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Azienda Provinciale per i Servizi Sanitari
Provincia Autonoma di Trento

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UNIVERSITÀ DI TRENTO

UNIVERSITÀ di VERONA
Facoltà di MEDICINA E CHIRURGIA

La Sindrome Cardio-Nefro-Metabolica: Un Connubio Mortale

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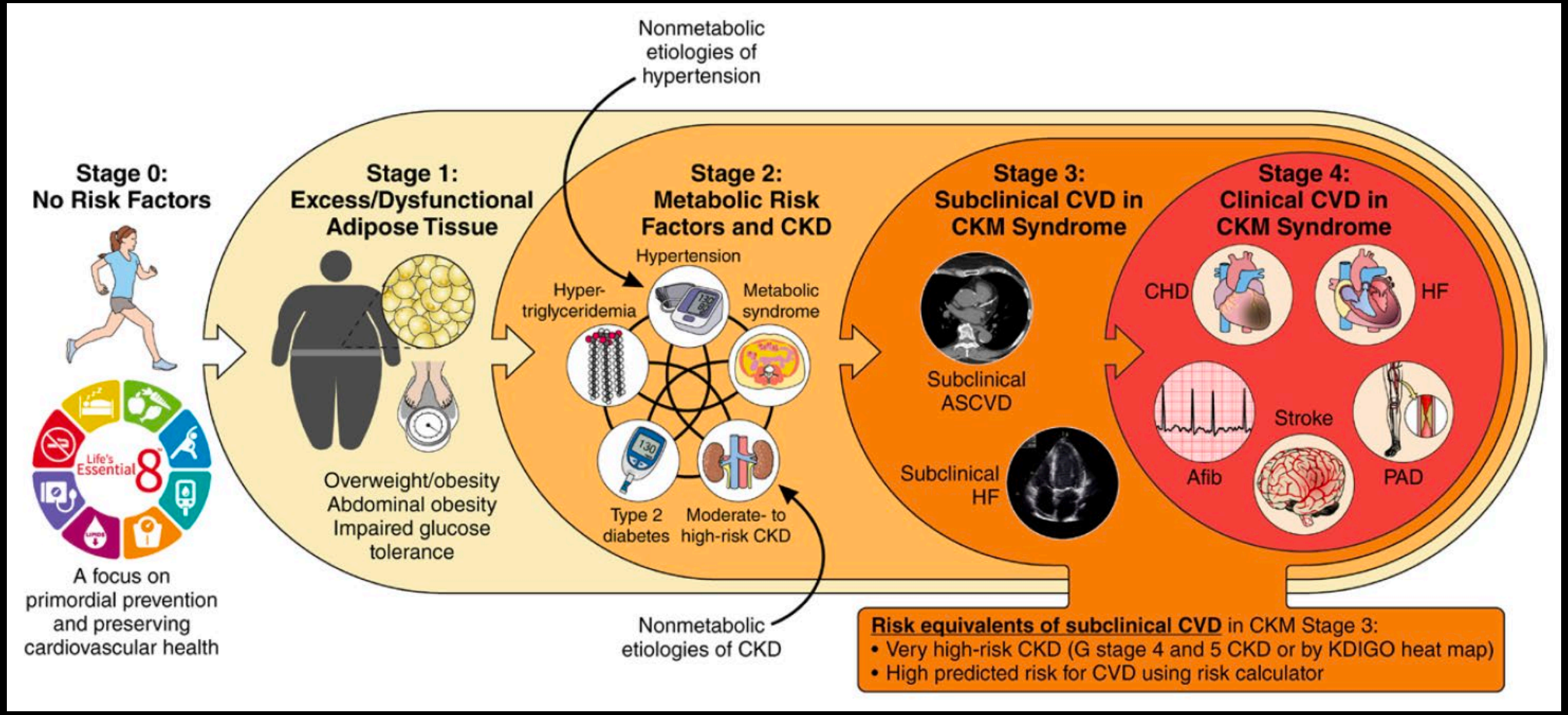
PRESENTER FINANCIAL DISCLOSURE

Over the past 2 calendar years, dr. M. Dauriz occasionally served as Consultant and/or Member of the Advisory Board for

NOVONORDISK, ASTRAZENECA, ELI LILLY, BOEHRINGER, SANOFI, GUIDOTTI, DAIICHI SANKYO

Stages of the CKM Syndrome



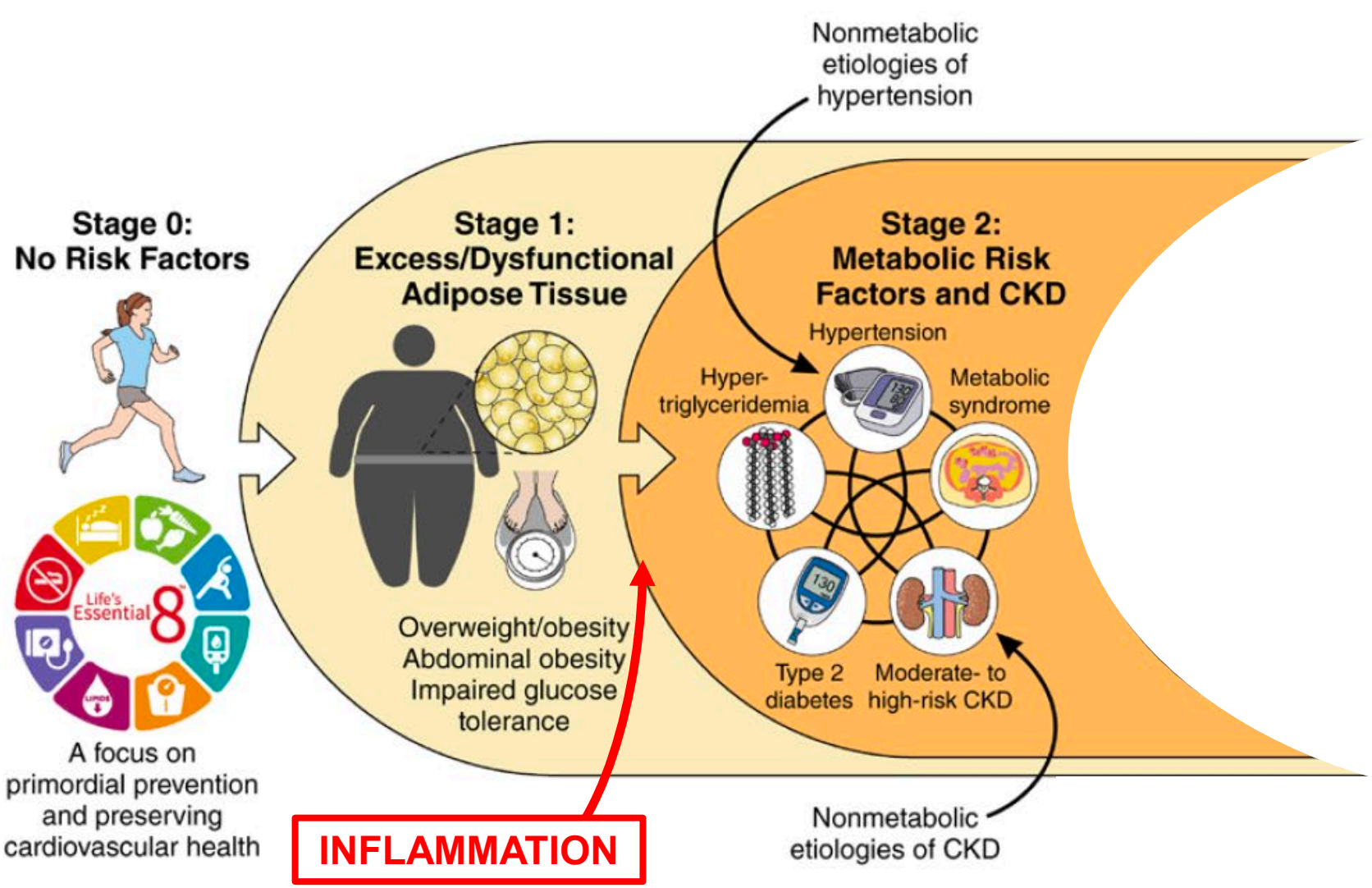
Ndumele CE, *Circulation*. 2023;148:1606–1635

Definition of the CKM Syndrome Stages (I)

CKM syndrome stages	Definition
Stage 0: No CKM risk factors	Individuals with normal BMI and waist circumference, normoglycemia, normotension, a normal lipid profile, and no evidence of CKD or subclinical or clinical CVD
Stage 1: Excess or dysfunctional adiposity	Individuals with overweight/obesity, abdominal obesity, or dysfunctional adipose tissue, without the presence of other metabolic risk factors or CKD BMI ≥25 kg/m^2 (or ≥23 kg/m^2 if Asian ancestry), Waist circumference ≥88/102 cm in women/men (or if Asian ancestry ≥80/90 cm in women/men), or Fasting blood glucose ≥100–124 mg/dL or HbA1c between 5.7% and 6.4%*

Ndumele CE, *Circulation*. 2023;148:1606–1635

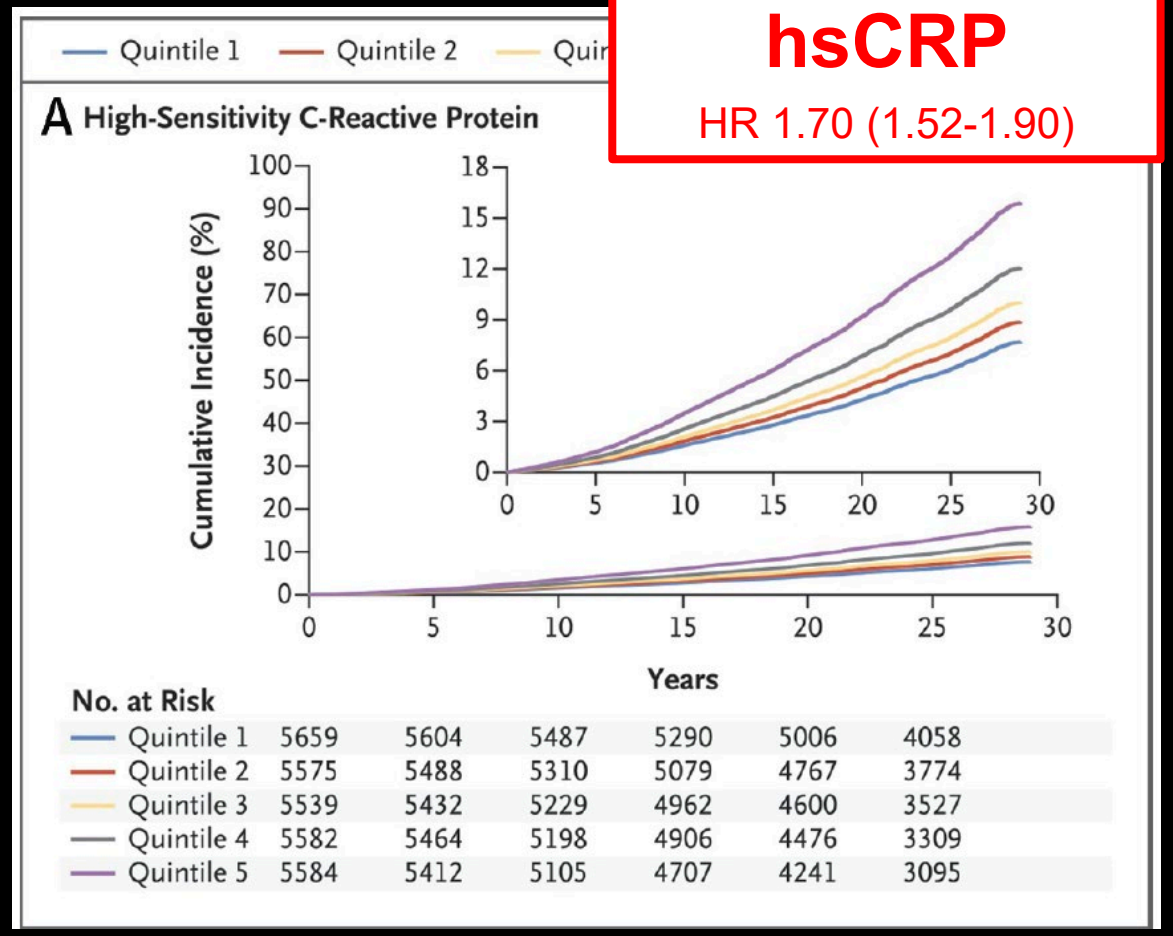
Subclinical, chronic inflammation as key mediator along the CKM continuum



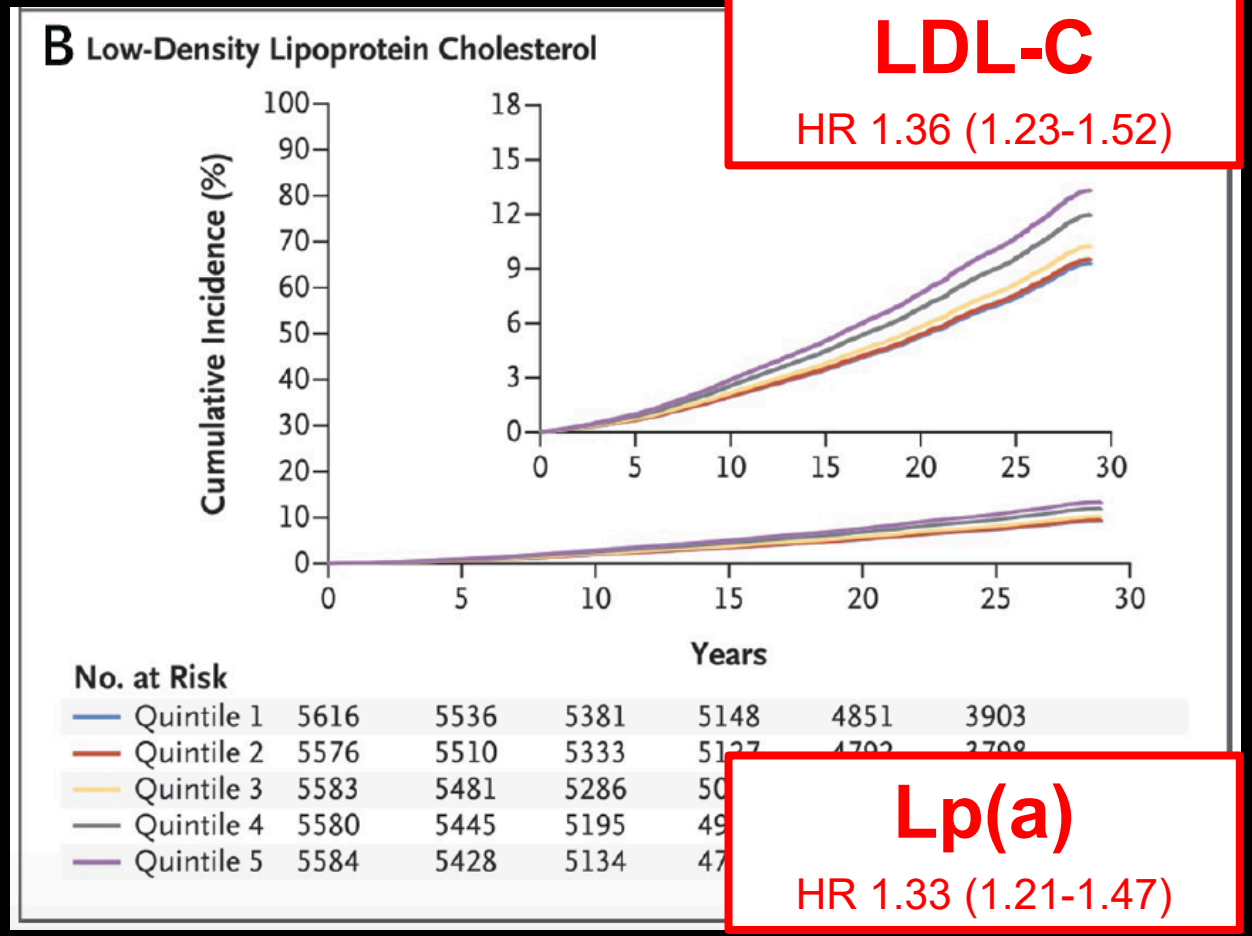
Ndumele CE, *Circulation*. 2023;148:1606–1635

Cumulative Incidence of First Major Cardiovascular Events According to Baseline Levels of hsCRP and LDL-C

30-year HRs and cumulative incidence for first major adverse cardiovascular events among 27,939 initially healthy American women



hsCRP
HR 1.70 (1.52-1.90)

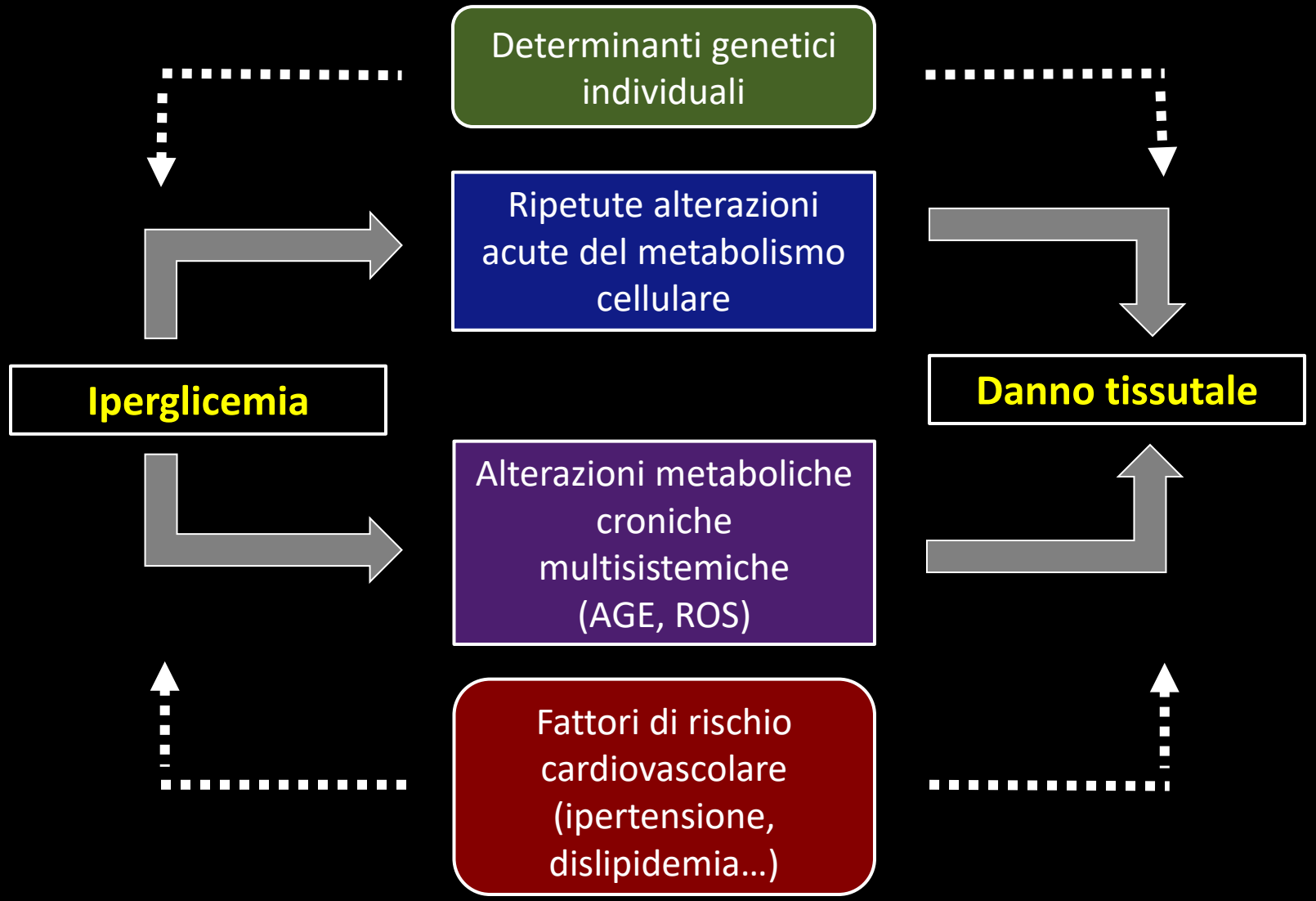


LDL-C
HR 1.36 (1.23-1.52)

Lp(a)
HR 1.33 (1.21-1.47)

N Engl J Med. 2024;391:2087–2097

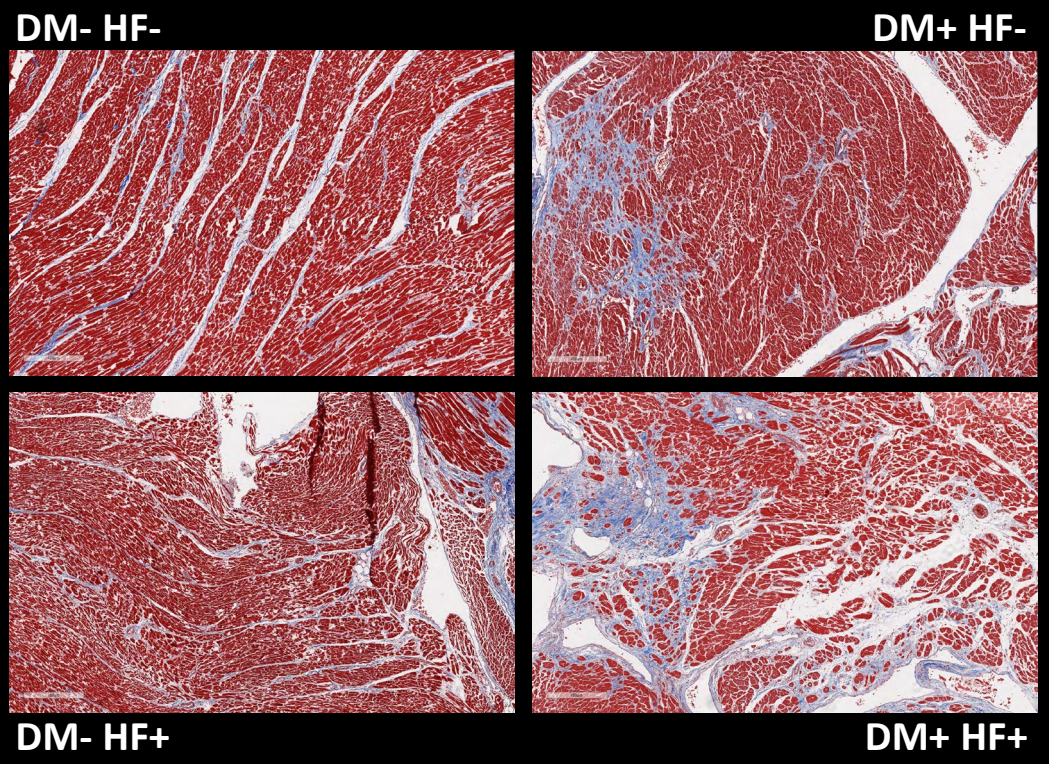
IPERGLICEMIA E DANNO MULTISISTEMICO: FISIOPATOLOGIA

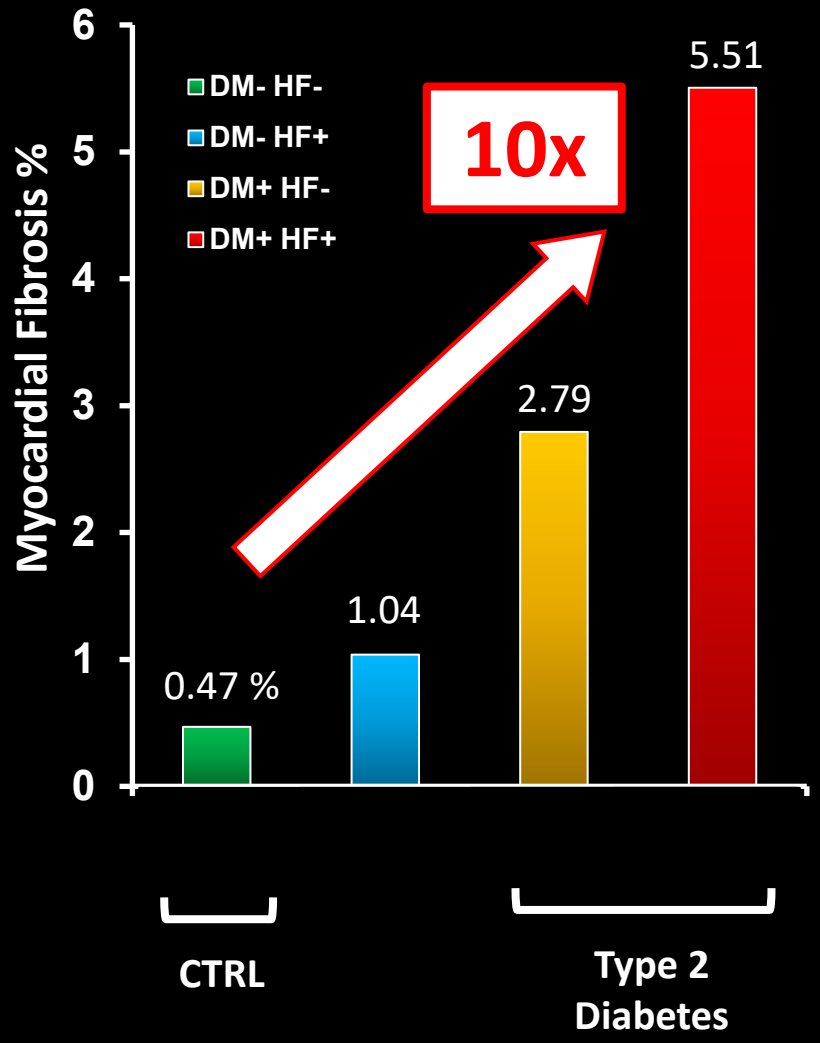


Adattata da Brownlee M., Diabetes (2005)

Structural and Functional Changes Occur in the Failing Heart

Proportion of Myocardial Fibrosis Area* according to Diabetes Status and Clinical HF Diagnosis

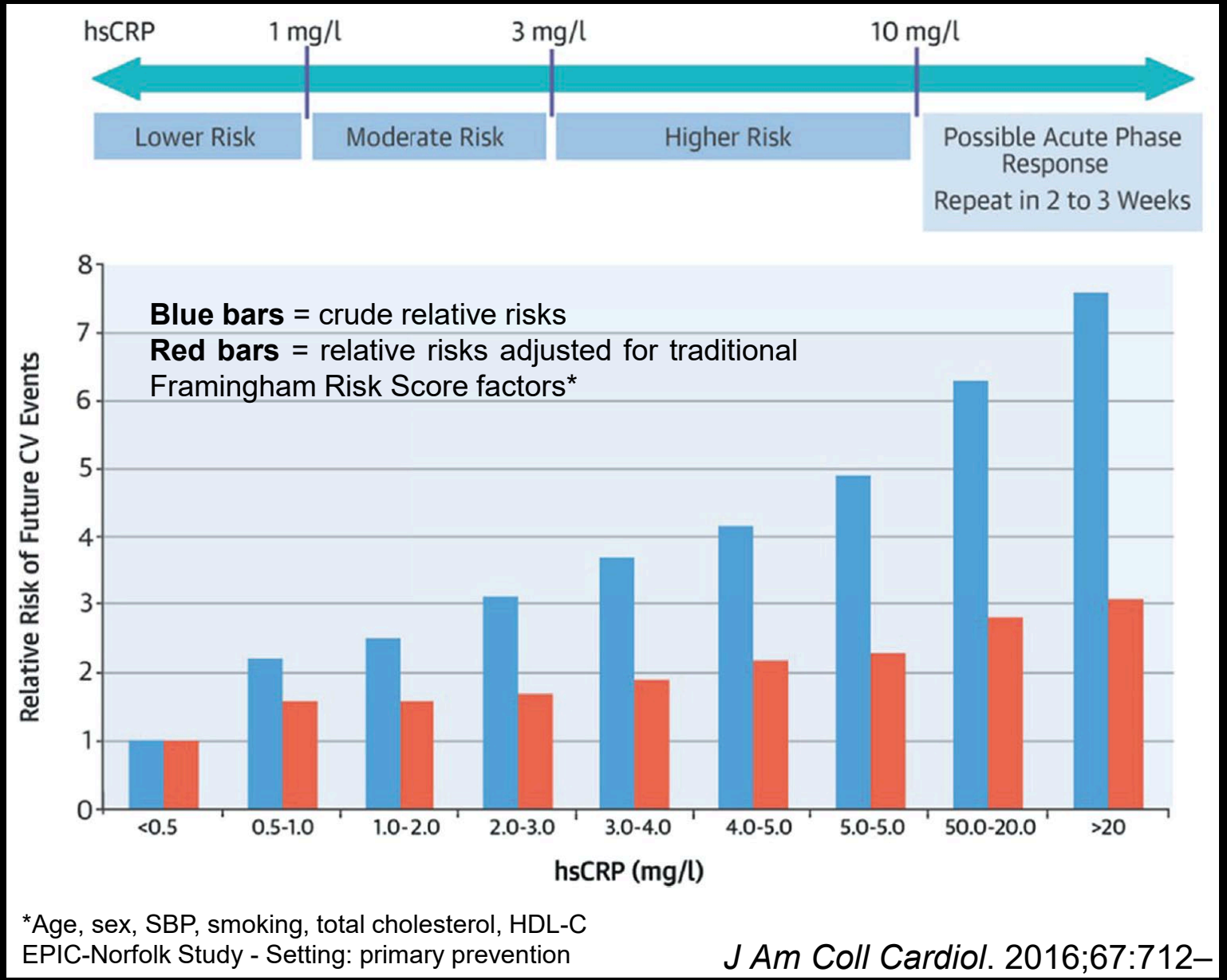




***NOTE:** estimates of cardiac fibrosis are calculated on the entire heart slide as the ratio of Masson-stained fibrosis area-to-total myocardium area with Photoshop CS5 (Adobe Systems Inc.)

Dauriz M. et al., preliminary data

Clinical Interpretation of hsCRP for Cardiovascular Risk Prediction



*Age, sex, SBP, smoking, total cholesterol, HDL-C
EPIC-Norfolk Study - Setting: primary prevention

J Am Coll Cardiol. 2016;67:712–

ACC SCIENTIFIC STATEMENT

Inflammation and Cardiovascular Disease: 2025 ACC Scientific Statement

A Report of the American College of Cardiology

Evaluation and Risk Assessment Biomarkers

- Because clinicians will not treat what they do not measure, universal screening of hsCRP in both primary and secondary prevention patients, in combination with cholesterol, represents a major clinical opportunity and is therefore recommended.
- Other inflammatory biomarkers such as serum amyloid A, IL-6, fibrinogen, white blood cell count, neutrophil-to-lymphocyte ratio, and EPA/AA ratio also predict cardiovascular risk; however, routine evaluation of these adds little to hsCRP and only hsCRP is recognized by regulatory agencies and has consistently been used in major cardiovascular outcome trials.

Imaging biomarkers

- Imaging biomarkers to detect vascular inflammation are promising in research but should not be used in routine clinical settings.

hsCRP screening and inflammation inhibition in primary prevention

- A single measurement of hsCRP (>3 mg/L) can be used in routine clinical practice to identify individuals at increased inflammatory risk if the patient is not acutely ill.
- In individuals with increased inflammatory burden, an early initiation of lifestyle interventions is recommended to reduce inflammatory risk.
- In primary prevention, the finding of a persistently elevated hsCRP level should lead to consideration of initiation or intensification statin therapy, irrespective of LDL cholesterol.

hsCRP screening and anti-inflammatory approaches in secondary prevention

- Among individuals with known cardiovascular disease both treated and not treated with statins, hsCRP is at least as powerful a predictor of recurrent vascular events as that of LDL cholesterol, demonstrating the importance of "residual inflammatory risk" in contemporary practice.
- Among individuals taking statin therapy, consideration should be given to increase dosage into the higher intensity range if hsCRP levels remain >2 mg/L, irrespective of LDL cholesterol.
- Low-dose colchicine reduces cardiovascular events among individuals with chronic stable atherosclerosis and is the first FDA approved anti-inflammatory agent for this purpose.
- Low-dose colchicine is intended to be used as an adjunct to lipid lowering; however, colchicine has not proven effective when initiated at the time of acute ischemia and should be avoided among individuals with significant liver or renal disease.
- Several novel anti-inflammatory agents, including IL-6 inhibitors, are now being evaluated in ongoing randomized trials in the settings of chronic kidney disease, dialysis, HFpEF, and acute coronary syndrome.

https://doi.org/10.1016/j.jacc.2025.08.047 -IN PRESS OCT 2025-

Diabetes Care
American Diabetes Association

Type 2 Diabetes Remission: A Systematic Review and Meta-analysis of Nonsurgical Randomized Controlled Trials

Diana T. Sherifali, Megan E. Racey, Michelle K. Greenway, Paige E. Alliston, Muhammad U. Ali, and Hertzel C. Gerstein, on behalf of the Integrated Knowledge Translation (iKT) Type 2 Diabetes Remission Advisory Team

Diabetes Care 2025;48(00):1–11 | https://doi.org/10.2337/dc25-0562

Aims

1) To assess the **effect** of pharmacological and nonpharmacological randomized controlled trials (RCTs) on type 2 diabetes (T2D) remission
2) To characterize the **components** of these T2D remission interventions

Methods

- Searched in MEDLINE and Embase to April 2025

Inclusion criteria:

- **Population**: Adults ≥18 years of age with T2D
- **Intervention**: Nonsurgical RCT for T2D remission
- **Outcomes**: T2D remission, weight loss, T2D relapse, glycated hemoglobin (A1C), patient-reported outcome measures (quality of life), and safety/adverse event
- Screened abstract and full-text articles in duplicate
- Random-effects multilevel meta-analytic modeling approach of outcomes

Results

18,355 studies

18 studies included

- Studies published between 2008 and 2025
- **Population**: Individuals with newly diagnosed T2D (14.6 months since diagnosis to 6.7 years); average age 53 years
- **Study duration**: 12 weeks to 18 months
- **Bias**: mostly low risk of bias
- Interdisciplinary teams using multimodal and tailored approaches

ODDS OF ACHIEVING T2D REMISSION

8 multimodal pharmacological RCTs	RR 1.75 (95% CI 1.49 to 2.04)
10 nonpharmacological RCTs	RR 5.80 (95% CI 4.28 to 7.87)

Significant decreases in body weight and significantly improved glucose control (A1C) and quality of life. RR, risk ratio.

Limitations and Next Steps

- Heterogeneity in our small pool of included studies (diversity of nonpharmacological components), stringent intervention protocols, narrow participant selection criteria, and lack of consistent remission definitions.
- Future research needs to consider **long-term sustainability** and effectiveness of these highly resourced and intensive interventions in real-world settings that include **diverse patient populations and unique individual preferences.**

Diabetes Remission Strategies

Pharmacological RCTs

RR 1.75 (95%CI 1.49 – 2.04)

Non pharmacological RCTs

RR 5.80 (95%CI 4.28 – 7.87)*

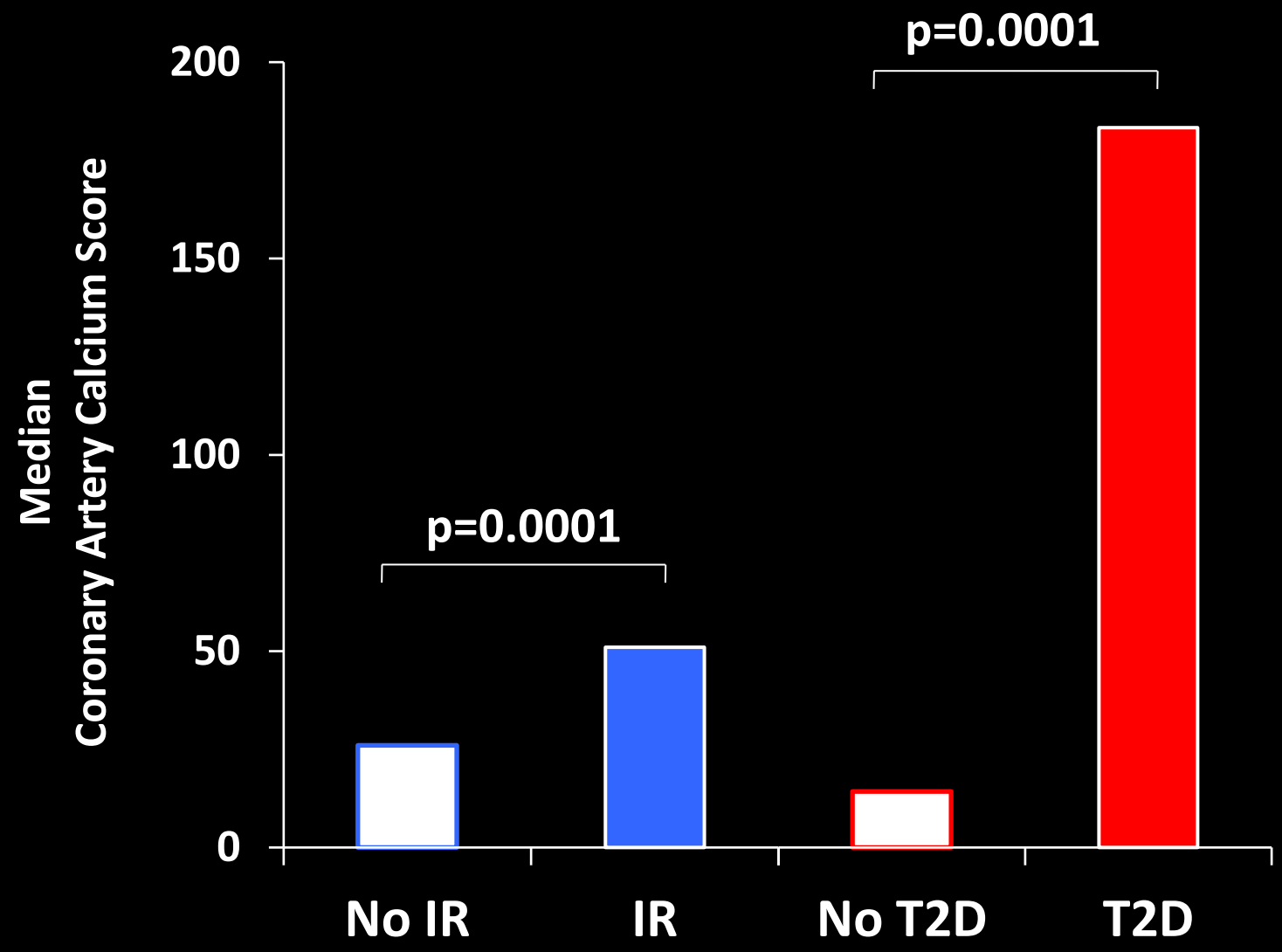
- (*) newly-diagnosed diabetes
- Average age 53 years
- treatment duration between 3 and 18 months

CKM syndrome stages	Definition
Stage 2: Metabolic risk factors and CKD	Individuals with metabolic risk factors (hypertriglyceridemia [≥135 mg/dL], hypertension, MetS.† diabetes). or CKD
Stage 3: Subclinical CVD in CKM	Subclinical ASCVD or subclinical HF among individuals with excess/dysfunctional adiposity, other metabolic risk factors, or CKD Subclinical ASCVD to be principally diagnosed by coronary artery calcification (subclinical atherosclerosis by coronary catheterization/CT angiography also meets criteria) Subclinical HF diagnosed by elevated cardiac biomarkers (NT-proBNP ≥125 pg/mL, hs-troponin T ≥14 ng/L for women and ≥22 ng/L for men, hs-troponin I ≥10 ng/L for women and ≥12 ng/L for men) or by echocardiographic parameters, with a combination of the 2 indicating highest HF risk.

Definition of the CKM Syndrome Stages (II)

Ndumele CE, *Circulation*. 2023;148:1606–1635

Atherosclerosis is higher in T2D but also in intermediate, Insulin Resistant (IR) phenotype



The Framingham Offspring Study

Meigs et al. Diabetes Care 2002

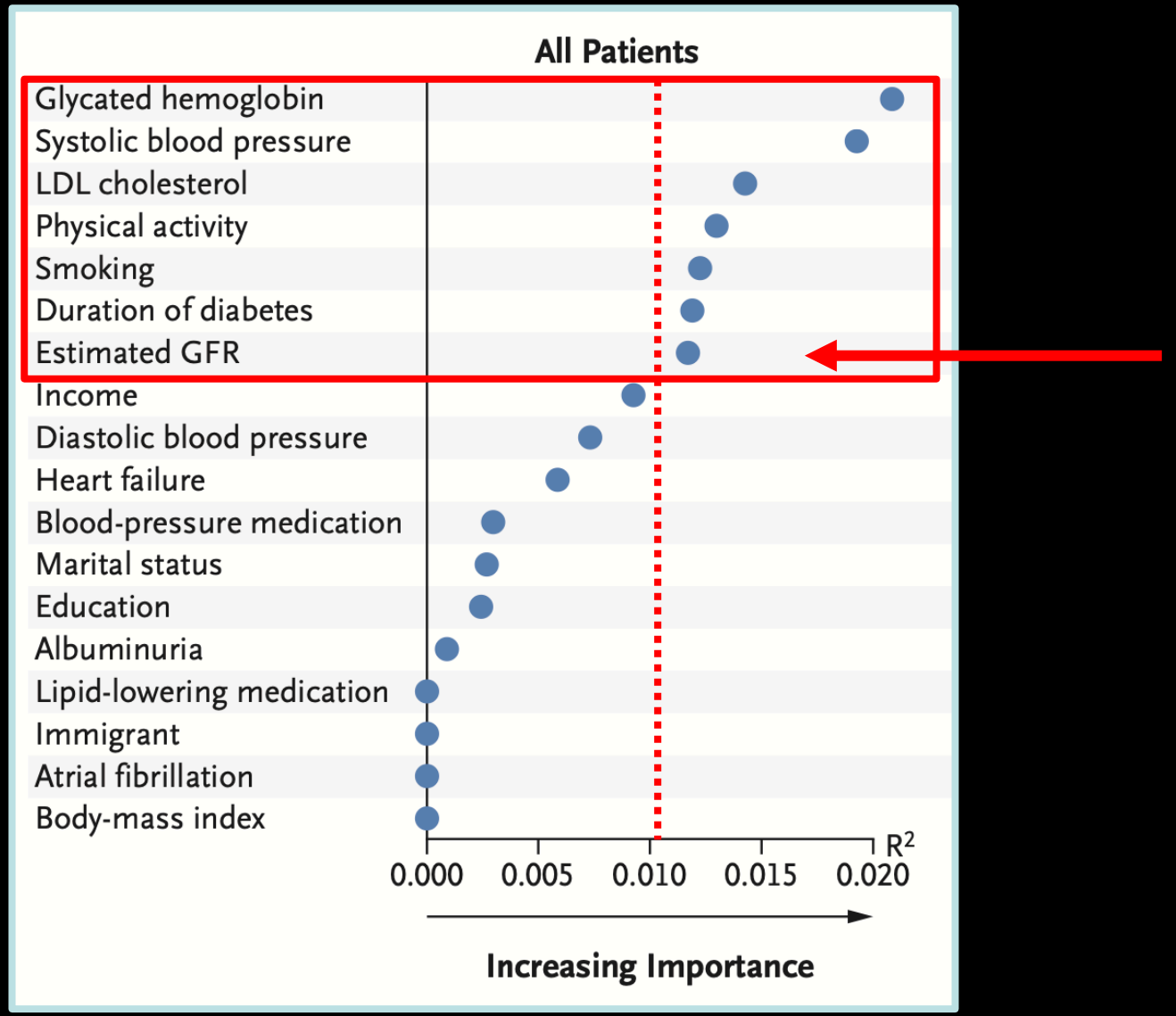
Definition of the CKM Syndrome Stages (III)

Ndumele CE, *Circulation*. 2023;148:1606–1635

CKM syndrome stages	Definition
Stage 2: Metabolic risk factors and CKD	Individuals with metabolic risk factors (hypertriglyceridemia [≥135 mg/dL], hypertension, MetS.† diabetes). or CKD
Stage 3: Subclinical CVD in CKM	Subclinical ASCVD or subclinical HF among individuals with excess/dysfunctional adiposity, other metabolic risk factors, or CKD Subclinical ASCVD to be principally diagnosed by coronary artery calcification (subclinical atherosclerosis by coronary catheterization/CT angiography also meets criteria) Subclinical HF diagnosed by elevated cardiac biomarkers (NT-proBNP ≥125 pg/mL, hs-troponin T ≥14 ng/L for women and ≥22 ng/L for men, hs-troponin I ≥10 ng/L for women and ≥12 ng/L for men) or by echocardiographic parameters, with a combination of the 2 indicating highest HF risk. Risk equivalents of subclinical CVD Very high-risk CKD (stage G4 or G5 CKD or very high risk per KDIGO classification) High predicted 10-y CVD risk
Stage 4: Clinical CVD in CKM	Clinical CVD (coronary heart disease, HF, stroke, peripheral artery disease, atrial fibrillation) among individuals with excess/dysfunctional adiposity, other CKM risk factors, or CKD Stage 4a: no kidney failure Stage 4b: kidney failure present

Relative importance of risk factors in predicting myocardial infarction mortality in subjects with type 2 diabetes

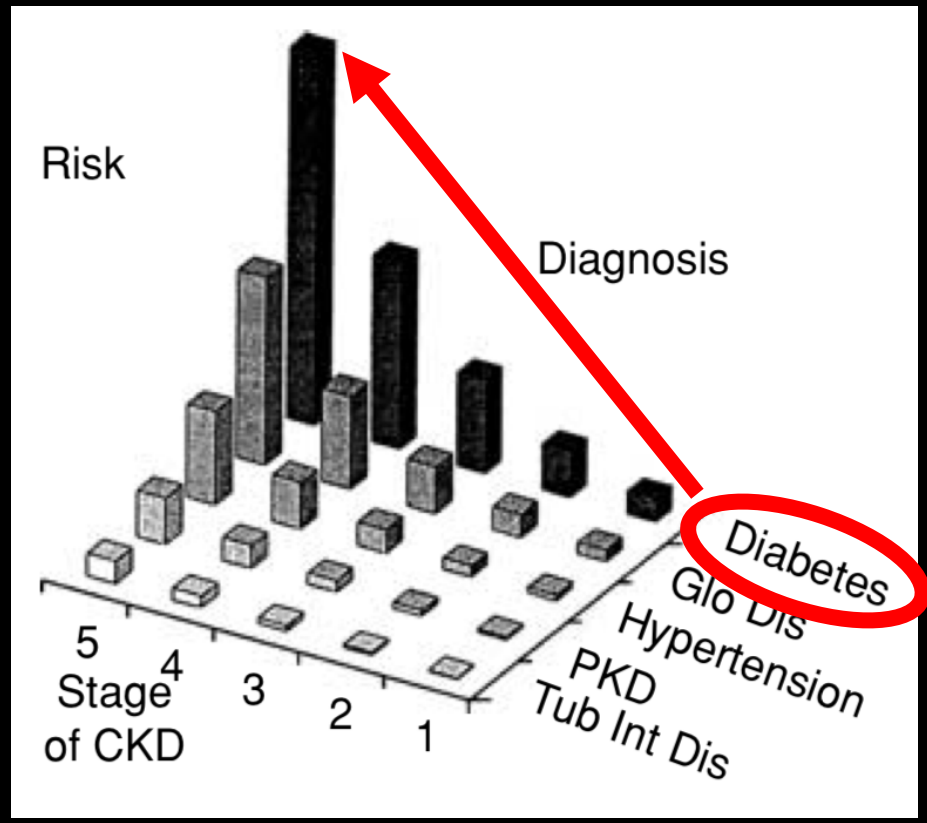
In a cohort study, were included 271,174 patients with type 2 diabetes who were registered in the Swedish National Diabetes Register and matched them with 1,355,870 controls on the basis of age, sex, and county.



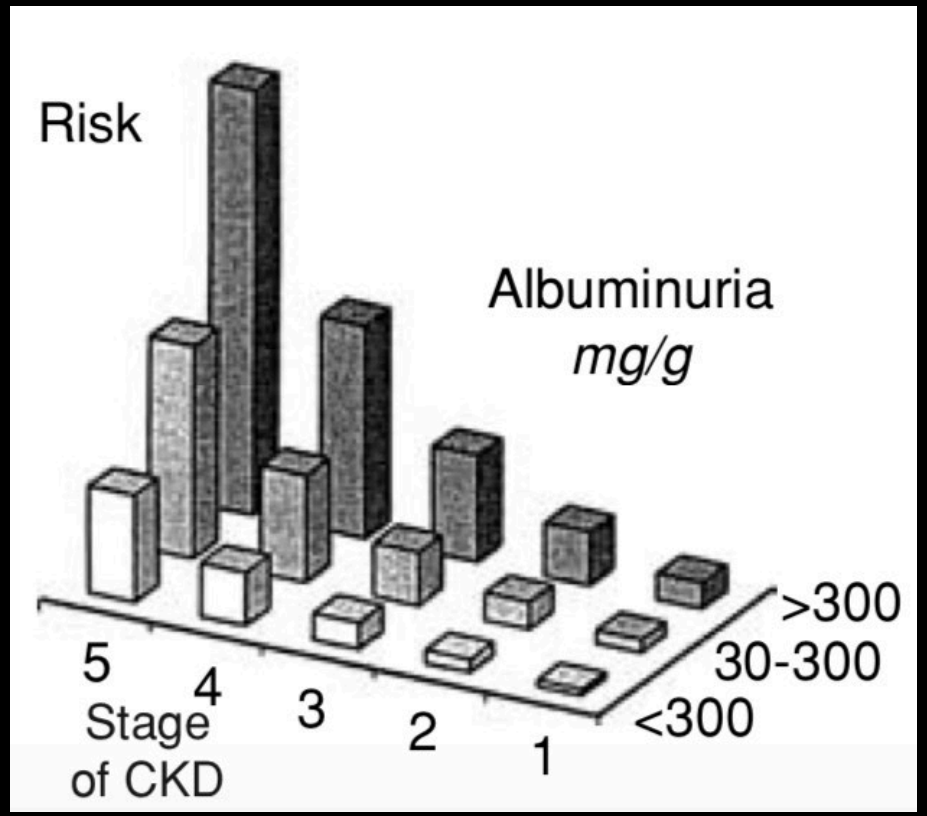
Rawshani A et al. *NEJM* 2018

STRATIFICAZIONE DEL RISCHIO DI MALATTIA RENALE CRONICA*

*progressione, mortalità e comorbidità



A.



B.

NKF Guidelines, *Am J Kidney Dis* 43 (Suppl 1):S1–S290, 2004

KDIGO heatmap for CKD classification and referral

CKD is classified based on:
Cause (C)*
GFR (G)†
Albuminuria (A)†

GFR categories (mL/min per 1.73 m²) Description and range				Albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30–299 mg/g 3–29 mg/mmol	≥300 mg/g ≥30 mg/mmol
	G1	Normal or high	≥90	Screen 1	Treat 1	Treat and refer 3
	G2	Mildly decreased	60–89	Screen 1	Treat 1	Treat and refer 3
	G3a	Mildly to moderately decreased	45–59	Treat 1	Treat 2	Treat and refer 3
	G3b	Moderately to severely decreased	30–44	Treat 2	Treat and refer 3	Treat and refer 3
	G4	Severely decreased	15–29	Treat and refer† 3	Treat and refer† 3	Treat and refer 4+
	G5	Kidney failure	<15	Treat and refer 4+	Treat and refer 4+	Treat and refer 4+

Low risk (if no other markers of kidney disease, no CKD)
Moderately increased risk
High risk
Very high risk

ONCE UPON A TIME

(early in the GWAS era)

the question was …

Which risk engines are best to assess CVD risk in diabetes?

NATURE REVIEWS | ENDOCRINOLOGY

Ray K. K. & Sattar, N. *Nat. Rev. Endocrinol.* 5, 302–303 (2009).

Chamnan P. , Simmons R.K. & Griffin S.J., *Nat. Rev. Endocrinol.* 6, Feb (2010).

ESC CVD Risk Calculation

For healthcare professionals

Designed for iPad. Not verified for macOS.

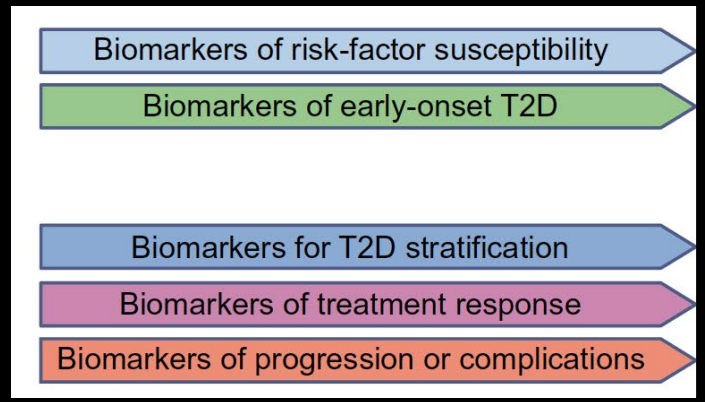
TODAY

(amidst the GWAS wave and at the beginning of metabolomics)

the question is …

“What can we reasonably add on top of clinical predictors to improve CVD risk assessment?”

Precision medicine for type 2 diabetes



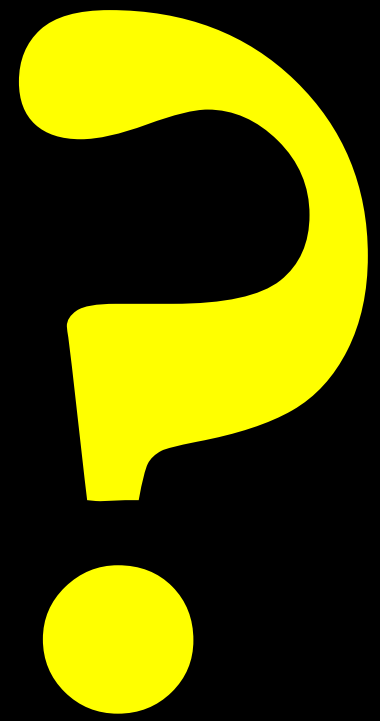
Diabetologia (2017) 60:784–792

TRANSLATIONAL GENETICS

Bringing genome-wide association findings into clinical use

Teri A. Manolio

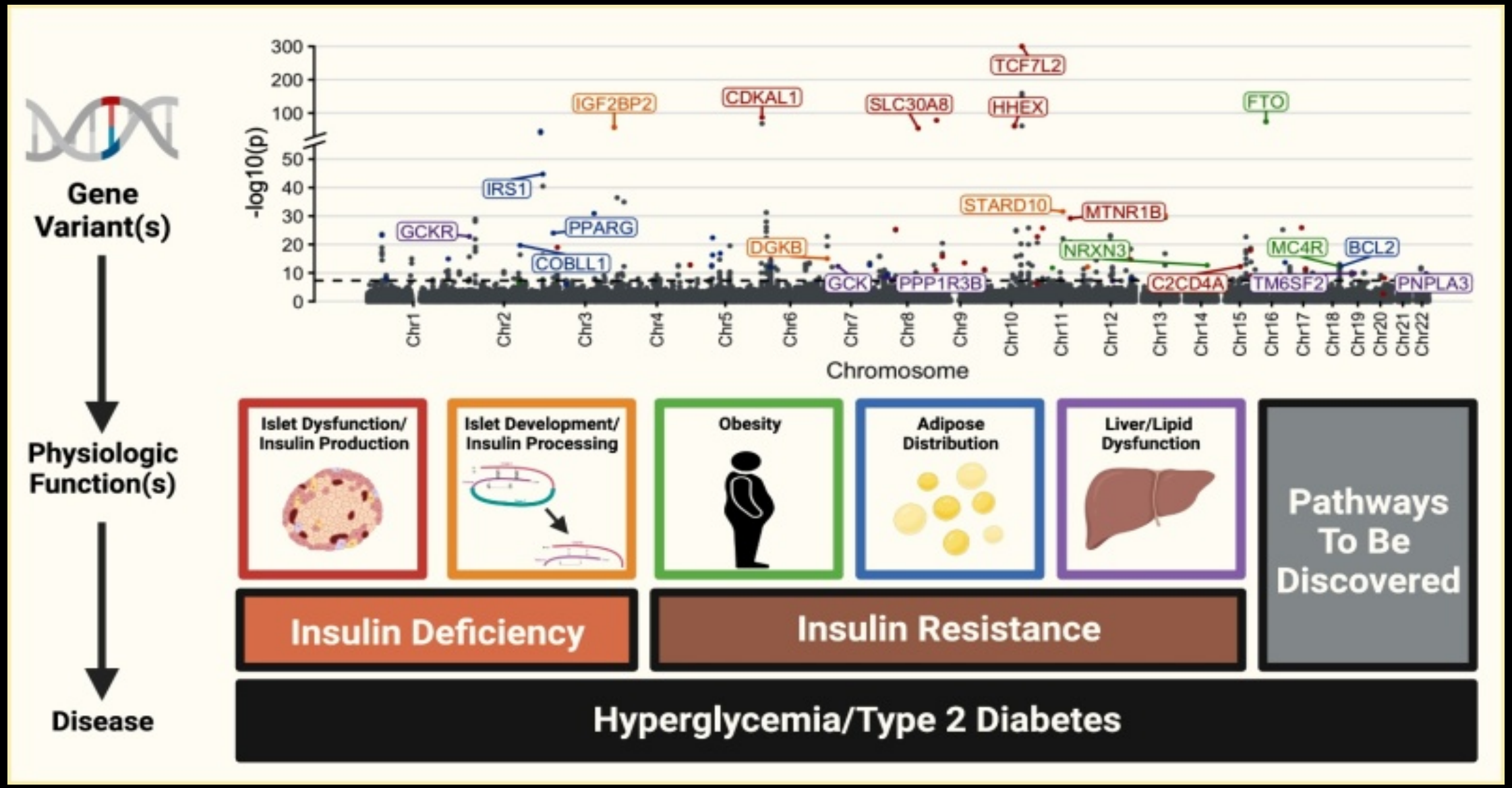
NATURE REVIEWS | GENETICS



Manhattan Plot & Q-Q Plot

Turner, 2018 *Journal of Open Source Software* 3(25),731

Type 2 Diabetes Loci Can Be Grouped Into Clusters That Appear to Capture Mechanisms of Disease.



Udler MS, *PLoS Med*. 2018;15(9):e1002654

Metabolic Pleiotropy on Display

nature genetics

Article

https://doi.org/10.1038/s41588-025-02355-3

A genetic map of human metabolism across the allele frequency spectrum

Received: 5 November 2024

Accepted: 29 August 2025

Published online: 03 October 2025

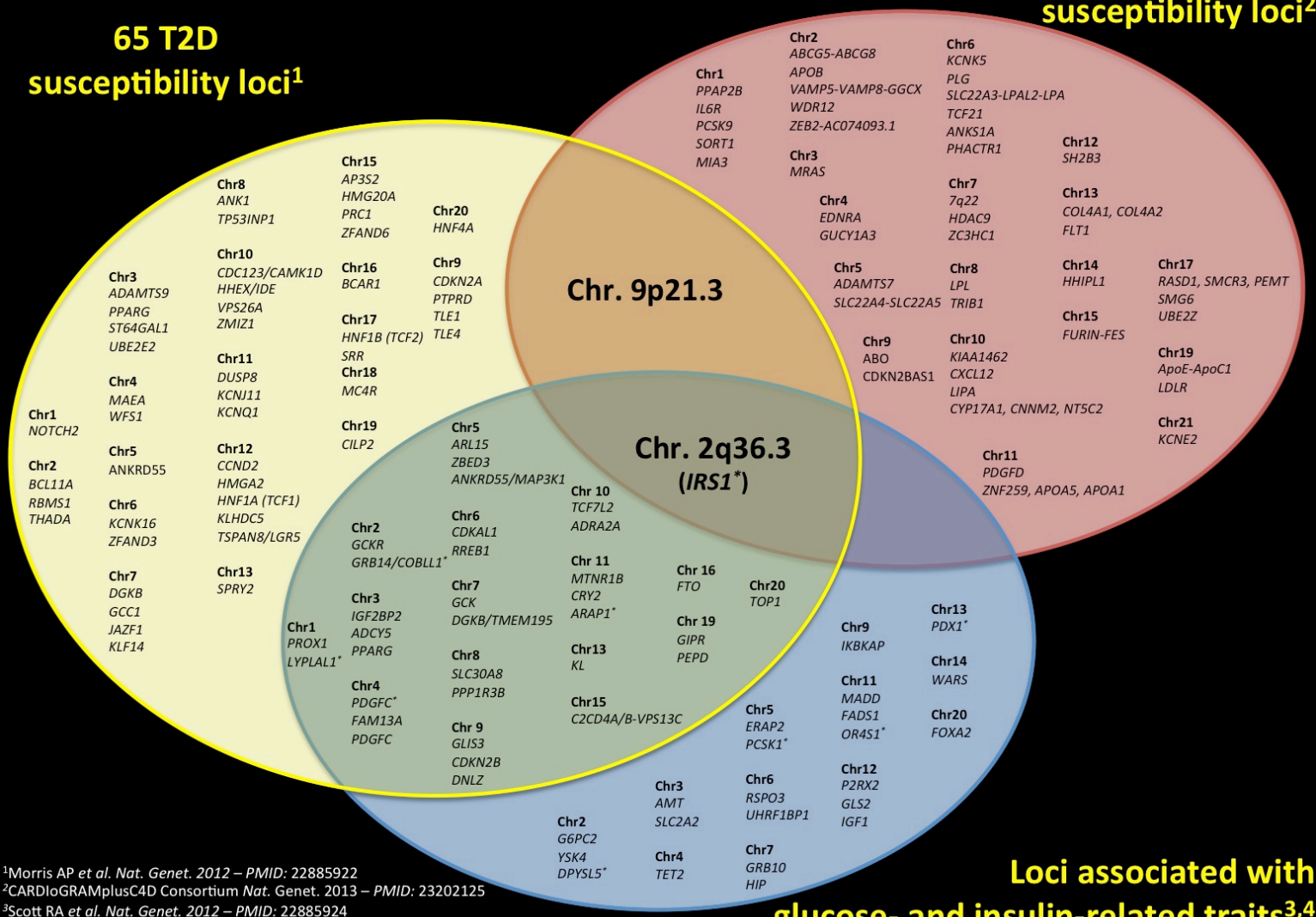
Martijn Zoodsma[1,2], Carl Beuchel[1,2], Summaira Yasmeen[1], Leonhard Kohleick[1], Aakash Nepal[1], Mine Koprulu[3], Florian Kronenberg[4], Manuel Mayr[5], Alice Williamson[1,3,6], Maik Pietzner[1,2,3,7] & Claudia Langenberg[1,2,3,7]

KEY MESSAGES

- Genetic regulation of circulating small molecules and lipoprotein characteristics (249 traits) in 500K UK Biobank individuals is shown
- The same variant associates with multiple metabolites in a coherent or divergent manner
- VEGFA appears a potential target to mitigate risk for CVD

There is evidence for overlapping associations among currently known T2D, CHD and glycaemic quantitative trait susceptibility loci from recent GWAS.

Dauriz & Meigs, *Curr. Cardiov. Risk Rep. 2014*



[1]Morris AP *et al. Nat. Genet. 2012 – PMID:* 22885922
[2]CARDIoGRAMplusC4D Consortium *Nat.* Genet. 2013 – *PMID:* 23202125
[3]Scott RA *et al. Nat. Genet. 2012 – PMID:* 22885924
[4]Manning AK *et al. Nat. Genet. 2012 – PMID:* 22581228 (*)

The impact of supplementing traditional risk information with polygenic risk score concerning type 2 diabetes and coronary heart disease on health behavior: a randomized controlled trial

Otto Halmesvaara[1] · Marleena Lonna[2,3] · Helena Kääriäinen[3] · Markus Perola[2,3] · Kati Kristiansson[2,3] · Hanna Konttinen[1]

Accepted: 19 March 2025 Journal of Community Genetics https://doi.org/10.1007/s12687-025-00790-7

STUDY HYPOTHESIS:

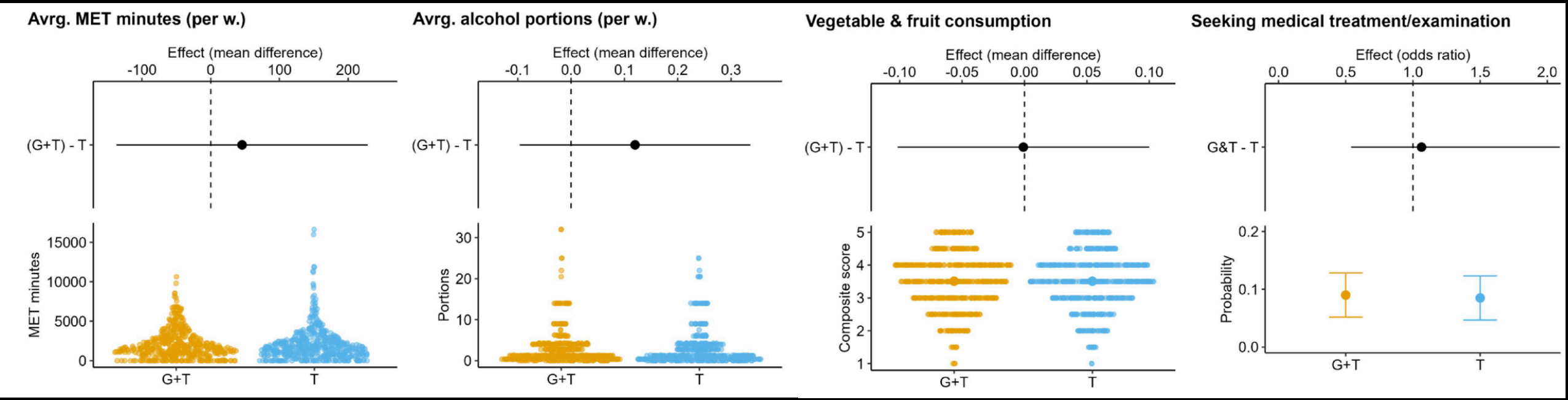
Supplementing risk estimates of type 2 diabetes and coronary heart disease based on traditional risk factors with PRS influences respondents' self-reported physical activity, alcohol and fruit/ vegetable consumption or prompts the respondents to seek medical treatment / examination.

RCT STUDY DESIGN:

The experimental group (n = 216) received risk estimates based on traditional risk and PRS, and the control group (n= 216) based solely on traditional risk factors.

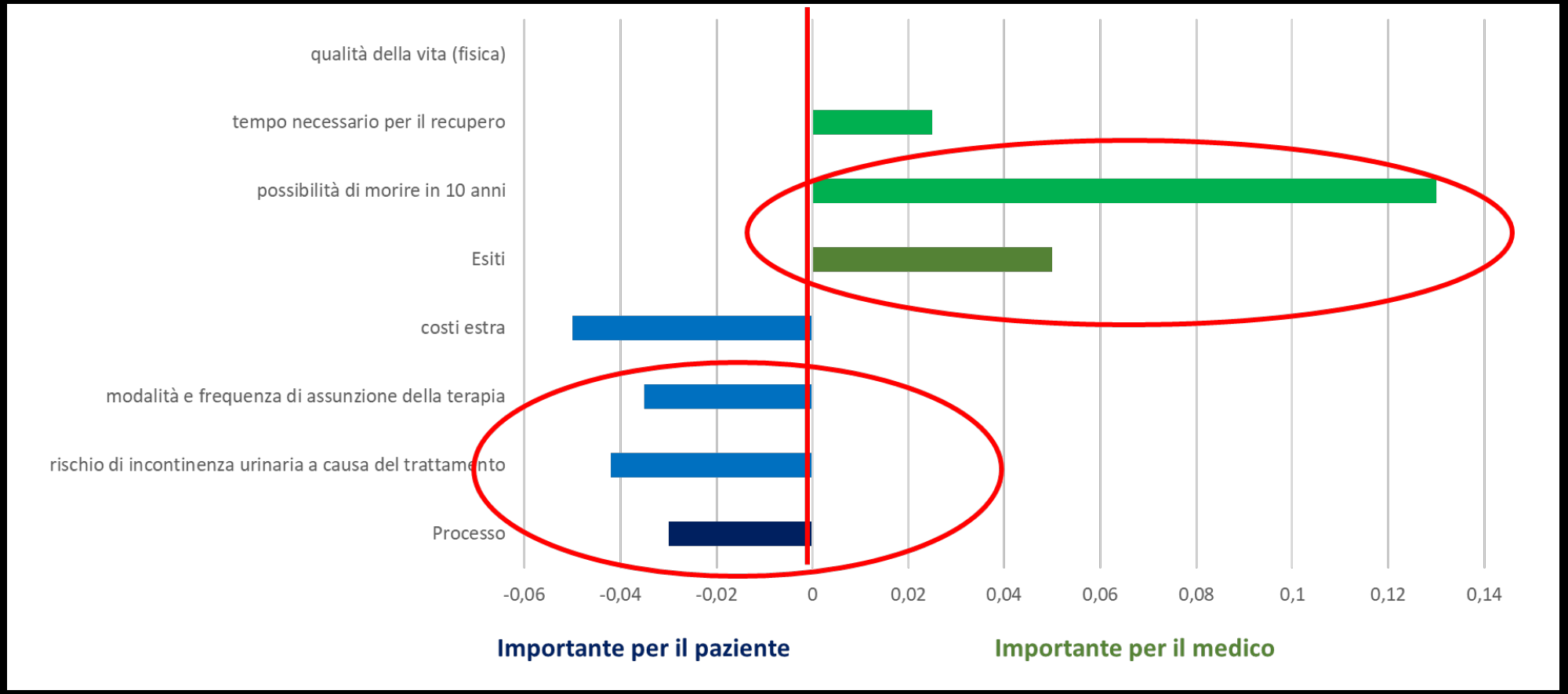
RESULTS:

After approximately 80 days between risk disclosure and outcome measurements, the study found no significant difference between the groups regarding health behavior or likelihood of seeking medical treatment/examination).



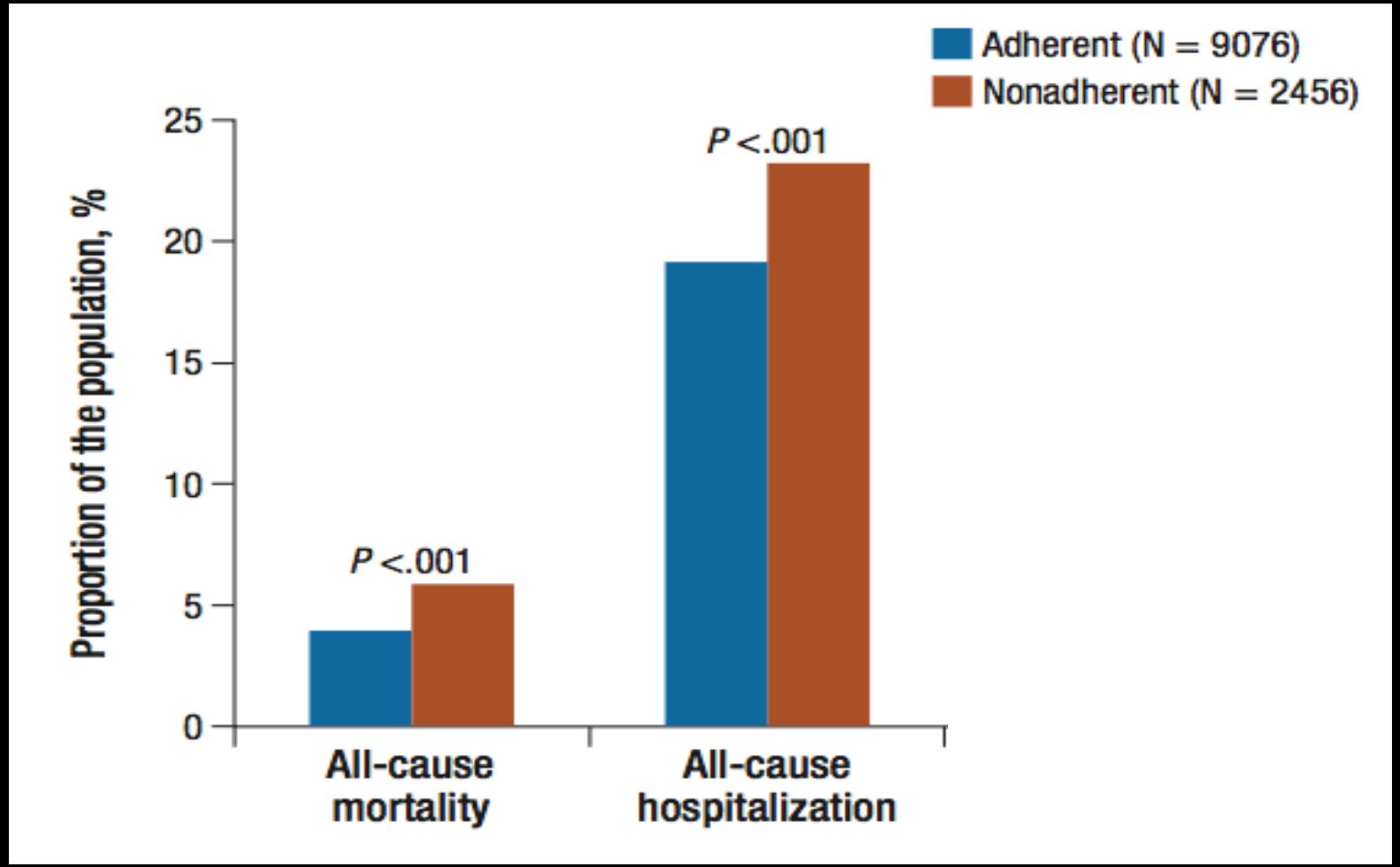
Differenza di importanza di alcuni attributi del trattamento tra medico e paziente: non sempre sono in accordo

Molto spesso il paziente valuta maggiormente importante l'impatto della terapia sulla sua quotidianità rispetto agli esiti clinici



Harrison M et al. BMJ Open 2017;7:e014719

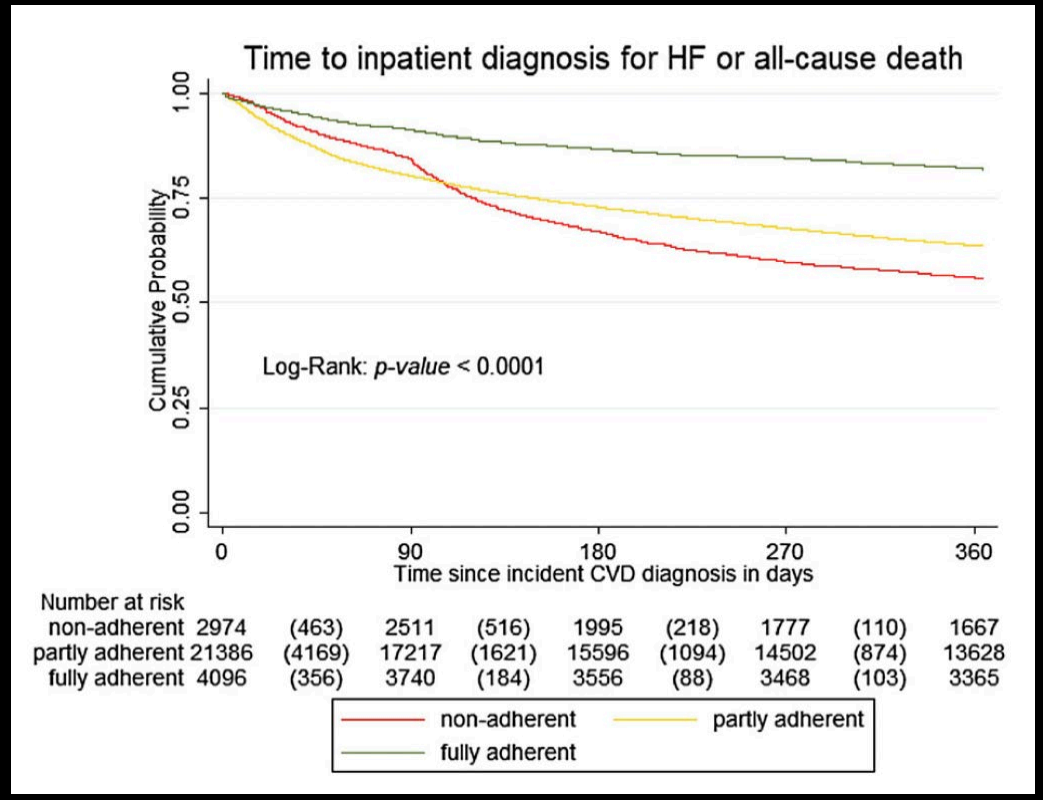
Impatto dell'aderenza sulla mortalità per tutte le cause e sull'ospedalizzazione nel T2DM



Ho PM et al - Arch Intern Med 2006; 166:1836

Guideline Adherence in Germany (II)

Impact on 1-year survival and complication outcomes



"**green**" → receiving at least 185 DDDs (defined daily doses) of each of the recommended agents per observed patient-year

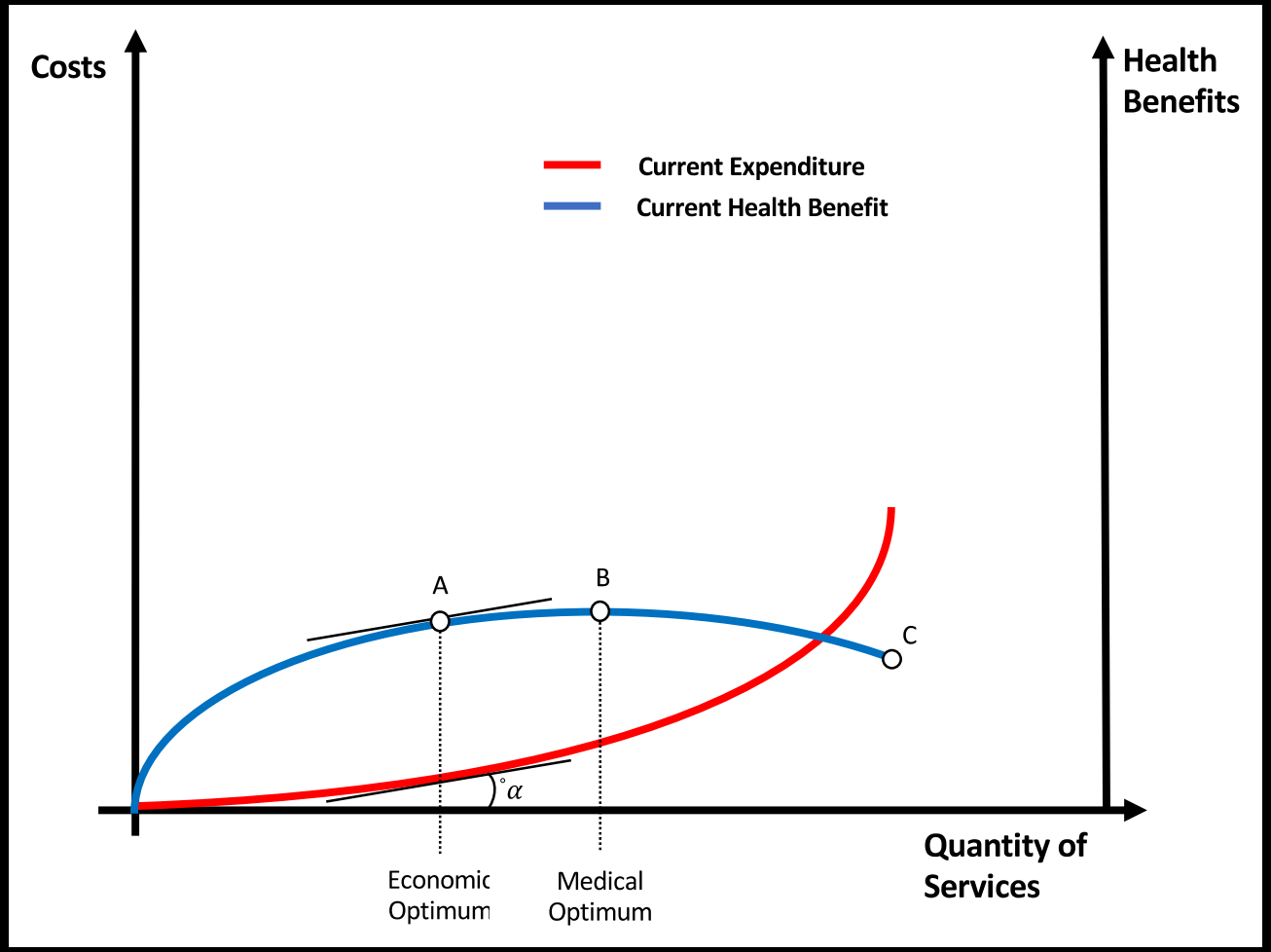
"**yellow**" → received at least two prescriptions of at least one of the recommended agents

"**red**" → did not receive at least two prescriptions of any of the recommended agents

Patient characteristics[a]	Guideline adherence subgroups[b]		
	"Green" level of guideline adherence	"Yellow" level of guideline adherence	"Red" level of guideline adherence
N (%)	4096 (14.4%)	21,386 (75.2%)	2974 (10.5%)
With incident IS	1949 (42.6%)	2277 (49.8%)	346 (7.6%)
With incident MI	599 (21.2%)	2140 (75.8%)	83 (2.9%)
With incident HF	1982 (11.2%)	14,609 (82.7%)	1084 (6.1%)
With incident CAD	1561 (15.2%)	7898 (76.7%)	833 (8.1%)
Age (years)	71.9 ± 10.6	74.5 ± 10.8	75.6 ±

Gabler M. et al., Diabetes Therapy (2021) 12:1209-1226

Canonical model (M_0) linking costs, health benefits and resource use (quantity of services)



Glycaemic control and macrovascular and microvascular outcomes:

A systematic review and meta-analysis of trials investigating intensive glucose-lowering strategies in people with type 2 diabetes (1998-2021)

Kunutsor SK et al. - Diabetes Obes Metab. 2024;26:2069–2081

STUDY SELECTION and ELIGIBILITY CRITERIA

- Eligible studies were CVOTs (open or blinded) of intensive glucose-lowering interventions of any duration in adult people with T2D that randomly assigned participants to intensive and standard glucose control and reported macrovascular and/or microvascular outcomes.
- These “strategy-driven trials” were designed to assess directly the impact of achieving higher versus lower levels of glycaemia on cardiovascular outcomes in patients with T2D.
- CVOTs of newer glucose-lowering agents were not included because designed to achieve ‘glycaemic equipoise’ to minimize the influence of different glucose levels between treatment and placebo groups.
- **Only RCTs that targeted measures of glycaemia (HbA1c) and also reported their values at follow-up were considered**

Glycaemic control and macrovascular and microvascular outcomes:

A systematic review and meta-analysis of trials investigating intensive glucose-lowering strategies in people with type 2 diabetes

Outcome	No. of studies	Intensive Therapy Events/Participants	Standard Therapy Events/Participants	HR (95% CI)
Macrovascular outcomes				
3-point MACE	4	2217/19533	2257/19540	0.97 (0.92, 1.03)
4-point MACE	1	403/2570	418/2575	0.95 (0.83, 1.09)
5-point MACE	1	1792/6264	1727/6273	1.04 (0.97, 1.11)
MACE plus amputation	1	12/80	23/80	0.45 (0.23, 0.90)
MACE plus amputation/revascularisation	1	19/80	35/80	0.47 (0.26, 0.86)
CVD death	6	1084/22103	1067/21816	1.03 (0.89, 1.19)
Heart failure	6	937/23154	935/21577	0.94 (0.85, 1.04)
Myocardial infarction	5	979/14133	813/12262	0.92 (0.80, 1.05)
Fatal MI	2	212/5299	101/3713	0.77 (0.40, 1.48)
Non-fatal MI	5	710/16435	693/14798	0.84 (0.75, 0.94)
Coronary events	2	608/6840	627/6840	0.91 (0.80, 1.05)
Coronary revascularisation	4	1315/11404	1300/11124	1.00 (0.88, 1.13)
Angina pectoris	5	1265/12826	1173/11231	0.99 (0.91, 1.07)
Stroke	7	984/20973	878/19102	0.95 (0.82, 1.11)
Fatal stroke	1	43/2729	15/1138	1.17 (0.54, 2.54)
Non-fatal stroke	4	413/13874	330/12235	1.03 (0.88, 1.20)
Peripheral vascular disease	5	393/9006	425/9012	0.91 (0.80, 1.05)
Amputations	5	128/12914	121/11299	0.89 (0.63, 1.26)
All-cause mortality	10	>2840/26823	>2559/24919	0.98 (0.92, 1.04)
Microvascular outcomes				
Composite microvascular outcome	3	2074/14564	2089/12980	0.88 (0.77, 1.00)
Neuropathy	4	2687/7706	2658/7412	1.03 (0.98, 1.08)
Peripheral neuropathy	2	218/544	236/578	0.97 (0.83, 1.12)
Autonomic neuropathy	2	62/544	69/578	0.78 (0.19, 3.23)
Retinopathy	8	1366/11441	1241/9561	0.85 (0.78, 0.93)
Nephropathy	3	427/6920	580/6920	0.71 (0.58, 0.87)
Macroalbuminuria	3	194/7282	273/7303	0.70 (0.55, 0.90)
Microalbuminuria	4	1556/7531	1764/7537	0.77 (0.63, 0.94)
Albuminuria	2	379/2085	366/1804	0.78 (0.59, 1.01)
Doubling of serum creatinine	4	>156/7795	>161/7804	0.92 (0.70, 1.21)
ESKD, dSCr or death	1	51/73	57/80	0.69 (0.43, 1.11)
Safety outcomes				
Any adverse events	2	1162/1343	1170/1351	1.00 (0.98, 1.03)
Serious adverse events	3	250/6471	232/6474	1.04 (0.76, 1.44)
Any hypoglycaemia	2	563/1349	322/1351	1.44 (0.85, 2.42)
Severe hypoglycaemia	7	1293/21774	563/21790	1.88 (1.24, 2.84)

Kunutsor SK et al. - Diabetes Obes Metab. 2024;26:2069–2081

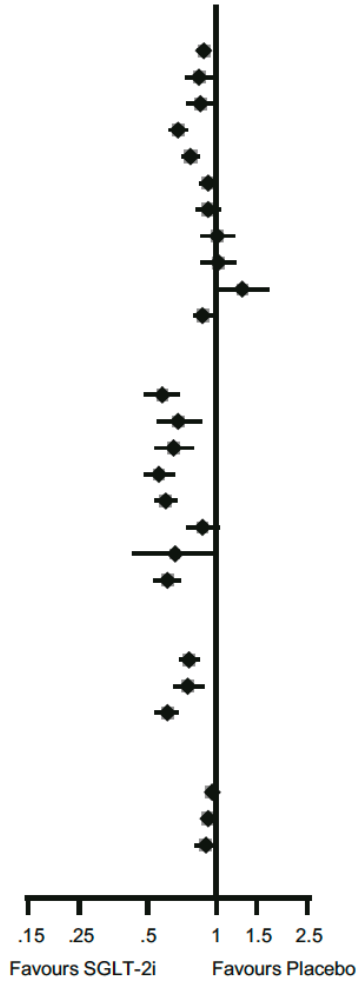
Glycaemic control and macrovascular and microvascular outcomes:

A systematic review and meta-analysis of trials investigating intensive glucose-lowering strategies in people with type 2 diabetes (2009-2020)

Kunutsor SK et al. - Diabetes Obes Metab. 2024;26:1837–1849.

SGLT-2is and Outcomes

Outcome	No. of studies	SGLT-2i Events / Participants	Placebo Events / Participants	HR (95% CI)
Macrovascular outcomes				
3-point MACE	6	2459 / 32051	2123 / 25494	0.88 (0.82, 0.94)
4-point MACE	3	1963 / 15478	1510 / 10372	0.84 (0.73, 0.97)
CVD death	6	1023 / 32057	880 / 25496	0.85 (0.74, 0.96)
Hospitalization for HF	6	>811 / 32057	>981 / 25496	0.68 (0.62, 0.75)
Hospitalization for HF or CVD death	6	>1705 / 32057	>1727 / 25496	0.77 (0.71, 0.84)
Myocardial infarction	4	>946 / 24563	>725 / 18005	0.92 (0.84, 1.00)
Nonfatal MI	3	>523 / 15981	>269 / 9427	0.92 (0.81, 1.05)
Fatal or nonfatal stroke	3	>2022 / 15981	>156 / 9427	1.01 (0.85, 1.21)
Nonfatal stroke	3	>307 / 15981	>138 / 9427	1.02 (0.85, 1.22)
Amputations	4	>307 / 22062	>221 / 17858	1.30 (0.99, 1.70)
All-cause mortality	6	>1685 / 32057	>1465 / 25496	0.87 (0.79, 0.96)
Microvascular outcomes				
Doubling of serum creatinine	3	>118 / 12642	>188 / 8869	0.58 (0.48, 0.69)
ESKD	2	>116 / 7997	>165 / 6546	0.68 (0.55, 0.86)
Composite of dSCr, ESKD, or death from renal causes	4	>409 / 18141	>403 / 11626	0.65 (0.54, 0.79)
Composite of 40% reduction in eGFR, ESKD, or death from renal causes	2	>211 / 14377	>238 / 12925	0.56 (0.48, 0.66)
Macroalbuminuria	2	459 / 9886	330 / 6380	0.60 (0.54, 0.67)
Albuminuria	2	1430 / 8574	703 / 5721	0.87 (0.74, 1.03)
RRT	2	89 / 6889	114 / 4532	0.66 (0.43, 1.00)
Nephropathy	1	525 / 4124	388 / 2061	0.61 (0.53, 0.70)
Combined micro and macrovascular outcomes				
Composite of 40% reduction in eGFR, ESKD, or death from renal or CV causes	2	>370 / 14377	>480 / 12925	0.76 (0.69, 0.84)
Composite of dSCr, ESKD, or death from renal or CV causes	2	>245 / 7997	>340 / 6546	0.75 (0.65, 0.88)
Nephropathy or CVD death	1	675 / 4170	497 / 2102	0.61 (0.54, 0.68)
Safety outcomes				
Any adverse events	3	10696 / 12380	6348 / 7275	0.96 (0.92, 1.00)
Serious adverse events	7	11507 / 40614	10315 / 34046	0.92 (0.90, 0.94)
Severe hypoglycaemia	4	458 / 24045	336 / 18933	0.90 (0.80, 1.01)



SGLT2i

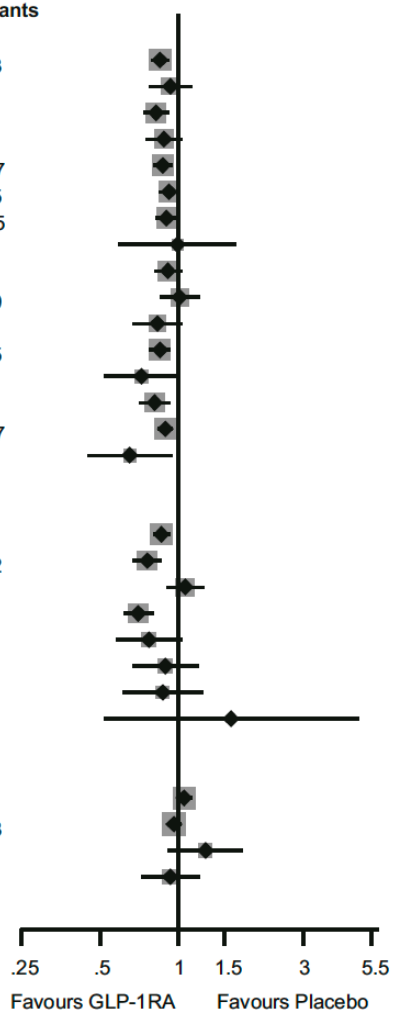
Glycaemic control and macrovascular and microvascular outcomes:

A systematic review and meta-analysis of trials investigating intensive glucose-lowering strategies in people with type 2 diabetes (2009-2020)

Kunutsor SK et al. - Diabetes Obes Metab. 2024;26:1837–1849.

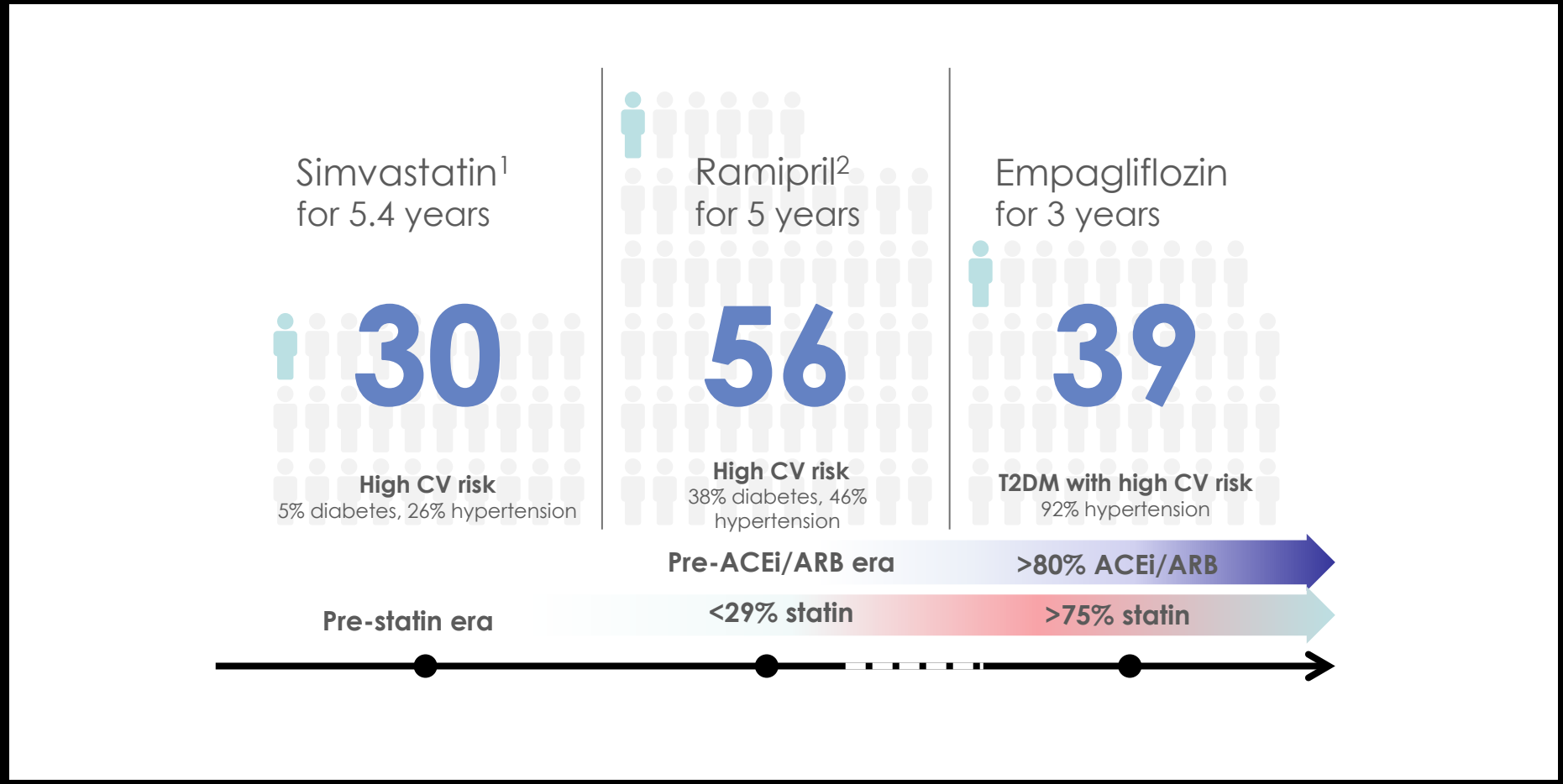
GLP-1RAs and Outcomes

Outcome	No. of studies	GLP-1RA Events / Participants	Placebo Events / Participants	HR (95% CI)
Macrovascular outcomes				
3-point MACE	8	2822 / 29735	3106 / 28433	0.85 (0.79, 0.92)
4-point MACE	4	551 / 11431	647 / 11439	0.93 (0.77, 1.13)
5-point MACE	3	1404 / 9033	1484 / 7680	0.82 (0.74, 0.92)
Composite of all-cause mortality, nonfatal MI, or nonfatal stroke	3	296 / 5314	334 / 5322	0.88 (0.75, 1.03)
CVD death	9	>1160 / 32769	>1286 / 31467	0.87 (0.80, 0.95)
Hospitalization for HF	8	>786 / 28038	>831 / 26735	0.92 (0.84, 1.00)
Myocardial infarction	6	>1270 / 27455	>1361 / 26145	0.90 (0.82, 1.00)
Fatal MI	3	60 / 16973	61 / 17020	0.99 (0.59, 1.65)
Nonfatal MI	6	692 / 17648	705 / 16305	0.91 (0.81, 1.03)
Unstable angina	7	>261 / 20682	>254 / 19339	1.01 (0.85, 1.20)
Coronary revascularization procedure	3	614 / 9033	633 / 7680	0.83 (0.67, 1.03)
Stroke	6	>659 / 27455	>761 / 26145	0.85 (0.77, 0.93)
Fatal stroke	3	60 / 16973	83 / 17020	0.72 (0.52, 1.00)
Nonfatal stroke	6	397 / 17648	460 / 16305	0.81 (0.71, 0.93)
All-cause mortality	9	>1865 / 32769	>2043 / 31467	0.89 (0.83, 0.95)
Amputation	1	60 / 4668	78 / 4672	0.65 (0.45, 0.95)
Microvascular outcomes				
Composite microvascular outcome	2	1265 / 9617	1435 / 9624	0.86 (0.80, 0.93)
Nephropathy	4	1531 / 13982	1657 / 12632	0.76 (0.67, 0.86)
Retinopathy	7	736 / 27646	651 / 26335	1.06 (0.90, 1.25)
Macroalbuminuria	2	509 / 7385	459 / 6031	0.70 (0.62, 0.80)
Kidney function outcome	1	121 / 2717	76 / 1359	0.77 (0.58, 1.03)
dSCr	1	87 / 4668	97 / 4672	0.89 (0.67, 1.19)
RRT	1	56 / 4668	64 / 4672	0.87 (0.61, 1.24)
Death from renal disease	1	8 over 4668	5 over 4672	1.59 (0.52, 4.87)
Safety outcomes				
Any adverse events	3	5872 / 8391	5648 / 8402	1.05 (0.98, 1.12)
Serious adverse events	6	5380 / 20357	5528 / 20398	0.96 (0.91, 1.02)
Any hypoglycaemia	3	2607 / 8391	2572 / 8402	1.27 (0.91, 1.75)
Severe hypoglycaemia	7	511 / 28061	531 / 26743	0.93 (0.72, 1.20)



GLP1-RA

Number needed to treat (NNT) to prevent one death across landmark trials in patients with high CV risk (I)



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1. 4S investigator. Lancet 1994; 344: 1383-89, http://www.trialresultscenter.org/study2590-4S.htm;
2. HOPE investigator N Engl J Med 2000;342:145-53, http://www.trialresultscenter.org/study2606-HOPE.htm

Number needed to treat (NNT) to prevent one death across landmark trials in patients with high CV risk (II)

	Dulaglutide*	Semaglutide$	Semaglutide**	Tirzepatide§
Trial name	REWIND	SUSTAIN-6	SELECT	SURPASS-CVOT^^
Follow-up duration	median 5.4 yrs	2.1 yrs	median 3.3 yrs	median 4 yrs
NNT	83	45	34	n/d
Condition	T2D	T2D	Overweight/obesity. No T2D	T2D with ASCVD
Setting	Primary prevention	Primary prevention	Secondary prevention	Primary and secondary prev.
Established CVD	31%	83%	100%	>90%
Statins	66%	77%	87%	>90%
ACEi/ARBs	81%	79%	75%	>80%

* Gerstein HC, Lancet 2019 Jul 13;394(10193):121-130

$ Marso PM, NEJM 2016;375:1834-1844

** Lincoff MA, NEJM 2023;389:2221-2232

§ 2025 EASD Scientific Meeting; Clinicaltrials.gov ID: NCT04255433

^^post-SGLT2i/GLP1-RA Era – active comparator, non-inferiority trial)

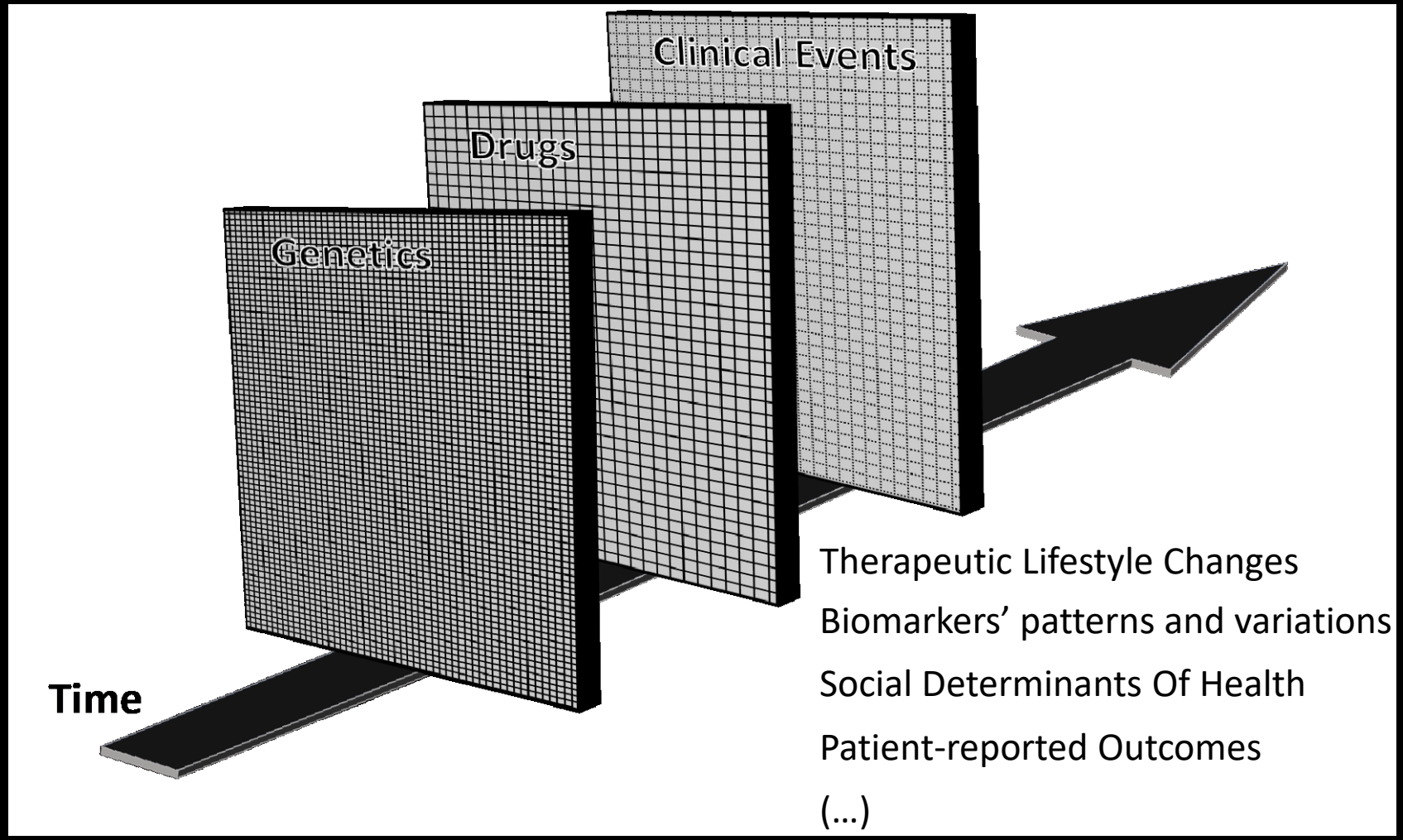
Relative risk reduction of renal endpoints and cardiovascular death across landmark trials in CKD patients with and without T2D

	Empagliflozin*	Dapagliflozin**
Trial name	EMPA-KIDNEY	DAPA-CKD
Key population	Individuals with CKD (eGFR ≥20 mL/min/BSA) with and without T2D	Similar CKD population with and without T2D
Key results	**28% RRR** (relative risk reduction) in the composite primary outcome (kidney disease progression or cardiovascular death).	**39% RRR** in the composite kidney and cardiovascular death outcome.

* NEJM 2023;388:117-127

** NEJM 2020;383:1436-1446

N-layer Structure of (binary) Variables along the Integrated Healthcare Records Continuum



Dauriz M, *Frankfurt School MBA IHM 2023*


The
End