnings and precautions for use, Interaction with other medicinal products and other forms of interactions, and Pharmacodynamics properties. CV, cardiovascular; HHF, hospitalization for heart failure; MACE, major adverse cardiovascular events.

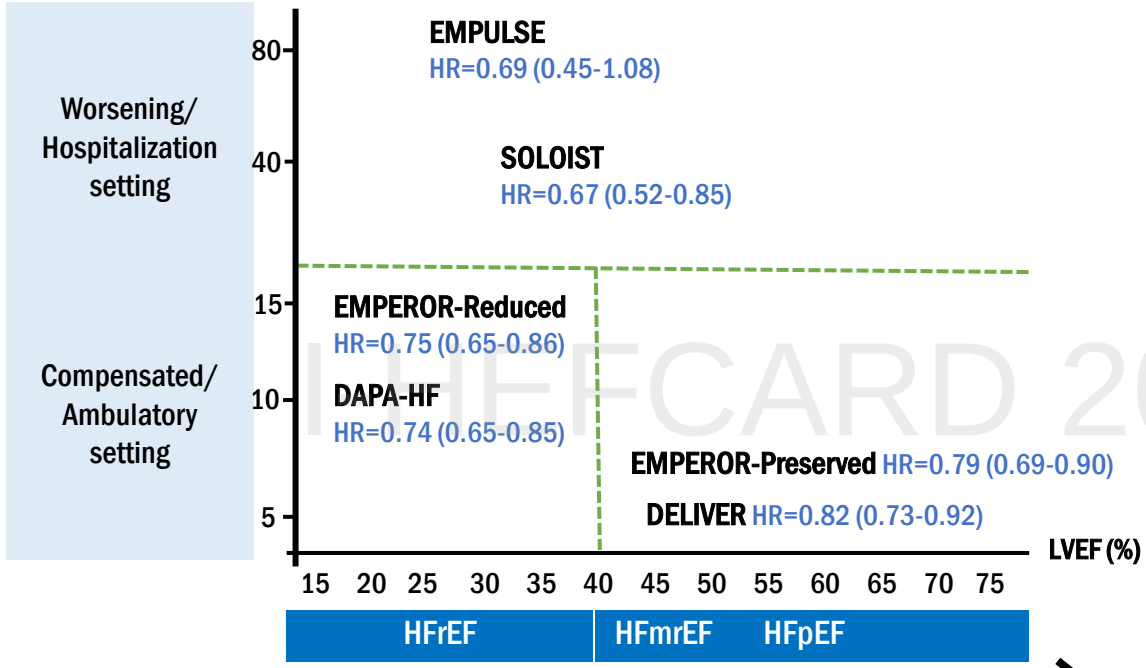
1. Zinman B *et al. N Engl J Med* 2015;373:2117 (supplemental appendix); 2. Wiviott S *et al. N Engl J Med* 2018;DOI: 10.1056/NEJMoa1812389; 3. Neal B *et al. N Engl J Med* 2017;377:644 (supplementary appendix); 4. Cannon CP et al. N Engl J Med 2020;383:1425-35

Integrative representation of available evidence in heart failure (HF) according to patients' left ventricle ejection fraction and level of risk and profiles supporting its use.

Girerd and Zannad. J Intern Med 2023; **293**:550–558.

Homogeneous effect of SGLT2i across the spectrum of heart failure severity and ejection fraction

Effect of SGLT2i on CV death and HF hospitalization



Good safety profile of SGLT2i in heart failure

Ketoacidosis
HR=0.90 (0.30-2.77)

Amputations
HR=1.00 (0.66-1.55)

Genital infection
HR=2.97 (2.02-4.36)/absoulute risk <2%

Acute kidney injury
HR=0.81 (0.58-1.12)

Younes, IJC, 2022

Effect of SGLT2i across the spectrum of heart failure profile

Disregarding of

Type 2 diabetic status
Ref. DAPA-HF. McMurray NEJM 2019; EMPEROR-Reduced, Packer NEJM 2020; EMPEROR-Preserved, Anker NEJM 2021; DELIVER, Solomon NEJM 2022

Baseline eGFR
(exclusion criteria eGFR <20 ml/min in Empagliflozin trials and <30 ml/min in Dapagliflozin trials)
Ref. DAPA-HF. McMurray NEJM 2019; EMPEROR-Reduced, Packer NEJM 2020; EMPEROR-Preserved, Anker NEJM 2021; DELIVER, Solomon NEJM 2022; DAPA-HF, Jhund Cisrculation 2021

Baseline blood presuure
(exclusion criteria <100 mmHg in Empagliflozin trials and <95 mmHg in Dapagliflozin trials)
Ref. DAPA-HF. Serenelli EHJ 2020; EMPEROR-Reduced, Bohm JACC 2021

Baseline atrial fibrillation
Ref. DELIVER, Butt JACC 2020

Baseline heart rate
Ref. EMPEROR-Preserved, Bohm EJHF 2022

All heart failure patients are eligible for SGLT2i therapy

Exception: Type 1 diabetes
Gaps in evidence: Pregnancy and end stage renal diasease

Acute HF Setting

ESC European Society of Cardiology
European Journal of Heart Failure (2020) 22, 713–722
doi:10.1002/ejhf.1713

RESEARCH ARTICLE

Randomized, double-blind, placebo-controlled, multicentre pilot study on the effects of empagliflozin on clinical outcomes in patients with acute decompensated heart failure (EMPA-RESPONSE-AHF)

Kevin Damman[1], Joost C. Beusekamp[1], Eva M. Boorsma[1], Henk P. Swart[2], Tom D.J. Smilde[3], Arif Elvan[4], J.W. Martijn van Eck[5], Hiddo J.L. Heerspink[1,6], and Adriaan A. Voors[1]*

[1]University of Groningen, University Medical Center Groningen, Groningen, The Netherlands; [2]Antonius Ziekenhuis Sneek, Sneek, The Netherlands; [3]TREANT zorggroep, Emmen, The Netherlands; [4]Department of Cardiology, ISALA, Zwolle, The Netherlands; [5]Jeroen Bosch Ziekenhuis, Den Bosch, The Netherlands; and [6]The George Institute for Global Health, Sydney, Australia

Received 6 November 2019; revised 19 November 2019; accepted 22 November 2019; online publish-ahead-of-print 7 January 2020

Aims Inhibition of sodium–glucose co-transporter 2 (SGLT2) reduces the risk of death and heart failure (HF) admissions in patients with chronic HF. However, safety and clinical efficacy of SGLT2 inhibitors in patients with acute decompensated HF are unknown.

Methods and results In this randomized, placebo-controlled, double-blind, parallel group, multicentre pilot study, we randomized 80 acute HF patients with and without diabetes to either empagliflozin 10 mg/day or placebo for 30 days. The primary outcomes were change in visual analogue scale (VAS) dyspnoea score, diuretic response (weight change per 40 mg furosemide), change in N-terminal pro brain natriuretic peptide (NT-proBNP), and length of stay. Secondary outcomes included safety and clinical endpoints. Mean age was 76 years, 33% were female, 47% had *de novo* HF and median NT-proBNP was 5236 pg/mL. No difference was observed in VAS dyspnoea score, diuretic response, length of stay, or change in NT-proBNP between empagliflozin and placebo. Empagliflozin reduced a combined endpoint of in-hospital worsening HF, rehospitalization for HF or death at 60 days compared with placebo [4 (10%) vs. 13 (33%); $P = 0.014$]. Urinary output up until day 4 was significantly greater with empagliflozin vs. placebo [difference 3449 (95% confidence interval 578–6321) mL; $P < 0.01$]. Empagliflozin was safe, well tolerated, and had no adverse effects on blood pressure or renal function.

Conclusions In patients with acute HF, treatment with empagliflozin had no effect on change in VAS dyspnoea, diuretic response, NT-proBNP, and length of hospital stay, but was safe, increased urinary output and reduced a combined endpoint of worsening HF, rehospitalization for HF or death at 60 days.

Keywords Acute heart failure • Empagliflozin • Sodium–glucose co-transporter 2 • Hospital readmission • Dyspnoea • Diuresis • Renal function • Blood pressure

In patients with acute HF, treatment with empagliflozin had no effect on change in VAS dyspnoea, diuretic response, NT-proBNP, and length of hospital stay, but was safe, increased urinary output and reduced a combined endpoint of worsening HF, rehospitalization for HF or death at 60 days.

Sotagliflozin in Patients with Diabetes and Recent Worsening Heart Failure

D.L. Bhatt, M. Szarek, P.G. Steg, C.P. Cannon, L.A. Leiter, D.K. McGuire, J.B. Lewis, M.C. Riddle, A.A. Voors, M. Metra, L.H. Lund, M. Komajda, J.M. Testani, C.S. Wilcox, P. Ponikowski, R.D. Lopes, S. Verma, P. Lapuerta, and B. Pitt, for the SOLOIST-WHF Trial Investigators*

ABSTRACT

BACKGROUND
Sodium–glucose cotransporter 2 (SGLT2) inhibitors reduce the risk of hospitalization for heart failure or death from cardiovascular causes among patients with stable heart failure. However, the safety and efficacy of SGLT2 inhibitors when initiated soon after an episode of decompensated heart failure are unknown.

METHODS
We performed a multicenter, double-blind trial in which patients with type 2 diabetes mellitus who were recently hospitalized for worsening heart failure were randomly assigned to receive sotagliflozin or placebo. The primary end point was the total number of deaths from cardiovascular causes and hospitalizations and urgent visits for heart failure (first and subsequent events). The trial ended early because of loss of funding from the sponsor.

RESULTS
A total of 1222 patients underwent randomization (608 to the sotagliflozin group and 614 to the placebo group) and were followed for a median of 9.0 months; the first dose of sotagliflozin or placebo was administered before discharge in 48.8% and a median of 2 days after discharge in 51.2%. Among these patients, 600 primary end-point events occurred (245 in the sotagliflozin group and 355 in the placebo group). The rate (the number of events per 100 patient-years) of primary

In patients with diabetes and recent worsening heart failure, sotagliflozin therapy, initiated before or shortly after discharge, resulted in a significantly lower total number of deaths from cardiovascular causes and hospitalizations and urgent visits for heart failure than placebo.

ARTICLES
https://doi.org/10.1038/s41591-021-01659-1
nature medicine
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OPEN

The SGLT2 inhibitor empagliflozin in patients hospitalized for acute heart failure: a multinational randomized trial

Adriaan A. Voors[1]✉, Christiane E. Angermann[2], John R. Teerlink[3], Sean P. Collins[4], Mikhail Kosiborod[5,6,7,8], Jan Biegus[9], João Pedro Ferreira[10,11], Michael E. Nassif[5,6], Mitchell A. Psotka[12], Jasper Tromp[13], C. Jan Willem Borleffs[14], Changsheng Ma[15], Joseph Comin-Colet[16], Michael Fu[17], Stefan P. Janssens[18], Robert G. Kiss[19], Robert J. Mentz[20,21], Yasushi Sakata[22], Henrik Schirmer[23], Morten Schou[24], P. Christian Schulze[25], Lenka Spinarova[26], Maurizio Volterrani[27], Jerzy K. Wranicz[28], Uwe Zeymer[29], Shelley Zieroth[30], Martina Brueckmann[31,32], Jonathan P. Blatchford[33], Afshin Salsali[34,35] and Piotr Ponikowski[9]

The sodium–glucose cotransporter 2 inhibitor empagliflozin reduces the risk of cardiovascular death or heart failure hospitalization in patients with chronic heart failure, but whether empagliflozin also improves clinical outcomes when initiated in patients who are hospitalized for acute heart failure is unknown. In this double-blind trial (EMPULSE; NCT04157751), 530 patients with a primary diagnosis of acute de novo or decompensated chronic heart failure regardless of left ventricular ejection fraction were randomly assigned to receive empagliflozin 10 mg once daily or placebo. Patients were randomized in-hospital when clinically stable (median time from hospital admission to randomization, 3 days) and were treated for up to 90 days. The primary outcome of the trial was clinical benefit, defined as a hierarchical composite of death from any cause, number of heart failure events and time to first heart failure event, or a 5 point or greater difference in change from baseline in the Kansas City Cardiomyopathy Questionnaire Total Symptom Score at 90 days, as assessed using a win ratio. More patients treated with empagliflozin had clinical benefit compared with placebo (stratified win ratio, 1.36; 95% confidence interval, 1.09–1.68; $P = 0.0054$), meeting the primary endpoint. Clinical benefit was observed for both acute de novo and decompensated chronic heart failure and was observed regardless of ejection fraction or the presence or absence of diabetes. Empagliflozin was well tolerated; serious adverse events were reported in 32.3% and 43.6% of the empagliflozin- and placebo-treated patients, respectively. These findings indicate that initiation of empagliflozin in patients hospitalized for acute heart failure is well tolerated and results in significant clinical benefit in the 90 days after starting treatment.

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Pleiotropic effects of sodium-glucose co-transporter-2 (SGLT-2) inhibitors

Received: 17 April 2019 | Revised: 16 June 2019 | Accepted: 26 June 2019
DOI: 10.1111/dom.13819

REVIEW ARTICLE

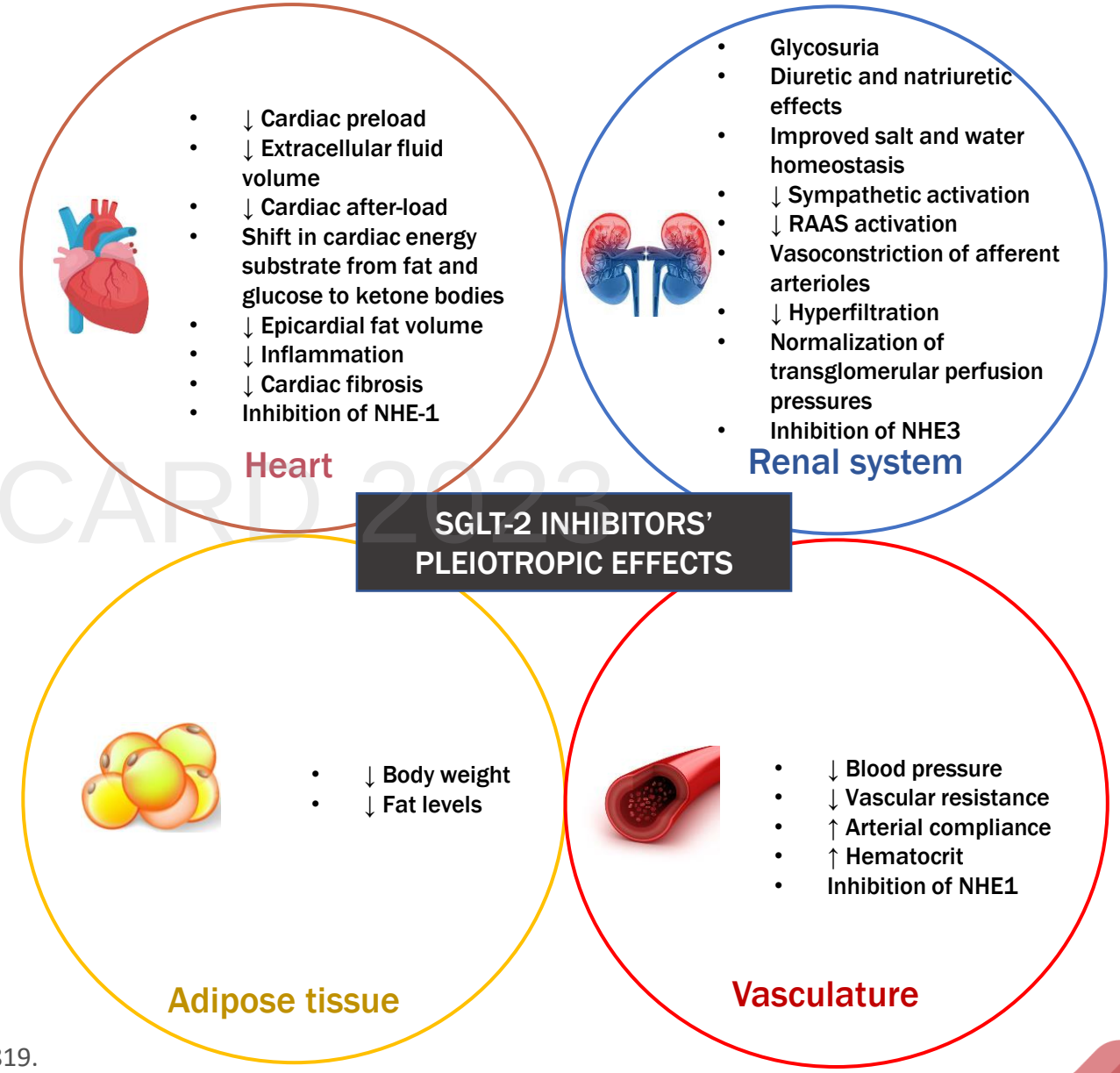
WILEY

Use of sodium-glucose co-transporter-2 inhibitors in patients with type 2 diabetes mellitus and multiple cardiovascular risk factors: An Asian perspective and expert recommendations

Chaicharn Deerochanawong MD[1] | Siew P. Chan MD[2] | Bien J. Matawaran MD[3] | Wayne H.-H. Sheu MD[4] | Juliana Chan MD[5] | Nguyen H. Man MD[6] | Ketut Suastika MD[7] | Chin M. Khoo MD[8] | Kun-Ho Yoon MD[9] | Andrea Luk MD[5] | Ambrish Mithal MD[10] | Ji Linong MD[11]

In addition to lowering blood glucose, SGLT-2 inhibitors exert favourable effects on multiple risk factors (including blood pressure, body weight and renal function) and provide an opportunity to reduce the risk of CVD in patients with T2DM.

Deerochanawong C *et al. Diabetes Obes Metab.* 2019. doi: 10.1111/dom.13819.



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PROFILES OF ANTIHYPERGLYCEMIC MEDICATIONS

		MET	GLP-1 RA	DUAL GIP/ GLP-1 RA	SGLT2i	TZD	INSULIN (basal & basal bolus)	DPP-4i	SU	GLN	AGi	COLSVL	BRC	PRAML
EFFICACY FOR GLUCOSE LOWERING		++	+++	+++	++	++	+++/++++	+	++	+	+	+	+	+
ASCVD	MACE	Neutral	Benefit[1,3]	Safe	Benefit[2]	Neutral[3]	Neutral	Neutral	Possible Increased Risk	Neutral	Insufficient Evidence	Neutral[3]	Safe	Insufficient Evidence
	CHF		Unclear		Reduced Risk	Moderate to Severe[4]	Moderate	Moderate[4]						
	STROKE		Benefit[5]		Possible Benefit[2]	Benefit	Neutral	Neutral						
CKD		CKD3a/3b[6]	Benefit[7]	Insufficient Evidence	Benefit		Increased	Neutral			Not recommended SCR >2 mg/dL or CrCl <25	Neutral	Neutral	Neutral
RENAL ADJUSTMENT		Not with CKD4 eGFR <30[6]	Exenatide not recommended eGFR <45											
HYPOGLYCEMIA RISK[14]		Neutral	Neutral	Neutral						Mild	Neutral	Neutral	Neutral	Neutral
WEIGHT		Slight loss	Loss	Loss						Neutral	Neutral	Neutral	Neutral	Loss
NAFLD		Neutral	Benefit	Benefit	Potential Benefit	Benefit	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Benefit
GI ADVERSE SYMPTOMS		Mild to Moderate	Moderate[10]	Moderate[10]	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Moderate	Mild	Moderate	Moderate
OTHER CONSIDERATIONS			Medullary Thyroid Carcinoma/ MEN2	Medullary Thyroid Carcinoma/ MEN2	GU infections DKA[11] Fracture Risk[12]	Fracture Risk		Rare Arthralgias/ Myalgias						
ACCESS/COST		$	$$$	$$$	$$$	$	$ - $$$[13]	$-$$	$	$-$$	$-$$	$$$	$$$	$$$

- TZD
- Saxagliptin

Possible benefits | Use with caution | Likelihood of adverse events | Neutral, not studied, insufficient evidence

[1]GLP-1 RA MACE benefits with liraglutide, semaglutide, dulaglutide. [2]SGLT2i MACE benefits with empagliflozin, canagliflozin. Possible benefit for hemorrhagic stroke. [3]GLP-1 RA, TZD, COLSVL can lower LDL. [4]TZDs increase fluid retention and edema and are contraindicated in persons with NYHA Class III/IV CHF. There is Increased risk of hospitalization for CHF with saxagliptin, and limited experience for persons with NYHA Class II/IV CHF with alogliptin [5]GLP-1 RA stroke benefits observed with semaglutide and dulaglutide. [6]CKD3a no adjustment with monitoring, CKD3b decrease dose and do not initiate, CKD4 contraindicated. Hold for acute kidney injury, IV contrast. [7]Dulaglutide, semaglutide decrease CKD progression. [8]The eGFR thresholds for initiation and/or continuation of therapy in CKD vary among SGLT2i. Check medication-specific eGFR levels. [9]Only linagliptin does not require adjustment. [10]Slow titration, portion control, and consider reducing to prior tolerated dose. [11]Precipitants include significant current illness, surgery, inappropriate or rapid insulin dose reduction. [12]Reported with canagliflozin, dapagliflozin. [13]Cost varies widely with devices (e.g., pens), formulations (e.g., analogues), and combinations (e.g., 70/30). [14]SIngle-agent risks of hypoglycemia may be low but increases when combined with other agents.

Algorithm Figure 9-Antihyperglycemic Medications

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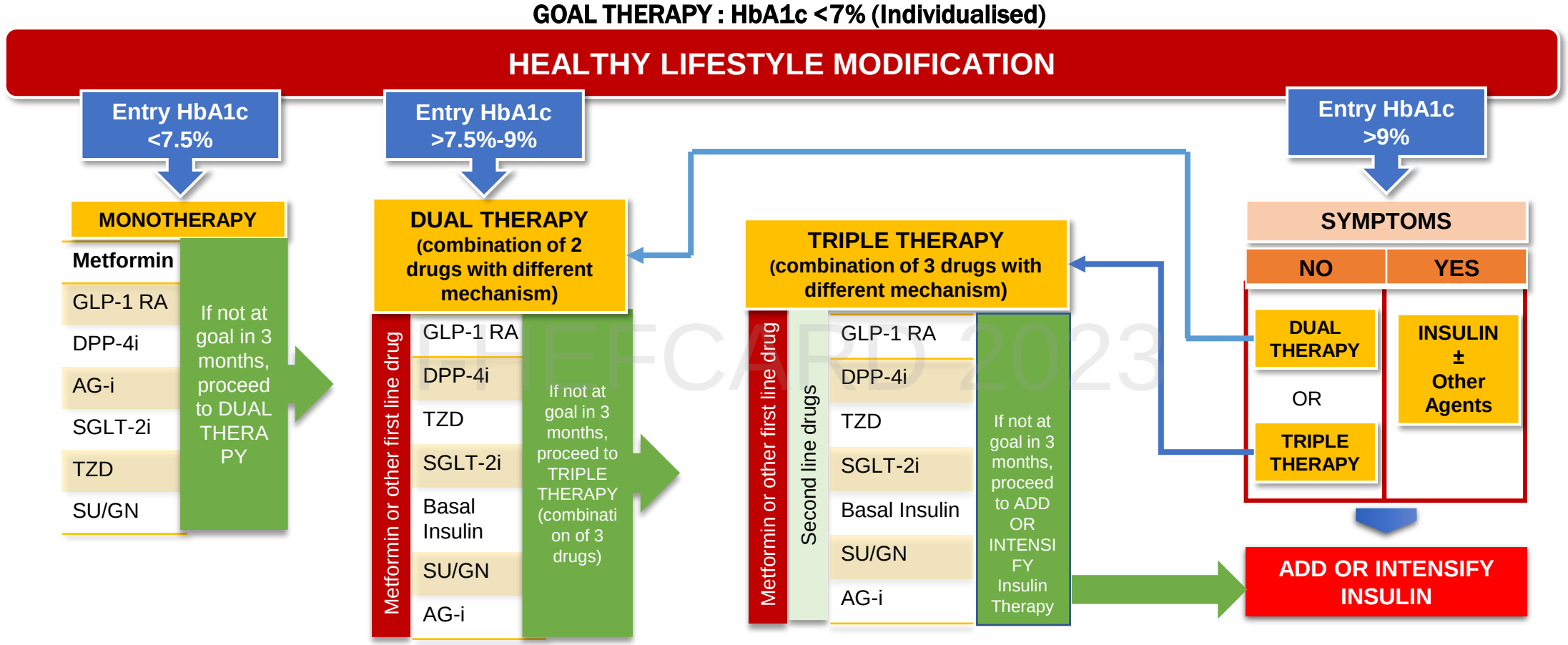
Algorithm of Type 2 Diabetes management in Indonesia (Perkeni, 2019)



1. Pemilihan dan penggunaan obat mempertimbangkan faktor pembiayaan, ketersediaan obat, efektifitas, manfaat kardiorenal, efek samping, efek terhadap berat badan, serta pilihan pasien.
2. Pengelolaan bukan hanya meliputi gula darah, tetapi juga penanganan faktor – faktor resiko kardiorenal yang lain secara terintegrasi.
3. **Obat Agonis GLP-1 dan penghambat SGLT-2 tertentu menunjukkan manfaat untuk pasien dengan komorbid penyakit kardiovaskular aterosklerotik, gagal jantung dan gagal ginjal. Kedua golongan obat ini disarankan menjadi pilihan untuk pasien dengan komorbid/komplikasi penyakit tersebut.**
4. Bila HbA1C tidak bisa diperiksa maka sebagai pedoman dipakai glukosa darah rerata yang dikonversikan ke HbA1C (poin 7 penjelasan algoritma).

USE OF GLUCOSE-LOWERING MEDICATIONS IN THE MANAGEMENT OF TYPE 2 DIABETES

HEALTHY LIFESTYLE BEHAVIORS; DIABETES SELF-MANAGEMENT EDUCATION AND SUPPORT (DSMES); SOCIAL DETERMINANTS OF HEALTH (SDOH)

TO AVOID THERAPEUTIC INERTIA REASSESS AND MODIFY TREATMENT REGULARLY (3–6 MONTHS)

Goal: Cardiorenal Risk Reduction in High-Risk Patients with Type 2 Diabetes (in addition to comprehensive CV risk management)*

+ASCVD†

Defined differently across CVOTs but all included individuals with established CVD (e.g., MI, stroke, any revascularization procedure). Variably included: conditions such as transient ischemic attack, unstable angina, amputation, symptomatic or asymptomatic coronary artery disease.

+Indicators of high risk

While definitions vary, most comprise ≥55 years of age with two or more additional risk factors (including obesity, hypertension, smoking, dyslipidemia, or albuminuria)

+ASCVD/Indicators of High Risk

GLP-1 RA# with proven CVD benefit — EITHER/OR — SGLT2i§ with proven CVD benefit

If A1C above target

- For patients on a GLP-1 RA, consider adding SGLT2i with proven CVD benefit or vice versa
- TZD^

+HF

Current or prior symptoms of HF with documented HFrEF or HFpEF

+HF

SGLT2i§ with proven HF benefit in this population

+CKD

eGFR <60 mL/min per 1.73 m² OR albuminuria (ACR ≥3.0 mg/mmol [30 mg/g]). These measurements may vary over time; thus, a repeat measure is required to document CKD.

+CKD (on maximally tolerated dose of ACEi/ARB)

PREFERABLY

SGLT2i§ with primary evidence of reducing CKD progression

Use SGLT2i in people with an eGFR ≥20 mL/min per 1.73 m²; once initiated should be continued until initiation of dialysis or transplantation

OR

GLP-1 RA with proven CVD benefit if SGLT2i not tolerated or contraindicated

If A1C above target, for patients on SGLT2i, consider incorporating a GLP-1 RA or vice versa

If additional cardiorenal risk reduction or glycemic lowering needed

Goal: Achievement and Maintenance of Glycemic and Weight Management Goals

Glycemic Management: Choose approaches that provide the efficacy to achieve goals:

Metformin OR Agent(s) including COMBINATION therapy that provide adequate EFFICACY to achieve and maintain treatment goals

Consider avoidance of hypoglycemia a priority in high-risk individuals

In general, higher efficacy approaches have greater likelihood of achieving glycemic goals

Efficacy for glucose lowering

Very High:
Dulaglutide (high dose), Semaglutide, Tirzepatide

Insulin

Combination Oral, Combination Injectable (GLP-1 RA/Insulin)

High:
GLP-1 RA (not listed above), Metformin, SGLT2i, Sulfonylurea, TZD

Intermediate:
DPP-4i

Achievement and Maintenance of Weight Management Goals:

Set individualized weight management goals

General lifestyle advice: medical nutrition therapy/eating patterns/ physical activity

Intensive evidence-based structured weight management program

Consider medication for weight loss

Consider metabolic surgery

When choosing glucose-lowering therapies:

Consider regimen with high-to-very-high dual glucose and weight efficacy

Efficacy for weight loss

Very High:
Semaglutide, Tirzepatide

High:
Dulaglutide, Liraglutide

Intermediate:
GLP-1 RA (not listed above), SGLT2i

Neutral:
DPP-4i, Metformin

If A1C above target

Identify barriers to goals:

- Consider DSMES referral to support self-efficacy in achievement of goals
- Consider technology (e.g., diagnostic CGM) to identify therapeutic gaps and tailor therapy
- Identify and address SDOH that impact achievement of goals

* In people with HF, CKD, established CVD or multiple risk factors for CVD, the decision to use a GLP-1 RA or SGLT2i with proven benefit should be independent of background use of metformin; † A strong recommendation is warranted for people with CVD and a weaker recommendation for those with indicators of high CV risk. Moreover, a higher absolute risk reduction and thus lower numbers needed to treat are seen at higher levels of baseline risk and should be factored into the shared decision-making process. See text for details; ^ Low-dose TZD may be better tolerated and similarly effective; § For SGLT2i, CV/renal outcomes trials demonstrate their efficacy in reducing the risk of composite MACE, CV death, all-cause mortality, MI, HHF, and renal outcomes in individuals with T2D with established/high risk of CVD; # For GLP-1 RA, CVOTs demonstrate their efficacy in reducing composite MACE, CV death, all-cause mortality, MI, stroke, and renal endpoints in individuals with T2D with established/high risk of CVD.

ADA, 2023
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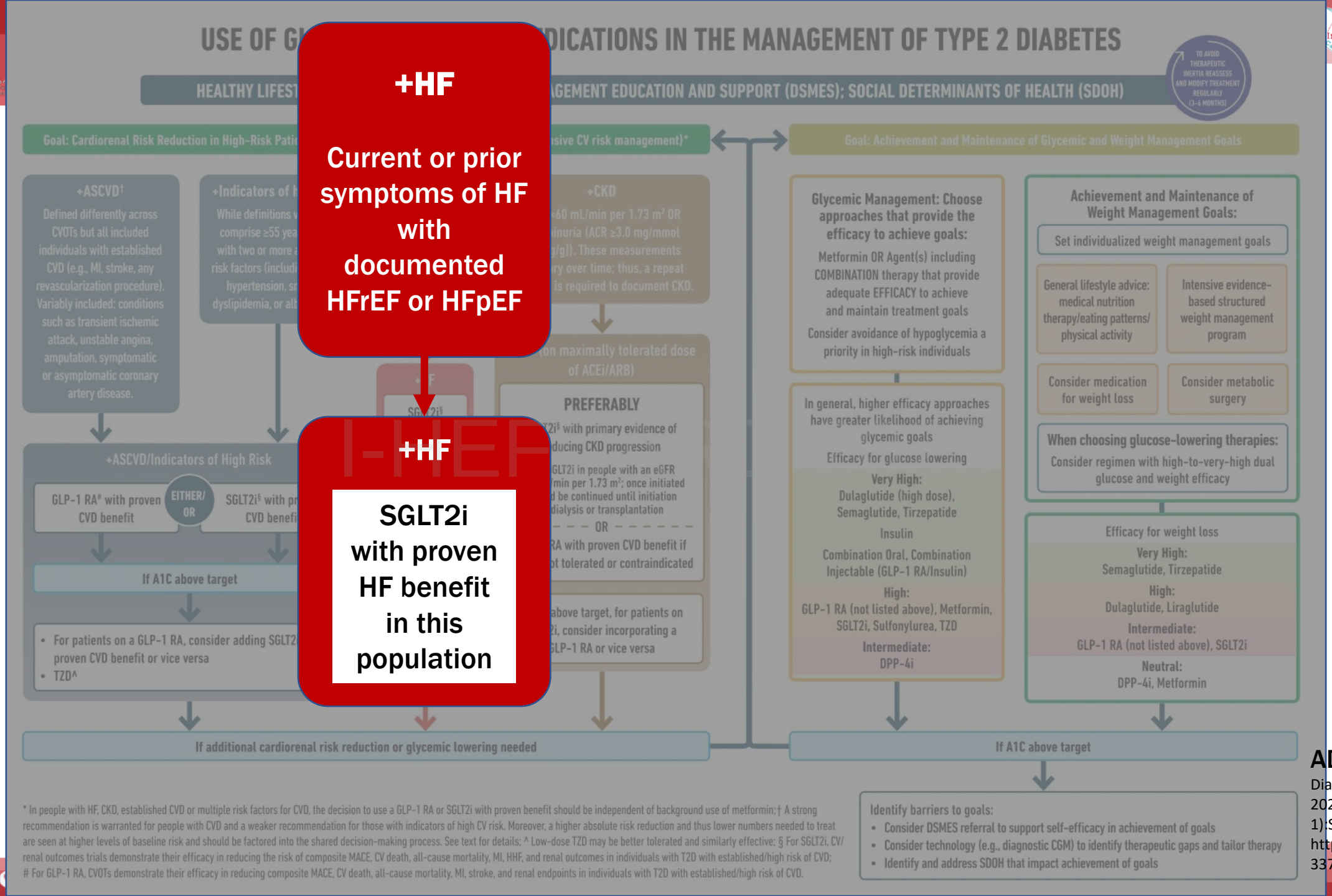

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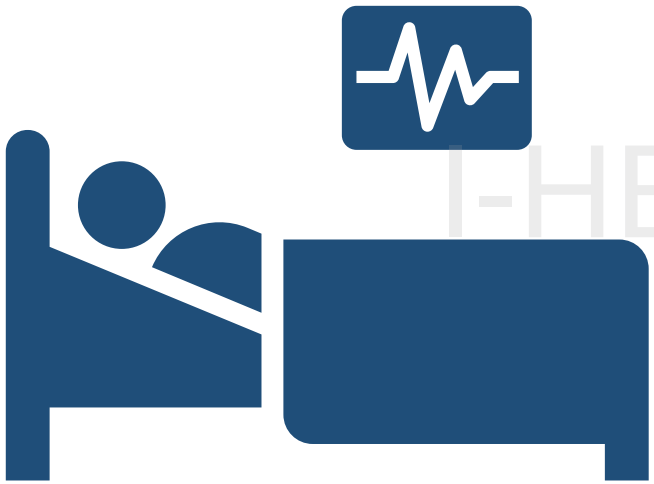
Case



- Men, 56 y.
- ICCU due to HFrEF (LVEF Biplane 30%)
- T2DM for 9 y.
- BP: 110/70 mmHg
- Random PG: 290 mg/dL
- HbA1c: 8.9%
- eGFR 50
- Last medications:
  - Metformin 2x500 and Glimepiride 4 mg per day
  - Ramipril 1x5 mg, bisoprolol 1x5 mg, spironolactone 1x50 mg