The management of Cardiovascular Disease in patients with Diabetes

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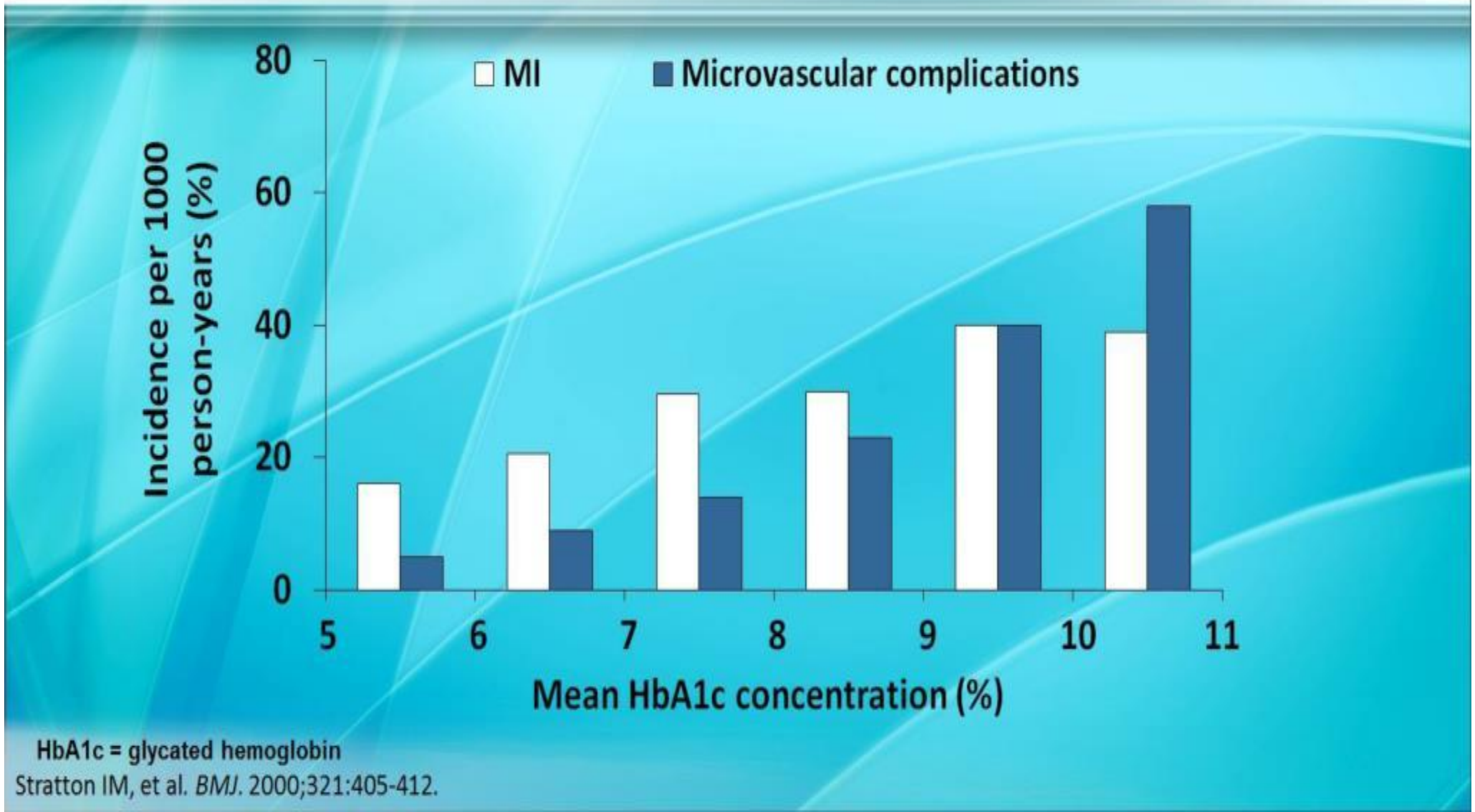
UKPDS 35: The Relationship Between Glycemia and the Risk of Complications in T2DM

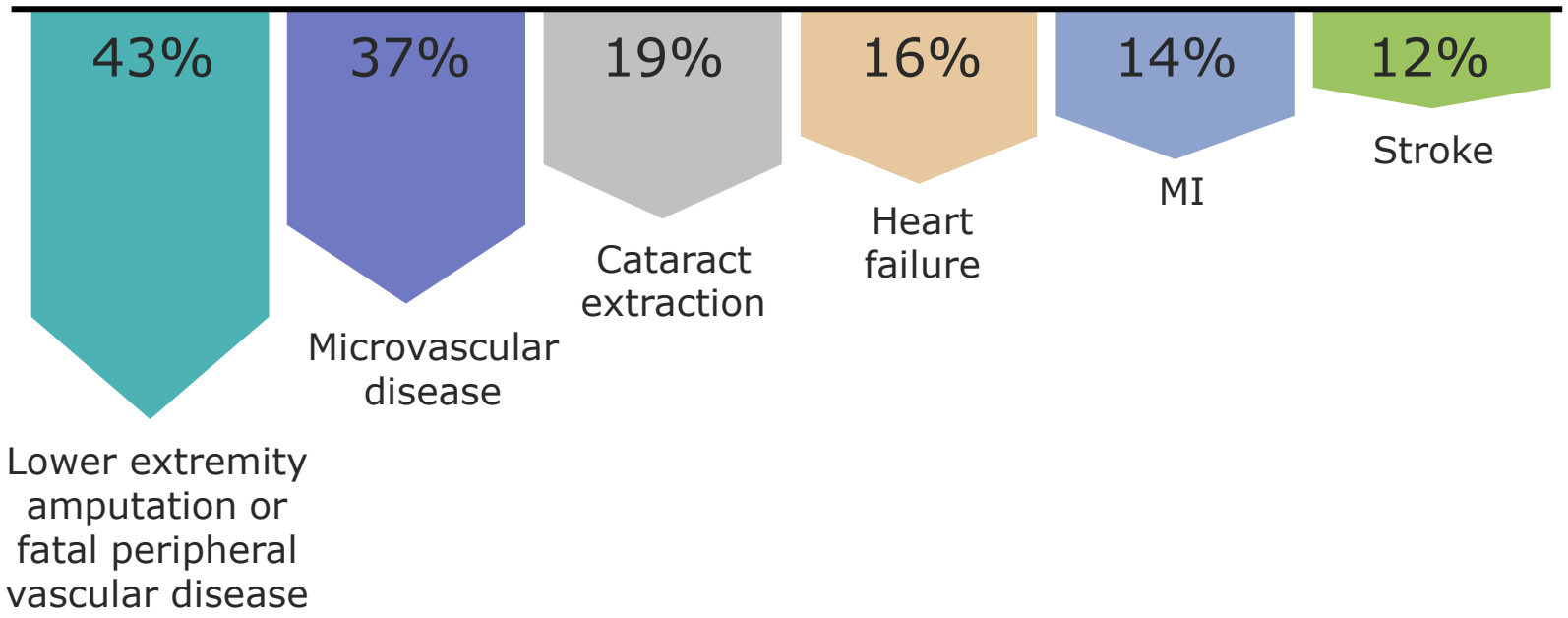


HbA1c = glycated hemoglobin

Stratton IM, et al. *BMJ*. 2000;321:405-412.

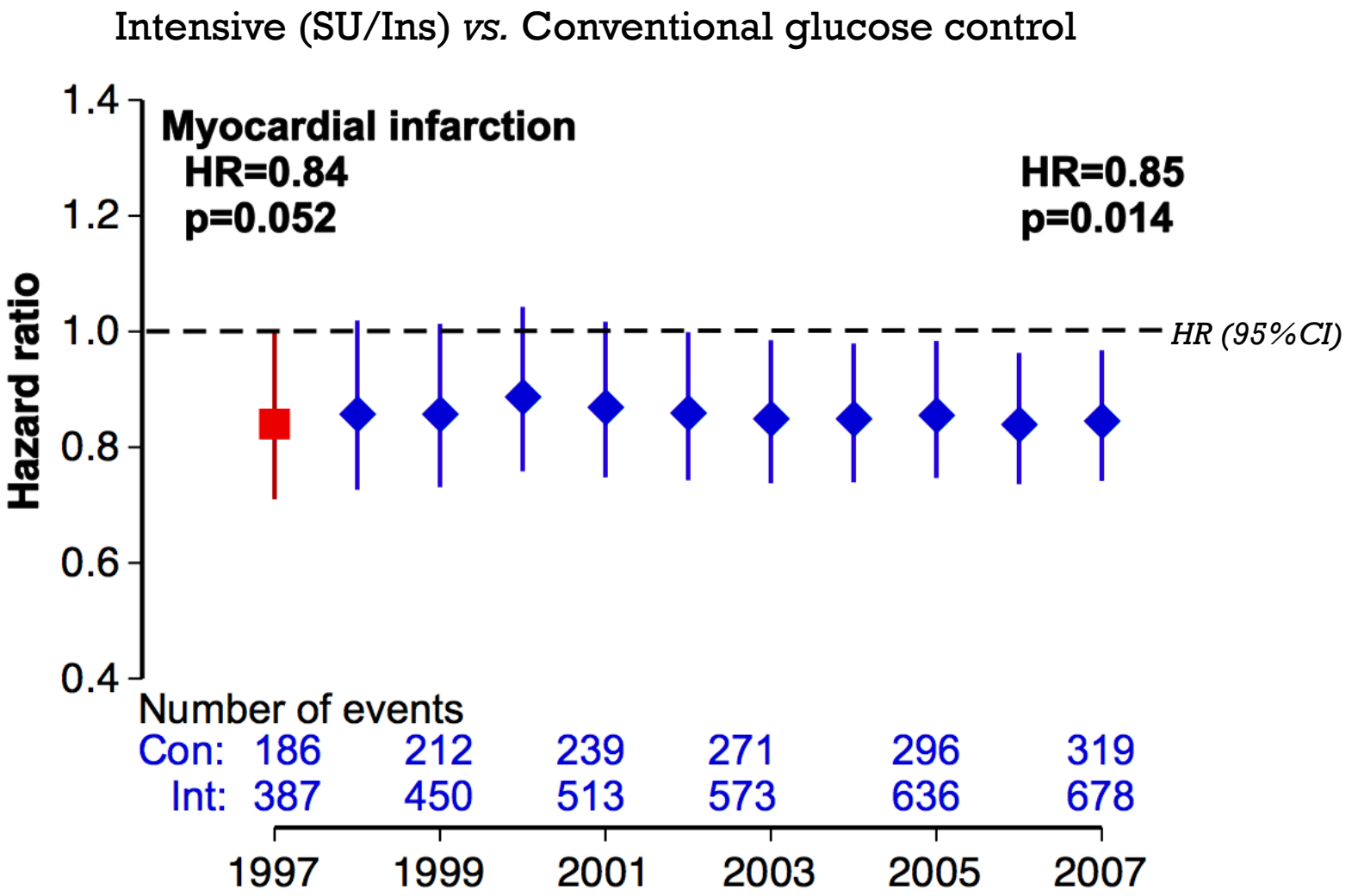
Improving control reduces risks of long-term complications

Every 1% drop in HbA_{1c} can reduce long-term diabetes complications



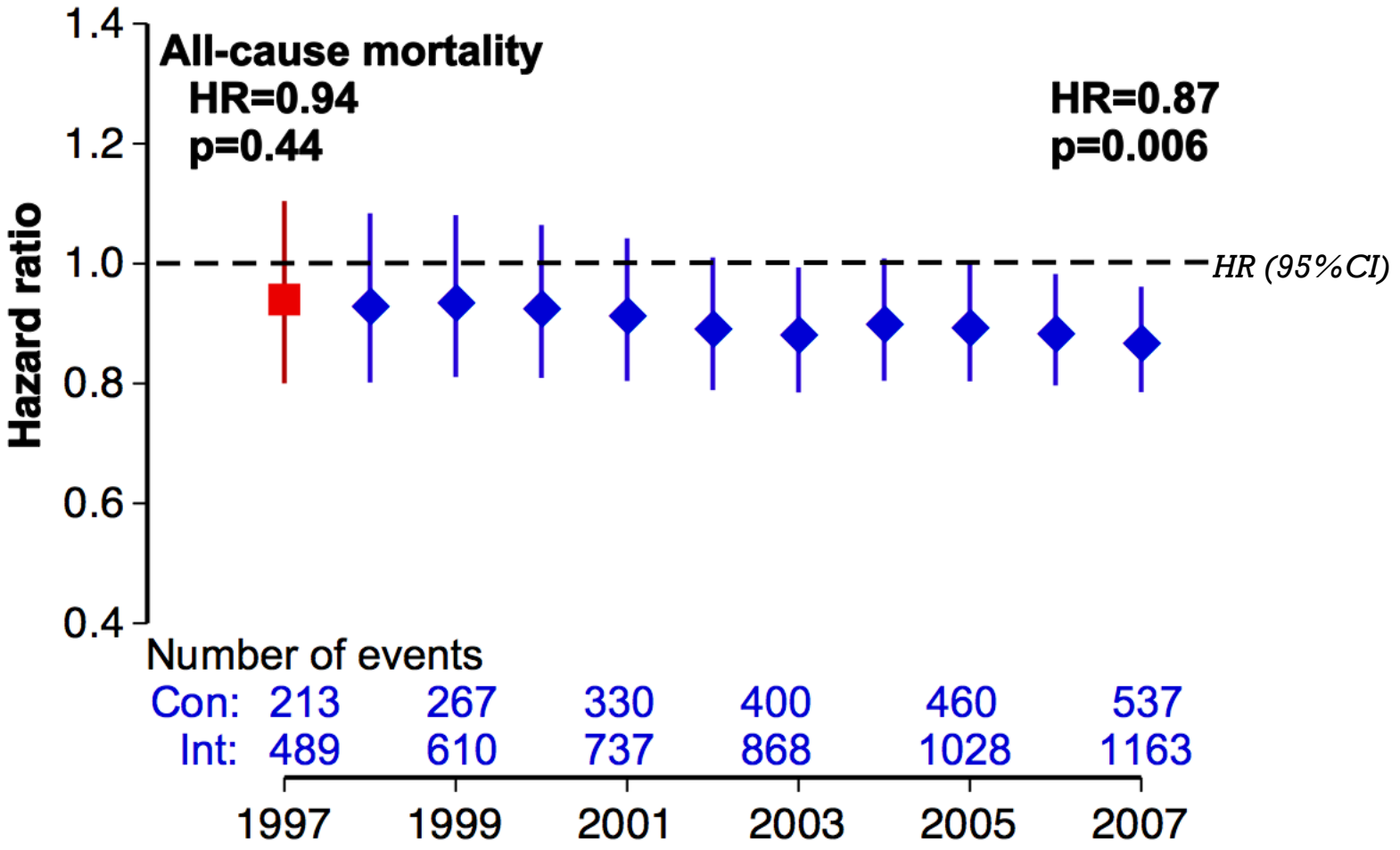
UKPDS: Stratton *et al. BMJ* 2000;32:405–12

Myocardial Infarction Hazard Ratio
(fatal or non-fatal myocardial infarction or sudden death)

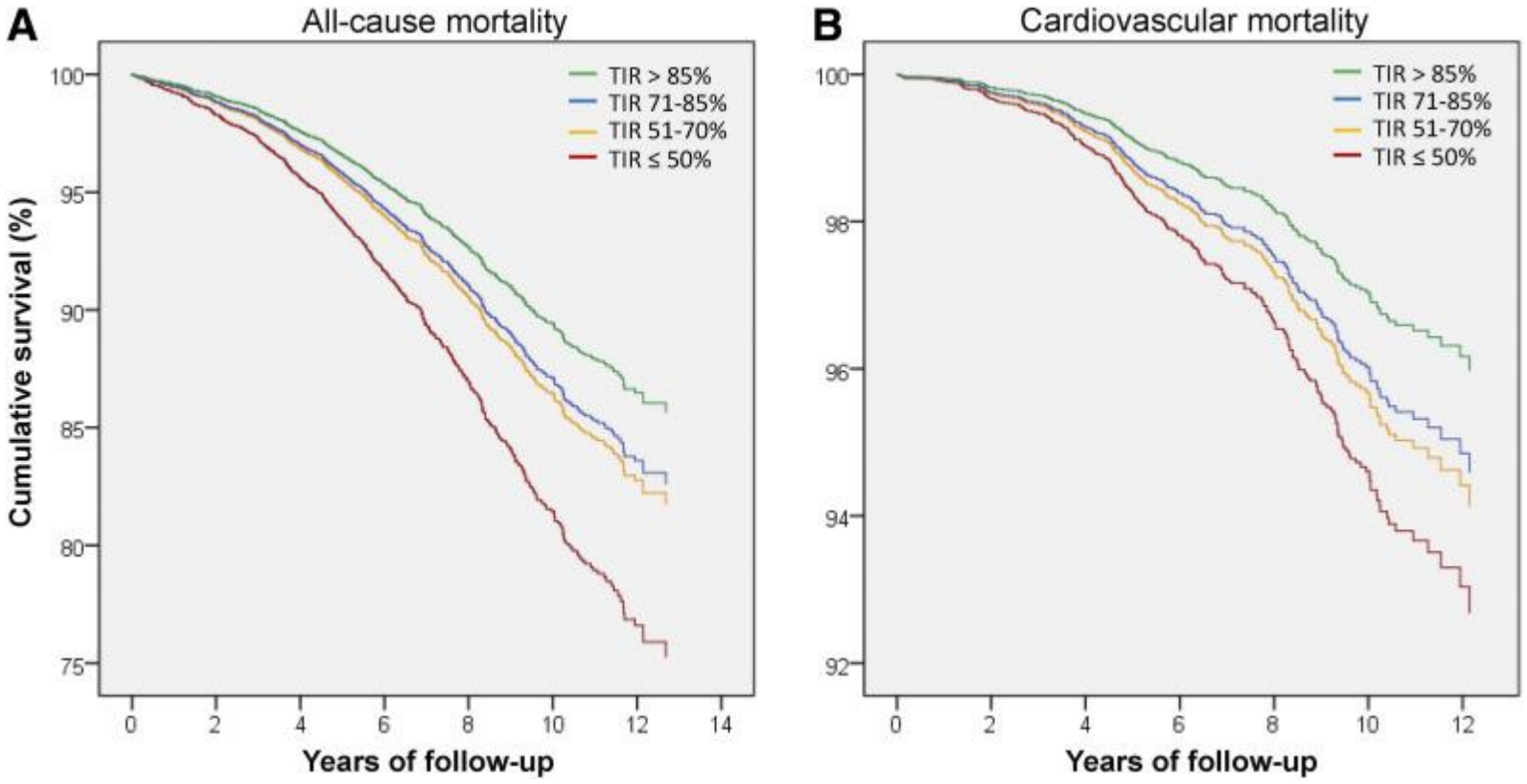


All-cause Mortality Hazard Ratio

Intensive (SU/Ins) *vs.* Conventional glucose control

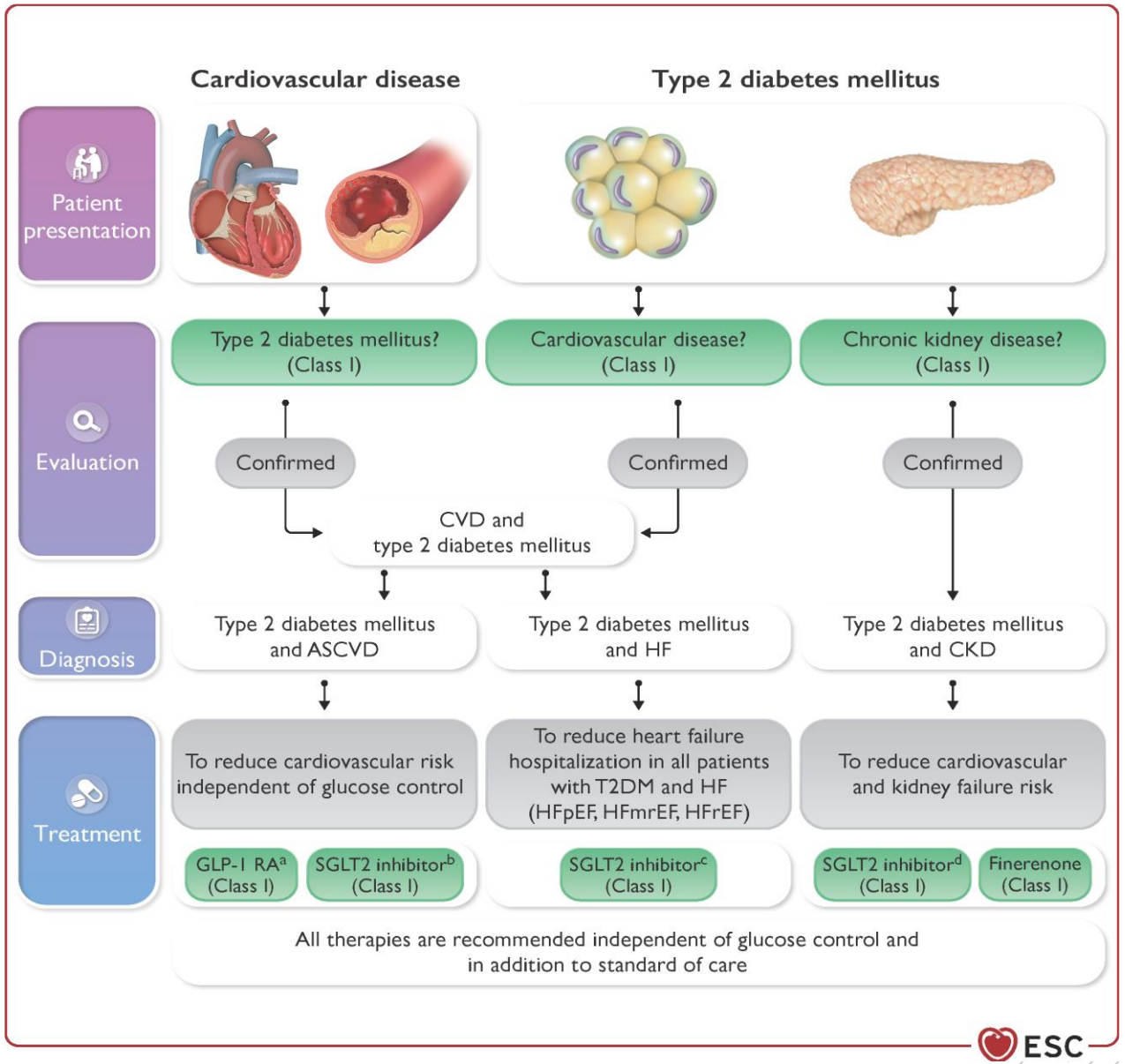


TIR & MORTALITY IN T2 DIABETES

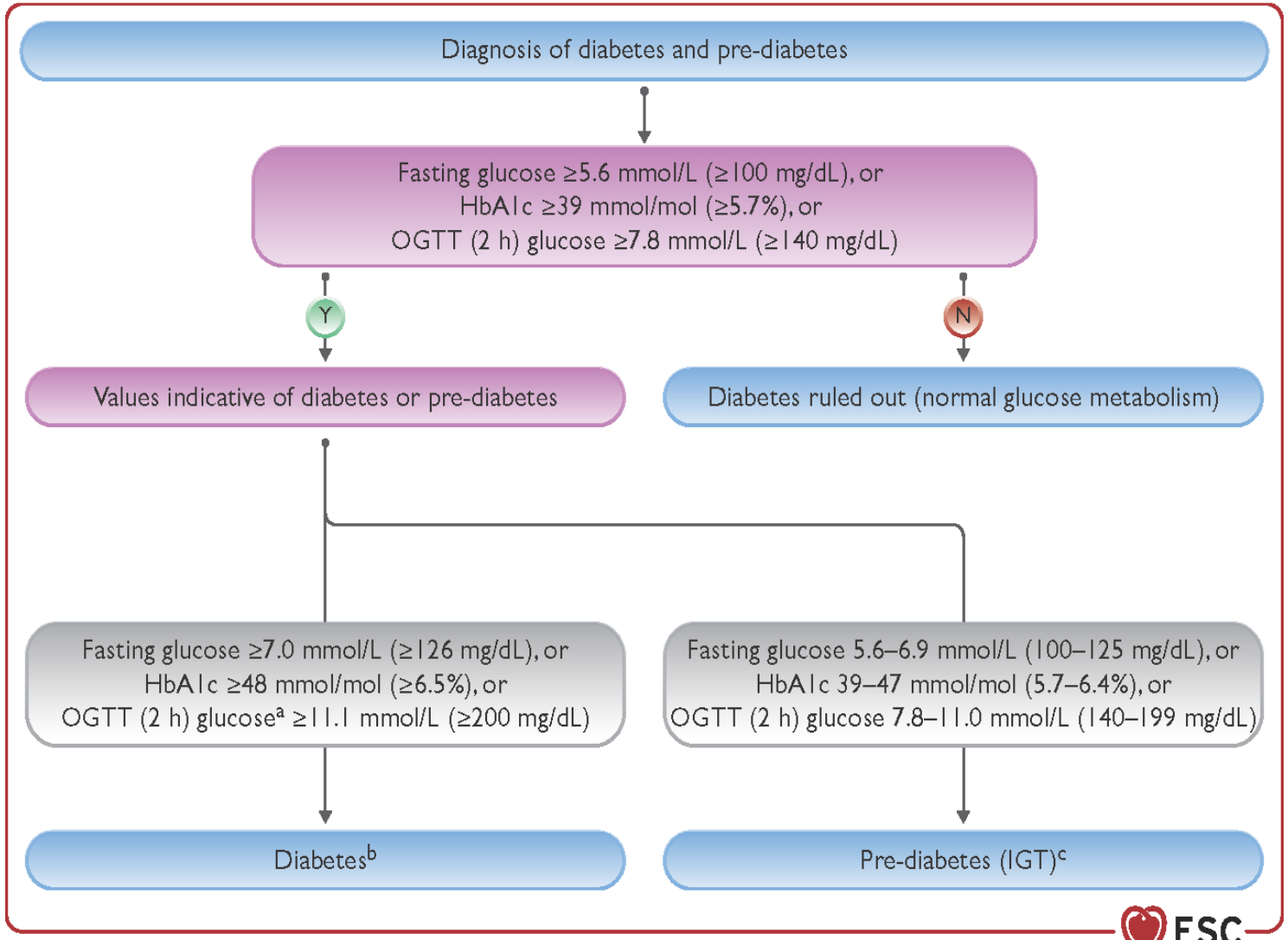


Lu J et al. Time in Range in Relation to All-Cause and Cardiovascular Mortality in Patients With Type 2 Diabetes: A Prospective Cohort Study. Diabetes Care. 2021 Feb;44(2):549-555. doi: 10.2337/dc20-1862.

Clinical Approach & Key Recommendations



Diagnosis of diabetes & pre-diabetes



Recommendations for diagnosing diabetes

Recommendations	Class	Level
Screening for diabetes is recommended in all individuals with CVD, using fasting glucose and/or HbA1c.	I	A
It is recommended that the diagnosis of diabetes is based on HbA1c and/or fasting plasma glucose, or on an OGTT if still in doubt.	I	B

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

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Recommendations for assessing cardiovascular 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

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Recommendations for reducing weight in patients with type 2 diabetes with or without cardiovascular disease

Recommendations	Class	Level
It is recommended that individuals living with overweight or obesity aim to reduce weight and increase physical exercise to improve metabolic control and overall CVD risk profile.	I	A
Glucose-lowering medications with effects on weight loss (e.g. GLP-1 RAs) should be considered in patients with overweight or obesity to reduce weight.	IIa	B
Bariatric surgery should be considered for high and very high risk patients with BMI ≥35 kg/m^2 (≥Class II) when repetitive and structured efforts of lifestyle changes combined with weight-reducing medications do not result in maintained weight loss.	IIa	B

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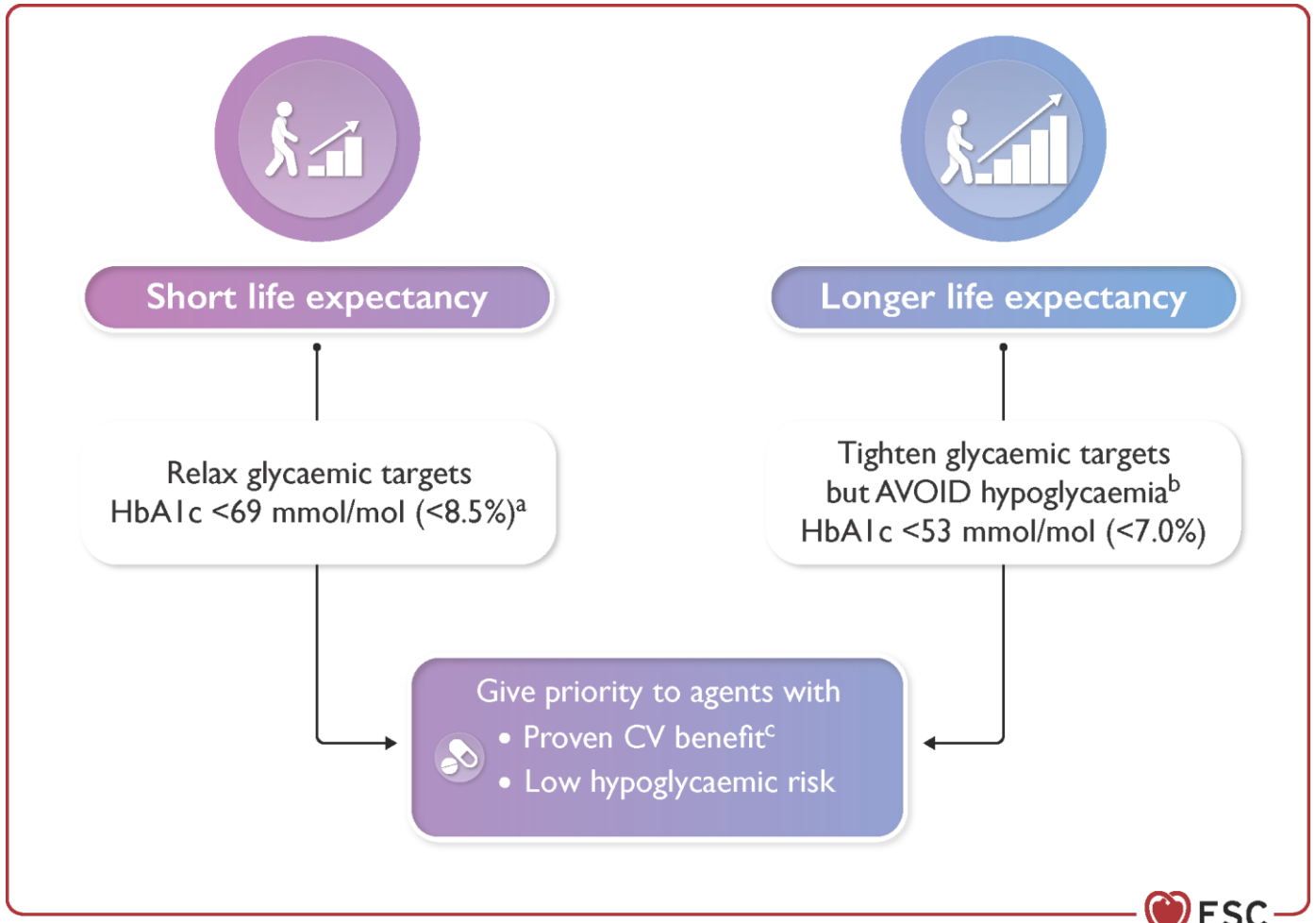
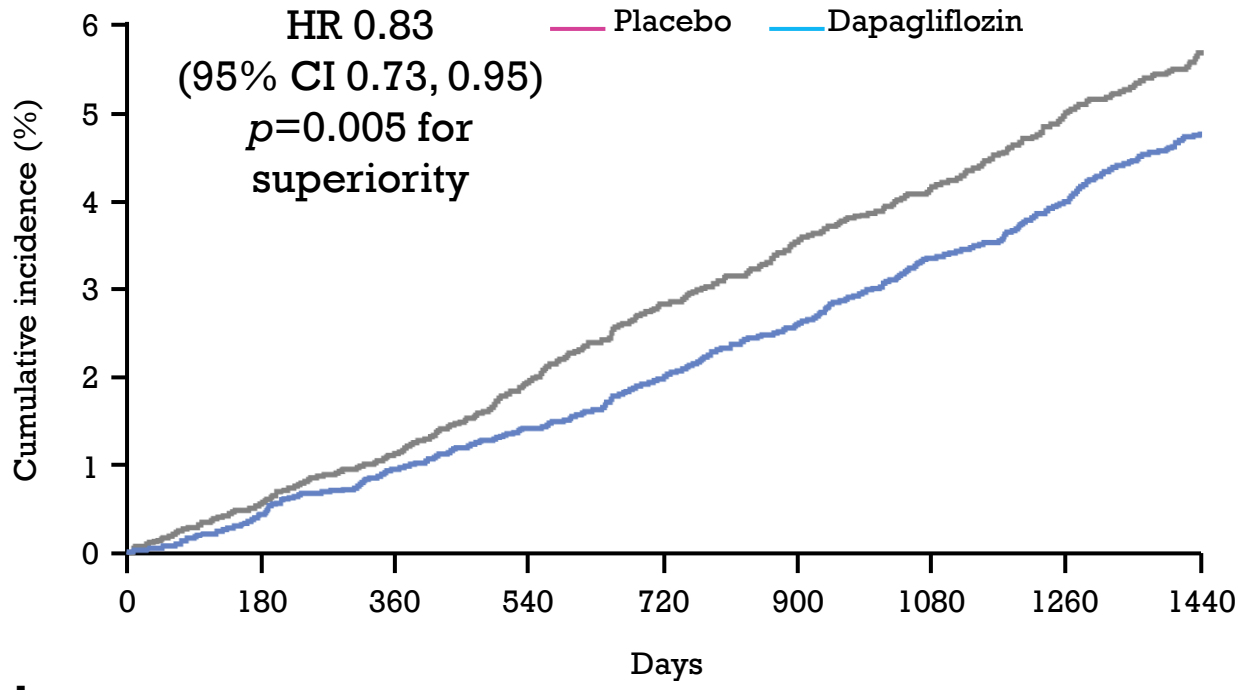
Glycaemic targets in patients with T2DM & CVD



DAPAGLIFLOZIN: DECLARE-TIMI 58: composite of CV death or HHF co-primary outcome



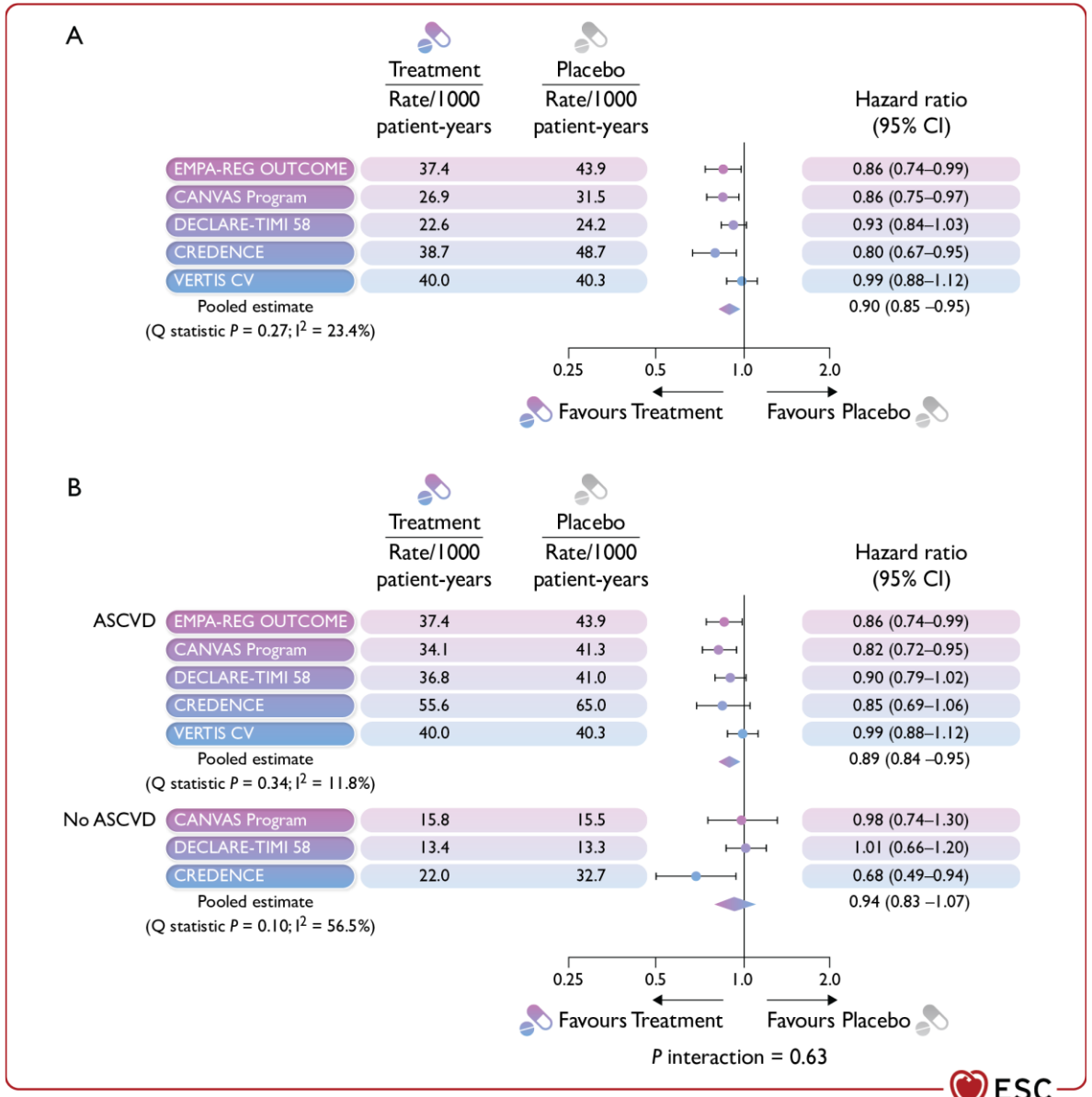
No. at risk									
Placebo	8578	8485	8387	8259	8127	8003	7880	7367	5362
Dapagliflozin	8582	8517	8415	8322	8224	8110	7970	7497	5445

Wiviott SD *et al. N Engl J Med* 2018;380:347

Dapagliflozin demonstrated a 17% RRR in CV death or HHF

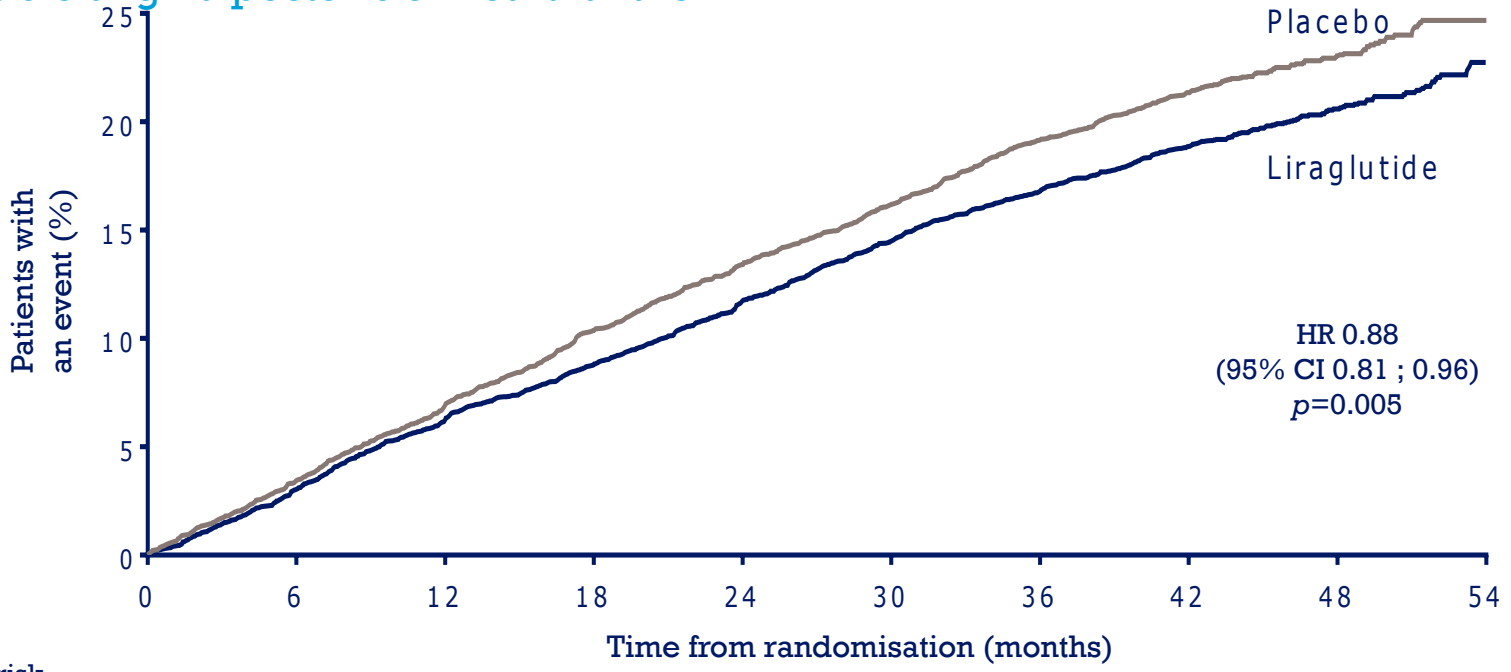
Meta-analysis of CVOT trials with SGLT2i

A. Overall MACE
B. MACE by ASCVD status



Expanded MACE

CV death, non-fatal MI, non-fatal stroke, coronary revascularisation or hospitalisation for unstable angina pectoris or heart failure



No. at risk

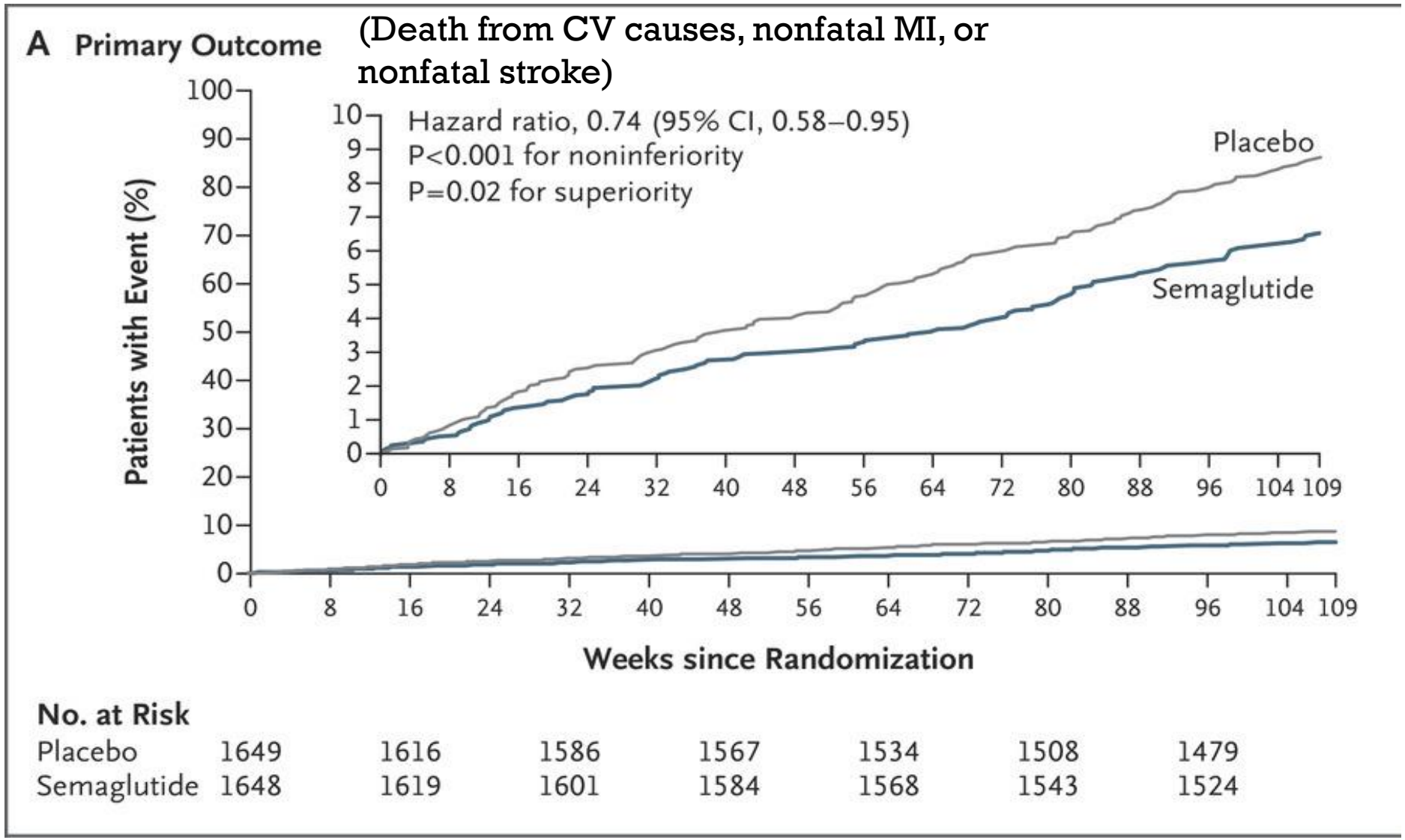
Liraglutide	4668	4515	4356	4221	4063	3914	3793	3682	1452	395
Placebo	4672	4506	4336	4157	4002	3857	3697	3581	1410	366

The cumulative incidences were estimated using the Kaplan–Meier method, and the HRs using the Cox proportional-hazard regression model The data analyses are truncated at 54 months, because less than 10% of the patients had an observation time beyond 54 months

CI, confidence interval; CV, cardiovascular; HR, hazard ratio; MACE, major adverse cardiac event; MI, myocardial infarction

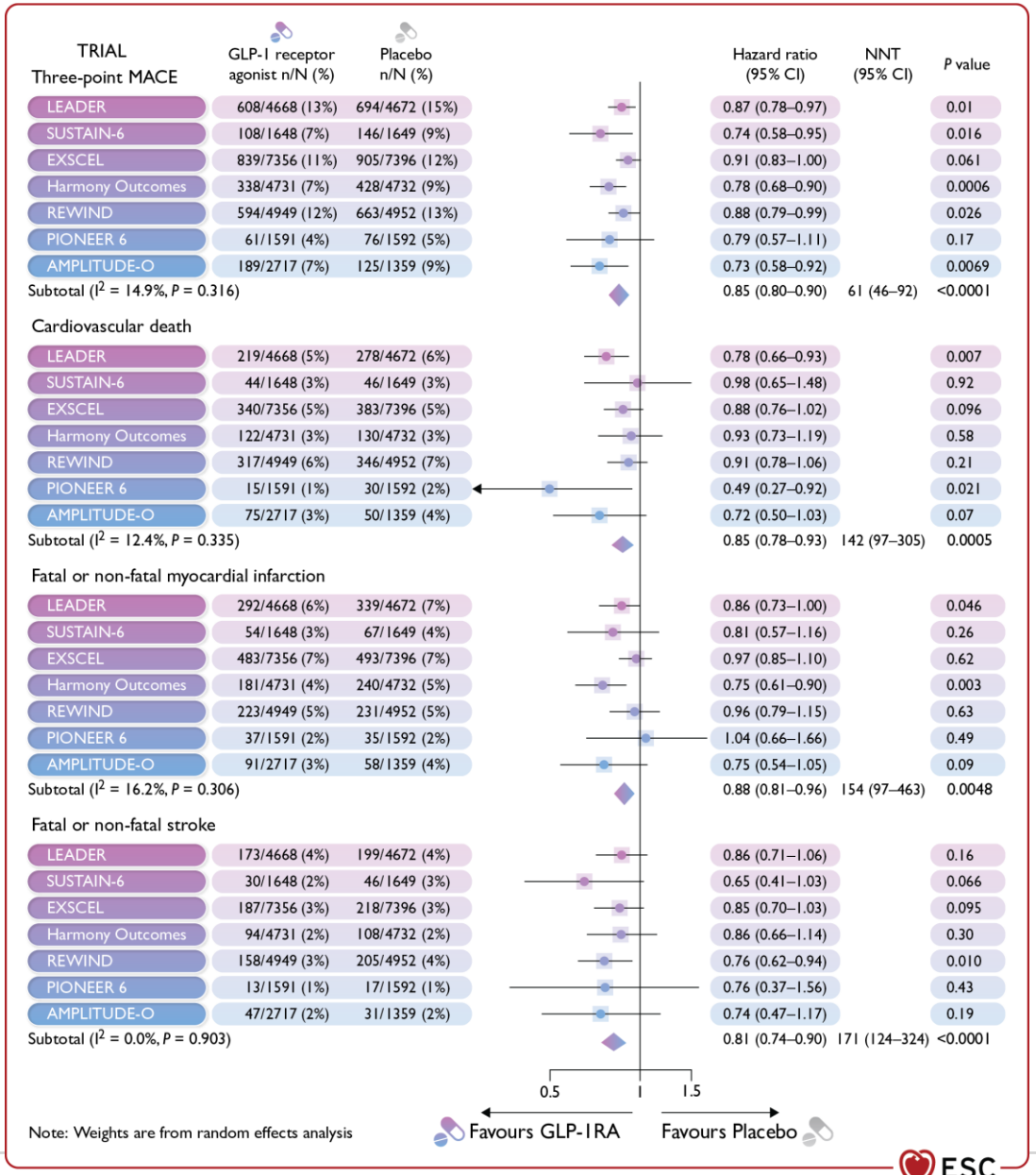
Marso SP et al. *N Engl J Med* 2016;375:311–322

SUSTAIN-6 (Semaglutide)



Marso SP et al SUSTAIN-6 Investigators. Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. N Engl J Med. 2016 Nov 10;375(19):1834-1844.

Meta-analysis of CVOT trials with GLP-1 receptor agonists



ESC

(European Heart Journal: 20

Recommendations for glucose-lowering treatment for patients with type 2 diabetes and ASCVD to reduce cardiovascular risk (1)

Recommendations	Class	Level
It is recommended to prioritize the use of glucose-lowering agents with proven CV benefits followed by agents with proven CV safety over agents without proven CV benefit or proven CV safety.	I	C
Sodium–glucose co-transporter-2 inhibitors		
SGLT2 inhibitors with proven CV benefit are recommended in patients with T2DM and ASCVD to reduce CV events, independent of baseline or target HbA1c and independent of concomitant glucose-lowering medication.	I	A
Glucagon-like peptide-1 receptor agonists		
GLP-1 RAs with proven CV benefit are recommended in patients with T2DM and ASCVD to reduce CV events, independent of baseline or target HbA1c and independent of concomitant glucose-lowering medication.	I	A

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Recommendations for glucose-lowering treatment for patients with type 2 diabetes and ASCVD to reduce cardiovascular risk (2)

Recommendations (continued)	Class	Level
Other glucose-lowering medications to reduce cardiovascular risk		
If additional glucose control is needed, metformin should be considered in patients with T2DM and ASCVD.	IIa	C
If additional glucose control is needed, pioglitazone may be considered in patients with T2DM and ASCVD without HF.	IIb	B

2023 ESC Guidelines for the management of cardiovascular disease in patients with diabetes
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Recommendation for glucose-lowering treatment for patients with type 2 diabetes without ASCVD or severe TOD to reduce cardiovascular risk

Recommendations	Class	Level
In patients with T2DM without ASCVD or severe TOD at low or moderate risk, treatment with metformin should be considered to reduce CV risk.	IIa	C
In patients with T2DM without ASCVD or severe TOD at high or very high risk, treatment with metformin may be considered to reduce CV risk.	IIb	C
In patients with T2DM without ASCVD or severe TOD but with a calculated 10-year CVD risk≥10%, treatment with a SGLT2 inhibitor or GLP-1 RA may be considered to reduce CV risk.	IIb	C

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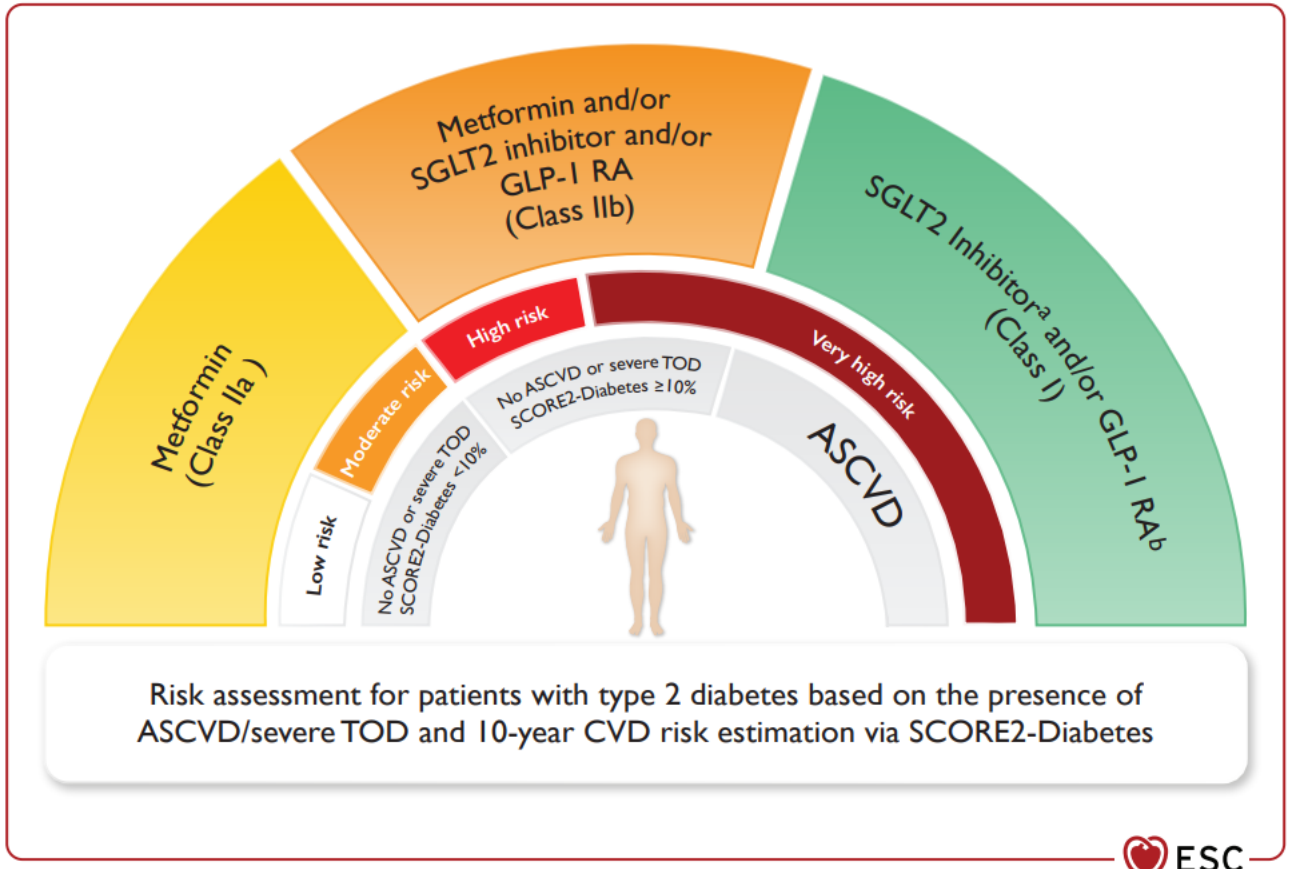
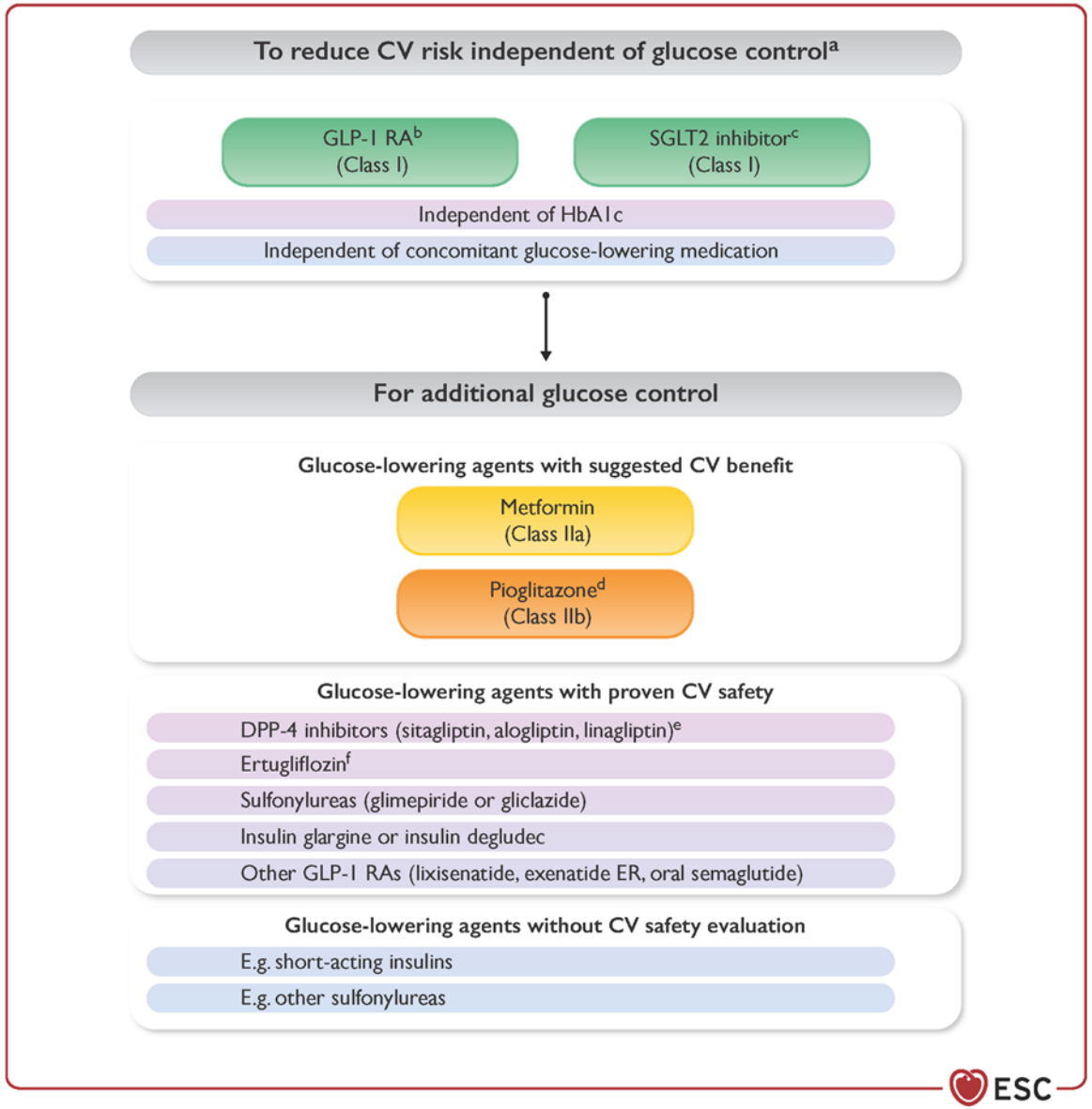
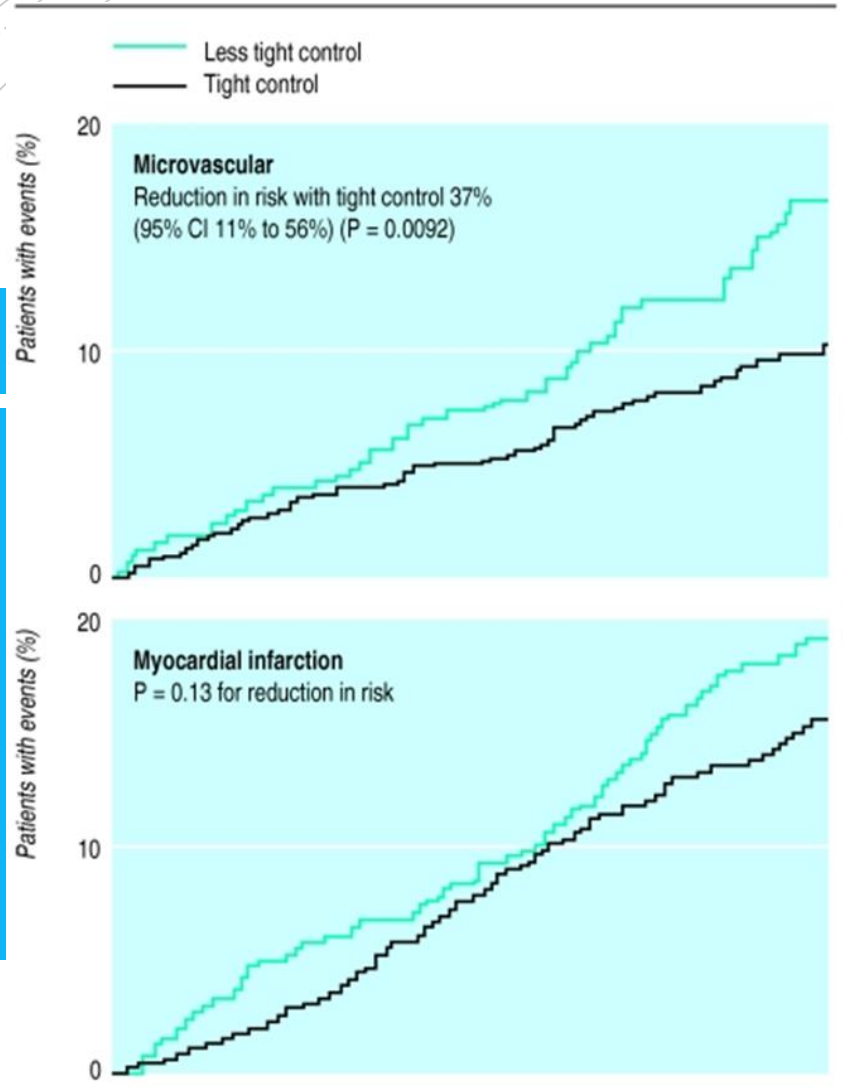
Glucose-lowering treatment for patients with T2DM to reduce cardiovascular risk

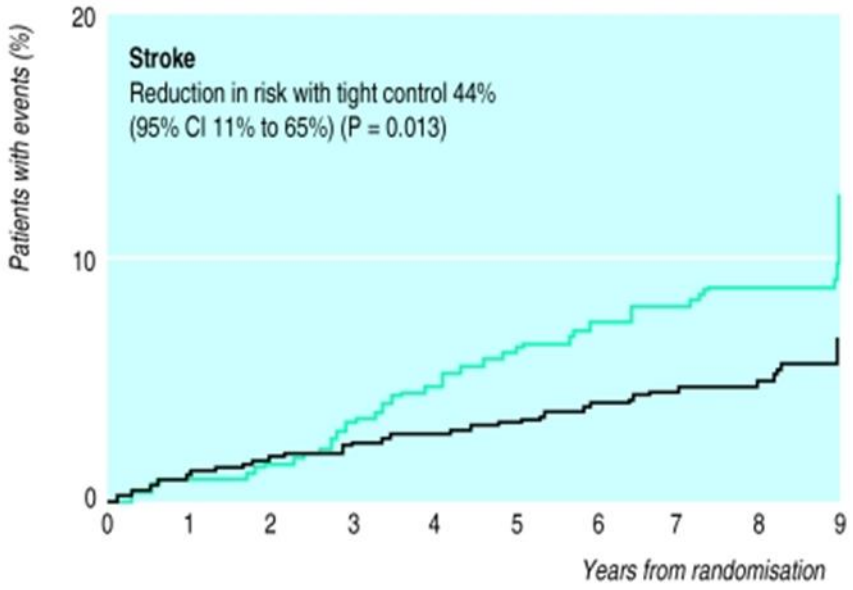


Glucose-lowering treatment for patients with T2DM & ASCVD to reduce cardiovascular risk



Blood Pressure





UK Prospective Diabetes Study Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. UK Prospective Diabetes Study Group. BMJ. 1998 Sep 12;317(7160):703-13.

Recommendations for blood pressure management in patients with diabetes (1)

Recommendations	Class	Level
Screening for hypertension		
Regular BP measurements are recommended in all patients with diabetes to detect and treat hypertension to reduce CV risk.	I	A
Treatment targets		
Anti-hypertensive drug treatment is recommended for people with diabetes when office BP is ≥140/90 mmHg.	I	A
It is recommended to treat hypertension in patients with diabetes in an individualized manner. The BP goal is to target SBP to 130 mmHg and <130 mmHg if tolerated, but not <120 mmHg. In older people (age >65 years), it is recommended to target SBP to 130–139 mmHg.	I	A

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Recommendations for blood pressure management in patients with diabetes (2)

Recommendations	Class	Level
Treatment targets (continued)		
An on-treatment SBP target of <130 mmHg may be considered in patients with diabetes at particularly high risk of a cerebrovascular event to further reduce their risk of stroke.	IIb	B
Treatment and evaluation		
Lifestyle changes (weight loss if overweight, physical activity, alcohol restriction, sodium restriction, increased consumption of vegetables, using low-fat dairy products) are recommended in patients with diabetes and hypertension.	I	A
It is recommended to initiate treatment with a combination of a RAS inhibitor and a CCB or thiazide/thiazide-like diuretic.	I	A

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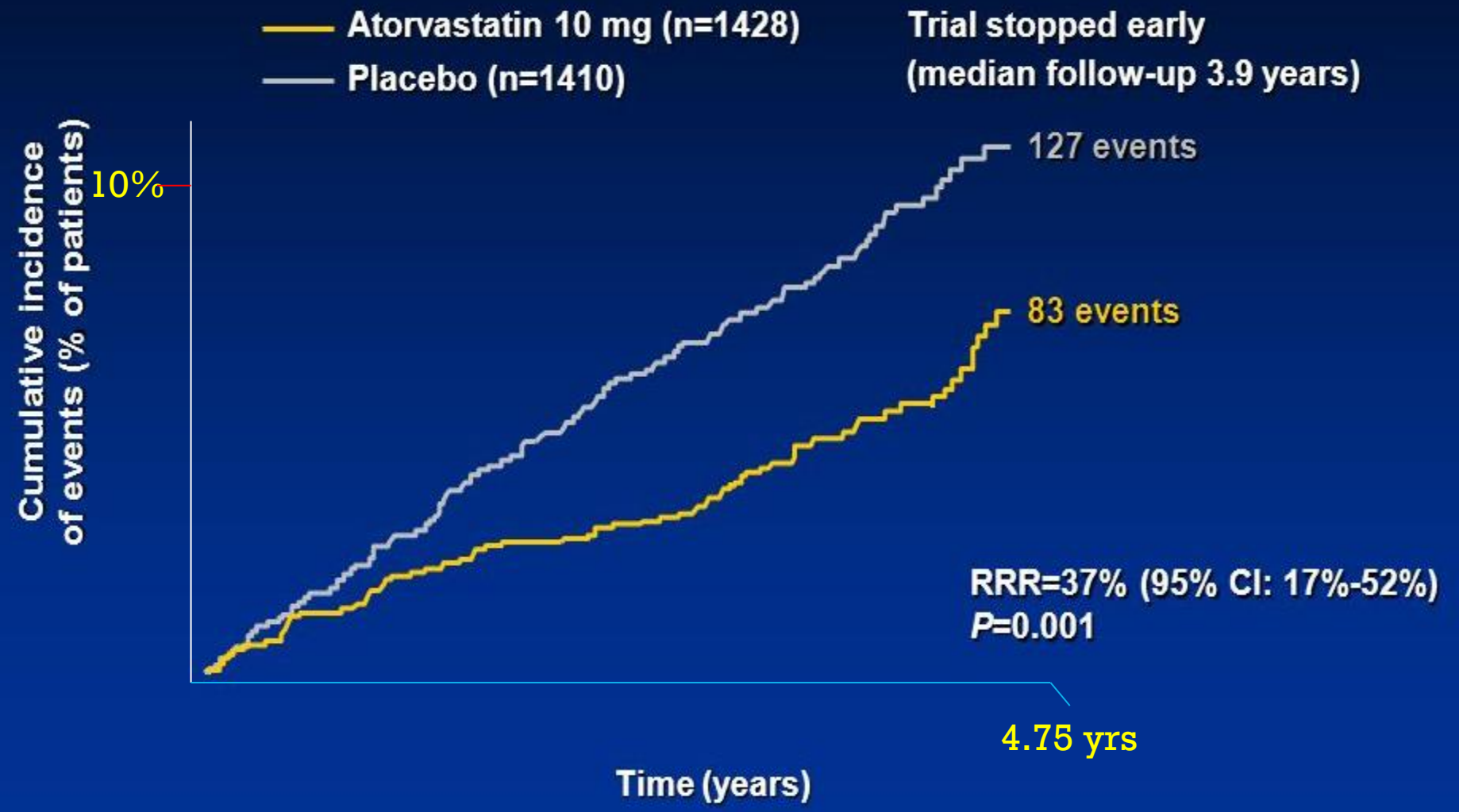
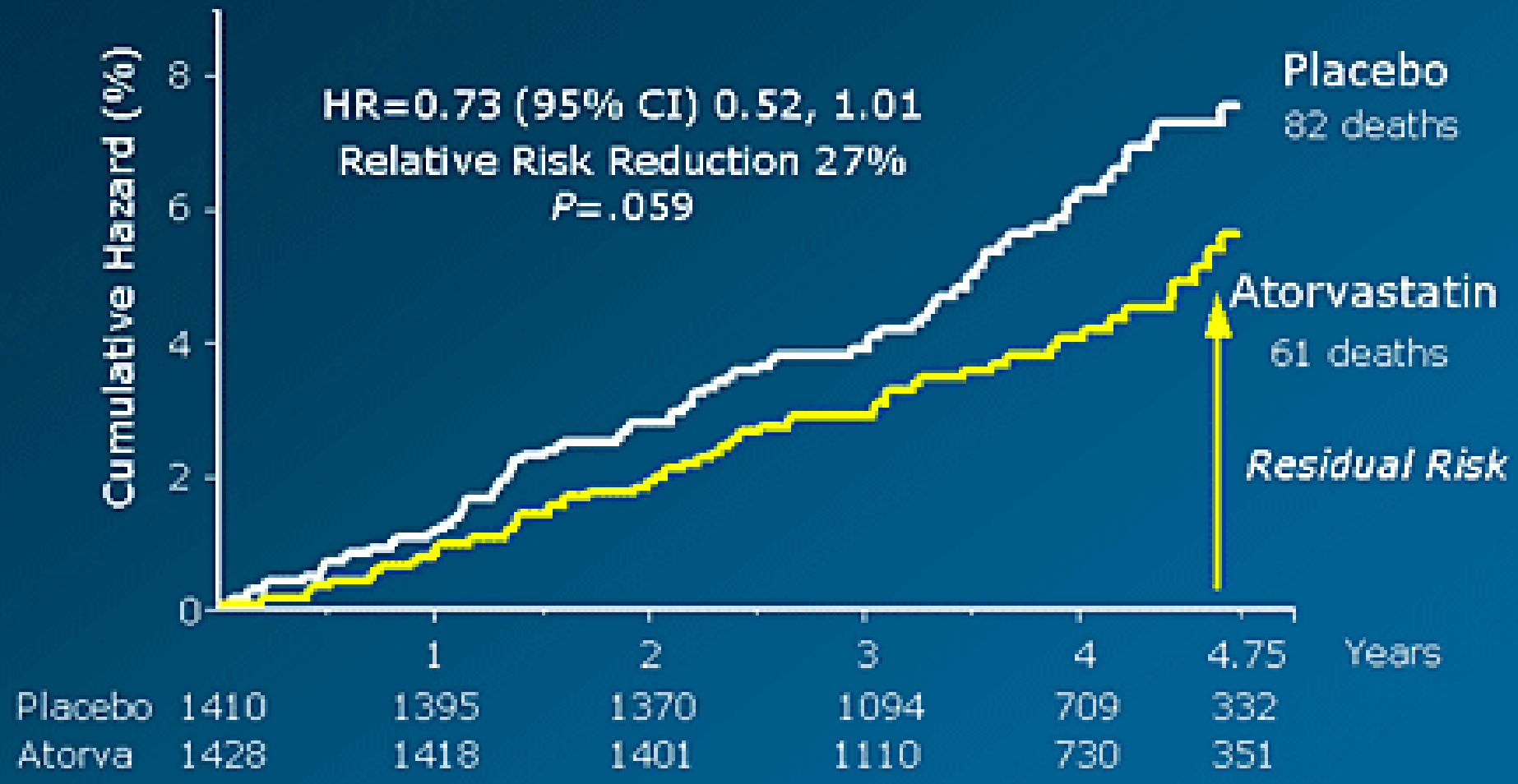
CARDS: Atorvastatin Significantly Reduces Risk of Major CV Events*



*Acute CHD event, coronary revascularization, stroke.

Colhoun HM et al. *Lancet*. 2004;364:685-696.

CARDS: Atorvastatin (10 mg qd) Reduces Death in Diabetes



Calhoun HM et al. *Lancet*. 2004;364:685-696.

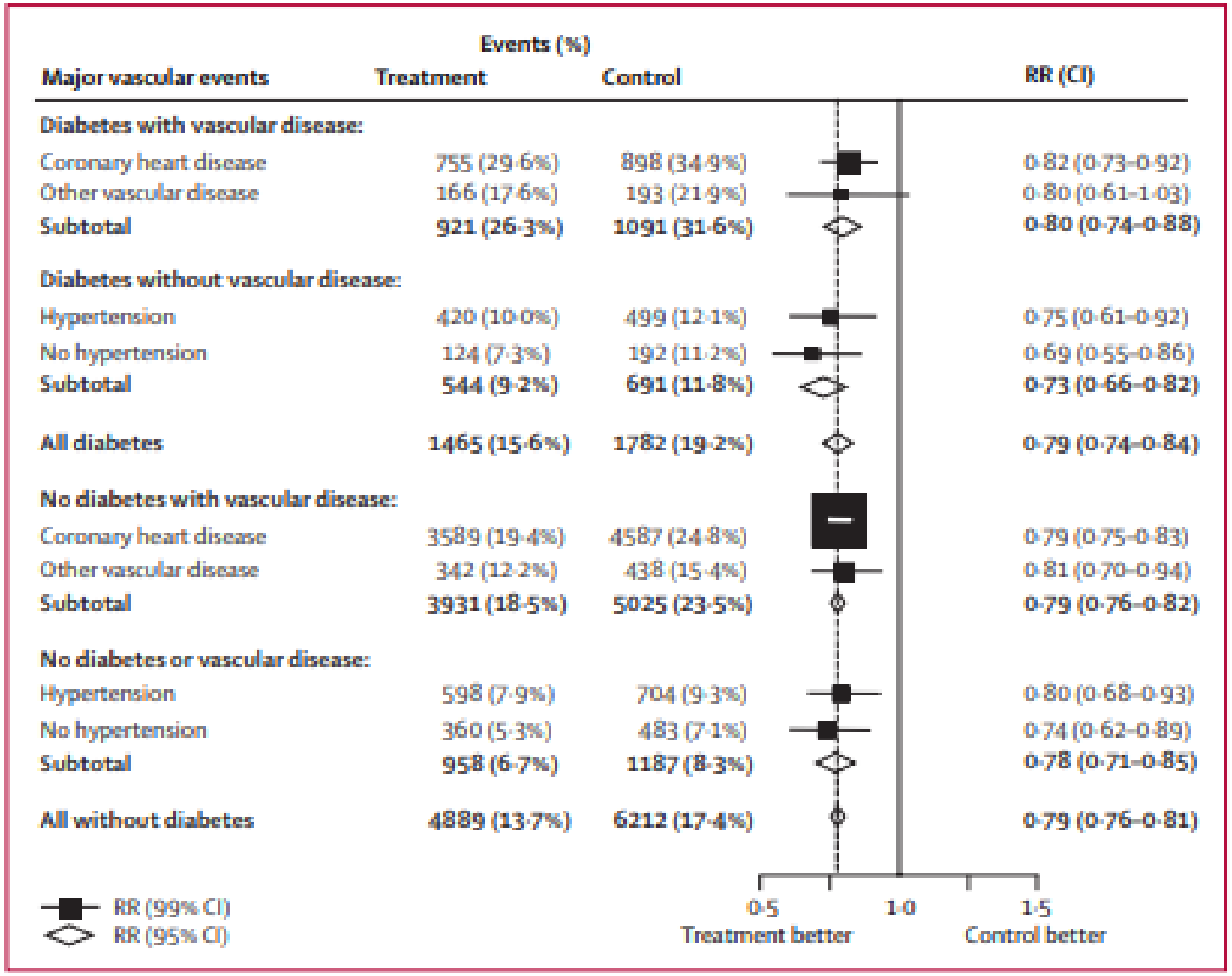


Figure 3: Proportional effects on major vascular events per mmol/L reduction in LDL cholesterol in participants with and without diabetes by history of vascular disease

Cholesterol Treatment Trialists' (CTT) Collaborators. Lancet. 2008;371(9607):117-25

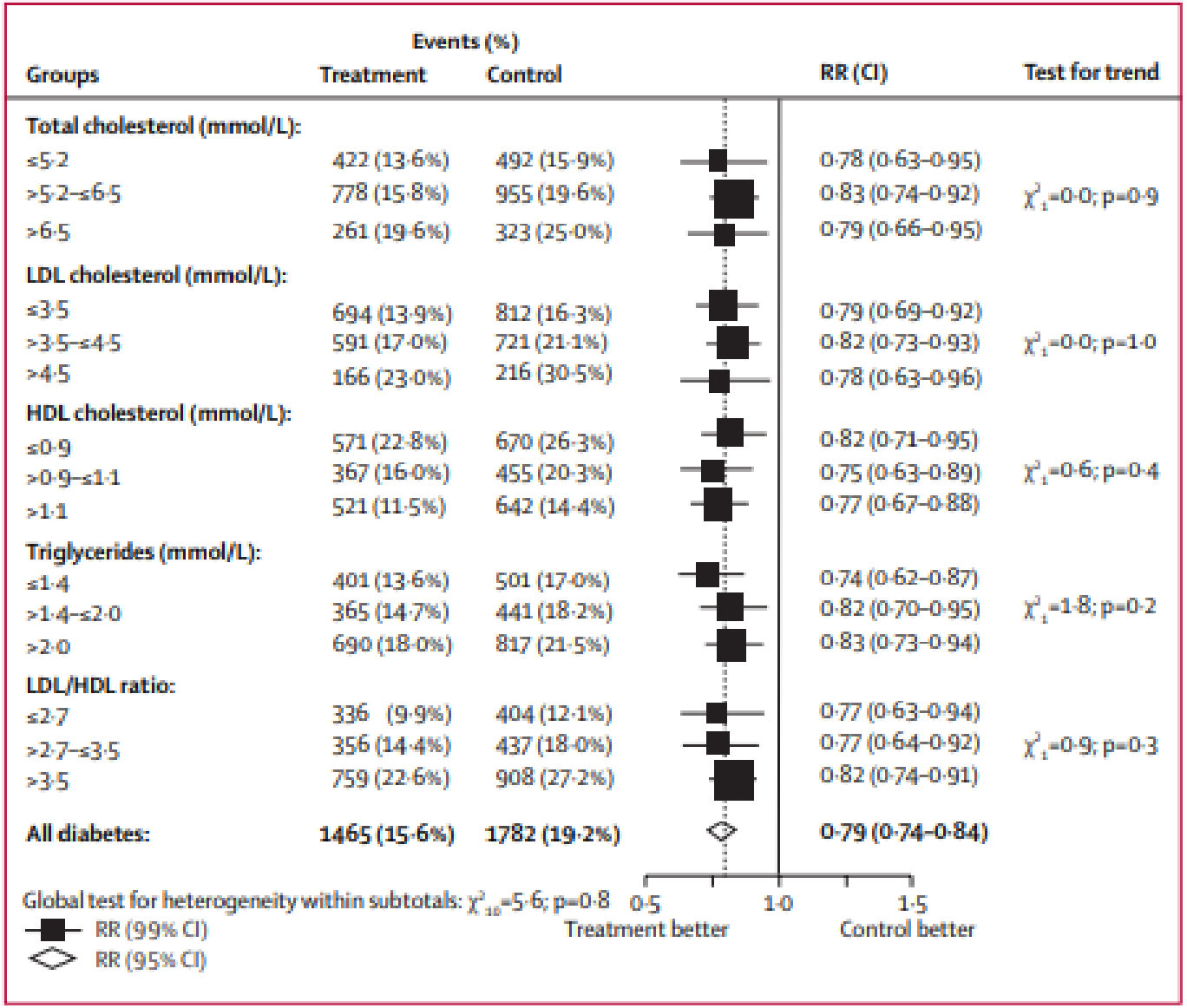
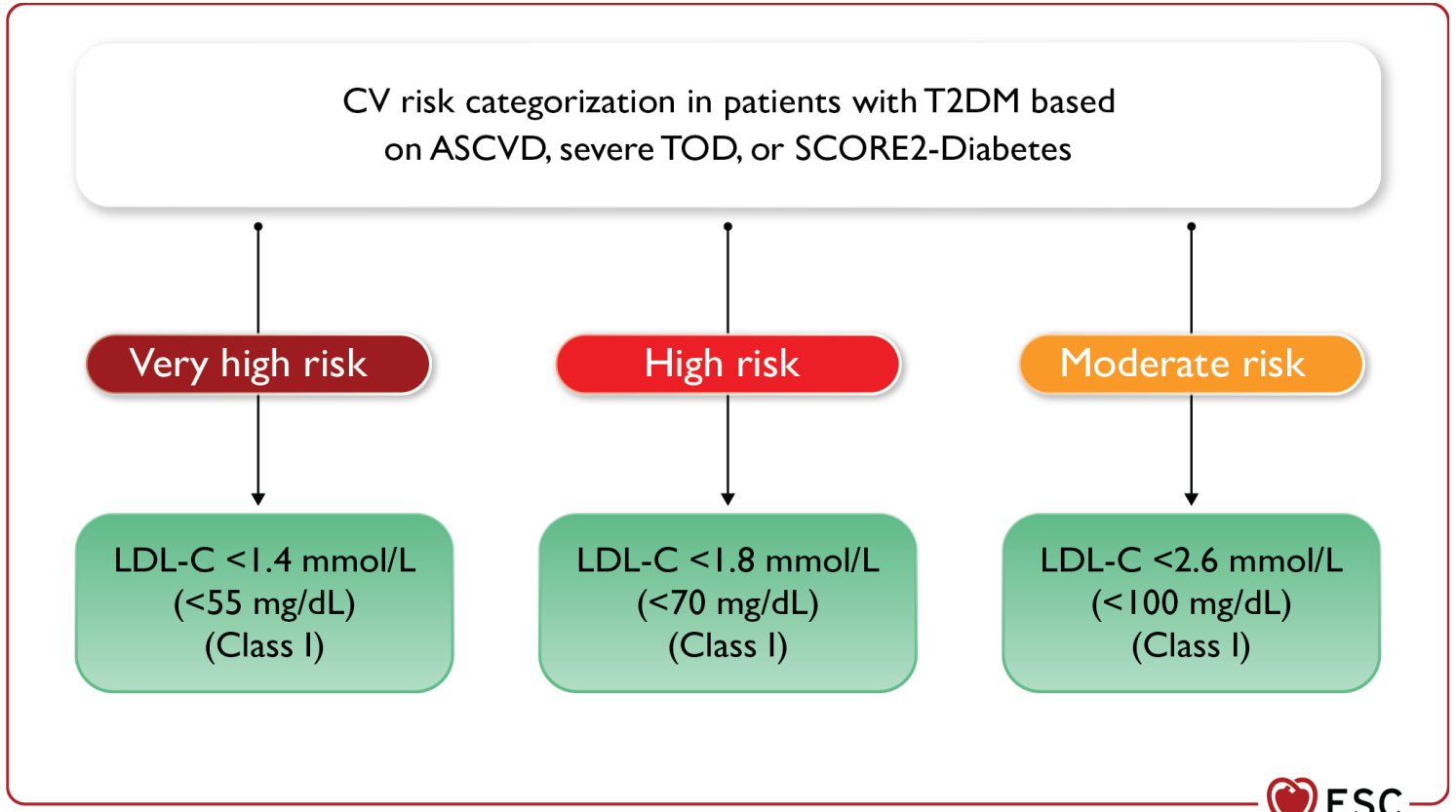


Figure 5: Proportional effects on major vascular events per mmol/L reduction in LDL cholesterol by baseline lipid profile in participants with diabetes

Cholesterol Treatment Trialists' (CTT) Collaborators. Lancet. 2008;371(9607):117-25

Recommended LDL-C targets



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

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Recommendations for the management of dyslipidaemia in patients with diabetes (3)

Recommendations	Class	Level
Lipid-lowering treatment (continued)		
If a statin-based regimen is not tolerated at any dosage (even after re-challenge), a PCSK9 inhibitor added to ezetimibe should be considered.	IIa	B
If a statin-based regimen is not tolerated at any dosage (even after re-challenge), ezetimibe should be considered.	IIa	C
High-dose icosapent ethyl (2 g b.i.d.) may be considered in combination with a statin in patients with hypertriglyceridaemia.	IIb	B

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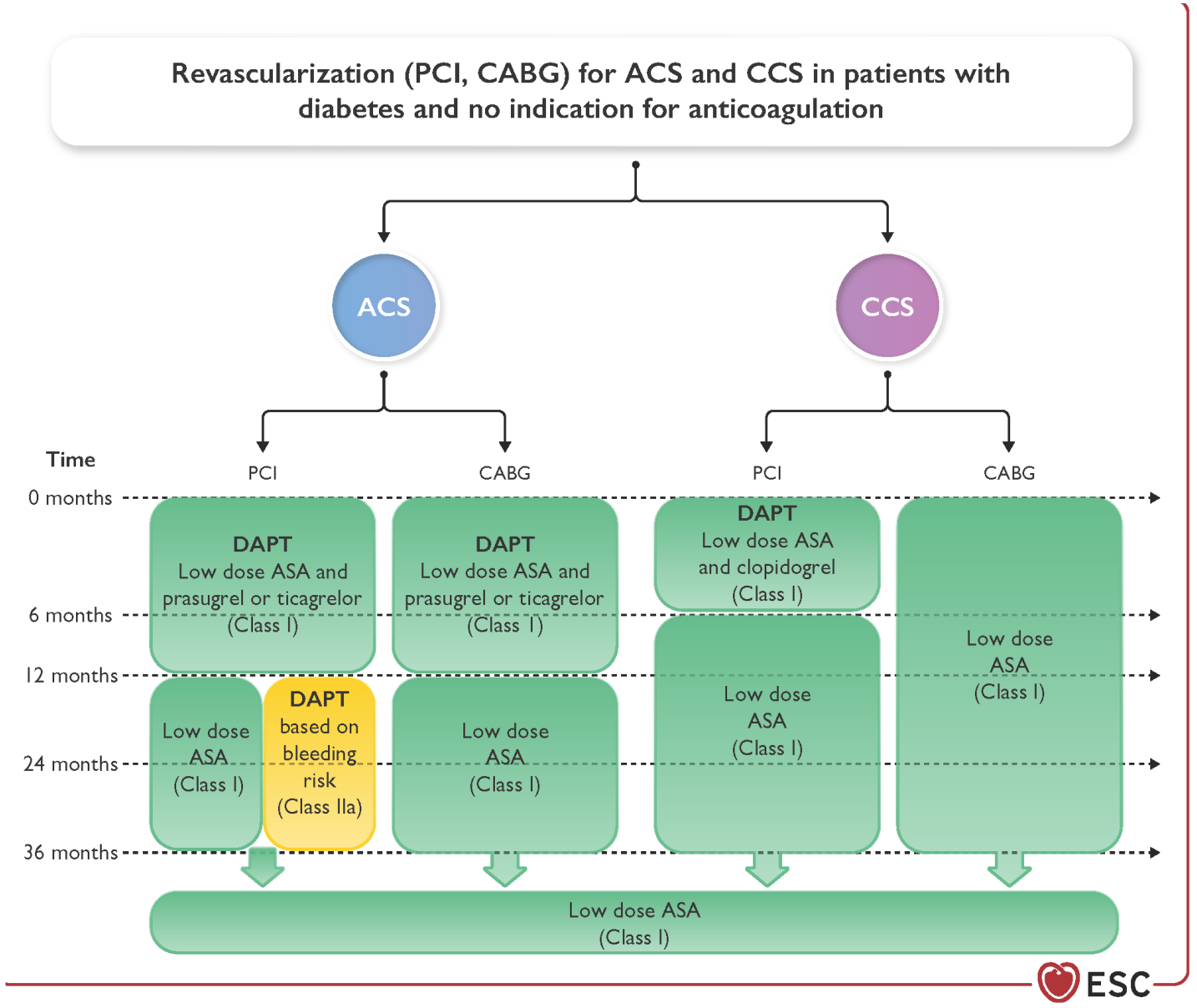
Recommendations for antiplatelet therapy



Recommendations for gastric protection in patients with diabetes taking antithrombotic drugs

Recommendations	Class	Level
When antithrombotic drugs are used in combination, proton pump inhibitors are recommended to prevent gastrointestinal bleeding.	I	A
When a single antiplatelet or anticoagulant drug is used, proton pump inhibitors should be considered to prevent gastrointestinal bleeding, considering the bleeding risk of the individual patient.	IIa	A
When clopidogrel is used, omeprazole and esomeprazole are not recommended for gastric protection.	III	B

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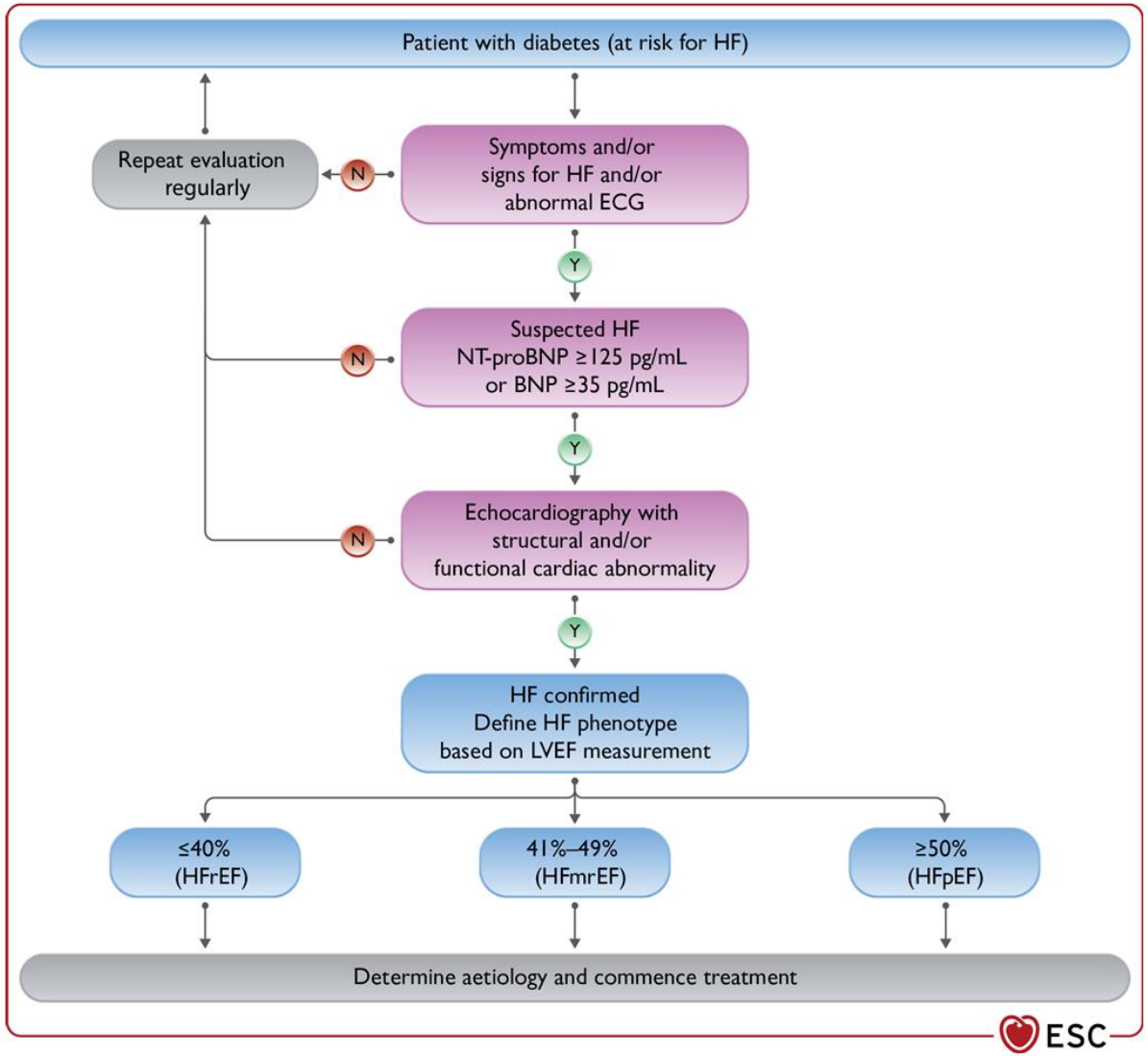
Chronic Coronary Syndrome

- Myocardial revascularisation is recommended when angina persists despite treatment with anti-anginal drugs or in patients with a documented large area of ischaemia (>10%LV).
- When myocardial revascularisation is not possible, one needs to target symptom relief:
  - increasing myocardial oxygen supply with long-acting nitrates or CCBs
  - decreasing oxygen demand with the help of beta-blockers, non-dihydropyridine CCBs, ranolazine, or ivabradine.
- Ranolazine, a drug that reduces myocardial ischaemia at the cellular level, also has the unique effect of reducing HbA1c, especially in patients with poor metabolic control.

Diagnostic algorithm for patients with diabetes



Recommendations for heart failure treatments in patients with heart failure with reduced ejection fraction and diabetes (1)

Recommendations	Class	Level
Recommendations for the pharmacological treatment indicated in patients with HFrEF (NYHA class II–IV) and diabetes		
SGLT2 inhibitors (dapagliflozin, empagliflozin, or sotagliflozin) are recommended in all patients with HFrEF and T2DM to reduce the risk of HF hospitalization and CV death.	I	A
Sacubitril/valsartan or an ACE-I is recommended in all patients with HFrEF and diabetes to reduce the risk of HF hospitalization and death.	I	A
Beta-blockers are recommended in patients with HFrEF and diabetes to reduce the risk of HF hospitalization and death.	I	A

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Recommendations for heart failure treatments in patients with heart failure with reduced ejection fraction and diabetes (2)

Recommendations	Class	Level
Recommendations for the pharmacological treatment indicated in patients with HFrEF (NYHA class II–IV) and diabetes (continued)		
MRAs are recommended in patients with HFrEF and diabetes to reduce the risk of HF hospitalization and death.	I	A
An intensive strategy of early initiation of evidence-based treatment (SGLT2 inhibitors, ARNI/ACE-Is, beta-blockers, and MRAs), with rapid up-titration to trial-defined target doses starting before discharge and with frequent follow-up visits in the first 6 weeks following a HF hospitalization is recommended to reduce re-admissions or mortality.	I	B

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Recommendations for heart failure treatments in patients with heart failure with reduced ejection fraction and diabetes (3)

Recommendations	Class	Level
Recommendations for other treatments indicated in selected patients with HFrEF (NYHA class II–IV) and diabetes		
Device therapy with an ICD, CRT-P, or CRT-D is recommended in patients with diabetes, as in the general population with HFrEF.	I	A
ARBs are recommended in symptomatic patients with HFrEF and diabetes who do not tolerate sacubitril/valsartan or ACE-Is, to reduce the risk of HF hospitalization and CV death.	I	A
Diuretics are recommended in patients with HFrEF and diabetes with signs and/or symptoms of fluid congestion to improve symptoms, exercise capacity, and HF hospitalization.	I	C

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Recommendations for heart failure treatments in patients with heart failure with reduced ejection fraction and diabetes (4)

Recommendations	Class	Level
Recommendations for other treatments indicated in selected patients with HFrEF (NYHA class II–IV) and diabetes (continued)		
Ivabradine should be considered to reduce the risk of HF hospitalization and CV death in patients with HFrEF and diabetes in sinus rhythm, with a resting heart rate ≥70 b.p.m., who remain symptomatic despite treatment with beta-blockers (maximum tolerated dose), ACE-Is/ARBs, and MRAs.	IIa	B
Hydralazine and isosorbide dinitrate should be considered in self-identified Black patients with diabetes and LVEF ≤ 35% or with LVEF <45% combined with a dilated left ventricle in NYHA class III–IV despite treatment with an ACE-I (or ARNI), a beta-blocker, and an MRA, to reduce the risk of HF hospitalization and death.	IIa	B

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Recommendations for heart failure treatments in patients with heart failure with reduced ejection fraction and diabetes (5)

Recommendations	Class	Level
Recommendations for other treatments indicated in selected patients with HFrEF (NYHA class II–IV) and diabetes (continued)		
Digoxin may be considered in patients with symptomatic HFrEF in sinus rhythm despite treatment with sacubitril/valsartan or an ACE-I, a beta-blocker, and an MRA, to reduce the risk of hospitalization.	IIb	B

2023 ESC Guidelines for the management of cardiovascular disease in patients with diabetes
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Recommendations for heart failure treatments in patients with diabetes and left ventricular ejection fraction over 40%

Recommendations	Class	Level
Empagliflozin or dapagliflozin are recommended in patients with T2DM and LVEF >40% (HFmrEF and HFpEF) to reduce the risk of HF hospitalization or CV death.	I	A
Diuretics are recommended in patients with HFpEF or HFmrEF and diabetes with signs and/or symptoms of fluid congestion to improve symptoms, exercise capacity, and HF hospitalization.	I	C

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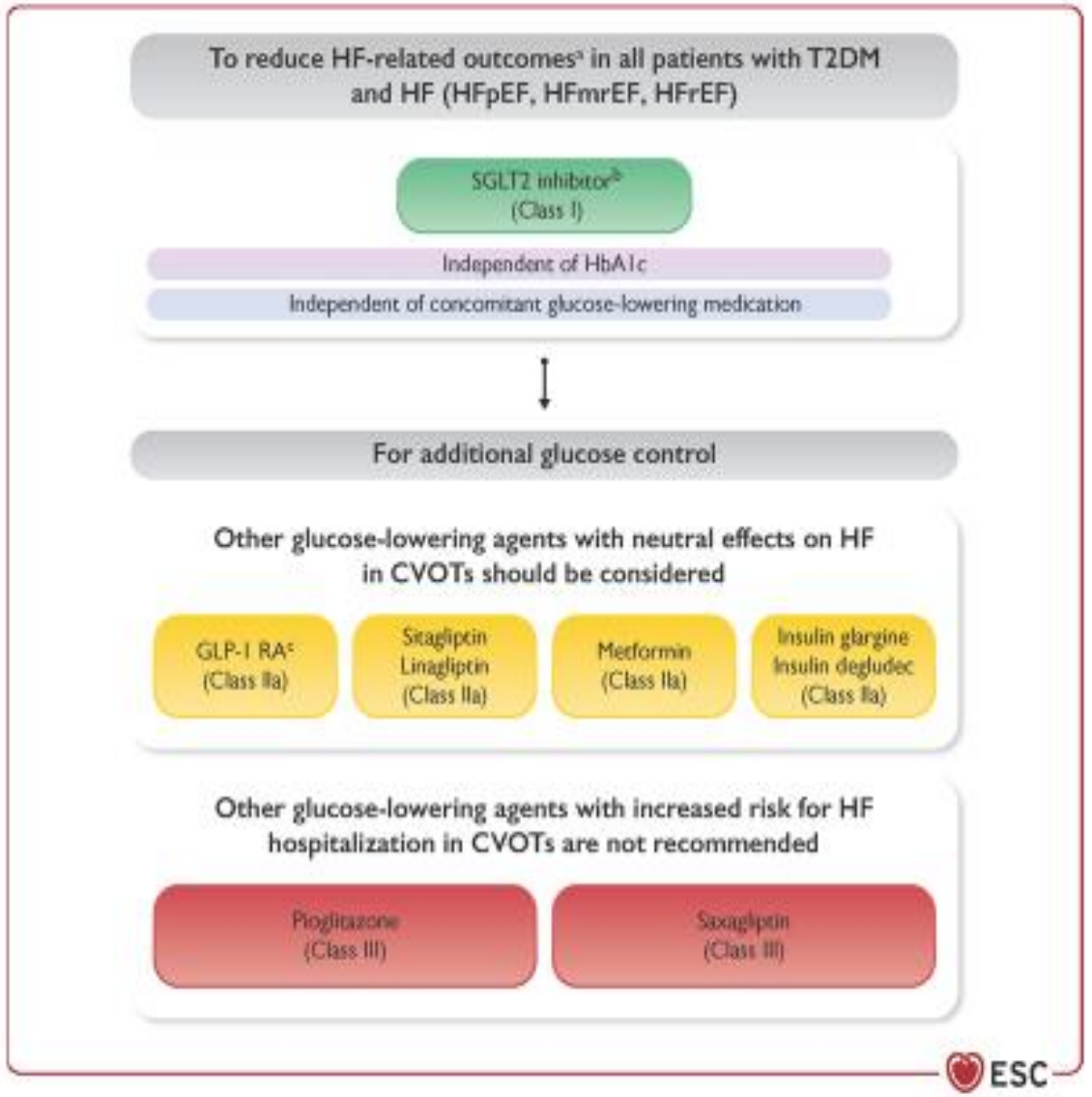
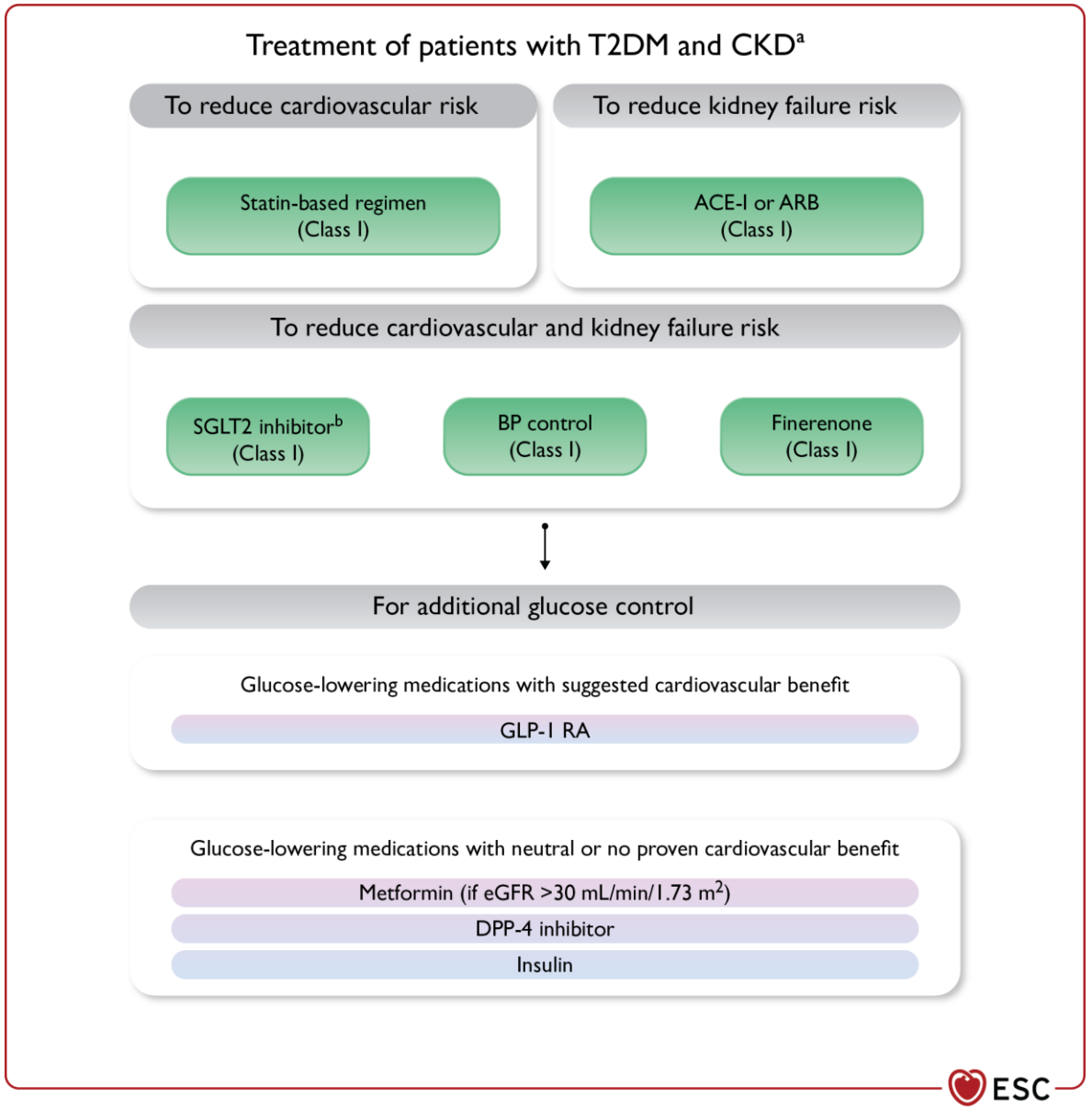
Glucose-lowering treatment of patients with heart failure and type 2 diabetes



Treatment of patients with T2DM & CKD



Recommendations for patients with chronic kidney disease and diabetes (1)

Recommendations	Class	Level
Intensive LDL-C lowering with statins or a statin/ezetimibe combination is recommended.	I	A
A BP target of ≤130/80 mmHg is recommended to reduce risk of CVD and albuminuria.	I	A
Personalized HbA1c targets 6.5–8.0% (48–64 mmol/mol) are recommended, with a target <7.0% (<53 mmol/mol) to reduce microvascular complications, wherever possible.	I	A
The maximum tolerated dose of an ACE-I or ARB is recommended.	I	A
A SGLT2 inhibitor (canagliflozin, empagliflozin, or dapagliflozin) is recommended in patients with T2DM and CKD with an eGFR ≥20 mL/min/1.73 m^2 to reduce the risk of CVD and kidney failure.	I	A

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(European Heart Journal; 2023 – doi:10.1093/eurheartj/ehad192)

Recommendations for patients with chronic kidney disease and diabetes (2)

Recommendations	Class	Level
Finerenone is recommended in addition to an ACE-I or ARB in patients with T2DM and eGFR >60 mL/min/1.73 m^2 with a UACR ≥30 mg/mmol (≥300 mg/g), or eGFR 25–60 mL/min/1.73 m^2 and UACR ≥3 mg/mmol (≥30 mg/g) to reduce CV events and kidney failure.	I	A
A GLP-1 RA is recommended at eGFR >15 mL/min/1.73 m^2 to achieve adequate glycaemic control, due to low risk of hypoglycaemia and beneficial effects on weight, CV risk, and albuminuria.	I	A
Low-dose ASA (75–100 mg o.d.) is recommended in patients with CKD and ASCVD.	I	A
It is recommended that patients with diabetes are routinely screened for kidney disease by assessing eGFR defined by CKD-EPI and UACR.	I	B

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Recommendations for patients with chronic kidney disease and diabetes (3)

Recommendations	Class	Level
Treatment with intensive medical or an initial invasive strategy is recommended in people with CKD, diabetes, and stable moderate or severe CAD, due to similar outcomes.	I	B
Kidney specialist advice may be considered for managing a raised serum phosphate, other evidence of CKD-MBD, and renal anaemia.	IIb	C
Combined use of an ARB with an ACE-I is not recommended.	III	B

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Patient-centred care approach