5th IHEF CARD

The 5th Indonesian Symposium on Heart Failure and Cardiometabolic Disease

Cardiovascular-Kidney-Metabolic (CKM) Syndrome:

What do We Need to Know?

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Sheraton Grand Jakarta Gandaria City, Jakarta, Indonesia
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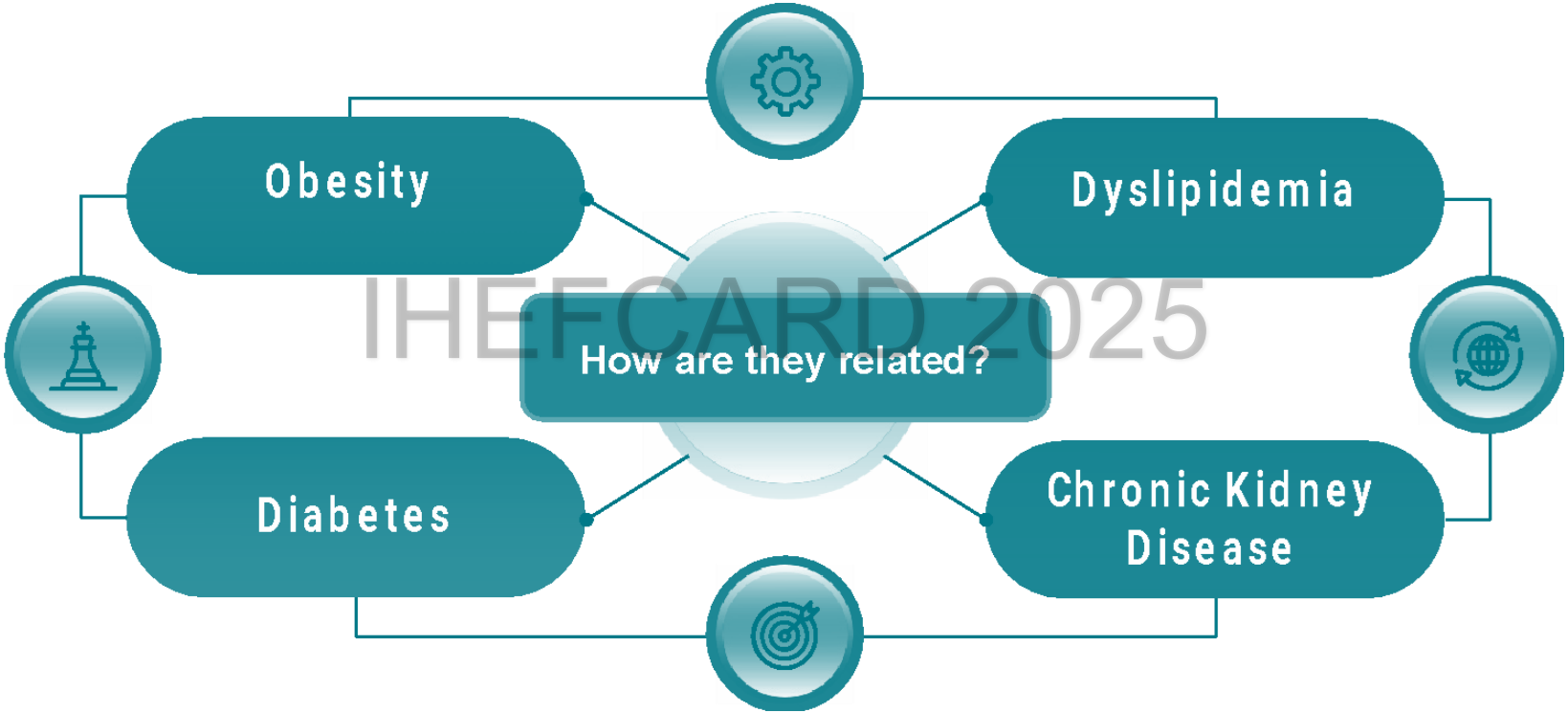
Let Us Ponder Something...



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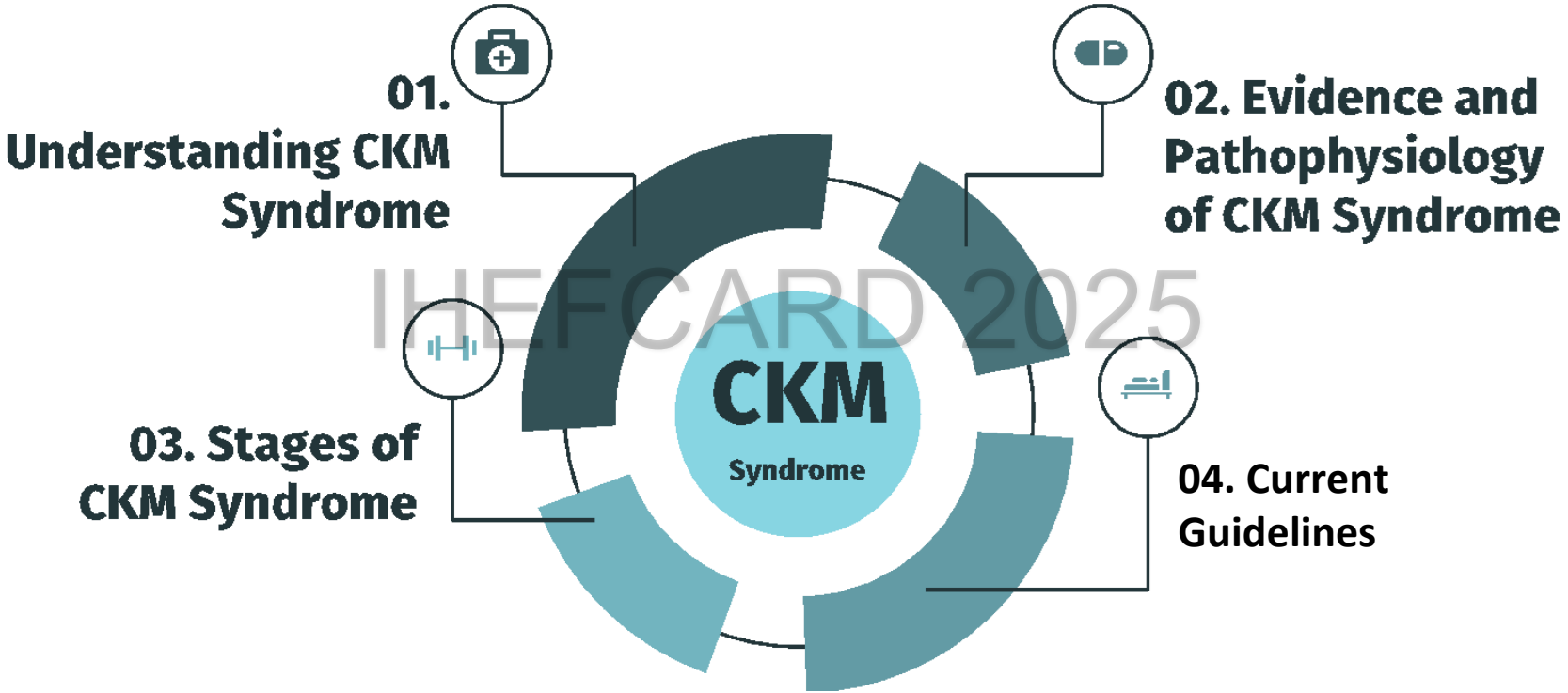
To Discuss



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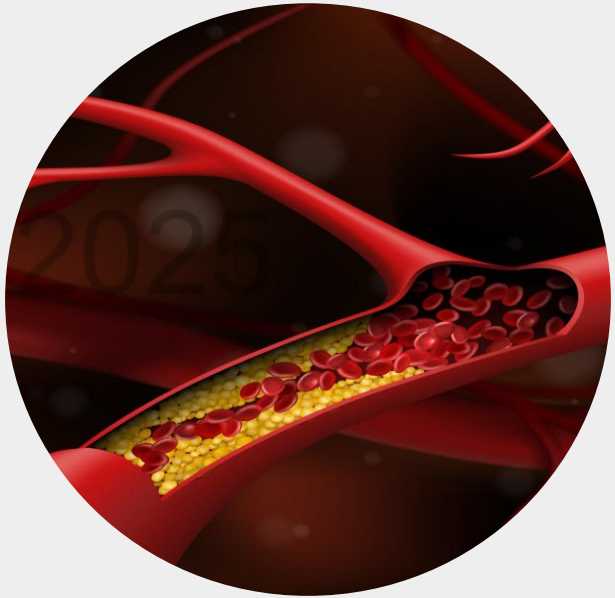
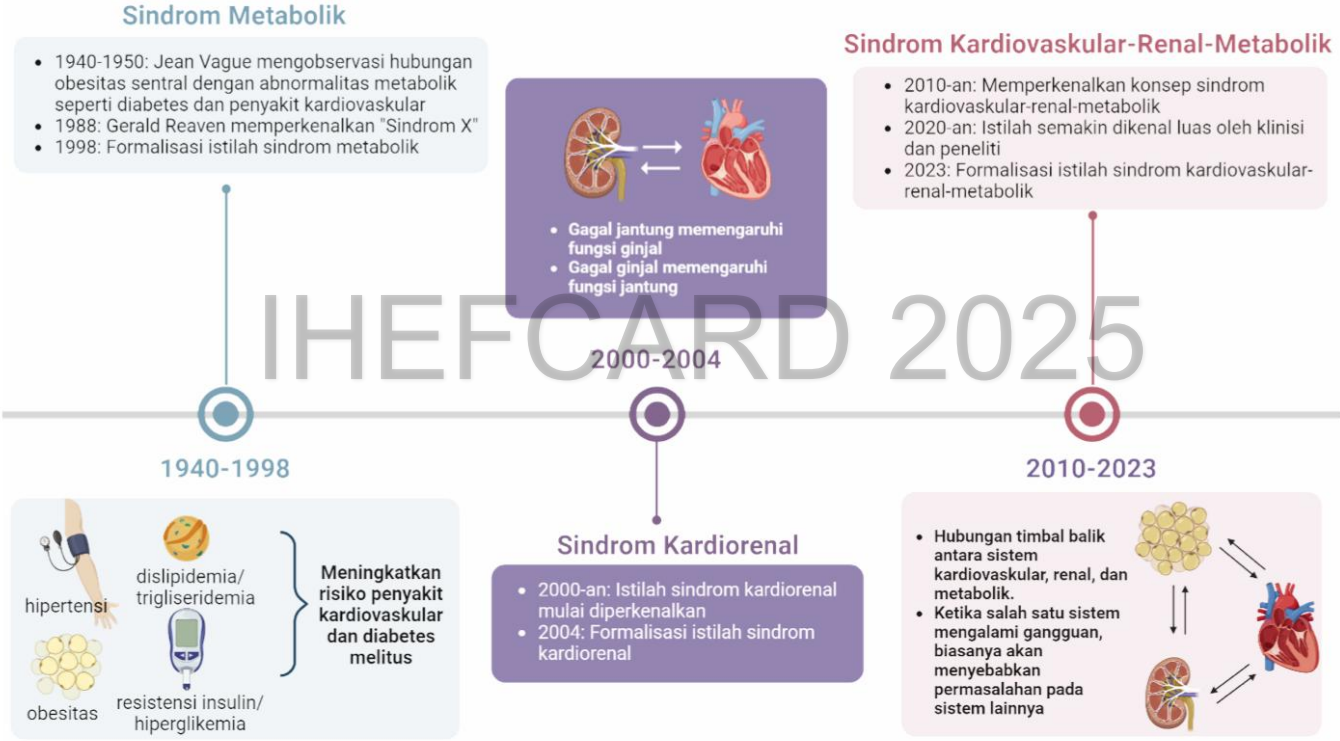
Understanding CKM Syndrome



Evolving Understanding of CKM Syndrome



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Konsensus Sindrom Kardiovaskular-Renal-Metabolik. PAPDI 2024.

CKM Syndrome: Definition

CKM Syndrome

a **systemic disorder** characterized by pathophysiological interactions among **metabolic risk factors, CKD, and the cardiovascular system**, leading to multiorgan dysfunction and a high rate of **adverse cardiovascular outcomes**.

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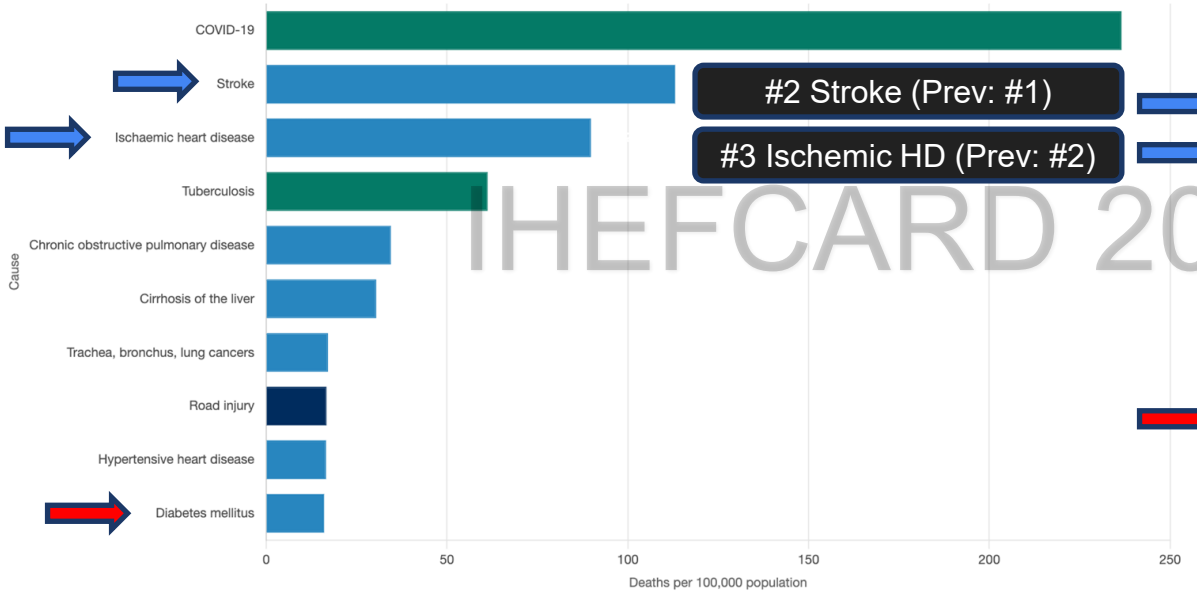
Ndumele CE, Neeland IJ, Tuttle KR, Chow SL, Mathew RO, Khan S, et al; American Heart Association. A Synopsis of the Evidence for the Science and Clinical Management of Cardiovascular-Kidney-Metabolic (CKM) Syndrome: A Scientific Statement From the American Heart Association. Circulation. 2023 Nov 14;148(20):1636-64.

ASCVDs Remain the Leading Cause of Death in the World

WHO, 2021



#2 Stroke (Prev: #1)

#3 Ischemic HD (Prev: #2)

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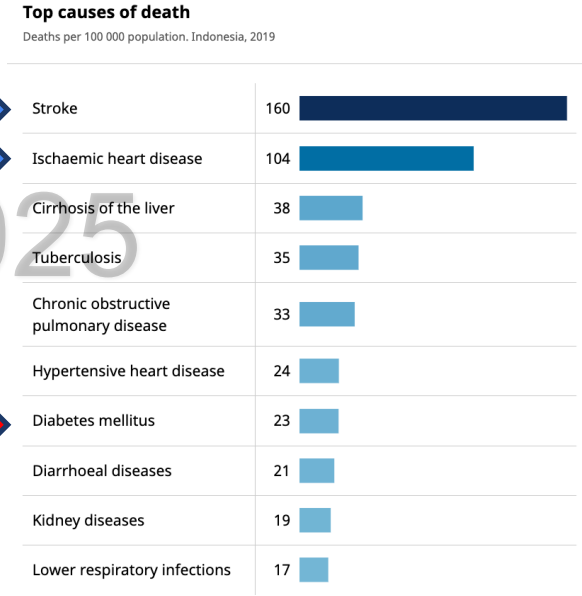
WHO 2019



https://data.who.int/countries/360
https://www.who.int/data/gho/data/themes/mortality-and-global-health-estimates/ghe-leading-causes-of-death

The Burden of ASCVDs in Indonesia Remains High

Second worst CVD-related DALYs compared to other ASEAN countries after Laos

Stroke and **Ischemic Heart Disease** remain as the leading cause of death (both are ASCVDs)

More than twofold increase in all-age CVD deaths from 292.000 in 1990 to 659.000 in 2019

120% increase in **all-age CVD prevalence** from 6,968,000 in 1990 to 15,348,000 in 2019

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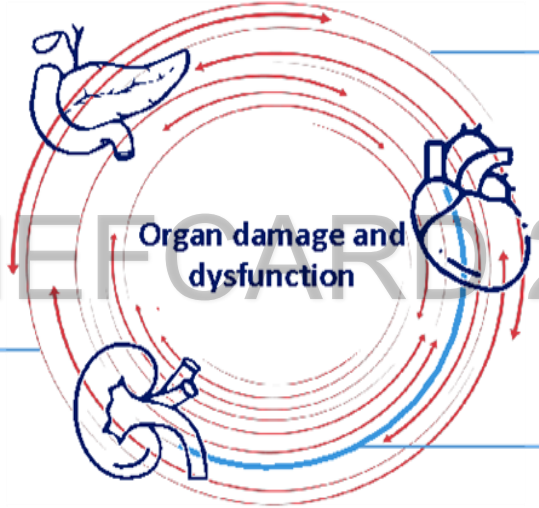
Muharram FR, Multazam CECZ, Mustofa A, Socha W, Andrianto, Martini S, et al. The 30 Years of Shifting in The Indonesian Cardiovascular Burden-Analysis of The Global Burden of Disease Study. J Epidemiol Glob Health. 2024 Mar;14(1):193-212.

CKM Syndrome: Integrated Evidence

Conditions of the cardio-kidney-metabolic systems affect more than 1 billion people worldwide[3,4]

~37% of adults with diabetes have been diagnosed with CKD*[1]

Diabetes and/or hypertension is the primary cause of ~75% of ESKD prevalent cases in the US[2]



~One-third of patients with T2D have CV disease[3,4]

CV disease is the leading cause of mortality in patients with T2D[5,6]

CV mortality accounts for 40-50% of deaths in patients with advanced CKD or ESKD (compared to 26% in controls with normal kidney function)[7]

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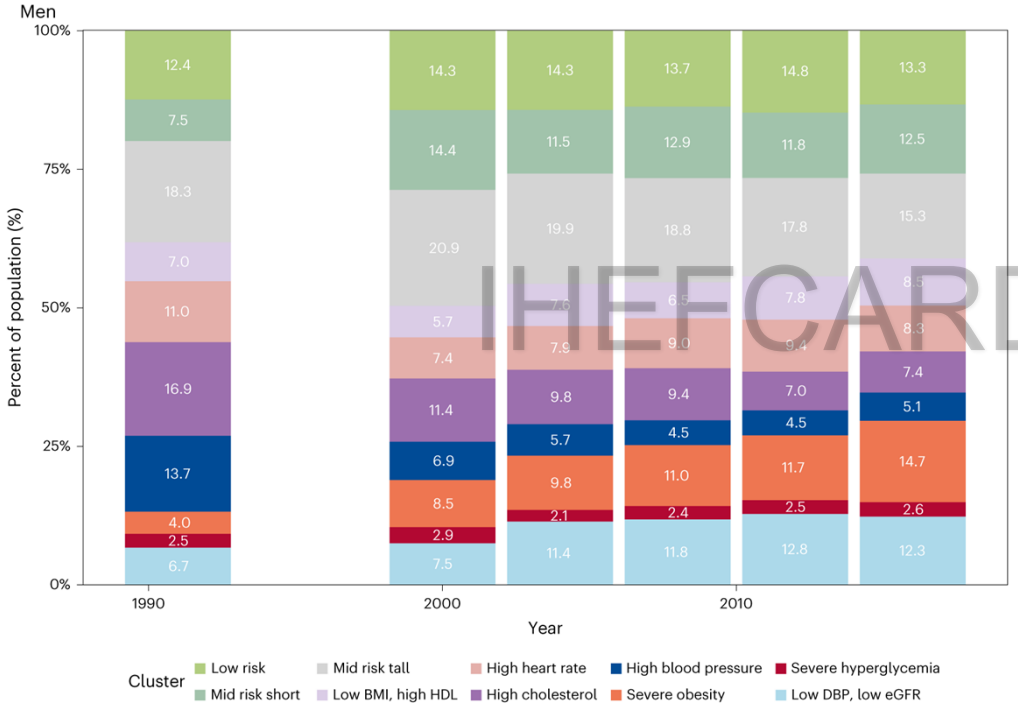
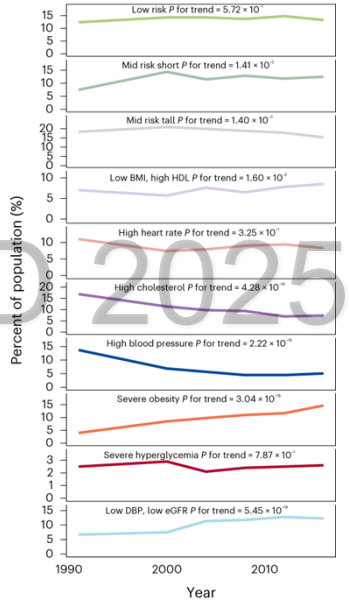
*As per NHANES 2011–2012 data.

CKD, chronic kidney disease; CV, cardiovascular; ESKD, end-stage kidney disease; HF, heart failure; NHANES, National Health and Nutrition Examination Survey; T2D, type 2 diabetes

1. Murphy D et al. Ann Intern Med 2016; 165(7):473-481; 2. Saran R et al. Am J Kidney Dis 2019; S0272-6386(19)31008-X; 3. Einarson TR et al. Cardiovasc Diabetol 2018; 17(1):83; 4. International Diabetes Federation. IDF Diabetes Atlas. 9th edn. 2019. https://www.diabetesatlas.org/ (accessed August 2020); 5. Morrish NJ et al. Diabetologia 2001; 44(Suppl. 2):S14; 6. American Diabetes Association. Diabetes Care 2020; 43(S1):S1-S212; 7. Jankowski J et al. Circulation. 2021; 143:1157-1172

Changing Trends in CV Risk Factors





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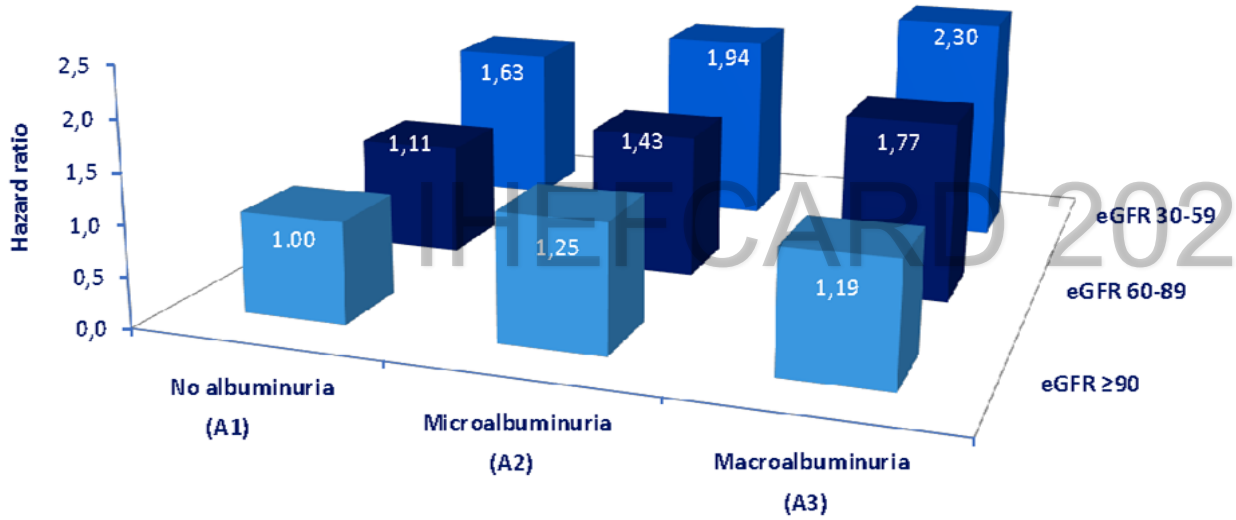
In 20 years, major cardiovascular related risk factors **changed**, from those with **high blood pressure and cholesterol level** 20 years ago to the predominant **obesity, diabetic, and low eGFR** cohort nowadays

Lhoste VPF, Zhou B, Mishra A, Bennett JE, Filippi S, Asaria P, Gregg EW, Danaei G, Ezzati M. Cardiometabolic and renal phenotypes and transitions in the United States population. Nat Cardiovasc Res. 2023 Dec 15;3(1):46-59.

CKM Syndrome: Integrated Evidence: CKD and CVD



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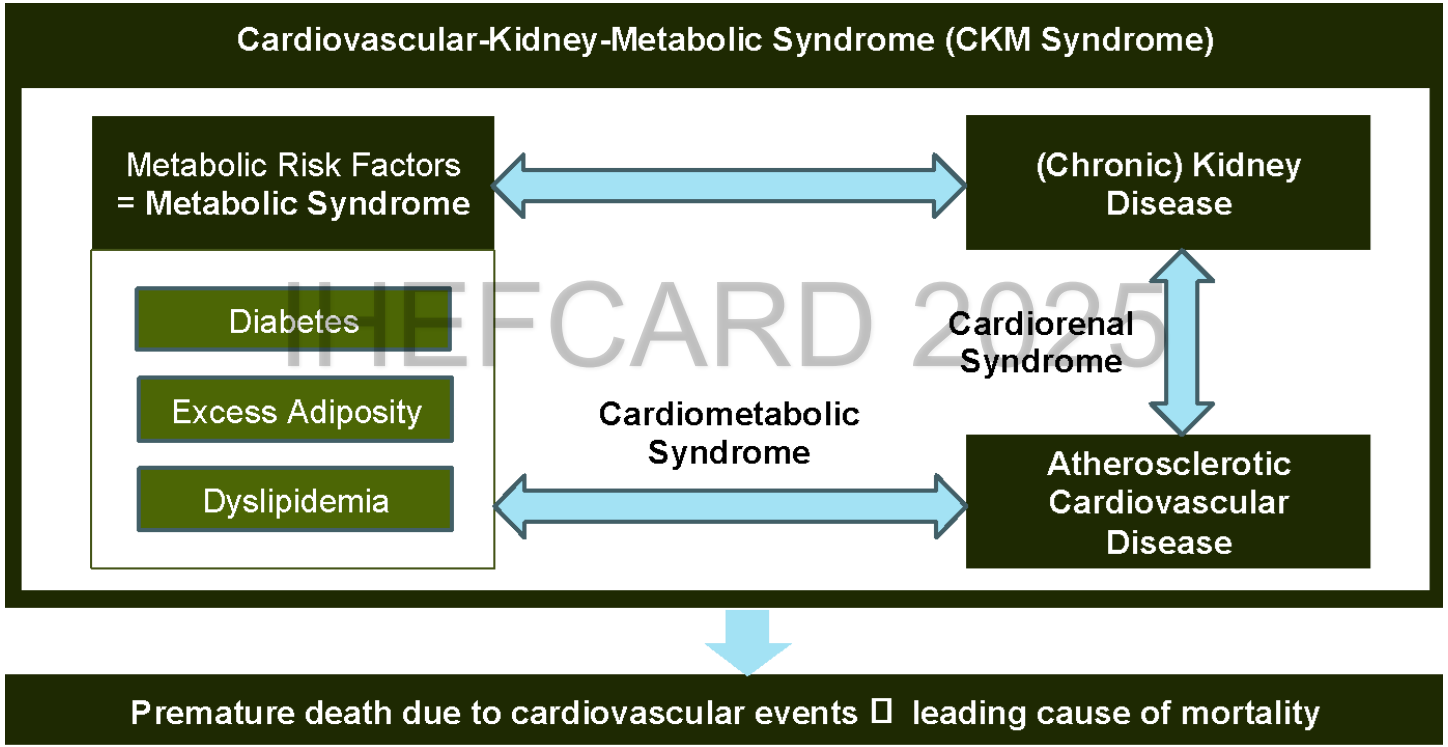
- CKD is associated with an increased risk of CV morbidity and mortality compared to the general population - the risk is even higher in peoples with CKD and diabetes[1,2]
- UACR and eGFR are independently associated with both CV and all-cause mortality[3,4]

CKD, chronic kidney disease; CV, cardiovascular; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; UACR, urinary albumin:creatinine ratio; T2D, type 2 diabetes

1. Foley RN et al. Am J Kidney Dis 1998; 32:S112–S119; 2. Alani H et al. World J Nephrol 2014; 3:156–168; 3. Drury PL et al. Diabetologia 2011; 54:32–43; 4. Tuttle KR et al. Diabetes Care 2014; 37:2864–2883

The Interrelation Between Risk Factors Contributing to CVD



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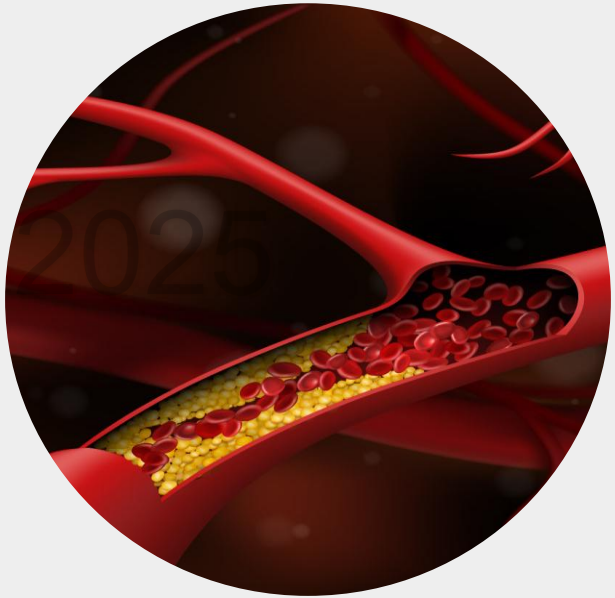
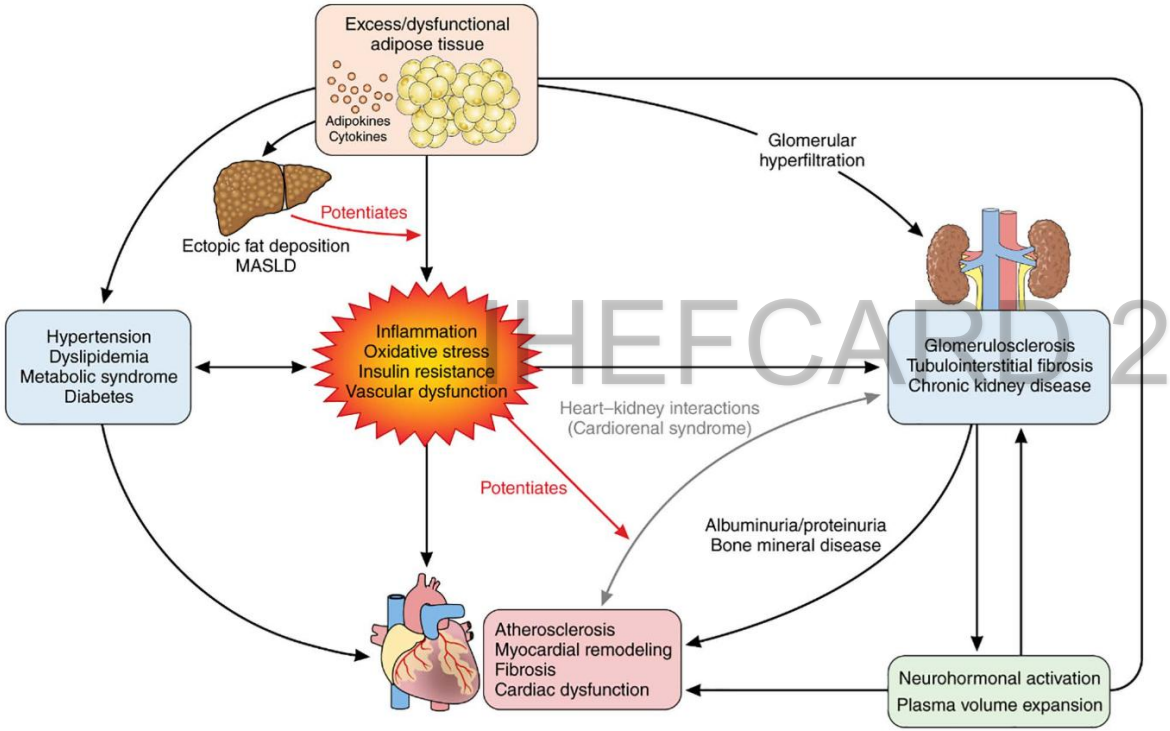
Pathophysiology of CKM Syndrome



Integrated Pathophysiology of the CKM Syndrome



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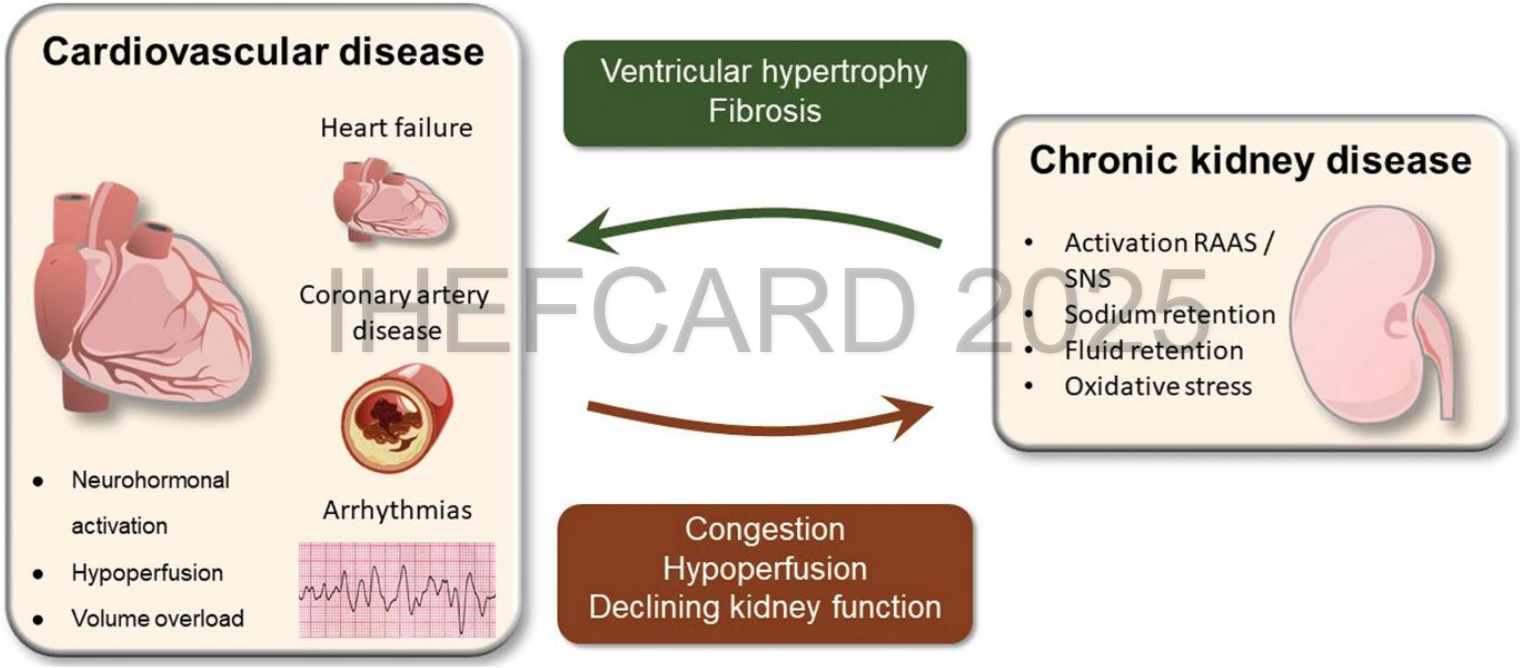
CKM syndrome most likely originates from excess and dysfunctional adipose tissue

These result in insulin resistance and hyperglycemia, propagating inflammatory reactions, oxidative stress, and vascular dysfunction

The central pathobiology contribute to the development of CKD and CVD as well as potentiating CKD-CVD pathology

Ndumele CE, Neeland IJ, Tuttle KR, Chow SL, Mathew RO, Khan SS, et al; American Heart Association. A Synopsis of the Evidence for the Science and Clinical Management of Cardiovascular-Kidney-Metabolic (CKM) Syndrome: A Scientific Statement From the American Heart Association. Circulation. 2023 Nov 14;148(20):1636-1664. doi: 10.1161/CIR.0000000000001186

Deadly Duo: CKD and CVD



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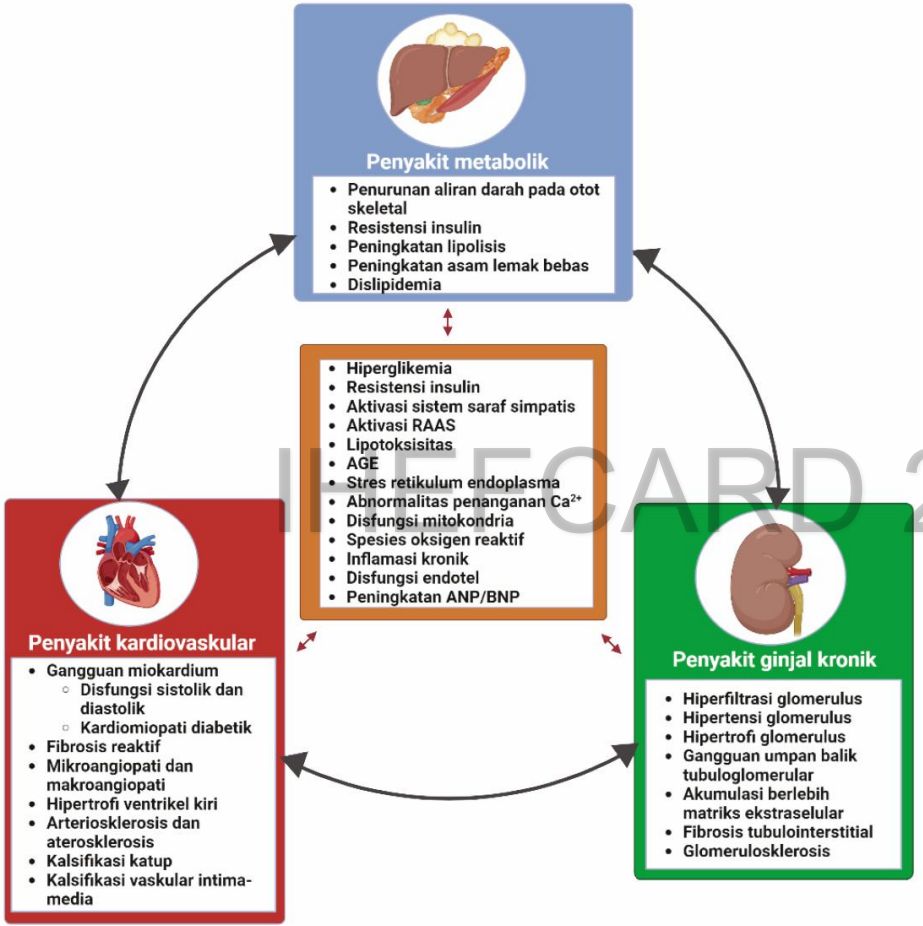
Schuett K, Marx N, Lehrke M. The Cardio-Kidney Patient: Epidemiology, Clinical Characteristics and Therapy. Circ Res. 2023 Apr 14;132(8):902-14.



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Integrated Pathophysiology

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03

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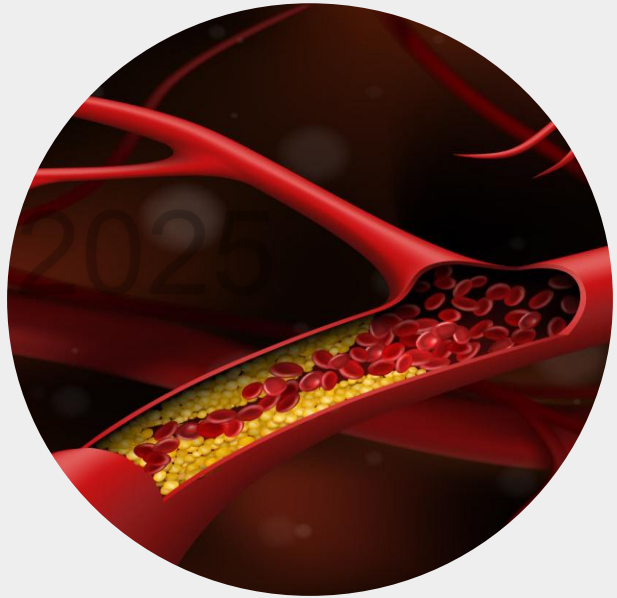
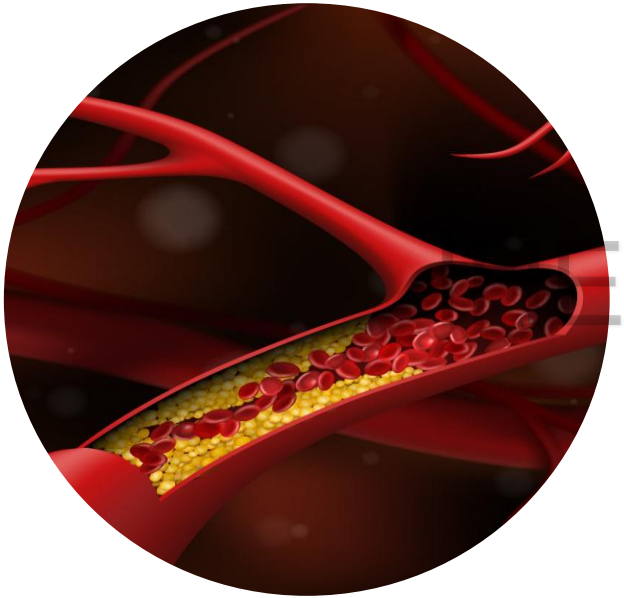
Screening, Diagnosis, and Stages of CKM Syndrome



CKM Syndrome: Definition



It is important to note that the current understanding of CKM syndrome includes those **at risk** for CVD and those with **existing** CVD → **emphasizing preventive efforts at all level**

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Ndumele CE, Neeland IJ, Tuttle KR, Chow SL, Mathew RO, Khan S, et al; American Heart Association. A Synopsis of the Evidence for the Science and Clinical Management of Cardiovascular-Kidney-Metabolic (CKM) Syndrome: A Scientific Statement From the American Heart Association. Circulation. 2023 Nov 14;148(20):1636-64.

Risk Stratification, Screening, and Diagnosis of CKM Syndrome

Melakukan Penapisan Risiko Kardiovaskular-Renal-Metabolik

CERDIK

- Menilai CERDIK (cek kesehatan secara berkala, enyahkan asap rokok, rajin aktivitas fisik/olahraga, diet sehat dan seimbang dengan mengurangi gula, garam, dan lemak, istirahat yang cukup, dan kelola stres)
- Mempertimbangkan pemeriksaan tambahan sesuai indikasi: HbA1c, UACR, dan lain-lain

Menilai Risiko Penyakit Kardiovaskular

Di antara individu usia 30-79 tahun:

- Hitung risiko absolut PKV, PKVAS, gagal jantung dengan PREVENT (10- dan 30-tahun)
- Personalisasi dalam *setting* diskusi dokter-pasien, pertimbangkan faktor risiko yang meningkatkan PKV untuk penentuan keputusan
- Klasifikasi ulang pada individu risiko sedang atau ketika terdapat ketidakpastian, pertimbangkan pemeriksaan berkelanjutan dengan biomarker atau pencitraan.

Menentukan Stadium Sindrom Kardiovaskular-Renal-Metabolik

- KRM Stadium 0 : Tidak ada faktor risiko KRM
- KRM Stadium 1 : Jaringan adiposa berlebih atau disfungsi
- KRM Stadium 2 : Faktor risiko metabolik atau PGK
- KRM Stadium 3 : PKV subklinis, PGK risiko sangat tinggi, atau prediksi risiko sangat tinggi terhadap PKV berdasarkan PREVENT
- KRM Stadium 4 : PKV klinis
  - Stadium 4a : Tidak ada gagal ginjal
  - Stadium 4b : Ada gagal ginjal

Menurunkan Risiko Sindrom Kardiovaskular-Renal-Metabolik

- Mempromosikan kesehatan KRM, mencegah progresi KRM, memprioritaskan regresi KRM
- Mengatasi faktor KRM dan mempertimbangkan terapi kardioprotektif berdasarkan rekomendasi panduan sesuai indikasi (contoh: statin, SGLT2i, GLP-1RA)
- Melakukan penapisan dan penekanan terhadap determinan sosial kesehatan
- Menilai ulang faktor KRM sesuai rentang waktu yang direkomendasikan
- Penggunaan antiplatelet disesuaikan dengan stadium KRM
  - Stadium 3 : dipertimbangkan pemberian antiplatelet jika risiko perdarahan rendah dan skor kalsium arteri koroner > 100
  - Stadium 4 : wajib diberikan antiplatelet selama tidak ada kontraindikasi

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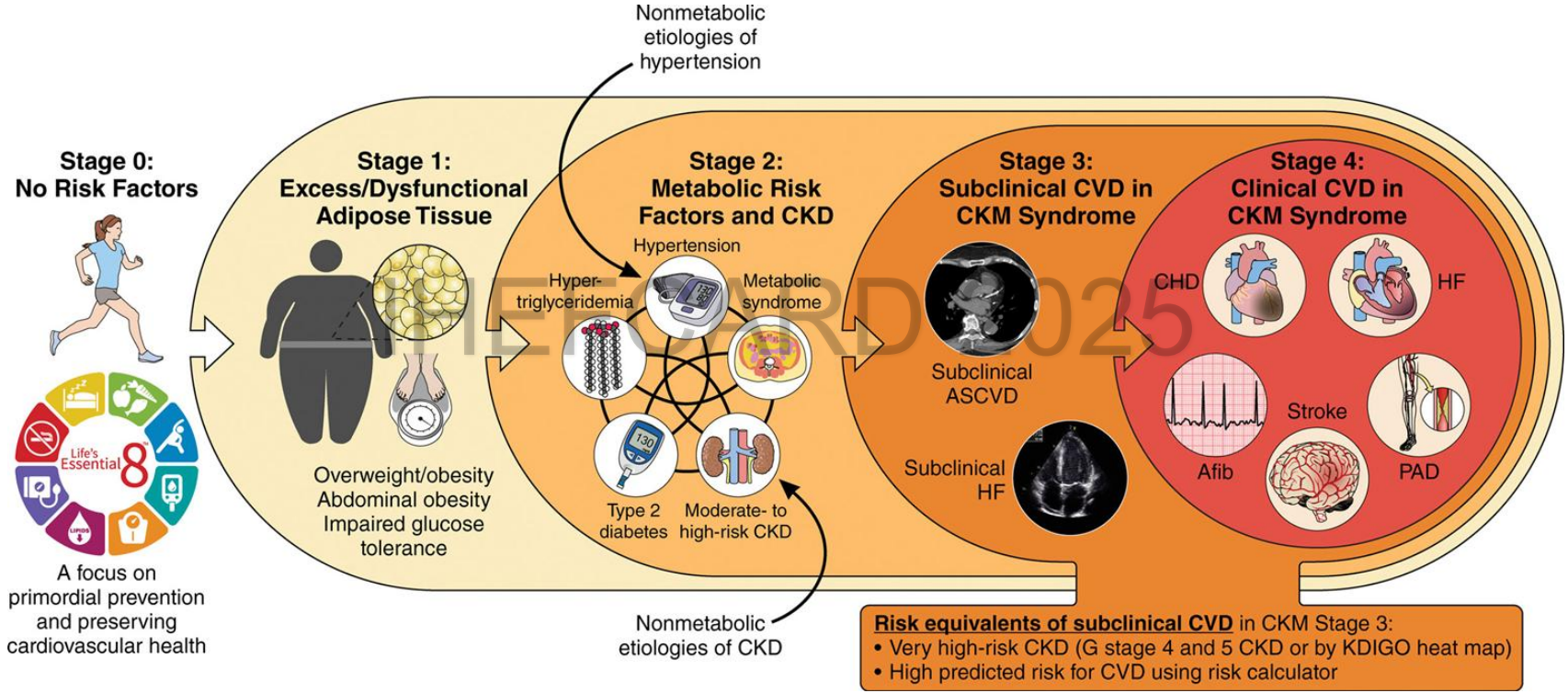
Konsensus Sindrom Kardiovaskular-Renal-Metabolik. PAPDI 2024.

Stages of the CKM Syndrome



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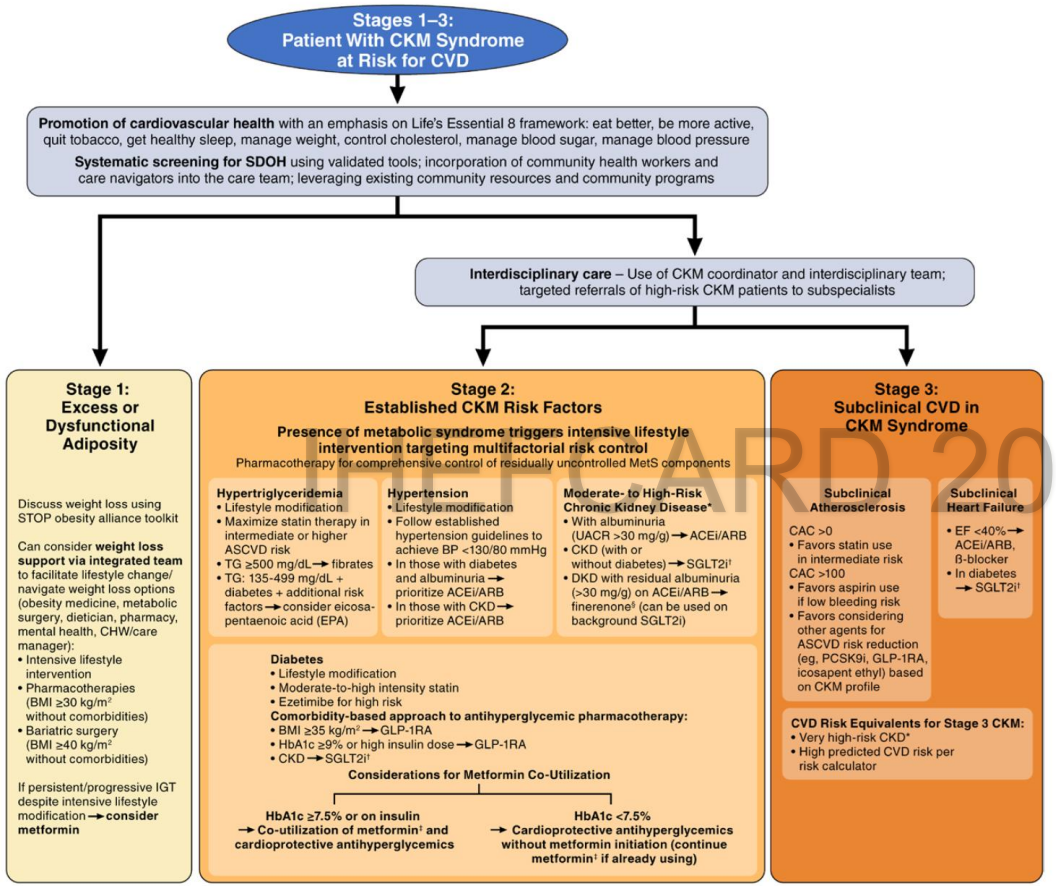

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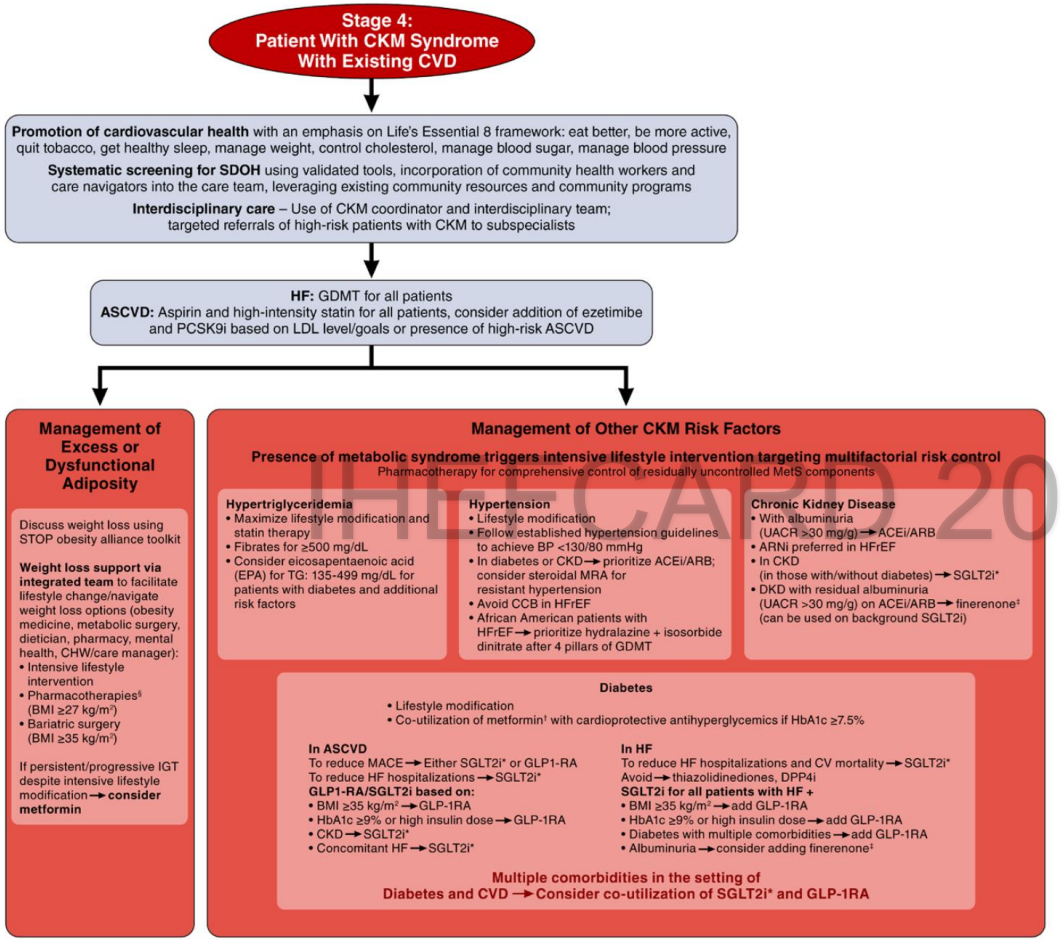
Management of CKM Syndrome: Stage 1 to 3

Management of CKM Syndrome



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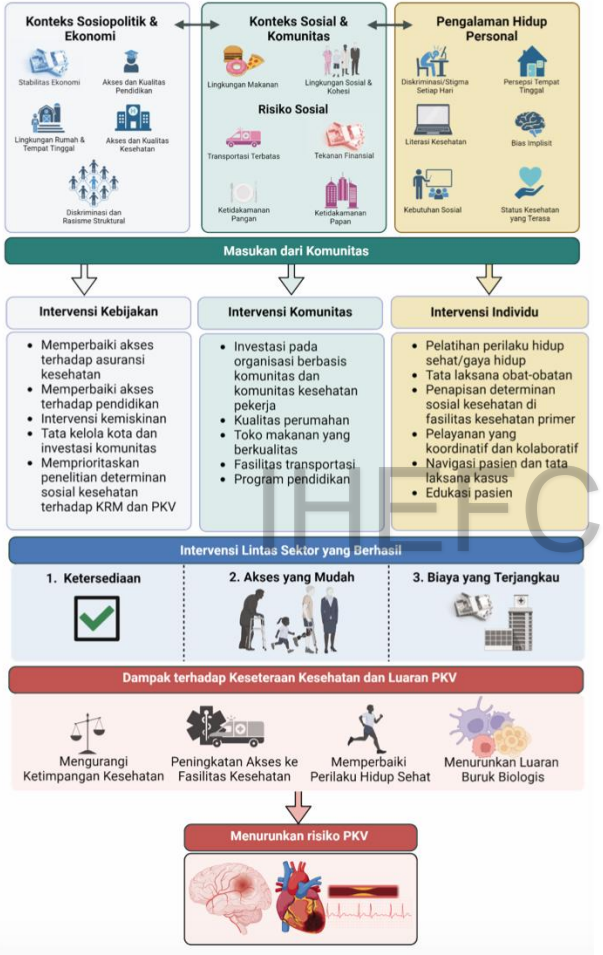

Promosi kesehatan kardiovaskular sepanjang masa kehidupan

Penapisan/Stadium KRM

Penilaian risiko PKV dengan PREVENT

Pencegahan berbasis risiko dengan pedoman terapi medis terarah

Lahir* | Remaja | Dewasa muda | Paruh baya | Lanjut usia

Faktor yang dapat dimodifikasi dari sindrom KRM (sosial/perilaku/biologi)

Determinan PKV pada sindrom KRM (faktor risiko)

PKV subklinis/klinis pada sindrom KRM (PKVAS, gagal jantung)

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Indonesian Working Group on Heart Failure and Cardiometabolic Disease

04

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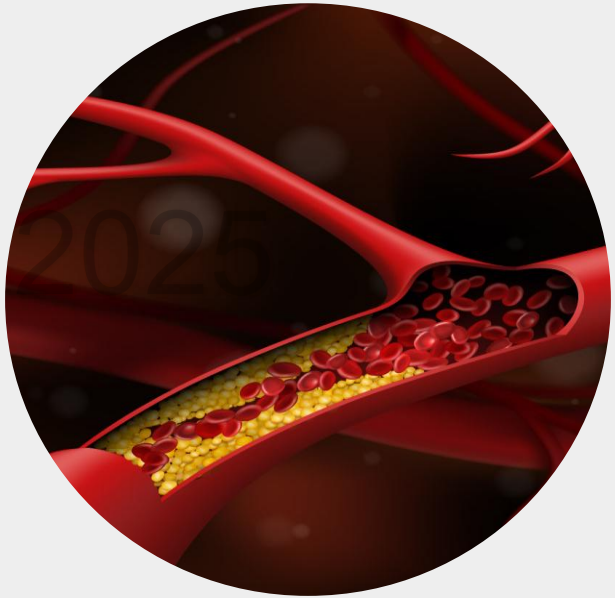
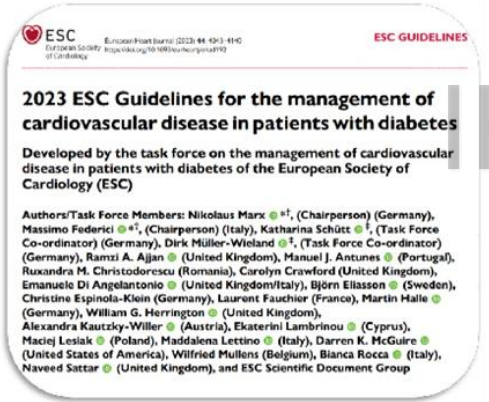
Current Guidelines

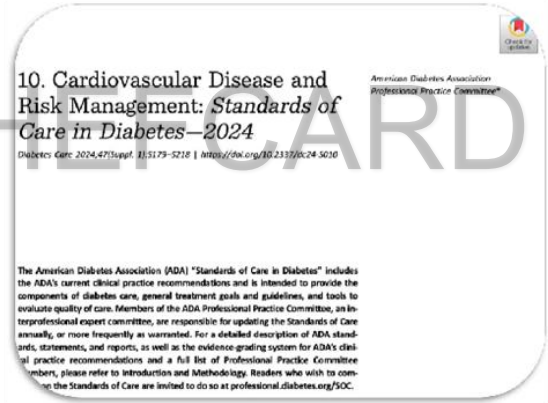


The Current Guidelines Say…

Current Guidelines Highlight the Importance of Agents with Proven Cardiovascular Benefits to Reduce the Burden of DM-ASCVDs



ESC 2023



ADA 2024

PAPDI 2024

PERKI 2022

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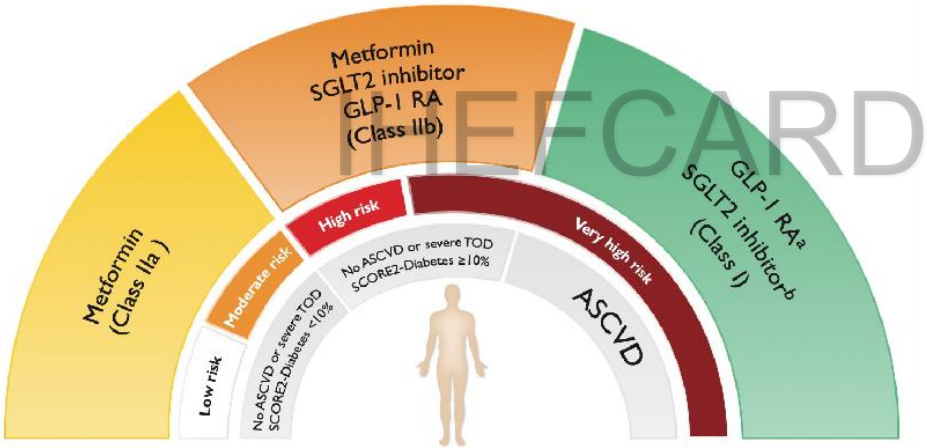
The Current Guidelines Say…

GLP-1RA and SGLT2i Are the Agents of Choice to Manage Co-Burden of T2DM and CVD—ESC 2023



Risk assessment for patients with type 2 diabetes based on the presence of ASCVD/severe TOD and 10-year CVD risk estimation via SCORE2-Diabetes

To reduce CV risk independent of glucose control[a]

- GLP-1 RA[b] (Class I)
- SGLT2 inhibitor[c] (Class I)
- Independent of HbA1c
- Independent of concomitant glucose-lowering medication

For additional glucose control

Glucose-lowering agents with suggested CV benefit

- Metformin (Class IIa)
- Pioglitazone[d] (Class IIb)

Glucose-lowering agents with proven CV safety

- DPP-4 inhibitors (sitagliptin, alogliptin, linagliptin)[e]
- Ertugliflozin[f]
- Sulfonylureas (glimepiride or gliclazide)
- Insulin glargine or insulin degludec
- Other GLP-1 RAs (lixisenatide, exenatide ER, oral semaglutide)

Glucose-lowering agents without CV safety evaluation

- E.g. short-acting insulins
- E.g. other sulfonylureas

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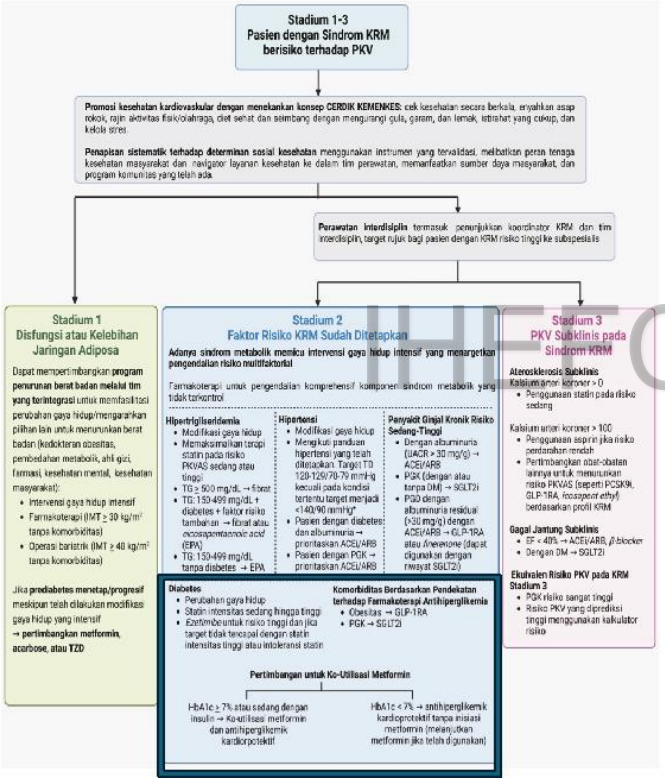
GLP-1RA and SGLT2i Are the Agents of Choice to Manage Co-Burden of T2DM and CVD



Diabetes
- Perubahan gaya hidup
- Statin intensitas sedang hingga tinggi
- *Ezetimibe* untuk risiko tinggi dan jika target tidak tercapai dengan statin intensitas tinggi atau intoleransi statin

Komorbiditas Berdasarkan Pendekatan terhadap Farmakoterapi Antihiperglikemia
- Obesitas → GLP-1RA
- PGK → SGLT2i

Pertimbangan untuk Ko-Utilisasi Metformin

HbA1c ≥ 7% atau sedang dengan insulin → Ko-utilisasi metformin dan antihiperglikemik kardiorpotektif

HbA1c < 7% → antihiperglikemik kardioprotektif tanpa inisiasi metformin (melanjutkan metformin jika telah digunakan)

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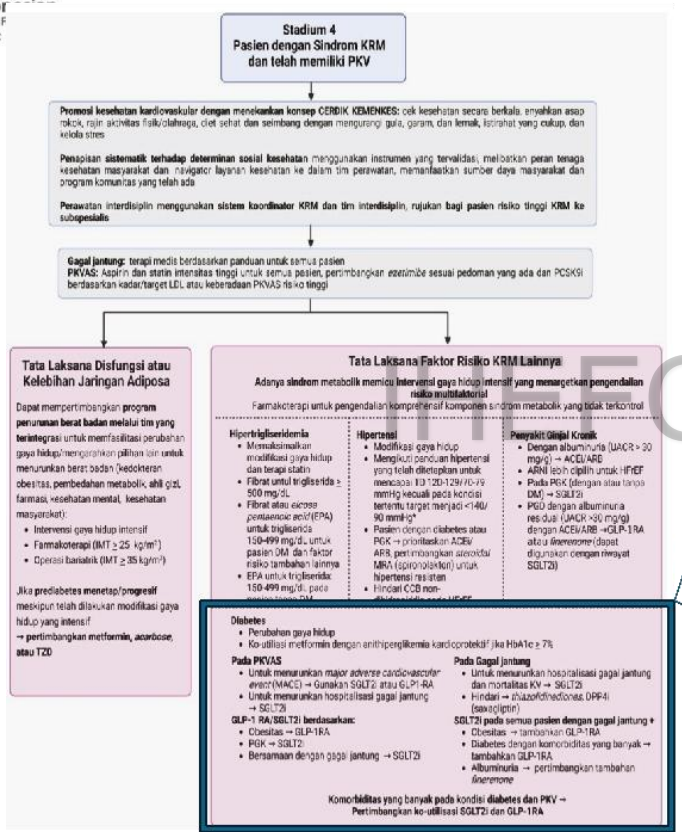
Recommended use of GLP-1RA and/or SGLT2i in patients **with stage 2 CRM syndrome with hyperglyvemia and obesity**

GLP-1RA and SGLT2i Are the Agents of Choice to Manage Co-Burden of T2DM and CVD



Diabetes
- Perubahan gaya hidup
- Ko-utiliasi metformin dengan anithiperglikemia kardioprotektif jika HbA1c ≥ 7%

Pada PKVAS
- Untuk menurunkan *major adverse cardiovascular event* (MACE) → Gunakan SGLT2i atau GLP1-RA
- Untuk menurunkan hospitalisasi gagal jantung → SGLT2i

GLP-1 RA/SGLT2i berdasarkan:
- Obesitas → GLP-1RA
- PGK → SGLT2i
- Bersamaan dengan gagal jantung → SGLT2i

Pada Gagal jantung
- Untuk menurunkan hospitalisasi gagal jantung dan mortalitas KV → SGLT2i
- Hindari → *thiazolidinediones*, DPP4i (saxagliptin)

SGLT2i pada semua pasien dengan gagal jantung +
- Obesitas → tambahkan GLP-1RA
- Diabetes dengan komorbiditas yang banyak → tambahkan GLP-1RA
- Albuminuria → pertimbangkan tambahan *finerenone*

Komorbiditas yang banyak pada kondisi diabetes dan PKV → Pertimbangkan ko-utilisasi SGLT2i dan GLP-1RA

Recommended use of GLP-1RA and/or SGLT2i in patients **with stage 4 CRM syndrome or with existing CVD**

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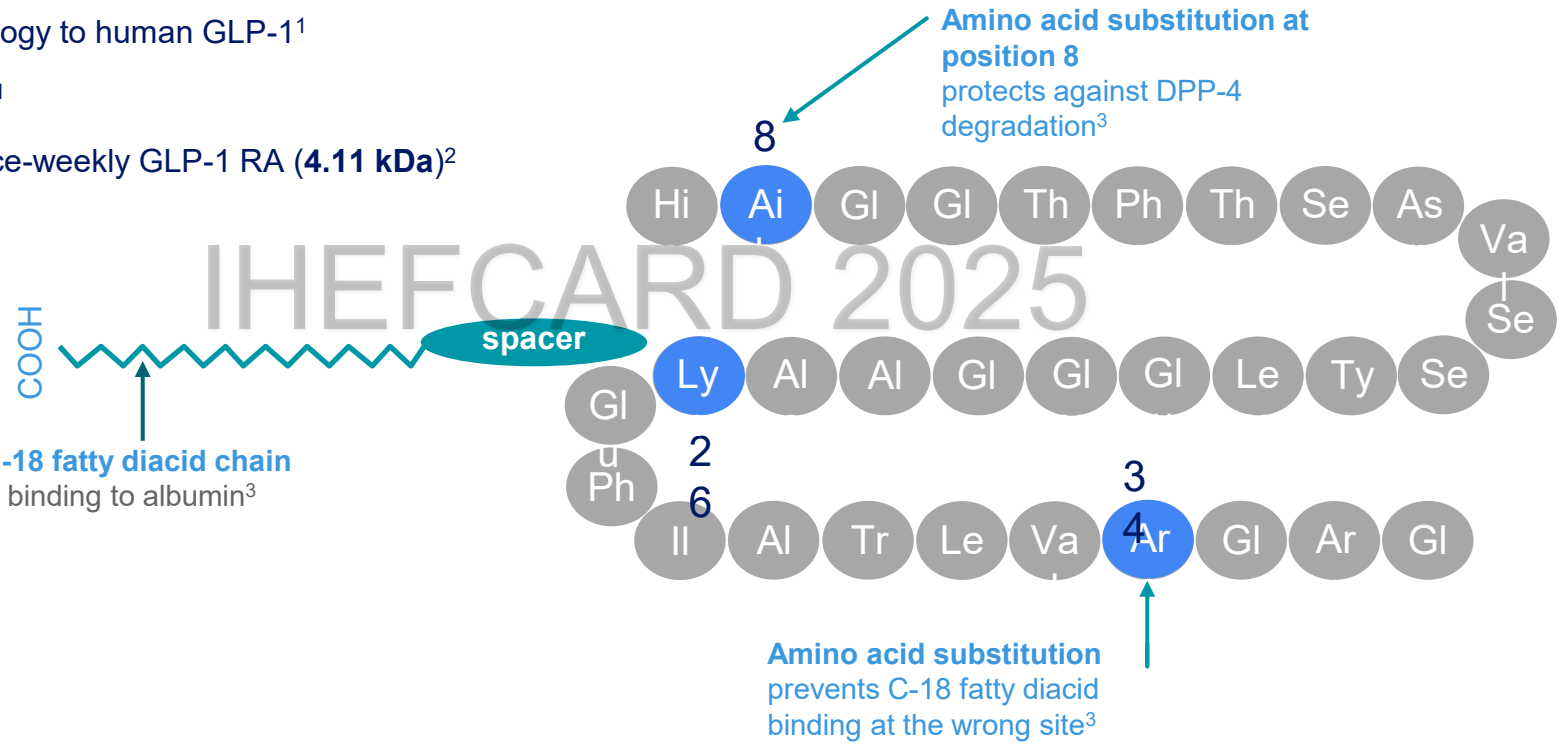
GLP-1 RA Semaglutide

Half-life of one week allowing a convenient once-weekly dosing

- **94%** homology to human GLP-1[1]
- $t_{1/2}$ **~1 week**[1]
- Smallest once-weekly GLP-1 RA (**4.11 kDa**)[2]



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GLP-1 RA=glucagon-like peptide-1 receptor agonist; t1/2= half-life; DPP-4=dipeptidyl peptidase-4.

***References:* 1.** *Ozempic® Prescribing Information, Indonesia 2023;* **2.** *Dhruv UA et al. JCD. 2016;2:18-25.* **3.** *Kapitza C et al. J Clin Pharmacol. 2015;55(5):497-504;* **4.** *Lau J et al. J Med Chem 2015;58:7370–80.*

Semaglutide improves metabolic health and slows down disease progression

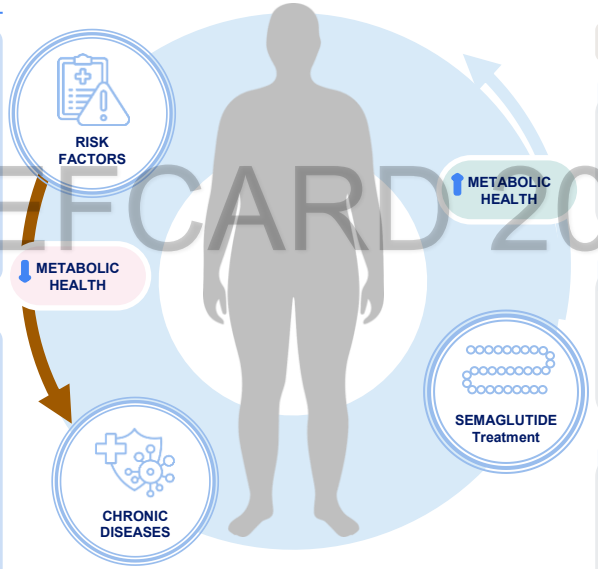
COMMON RISK FACTORS & LINKED CHRONIC DISEASES

Many people today live with a combination of **risk factors** like inflammation, adiposity, hypertension and insulin resistance that can **trigger a decline in metabolic health**[1-3]

- Inflammation
- Adiposity
- Hypertension
- Insulin resistance

This translates to an **increasing risk of developing interlinked diseases** within the **cardiometabolic spectrum**, such as:[4-8]

- T2D
- CKD
- MASH
- Obesity
- CVD



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MULTIFACTORIAL EFFECTS OF SEMAGLUTIDE

Non-exhaustive overview

Brain
- ⬇ Food intake[9-11]
- ⬇ Appetite[9-11]

Liver
- ⬇ Glucose production[12]
- ⬇ Accumulation of lipids[13]

Kidneys
- ⬆ Natriuresis[14,15]; Diuresis[15]
- ⬇ Inflammation[14,15]

Blood Vessels
- ⬇ Inflammation[14,15]
- ⬇ Platelet aggregation[17]

Pancreas
- ⬆ Insulin production[18]
- ⬇ Glucagon secretion[18]

Heart
- ⬇ Systolic blood pressure[19]
- ⬇ Inflammation[14,15]

Semaglutide is recommended in guidelines and has a well-established safety and tolerability profile

>43,000 patients have been investigated with semaglutide in clinical trials[1]

Cumulative exposure of **>33 million patient-years** globally[1]

Semaglutide is a recommended treatment across the cardiometabolic spectrum and the only GLP-1 RA offering CVD protection in people with obesity[2-5]

INCLUDED IN…

ESC European Society of Cardiology

American Diabetes Association.

EASO

KDIGO

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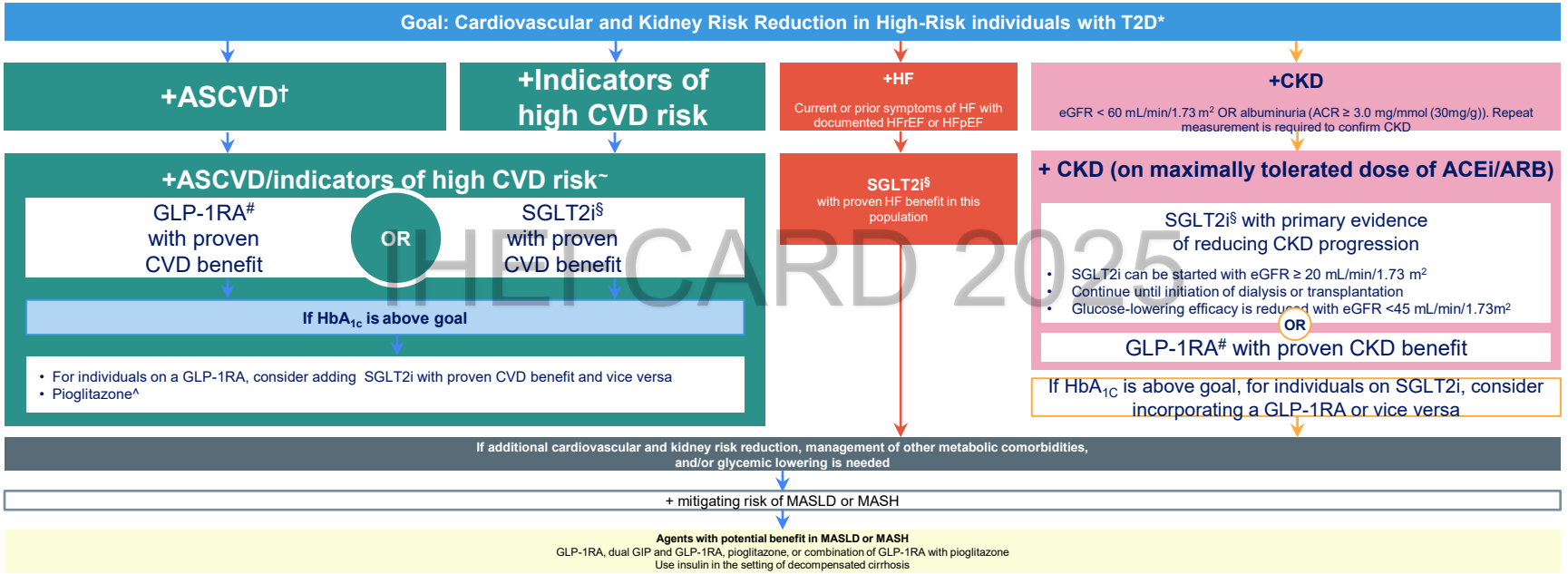
CVD, cardiovascular death; GLP-1 RA, glucagon-like peptide-1 receptor agonist; PwO, people with obesity

1. Novo Nordisk data on file. 2. Semaglutide (Rybelsus®) Summary of Product Characteristics, last revised September 2022. 3. Semaglutide (Ozempic®) Summary of Product Characteristics, last revised November 2022. 4. Semaglutide (Wegovy®) Summary of Product Characteristics, last revised October 2023. 5. Bergmann NC, et al. Diabetes Obes Metab. 2023;25:18-35.

T2D individuals with ASCVD/indicators of high risk for CVD, HF, CKD (ADA Standards of Care in Diabetes 2025)



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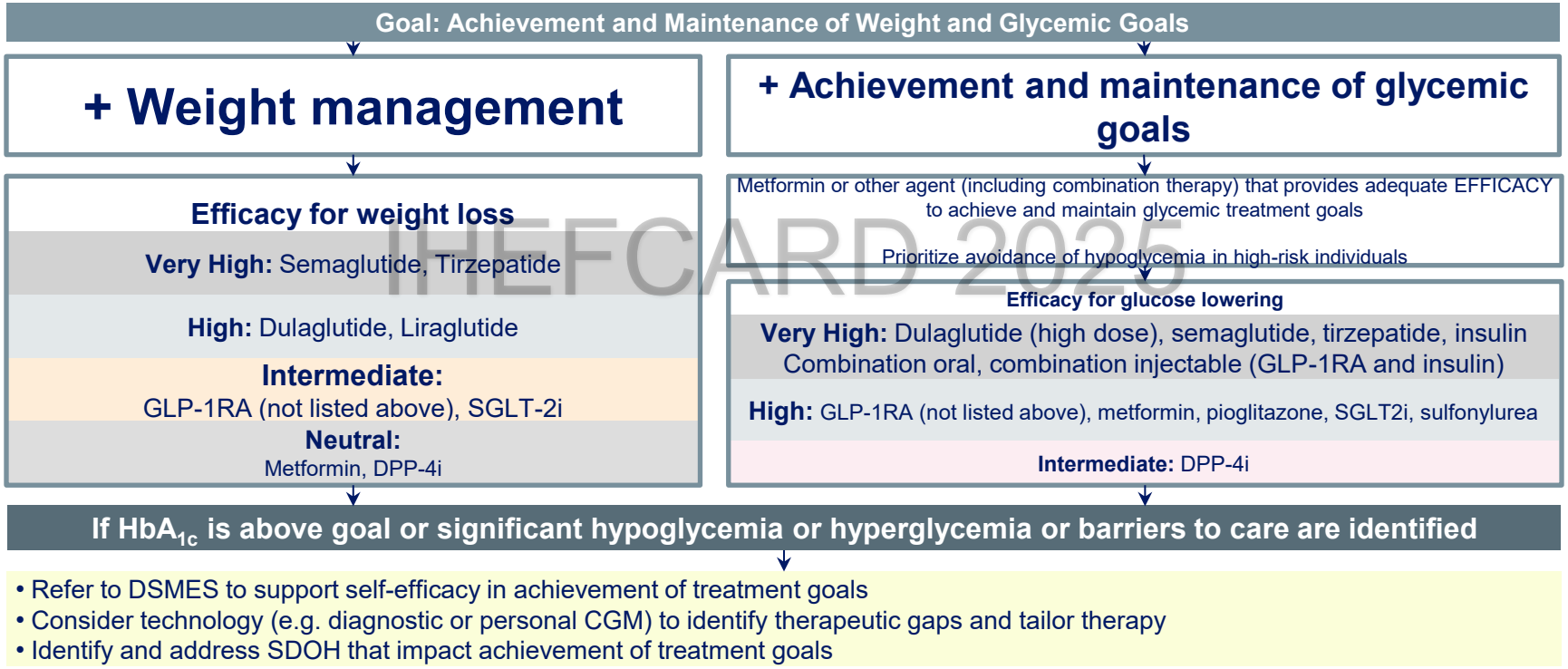
*In people with HF, CKD, established CVD or multiple risk factors for CVD, the decision to use a GLP-1RA or SGLT2i with proven benefit should be independent of background use of metformin;
†ASCVD: Defined differently across CVOTs but all included individuals with established CVD (e.g. MI, stroke, any revascularization procedure) and 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);
~ A strong recommendation is warranted for people with CVD and a weaker recommendation for those with indicators of high risk CVD. 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 shared decision-making process.
# For GLP-1RA, CVOTs demonstrate their efficacy in reducing composite MACE, CV death, all-cause mortality, MI, stroke and kidney endpoints in individuals with T2D with established/high risk of CVD. One kidney outcome trial demonstrated benefit in reducing persistent eGFR reduction and CV death for a GLP-1RA in individuals with CKD and T2D;
§ For SGLT2i, CV/kidney outcomes trials demonstrate their efficacy in reducing the risk of composite MACE, CV death, all-cause mortality, MI, HHF and kidney outcomes in individuals with T2D with established/high risk of CVD;
^Low-dose pioglitazone may be better tolerated and similarly effective as higher doses.
ASCVD, atherosclerotic cardiovascular disease; CV, cardiovascular; CKD, chronic kidney disease; HbA_{1c}, glycated hemoglobin; HF, heart failure; GLP-1RAs, glucagon-like peptide-1 receptor agonists; MACE, Major adverse cardiac events; MASH, metabolic dysfunction–associated steatohepatitis; MASLD, metabolic dysfunction-associated steatotic liver disease; SGLT2i, sodium–glucose cotransporter-2 inhibitors; T2D, type 2 diabetes; TZD, thiazolidinedione. Standards of Care in Diabetes - 2025: Diabetes Care, January 2025, Vol.48, Supplement 1; **Figure 9.3**

Achievement and maintenance of weight and glycemic management goals in those without established ASCVD, CKD or HF (ADA Standards of Care in Diabetes 2025)



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ASCVD, atherosclerotic cardiovascular disease; CV, cardiovascular; CKD, chronic kidney disease; DPP4i, Dipeptidyl peptidase-4 inhibitor; HbA1c, glycated hemoglobin; HF, heart failure; GLP-1RAs, glucagon-like peptide-1 receptor agonists; SGLT2i, sodium–glucose cotransporter-2 inhibitors; T2D, type 2 diabetes; TZD, thiazolidinedione. Standards of Care in Diabetes - 2025. Diabetes Care, January 2025, Vol.48, Supplement 1; ***Figure 9.3***

SUMMARY

- CKM syndrome is a heatlh disorder due to connections among heart disease, kidney disease, diabetes, and obesity leading to poor health outcomes
- CKM syndrome most likely originates from excess and dysfunctional adipose tissue effective approach to address excess adiposity and related insulin resistance provides the opportunity to address the root cause of CKD syndrome
- CKM staging model emphasizes the progressive pathophysiology of CKM syndrome, underscore the importance of early detection and intervention of CKM are often associated with greater clinical benefit
- Recent evidence demonstrates the benefit of an antihyperglycemic medication such as SGLT2 inhibitor and GLP-1 RA to manage and prevent adverse CVD events and CKD progression
- GLP-1 RA therapy plays a role in various pathophysiological in CKM syndrome (brain, liver, kidney, blood vessels, pancreas, and heart)

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Indonesian Working Group on Heart Failure and Cardiometabolic Disease

Thank You

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