Optimization in Management of Coronary Artery Disease

Dr. Yin Nwe Tun
Associate Professor/
Senior Consultant Cardiologist
Department of Cardiology
University of Medicine (1)

31.3.24

Outline:

1. Introduction of Coronary Artery Disease(CAD)
2. Guideline directed management and therapy of CAD
3. Role of SGLT2 inhibitors in Management of CAD

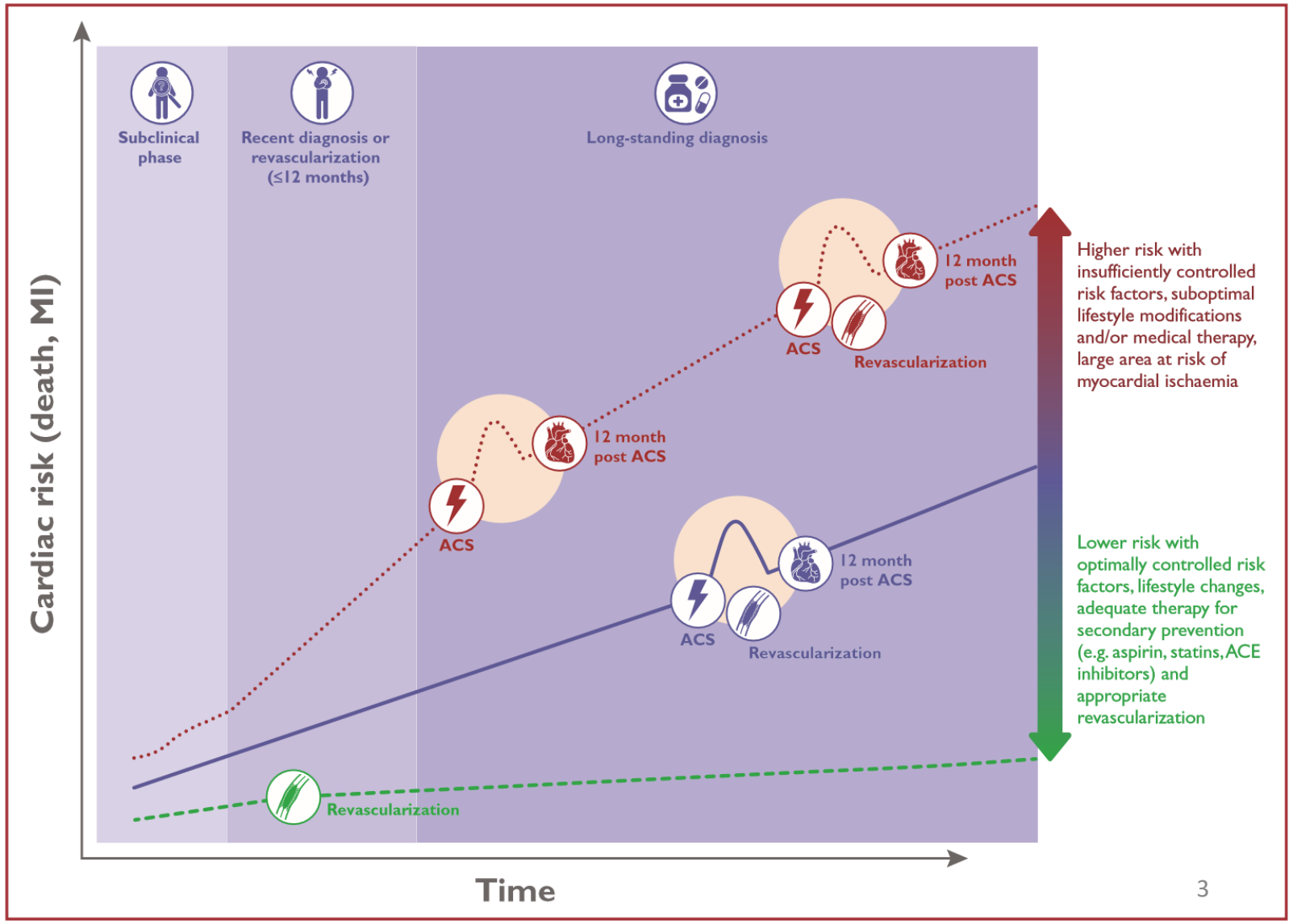
CAD: ACS and CCS "Dynamic Nature"

Coronary artery disease (CAD) is a pathological process characterized by atherosclerotic plaque accumulation in the epicardial arteries, obstructive or non obstructive.

Clinical presentation - either acute coronary syndromes (ACS) or chronic coronary syndromes (CCS).

"dynamic process" of atherosclerosis and altered arterial function "

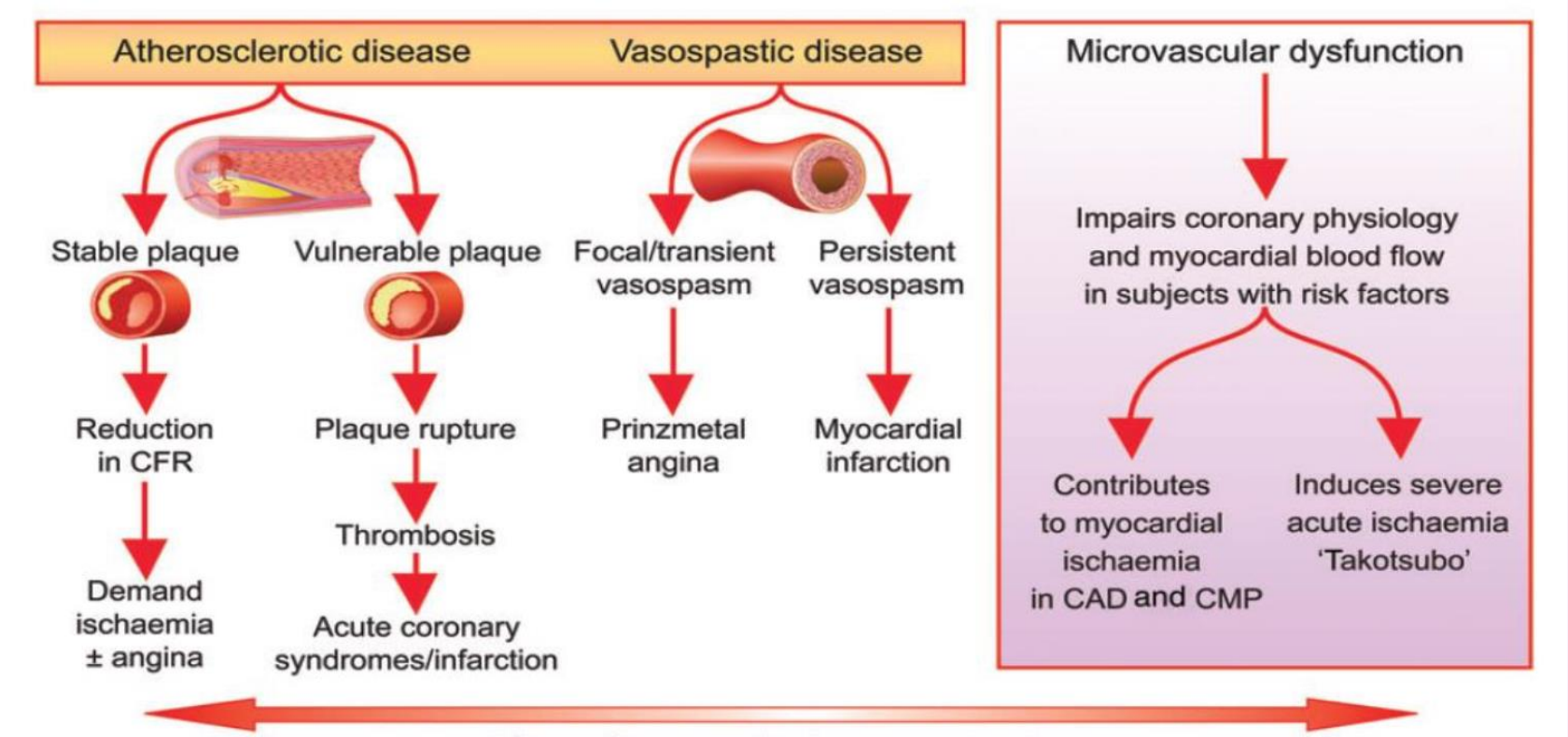
Having long, stable periods - become unstable at any time



Mechanisms of Myocardial Ischaemia in CAD

Epicardial coronary arteries

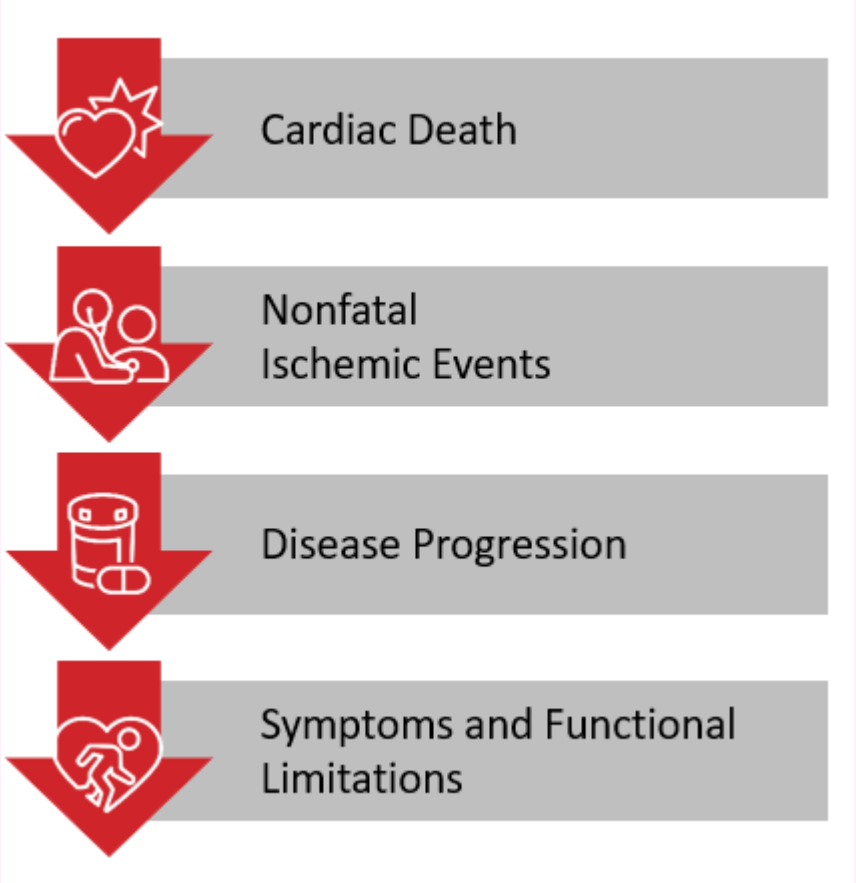
Coronary Microcirculation



These 3 mechanisms can co-exist in the same patient

Crea F et al. *Eur Heart J.* 2014;35(17):1101-11

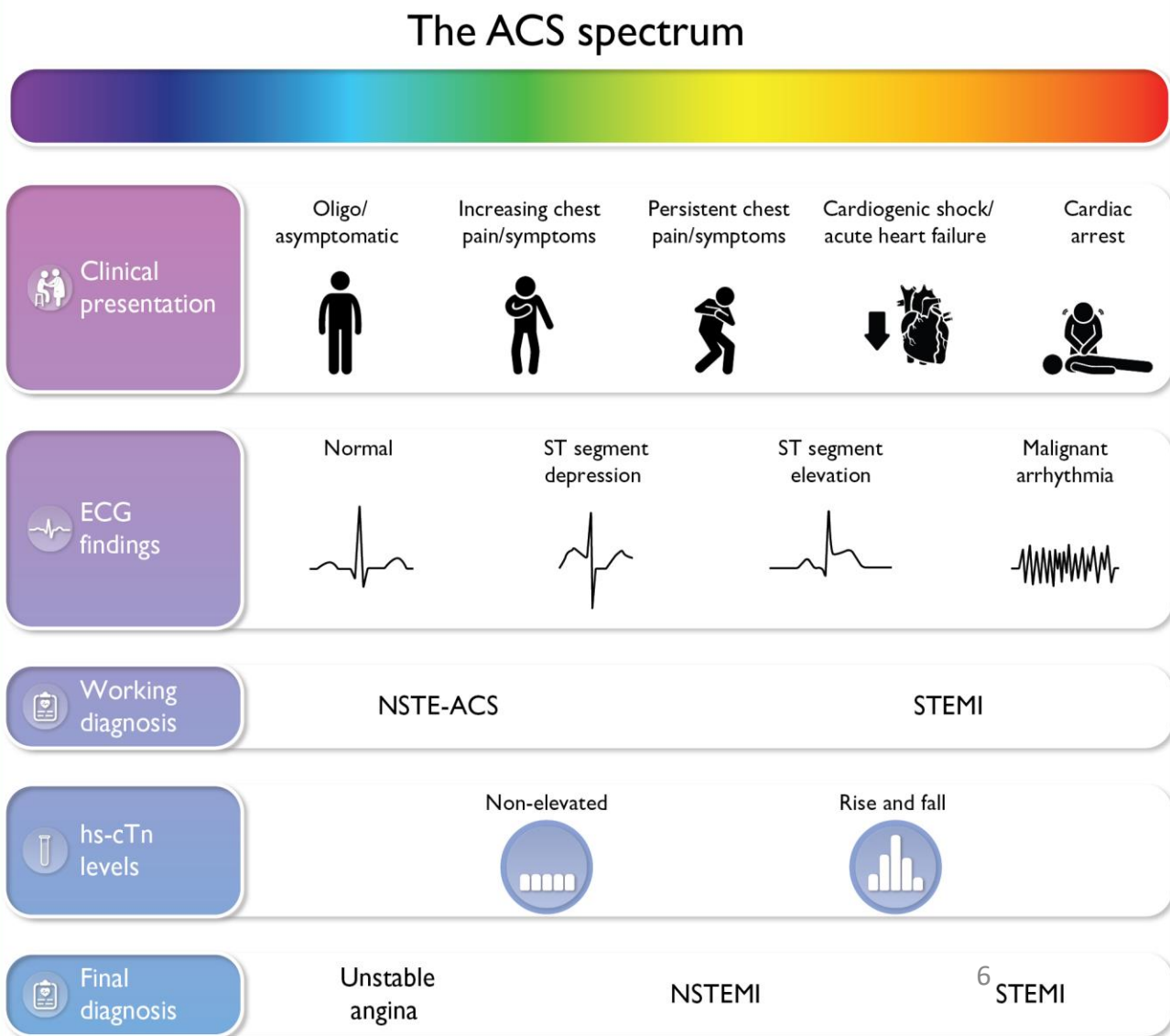
Goals of Treatment in Management of CAD



Acute Coronary Syndrome - ACS

- Spectrum of conditions - include patients with recent change in clinical symptoms or signs, with or without changes on 12-lead ECG and with or without acute elevations in cardiac troponin concentrations

- Commonly classified based on ECG at presentation and the presence or absence of troponin elevation into UA, NSTEMI, or STEMI



Overview of Initial triage, Management and Investigation of patients with signs and symptoms potentially consistent with ACS

ECG - interpreted within 10 min.

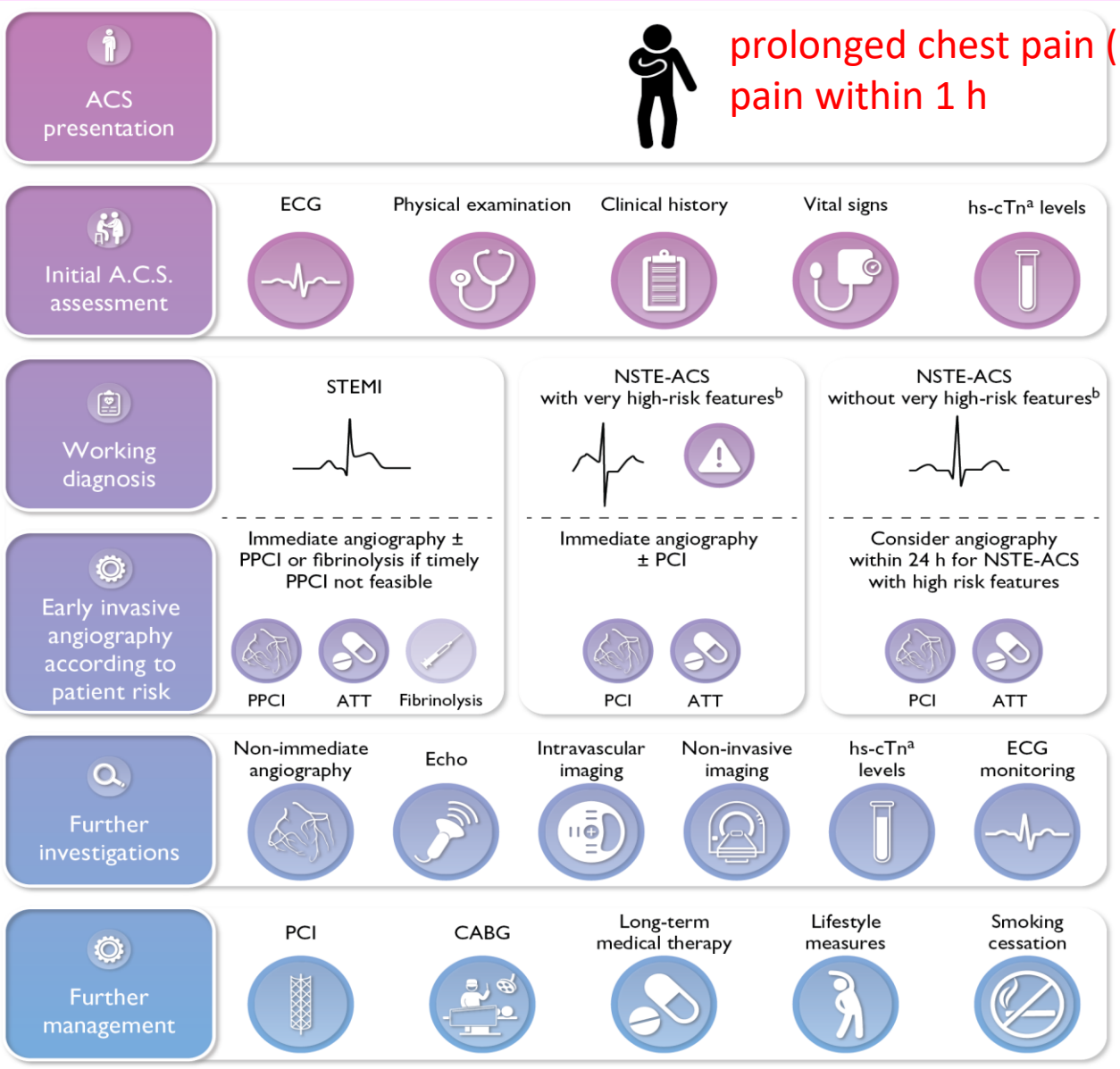
Focused physical examination –

1 .checking for the presence of all major pulses

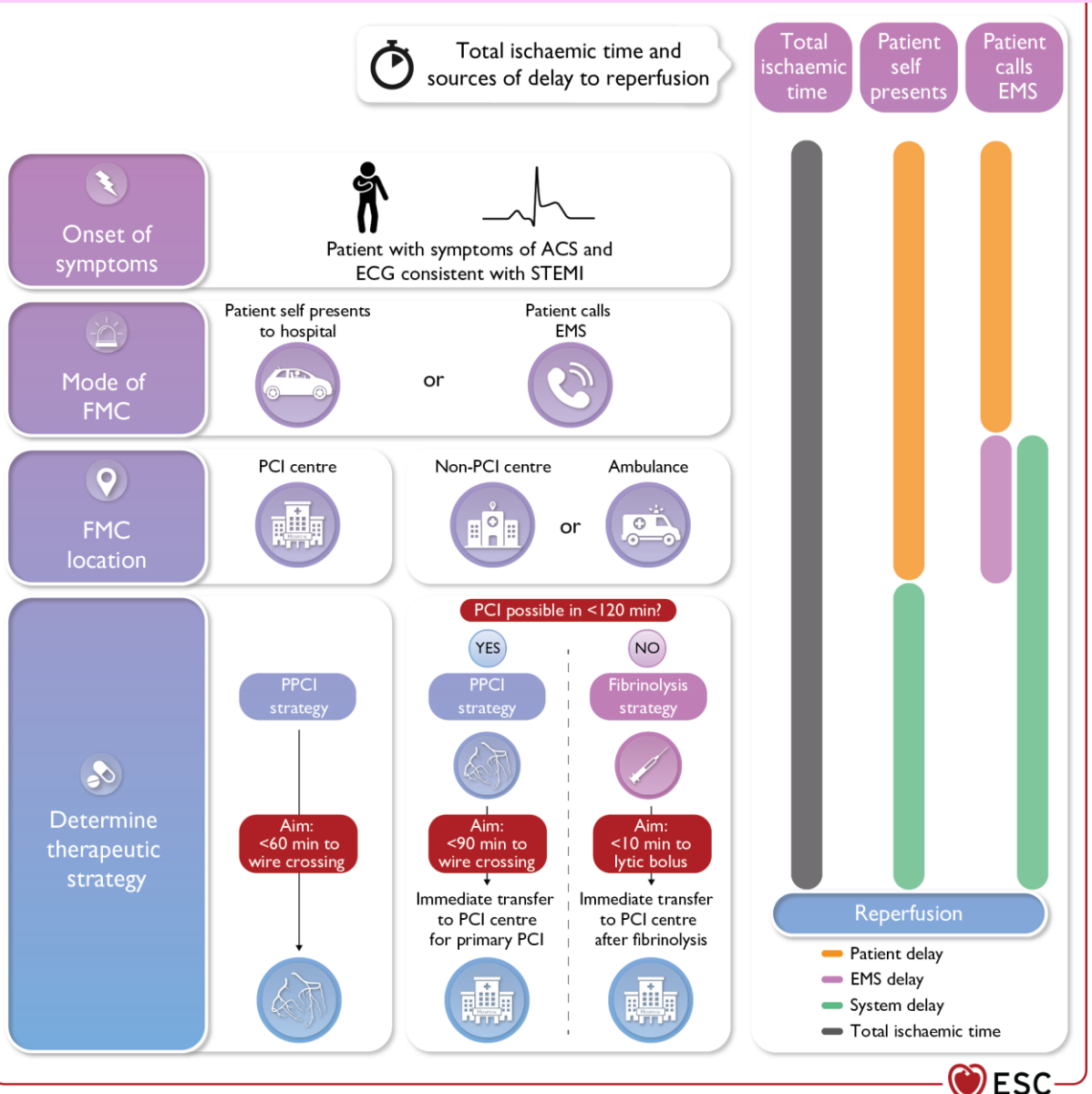
2. measurement of blood pressure in both arms

3. auscultation of the heart and lungs

4. assessing for signs of HF or circulatory compromise



Modes of presentation and pathways to invasive management and myocardial revascularization in patients presenting with STEMI



Invasive management strategies are time sensitive

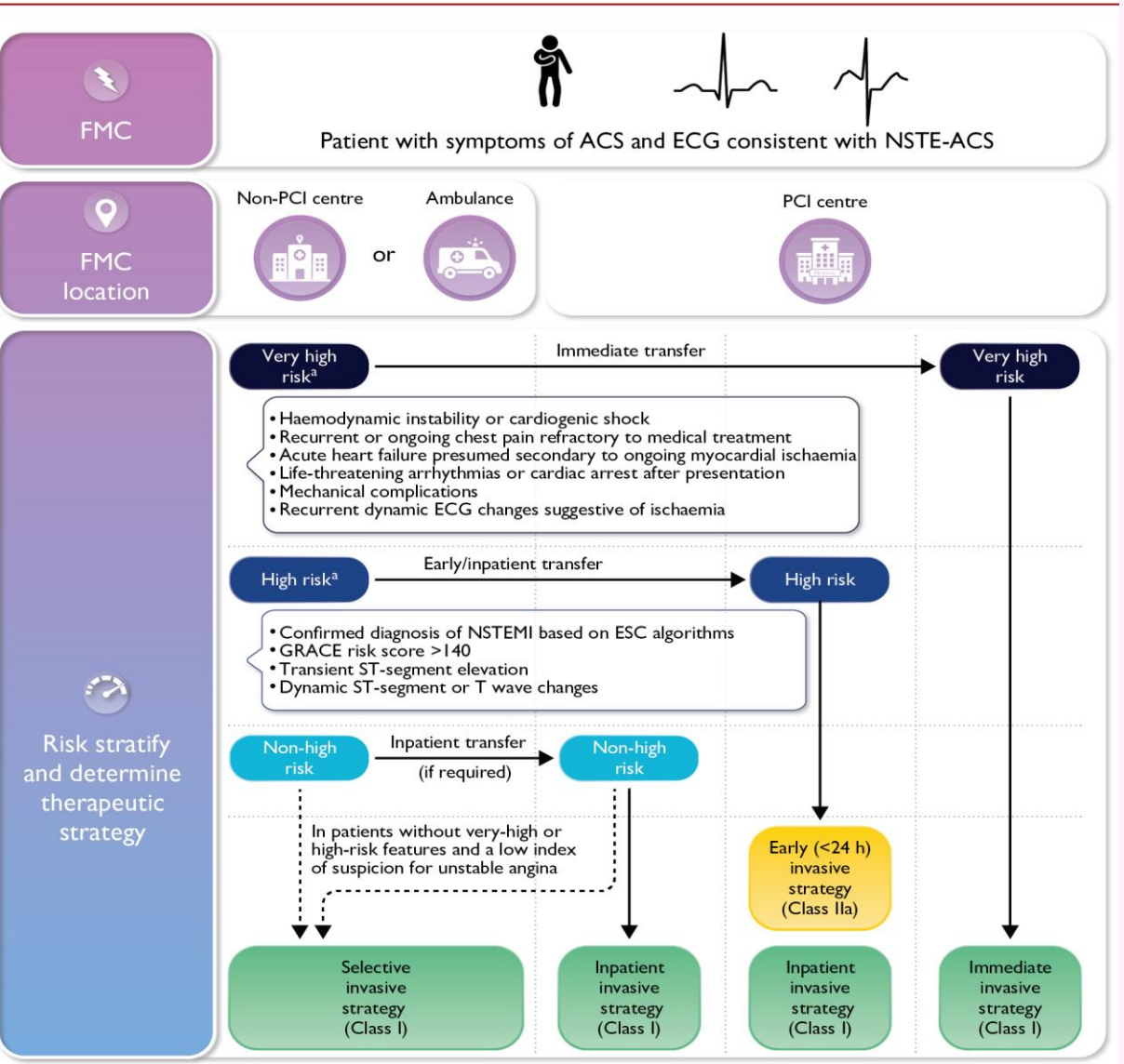
Timely PCI with concomitant antithrombotic drugs – key to reduce the ischemic risk in patients with ACS

PCI with stent deployment in the IRA during the index procedure is recommended in patients undergoing PPCI.[490–494]	I	A

Emergency CABG-

Occluded IRA when PPCI not feasible/ unsuccessful and large area of myocardium in jeopardy

Selection of invasive strategy and reperfusion therapy in patients presenting with NSTE-ACS



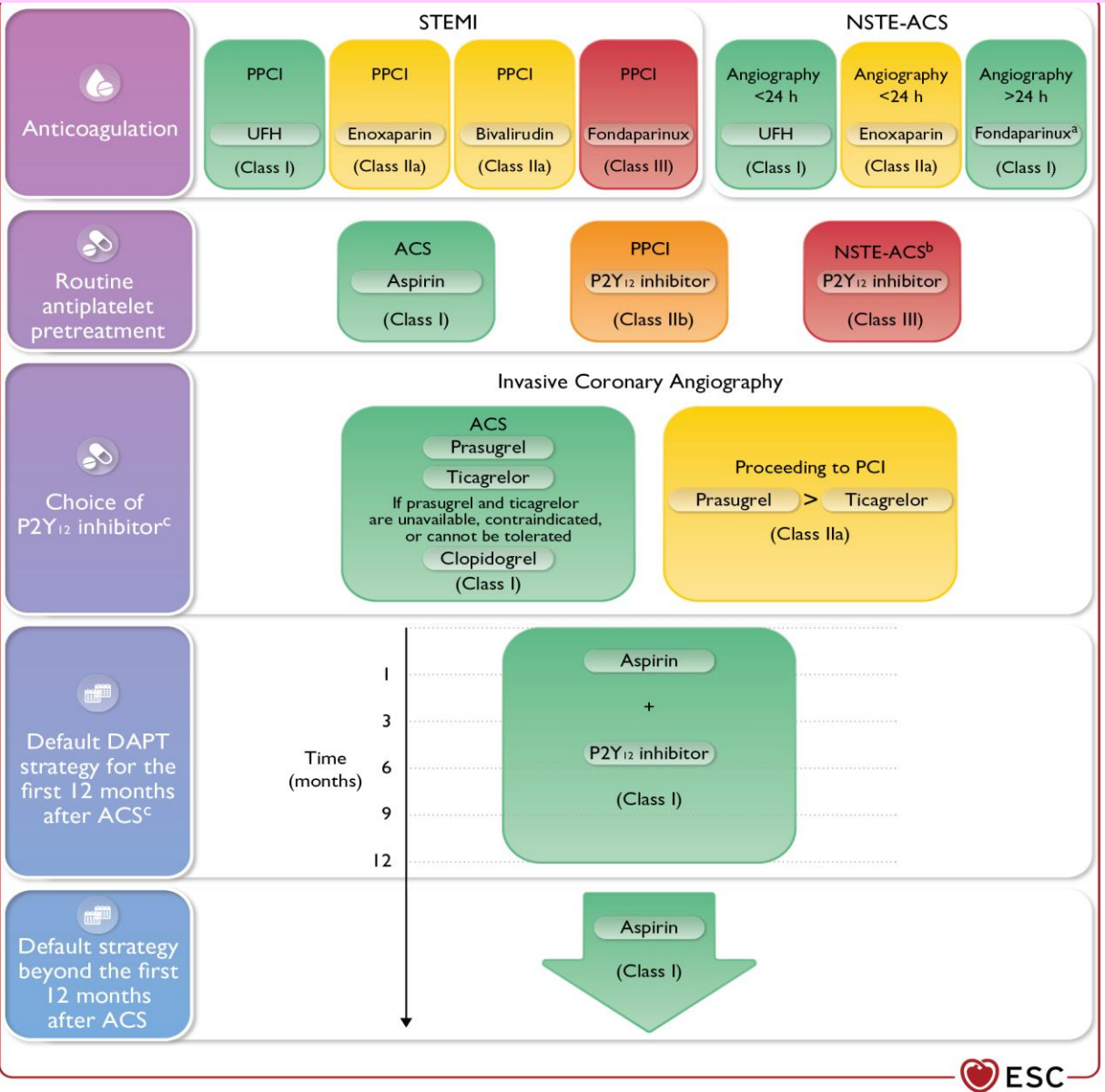
Very high-risk criteria:

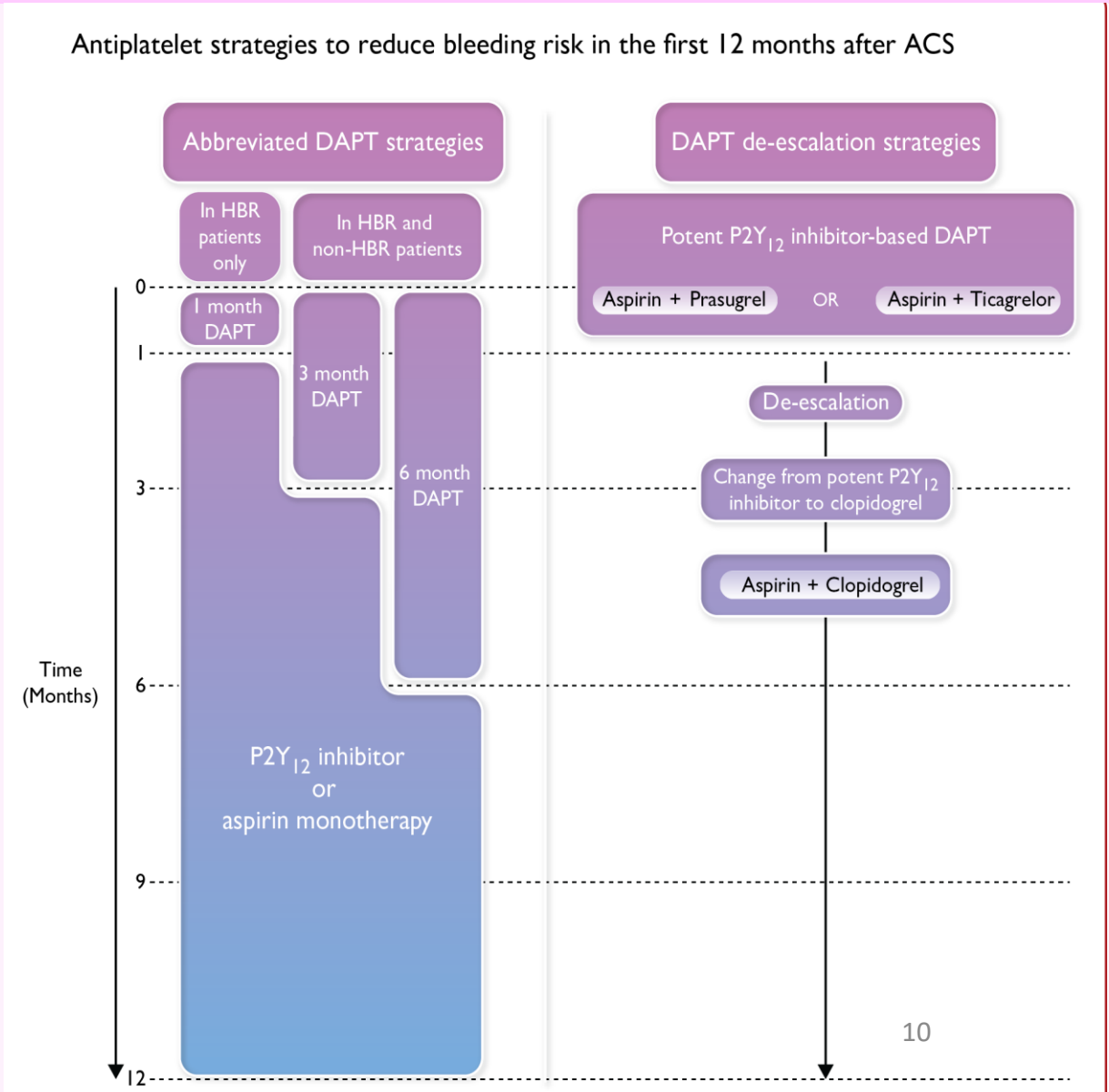
- Hemodynamic instability or Cardiogenic Shock
- Recurrent or ongoing chest pain refractory to medical treatment
- Acute HF presumed secondary to ongoing myocardial ischemia
- Life-threatening arrhythmias or cardiac arrest after presentation
- Mechanical complications
- Recurrent dynamic ECG changes suggestive of ischemia (particularly with intermittent ST-segment elevation)

High-risk criteria:

- A confirmed diagnosis of NSTEMI
- Dynamic ST-segment or T wave changes.
- Transient ST-segment elevation.
- A GRACE risk score >140

Recommended default antithrombotic therapy regimens in acute coronary syndrome patients





Chronic Coronary Syndrome - CCS

- Defined by the different evolutionary phases of CAD, excluding situations in which an acute coronary artery thrombosis dominates the clinical presentation. (i.e. ACS)
- Most frequently encountered clinical scenarios are:

  (i) patients with suspected CAD and 'stable' anginal symptoms, and/or dyspnoea

  (ii) patients with new onset HF or LV dysfunction and suspected CAD

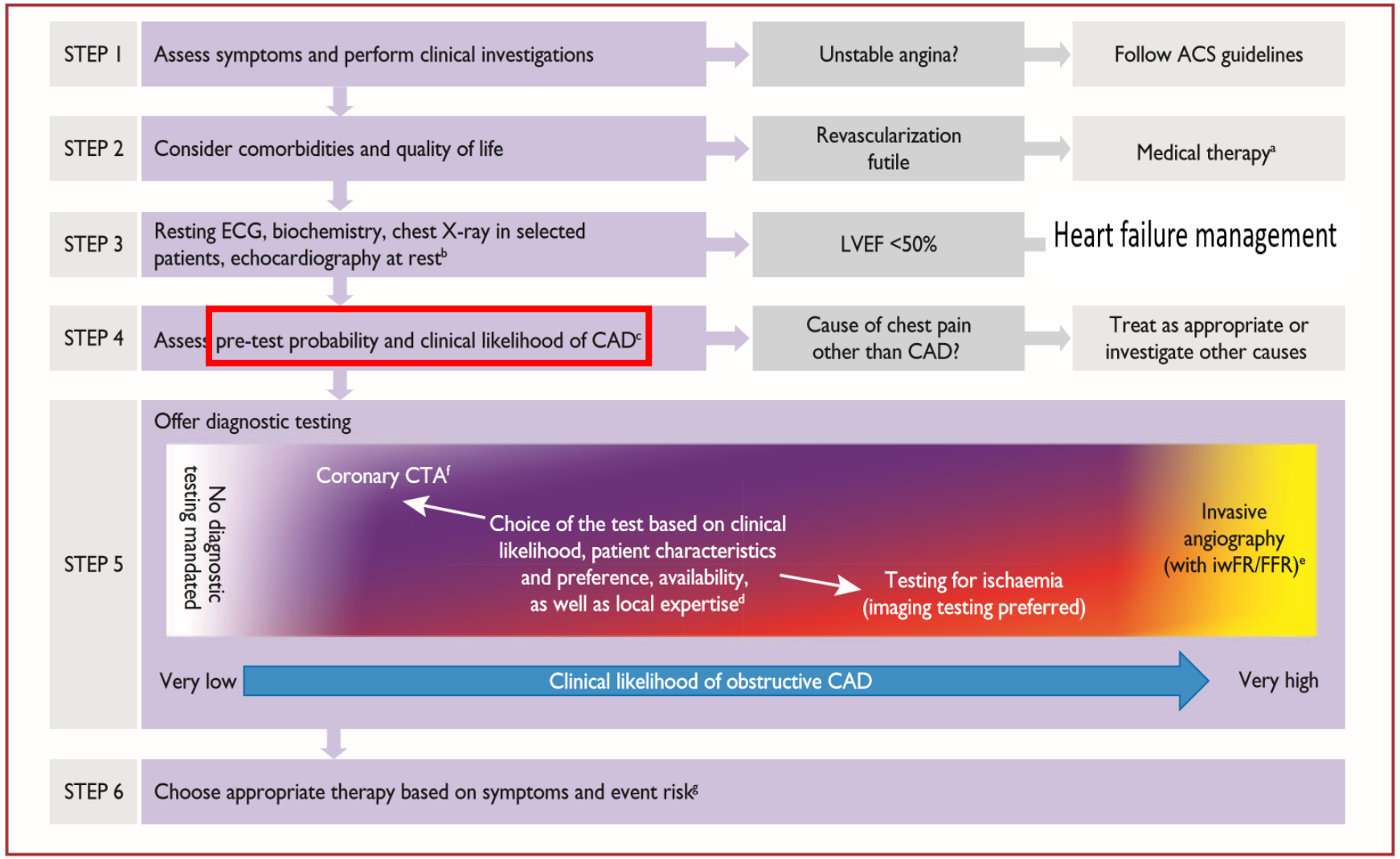
  (iii) asymptomatic and symptomatic patients with stabilized symptoms <1 year after an ACS, or patients with recent revascularization

  (iv) asymptomatic and symptomatic patients >1 year after initial diagnosis or revascularization

  (v) patients with angina and suspected vasospastic or microvascular d/s

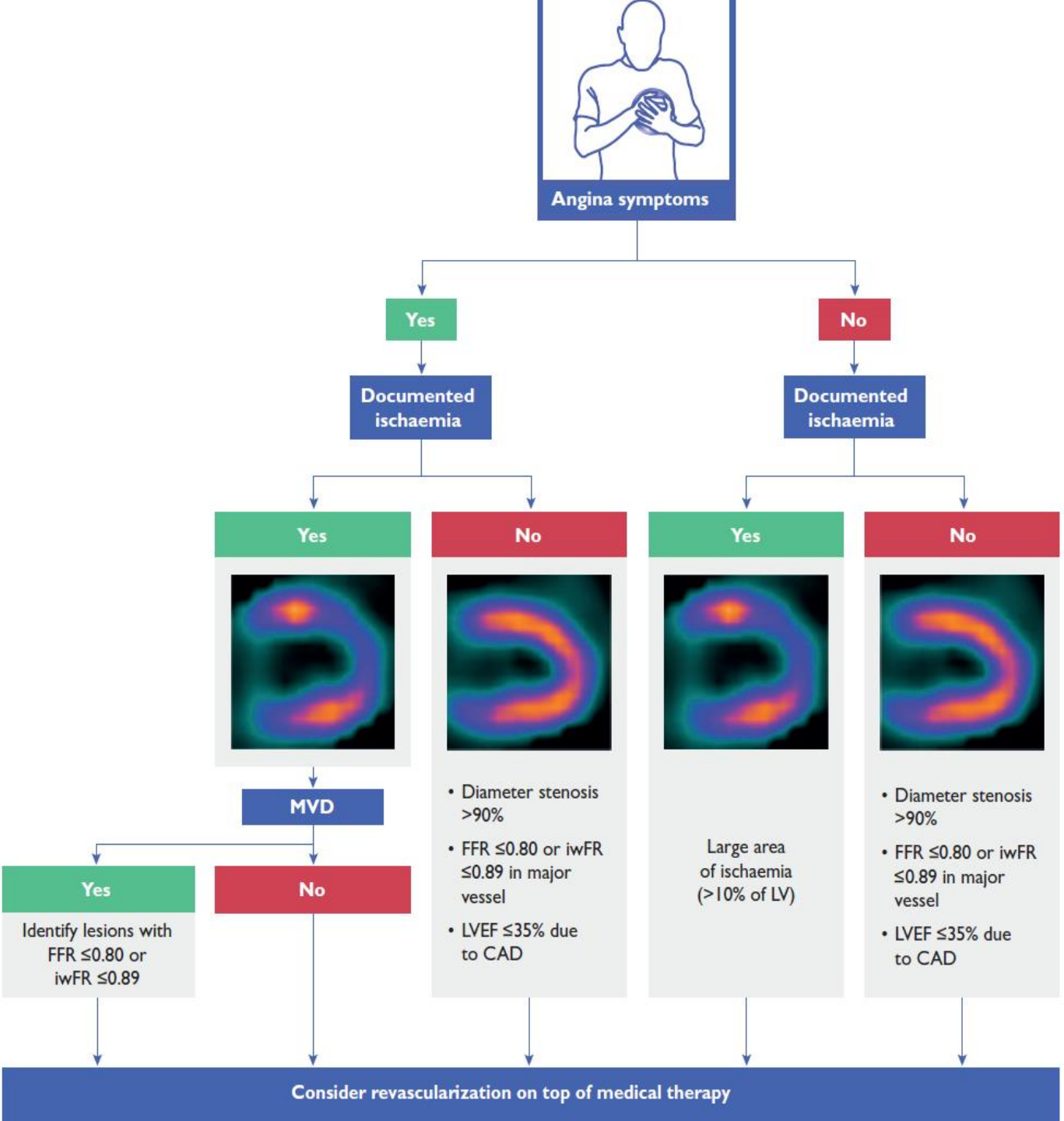
  (vi) asymptomatic subjects in whom CAD is detected at screening

Approach for the initial diagnostic management of patients with angina/Dyspnoea and suspected coronary artery disease



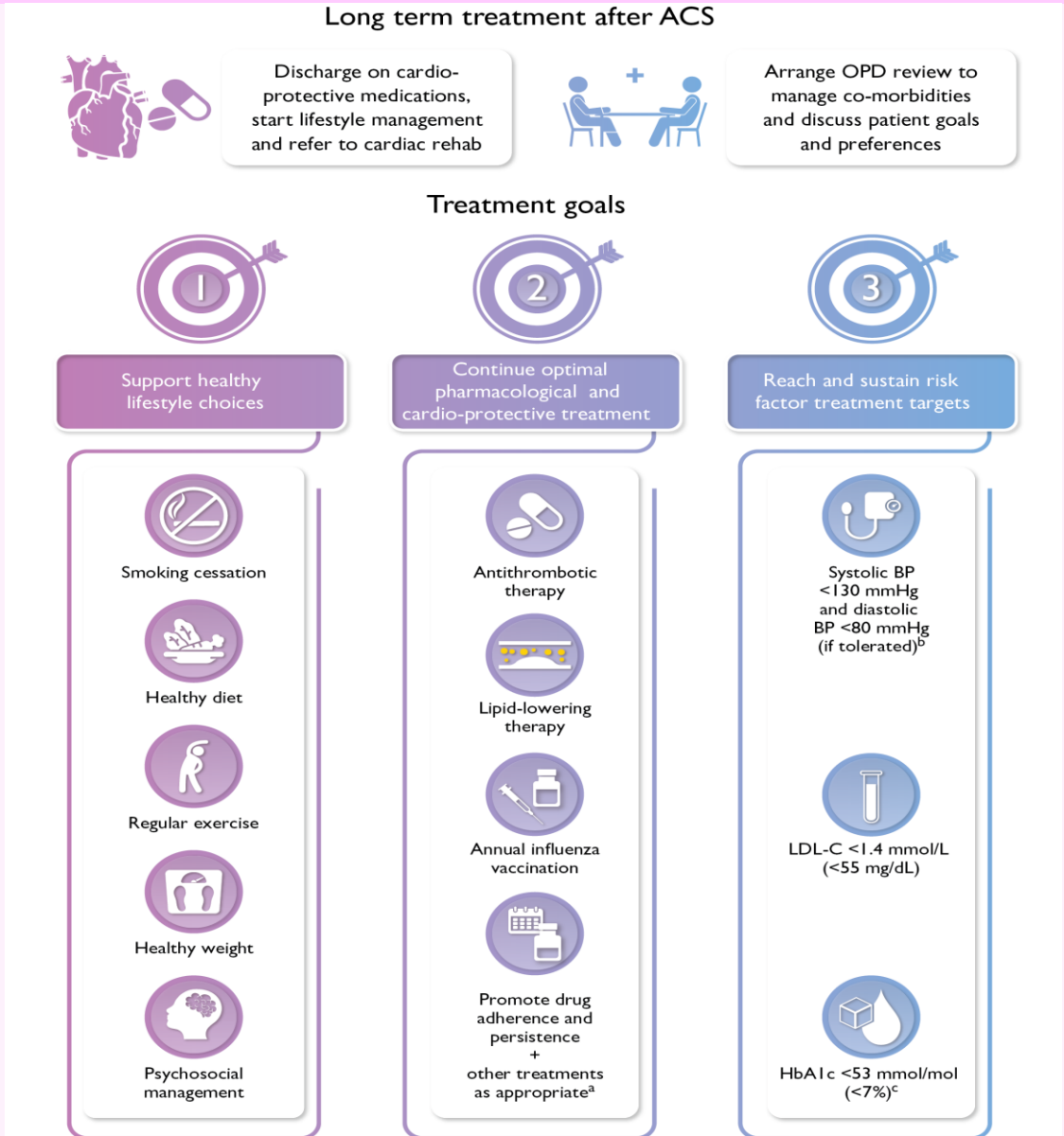
- **Functional non invasive test - stress CMR or stress echocardiography, SPECT, PET, myocardial contrast echocardiography, or contrast CMR.**
- **Anatomical non invasive test - coronary CTA**
- **Exercise ECG**

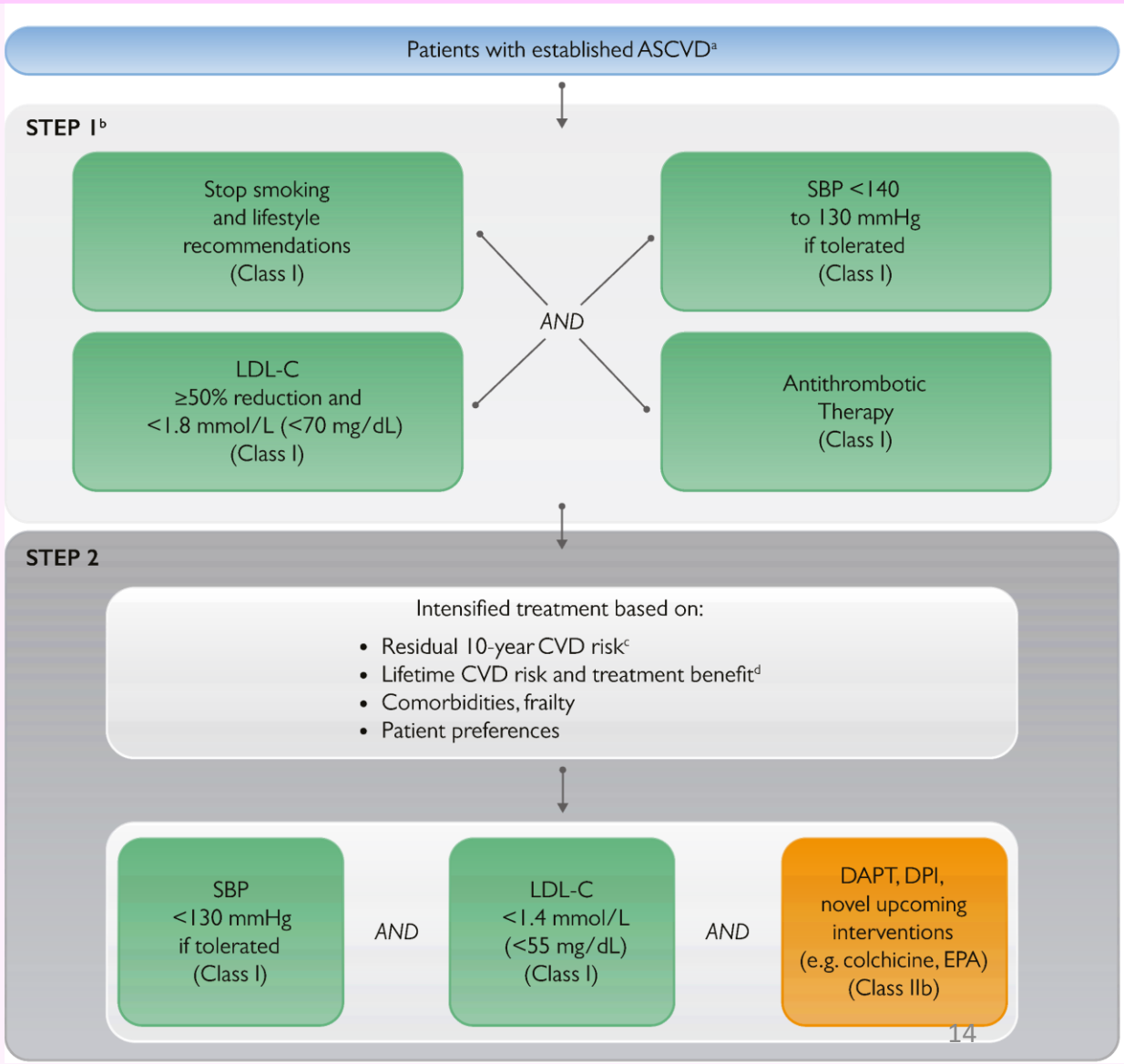
Decision tree for patients undergoing invasive coronary angiography



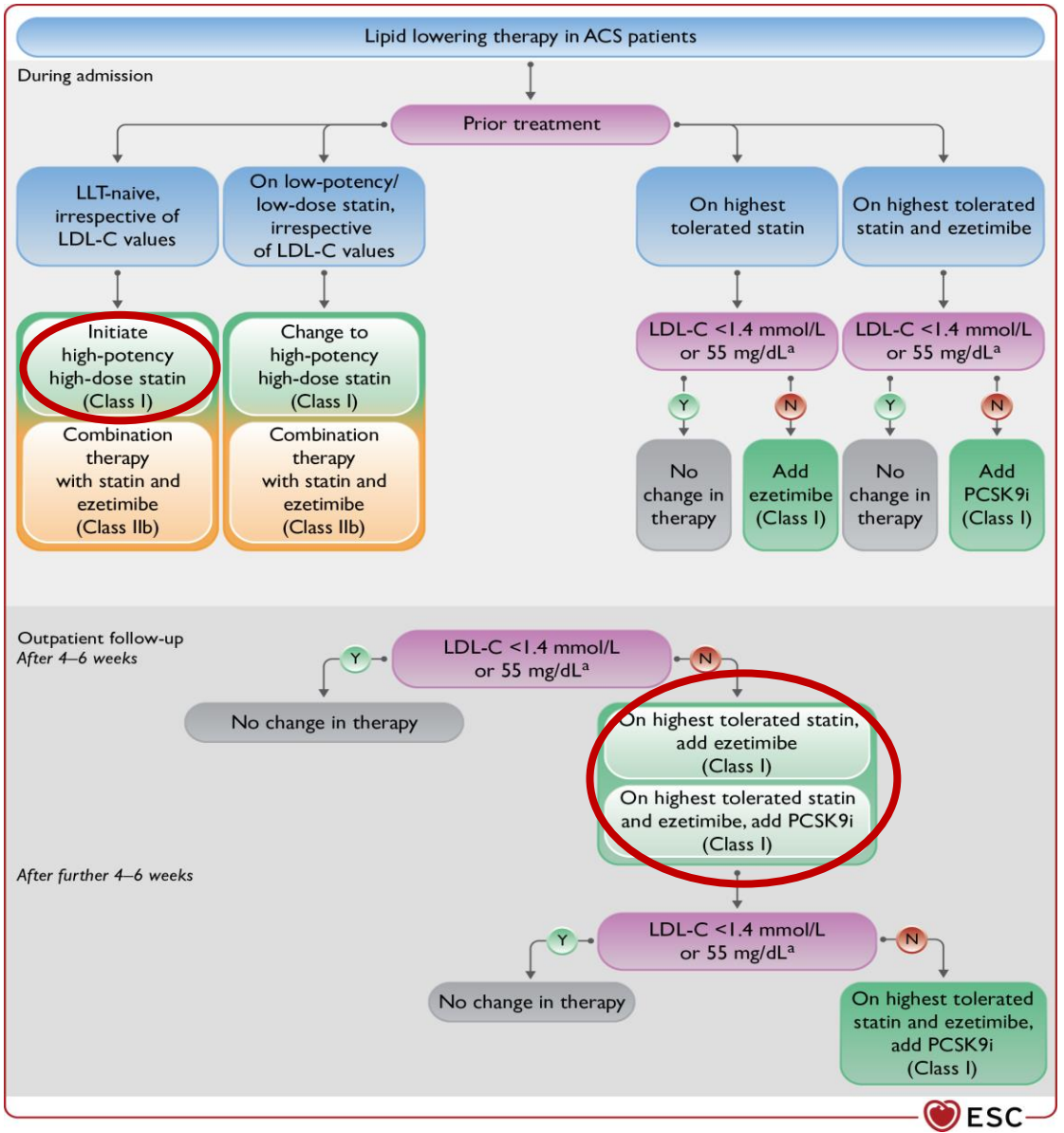
- Documented ischemia - Large area of ischemia (>10% of LV)
- Diameter stenosis >90%
- FFR ≤0.80 or iwFR ≤0.89 in major vessel
- LVEF ≤35% due to CAD

Long-term Management after ACS and in CCS

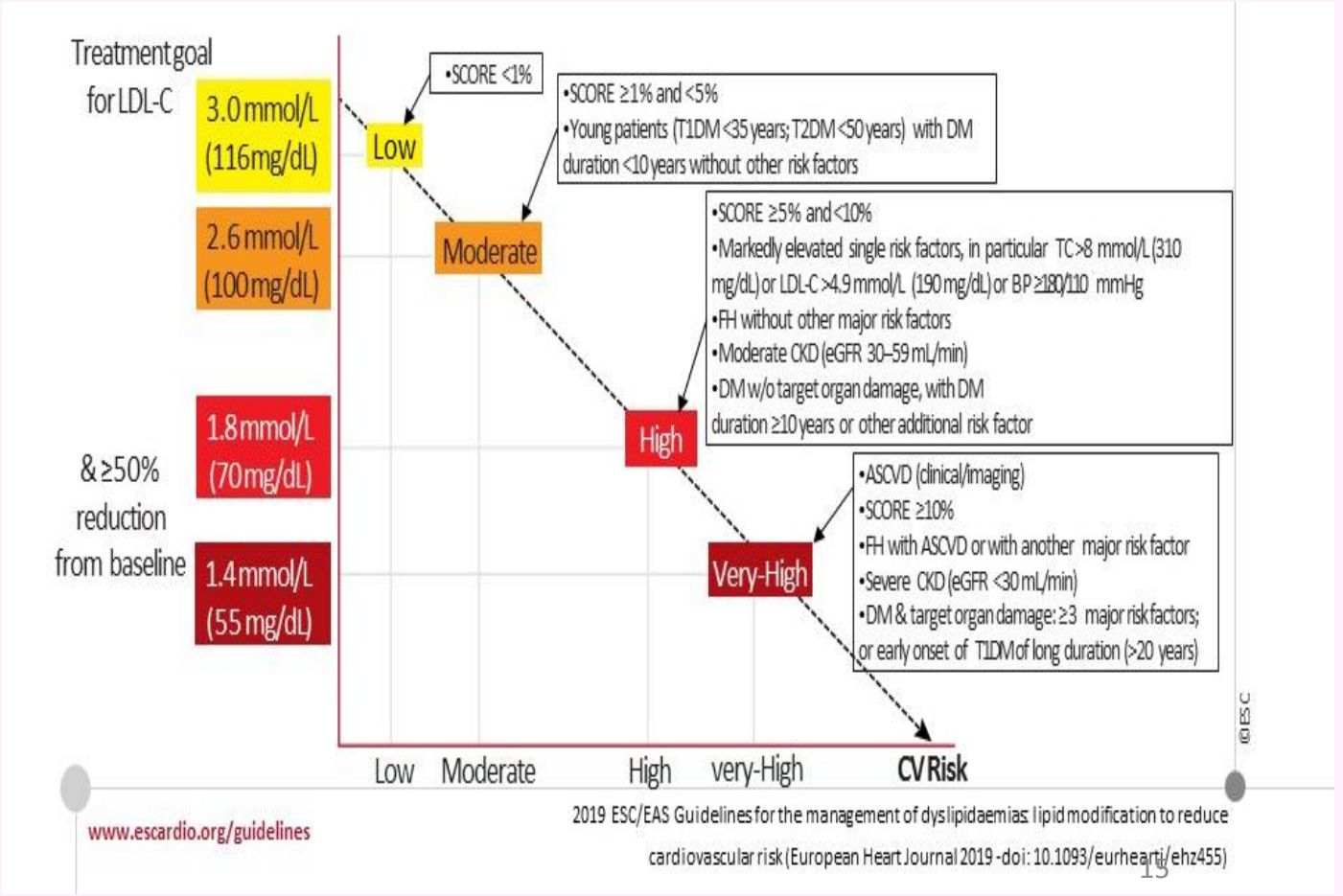




Lipid lowering therapy



Statins are recommended in all patients with CCS.[c] [341,342]	I	A
If a patient's goal[c] is not achieved with the maximum tolerated dose of statin, combination with ezetimibe is recommended.[317,320]	I	B
For patients at very high risk who do not achieve their goal[c] on a maximum tolerated dose of statin and ezetimibe, combination with a PCSK9 inhibitor is recommended.[320,323]	I	A



Recommendations of cardio-protective treatment for event prevention in ACS and CCS

Beta-blockers		
Beta-blockers are recommended in ACS patients with LVEF ≤40% regardless of HF symptoms.[801,870–872]	I	A
Routine beta-blockers for all ACS patients regardless of LVEF should be considered.[798,873–878]	IIa	B
RAAS system inhibitors		
Angiotensin-converting enzyme (ACE) inhibitors[d] are recommended in ACS patients with HF symptoms, LVEF ≤40%, diabetes, hypertension, and/or CKD.[195,813–817,879]	I	A
Mineralocorticoid receptor antagonists are recommended in ACS patients with an LVEF ≤40% and HF or diabetes.[826,880]	I	A
Routine ACE inhibitors for all ACS patients regardless of LVEF should be considered.[816,817]	IIa	A

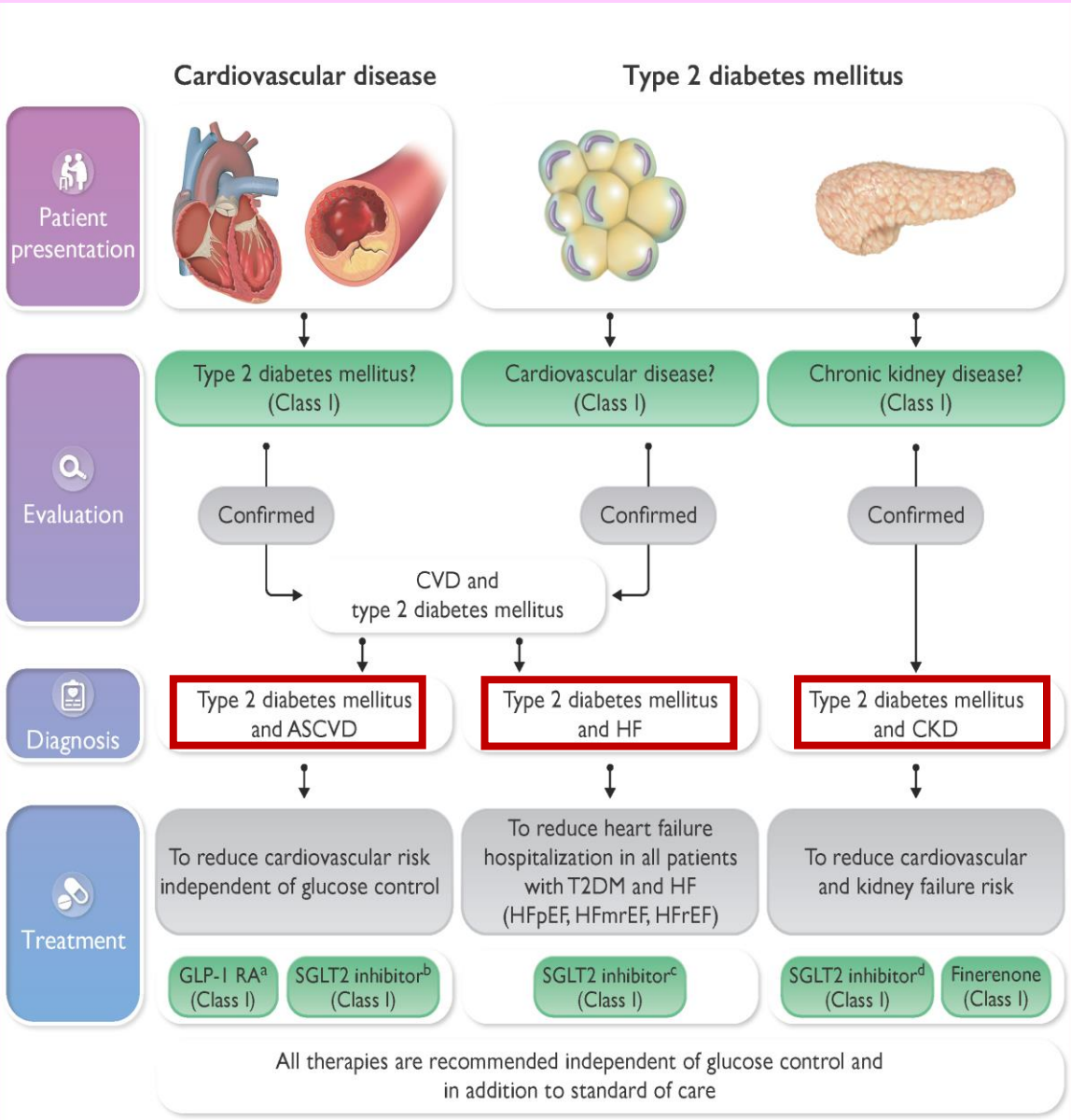
Other drugs		
Beta-blockers are recommended in patients with LV dysfunction or systolic HF.	I	A
In patients with a previous STEMI, long-term oral treatment with a beta-blocker should be considered.	IIa	B

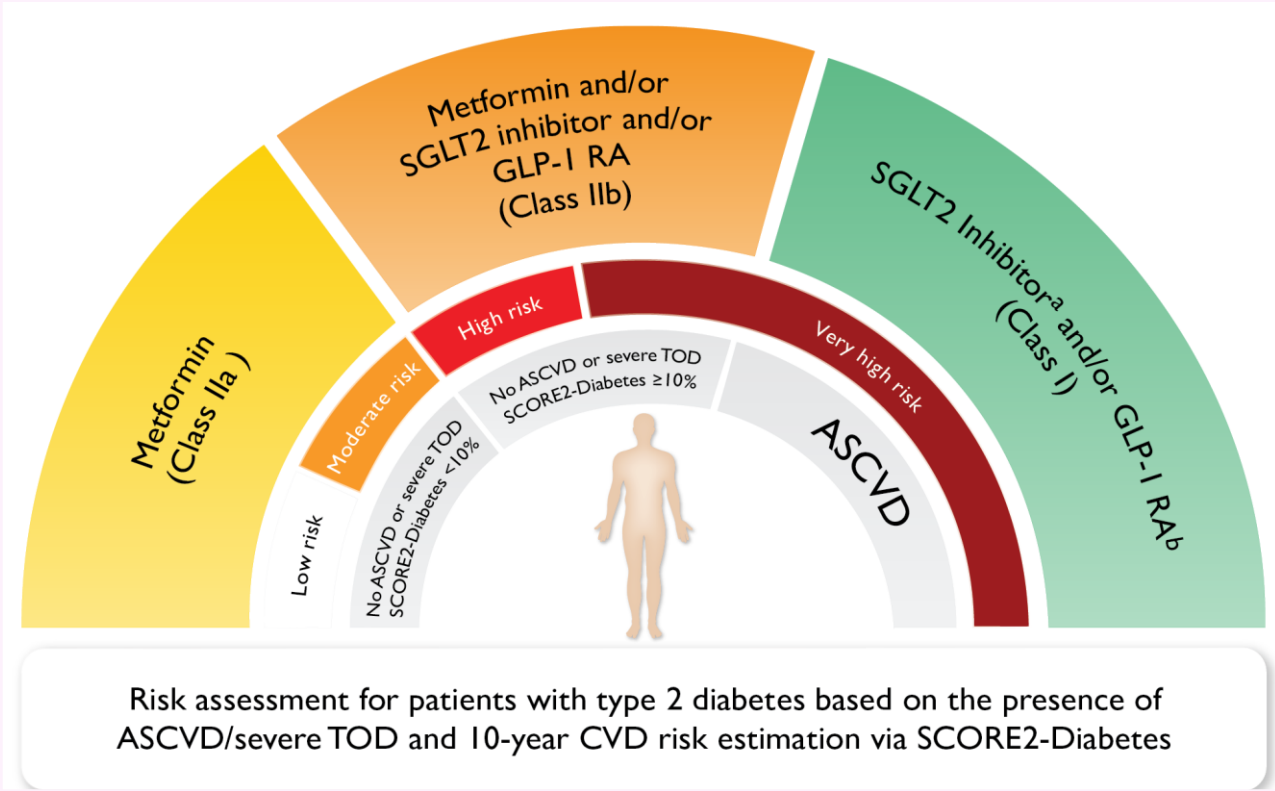
ACE inhibitors		
ACE inhibitors (or ARBs) are recommended if a patient has other conditions (e.g. heart failure, hypertension, or diabetes).	I	A
ACE inhibitors should be considered in CCS patients at very high risk of cardiovascular events.	IIa	A

Diabetes and CAD

- ACS patients with DM- more commonly present with non-specific symptoms → delays in both diagnosis and access to treatment
- Have more advanced CAD at diagnosis and worse long-term prognosis
- All patients with ACS, regardless of a history of DM, should have their glycemic status evaluated during hospitalization
- Recent trial evidence shown that reduction in the risk of new ACS events, HF, and renal impairment with SGLT2 inhibitors and GLP-1-RA - independent of baseline HbA1c levels

Management of CAD in DM





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

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

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

Glucose lowering treatment in DM with CAD based on evidence

To reduce CV risk independent of glucose control[a]

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

↓

For additional glucose control

Glucose-lowering agents with suggested CV benefit

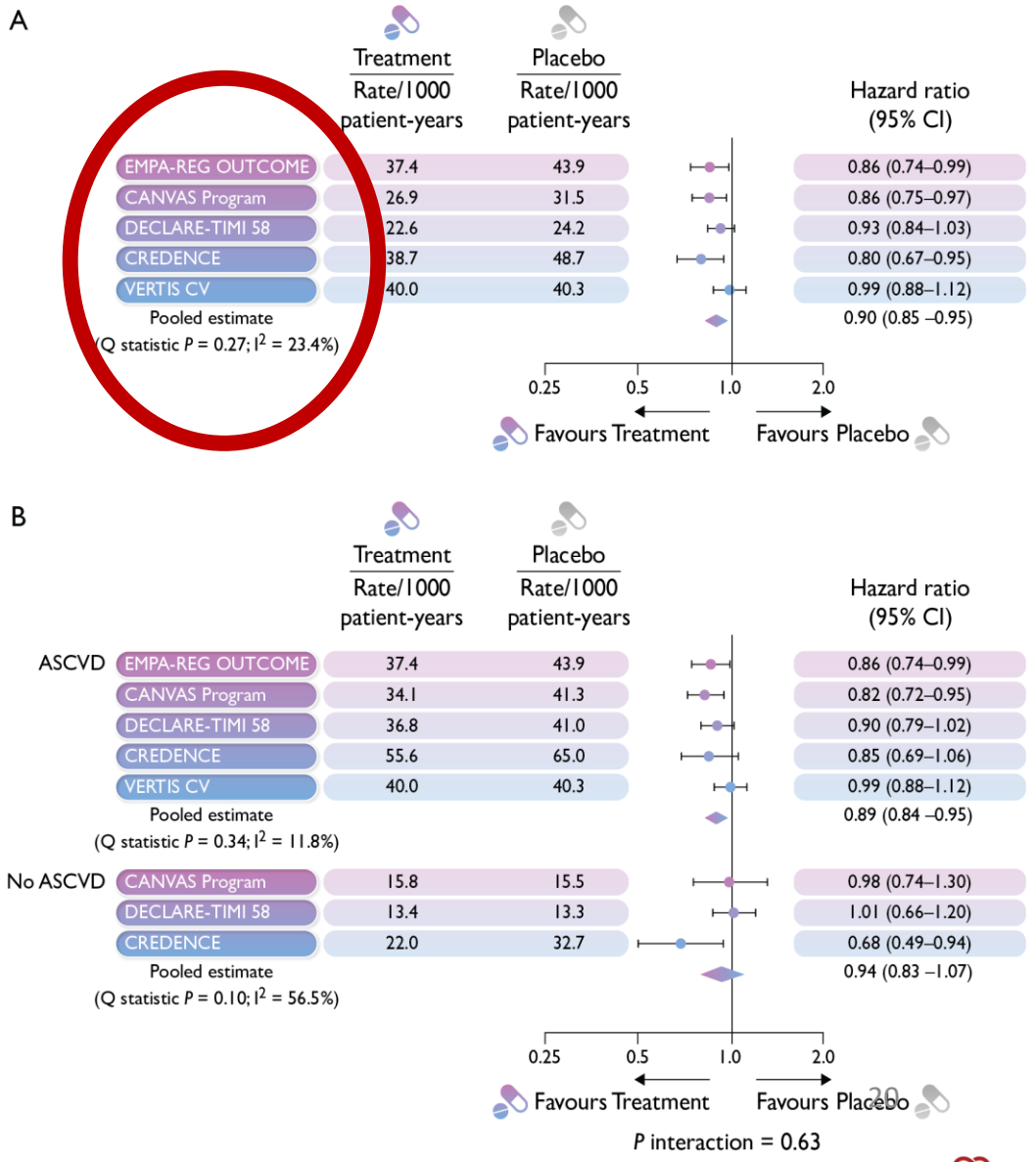
- Metformin (Class IIa)
- Pioglitazone[d] (Class IIb)

Glucose-lowering agents with proven CV safety

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

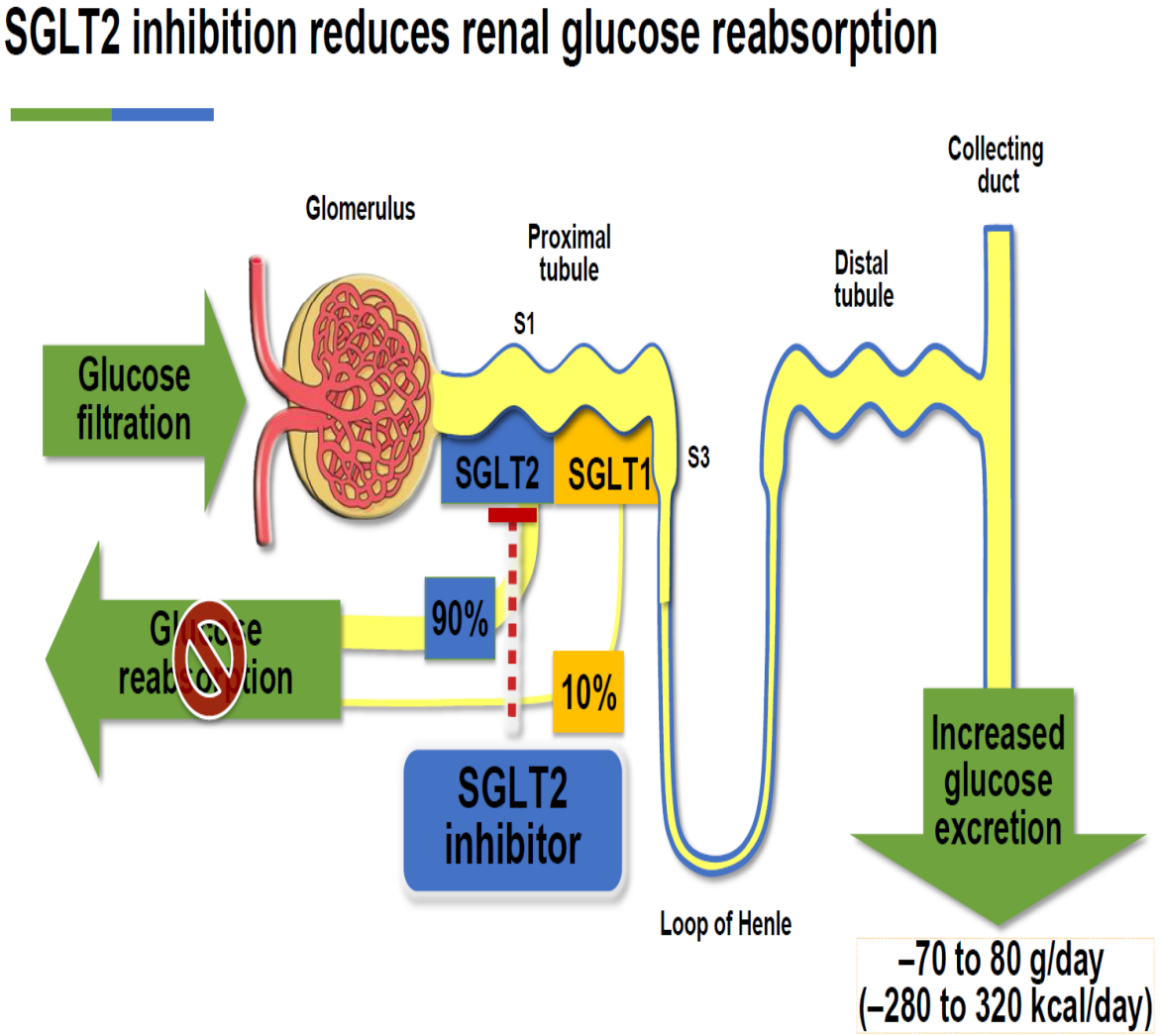
Glucose-lowering agents without CV safety evaluation

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



Evidence of SGLT-2 inhibitors in Mx of CAD

- SGLT2 is the glucose transporter, reabsorbs approximately 90% of glucose in the proximal tubule
- Little glucose excreted in the urine through sodium glucose co-transporters (SGLTs)
- Type 2 diabetes - dysregulation of glucose homeostasis
- SGLT2 is a therapeutic target for the management of type 2 diabetes



SGLT1, sodium-glucose cotransporter 1; SGLT2, sodium-glucose cotransporter 2.
Wright EM. *Am J Physiol Renal Physiol* 2001;280:F10-F18. Lee YJ et al. *Kidney Int Suppl* 2007;106:S27-S35.
Han S et al. *Diabetes* 2008;57:1723-1729. Inzucchi SE et al. *Diabetes Care* 2015;38:140-149.

Various types of SGLTs

Transporter	Substrate	Distribution
SGLT1	Glucose, galactose	Intestine, trachea, kidney, heart, brain, testis, and prostate
SGLT2	Glucose Galactose	Kidney, brain, liver, thyroid, muscle, and heart
SGLT4	Glucose and mannose	Intestine, kidney, liver, brain, lung, trachea, uterus, and pancreas
SGLT5	Not known	Kidney
SGLT6	Myo-inositol, glucose	Brain, kidney, and intestine
SMIT1	Myo-inositol, glucose	Brain, heart, kidney, and lung

The definitions of balanitis, dysuria, hyperhidrosis, myo-inositol, and nocturia can be found in the glossary.

- **Two types of SGLTs, SGLT1 and SGLT2, important for the reabsorption of filtered glucose from the kidney with different functions**

SGLT2 vs SGLT1

SGLT2

- **High-capacity transporter, but low affinity for glucose.**
- **One molecule of glucose is co-transported for each Na^+ ion.**
- **About 90% of renal glucose reabsorption is carried out by SGLT2 in first segment of the proximal tubule.**
- **Major transporter of glucose in the kidney.**

SGLT1

- **Low-capacity transporter, but high affinity for glucose.**
- **One molecule of glucose is co-transported for 2 Na^+ ions.**
- **About 10% of renal glucose reabsorption is carried out by SGLT1 located in the third segment of the proximal tubule.**
- **Major transporter of glucose in the intestines.**

SGLT2 inhibitors

MOA of SGLT2 inhibition:

- SGLT2 inhibitors block transport of glucose by SGLT2 competing with glucose for binding sites
- They reduce the T_{max} of glucose reabsorption in the proximal tubule, leading to urinary glucose excretion at a lower threshold concentration

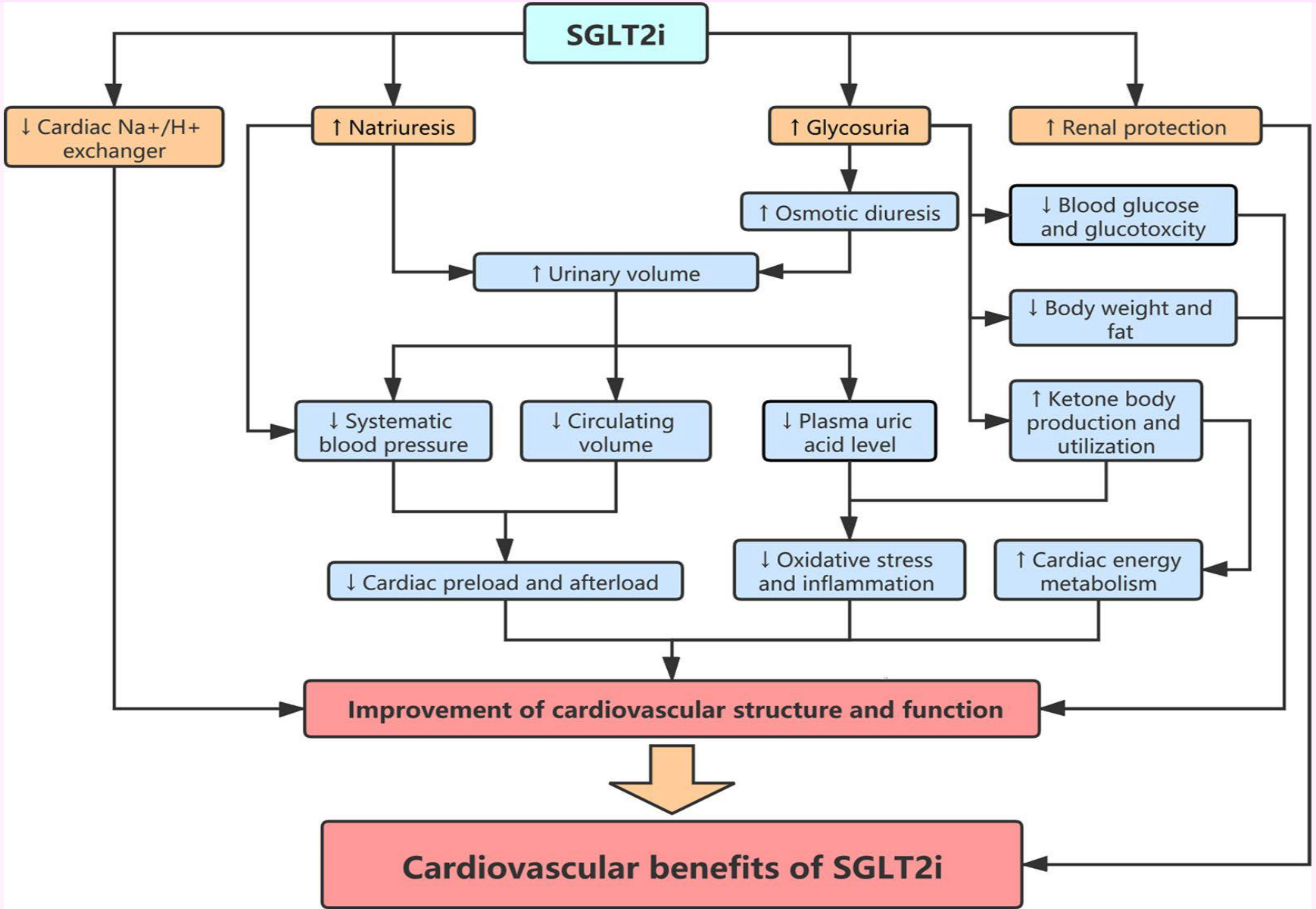
Potential benefits of SGLT2 inhibitors:

- Lowers plasma glucose
- Weight loss
- Improves β-cell function and insulin resistance
- Lowers blood pressure

Cardiovascular protection mechanisms of SGLT2 inhibitors

- Multiple direct & indirect mechanisms
- Improve many aspects : hemodynamics, metabolism, oxidative stress & inflammation
- Cardiovascular benefits are not related to anti-hyperglycemic effect of SGLT2i.

Cardiovascular protection mechanisms of SGLT2 inhibitors



Cardiovascular benefits

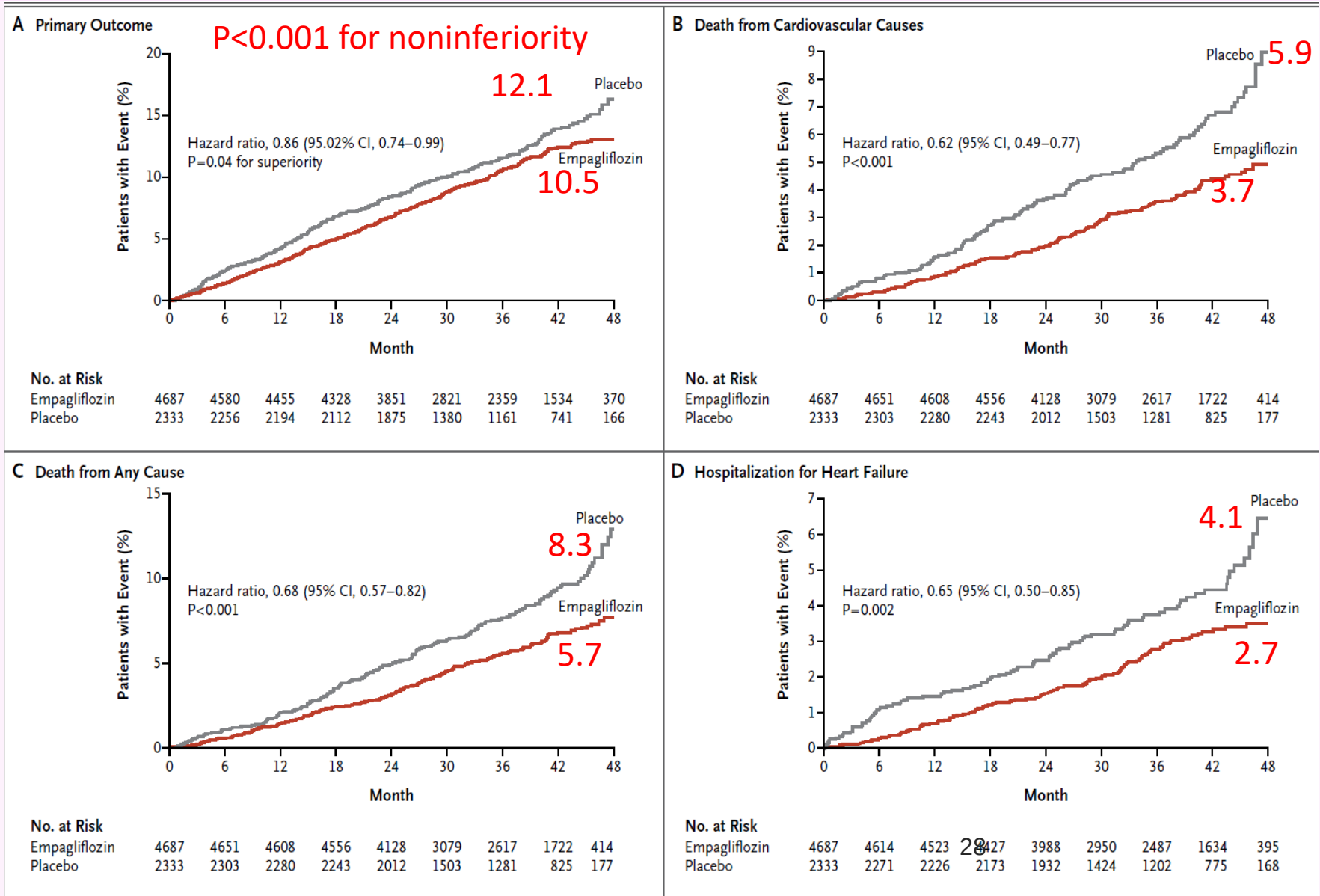
- Glycemic control & attenuation of glucotoxicity
- Natriuresis, diuresis & reduction in plasma volume
- Reduction in BP
- Amelioration of endothelial dysfunction & vascular stiffness
- Improvement of cardiac energy metabolism
- Inhibition of cardiac Na+/H+ (attenuation of cardiac remodeling & fibrosis)
- Improvements in cardiac structure & function
- Attenuation of inflammation
- Reduction in serum uric acid level

Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes EMPA REG OUTCOME

Pt with type 2 DM at high risk for CV events (7020)– randomized 1:1:1 fashion to Empagliflozin 10mg/25mg/Placebo
Followed up – 3.1 yrs
590sites/42 countries

Primary composite outcome - Death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke

Key secondary composite outcome - Primary outcome plus hospitalization for unstable angina



EMPA-REG OUTCOME: Summary

Patients with type 2 diabetes at high risk for cardiovascular events who received empagliflozin, as compared with placebo, had a lower rate of the primary composite cardiovascular outcome and of death from any cause when the study drug was added to standard care

14%

↓ 3P-MACE

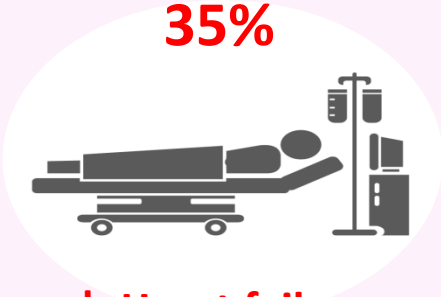
38%

↓ CV death

32%

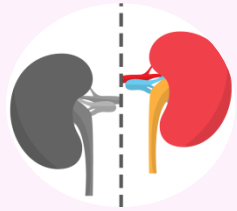
↓ All-cause mortality

35%



↓ Heart failure hospitalisations

39%



↓ Incident or worsening nephropathy

The overall safety profile of empagliflozin was consistent with previous clinical trials and current label information

Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes (CANVAS Program)

- Integrated data from two trials

-Total of 10,142 participants with type 2 diabetes and high cardiovascular risk

-Randomly assigned to receive canagliflozin or placebo

- Followed up for 188.2 weeks

- Primary outcome - composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke

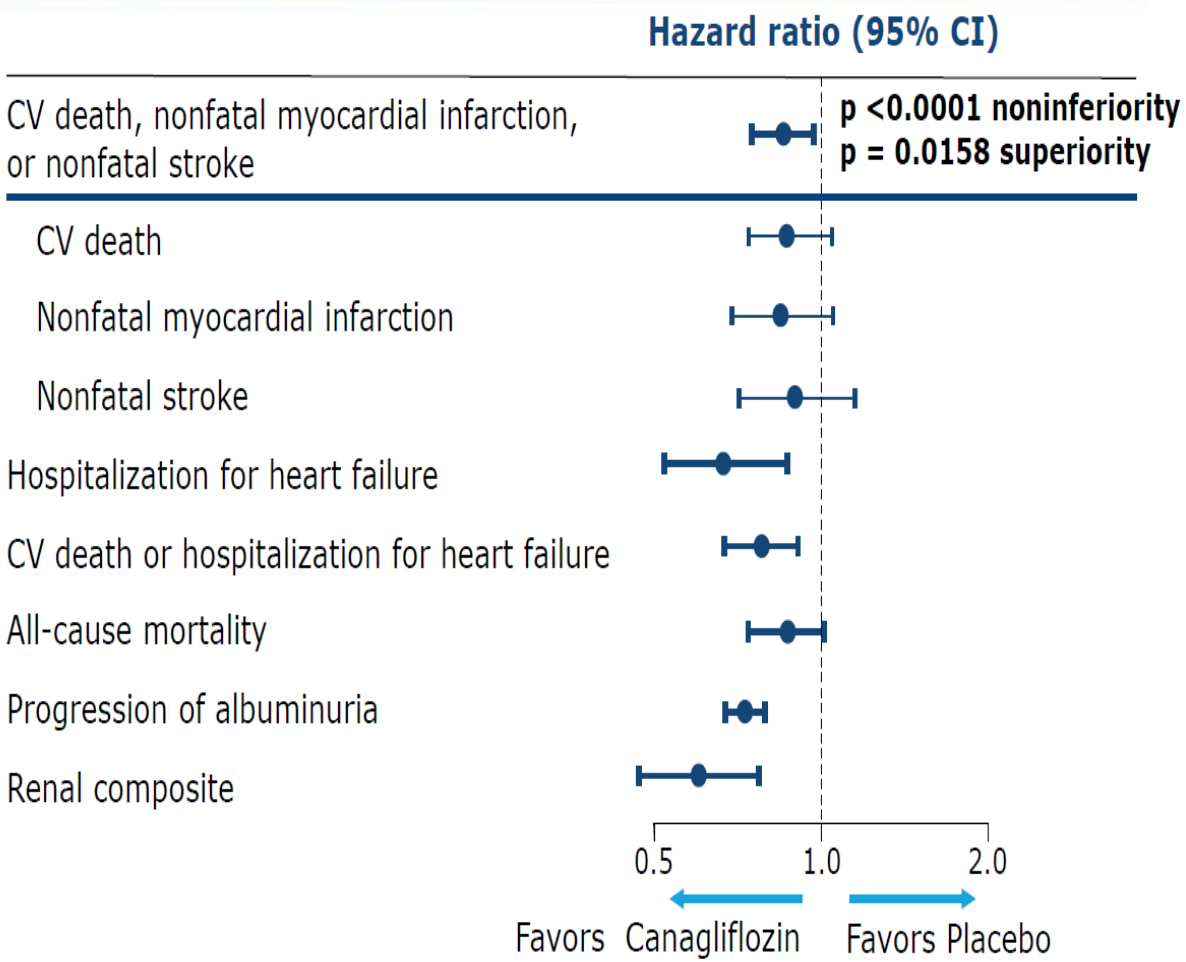
- Rate of the primary outcome was lower with canagliflozin than with placebo (occurring in 26.9 vs. 31.5, $P<0.001$ for noninferiority; $P=0.02$ for superiority).

-Possible benefit of progression of albuminuria and composite outcome of a sustained 40% reduction in the estimated glomerular filtration rate, the need for renal-replacement therapy, or death from renal causes

-Increased risk of amputation primarily at the level of the toe or metatarsal.

Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes (CANVAS Program)

Key Efficacy Outcomes in the CANVAS Program

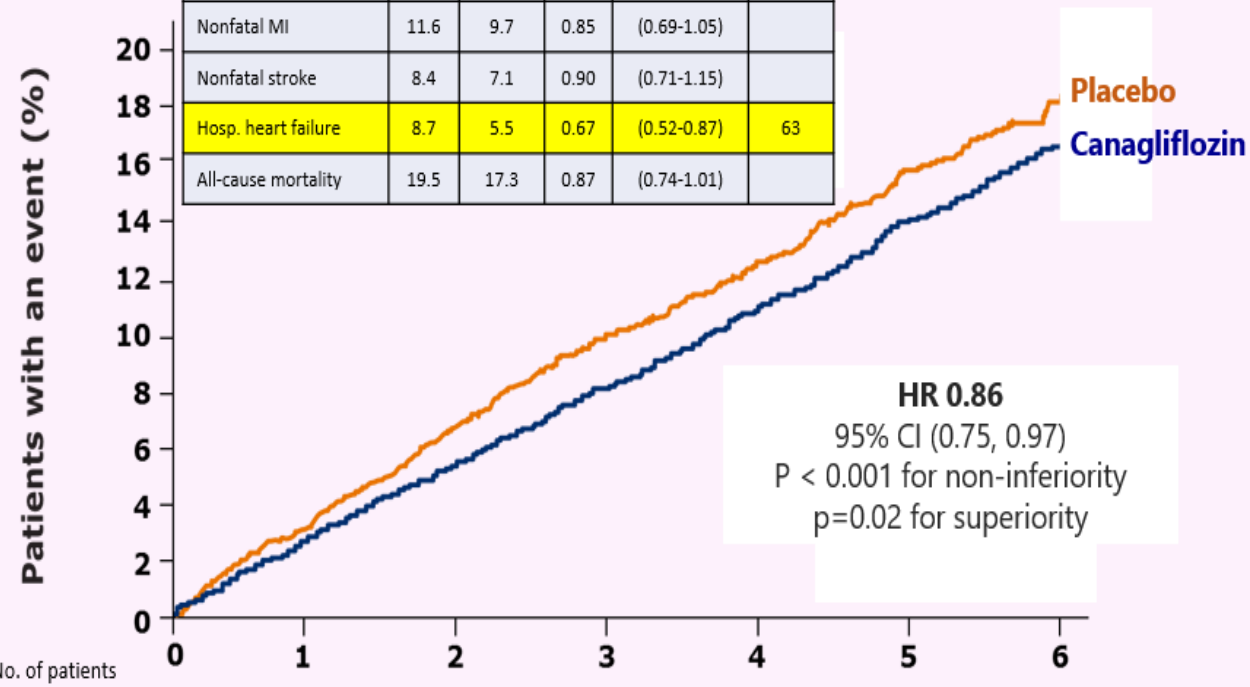


2018 Diabetes Canada CPG – Chapter 23. Cardiovascular Protection in People with Diabetes

Canagliflozin reduced CV events

CV death, non-fatal MI, or non-fatal stroke

Outcome (per 1000 pt-y)	PBO	CANA	HR	P or 95% CI	NNT 5
CV death, MI, stroke	31.5	26.9	0.86	0.02	44
CV deaths	12.8	11.6	0.87	(0.72-1.06)	
Nonfatal MI	11.6	9.7	0.85	(0.69-1.05)	
Nonfatal stroke	8.4	7.1	0.90	(0.71-1.15)	
Hosp. heart failure	8.7	5.5	0.67	(0.52-0.87)	63
All-cause mortality	19.5	17.3	0.87	(0.74-1.01)	



No. of patients							
Canagliflozin	5795	5566	4343	2555	2460	2363	1661
Placebo	4347	4153	2942	1240	1187	1120	789

Neal B et al. N Engl J Med 2017; DOI:10.1056/NEJMoa1611925

Dapagliflozin and Cardiovascular Outcomes in Type 2 DM patients DECLARE – TIMI 58

- 17160 patients with type 2 diabetes with established CV Disease (6974) or Multiple Risk Factors (10186), receive either dapagliflozin 10 mg or placebo, follow up – 4.2 years, 882 sites in 33 countries

- Primary safety outcome - composite of major adverse cardiovascular events (MACE), defined as cardiovascular death, myocardial infarction, or ischemic stroke

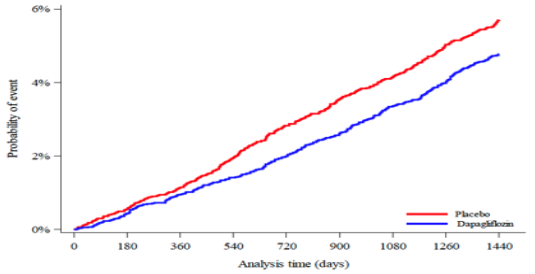
- Primary efficacy outcomes - MACE and a composite of cardiovascular death or hospitalization for heart failure

- Secondary efficacy outcomes - Renal composite (≥40% decrease in estimated GFR to <60, new end-stage renal disease, or death from renal or cardiovascular causes) and death from any cause

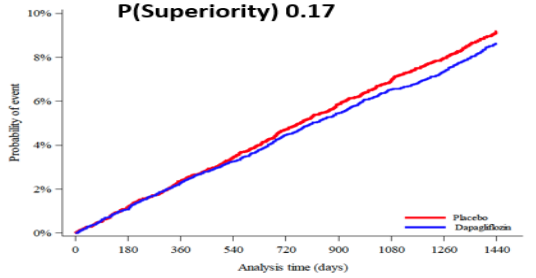
Dapagliflozin and Cardiovascular Outcomes in Type 2 DM patients DECLARE – TIMI 58

Primary Endpoints

CVD/HHF
4.9% vs 5.8%
HR 0.83 (0.73-0.95)
P(Superiority) 0.005



MACE
8.8% vs 9.4%
HR 0.93 (0.84-1.03)
P(Noninferiority) <0.001
P(Superiority) 0.17



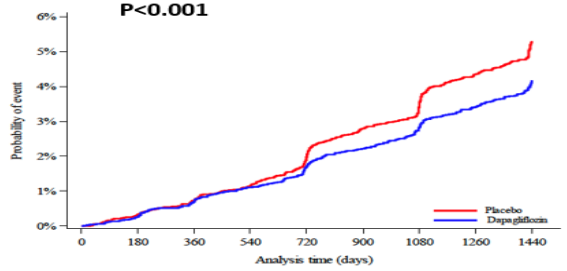
BRIGHAM AND WOMEN'S HOSPITAL — HARVARD MEDICAL SCHOOL TEACHING HOSPITAL

Significantly lower rate of cardiovascular death and hospitalization for heart failure than placebo but did not result in a significantly lower rate of MACE

Dapagliflozin was noninferior to placebo with respect to the composite safety outcome of cardiovascular death, myocardial infarction, or ischemic stroke (MACE)

Secondary Endpoints

1st Renal Composite EP
40%↓ eGFR, ESRD, Renal or CV death
4.3% vs. 5.6%
HR 0.76 (0.67-0.87)
P<0.001



All-Cause Mortality
6.2% vs 6.6%
HR 0.93 (0.82-1.04)
P=0.20

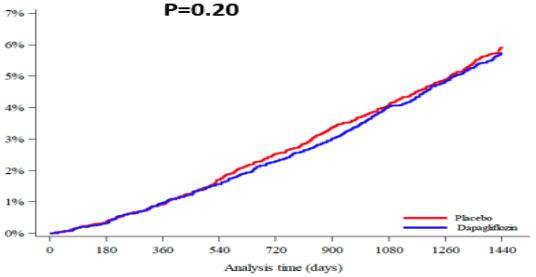


Table 2. Safety Events.*

Event	Dapagliflozin (N=8574)	Placebo (N=8569)	Hazard Ratio (95% CI)	P Value
	no. (%)			
Serious adverse event	2925 (34.1)	3100 (36.2)	0.91 (0.87–0.96)	<0.001
Adverse event leading to discontinuation of trial regimen	693 (8.1)	592 (6.9)	1.15 (1.03–1.28)	0.01
Major hypoglycemic event	58 (0.7)	83 (1.0)	0.68 (0.49–0.95)	0.02
Diabetic ketoacidosis	27 (0.3)	12 (0.1)	2.18 (1.10–4.30)	0.02
Amputation	123 (1.4)	113 (1.3)	1.09 (0.84–1.40)	0.53
Fracture	457 (5.3)	440 (5.1)	1.04 (0.91–1.18)	0.59
Symptoms of volume depletion	213 (2.5)	207 (2.4)	1.00 (0.83–1.21)	0.99
Acute kidney injury	125 (1.5)	175 (2.0)	0.69 (0.55–0.87)	0.002
Genital infection	76 (0.9)	9 (0.1)	8.36 (4.19–16.68)	<0.001
Urinary tract infection	127 (1.5)	133 (1.6)	0.93 (0.73–1.18)	0.54
Cancer	481 (5.6)	486 (5.7)	0.99 (0.87–1.12)	0.83
Bladder cancer	26 (0.3)	45 (0.5)	0.57 (0.35–0.93)	0.02
Breast cancer	36 (0.4)	35 (0.4)	1.02 (0.64–1.63)	0.92
Hypersensitivity	32 (0.4)	36 (0.4)	0.87 (0.54–1.40)	0.57
Hepatic event	82 (1.0)	87 (1.0)	0.92 (0.68–1.25)	0.60

Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE Trial)

Objectives

In people with T2DM, eGFR 30 to 90 mL/min/1.73 m^2, and UACR 300 to 5000 mg/g who are receiving standard of care including a maximum tolerated dose of an ACEi or ARB, to assess whether canagliflozin compared with placebo reduces

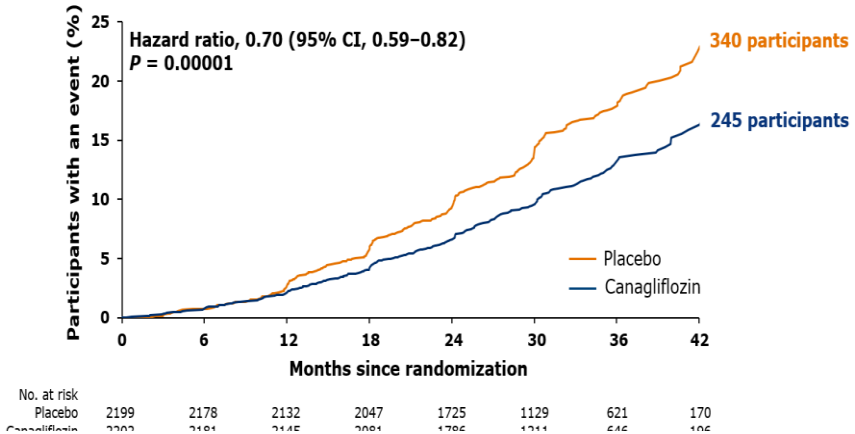
Primary:

- Composite outcome of ESKD, doubling of serum creatinine, or renal or CV death

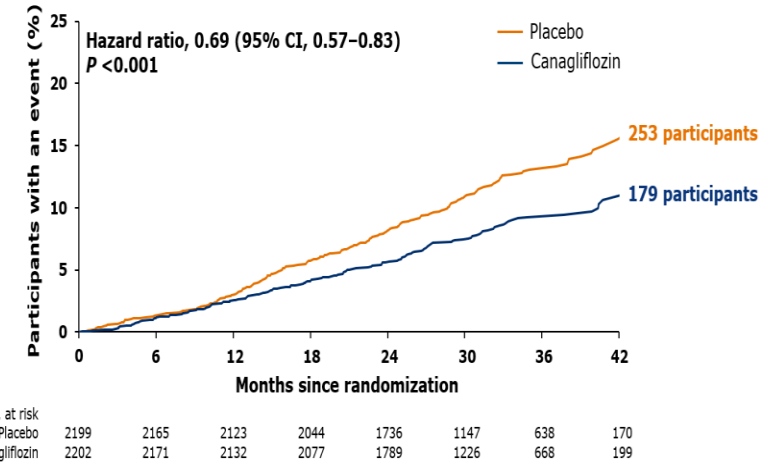
Secondary:

- CV death or hospitalization for heart failure
- Major cardiovascular events (3-point MACE: CV death, MI, or stroke)
- Hospitalization for heart failure
- ESKD, doubling of serum creatinine, or renal death
- CV death
- All-cause mortality
- CV death, MI, stroke, hospitalization for heart failure, or hospitalization for unstable angina

Primary Outcome: ESKD, Doubling of Serum Creatinine, or Renal or CV Death



CV Death or Hospitalization for Heart Failure



Summary

Primary	Hazard ratio (95% CI)	*P* value	
1. ESKD, doubling of serum creatinine, or renal or CV death	0.70 (0.59–0.82)	0.00001	✔
Secondary			
2. CV death or hospitalization for heart failure	0.69 (0.57–0.83)	<0.001	✔
3. CV death, MI, or stroke	0.80 (0.67–0.95)	0.01	✔
4. Hospitalization for heart failure	0.61 (0.47–0.80)	<0.001	✔
5. ESKD, doubling of serum creatinine, or renal death	0.66 (0.53–0.81)	<0.001	✔
6. CV death	0.78 (0.61–1.00)	0.0502	Not significant
7. All-cause mortality	0.83 (0.68–1.02)	–	Not formally tested
8. CV death, MI, stroke, hospitalization for heart failure, or hospitalization for unstable angina	0.74 (0.63–0.86)	–	Not formally tested

CREDENCE

The VERTIS CV Trial
Cardiovascular Outcomes Following Ertugliflozin Treatment in Patients with Type 2 Diabetes Mellitus and Atherosclerotic Cardiovascular Disease

Study design

Multicenter, randomized, double-blind, placebo-controlled, event-driven trial

Randomization 1:1:1

Placebo | Ertugliflozin 5 mg | Ertugliflozin 15 mg

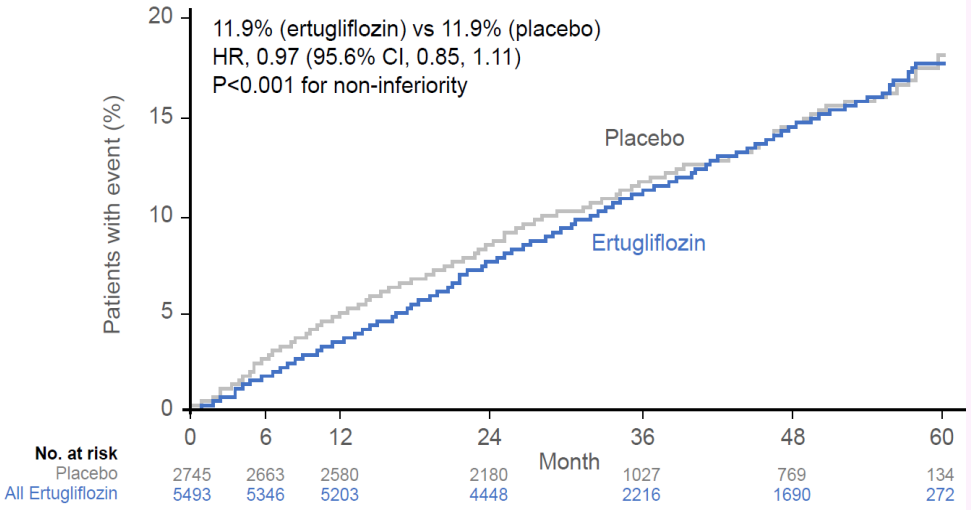
Primary endpoint (non-inferiority):
- Composite outcome of MACE (CV death, nonfatal MI, nonfatal stroke)

Secondary endpoints (superiority):
- Composite outcome of CV death/HHF
- CV death
- Renal composite (renal death, dialysis/transplant, doubling of serum creatinine)

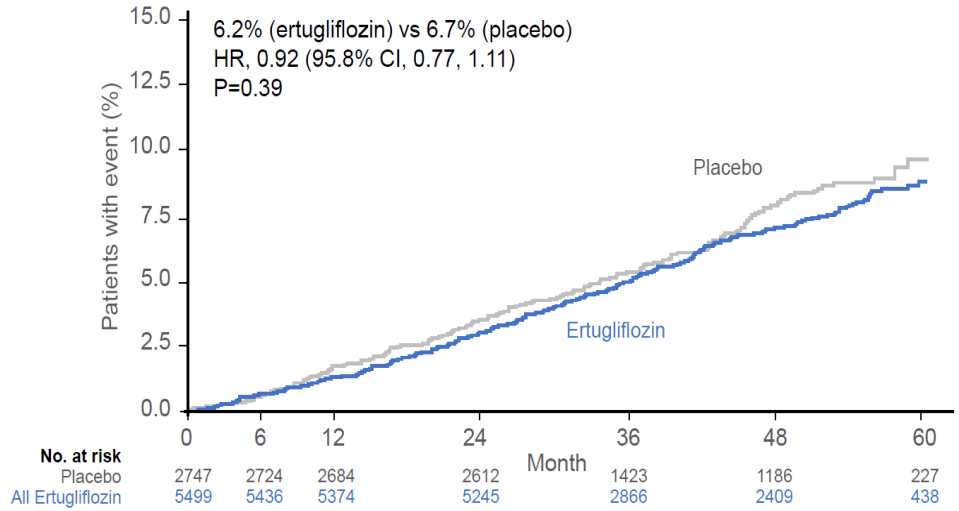
Other prespecified endpoints:
- Individual components of MACE
- Composite of MACE-plus (MACE plus hospitalization for unstable angina)
- Fatal or nonfatal MI
- Fatal or nonfatal stroke
- HHF
- All-cause mortality

Primary outcome: MACE*

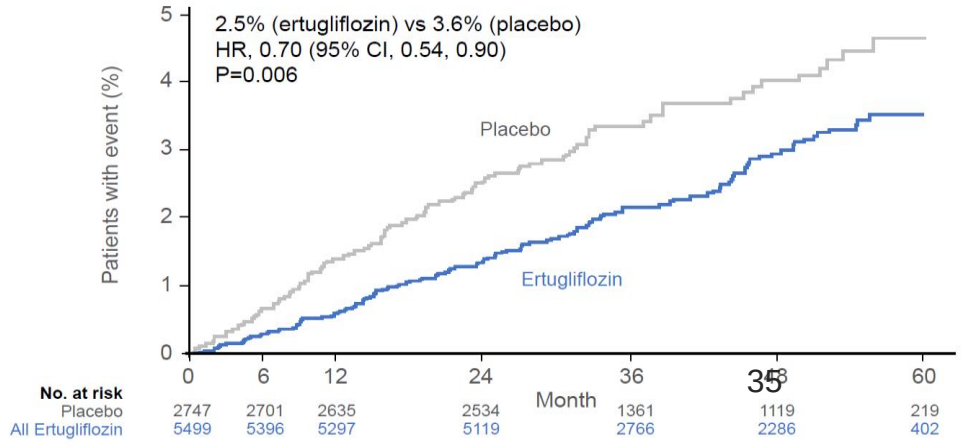
CV death, nonfatal MI, or nonfatal stroke



CV death*



HHF*



SGLT2 Inhibitors, Cardiovascular and Renal Outcomes in Patients with Type 2 Diabetes

Systematic Review and Meta-analysis

Studies included

- All analyses were primarily conducted on the total patient population of each of the 6 trials identified:
  - EMPA-REG OUTCOME[1]
  - CANVAS Trials Program[2]
    - CANVAS
    - CANVAS-R
  - DECLARE-TIMI 58[3]
  - CREDENCE[4]
  - VERTIS CV

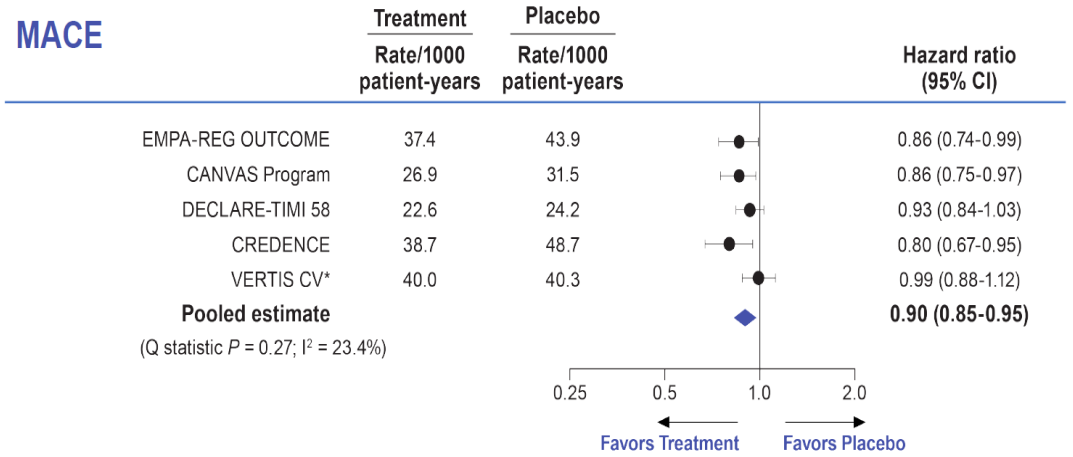
Baseline characteristics of patient populations by trial

	EMPA-REG OUTCOME[1]	CANVAS Program[2]	DECLARE-TIMI 58[3]	CREDENCE[4]	VERTIS CV
SGLT2 inhibitor	Empagliflozin	Canagliflozin	Dapagliflozin	Canagliflozin	Ertugliflozin
N	7020	10,142	17,160	4401	8246
Duration of follow-up, median, years	3.1	2.4	4.2	2.6	3.0
Age, mean ± SD, years	63.1 ± 8.6	63.3 ± 8.3	63.9 ± 6.8	63.0 ± 9.2	64.4 ± 8.1
Female, %	28.5	35.8	37.4	33.9	30.0
HbA1c, mean ± SD, %	8.1 ± 0.8	8.2 ± 0.9	8.3 ± 1.2	8.3 ± 1.3	8.2 ± 1.0
Diabetes duration, mean ± SD, years	NA	13.5 ± 7.8	11.8 ± 7.8	15.8 ± 8.6	13.0 ± 8.3
Established CV disease, %	100	65.6	40.6	50.4	100
History of HF, %	10.1	14.4	10.0	14.8	23.7
Reduced kidney function (eGFR <60 mL/min/1.73 m^2), %	25.9	20.1	7.4	59.8	21.9

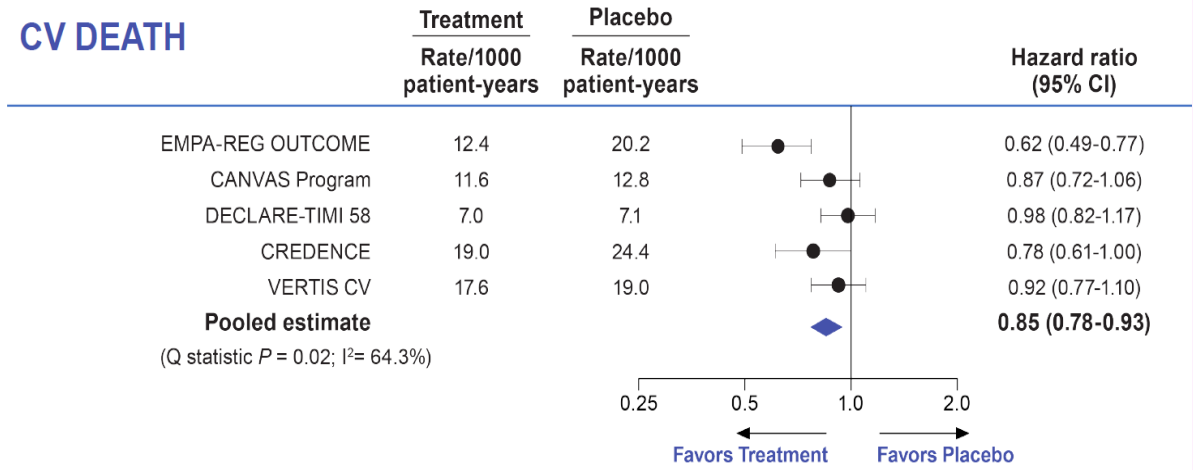
CV, cardiovascular; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; HF, heart failure; NA, not available; SD, standard deviation.

1. Zinman B et al. *N Engl J Med* 2015;373:2117-2128. 2. Neal B et al. *N Engl J Med* 2017;377:644-657. 3. Wiviott SD et al. *N Engl J Med* 2019;380:347-357. 4. Perkovic V et al. *N Engl J Med* 2019; 380:2295-306.

Time to first MACE



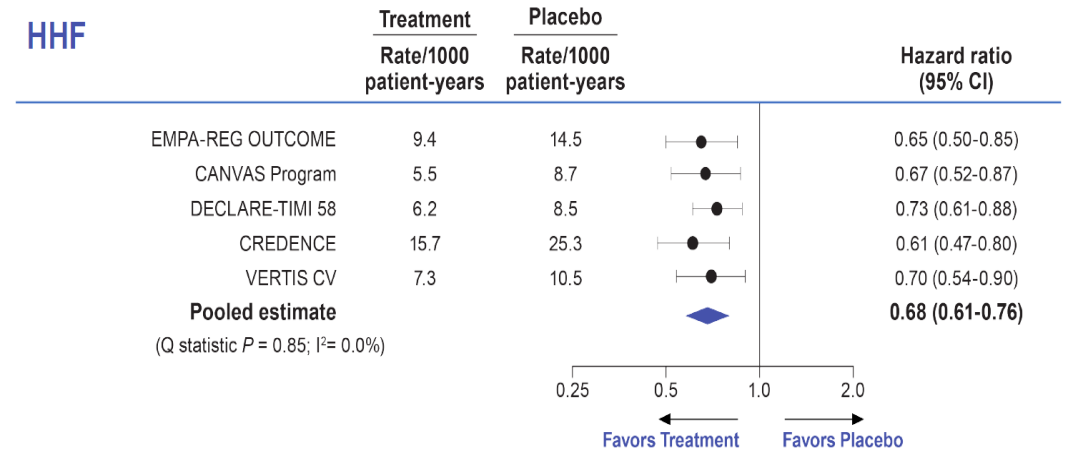
Time to CV death



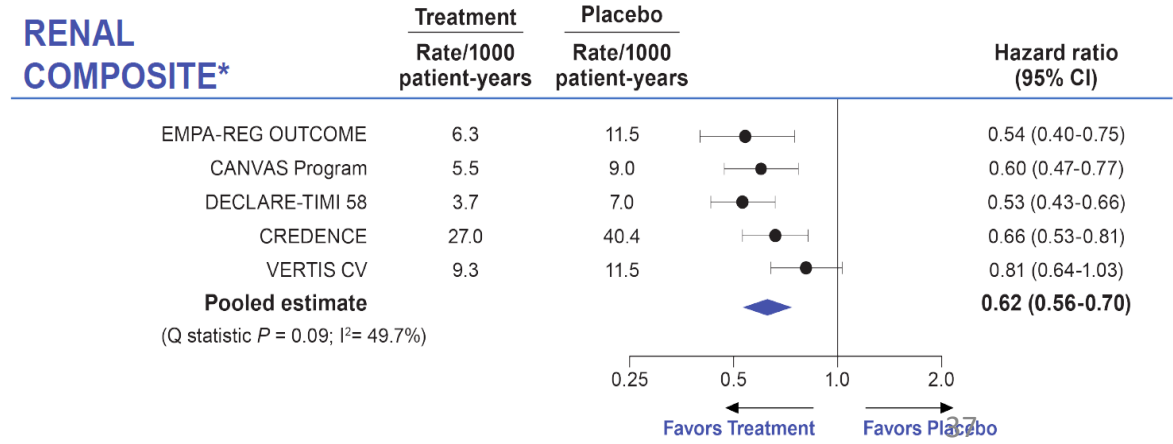
Meta-analysis of SGLT2 inhibitor trials demonstrated a reduction in the primary ASCVD-based composite of time to first event of CV death, MI, or stroke

Neither Dapa nor Ertu reduced the risk of MACE, but both reduced risk of HF hospitalization

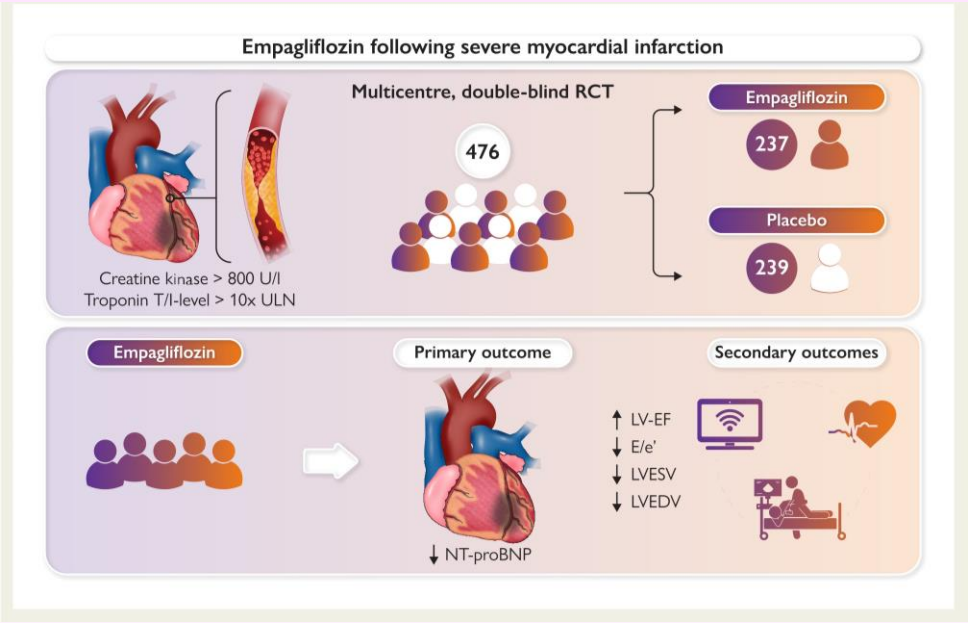
Time to first HHF



Time to first renal composite outcome



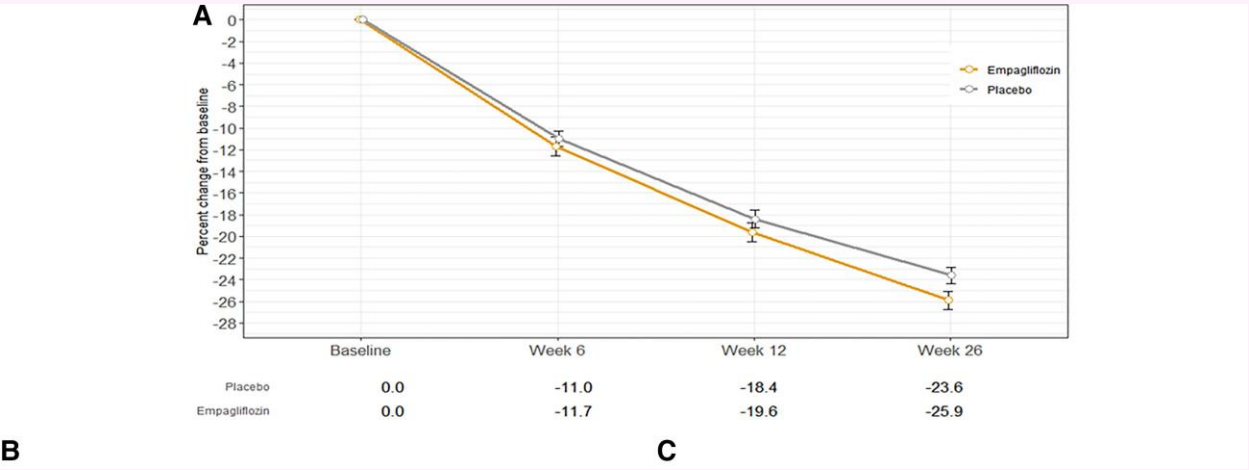
Empagliflozin in acute myocardial infarction: the EMMY trial



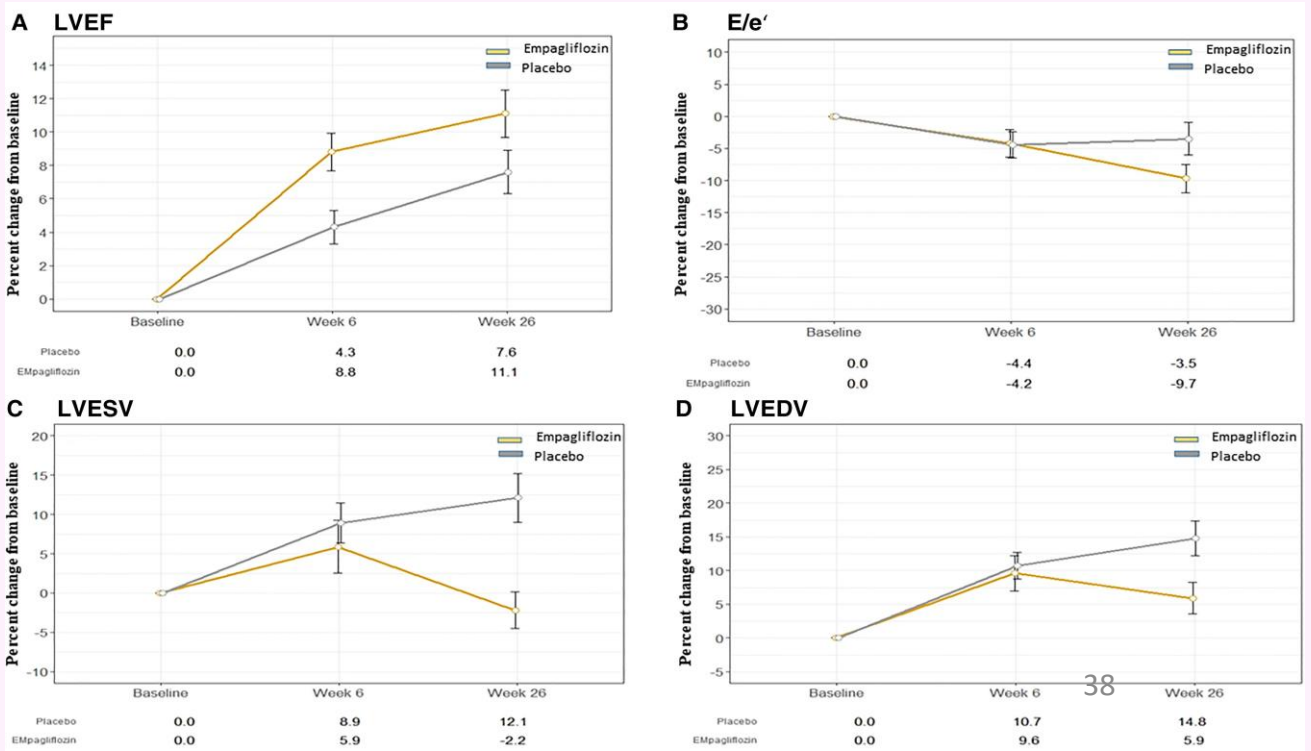
-Total of 476 people with acute myocardial infarction were randomized to either empagliflozin 10 mg or matching placebo once daily within 72 h of acute percutaneous coronary intervention

-The change in NT-pro BNP concentrations, echocardiographic functional and structural parameters (LVEF, E/è, LVEDV, LVESV) over 26 weeks of treatment was evaluated

% decline across all visits in NT pro BNP concentration



Changes in echocardiographic parameters by treatment group



Dapagliflozin in MI without DM or HF
DAPA MI

- MI (STEMI/NSTEMI) within 7 (+3) days
- Impaired LV systolic function or Q-wave
- No known T1DM or T2DM or established HF and no clear indication for SGLT2 inhibition

R

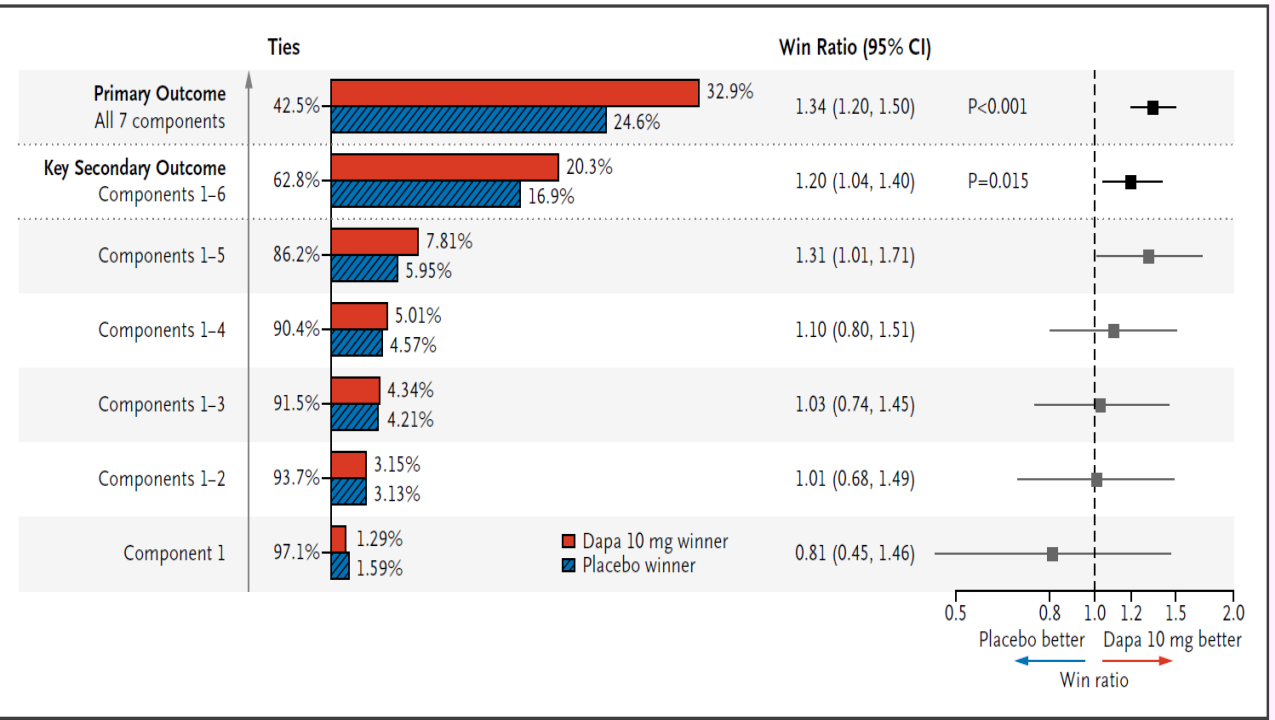
Dapagliflozin 10 mg once daily on top of SoC

Placebo once daily on top of SoC

On-site visits at 8 (±2) weeks post-randomization and at 1 year, thereafter every 10 months until study closure visit

Key assumptions
- ~4000 patients
- Assumed true Win-Ratio 1.20
- Power: 80%
- P < 0.05

Minimum follow-up: 3 months
Total trial duration: 2.5 years
39 sites in Sweden connected to the SWEDEHEART registry
64 sites in the UK connected to the MINAP registry



Primary composite outcome

The hierarchical composite outcome of:

1. Death (first CV death, followed by non-CV death)
2. Hospitalization due to heart failure (first adjudicated, followed by investigator reported)
3. Non-fatal MI
4. AF/flutter event
5. New onset of T2DM
6. NYHA Functional Classification at last visit
7. Body weight decrease of at least 5% at last visit

Secondary outcomes

- The hierarchical composite outcome of:
  1. Death (first CV death, followed by non-CV death)
  2. Hospitalization due to heart failure (first adjudicated, followed by investigator reported)
  3. Non-fatal MI
  4. AF/flutter event
  5. New onset of T2DM
  6. NYHA Functional Classification at last visit

- Primary hierarchical composite outcome including all seven components resulted in 32.9% wins for dapagliflozin and 24.6% wins for placebo
- benefit was mainly driven by the cardiometabolic components
- the rates of the composite of time to cardiovascular death/ hospitalization for HF were similar in both treatment groups

Empagliflozin in patients post myocardial infarction rationale and design of the EMPACT-MI trial

- Will evaluate safety and efficacy of empagliflozin compared with placebo in patients hospitalized for MI with or at high risk of new onset HF, in addition to standard care.
- Streamlined, multinational, randomized, double-blind, placebo-controlled trial randomizing 5,000 participants at 480 centers in 22 countries
- Eligible patients with spontaneous MI having new signs or symptoms of pulmonary congestion or LVEF < 45%, and at least 1 additional risk factor for development of future HF
- Randomized to empagliflozin 10mg or placebo daily in addition to standard of care within 14 days of hospital admission for MI
- The primary composite end point is time to first hospitalization for HF or all-cause mortality
- EMPACT-MI will inform clinical practice regarding the role of empagliflozin in patients after an MI with high-risk for the development of future HF and mortality

Conclusion

- SGLT2 inhibitors were developed as anti-diabetic agents but cumulating evidence has shown their beneficial effects on CV system
- Therapeutic spectrum of SGLT2i are extended to non-diabetic patients since CV benefits are independent of glycemic control
- Extensive clinical studies demonstrated that SGLT2i reduced the risk of CV death & hospitalization for HF in broad range of DM patients with all stages of HF with/without established CAD
- The use of SGLT2i is also safe in patients with CKD

Conclusion

- **The difference in Primary outcome- became evident approximately 3 months after starting Empa**
- **The impressive outcome results occurred in addition to background of near-optimal treatment of BP, lipid, anticoagulation by standard of care**
- **Speaks the ability of Empa to tackle some of the residual CV risk**
- **Whether Empa can improve CV outcome in pt with DM without pre-existing CV disease ???**
- **Whether Empa can improve CV outcome in pt with pre-existing CV disease without DM ???**

THANK YOU