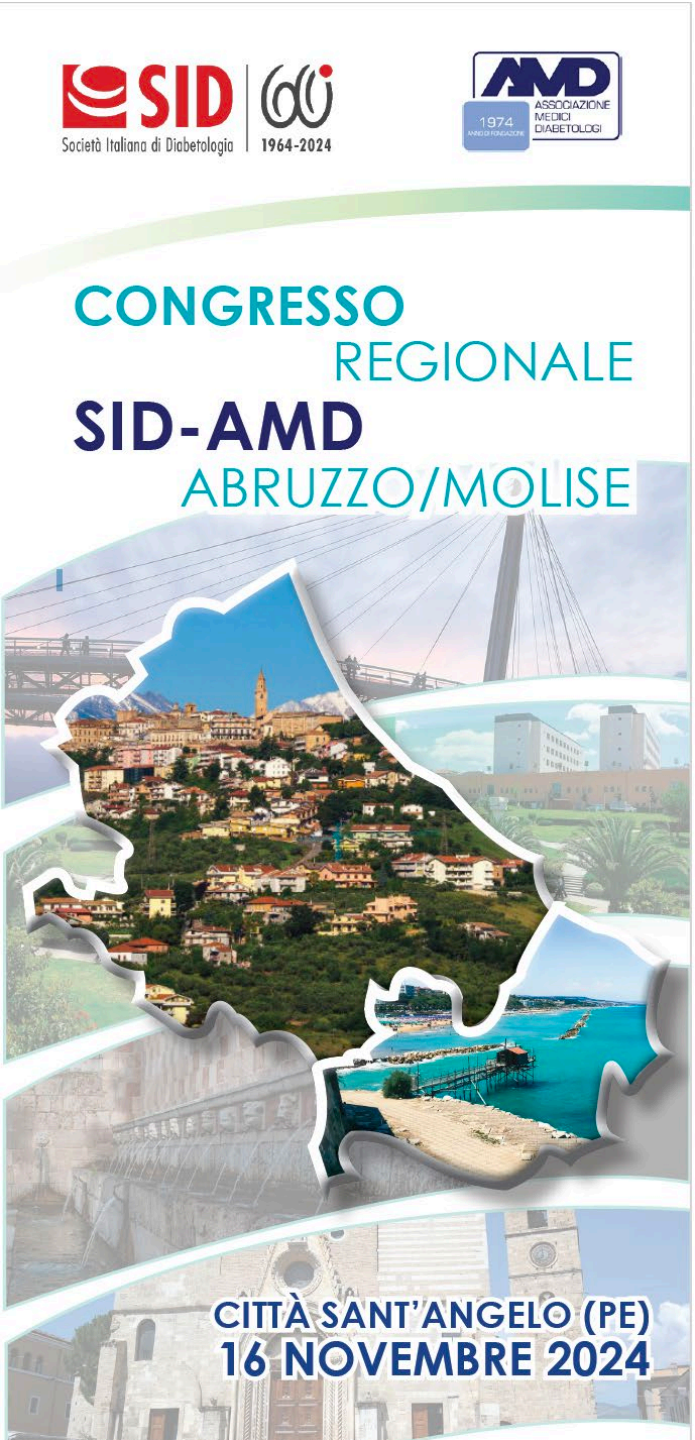


La gestione olistica della persona con diabete: confronto fra gli algoritmi proposti dalle Linee Guida Protezione Vascolare

Prof Francesca Santilli

Clinica Medica

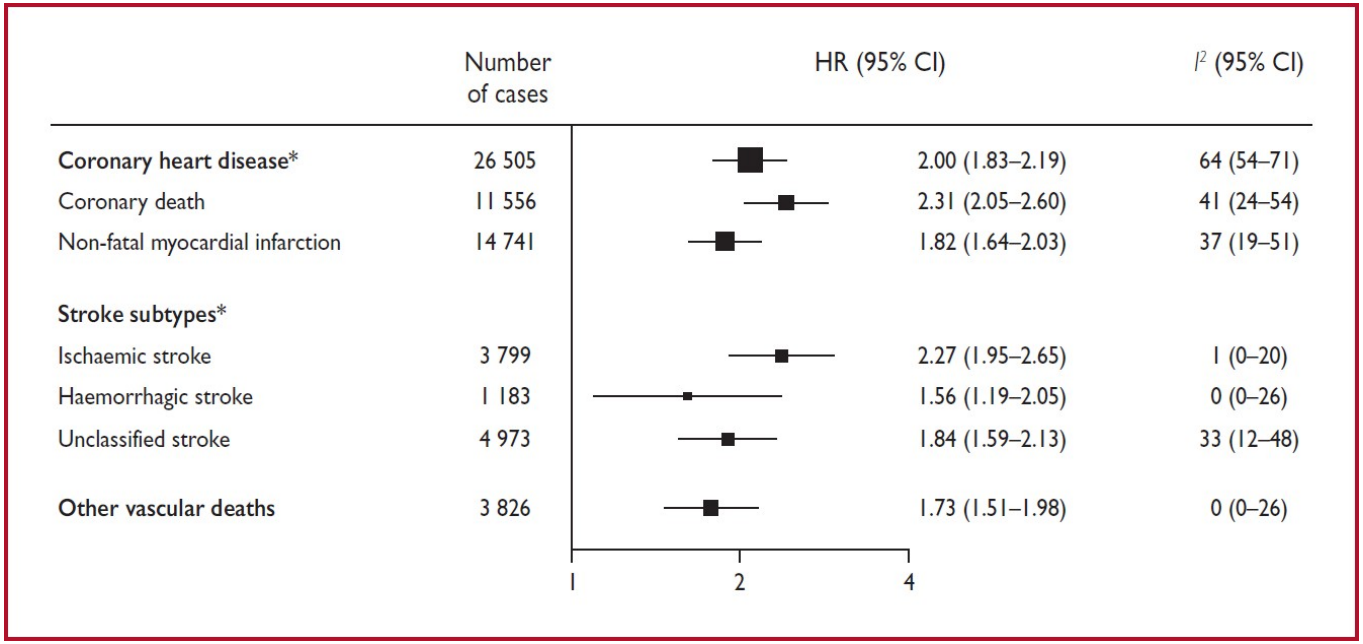
Dipartimento di Medicina e Scienze dell'invecchiamento

Università G. d'Annunzio Chieti-Pescara

People with diabetes have a two-fold higher risk of coronary heart disease and stroke

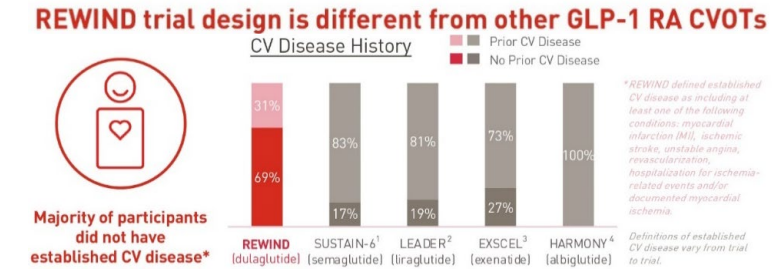
Collaborative meta-analysis of 102 prospective studies

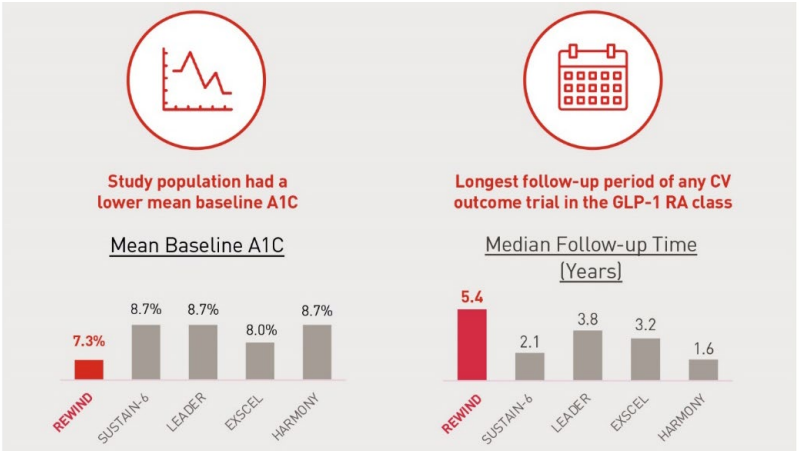
(n=698,782; 52,765 non-fatal or fatal vascular outcomes; 8.49 million person-years at risk)



Emerging Risk Factors Collaboration. Lancet. 2010;375:22152222

REWIND: the latest primary prevention trial in T2DM



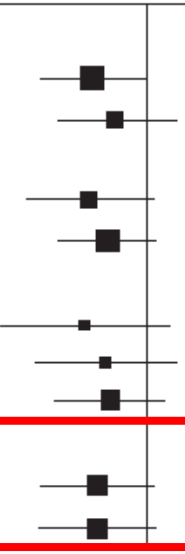


	Dulaglutide (n=4949)	Placebo (n=4952)
Cardiovascular		
Body-mass index (kg/m²)	32·3 (5·7)	32·3 (5·8)
Systolic blood pressure (mm Hg)	137·1 (16·6)	137·3 (17·0)
Diastolic blood pressure (mm Hg)	78·4 (9.8)	78·5 (9.9)
Heart rate (beats per min)	71·4 (10·7)	71·6 (11·0)
Serum creatinine (µmol/L)	83·7 (27·4)	84·5 (27·3)
eGFR (mL/min per 1·73 m²)	75·3 (61·6–91·8)	74·7 (61·2–90·6)
UACR (mg/mmol)	1·80 (0·70–6·60)	1·88 (0·70–7·38)
Cholesterol (mmol/L)	4·52 (1·16)	4·52 (1·16)
LDL cholesterol (mmol/L)	2·56 (0·98)	2·56 (0·98)
HDL cholesterol (mmol/L)	1·18 (0·33)	1·18 (0·36)
Triglycerides (mmol/L)	1·60 (1·15–2·20)	1·60 (1·20–2·25)
Cardiovascular medications		
ACE inhibitor or ARB	4009 (81·0%)	4059 (82·0%)
β blocker	2237 (45·2%)	2274 (45·9%)
Other blood pressure drug	2767 (55·9%)	2833 (57·2%)
Statin	3279 (66·3%)	3268 (66·0%)
Fibrate	452 (9·1%)	446 (9·0%)
Antiplatelet	2662 (53·8%)	2680 (54·1%)

Gerstein HC et al, Lancet 2019.

The annual rate of major vascular events in the placebo arm is high despite state-of-the art therapy

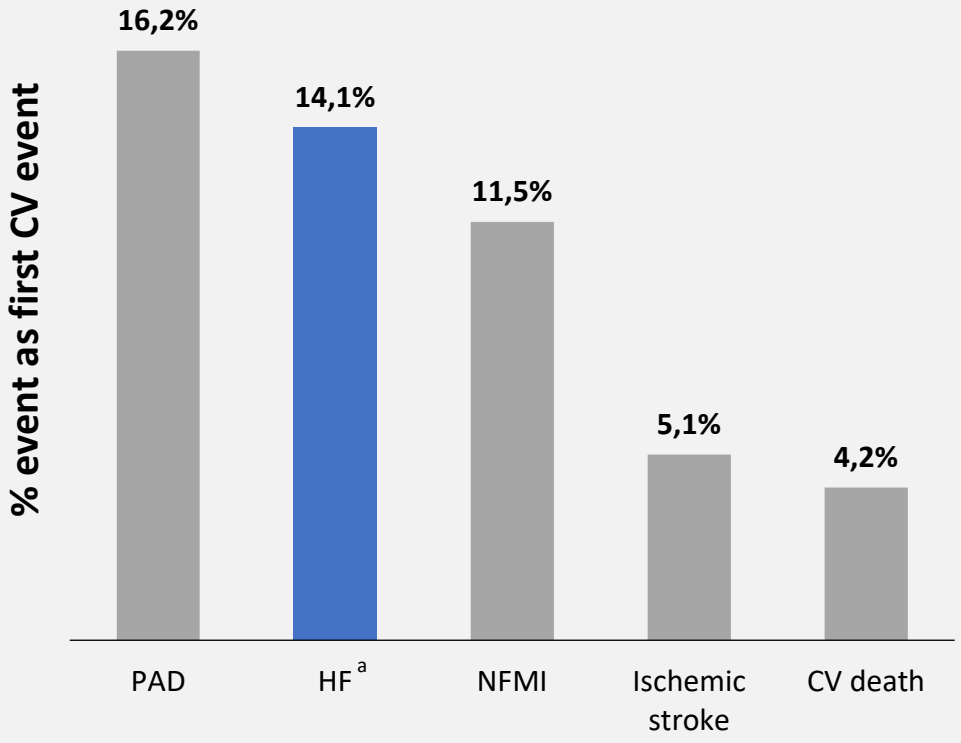
	Dulaglutide		Placebo		Hazard ratio (95% CI)	$p_{interaction}$
	Events/patients (%)	Incidence (per 100 person–years)	Events/patients (%)	Incidence (per 100 person–years)		
Age (years)						0·57
≥66	331/2314 (14·3%)	2·9	384/2350 (16·3%)	3·3	0·86 (0·74–1·00)	
<66	263/2635 (10·0%)	1·9	279/2602 (10·7%)	2·1	0·92 (0·78–1·09)	
Sex						0·60
Female	218/2306 (9·5%)	1·8	249/2283 (10·9%)	2·1	0·85 (0·71–1·02)	
Male	376/2643 (14·2%)	2·8	414/2669 (15·5%)	3·1	0·90 (0·79–1·04)	
Duration of diabetes (years)						0·88
<5	128/1227 (10·4%)	2·0	146/1192 (12·2%)	2·4	0·84 (0·66–1·06)	
5–10	174/1446 (12·0%)	2·3	196/1476 (13·3%)	2·6	0·89 (0·73–1·09)	
≥10	292/2276 (12·8%)	2·5	321/2284 (14·1%)	2·8	0·90 (0·77–1·06)	
History of cardiovascular disease*						0·97
Yes	280/1560 (17·9%)	3·7	315/1554 (20·3%)	4·2	0·87 (0·74–1·02)	
No	277/3093 (8·9%)	1·7	317/3128 (10·1%)	2·0	0·87 (0·74–1·02)	



Gerstein HC et al, Lancet 2019.

HF was the first manifestation of T2D-related CV disease more often than was MI or stroke

Cohort study of patients (N~1.9 million) with T2D and incidence of CV disease[1]



T2D and HF often coexist:[2]

- **T2D trials: HF prevalence 10% to 30%**
- **Chronic HF trials: T2D prevalence ~30%**

- In this large cohort, PAD and HF were the two most common first presentations of T2D-related CV disease
- Yet, myocardial infarction and stroke continue to be chosen as primary outcomes of major type 2 diabetes trials, as part of the MACE endpoint
- This suggests that future studies should assess CV events that occur earlier in patients with T2D such as HF and PAD

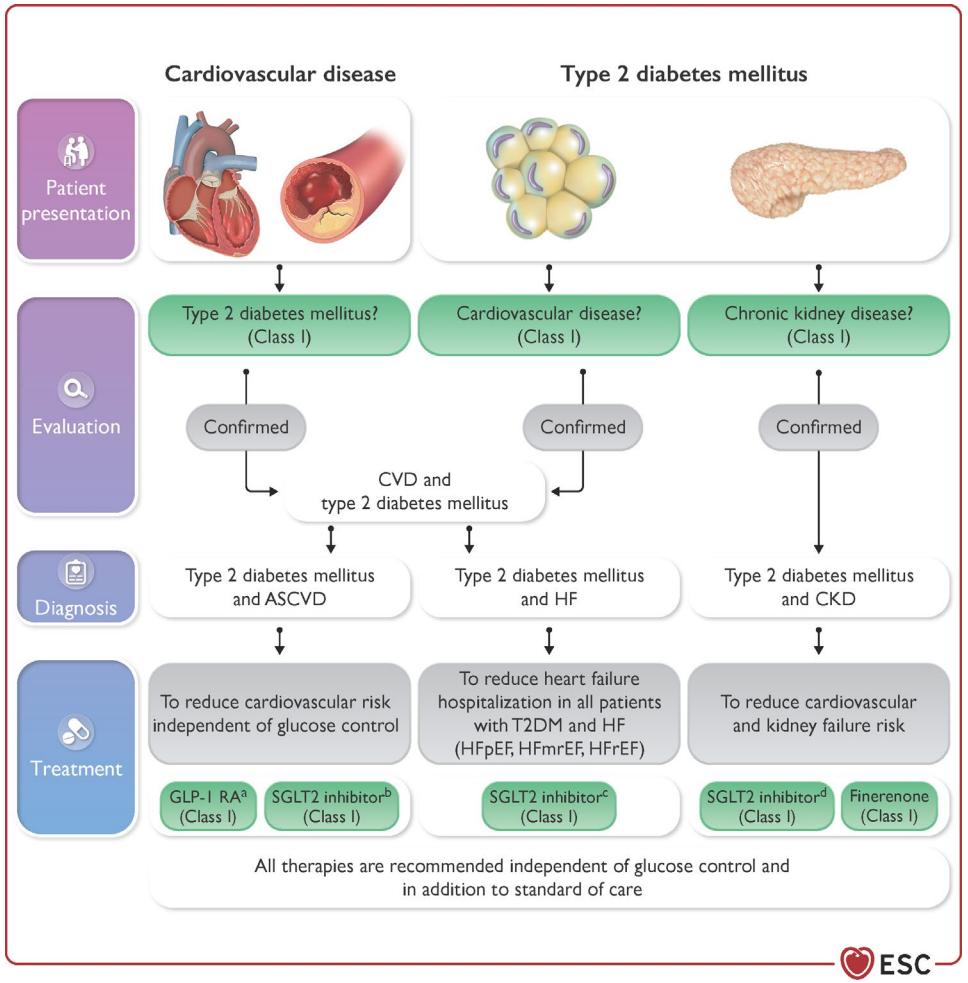
[a]Heart failure post MI was not included in this definition of HF

CV = cardiovascular; HF = heart failure; NFMI = nonfatal myocardial infarction; PAD = peripheral arterial disease; T2D = type 2 diabetes.

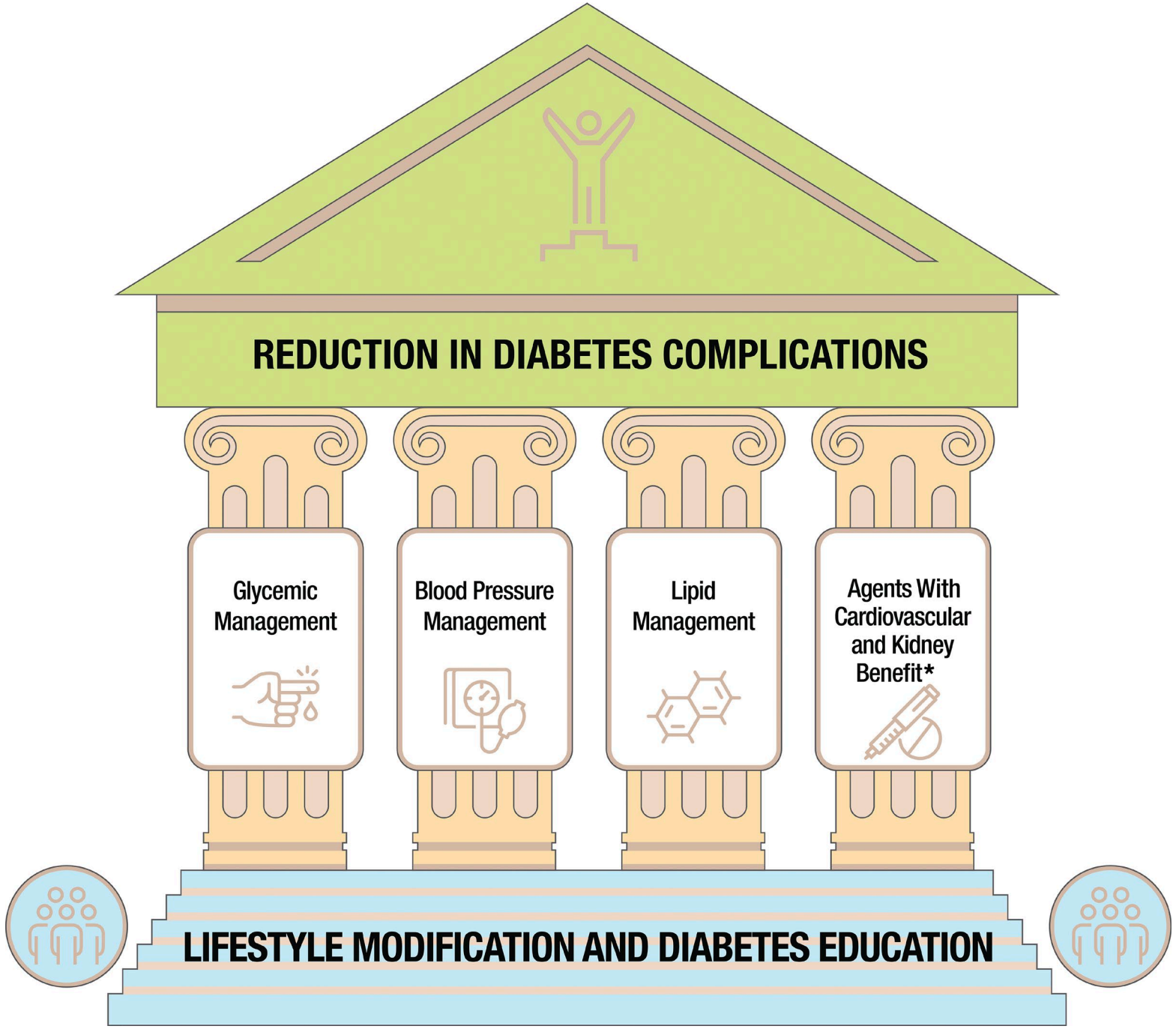
1. Shah AD et al. Article and appendix. *Lancet Diabetes Endocrinol*. 2015;3:105-113; 2. Seferović PM et al. *Eur J Heart Fail.* 2018;20:853-872.

Figure 1

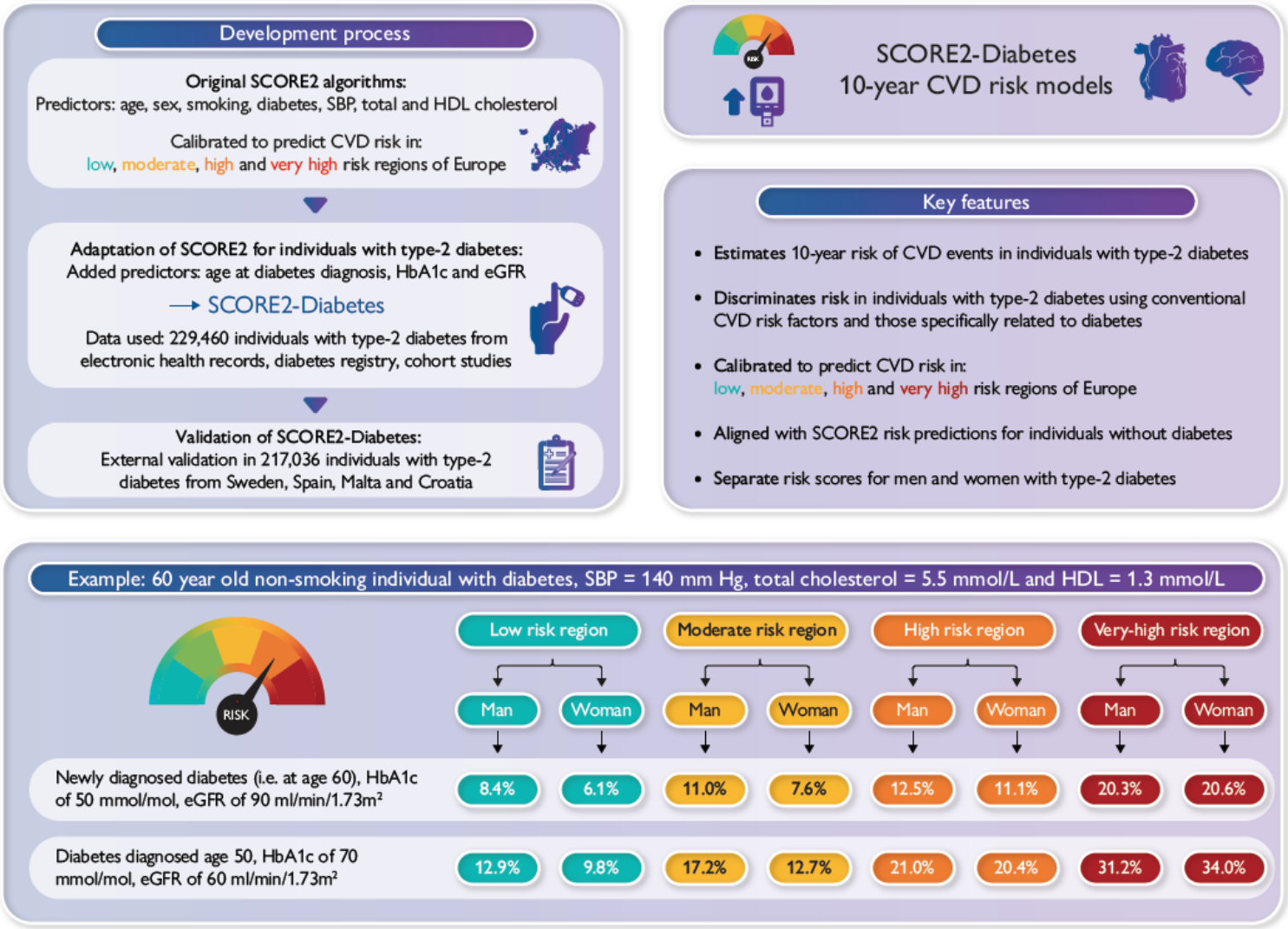
Management of cardiovascular disease in patients with type 2 diabetes: clinical approach and key recommendations



2023 ESC Guidelines for the management of cardiovascular disease in patients with diabetes
(European Heart Journal; 2023 – doi:10.1093/eurheartj/ehad192)

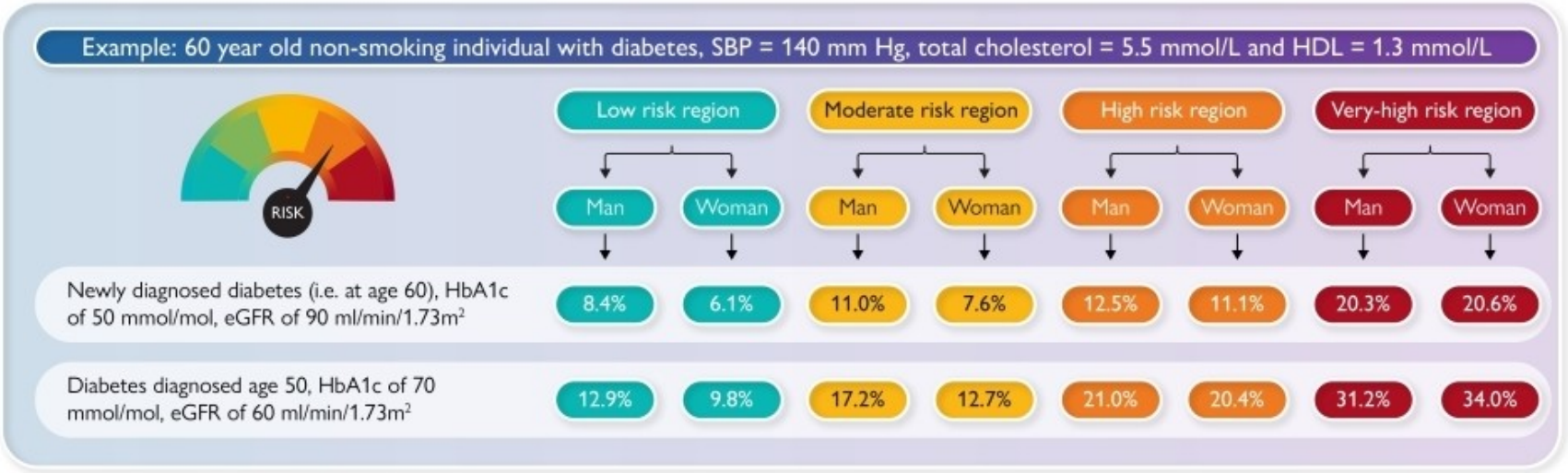

REDUCTION IN DIABETES COMPLICATIONS
Glycemic Management
Blood Pressure Management
Lipid Management
Agents With Cardiovascular and Kidney Benefit*
LIFESTYLE MODIFICATION AND DIABETES EDUCATION

SCORE2-Diabetes: 10-year cardiovascular risk estimation in type 2 diabetes in Europe



Eur Heart J 2023; 00, 1–14

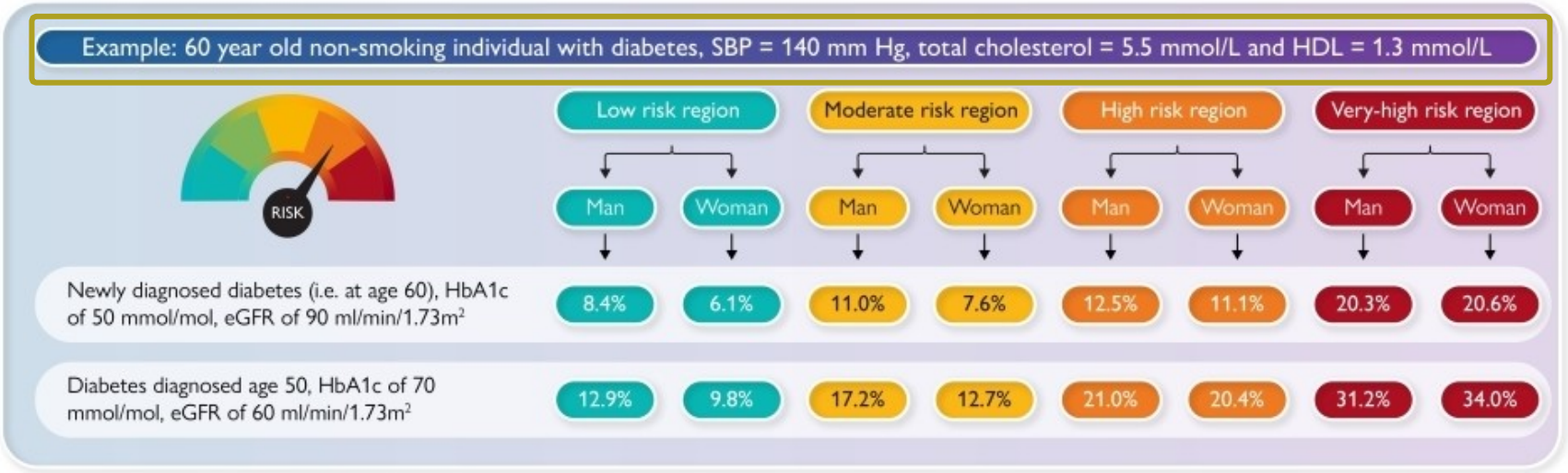
SCORE2-Diabetes: example of risk estimation



www.escardio.org/guidelines

2023 ESC Guidelines for the management of cardiovascular disease in patients with diabetes
(European Heart Journal; 2023 – doi:10.1093/eurheartj/ehad192)

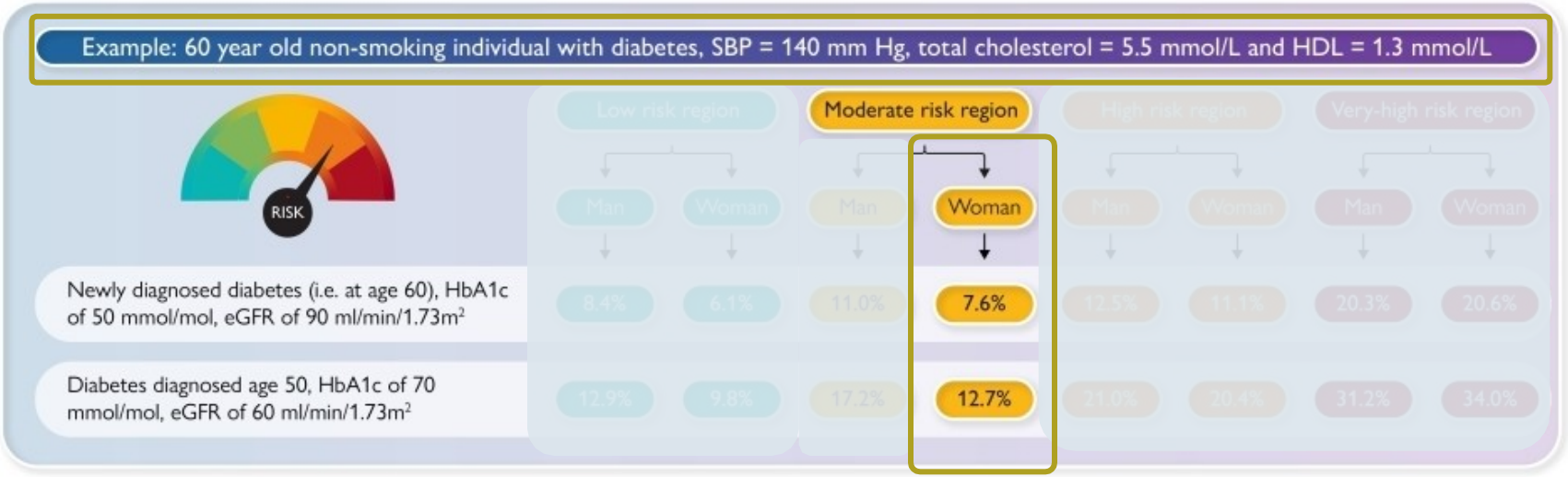
SCORE2-Diabetes: example of risk estimation



www.escardio.org/guidelines

2023 ESC Guidelines for the management of cardiovascular disease in patients with diabetes
(European Heart Journal; 2023 – doi:10.1093/eurheartj/ehad192)

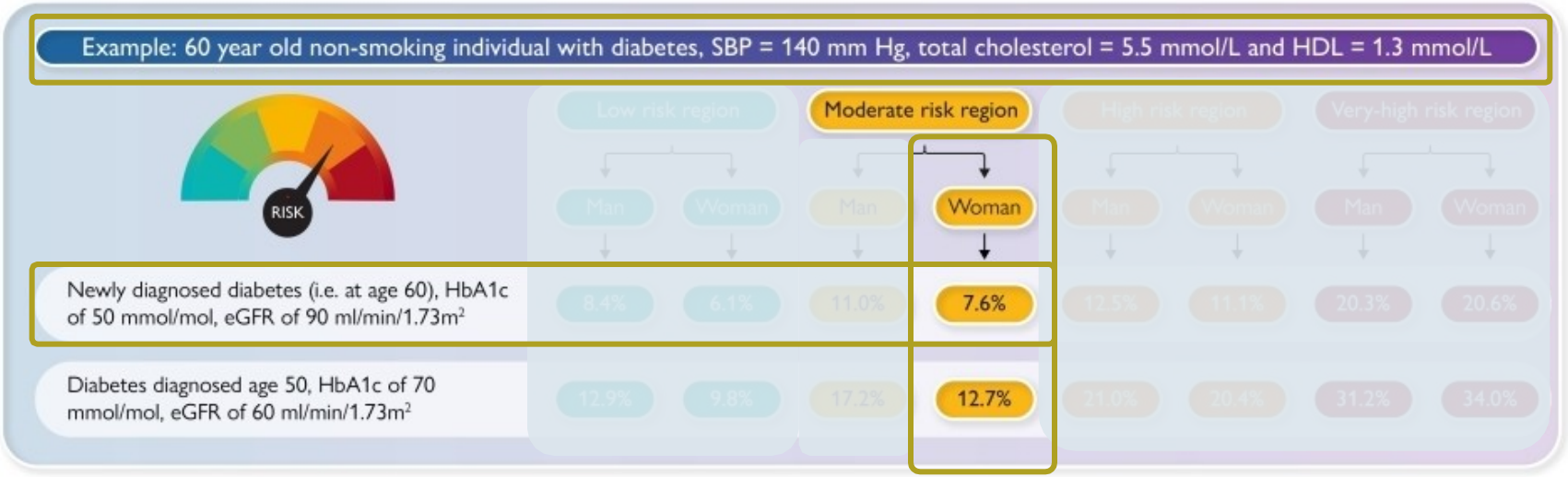
SCORE2-Diabetes: example of risk estimation



www.escardio.org/guidelines

2023 ESC Guidelines for the management of cardiovascular disease in patients with diabetes
(European Heart Journal; 2023 – doi:10.1093/eurheartj/ehad192)

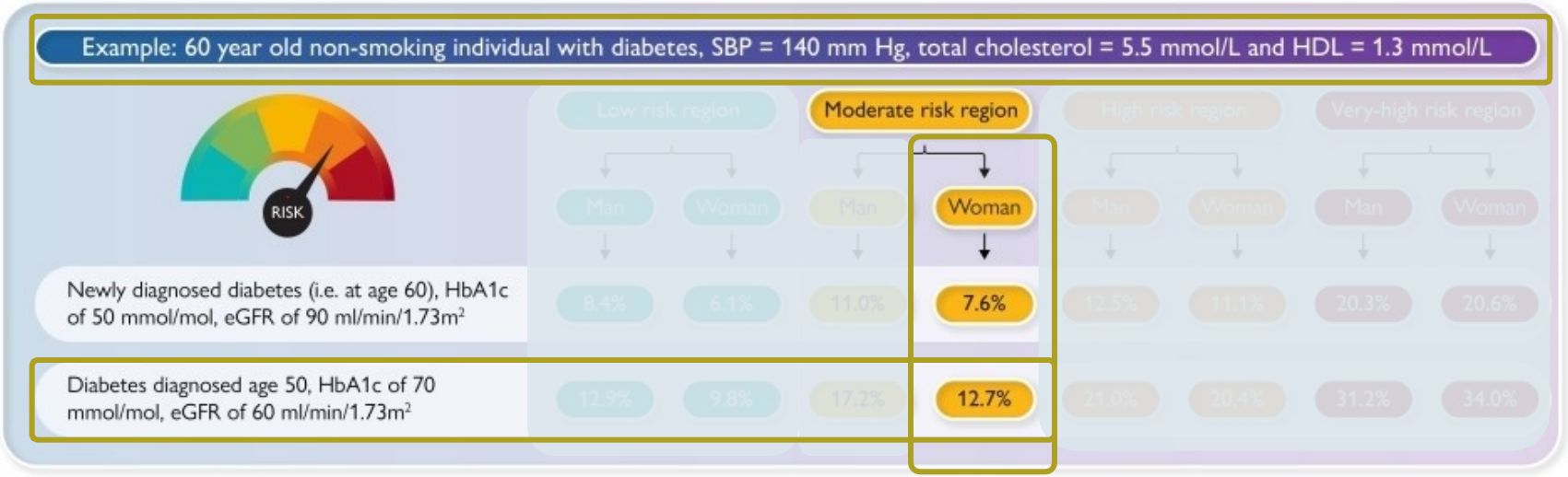
SCORE2-Diabetes: example of risk estimation



www.escardio.org/guidelines

2023 ESC Guidelines for the management of cardiovascular disease in patients with diabetes
(European Heart Journal; 2023 – doi:10.1093/eurheartj/ehad192)

SCORE2-Diabetes: example of risk estimation

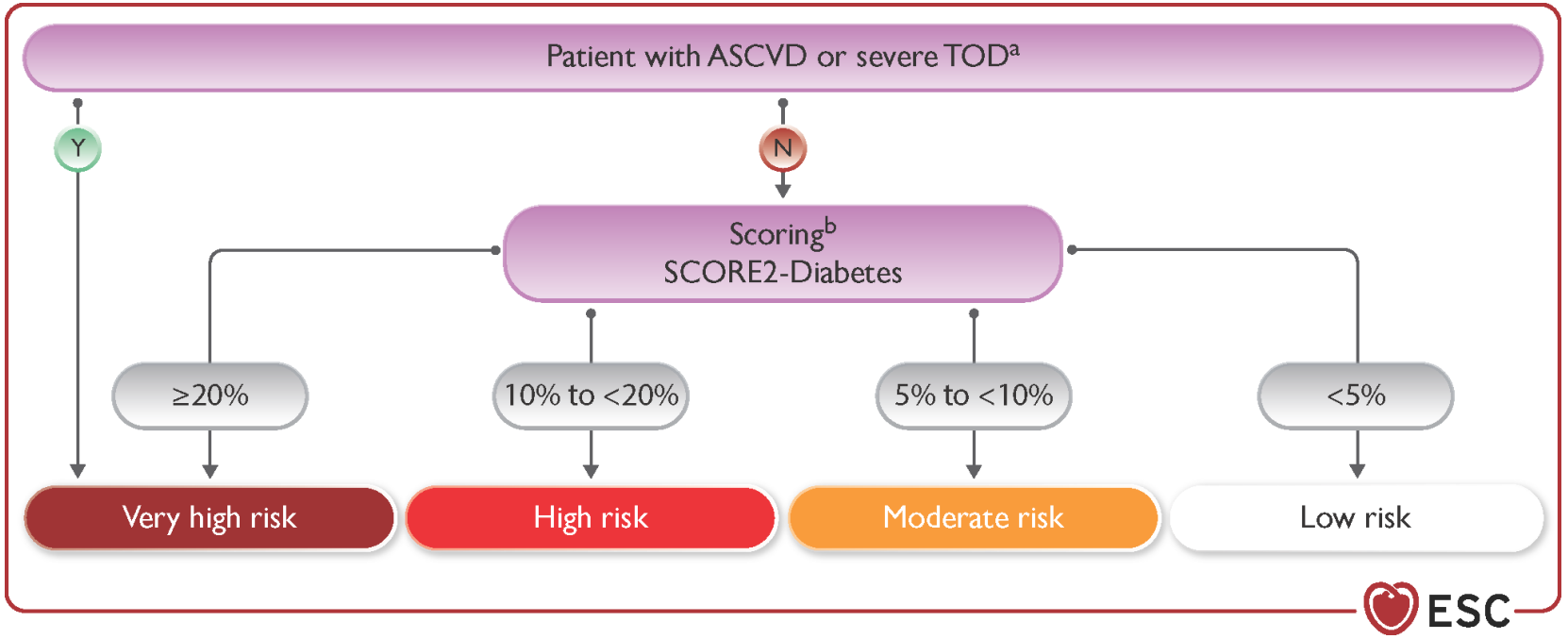


www.escardio.org/guidelines

2023 ESC Guidelines for the management of cardiovascular disease in patients with diabetes
(European Heart Journal; 2023 – doi:10.1093/eurheartj/ehad192)

When and how to use SCORE2-Diabetes

Cardiovascular risk categories in patients with type 2 diabetes



www.escardio.org/guidelines

2023 ESC Guidelines for the management of cardiovascular disease in patients with diabetes
(European Heart Journal; 2023 – doi:10.1093/eurheartj/ehad192)

Cardiovascular risk categories in type 2 diabetes

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

2023 ESC Guidelines for the management of cardiovascular disease in patients with diabetes
(European Heart Journal; 2023 – doi:10.1093/eurheartj/ehad192)

What is…?

ASCVD refers to all clinical conditions of atherosclerotic origin, including:

acute coronary syndrome (ACS), myocardial infarction (MI), stable or unstable angina, coronary artery disease documented using angiography, coronary or other arterial revascularization (coronary artery bypass graft surgery, femoral-popliteal bypass graft surgery, etc), stroke, transient ischemic attack, documented carotid disease, peripheral artery disease, and abdominal aortic aneurysm.

Severe TOD is defined as at least one of:

- eGFR <45 mL/min/1.73 m2 irrespective of the presence or absence of albuminuria;

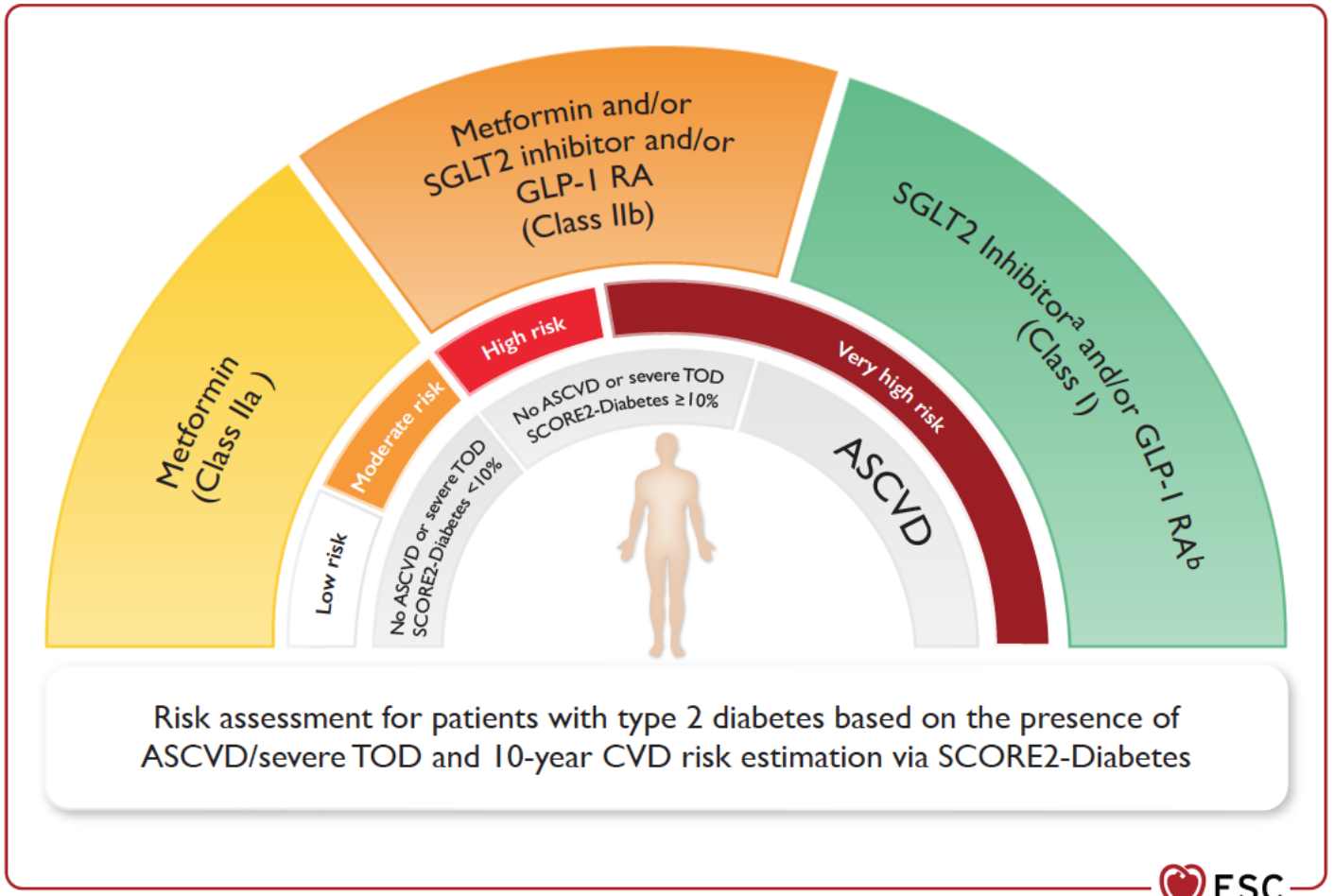
-eGFR 46-59 mL/min/1.73 m^2 and microalbuminuria (ACR 30-300 mg/g or 3-30 mg/mmol);

-proteinuria (ACR >300 mg/g or >30 mg/mmol);

- presence of microvascular disease in at least three different sites (e.g. microalbuminuria plus retinopathy plus neuropathy).

Glucose-lowering treatment for patients with type 2 diabetes to reduce cardiovascular risk based on the presence of atherosclerotic cardiovascular disease/severe target-organ damage and 10-year cardiovascular disease risk estimation via SCORE2-Diabetes

cSevere TOD defined as eGFR <45 mL/min/1.73 m2 irrespective of albuminuria; or eGFR 45–59 mL/min/1.73 m2 and microalbuminuria (UACR 30–300 mg/g; stage A2); or proteinuria (UACR >300 mg/g; stage A3); or presence of microvascular disease in at least three different sites [e.g. microalbuminuria (stage A2) plus retinopathy plus neuropathy].



European Heart Journal 2023; 00, 1–98

5.2.1. Si raccomanda l'uso di metformina, SGLT-2i e GLP-1 RA come farmaci di prima scelta per il trattamento a lungo termine in pazienti con diabete di tipo 2 con pregressi eventi cardiovascolari e senza scompenso cardiaco. Pioglitazone, DPP-4i, acarbosio ed insulina dovrebbero essere considerati farmaci di seconda scelta.

Forza della raccomandazione: forte. Qualità delle prove: moderata.

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 Individuals 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

Prioritize avoidance of hypoglycemia 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 go

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

Intensive eviden based structur weight managen program

Consider medication for weight loss

Consider metab surgery

When choosing glucose-lowering therap

Consider regimen with high-to-very-high 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

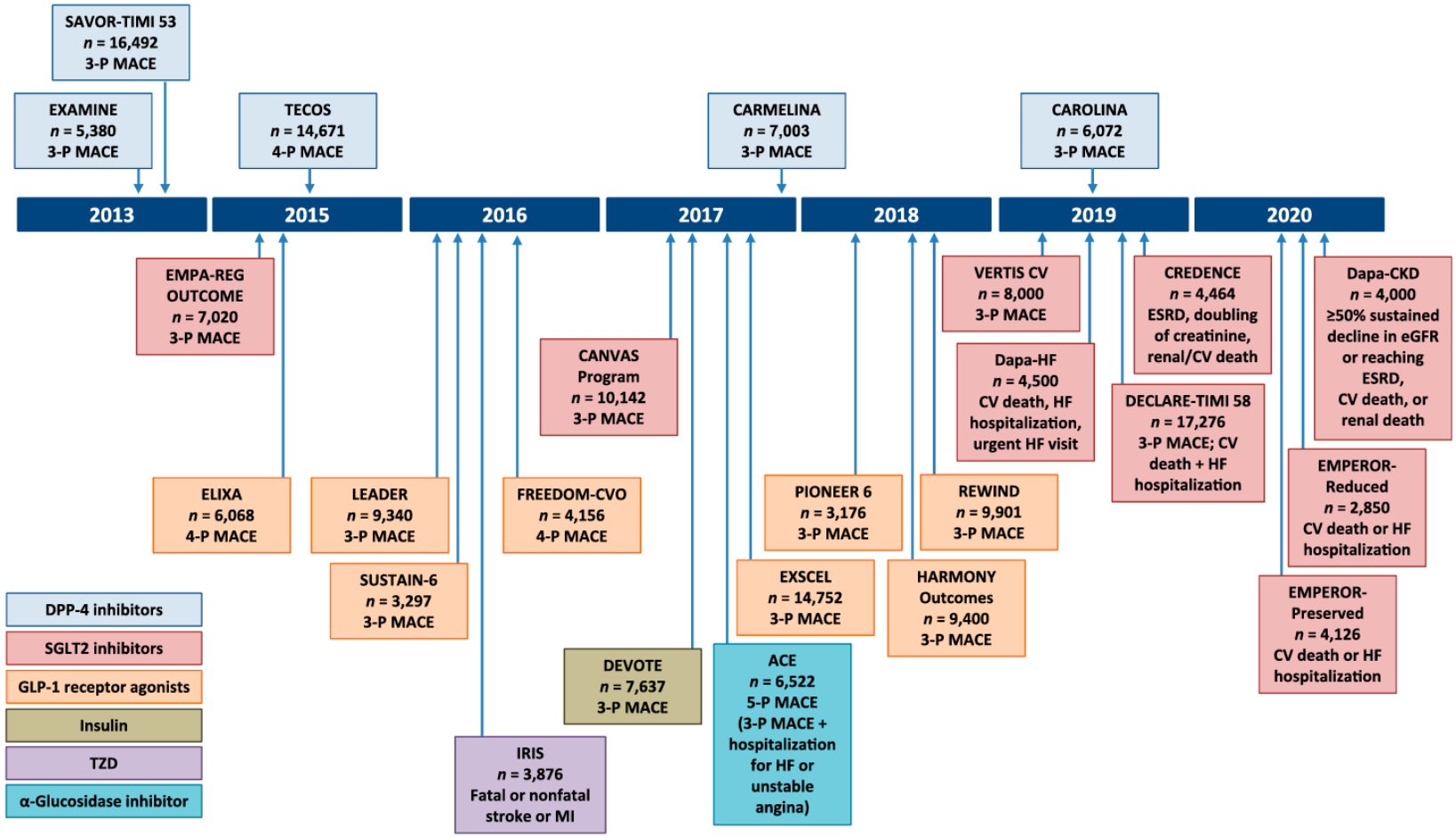
Identify barriers to goals:

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

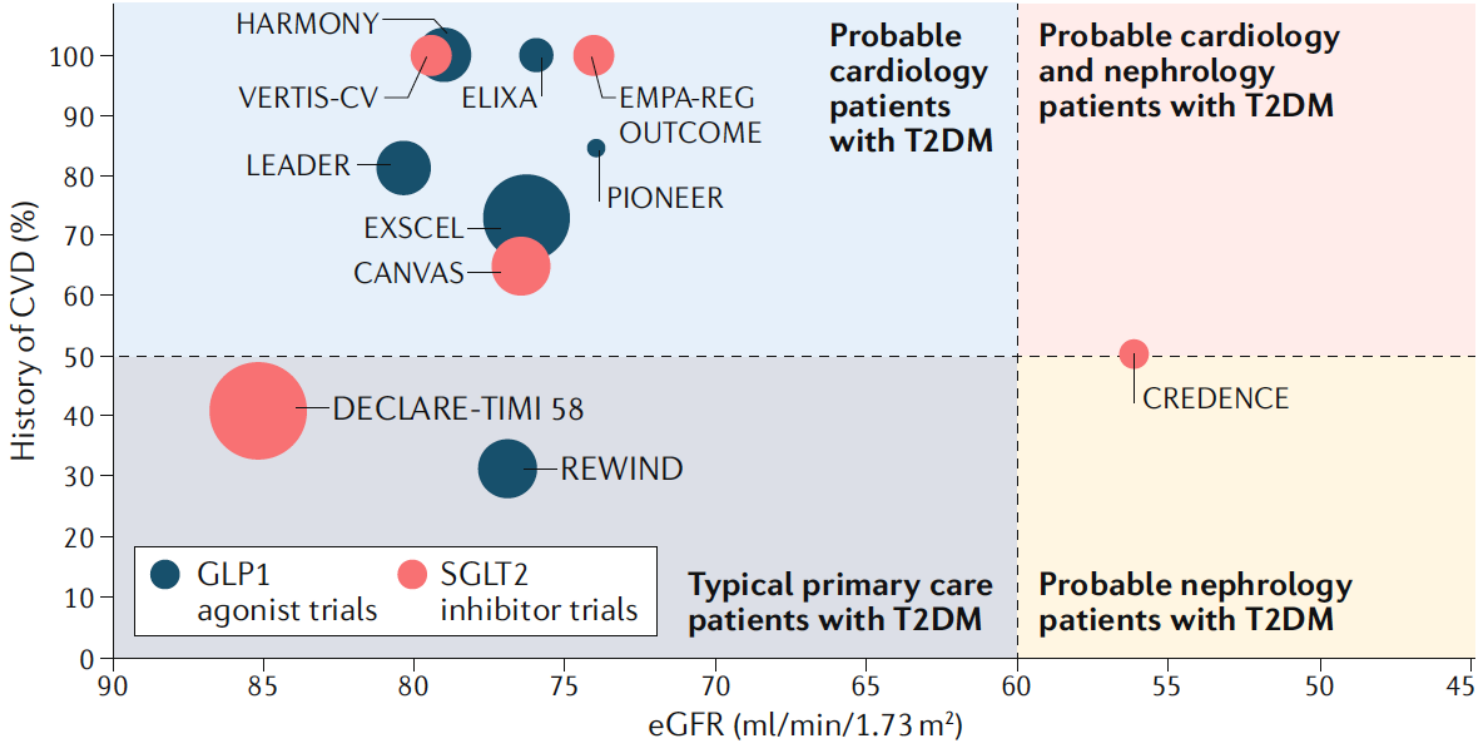
* In people with HF, CKD, established CVD, or multiple risk factors for CVD, the decision to use a GLP-1 RA or SGLT2i with proven benefit should be independent of background use of metformin; † A strong recommendation is warranted for people with CVD and a weaker recommendation for those with indicators 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.

Diabetes Care. 2023;47(Supplement_1):S158-S178. doi:10.2337/dc24-S009

Overview of CVOTs of glucose-lowering drugs

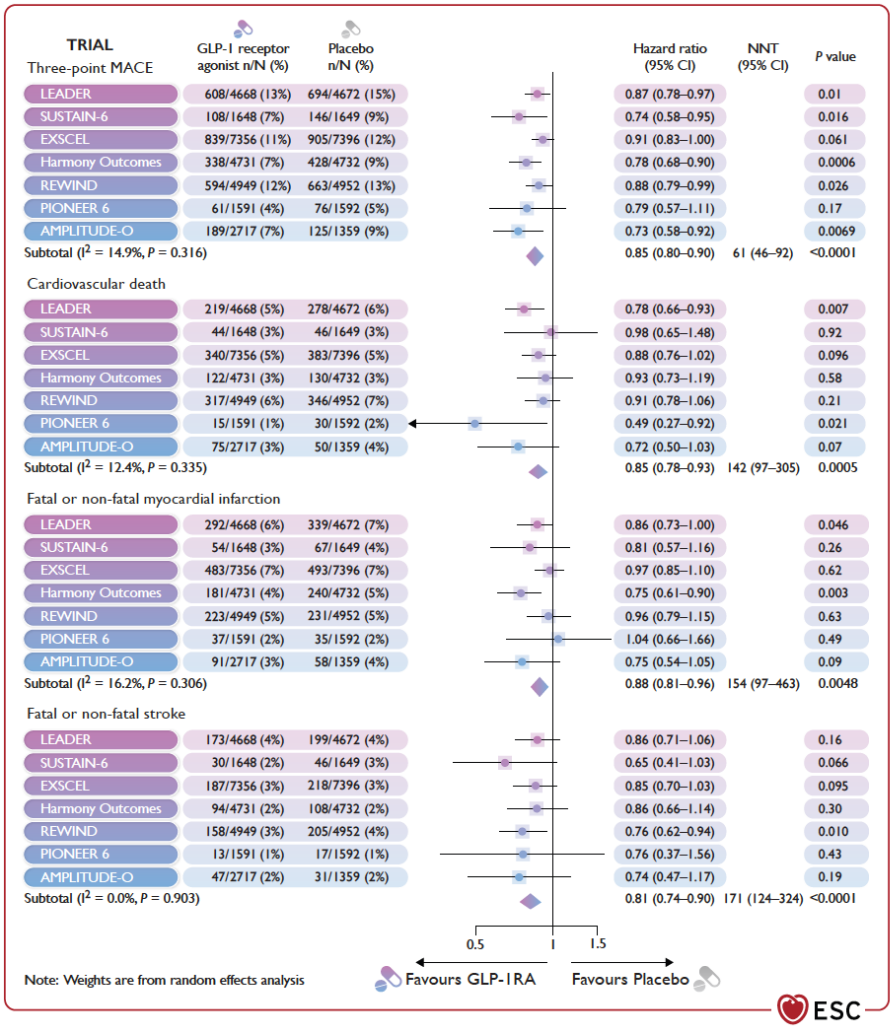


Patient cohorts enrolled in clinical trials with SGLT2 inhibitors and GLP1 receptor agonists



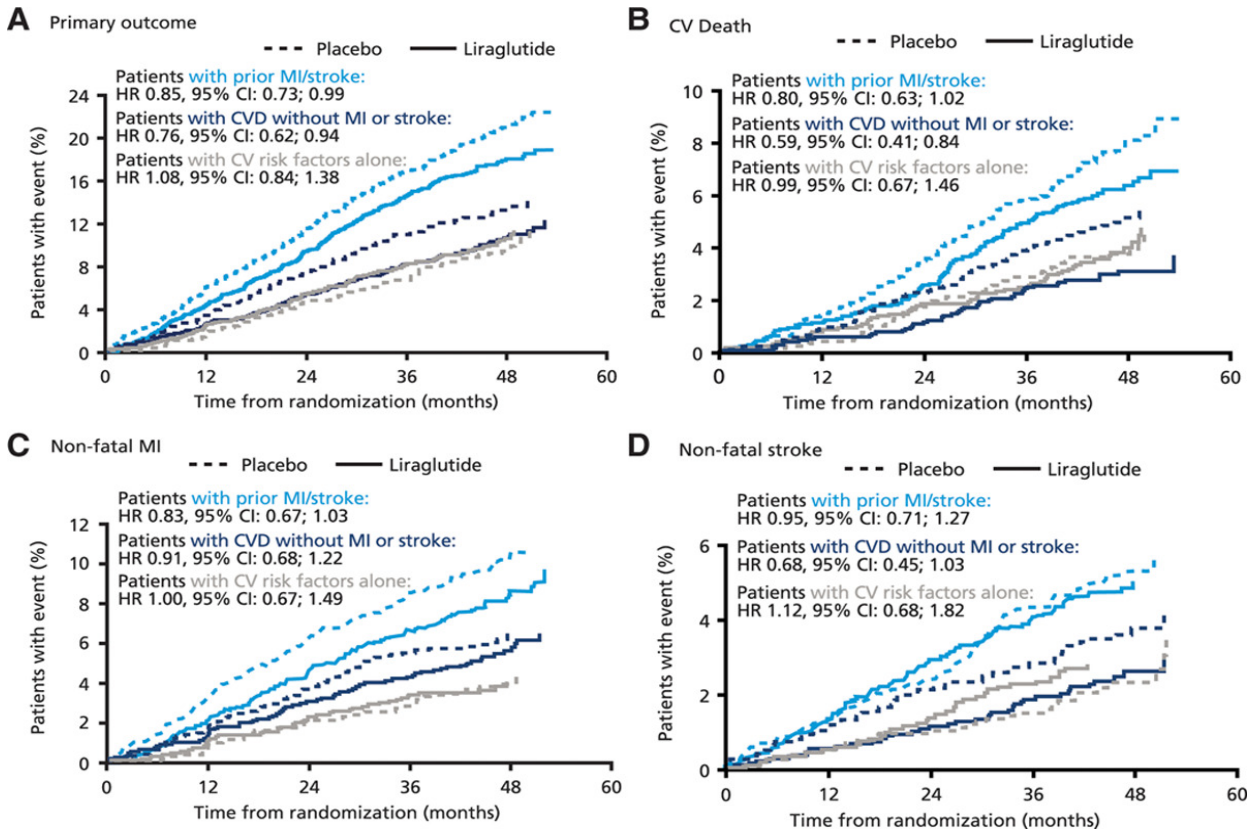
Nat Rev Nephrol 2020 Aug;16(8):433-434.

Meta-analysis of cardiovascular outcomes trials with glucagon-like peptide-1 receptor agonists



European Heart Journal 2023; 00, 1–98

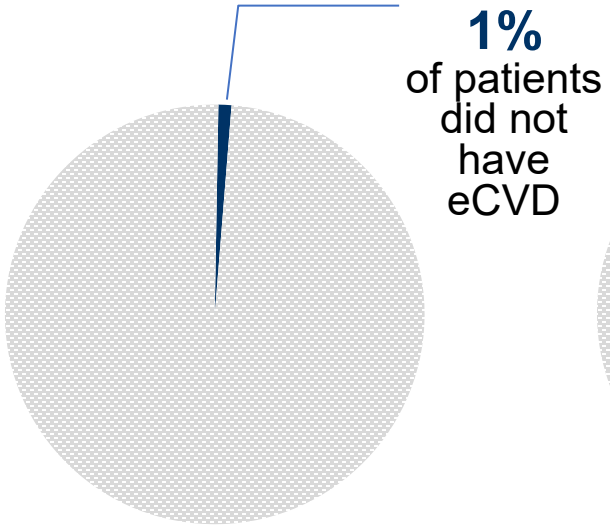
Effects of Liraglutide on Cardiovascular Outcomes in Patients With Type 2 Diabetes Mellitus With or Without History of Myocardial Infarction or Stroke



Subodh Verma. Circulation. Volume: 138, Issue: 25, Pages: 2884-2894, DOI: (10.1161/CIRCULATIONAHA.118.034516)

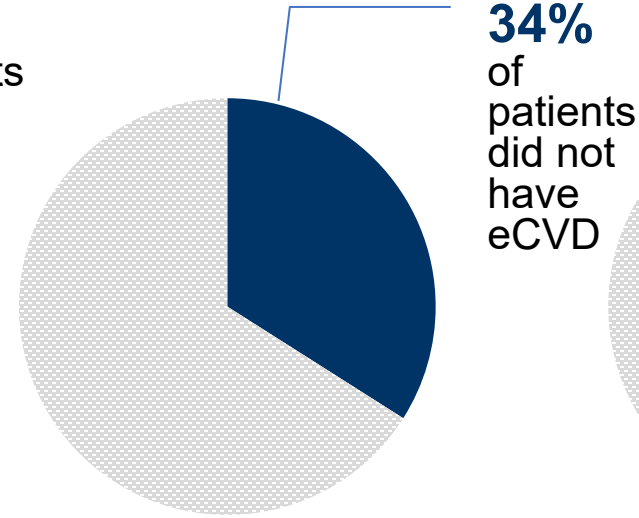
The proportion of patients with and without established CV disease varied across the three SGLT2 CV outcome studies

EMPA-REG OUTCOME
(N=7,020)



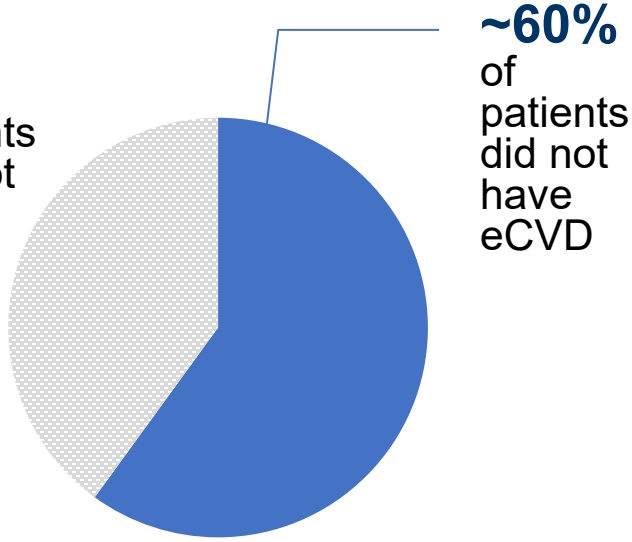
1% of patients did not have eCVD

CANVAS
(N=10,142)



34% of patients did not have eCVD

DECLARE
(N=17,160)

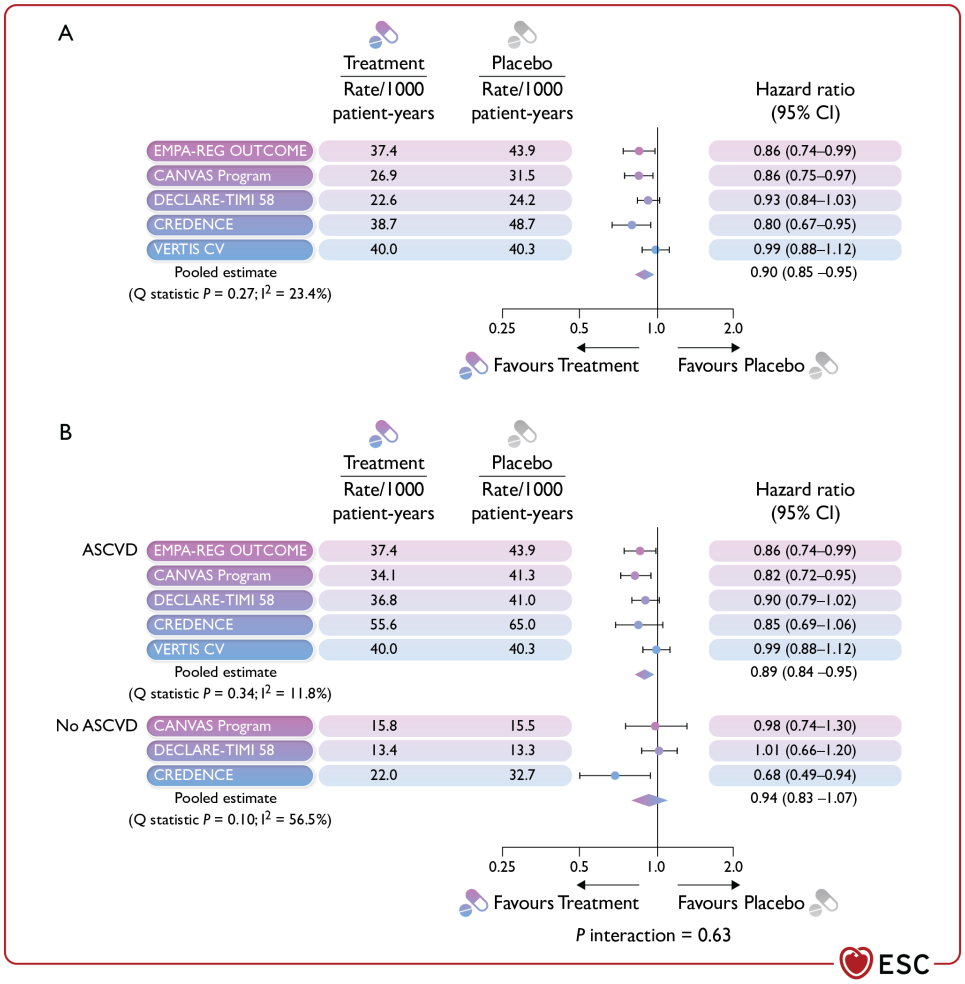


~60% of patients did not have eCVD

- CV, cardiovascular; SGLT2, sodium glucose co-transporter 2; T2D, type 2 diabetes; eCVD, established CV disease.
- 1. Zinman B, et al. *N Engl J Med* 2015;373:2117–2128;; 2. Neal B, et al. *N Engl J Med* 2017; DOI: 10.1056/NEJMoa1611925;3. Sattar Diabetologia (2013) 56:686–695 4. Raz I, et al. *Diabetes Obes Metab* 2018. http://dx.doi.org/10.1111/dom.13217

Figure 5

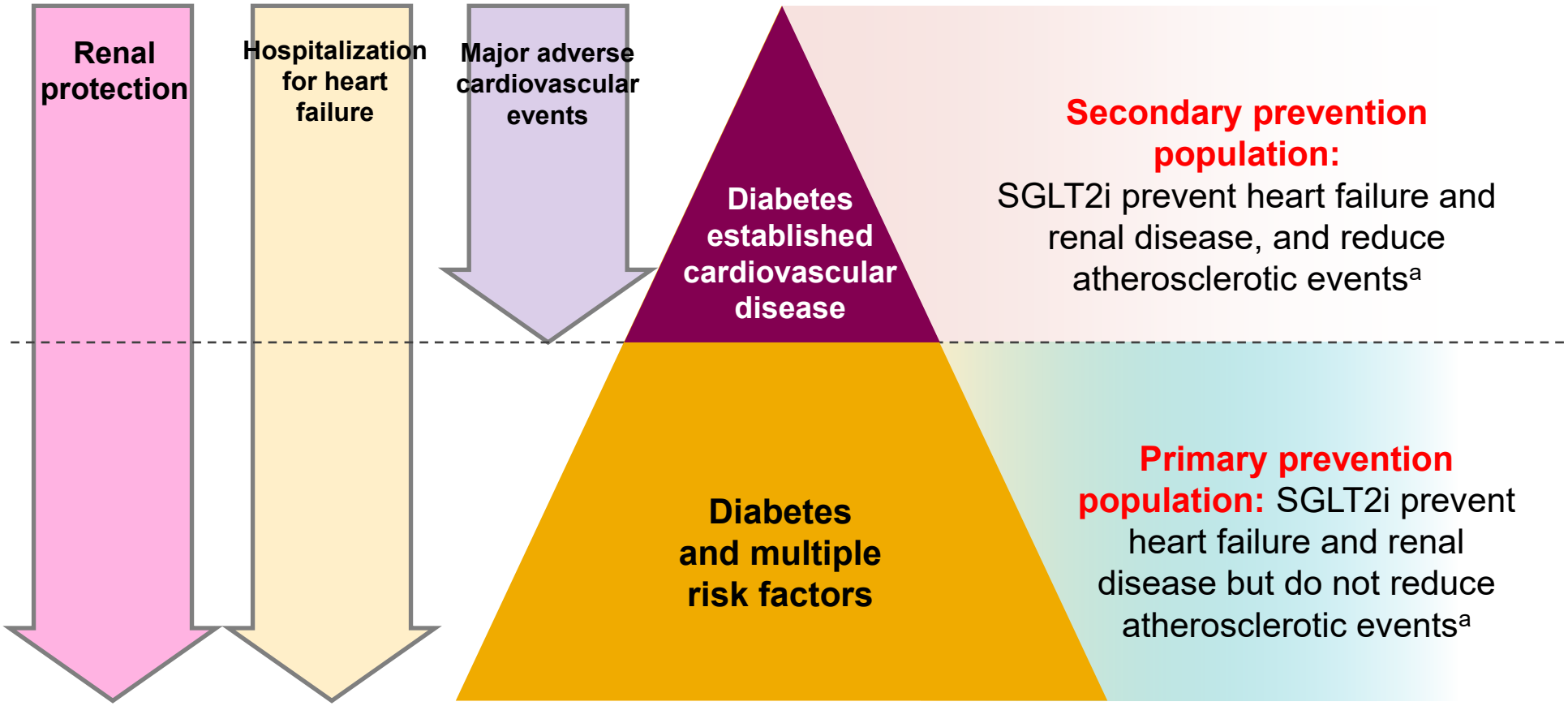
Meta-analysis of cardiovascular outcomes trials with sodium–glucose co-transporter-2 inhibitors. (A) Overall major adverse cardiovascular events; (B) Major adverse cardiovascular events by atherosclerotic cardiovascular disease status



2023 ESC Guidelines for the management of cardiovascular disease in patients with diabetes
(European Heart Journal; 2023 – doi:10.1093/eurheartj/ehad192)

Pump, pipes and filter: Do SGLT2 inhibitors cover it all?

Cardiorenal efficacy of SGLT2i

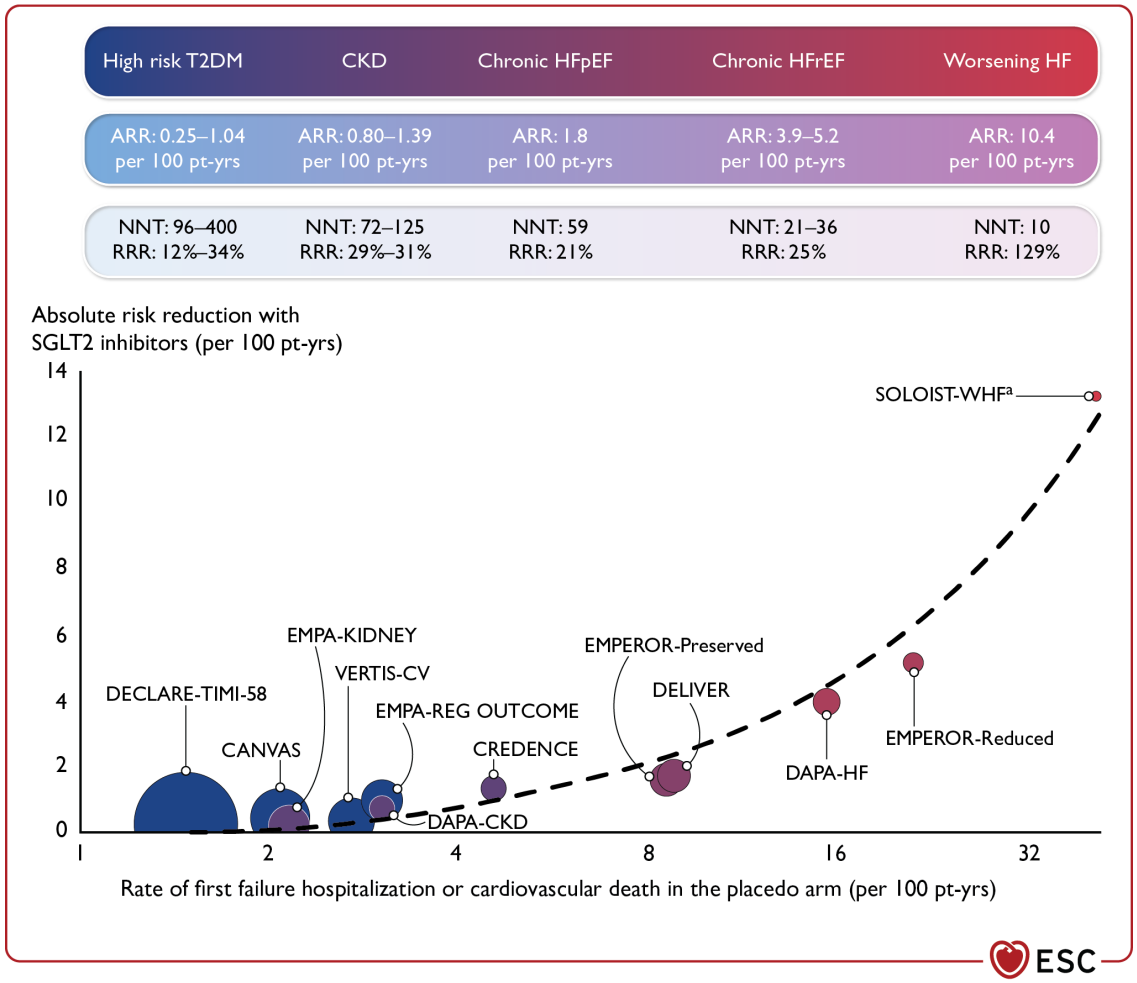


[a]Defined as MACE. MACE = major adverse cardiovascular events; SGLT2i = sodium-glucose cotransporter inhibitors.

Verma S et al. *Lancet*. 2019;393:3-5

Figure 15

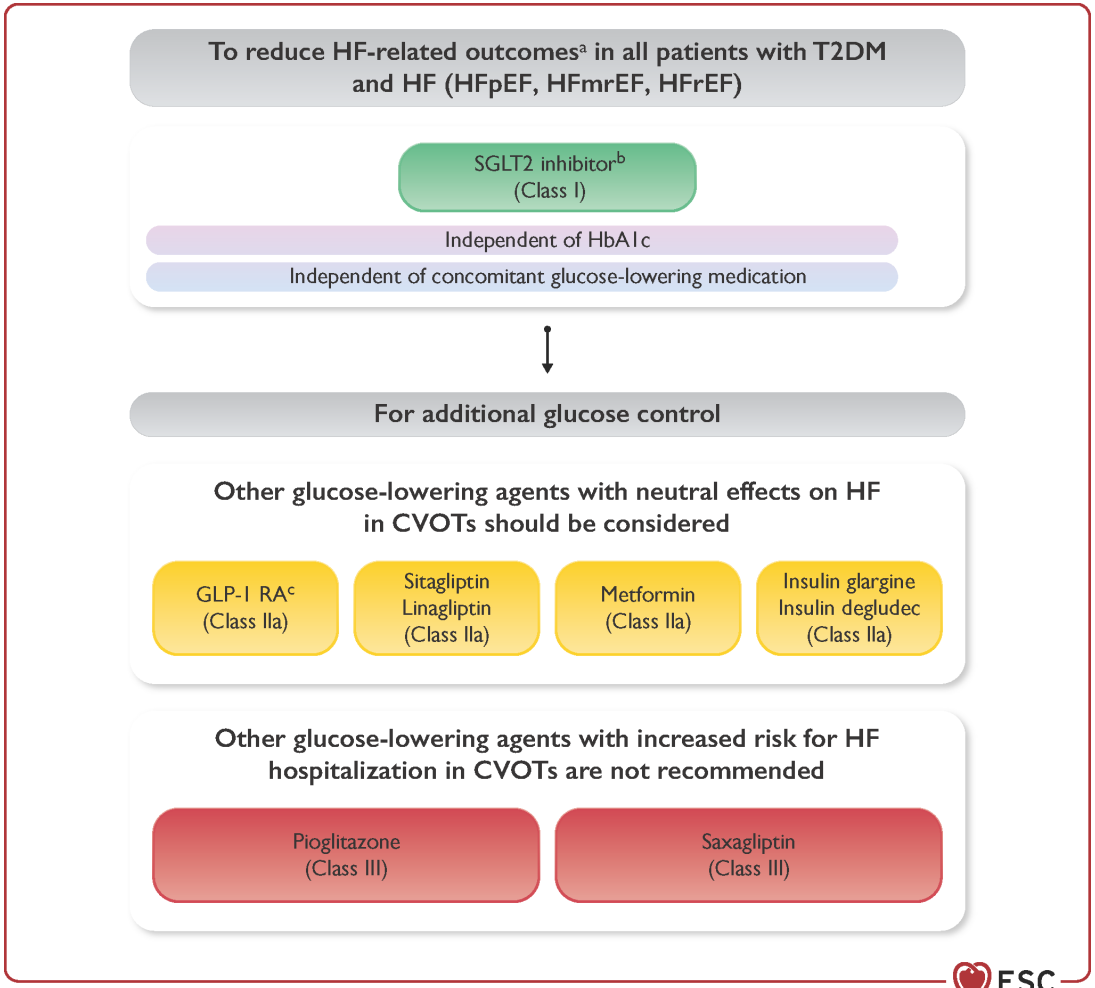
Absolute risk reduction with sodium–glucose co-transporter-2 inhibitors in relation to patient risk based on rate of heart failure-related endpoints in the placebo arm of the respective trials



2023 ESC Guidelines for the management of cardiovascular disease in patients with diabetes
(European Heart Journal; 2023 – doi:10.1093/eurheartj/ehad192)

Figure 16

Glucose-lowering treatment of patients with heart failure and type 2 diabetes



2023 ESC Guidelines for the management of cardiovascular disease in patients with diabetes
(European Heart Journal; 2023 – doi:10.1093/eurheartj/ehad192)

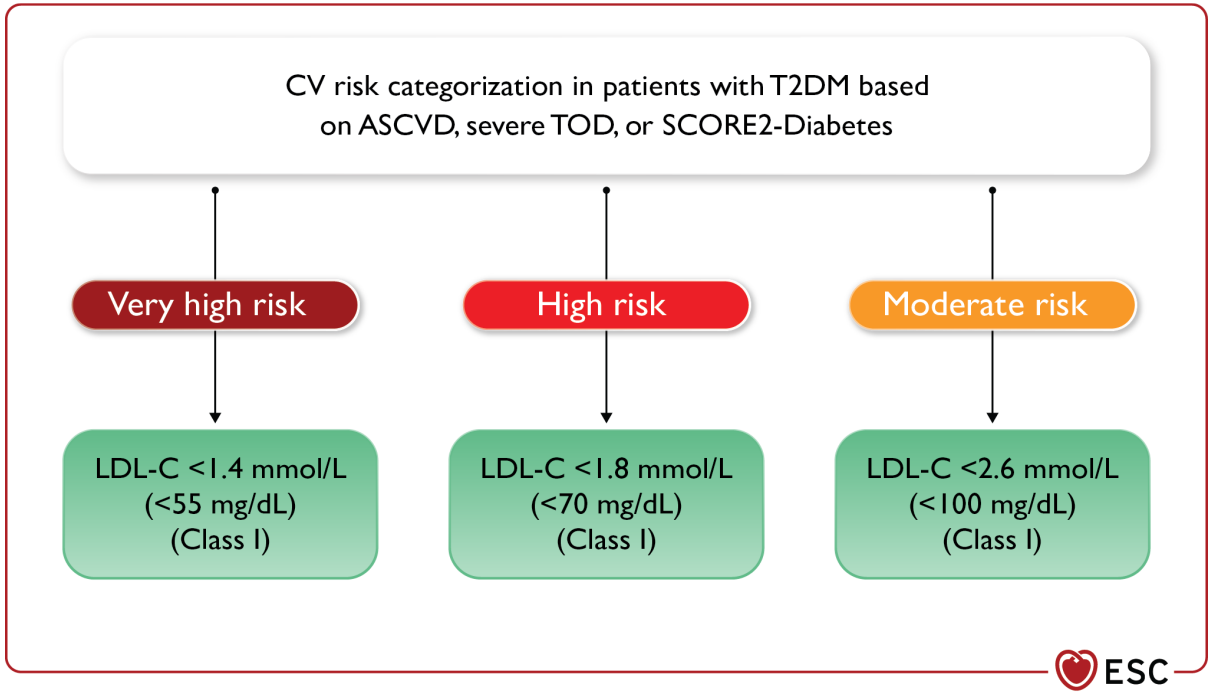
5.2.2. Si raccomanda l'uso di SGLT-2i come farmaci di prima scelta per il trattamento a lungo termine di pazienti con diabete di tipo 2 con scompenso cardiaco. I GLP-1 RA e metformina dovrebbero essere considerati come farmaci di seconda scelta, mentre DPP-4i, acarbosio ed insulina come farmaci di terza scelta.

Forza della raccomandazione: forte. Qualità delle prove: moderata.

Le associazioni tra più farmaci devono essere prescritte secondo le indicazioni delle rispettive schede tecniche.
** La metformina è controindicata in classe III e IV NYHA; ** Saxagliptin è associato ad un aumento di ricoveri per scompenso cardiaco*

Figure 10

Recommended low-density lipoprotein-cholesterol targets by cardiovascular risk categories in patients with type 2 diabetes



2023 ESC Guidelines for the management of cardiovascular disease in patients with diabetes
(European Heart Journal; 2023 – doi:10.1093/eurheartj/ehad192)

Recommendations for the management of dyslipidaemia in patients with diabetes (2)

Recommendations	Class	Level
Lipid-lowering treatment		
Statins are recommended as the first-choice LDL-C-lowering treatment in patients with diabetes and above-target LDL-C levels. Administration of statins is defined based on the CV risk profile of the patients and the recommended LDL-C (or non-HDL-C) target levels.	I	A
A PCSK9 inhibitor is recommended in patients at very high CV risk, with persistently high LDL-C levels above target despite treatment with a maximum tolerated statin dose, in combination with ezetimibe, or in patients with statin intolerance.	I	A
If the target LDL-C is not reached with statins, combination therapy with ezetimibe is recommended.	I	B

2023 ESC Guidelines for the management of cardiovascular disease in patients with diabetes
(European Heart Journal; 2023 – doi:10.1093/eurheartj/ehad192)

Table 10.2—High-intensity and moderate-intensity statin therapy

High-intensity statin therapy (lowers LDL cholesterol by ≥50%)	Moderate-intensity statin therapy (lowers LDL cholesterol by 30–49%)
Atorvastatin 40–80 mg	Atorvastatin 10–20 mg
Rosuvastatin 20–40 mg	Rosuvastatin 5–10 mg
	Simvastatin 20–40 mg
	Pravastatin 40–80 mg
	Lovastatin 40 mg
	Fluvastatin XL 80 mg
	Pitavastatin 1–4 mg

Once-daily dosing. XL, extended release.

Recommendations for patients with diabetes without a history of symptomatic atherosclerotic cardiovascular disease or revascularization

Recommendation	Class	Level
In adults with T2DM without a history of symptomatic ASCVD or revascularization, ASA (75–100 mg o.d.) may be considered to prevent the first severe vascular event, in the absence of clear contraindications.	IIb	A

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Effects of Aspirin for Primary Prevention in Persons with Diabetes Mellitus

The ASCEND Study Collaborative Group*

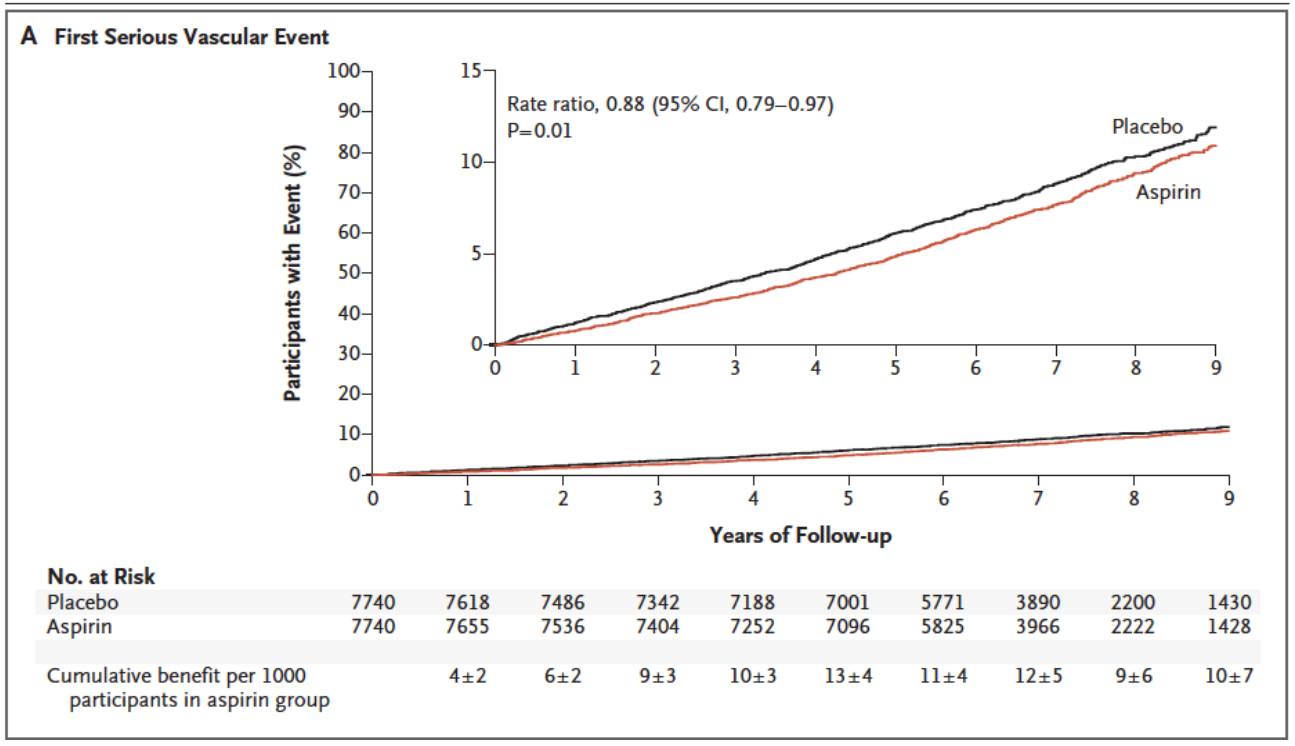
Baseline demographics (N=15,480)

Characteristic	Aspirin	Placebo
Age, years	63	63
Male	63%	63%
Type 2 diabetes	94%	94%
Diabetes duration, median years	7	7
Hypertension	62%	62%
Statin use	76%	75%
Body Mass Index, kg/m^2	31	31
Glycated haemoglobin, mmol/mol	55 (7.2%)	55 (7.2%)
PPI	1073 (14)	1181 (15)

ASCEND. N Engl J Med 2018

Effect of aspirin on serious vascular events

(non-fatal MI, stroke, TIA, CV death)



No. at Risk										
Placebo	7740	7618	7486	7342	7188	7001	5771	3890	2200	1430
Aspirin	7740	7655	7536	7404	7252	7096	5825	3966	2222	1428
Cumulative benefit per 1000 participants in aspirin group		4±2	6±2	9±3	10±3	13±4	11±4	12±5	9±6	10±7

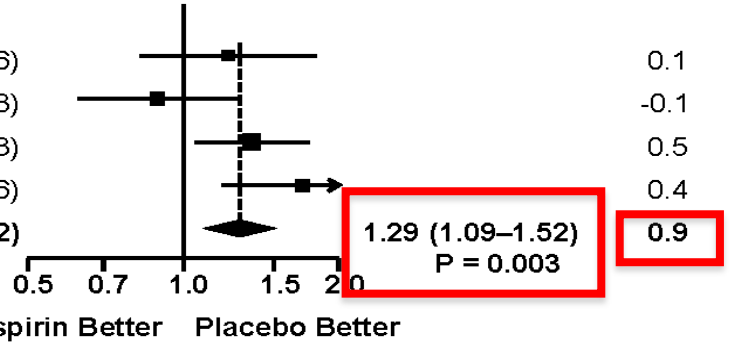
NNT=91

Event rate: 1.3%/year

ASCEND. N Engl J Med 2018

Effect of aspirin on major bleed

Type of Event	Aspirin (N=7740) no. of participants with events (%)	Placebo (N=7740) no. of participants with events (%)	Rate Ratio (95% CI)	Absolute Difference (%)
Major bleed				
Intracranial hemorrhage	55 (0.7)	45 (0.6)		0.1
Sight threatening eye bleed	57 (0.7)	64 (0.8)		-0.1
Serious gastrointestinal hemorrhage	137 (1.8)	101 (1.3)		0.5
Other major bleed	74 (1.0)	43 (0.6)		0.4
Any major bleed	**314 (4.1)**	**245 (3.2)**	**1.29 (1.09–1.52) P = 0.003**	**0.9**

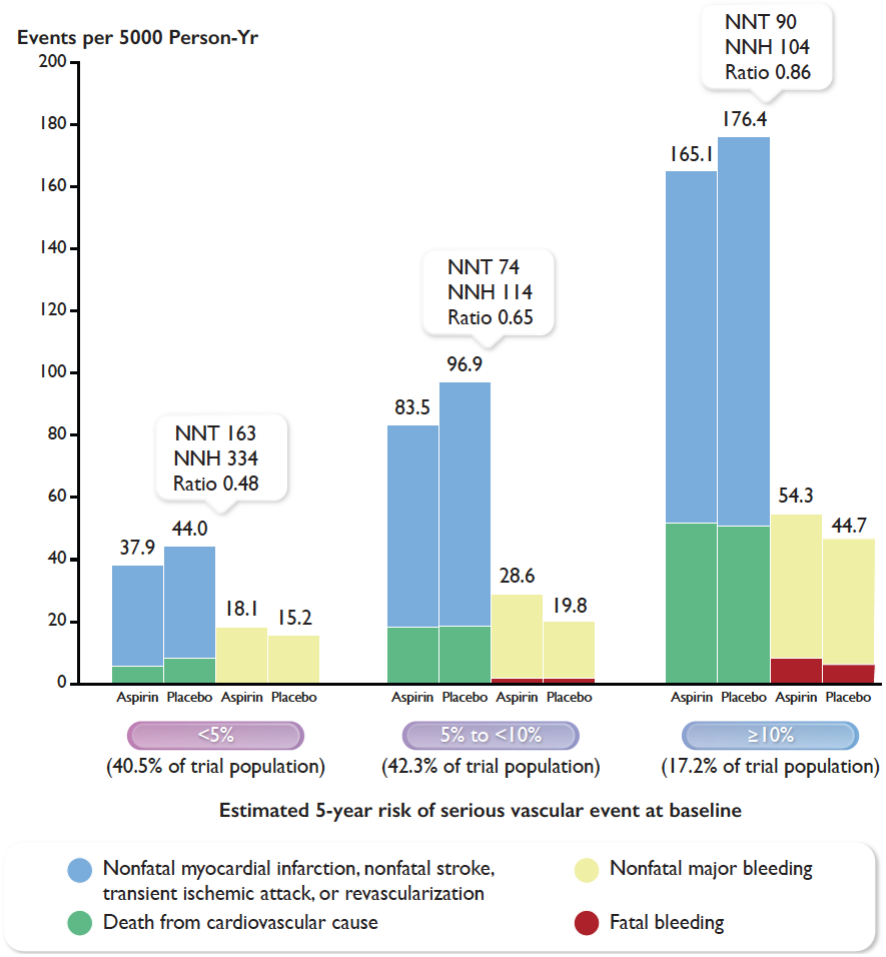


NNH=112

Approximately half the excess of bleeding was in the gastrointestinal tract, with approximately one third in the upper gastrointestinal tract

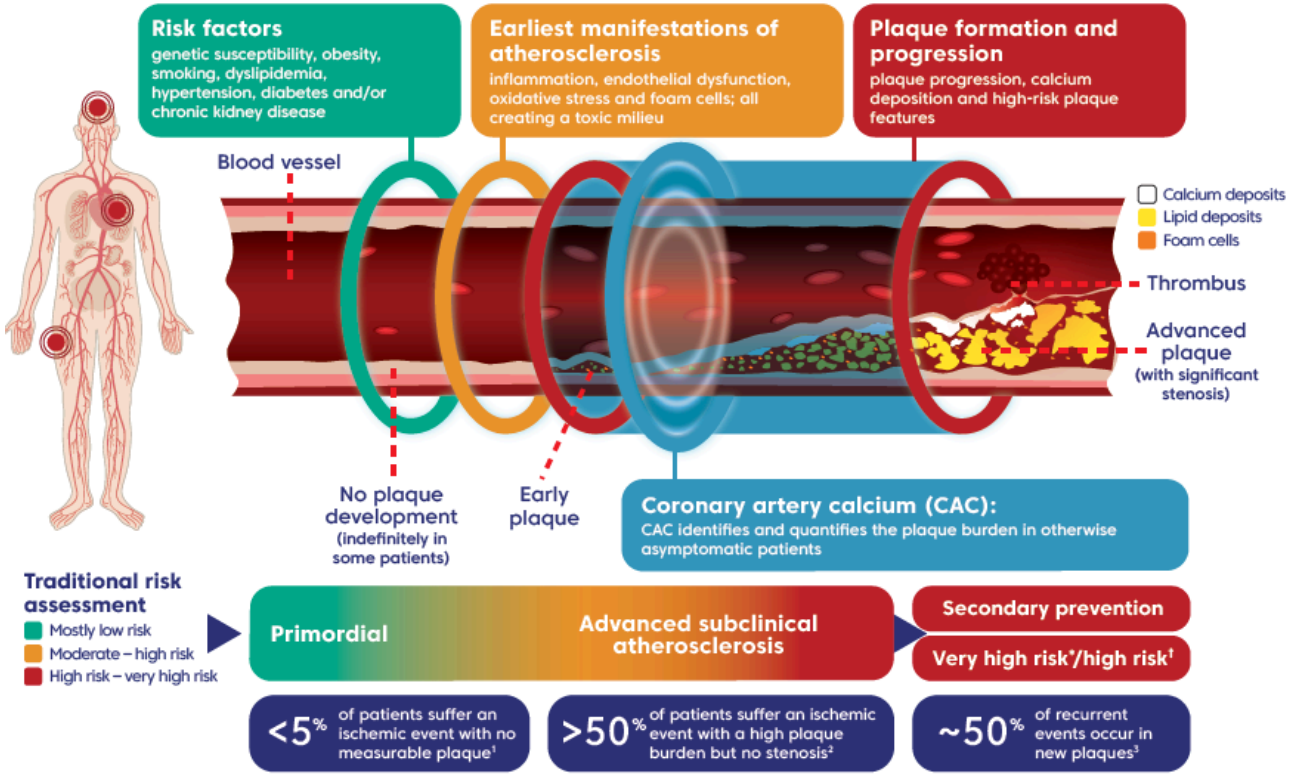
ASCEND. N Engl J Med 2018

Observed absolute effect in aspirin and placebo groups for serious vascular events, including major bleeding or revascularization. ASCEND, A Study of Cardiovascular Events iN Diabetes



European Heart Journal 2023; 00, 1–37 https://doi.org/10.1093/eurheartj/ehad192

Cardiovascular Risk Continuum



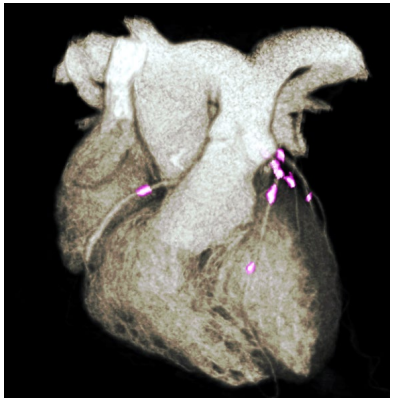
1. Mortensen MB, et al. *J Am Coll Cardiol.* 2020;76(24):2803–13; 2. Douglas P, et al. *N Engl J Med.* 2015;372(14):1291-300;
3. Stone G, et al. *N Engl J Med.* 2011;364:226-35.
*progression of polyvascular disease. †stabilization of disease or complete revascularization.

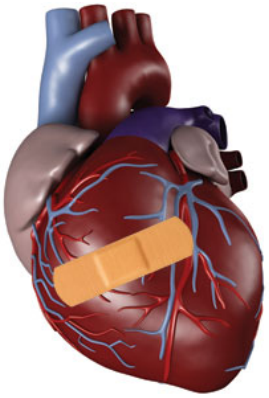
Michael J. Blaha[a,*], Magdy Abdelhamid[b], Francesca Santilli[c], Zhongwei Shi[d], Dirk Sibbing[e]

Am J Prev Cardiol. 2022;13:100456

Continuum of ASCVD Risk

Subclinical atherosclerosis shortens the gap between primary and secondary prevention





Primary Prevention → **Advanced Subclinical Atherosclerosis?** → **Secondary Prevention**

Blaha MJ, *AJC* 2016

New recommendations for stratification of CV risk in patients with diabetes

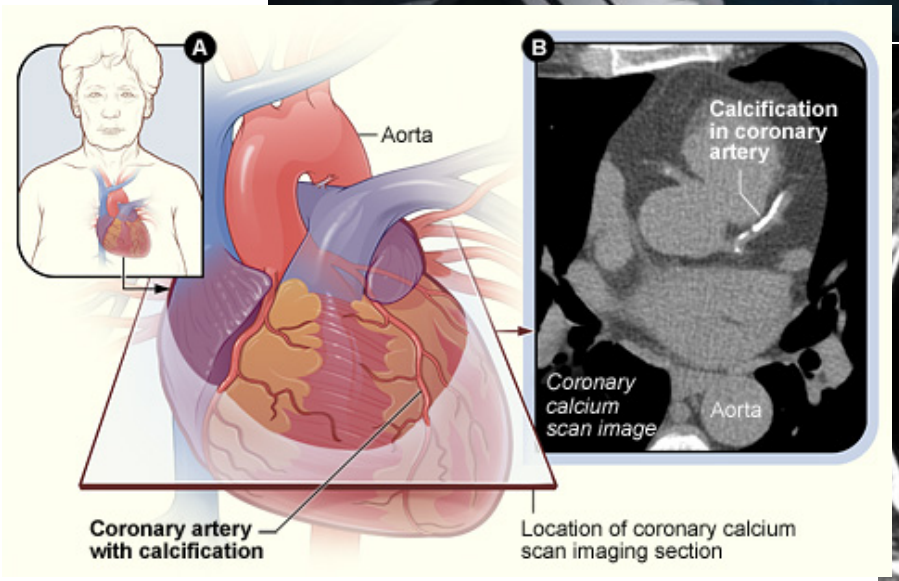
Assessment of atherosclerosis: imaging techniques

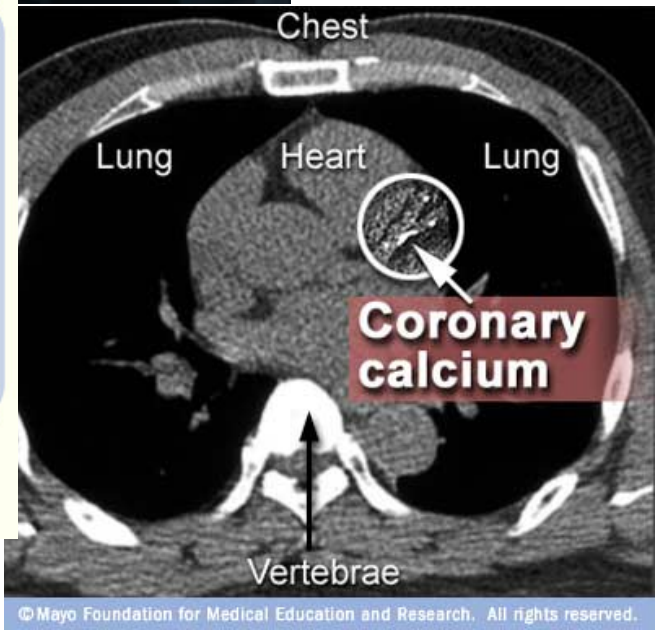
CV risk assessment
Carotid or femoral ultrasound for plaque detection as CV risk modifier
Screening for CAD with coronary CT angiography and functional imaging
CAC scoring as risk modifier
ABI as riskmodifier
Carotid ultrasound intima-media thickness for CV risk is not recommended

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

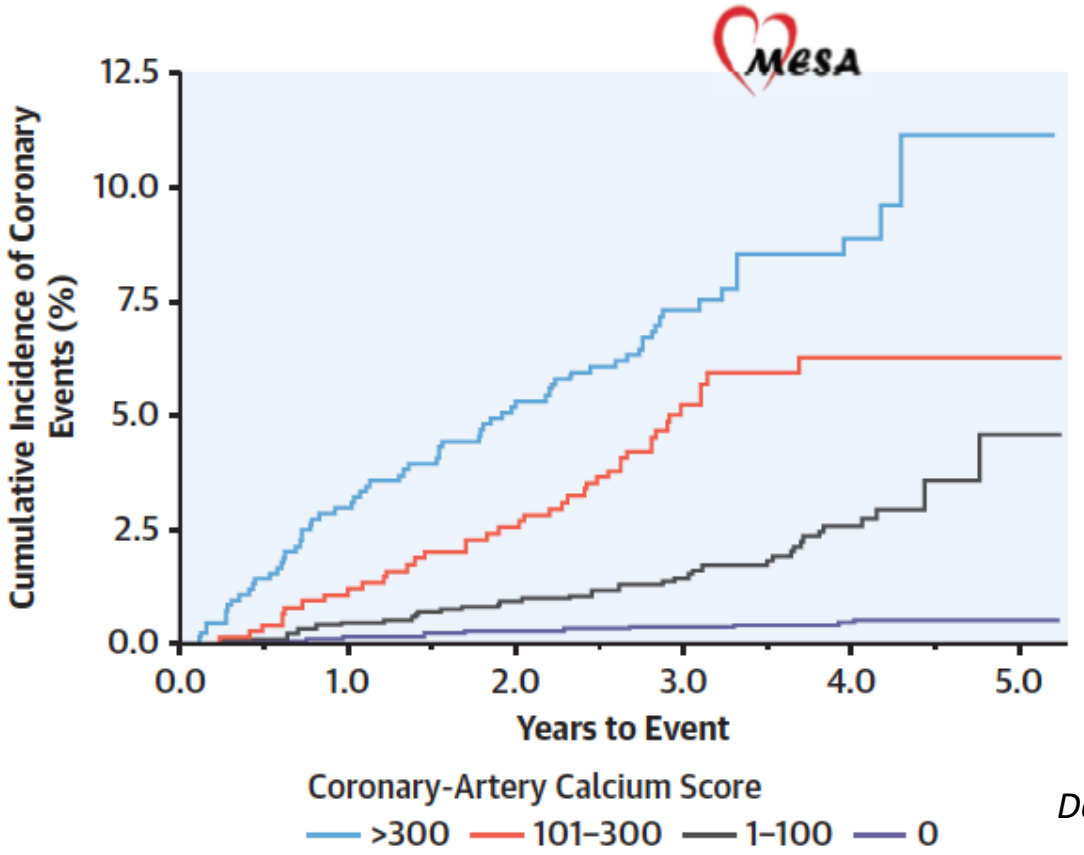
Coronary Artery Calcium

~1 mSv



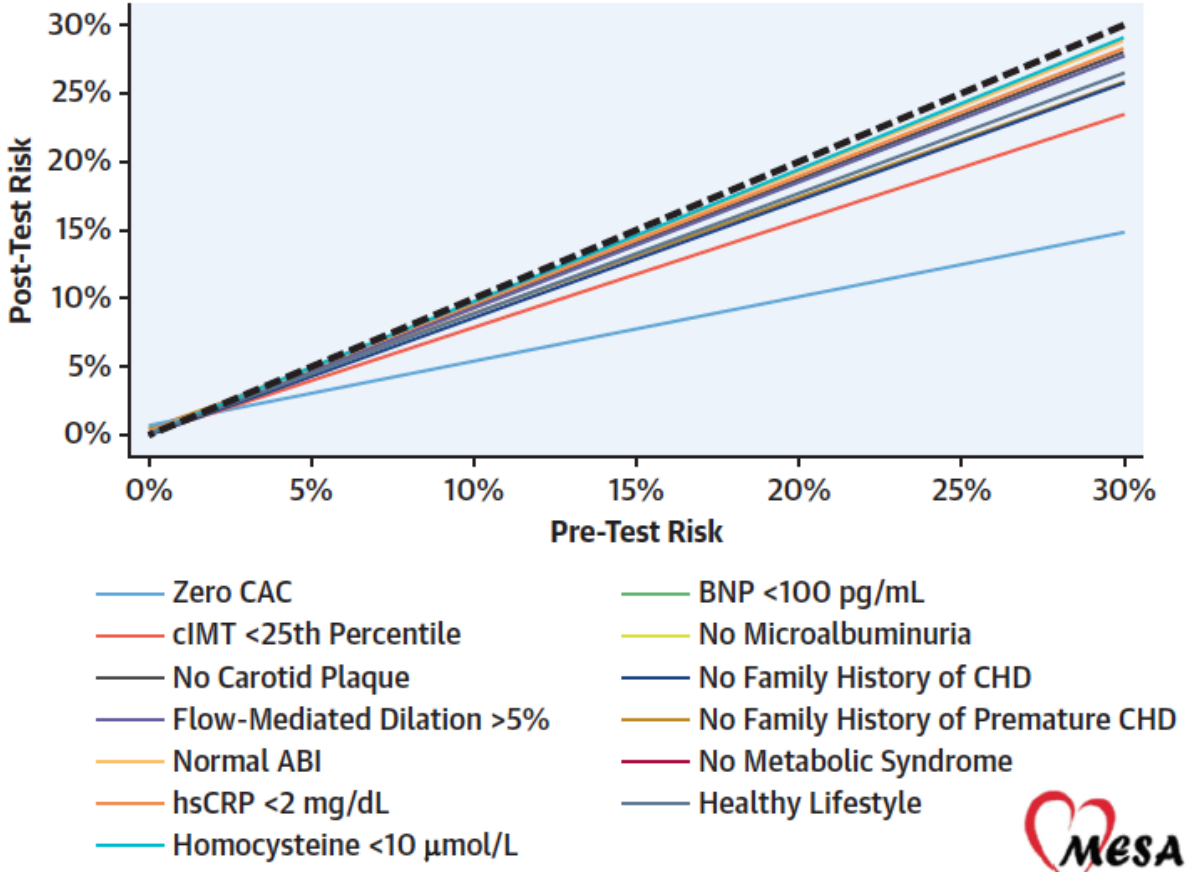


Coronary Artery Calcium and Coronary Events in 4 Race/Ethnic Groups



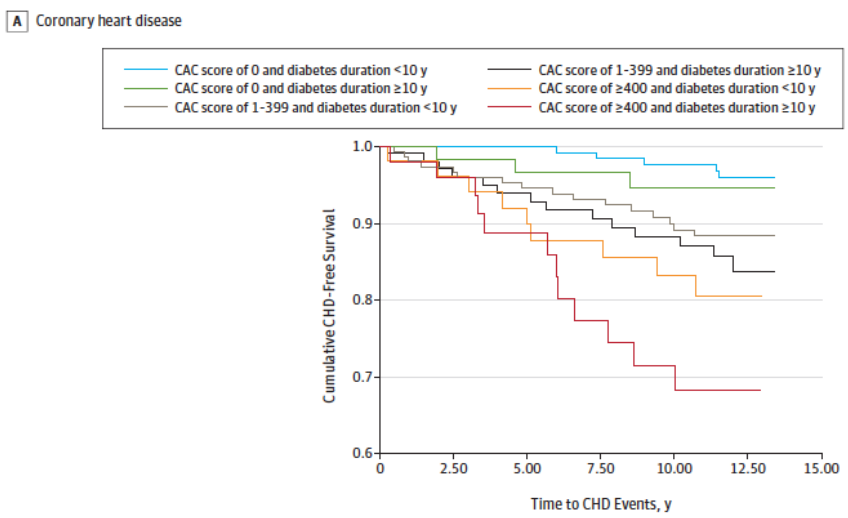
Detrano R. N Engl J Med 2008

CAC = 0 Versus Other Negative Risk Markers in MESA



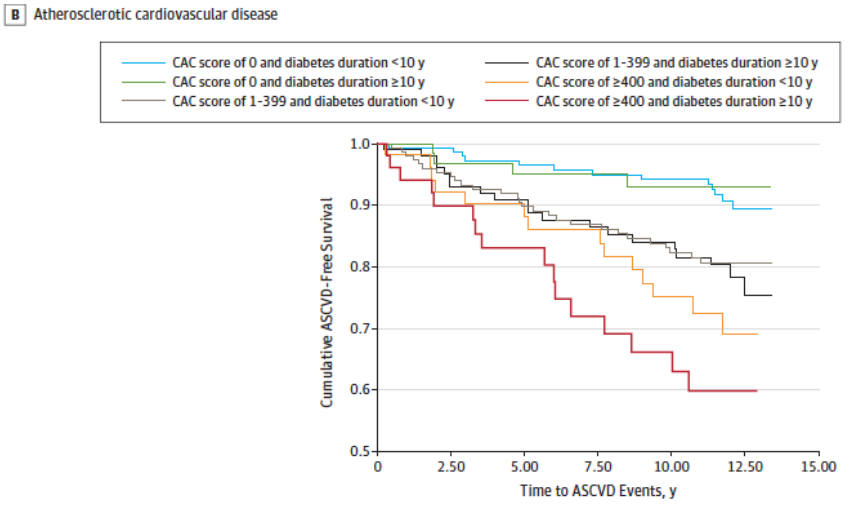
Blaha MJ. Circulation 2016

Event-Free Survival for CHD and ASCVD in Those With Type 2 Diabetes by Diabetes Duration and CAC Score



No. at risk

CAC score of 0 and diabetes duration <10 y	151	141	131	121	118	47
CAC score of 0 and diabetes duration ≥10 y	64	60	54	52	47	15
CAC score of 1-399 and diabetes duration <10 y	149	141	131	123	110	35
CAC score of 1-399 and diabetes duration ≥10 y	105	95	84	78	72	28
CAC score of ≥400 and diabetes duration <10 y	54	47	42	40	34	12
CAC score of ≥400 and diabetes duration ≥10 y	52	44	36	27	22	7



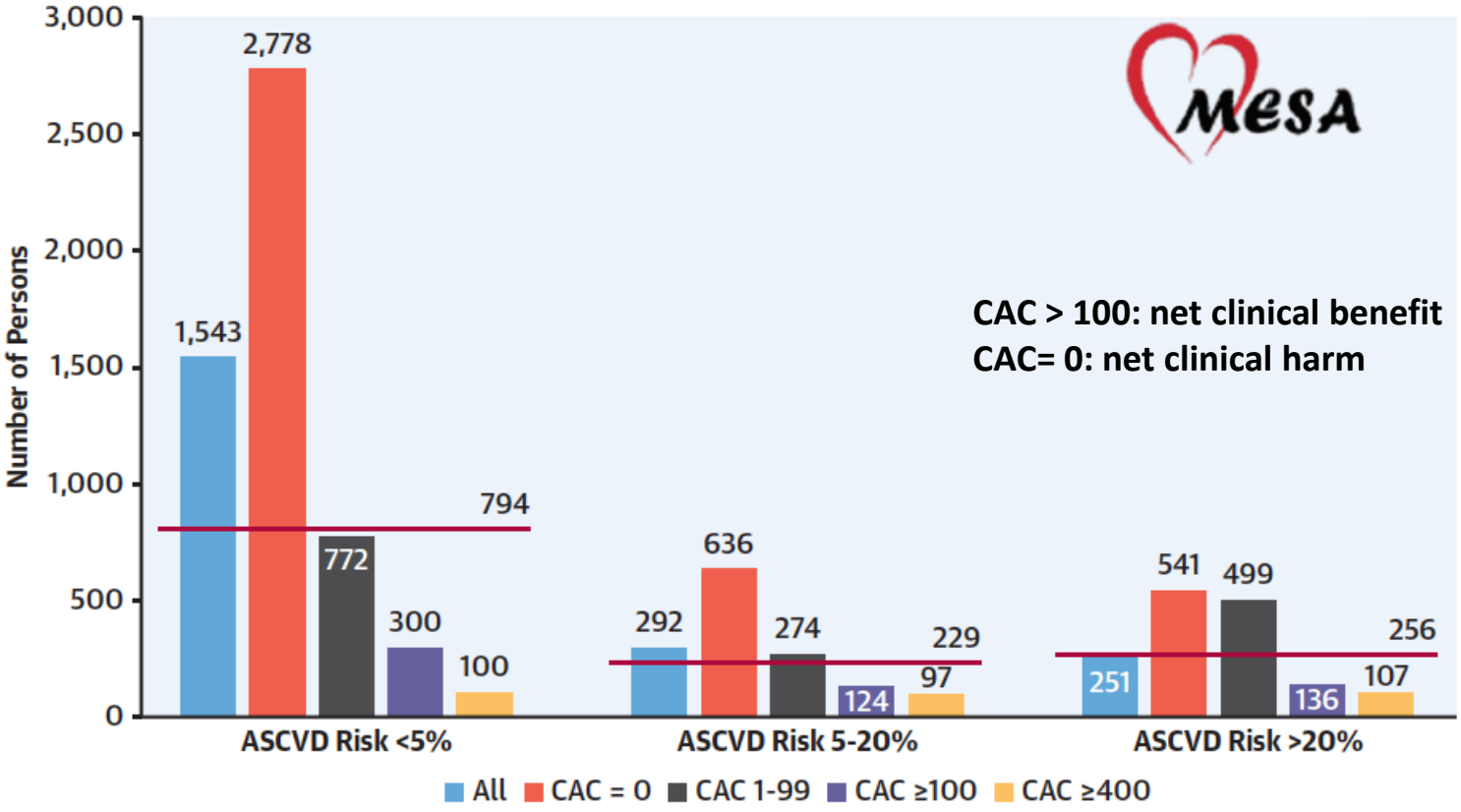
No. at risk

CAC score of 0 and diabetes duration <10 y	151	142	130	120	117	45
CAC score of 0 and diabetes duration ≥10 y	64	59	53	51	46	14
CAC score of 1-399 and diabetes duration <10 y	149	139	125	117	103	33
CAC score of 1-399 and diabetes duration ≥10 y	105	92	81	74	68	25
CAC score of ≥400 and diabetes duration <10 y	54	46	42	40	32	10
CAC score of ≥400 and diabetes duration ≥10 y	52	41	35	26	21	7

Malik s. JAMA Cardiol 2017

Using 10-year ASCVD risk estimate plus CAC score to guide aspirin treatment

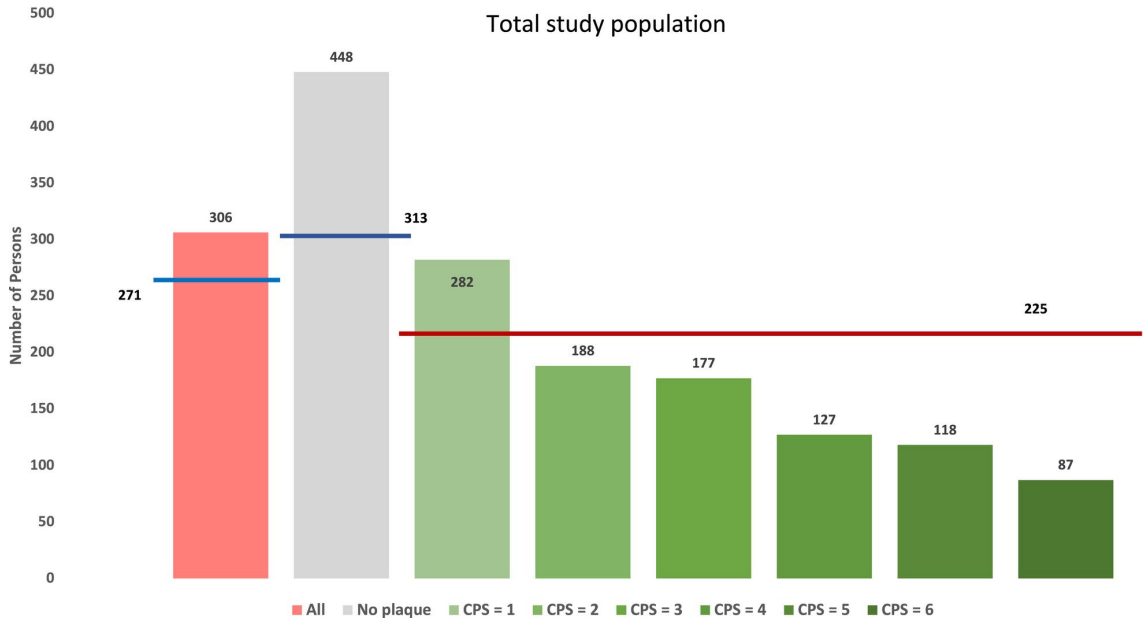
Cainzos-Aichirica M. Circulation 2020

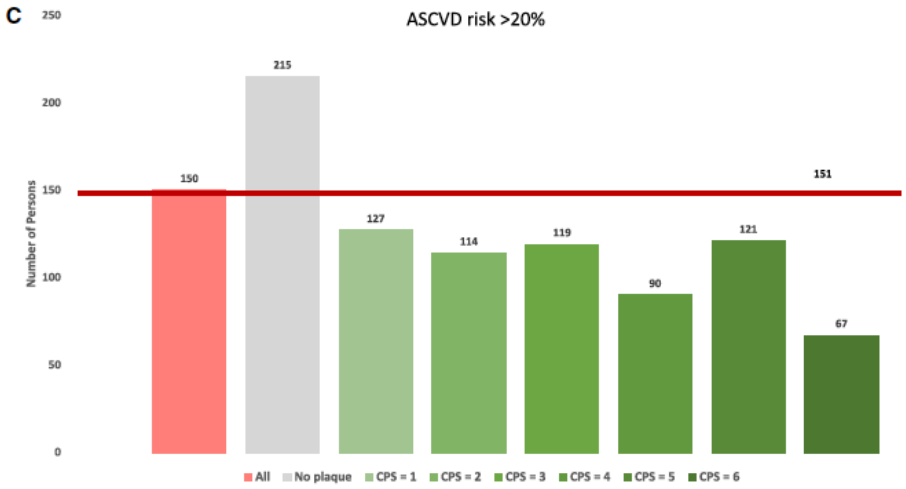


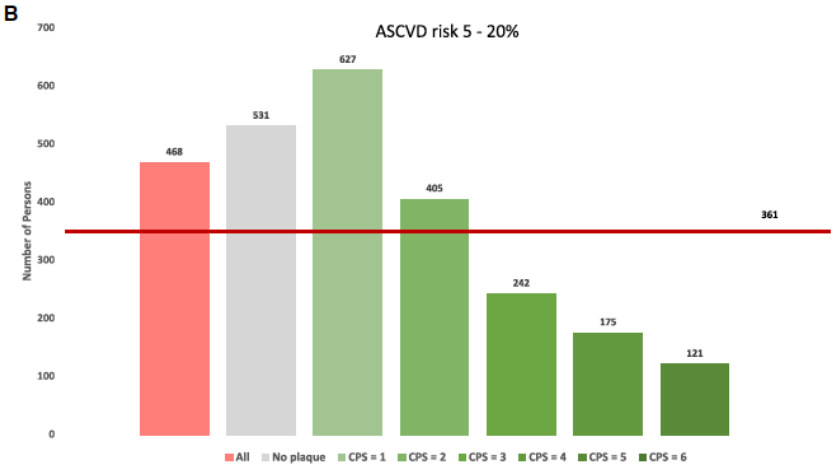
New guidelines from the National Lipid Association (NLA), released December 2020, have endorsed use of CAC≥100 to identify those who benefit from aspirin in primary prevention

Carotid Ultrasound-Based Plaque Score for the Allocation of Aspirin for the Primary Prevention of Cardiovascular Disease Events: The Multi-Ethnic Study o Atherosclerosis and the Atherosclerosis Risk in Communities Study

Omar Dzaye, MD, MPH, PhD; Alexander C. Razavi, MD, MPH, PhD; Zeina A. Dardari, MS; Khurram Nasir, MD, MPH, MSc; Kunihiro Matsushita, MD, PhD; Yejin Mok, PhD, MPH; Francesca Santilli, MD; Augusto María Lavalle Cobo, MD; Amer M. Johri, MD, MSc; Gerhard Albrecht, MD; Michael J. Blaha, MD, MPH







Plaque score ≥2 (at least 2 carotid segments with plaque)

J Am Heart Assoc. 2024;13:e034718

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

Developed by the task force on the management of cardiovascular disease in patients with diabetes of the European Society of Cardiology (ESC)

In patients with diabetes with asymptomatic ASCVD (including documented CAD confirmed by imaging) and a higher CV risk, the net benefit of platelet inhibition by ASA may be higher and thus, therapy needs to be individualized.

Recommendations for assessing CVD risk in patients with type 2 diabetes

Recommendations	Class	Level
It is recommended to screen patients with diabetes for the presence of severe TOD.	I	A
It is recommended to assess medical history and the presence of symptoms suggestive of ASCVD in patients with diabetes.	I	B
In patients with T2DM without symptomatic ASCVD or severe TOD, it is recommended to estimate 10-year CVD risk via SCORE2-Diabetes.	I	B

⇩

New recommendation

Severe TOD defined as eGFR <45 mL/min/1.73m^2 irrespective of albuminuria; or eGFR 45–59 mL/min/1.73m^2 and microalbuminuria (UACR 30–300 mg/g; stage A2); or proteinuria (UACR >300 mg/g; stage A3); or presence of microvascular disease in at least three different sites [e.g. microalbuminuria (stage A2) plus retinopathy plus neuropathy]

www.escardio.org/guidelines

2023 ESC Guidelines for the management of cardiovascular disease in patients with diabetes
(European Heart Journal; 2023 – doi:10.1093/eurheartj/ehad192)

Should we screen for CAD in asymptomatic patients with diabetes?

Schernthaner et al. Cardiovasc Diabetol (2018) 17:145
https://doi.org/10.1186/s12933-018-0788-7

Cardiovascular Diabetology

COMMENTARY Open Access

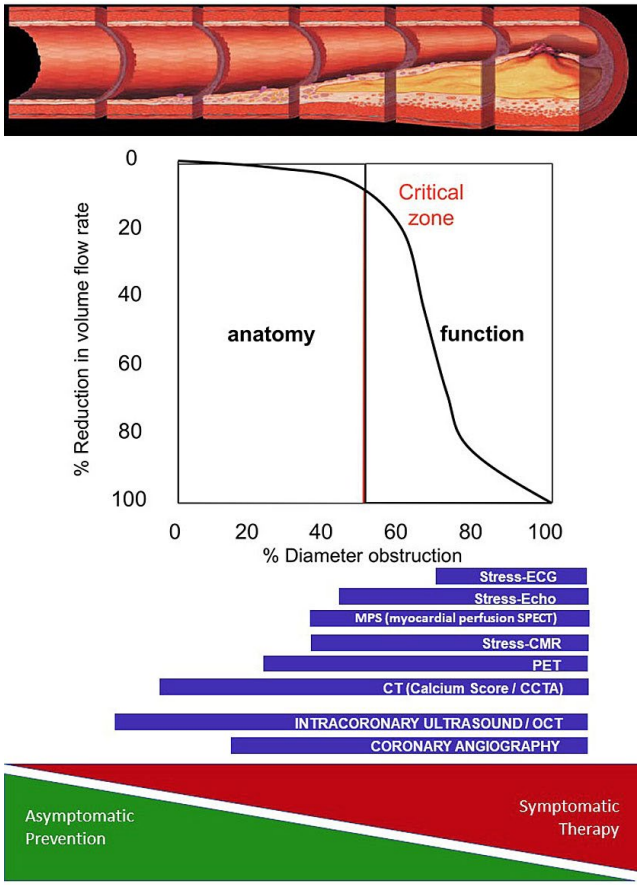
Unrecognised cardiovascular disease in type 2 diabetes: is it time to act earlier?

Review Article

Cardiovascular Screening for the Asymptomatic Patient with Diabetes: More Cons Than Pros

Konstantinos Makrilakis and Stavros Liatis

The Ischemic Cascade and imaging



The ischaemic cascade starts with changes in the coronary artery (i.e., noncalcified and calcified changes of the vessel wall).

As long as the luminal narrowing of the artery does not exceed 50%, no limitation of flow is expected. When the narrowing of the artery exceeds 50%, reduced myocardial blood flow with decreased myocardial perfusion can occur.

The decrease of myocardial perfusion results in diastolic and systolic dysfunction of the left ventricle. After this stage, ECG changes and chest pain can often be observed.

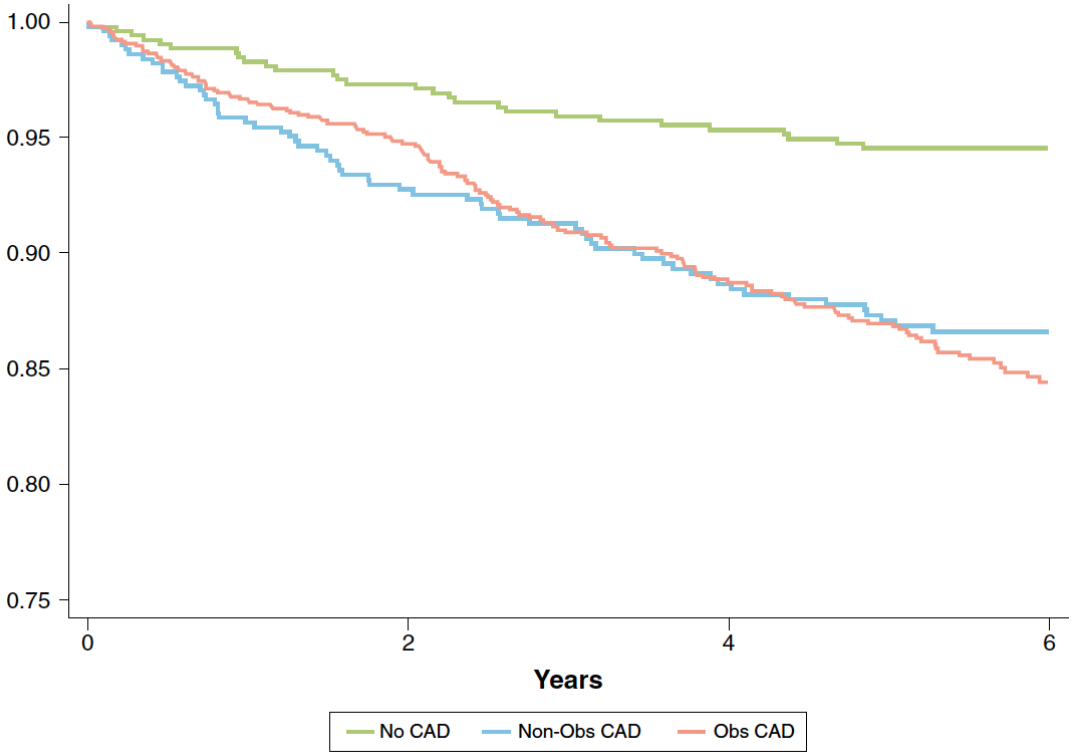
Swiss Med Wkly. 2019;149:w20014

Prevalence of silent CAD among diabetic subjects, observed in major studies

Author (ref.), publication year	Number of subjects	Type of diabetes	Prevalence of silent CAD (%)	Method
Wackers et al. [11], 2004	522	T2DM	22	Abnormal SPECT
Anand et al. [47], 2006	510	T2DM	46.3	Significant CAC
Lièvre et al. [51], 2011	316	T2DM	21.5	Exercise test or dipyridamole SPECT positive or uncertain
Davis et al. [33], 2013	1,967	T2DM	16.6	ECG evidence of SMI
Zellweger et al. [50], 2014	400	T2DM	22	Abnormal MPS
Muhlestein et al. [52], 2014	395	T1DM	10.7 severe stenosis	Abnormal coronary computed tomography angiography
		T2DM	11.9 moderate stenosis	
			46.1 mild stenosis	
Turrini et al. [37], 2015	262	T2DM	7.6	Silent CAD at exercise test
Zhu et al. [55], 2019	614	T2DM	21.3	Abnormal SPECT

Explor Med. 2021;2:1-19

Both nonobstructive and obstructive CAD according to coronary CTA confers an increased long-term risk of MACE and mortality in patients with DM

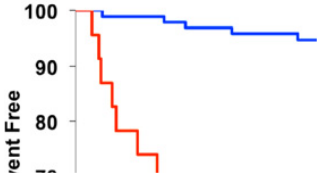


Adjusted Kaplan-Meier curve for survival on the basis of CAD severity among patients with DM and nondiabetic subjects. (A) Risk adjusted. Obs = obstructive; other abbreviations

JACC Cardiovasc Imaging 2016;9:1280-1288.

The presence of a small unrecognized MI confers an eight-fold higher risk for adverse outcome

DE-MRI



Independent of traditional cardiac risk factors, including age, sex, and Framingham risk score

Asymptomatic patients with diabetes and without a history of heart disease have a substantial prevalence of unrecognized MI, occurring in **19%** of the total study population. Often, these infarcts were small (5% of the left ventricle) and not identified by electro-cardiography.

Diabetes Care 2019;42:1290–1296

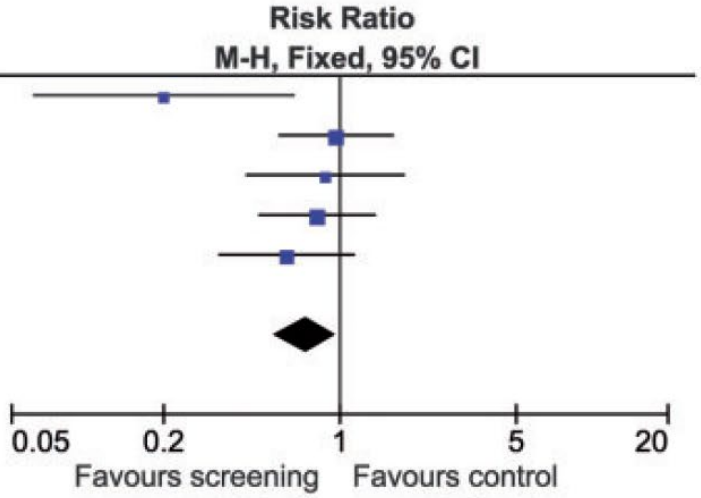
Meta-analysis of the primary endpoint: any cardiac event

3299 pts

Study or Subgroup	Screening Events	Screening Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
Faglia *et al.*	3	71	15	71	13.7%	0.20 [0.06, 0.66]	2005
DIAD	26	561	27	562	24.7%	0.96 [0.57, 1.63]	2009
DYNAMIT	13	306	15	309	13.7%	0.88 [0.42, 1.81]	2011
FACTOR-64	23	452	28	447	25.8%	0.81 [0.48, 1.39]	2014
DADDY-D	15	262	24	258	22.1%	0.62 [0.33, 1.15]	2015
Total (95% CI)		**1652**		**1647**	**100.0%**	**0.73 [0.55, 0.97]**	
Total events	80		109				

Heterogeneity: Chi² = 6.27, df = 4 (*P* = 0.18); I² = 36%

Test for overall effect: Z = 2.19 (*P* = 0.03)



Fifty-six asymptomatic Type 2 diabetics would have to undergo CAD screening to prevent one cardiac event over a 4-year follow-up.

European Heart Journal - Cardiovascular Imaging (2018) 19, 838–846

10. Cardiovascular Disease and Risk Management: *Standards of Care in Diabetes—2024*

Diabetes Care 2024;47(Suppl. 1):S179–S218 | https://doi.org/10.2337/dc24-S010

Recommendations

10.38a In asymptomatic individuals, routine screening for coronary artery disease is not recommended, as it does not improve outcomes as long as ASCVD risk factors are treated. **A**

10.38b Consider investigations for coronary artery disease in the presence of any of the following: atypical cardiac symptoms; signs or symptoms of associated vascular disease, including carotid bruits, transient ischemic attack, stroke, claudication, or PAD; or electrocardiogram abnormalities (e.g., Q waves). **E**

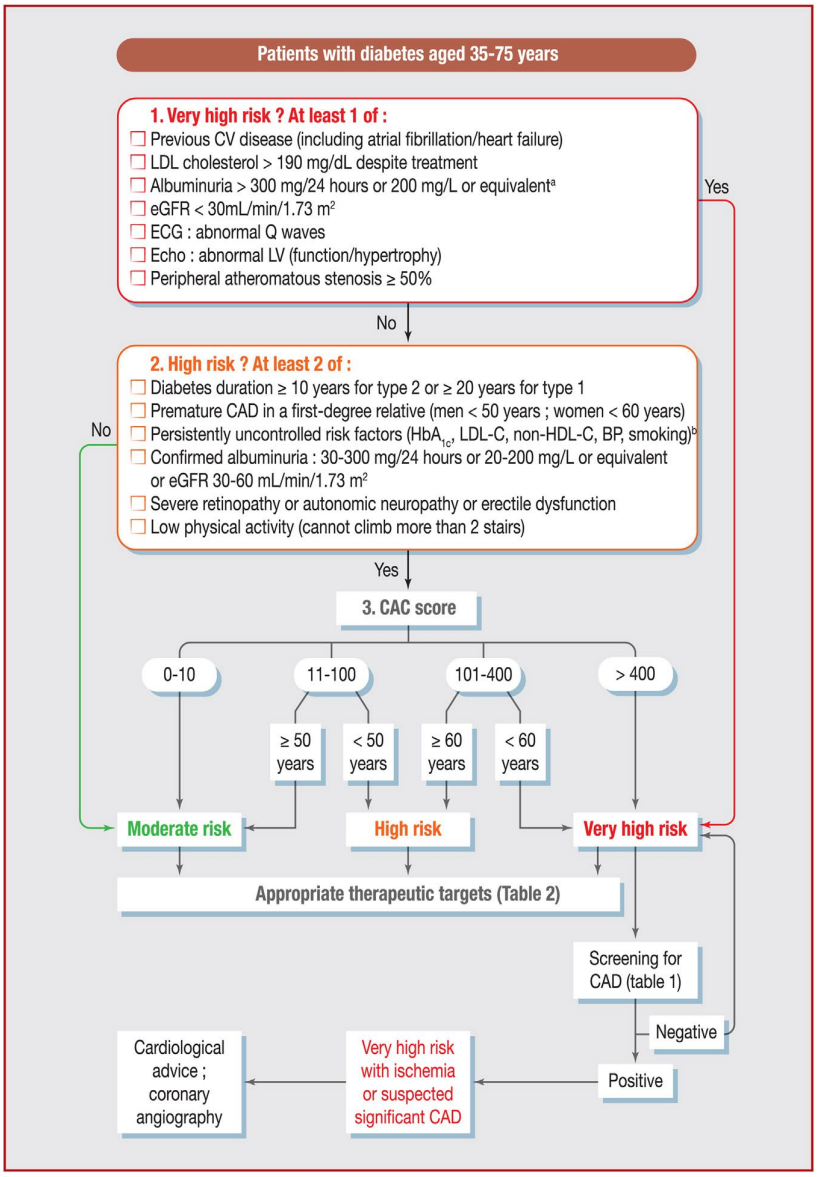
10. Cardiovascular Disease and Risk Management: *Standards of Care in Diabetes—2024*

Diabetes Care 2024;47(Suppl. 1):S179–S218 | https://doi.org/10.2337/dc24-S010

Against Screening of Asymptomatic Patients for ASCVD

- These high-risk patients **should already be receiving intensive medical therapy**—an approach that provides benefit similar to invasive revascularization.
- **Silent ischemia may reverse** over time

In prospective studies, coronary artery calcium has been established as an independent predictor of future ASCVD events in people with diabetes and is consistently superior to both the UK Prospective Diabetes Study (UKPDS) risk engine and the Framingham Risk Score in predicting risk in this population.



Position paper of the French Society of Cardiology

Algorithm for the stratification and management of the risk of coronary artery disease in asymptomatic patients with diabetes in 3 steps

Medical history, clinical examination, ECG and usual biological parameters are considered.

Cardiac echography or any exploration of peripheral arteries can be used if available

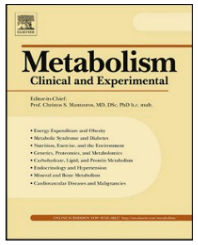
Archives of Cardiovascular Disease 2021;114: 150-172

Metabolism 159 (2024) 155931

Contents lists available at ScienceDirect

Metabolism

journal homepage: www.journals.elsevier.com/metabolism



DCRM 2.0: Multispecialty practice recommendations for the management of diabetes, cardiorenal, and metabolic diseases

Yehuda Handelsman [a,*], John E. Anderson [b], George L. Bakris [c], Christie M. Ballantyne [d], Deepak L. Bhatt [e], Zachary T. Bloomgarden [f], Biykem Bozkurt [g], Matthew J. Budoff [h], Javed Butler [i], David Z.I. Cherney [j], Ralph A. DeFronzo [k], Stefano Del Prato [l], Robert H. Eckel [m], Gerasimos Filippatos [n], Gregg C. Fonarow [h], Vivian A. Fonseca [o], W. Timothy Garvey [p], Francesco Giorgino [q], Peter J. Grant [r], Jennifer B. Green [s], Stephen J. Greene [t], Per-Henrik Groop [u,v], George Grunberger [w,x,y,z], Ania M. Jastreboff [aa], Paul S. Jellinger [ab], Kamlesh Khunti [ac], Samuel Klein [ad], Mikhail N. Kosiborod [ae], Pamela Kushner [af], Lawrence A. Leiter [ag], Norman E. Lepor [h], Christos S. Mantzoros [ah], Chantal Mathieu [ai], Christian W. Mende [aj], Erin D. Michos [ak], Javier Morales [al], Jorge Plutzky [am], Richard E. Pratley [an], Kausik K. Ray [ao], Peter Rossing [ap], Naveed Sattar [aq], Peter E.H. Schwarz [ar], Eberhard Standl [as], P. Gabriel Steg [at], Lale Tokgözoğlu [au], Jaakko Tuomilehto [av], Guillermo E. Umpierrez [aw], Paul Valensi [ax], Matthew R. Weir [ay], John Wilding [az], Eugene E. Wright Jr. [ba]

Lipid Disorders

Monitor Lipids Every 6–12 Weeks Until Individual Target Is Achieved

LDL-C Goal—Reduce LDL-C by ≥50% or Reach Risk-Based Goal, Whichever Leads to Lower LDL-C

mg/dL / mmol/L		
<100 / <2.6	**High**	≥2 RF + 10-y risk <10% Diabetes or CKD ≥3 with no other RF CAC <100[a]
<70 / <1.8	**Very high**	10-y risk >10% Diabetes or CKD ≥3 with ≥1 RF CAC >100[b] HeFH without ASCVD
<55 / <1.4	**Extreme**	Established ASCVD (CAD, PAD, TIA, ischemic stroke) CAC >300 Diabetes with target organ damage CKD ≥3 with albuminuria HeFH with FHx premature ASCVD (<55 years, male; <65 years, female)
<40 / <1.0	**Extreme-plus**	Progressive ASCVD despite LDL-C <55 mg/dL / <1.4 mmol/L

[a] And <75th age/sex percentile. [b] Or ≥75th age/sex percentile.

Expected Decrease in LDL-C						
Statin ↓ ~30–60%	**PCSK9i mAb** ↓ ~60%	**Eze** ↓ ~20%	**BA** ↓ ~20%	**Eze + BA** ↓ ~38%	**PCSK9i siRNA** ↓ ~50%	**BAS** ↓ ~20%

- An elevated Lp(a) is an important RF independent of other RFs
- Choose initial statin dose likely to achieve LDL-C goal
- Use combination therapy when LDL-C is >50% higher than goal
- Add treatments every 6–12 weeks until goal is achieved

Management of Hypertriglyceridemia

Reduce risk of ASCVD	
All patients with elevated TG	Moderate-CHO diet + weight reduction + max-tolerated statin
Patients with TG 135–499 mg/dL / 1.52–5.63 mmol/L+ ASCVD or diabetes + 2 RF	Add IPE
Reduce risk of pancreatitis	
All patients with TG ≥500 mg/dL / ≥5.65 mmol/L	Moderate-CHO, low-fat diet + alcohol avoidance + weight reduction + max-tolerated statin Add fibrate, IPE, other OM3[c], or niacin
Patients with insulin resistance	Consider adding pioglitazone
Patients with acute, severe hypertriglyceridemia	Consider insulin, apheresis

Expected Decrease in TG				
Statin ↓ ~20–30%	Fibrate ↓ ~30–50%	OM3[c] ↓ ~30–40%	Niacin ↓ ~20–30%	Pio ↓ ~10–15%

[c] EPA or EPA+DHA.

Proven ASCVD benefits in CVOTs

ASCVD = atherosclerotic cardiovascular disease; BA = bempedoic acid; BAS = bile acid sequestrant; CAC = coronary artery calcium; CAD = coronary artery disease; CHO = carbohydrate; CKD ≥3 = stage 3 or higher chronic kidney disease; CVOT = cardiovascular outcome trial; DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; Eze = ezetimibe; FHx = family history; HDL-C = high-density lipoprotein cholesterol; HeFH = heterozygous familial hypercholesterolemia; IPE = icosapent ethyl; LDL-C = low-density lipoprotein cholesterol; Lp(a) = lipoprotein (a); mAb = monoclonal antibody; OM3 = prescription-strength omega-3 fatty acid; PAD = peripheral artery disease; PCSK9i = proprotein convertase subtilisin/kexin type 9 inhibitor; Pio = pioglitazone; RF = major risk factors (i.e., advancing age, elevated non-HDL-C, elevated LDL-C, low HDL-C, diabetes, hypertension, CKD, cigarette smoking, pre-eclampsia, family history of ASCVD); siRNA = small interfering ribonucleic acid; TG = triglyceride; TIA = transient ischemic attack.

Hypertension

Goal BP[a]: <130/80 mm Hg

Assess BP at Home Weekly and in Office Every 3–12 Months[b]		
Office BP	**Seated**	Back supported, feet flat on ground with oscillometric device connected; let person rest quietly for >5 min before checking BP twice, 1–2 min apart, followed by 1 orthostatic reading. BP can also be measured with automated oscillometric device attended or unattended.
Office BP	**Orthostatic[c]**	Assess standing BP for evaluation of volume depletion and autonomic dysfunction[d]
Ambulatory BP		Train persons with HTN how to measure seated BP at home upon waking. Transmit BP data via Bluetooth or via fax to patient chart

Preferred BP-Lowering Agents	Treatment Regimen
1. ARB or ACEi at maximum tolerated dose[e]	• Maintain lifestyle therapy • Use initial combination therapy if BP >20/10 mm Hg above goal • Add medications as needed to reach goal • Use combination products to foster adherence • Assess adherence with medications and dietary sodium
2. Dihydropyridine CCB	
3. Thiazide-type and thiazide-like diuretic	
4. MRA for resistant hypertension	

[a] Individualize based on patient characteristics. Maintain DBP >60 mm Hg in older adults with diabetes.
[b] Check BP more frequently when starting or titrating therapy.
[c] BP decrease of ≥20/10 mm Hg within 3 minutes of standing.
[d] Indicates higher risk of cardiovascular events and mortality.
[e] Preferred for kidney and cardiovascular protection.

ACEi = angiotensin converting enzyme inhibitor; ARB = angiotensin II receptor blocker; BP = blood pressure; CCB = calcium channel blocker; DBP = diastolic blood pressure; HTN = hypertension; MRA = mineralocorticoid receptor antagonist.

Antihyperglycemic Therapy in Type 2 Diabetes

Lifestyle Therapy

Cardiorenal Track

Prevent ASCVD/HF/CKD Events Independent of Glycemic Status

ASCVD	HFpEF	HFrEF/HFmrEF	CKD	Stroke/TIA
GLP-1 RA[a,b]	SGLT2i[b]	SGLT2i[b]	SGLT2i[b]	GLP-1 RA[a]
SGLT2i[b]	GLP-1 RA[a,b]		GLP-1 RA[a,b]	Pio
Pio				

[a] GLP-1 RA with proven benefit.
[b] Combining GLP-1 RA and SGLT2i is encouraged to improve outcomes.
[c] GLP-1 RA or GIP/GLP-1 RA.
[d] If CKD, efficacy may be lower; consider using SGLT2i later in glucose hierarchy.
[e] Glycated albumin or fructosamine may also be considered for evaluation of glycemic control.
[f] Do not combine incretin classes (GLP-1 RA, GIP/GLP-1 RA, DPP4i). Use caution when combining insulin + SU, insulin + SGLT2i, or insulin + TZD.

AGI = alpha glucosidase inhibitor; ASCVD = atherosclerotic cardiovascular disease; CGM = continuous glucose monitoring; CKD = chronic kidney disease; CVOT = cardiovascular outcome trial; DPP4i = dipeptidyl peptide 4 inhibitor; GIP = glucose-dependent insulinotropic polypeptide; GLP-1 RA = glucagon-like peptide 1 receptor agonist; HF = heart failure; HFmrEF = heart failure with mildly reduced ejection fraction; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; MOA = mechanism of action; Pio = pioglitazone; QR = quick release; SGLT2i = sodium glucose cotransporter 2 inhibitor; SMBG = self-monitored blood glucose; SU = sulfonylurea; TIA = transient ischemic attack; TZD = thiazolidinedione.

Proven benefits in CVOTs Hypoglycemia and/or HF risk

Hyperglycemia Track

Manage Glycemia to Individualized Goals

Recently diagnosed, healthier, few to no comorbidities

A1C: 6.0 / 42 — 6.5 / 48 — 7.0 / 53 — 7.5 / 58 — % / mmol/mol

Limited life expectancy, frail, complex comorbidities

Most patients

↓ Glucose Hierarchy

Preferred
- GLP-1 RA-based[c]
- Metformin
- SGLT2i[d]
- TZD
- Insulin
- DPP4i
- SU

Less used
- Glinide
- Colesevelam
- AGI
- Bromocriptine QR
- Pramlintide

- **Generally, use initial combination therapy for patients with A1C >1–2% above individualized goal**
- Lower A1C goals can be achieved safely provided there is no hypoglycemia
- Assess glucose control with A1C plus CGM or SMBG and intensify therapy until goal achieved[e]
- Add agents with complementary MOA to maintain glucose control at goal[f]
- Choose agents according to recommended hierarchy, based on individual patient's risks and benefits, preferences, and access to therapies
- Consider initial insulin therapy in severe hyperglycemia/metabolic decompensation

Heart Failure Prevention and Management

Initial and Longitudinal Clinical Assessment

Serially assess for signs or symptoms of congestion/volume overload or inadequate perfusion

Prevention of Heart Failure

General Recommendations

All	• Lifestyle intervention (low-salt diet, smoking cessation, physical activity, maintaining healthy weight) • BP control; target SBP <130 mm Hg • ASCVD interventions as indicated
T2D **High HF risk**	Natriuretic peptide screening followed by team-based care, including cardiology referral, can be useful in preventing HF

Medication Recommendations

T2D + high CV risk or established CVD	SGLT2i
CKD with or without T2D	SGLT2i
T2D + CKD	Nonsteroidal MRA

[a] ARNI preferred over ACEi or ARB.
[b] Steroidal MRA.
[c] Select agent with proven benefits; recommended to improve symptoms and physical limitations.
[d] If T2D + CKD, consider nonsteroidal MRA.

ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; ARNI = angiotensin receptor neprilysin inhibitor; ASCVD = atherosclerotic cardiovascular disease; BMI = body mass index; BP = blood pressure; CKD = chronic kidney disease; CV = cardiovascular; CVD = CV disease; EF = ejection fraction; GLP-1 RA = glucagon-like peptide 1 receptor agonist with proven benefit; HF = heart failure; HFmrEF = HF with mildly reduced EF; HFpEF = HF with preserved EF; HFrEF = HF with reduced EF; MRA = mineralocorticoid receptor agonist; SBP = systolic blood pressure; SGLT2i = sodium glucose cotransporter 2 inhibitor; T2D = type 2 diabetes.

Strongly recommended | Reasonable to use | May be considered

Treatment of Heart Failure

Heart failure defined as:

- Signs and/or symptoms of HF caused by structural/functional cardiac abnormality

– plus –

- Elevated natriuretic peptides or objective evidence of congestion (eg, echocardiographic evidence, right heart catheterization)

HFrEF (EF ≤40%)

Diuretic (if congested) + quadruple therapy

ARNI (or ACEi/ARB)[a] + β-blocker + SGLT2i + MRA[b]

Follow HF guidelines for device and Class II therapy recommendations

HFmrEF (EF=41–49%)

Diuretic (if congested) + SGLT2i + consider additional therapies

GLP-1 RA[c] (if BMI ≥30 kg/m² and EF ≥45%) + ARNI or ACEi or ARB[a] + β-blocker + MRA[b,d]

HFpEF (EF ≥50%)

Diuretic (if congested) + SGLT2i + consider additional therapies

GLP-1 RA[c] (if BMI ≥30 kg/m²) + ARNI or ARB[a] (EF up to 55–60%) + MRA[b,d] (EF up to 55–60%)

Antiplatelet and Anticoagulation Therapy

	Condition	Risk Consideration	Recommended Medication
Primary Prevention	No known ASCVD but ≥2 RF	Low bleeding risk	• Aspirin 75–100 mg daily
	CAC ≥100	Low bleeding risk	• Aspirin 75–100 mg daily
Secondary prevention	ACS, within 1 year of event		• Aspirin 75–100 mg + P2Y12i
	Stable CAD with history of PCI or >12 months after ACS	High ischemic risk AND Low bleeding risk	• Aspirin 75–100 mg + ticagrelor 60 mg BID • Rivaroxaban 2.5 mg BID + aspirin 75–100 mg • Aspirin 75–100 mg + clopidogrel 75 mg
		Low ischemic risk OR High bleeding risk	• Clopidogrel 75 mg daily • Aspirin 75–100 mg daily
	Stable CAD, no PCI	High ischemic risk AND Low bleeding risk	• Rivaroxaban 2.5 mg BID + aspirin 75–100 mg
		Low ischemic risk OR High bleeding risk	• Clopidogrel 75 mg daily • Aspirin 75–100 mg daily
	PAD	Without limb revascularization	• Rivaroxaban 2.5 mg BID + aspirin 75–100 mg • Clopidogrel 75 mg daily
		After limb revascularization	• Rivaroxaban 2.5 mg BID + aspirin 75–100 mg

ACS = acute coronary syndrome; ASCVD = atherosclerotic cardiovascular disease; BID = twice daily; CAC = coronary artery calcium score; CAD = coronary artery disease; CKD = chronic kidney disease; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; PAD = peripheral artery disease; P2Y12i = P2Y12 inhibitor; PCI = percutaneous coronary intervention; RF = major risk factors (i.e., advanced age, elevated non-HDL-C, elevated LDL-C, low HDL-C, diabetes, hypertension, CKD, cigarette smoking, family history of ASCVD).

Inflammation

Evaluating Inflammation in ASCVD Risk Assessment

Assessments

hsCRP	>2.0 mg/L / >1.9 mmol/L (>1 measurement if asymptomatic)
UACR	>30 mg/g / >3 mg/mmol

Setting—Evaluate if:

Primary prevention	• ASCVD risk unclear
Secondary prevention	• Recurrent CV events despite optimal CV risk factor control • Unclear attributable CV risk in known ASCVD
All	• Patient preference/choice in shared decision making • Potential for residual risk reduction • Potential contributor to CV risk in rheumatologic and other chronic inflammatory conditions

If hsCRP >2.0 mg/L / >1.9 mmol/L, Consider

- CT-CAC, CTA for CV risk stratification in primary prevention
- Other potential causes of increased hsCRP

Managing Inflammation

Lifestyle Therapy

Weight Reduction

- If overweight or prediabetes, ≥5%–10% weight reduction with lifestyle
- If obesity, intensify to pharmacotherapy or other interventions as indicated

Treatment Options

Positive CVOT Benefits + Known hsCRP-Lowering Effect[a]	
ASCVD	Statin
	Ezetimibe
	Bempedoic acid
Hypertriglyceridemia	IPE
Overweight/obesity	GLP-1 RA-based[b]
T2D	GLP-1 RA-based[b]
	Pioglitazone
	SGLT2i
Direct Anti-inflammatory Medication	
ASCVD	Colchicine
Chronic inflammation	

[a] Residual CV risk reduction; no specific hsCRP indication.
[b] GLP-1 RA or GIP/GLP-1 RA.

ASCVD = atherosclerotic cardiovascular disease; CAC = coronary artery calcium; CT = computed tomography; CTA = computed tomography angiography; CV = cardiovascular; CVOT = cardiovascular outcome trial; GIP = glucose-dependent insulinotropic polypeptide; GLP-1 RA = glucagon-like peptide 1 receptor agonist; hsCRP = high-sensitivity C-reactive protein; IPE = icosapent ethyl; LDL-C = low-density lipoprotein cholesterol; SGLT2i = sodium glucose cotransporter 2 inhibitor; T2D = type 2 diabetes; UACR = urine-albumin creatinine ratio.

ASCVD Prevention and Management

	MI/CAD	Stroke/TIA	PAD
Standard of care	See Lipid, Hypertension, Anticoagulation, and Antihyperglycemic Therapy recommendations, depending on comorbidities		
Add for primary prevention in diabetes	GLP1-RA IPE[a] SGLT2i	GLP1-RA IPE[a]	
Add for secondary prevention			
Without diabetes	Aspirin IPE[a] Rivaroxaban + aspirin[b] PCSK9i GLP-1 RA (obesity only) Colchicine	Aspirin IPE[a] PCSK9i Pioglitazone[c] Clopidogrel + aspirin	PCSK9i Rivaroxaban + aspirin[b]
With diabetes	Aspirin Rivaroxaban + aspirin[b] PCSK9i GLP1-RA SGLT2i Pioglitazone Colchicine	Aspirin PCSK9i GLP1-RA Clopidogrel + aspirin Pioglitazone	PCSK9i Rivaroxaban + aspirin[b] GLP1-RA

[a] In patients with TG 135–499 mg/dL / 1.52–5.63 mmol/L + ASCVD or diabetes + 2 RF.
[b] Rivaroxaban 2.5 mg twice daily + aspirin 75–100 mg.
[c] In patients with insulin resistance.

ASCVD = atherosclerotic cardiovascular disease; CAD = coronary artery disease; CKD = chronic kidney disease; GLP1-RA = glucagon-like peptide1 receptor agonist with proven benefit in indicated population; HDL-C = high-density lipoprotein cholesterol; IPE = icosapent ethyl; LDL-C = low-density lipoprotein cholesterol; MI = myocardial infarction; PAD = peripheral artery disease; PCSK9i = proprotein convertase subtilisin/kexin type 9 inhibitor; RF = major risk factors (i.e., advancing age, elevated non-HDL-C, elevated LDL-C, low HDL-C, diabetes, hypertension, CKD, cigarette smoking, family history of ASCVD); SGLT2i = sodium glucose cotransporter 2 inhibitor; TG = triglyceride; TIA = transient ischemic attack.

Take-home messages

- Patients with diabetes have an heterogeneous CV risk, with many subjects without overt ASCVD presenting signs of advanced subclinical atherosclerosis, and may be at higher risk than appreciated
- Cardiovascular prevention strategies proposed by guidelines are largely based on clinical trials, which do not take into account subclinical atherosclerosis
- The intensity of prevention strategies is largely driven by cardiovascular risk stratification, which priorizes symptomatic ASCVD
- Silent or unrecognized coronary disease is at least 2-fold more frequent in patients with diabetes, and associated with poor prognosis
- Whether coronary revascularization and intensification of medical therapy based on routine CAD screening may improve outcomes of asymptomatic diabetic patients is still under debate
- A contemporary assessment of imaging-guided vs. unguided treatment leveraging the entirety of contemporary medical therapy is needed
- Contemporary agents such as GLP1RA, GLP1/GIP agonists, SGLT2-i, SGLT1/2 inhibitors,PCSK9i monoclonals, inclisiran, icosapent ethyl, bempedoic acid, low-dose rivaroxaban, and upcoming therapies targeting inflammation and lipoprotein(a) should help providing cardiovascular protection in higher risk subjects with diabetes