



Krónikus koszorúér szindróma (CCS) diagnosztikája és kezelése'20

Prof. Dr. Tóth Kálmán

PTE KK

I.sz. Belgyógyászati Klinika

Kardiológiai Tanszék

A mellkasi fájdalom epidemiológiája az alapellátásban és a sürgősségi betegellátó osztályokon

Diagnózis*	A mellkasi fájdalommal jelentkező betegek megoszlása (%)		
	Alapellátás, USA	Alapellátás, Európa	Sürgősségi betegellátó osztály ³
Muszkuloszkeletális elváltozás	36	29	7
Gasztrointesztinális betegség	19	10	3
Súlyos kardiovaszkuláris betegség [†]	16	13	54
→ Stabil coronaria-betegség	10	8	13
Instabil coronaria-betegség	1,5	—	13
Pszichoszociális vagy pszichiátriai betegség	8	17	9
Tüdőbetegség [‡]	5	20	12
Nem specifikus mellkasi fájdalom	16	11	15

*Az egyesült államokbeli prevalencia szerinti sorrendben

[†]Beleértve az infarctust, az instabil angina pectorist, a tüdő-emboliát és a szívelégtelenséget

[‡]Beleértve a pneumóniát, a pneumothoraxot és a tüdőrákot

Klinkman MS, Stevens D, Gorenflo DW. Episodes of care for chest pain: preliminary report from MIRNET (J Fam Pract 1994;38:349) nyomán, módosítva, a jogtulajdonos engedélyével; további irodalmi adatok³ felhasználásával

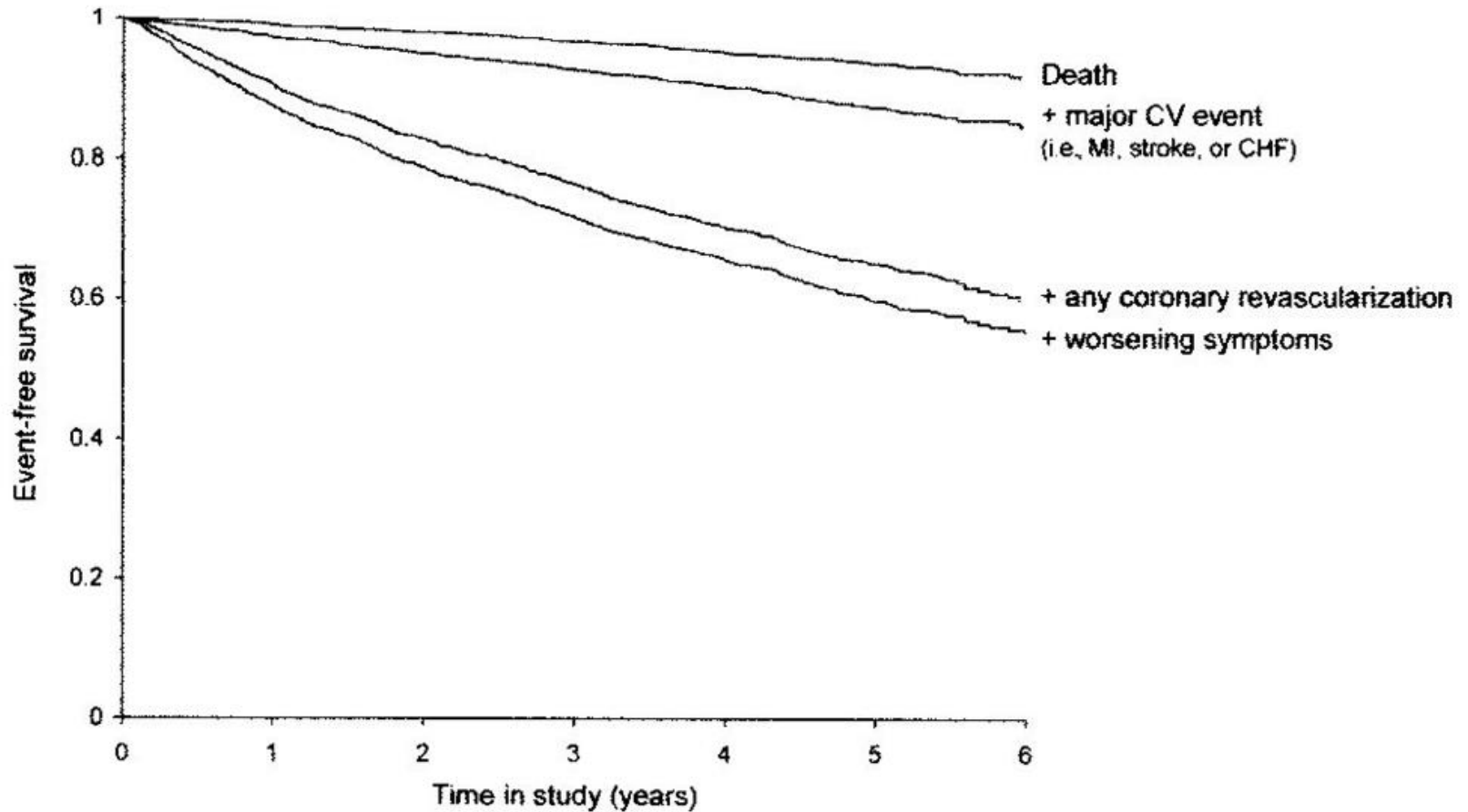
A stabil koszorúér betegség jelentősége

- Gyakori előfordulás: 20.000 – 40.000 / millió lakos
- Növekvő prevalencia a lakosság elöregedése miatt
- Jelentős gazdasági hatás: az egészségügyi kiadások 2.6%-a (az EU-ban 44.725 millió €)

Management of stable angina pectoris. Recommendations of the Task Force of the European Society of Cardiology. Eur. Heart J., 27, 1341-1381, 2006.

J Leal et al. Economic burden of cardiovascular diseases in the enlarged European Union. Eur. Heart J., 27,1610-1619, 2006.

Stabil angina prognózisa (ACTION)



A javallatok osztálya (ESC)

ESC Classes of recommendations



	Definition	Wording to use
Class I	Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective.	Is recommended or is indicated
Class II	Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure.	
Class IIa	Weight of evidence/opinion is in favour of usefulness/efficacy.	Should be considered
Class IIb	Usefulness/efficacy is less well established by evidence/opinion.	May be considered
Class III	Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful.	Is not recommended

Az evidenciaszintek (ESC)

ESC Levels of evidence



Level of evidence A	Data derived from multiple randomized clinical trials or meta-analyses.
Level of evidence B	Data derived from a single randomized clinical trial or large non-randomized studies.
Level of evidence C	Consensus of opinion of the experts and/or small studies, retrospective studies, registries.

Stabil angina/SCAD/CCS ajánlás ESC'2006-13-19



European Heart Journal
doi:10.1093/eurheartj/ehl002

ESC Guidelines

Guidelines on the management of stable angina pectoris: full text[†]

SCAD
CCS

The Task Force on the Management of Stable Angina Pectoris of the European Society of Cardiology

Authors/Task Force Members, Kim Fox, Chairperson, London (UK)*, Maria Angeles Alonso Garcia, Madrid (Spain), Diego Ardissino, Parma (Italy), Pawel Buszman, Katowice (Poland), Paolo G. Camici, London (UK), Filippo Crea, Roma (Italy), Caroline Daly, London (UK), Guy De Backer, Ghent (Belgium), Paul Hjelm Dahl, Stockholm (Sweden), José Lopez-Sendon, Madrid (Spain), Jean Marco, Toulouse (France), João Morais, Leiria (Portugal), John Pepper, London (UK), Udo Sechtem, Stuttgart (Germany), Maarten Simoons, Rotterdam (The Netherlands), Kristian Thygesen, Aarhus (Denmark)



Stabil angina/SCAD/CCS fogalmak

Stabil angina – klinikai tünetegyüttes

Stabil koszorúér betegség – kibővített fogalom: stabil angina, stabil állapotú post-MI, post-PCI, post-CABG betegek

CCS – minden, ami nem ACS

Új koncepciók'2019

New/revised concepts in 2019

The Guidelines have been revised to focus on CCS instead of stable CAD.

→ This change emphasizes the fact that the clinical presentations of CAD can be categorized as either ACS or CCS. CAD is a dynamic process of atherosclerotic plaque accumulation and functional alterations of coronary circulation that can be modified by lifestyle, pharmacological therapies, and revascularization which result in disease stabilization or regression.

→ In the current Guidelines on CCS, six clinical scenarios most frequently encountered in patients are identified: (i) patients with suspected CAD and 'stable' anginal symptoms, and/or dyspnoea; (ii) patients with new onset of 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 disease; (vi) asymptomatic subjects in whom CAD is detected at screening.

→ The PTP of CAD based on age, gender and nature of symptoms have undergone major revisions. In addition, we introduced a new phrase 'Clinical likelihood of CAD' that utilizes also various risk factors of CAD as PTP modifiers. The application of various diagnostic tests in different patient groups to rule-in or rule-out CAD have been updated.

→ The Guidelines emphasize the crucial role of healthy lifestyle behaviours and other preventive actions in decreasing the risk of subsequent cardiovascular events and mortality.

ACS = acute coronary syndromes; CAD = coronary artery disease; CCS = chronic coronary syndromes; HF = heart failure; LV = left ventricular; PTP = pre-test probability.

Aszimptómás egyének szűrése CAD irányában

Recommendations	Class ^a	Level ^b
Total risk estimation using a risk-estimation system such as SCORE is recommended for asymptomatic adults >40 years of age without evidence of CVD, diabetes, CKD, or familial hypercholesterolaemia.	I	C
Assessment of family history of premature CVD (defined as a fatal or non-fatal CVD event, or/and established diagnosis of CVD in first-degree male relatives before 55 years of age or female relatives before 65 years of age) is recommended as part of cardiovascular risk assessment.	I	C
It is recommended that all individuals aged <50 years with a family history of premature CVD in a first-degree relative (<55 years of age in men or <65 years of age in women) or familial hypercholesterolaemia are screened using a validated clinical score.	I	B
Assessment of coronary artery calcium score with computed tomography may be considered as a risk modifier ^c in the cardiovascular risk assessment of asymptomatic subjects.	IIb	B
Atherosclerotic plaque detection by carotid artery ultrasound may be considered as a risk modifier ^c in the cardiovascular risk assessment of asymptomatic subjects.	IIb	B
ABI may be considered as a risk modifier ^c in cardiovascular risk assessment.	IIb	B
In high-risk asymptomatic adults (with diabetes, a strong family history of CAD, or when previous risk-assessment tests suggest a high risk of CAD), functional imaging or coronary CTA may be considered for cardiovascular risk assessment.	IIb	C
In asymptomatic adults (including sedentary adults considering starting a vigorous exercise programme), an exercise ECG may be considered for cardiovascular risk assessment, particularly when attention is paid to non-ECG markers such as exercise capacity.	IIb	C
Carotid ultrasound IMT for cardiovascular risk assessment is not recommended.	III	A
In low-risk non-diabetic asymptomatic adults, coronary CTA or functional imaging for ischaemia are not indicated for further diagnostic assessment.	III	C
Routine assessment of circulating biomarkers is not recommended for cardiovascular risk stratification.	III	B

ECG = electrocardiogram; IMT = intima-media thickness; SCORE = Systematic COronary Risk Evaluation.

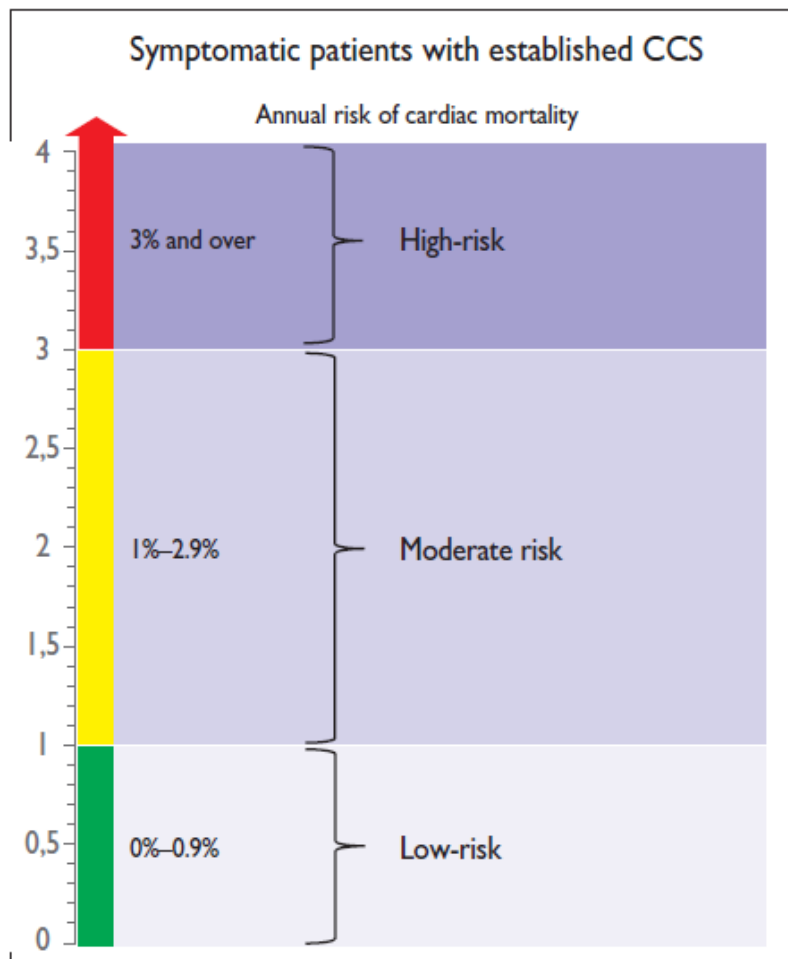
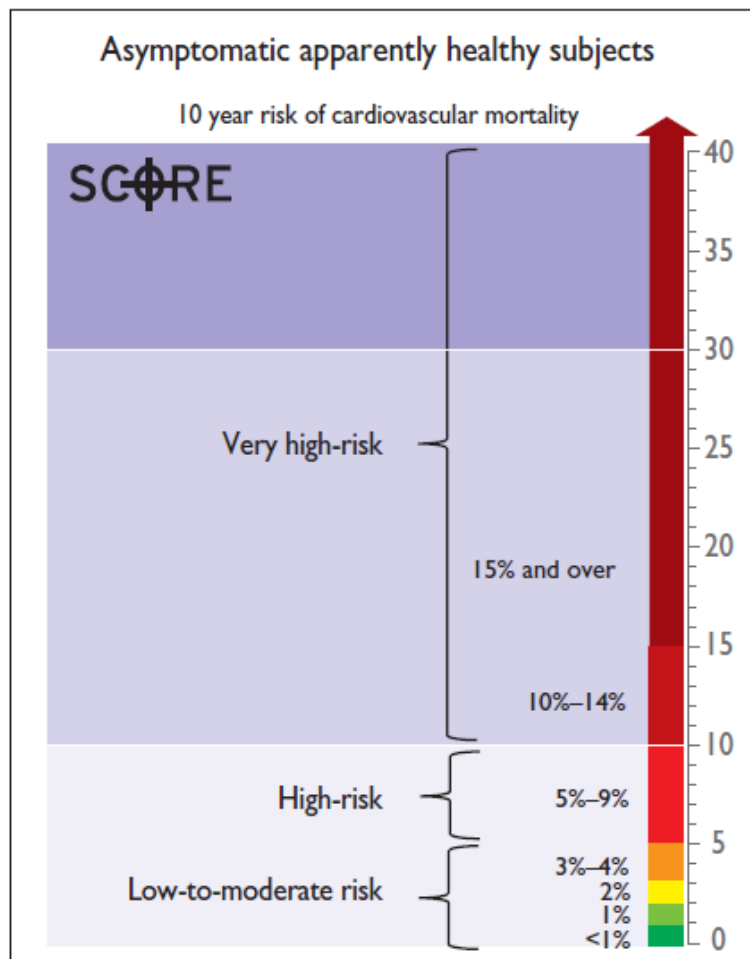
^aClass of recommendation.

^bLevel of evidence.

^cReclassifies patients better into low- or high-risk groups.

Rizikó becslés aszimptomatikus még egészséges egyéneknél (primer prevenció) és CCS-ben szenvedő betegekben (szekunder prevenció)

PRIMARY PREVENTION



SECONDARY PREVENTION

Mellkasi panaszokkal rendelkező betegek kivizsgálásának algoritmus (1)

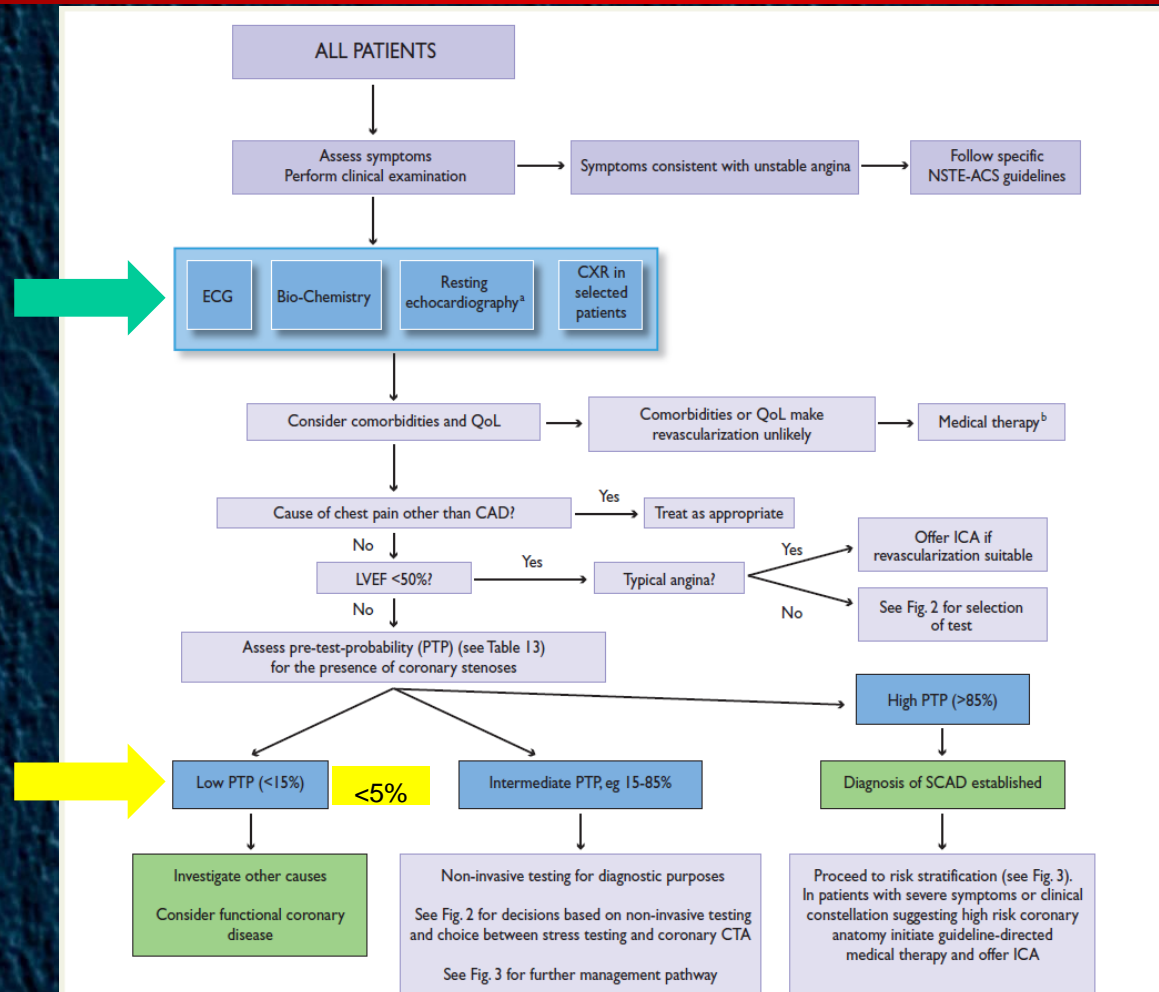


Figure 1 Initial diagnostic management of patients with suspected SCAD. CAD = coronary artery disease; CTA = computed tomography angiography; CXR = chest X-ray; ECG = electrocardiogram; ICA = invasive coronary angiography; LVEF = left ventricular ejection fraction; PTP = pre-test probability; SCAD = stable coronary artery disease.

^a May be omitted in very young and healthy patients with a high suspicion of an extracardiac cause of chest pain and in multimorbid patients in whom the echo result has no consequence for further patient management

^b If diagnosis of SCAD is doubtful, establishing a diagnosis using pharmacologic stress imaging prior to treatment may be reasonable.

Ambuláns EKG monitorozás, mint kezdő diagnosztikai lépés a mellkasi panaszok és feltételezett koszorúér betegség kivizsgálásában

Recommendations	Class^a	Level^b
Ambulatory ECG monitoring is recommended in patients with chest pain and suspected arrhythmias.	I	C
Ambulatory ECG recording, preferably monitoring with 12 lead ECG, should be considered in patients with suspected vasospastic angina.	IIa	C
Ambulatory ECG monitoring should not be used as a routine examination in patients with suspected CCS.	III	C
CAD = coronary artery disease; CCS = chronic coronary syndromes; ECG = electrocardiogram. ^a Class of recommendation. ^b Level of evidence.		

SCAD pre-teszt valószínűsége (13)

Table 13 Clinical pre-test probabilities^a in patients with stable chest pain symptoms¹⁰⁸

	Typical angina		Atypical angina		Non-anginal pain	
Age	Men	Women	Men	Women	Men	Women
30–39	59	28	29	10	18	5
40–49	69	37	38	14	25	8
50–59	77	47	49	20	34	12
60–69	84	58	59	28	44	17
→ 70–79	89	68	69	37	54	24
>80	93	76	78	47	65	32

ECG = electrocardiogram; PTP = pre-test probability; SCAD = stable coronary artery disease.

^a Probabilities of obstructive coronary disease shown reflect the estimates for patients aged 35, 45, 55, 65, 75 and 85 years.

- Groups in white boxes have a PTP <15% and hence can be managed without further testing.
- Groups in blue boxes have a PTP of 15–65%. They could have an exercise ECG if feasible as the initial test. However, if local expertise and availability permit a non-invasive imaging based test for ischaemia this would be preferable given the superior diagnostic capabilities of such tests. In young patients radiation issues should be considered.
- Groups in light red boxes have PTPs between 66–85% and hence should have a non-invasive imaging functional test for making a diagnosis of SCAD.
- In groups in dark red boxes the PTP is >85% and one can assume that SCAD is present. They need risk stratification only.

CAD preteszt valószínűsége 15.815 szimptómás betegben az életkor, nem és a szimptómák jellege alapján

	Typical		Atypical		Non-anginal			Dyspnoea ^a	
Age	Men	Women	Men	Women	Men	Women		Men	Women
30–39	3%	5%	4%	3%	1%	1%		0%	3%
→ 40–49	22%	10%	10%	6%	3%	2%		12%	3%
50–59	32%	13%	17%	6%	11%	3%		20%	9%
60–69	44%	16%	26%	11%	22%	6%		27%	14%
70+	52%	27%	34%	19%	24%	10%		32%	12%

CAD = coronary artery disease; PTP = pre-test probability.

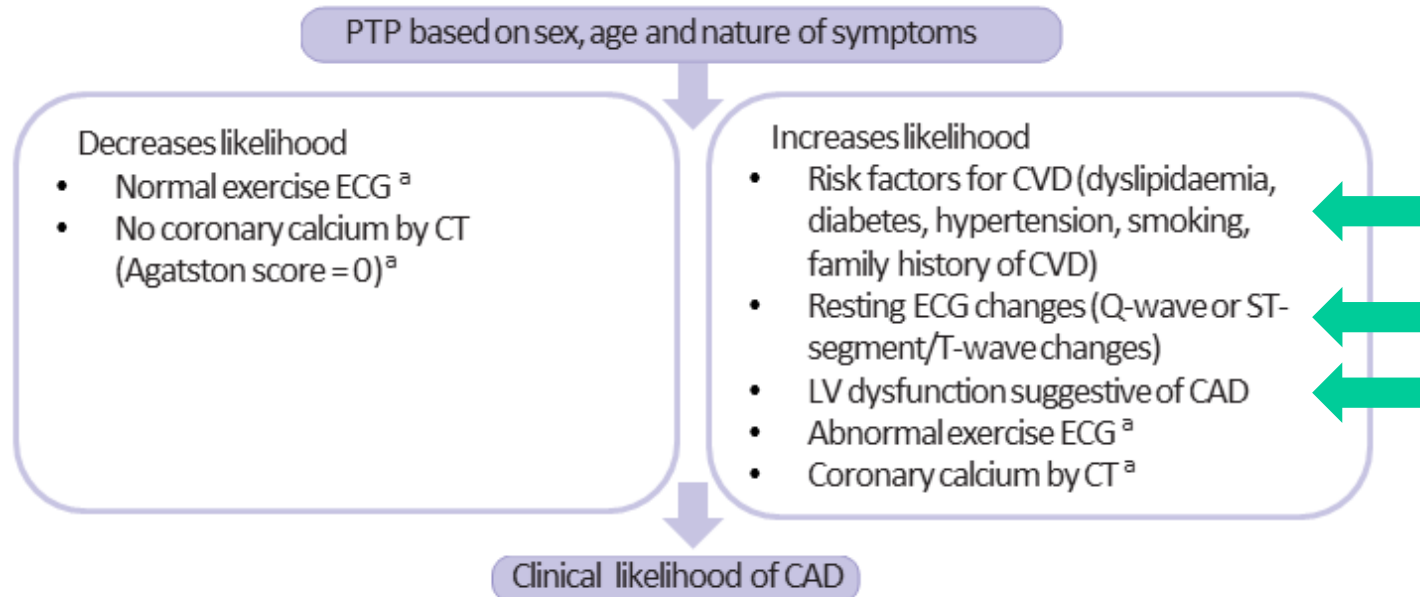
^aIn addition to the classic Diamond and Forrester classes, 59 patients with dyspnoea only or dyspnoea as the primary symptom are included. The regions shaded dark green denote the groups in which non-invasive testing is most beneficial (PTP >15%).

CAD klinikai valószínűsége

Patients with angina and/or dyspnoea and suspected coronary artery disease



Determinants of clinical likelihood of CAD



^a if available.

Mellkasi panaszokkal rendelkező betegek kivizsgálásának algoritmus (2)

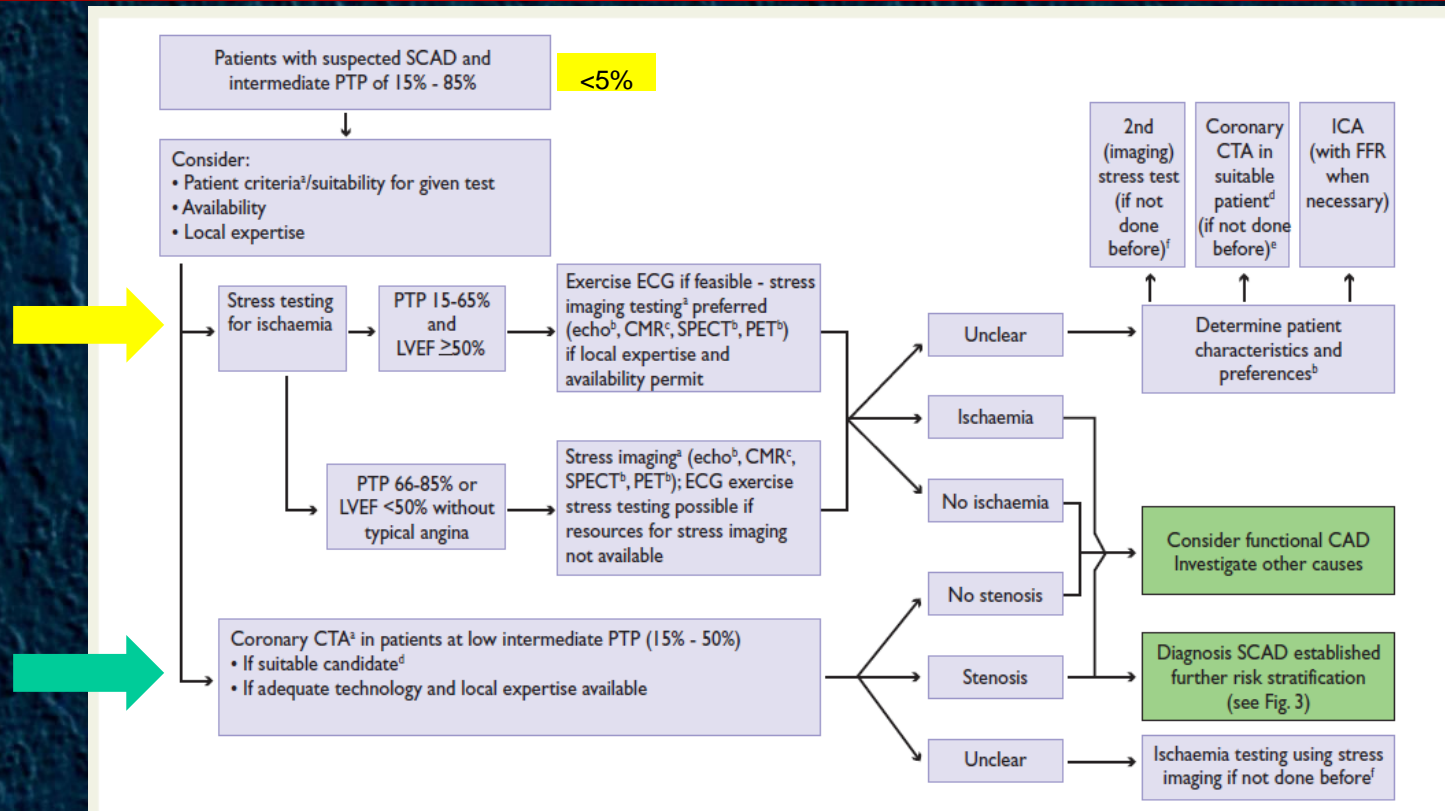


Figure 2 Non-invasive testing in patients with suspected SCAD and an intermediate pre-test probability. CAD = coronary artery disease; CTA = computed tomography angiography; CMR = cardiac magnetic resonance; ECG = electrocardiogram; ICA = invasive coronary angiography; LVEF = left ventricular ejection fraction; PET = positron emission tomography; PTP = pre-test probability; SCAD = stable coronary artery disease; SPECT = single photon emission computed tomography.

^aConsider age of patient versus radiation exposure.

^bIn patients unable to exercise use echo or SPECT/PET with pharmacologic stress instead.

^cCMR is only performed using pharmacologic stress.

^dPatient characteristics should make a fully diagnostic coronary CTA scan highly probable (see section 6.2.5.1.2) consider result to be unclear in patients with severe diffuse or focal calcification.

^eProceed as in lower left coronary CTA box.

^fProceed as in stress testing for ischaemia box.

Terheléses EKG, mint kezdő diagnosztikai lépés a mellkasi panaszok és feltételezett koszorúér betegség kivizsgálásában

Recommendations	Class ^a	Level ^b
→ Exercise ECG is recommended for the assessment of exercise tolerance, symptoms, arrhythmias, BP response, and event risk in selected patients. ^c	I	C
Exercise ECG may be considered as an alternative test to rule-in and rule-out CAD when non-invasive imaging is not available. ^{73,83}	IIb	B
Exercise ECG may be considered in patients on treatment to evaluate control of symptoms and ischaemia.	IIb	C
→ Exercise ECG is not recommended for diagnostic purposes in patients with ≥ 0.1 mV ST-segment depression on resting ECG or who are being treated with digitalis.	III	C

BP = blood pressure; CAD = coronary artery disease; ECG = electrocardiogram.

^aClass of recommendation.

^bLevel of evidence.

^cWhen this information will have an impact on diagnostic strategy or management.

Képzővizsgák a szimptomás betegek CAD diagnosztikájában

Recommendations	Class ^a	Level ^b
Non-invasive functional imaging for myocardial ischaemia ^c or coronary CTA is recommended as the initial test to diagnose CAD in symptomatic patients in whom obstructive CAD cannot be excluded by clinical assessment alone. ^{4,5,55,73,78–80}	I	B
It is recommended that selection of the initial non-invasive diagnostic test is done based on the clinical likelihood of CAD and other patient characteristics that influence test performance, ^d local expertise, and the availability of tests.	I	C
Functional imaging for myocardial ischaemia is recommended if coronary CTA has shown CAD of uncertain functional significance or is not diagnostic. ^{4,55,73}	I	B
Invasive coronary angiography is recommended as an alternative test to diagnose CAD in patients with a high clinical likelihood, severe symptoms refractory to medical therapy or typical angina at a low level of exercise, and clinical evaluation that indicates high event risk. Invasive functional assessment must be available and used to evaluate stenoses before revascularization, unless very high grade (>90% diameter stenosis). ^{71,72,74}	I	B
Invasive coronary angiography with the availability of invasive functional evaluation should be considered for confirmation of the diagnosis of CAD in patients with an uncertain diagnosis on non-invasive testing. ^{71,72}	IIa	B
Coronary CTA should be considered as an alternative to invasive angiography if another non-invasive test is equivocal or non-diagnostic.	IIa	C
Coronary CTA is not recommended when extensive coronary calcification, irregular heart rate, significant obesity, inability to cooperate with breath-hold commands, or any other conditions make obtaining good image quality unlikely.	III	C
Coronary calcium detection by CT is not recommended to identify individuals with obstructive CAD.	III	C

CAD = coronary artery disease; CT = computed tomography; CTA = computed tomography angiography.

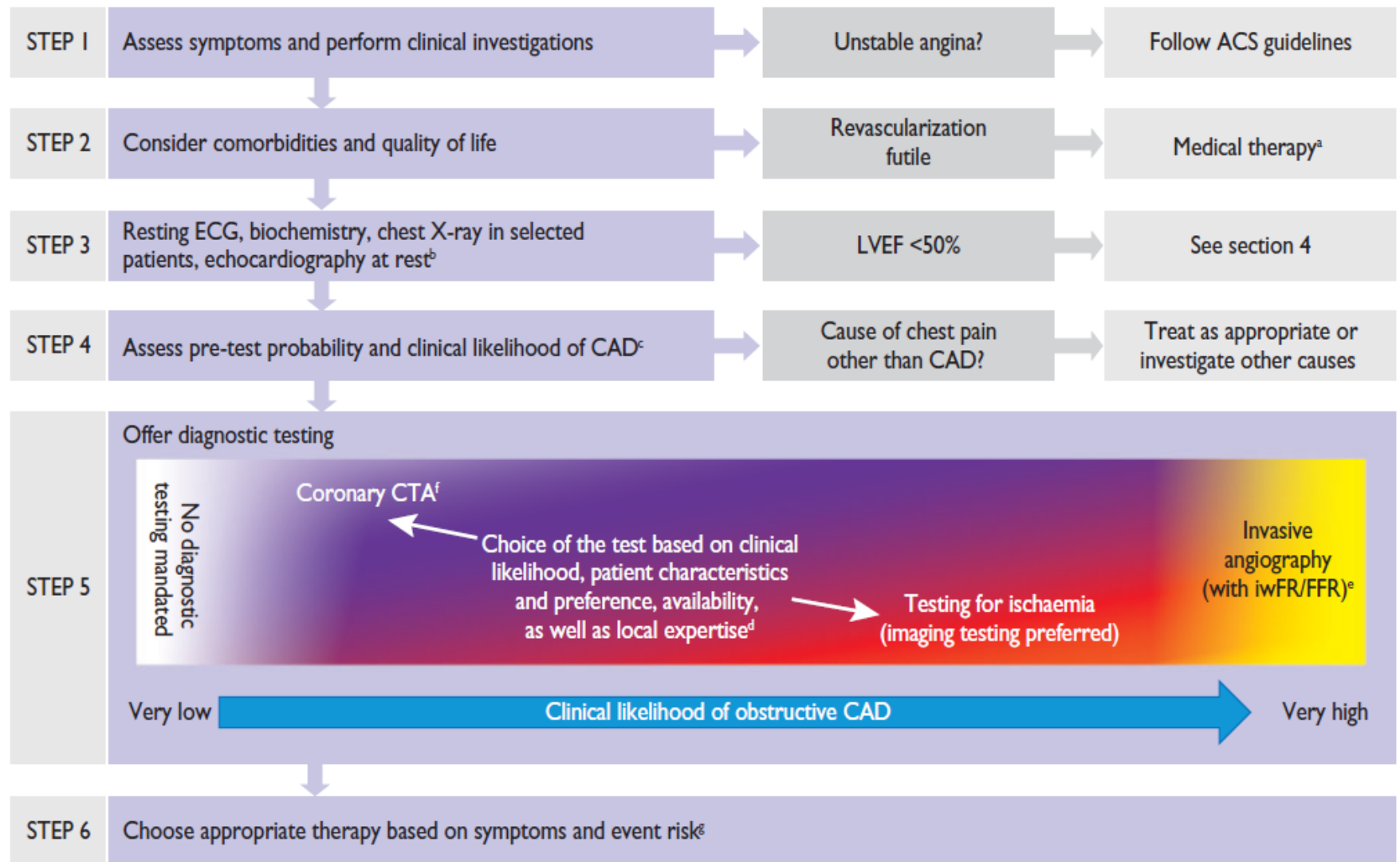
^aClass of recommendation.

^bLevel of evidence

^cStress echocardiography, stress cardiac magnetic resonance, single-photon emission CT, or positron emission tomography.

^dCharacteristics determining ability to exercise, likelihood of good image quality, expected radiation exposure, and risks or contraindications.

Diagnosztikai lépések a mellkasi panaszok és feltételezett koszorúér betegség kivizsgálására



A magas rizikójú CCS beteg

Exercise ECG	Cardiovascular mortality >3% per year according to Duke Treadmill Score
SPECT or PET perfusion imaging	Area of ischaemia $\geq 10\%$ of the left ventricle myocardium
Stress echocardiography	≥ 3 of 16 segments with stress-induced hypokinesia or akinesia
CMR	≥ 2 of 16 segments with stress perfusion defects or ≥ 3 dobutamine-induced dysfunctional segments
Coronary CTA or ICA	Three-vessel disease with proximal stenoses, LM disease, or proximal anterior descending disease
Invasive functional testing	FFR ≤ 0.8 , iwFR ≤ 0.89

CTA = computed tomography angiography; CMR = cardiac magnetic resonance; ECG = electrocardiogram; FFR = fractional flow reserve; ICA = invasive coronary angiography; iwFR = instantaneous wave-free ration (instant flow reserve); LM = left main; PET = positron emission tomography; SPECT; single-photon emission computed tomography.

^aFor detailed explanations, refer to the Supplementary Data.

Kezelési stratégiák

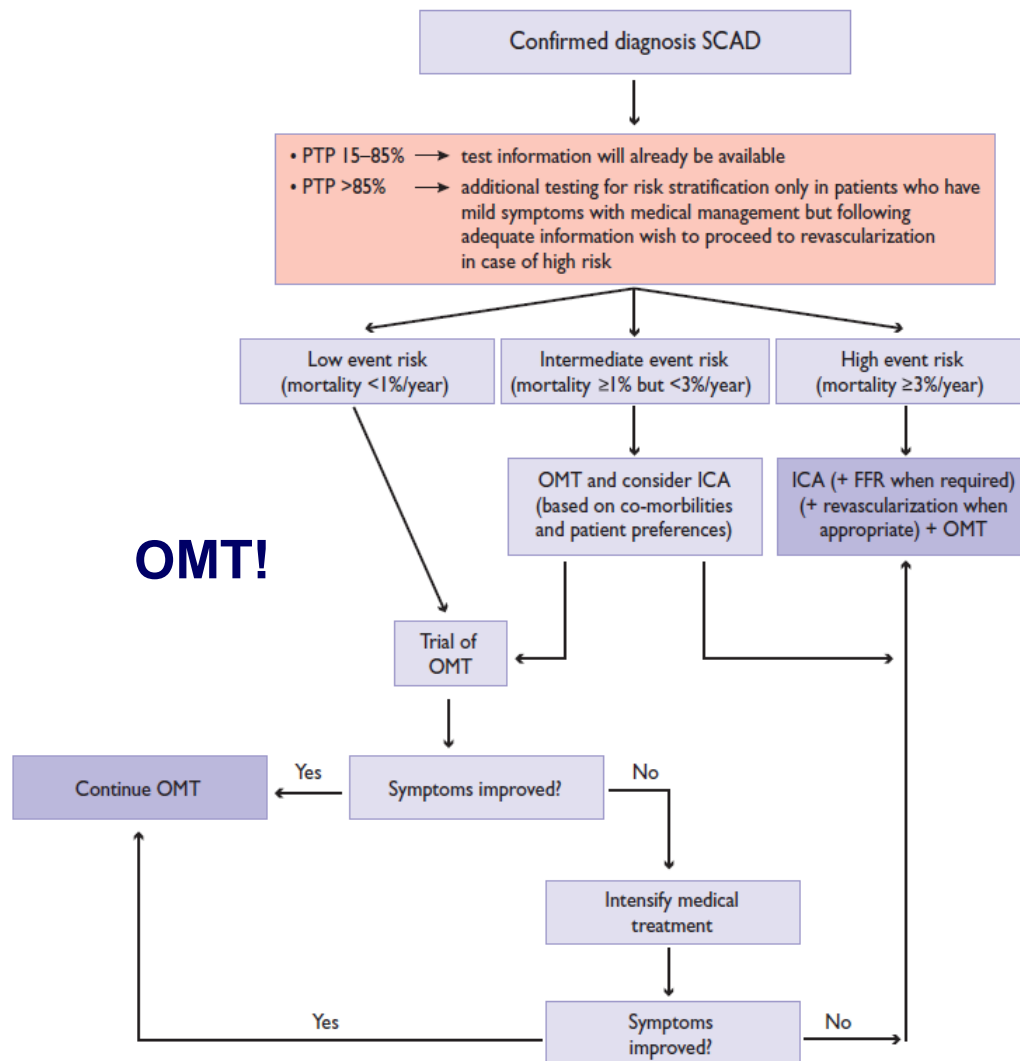
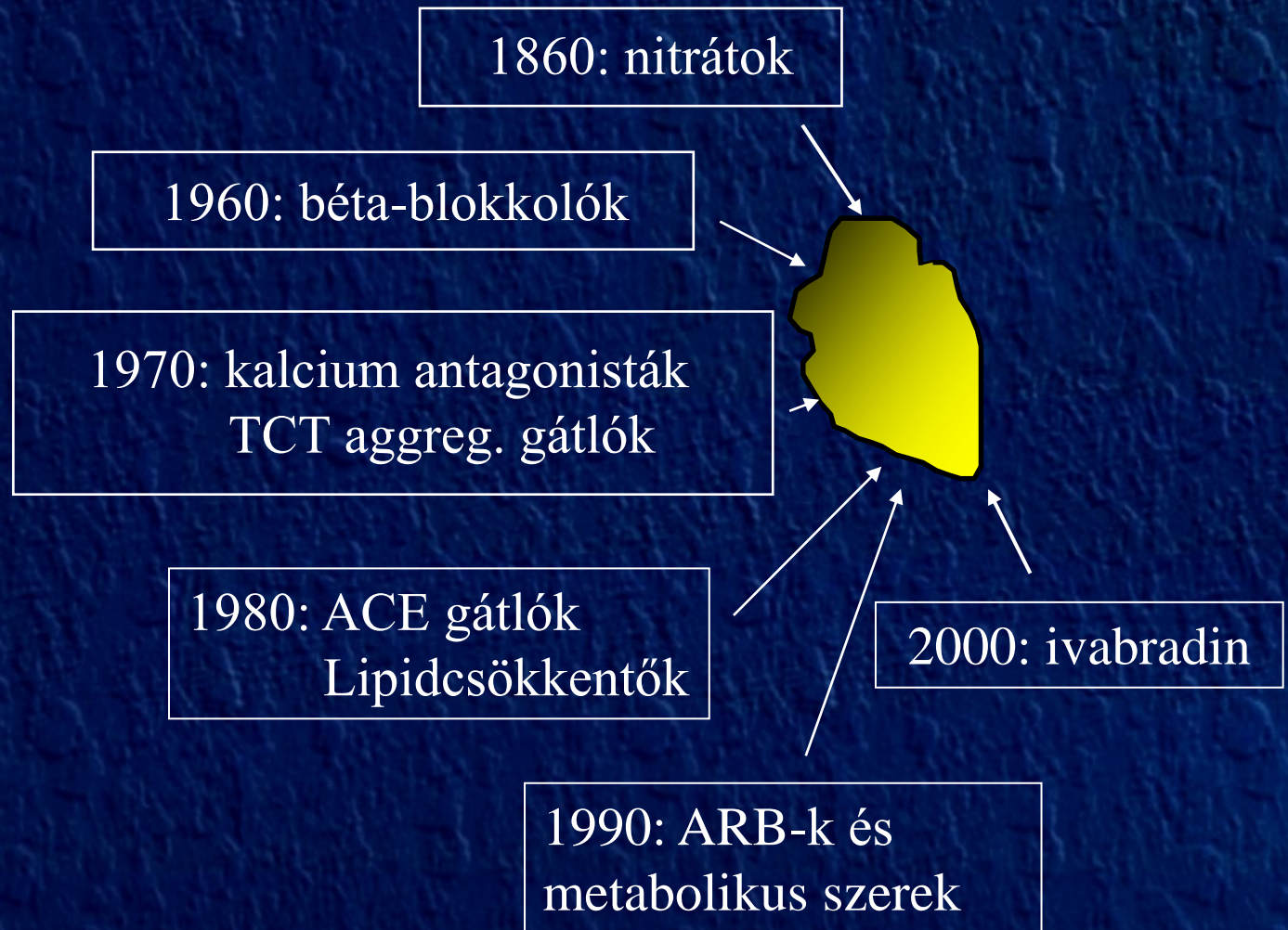


Figure 3 Management based on risk determination for prognosis in patients with chest pain and suspected SCAD (for choice of test see Fig. 2, for definitions of event risk see Table 17). ICA = invasive coronary angiography; OMT = optimal medical therapy; PTP = pre-test probability; SCAD = stable coronary artery disease.

Életmódi tanácsok CCS-ben

Lifestyle factor	
Smoking cessation	Use pharmacological and behavioural strategies to help patients quit smoking. Avoid passive smoking.
Healthy diet	Diet high in vegetables, fruit, and wholegrains. Limit saturated fat to <10% of total intake. Limit alcohol to <100 g/week or 15 g/day.
Physical activity	30 - 60 min moderate physical activity most days, but even irregular activity is beneficial.
Healthy weight	Obtain and maintain a healthy weight (<25 kg/m ²), or reduce weight through recommended energy intake and increased physical activity.
Other	Take medications as prescribed. Sexual activity is low risk for stable patients not symptomatic at low-to-moderate activity levels.

Gyógyszeres kezelés



A „mágikus” négyes/hármas/kettes

**TCT aggr.
gátló**

(rezisztencia,
dózis,
kombináció, GI
vérzés,
új szerek?)

**ACE-
inhibitor
(ARB?)**



**Béta-blockoló
(ivabradin?)**

**Statin
(új szerek!)**

PCI-CURE (2658 ACS beteg)

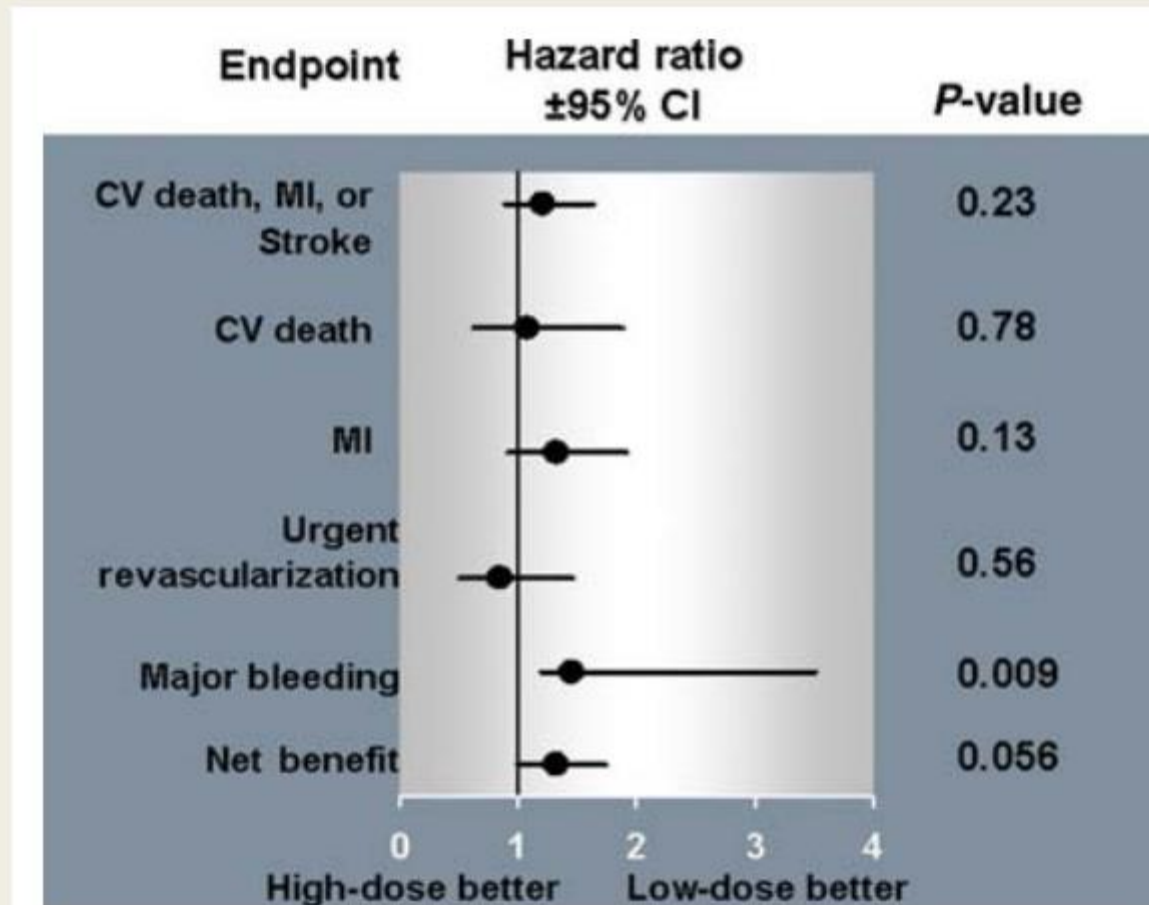


Figure 3 High- vs. low-dose aspirin comparison at long-term follow-up.

A P2Y₁₂ ADP receptor antagonisták

	Oral administration			Intravenous administration
	Clopidogrel	Prasugrel	Ticagrelor	Cangrelor
Drug class	Thienopyridine	Thienopyridine	Cyclopentyltriazolo-pyrimidine	ATP analogue
Reversibility	Irreversible	Irreversible	Reversible	Reversible
P2Y ₁₂ receptor interaction	Competitive	Competitive	Allosteric, non-competitive	Competitive
Bioactivation	Yes (pro-drug, CYP dependent, two steps)	Yes (pro-drug, CYP dependent, one step)	No*	No
(Pre-treatment)-dose	300/600 mg LD, 75 mg MD	60 mg LD, 5/10 mg MD	180 mg LD, 2 × 90 mg MD	30 µg/kg i.v. bolus, 4 µg/kg/min i.v. infusion for PCI
Onset of effect	Delayed: 2–6 h	Rapid: 30 min–4 h	Rapid: 30 min–2 h	Immediate: 2 min
Duration of effect	3–10 days	5–10 days	3–4 days	30–60 min
Delay to surgery	5 days	7 days	5 days	No significant delay
Price	0.50 €/day	2.88 €/day	3.34 €/day	350 €/vial

The table summarizes key characteristics of the available P2Y₁₂ receptor inhibitors. It also shows the average onset of action for the P2Y₁₂ inhibitors. The onset of action is significantly delayed in STEMI and cardiogenic shock patients for all oral P2Y₁₂ inhibitors.⁶ Following intestinal absorption, ticagrelor does not need to be metabolized to inhibit platelet aggregation. However, a metabolite (AR-C124910XX) is also active (*). Pricing are treatment costs per day (source: www.rote-liste.de) for the oral agents (generic drug price for clopidogrel) and price per vial for cangrelor. LD, loading dose; MD, maintenance dose.

Esemény megelőzés I (1/4)

Recommendations	Class ^a	Level ^b
Antithrombotic therapy in patients with CCS and in sinus rhythm		
Aspirin 75–100 mg daily is recommended in patients with a previous MI or revascularization.	I	A
Clopidogrel 75 mg daily is recommended as an alternative to aspirin in patients with aspirin intolerance.	I	B
Clopidogrel 75 mg daily may be considered in preference to aspirin in symptomatic or asymptomatic patients, with either PAD or a history of ischaemic stroke or transient ischaemic attack.	IIb	B
Aspirin 75–100 mg daily may be considered in patients without a history of MI or revascularization, but with definitive evidence of CAD on imaging.	IIb	C
Adding a second antithrombotic drug to aspirin for long-term secondary prevention should be considered in patients with a high risk of ischaemic events ^c and without high bleeding risk ^d (see Table 9 for options).	IIa	A
Adding a second antithrombotic drug to aspirin for long-term secondary prevention may be considered in patients with at least a moderately increased risk of ischaemic events ^e and without high bleeding risk ^d (see Table 9 for options).	IIb	A
Antithrombotic therapy post-PCI in patients with CCS and in sinus rhythm		
Aspirin 75–100 mg daily is recommended following stenting.	I	A
Clopidogrel 75 mg daily following appropriate loading (e.g. 600 mg or >5 days of maintenance therapy) is recommended, in addition to aspirin, for 6 months following coronary stenting, irrespective of stent type, unless a shorter duration (1–3 months) is indicated due to risk or the occurrence of life-threatening bleeding.	I	A
Clopidogrel 75 mg daily following appropriate loading (e.g. 600 mg or >5 days of maintenance therapy) should be considered for 3 months in patients with a higher risk of life-threatening bleeding.	IIa	A
Clopidogrel 75 mg daily following appropriate loading (e.g. 600 mg or >5 days of maintenance therapy) may be considered for 1 month in patients with very high risk of life-threatening bleeding.	IIb	C
Prasugrel or ticagrelor may be considered, at least as initial therapy, in specific high-risk situations of elective stenting (e.g. suboptimal stent deployment or other procedural characteristics associated with high risk of stent thrombosis, complex left main stem, or multivessel stenting) or if DAPT cannot be used because of aspirin intolerance.	IIb	C

Rizikó besorolás

Magas ischaemiás kockázat meghatározása:

- ◆ Diffúz, több eret érintő CAD és az alábbiak közül **legalább 1**:
 - Diabetes mellitus, amely gyógyszeres kezelést igényel
 - Ismétlődő MI
 - PAD
 - CKD, ha az eGFR 15–59 ml/min/1.73 m²

Mérsékelten magas ischaemiás kockázat meghatározása:

- ◆ **Legalább 1** az alábbiak közül:
 - Több eret érintő/diffúz CAD
 - Diabetes mellitus, amely gyógyszeres kezelést igényel
 - Ismétlődő MI
 - PAD
 - HF
 - CKD, ha az eGFR 15–59 ml/min/1.73 m²

Esemény megelőzés I (2/4)

Recommendations	Class ^a	Level ^b
Antithrombotic therapy in patients with CCS and AF		
→ When oral anticoagulation is initiated in a patient with AF who is eligible for a NOAC, ^f a NOAC is recommended in preference to a VKA. ^{299–301,308–311}	I	A
Long-term OAC therapy (NOAC or VKA with time in therapeutic range >70%) is recommended in patients with AF and a CHA ₂ DS ₂ -VASc score ^g ≥2 in males and ≥3 in females. ²⁹⁹	I	A
Long-term OAC therapy (NOAC or VKA with time in therapeutic range >70%) should be considered in patients with AF and a CHA ₂ DS ₂ -VASc score ^g of 1 in males and 2 in females. ²⁹⁹	IIa	B
→ Aspirin 75–100 mg daily (or clopidogrel 75 mg daily) may be considered in addition to long-term OAC therapy in patients with AF, history of MI, and at high risk of recurrent ischaemic events ^c who do not have a high bleeding risk. ^{d 295,297,299}	IIb	B

Esemény megelőzés I (3/4)

Recommendations	Class ^a	Level ^b
Antithrombotic therapy in post-PCI patients with AF or another indication for an OAC		
It is recommended that peri-procedural aspirin and clopidogrel are administered to patients undergoing coronary stent implantation.	I	C
In patients who are eligible for a NOAC, it is recommended that a NOAC (apixaban 5 mg b.i.d., dabigatran 150 mg b.i.d., edoxaban 60 mg o.d., or rivaroxaban 20 mg o.d.) ^f is used in preference to a VKA in combination with antiplatelet therapy. ^{300,301,308,310,311}	I	A
When rivaroxaban is used and concerns about high bleeding risk ^d prevail over concerns about stent thrombosis ^h or ischaemic stroke, ^g rivaroxaban 15 mg o.d. should be considered in preference to rivaroxaban 20 mg o.d. for the duration of concomitant single or dual antiplatelet therapy. ^{300,301,308,310}	IIa	B
When dabigatran is used and concerns about high bleeding risk ^d prevail over concerns about stent thrombosis ^h or ischaemic stroke, ^g dabigatran 110 mg b.i.d. should be considered in preference to dabigatran 150 mg b.i.d. for the duration of concomitant single or dual antiplatelet therapy. ^{300,301,308}	IIa	B
After uncomplicated PCI, early cessation (≤ 1 week) of aspirin and continuation of dual therapy with an OAC and clopidogrel should be considered if the risk of stent thrombosis ^h is low, or if concerns about bleeding risk prevail over concerns about the risk of stent thrombosis, ^h irrespective of the type of stent used. ^{301,308–310}	IIa	B
Triple therapy with aspirin, clopidogrel, and an OAC for ≥ 1 month should be considered when the risk of stent thrombosis ^h outweighs the bleeding risk, with the total duration (≤ 6 months) decided according to assessment of these risks and clearly specified at hospital discharge.	IIa	C
In patients with an indication for a VKA in combination with aspirin and/or clopidogrel, the dose intensity of the VKA should be carefully regulated with a target international normalized ratio in the range of 2.0–2.5 and with time in therapeutic range $>70\%$. ^{300,301,308–310}	IIa	B
Dual therapy with an OAC and either ticagrelor or prasugrel may be considered as an alternative to triple therapy with an OAC, aspirin, and clopidogrel in patients with a moderate or high risk of stent thrombosis, ^h irrespective of the type of stent used.	IIb	C
→ The use of ticagrelor or prasugrel is not recommended as part of triple antithrombotic therapy with aspirin and an OAC.	III	C

Esemény megelőzés I (4/4)

Recommendations	Class ^a	Level ^b
Use of proton pump inhibitors		
Concomitant use of a proton pump inhibitor is recommended in patients receiving aspirin monotherapy, DAPT, or OAC monotherapy who are at high risk of gastrointestinal bleeding.	I	A

AF = atrial fibrillation; b.i.d. = bis in die (twice a day); CAD = coronary artery disease; CCS = chronic coronary syndromes; CHA2DS2-VASc = Cardiac failure, Hypertension, Age >_75 [Doubled], Diabetes, Stroke [Doubled] Vascular disease, Age 65/74 and Sex category [Female]; CKD = chronic kidney disease; DAPT = dual antiplatelet therapy; eGFR = estimated glomerular filtration rate; HF = heart failure; MI = myocardial infarction; NOAC = non-vitamin K antagonist oral anticoagulant; OAC = oral anticoagulant; o.d. = omni die (once a day); PAD = peripheral artery disease; PCI = percutaneous coronary intervention; VKA = vitamin K antagonist.

^aClass of recommendation.

^bLevel of evidence.

^cDiffuse multivessel CAD with at least one of the following: diabetes mellitus requiring medication, recurrent MI, PAD, or CKD with eGFR 15-59 mL/min/1.73 m².

^dPrior history of intracerebral haemorrhage or ischaemic stroke, history of other intracranial pathology, recent gastrointestinal bleeding or anaemia due to possible gastrointestinal blood loss, other gastrointestinal pathology associated with increased bleeding risk, liver failure, bleeding diathesis or coagulopathy, extreme old age or frailty, or renal failure requiring dialysis or with eGFR <15 mL/min/1.73 m².

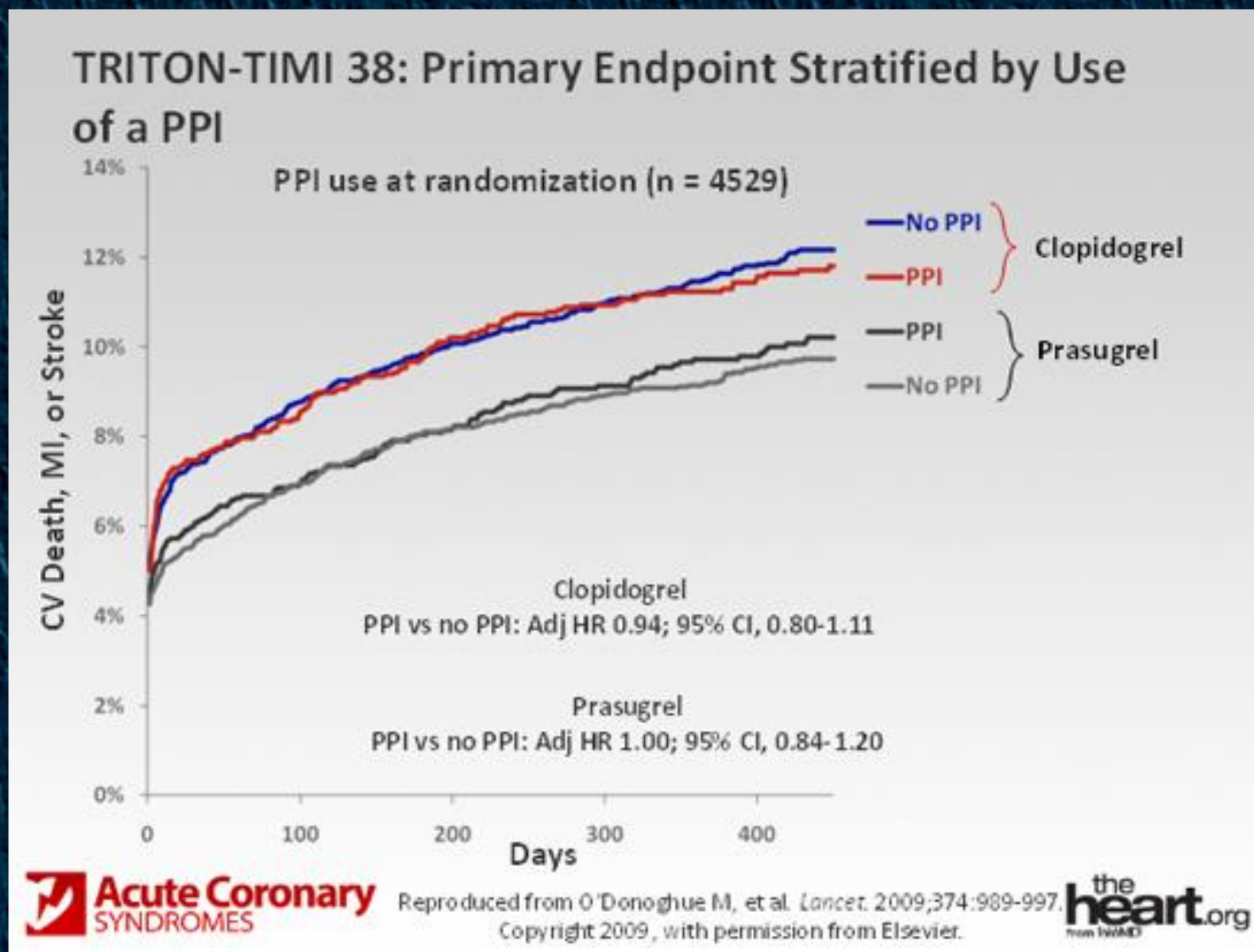
^eAt least one of the following: multivessel/diffuse CAD, diabetes mellitus requiring medication, recurrent MI, PAD, HF, or CKD with eGFR 15-59 mL/min/1.73 m².

^fSee summary of product characteristics for reduced doses or contraindications for each NOAC in patients with CKD, body weight <60 kg, age >75 years, and/or drug interactions.

^gCongestive HF, hypertension, age >_75 years (2 points), diabetes, prior stroke/transient ischaemic attack/embolus (2 points), vascular disease (CAD on imaging or angiography, 312 prior MI, PAD, or aortic plaque), age 65/74 years, and female sex.

^hRisk of stent thrombosis encompasses (i) the risk of thrombosis occurring and (ii) the risk of death should stent thrombosis occur, both of which relate to anatomical, procedural, and clinical characteristics. Risk factors for CCS patients include stenting of left main stem, proximal LAD, or last remaining patent artery; suboptimal stent deployment; stent length >60 mm; diabetes mellitus; CKD; bifurcation with two stents implanted; treatment of chronic total occlusion; and previous stent thrombosis on adequate antithrombotic therapy.

PPI és thienopyridinek



PPI kezelés algoritmus

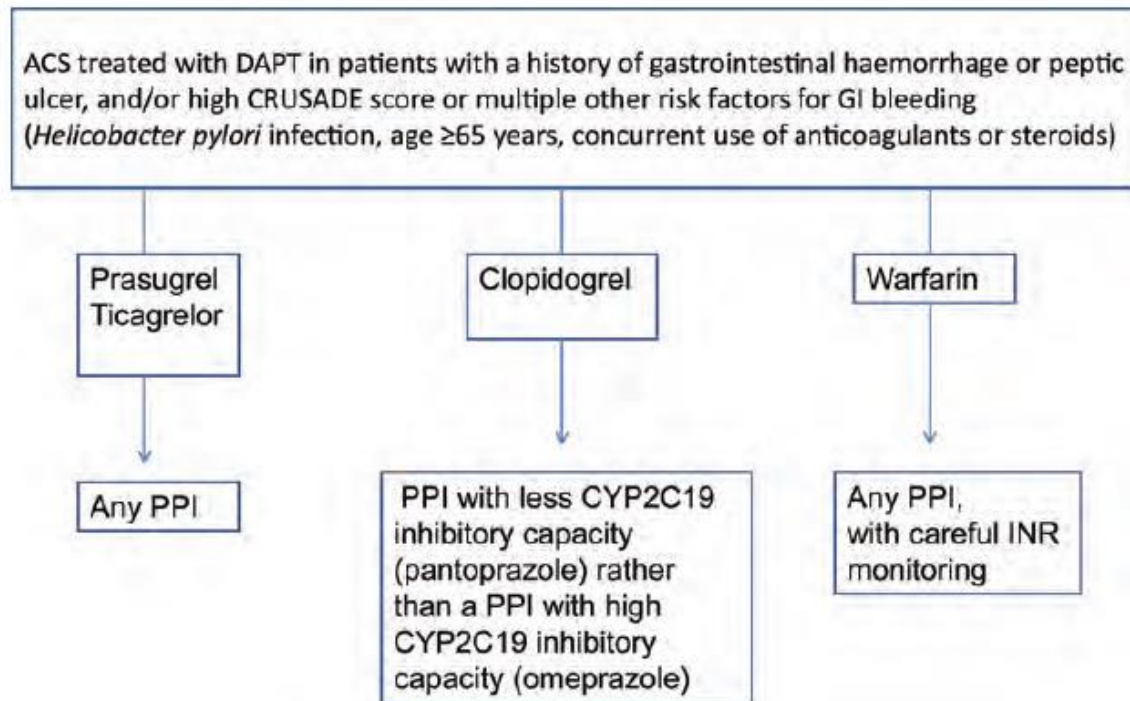
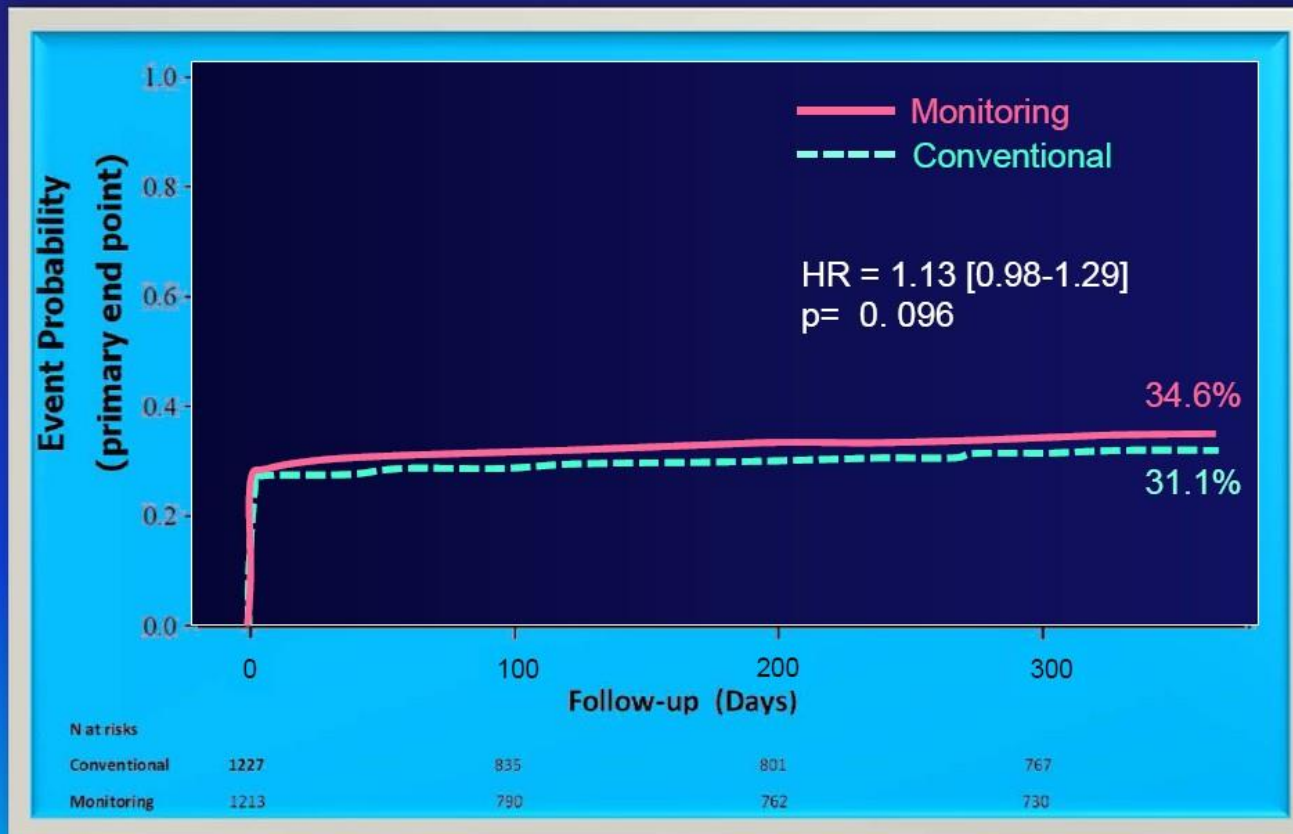


Figure 3 The proton pump inhibitor treatment algorithm in patients with acute coronary syndrome. ACS, acute coronary syndrome; GI, gastrointestinal; PPI, proton pump inhibitor.



Primary Endpoint to 1 year

Death, MI, stroke, stent thrombosis, urgent revascularization



ANTARCTIC



Criticism after ARCTIC → **ANTARCTIC**

- Low risk, stable patients → **Elderly, ACS patients**
- Elective PCI → **Urgent PCI**
- Predominant use of clopidogrel → **Predominant use of prasugrel**
- Old PRU thresholds → **New PRU thresholds**

Montalescot G et al. N Engl J Med 2013;368:871-2

Montalescot G et al. Circulation 2014;129:2136-43

ESC CONGRESS
ROME 2016



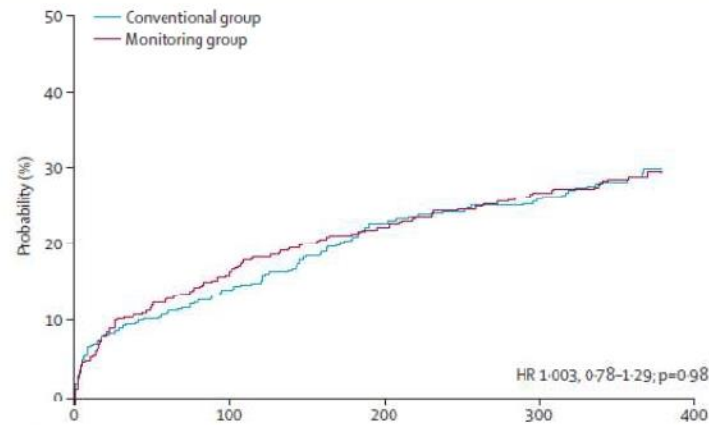
ANTARCTIC a study by the ACTION Group



ANTARCTIC



Primary Endpoint



CV death, MI, stroke,
stent thrombosis, urgent
revascularization *or*
BARC 2, 3 or 5

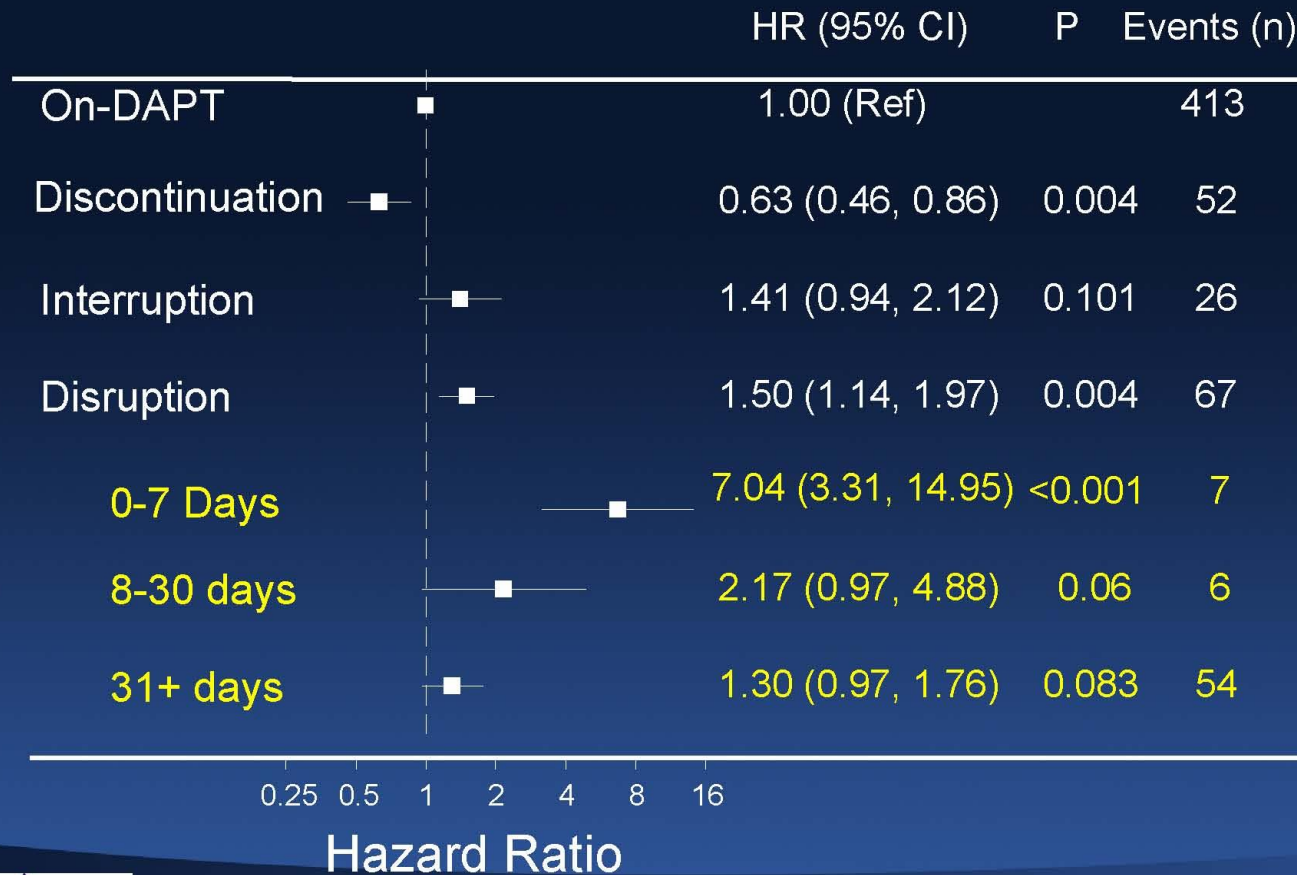
ESC CONGRESS
ROME 2016



ANTARCTIC a study by the ACTION Group

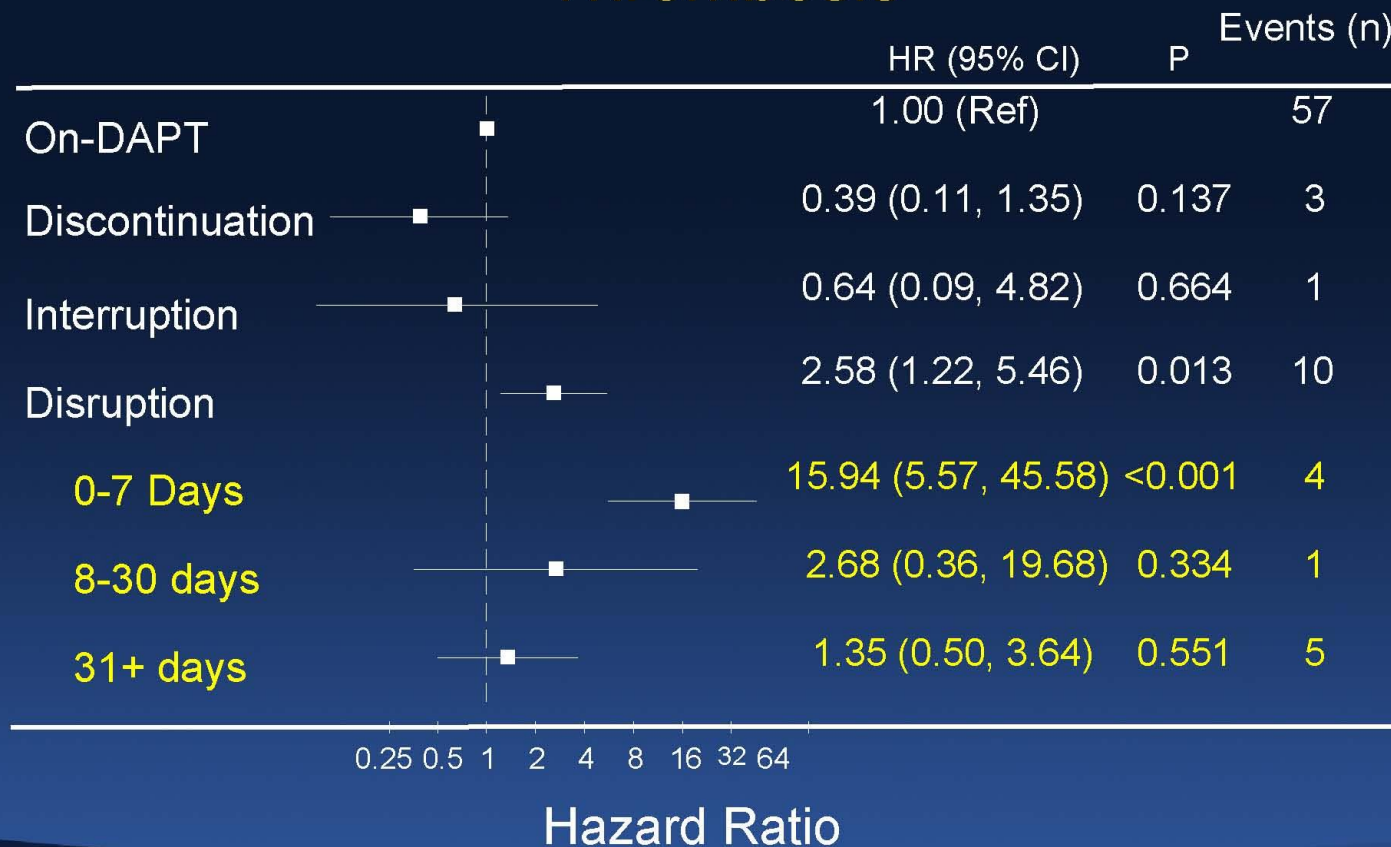


DAPT Cessation and MACE*



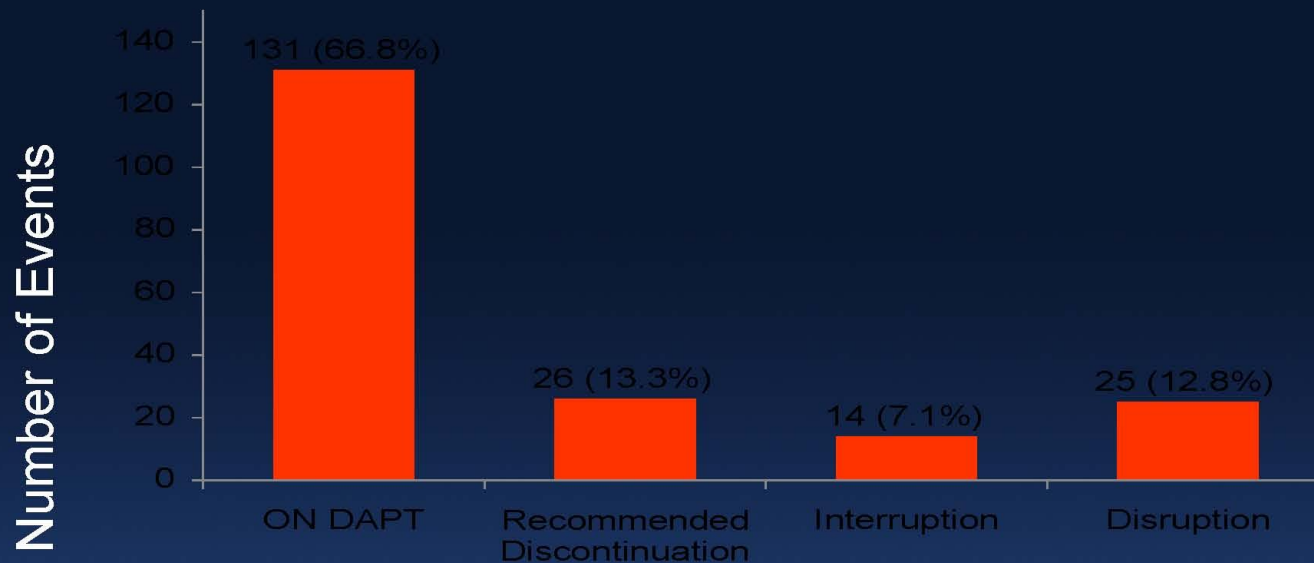
PARIS

DAPT Cessation and Def/Prob Stent Thrombosis



PARIS

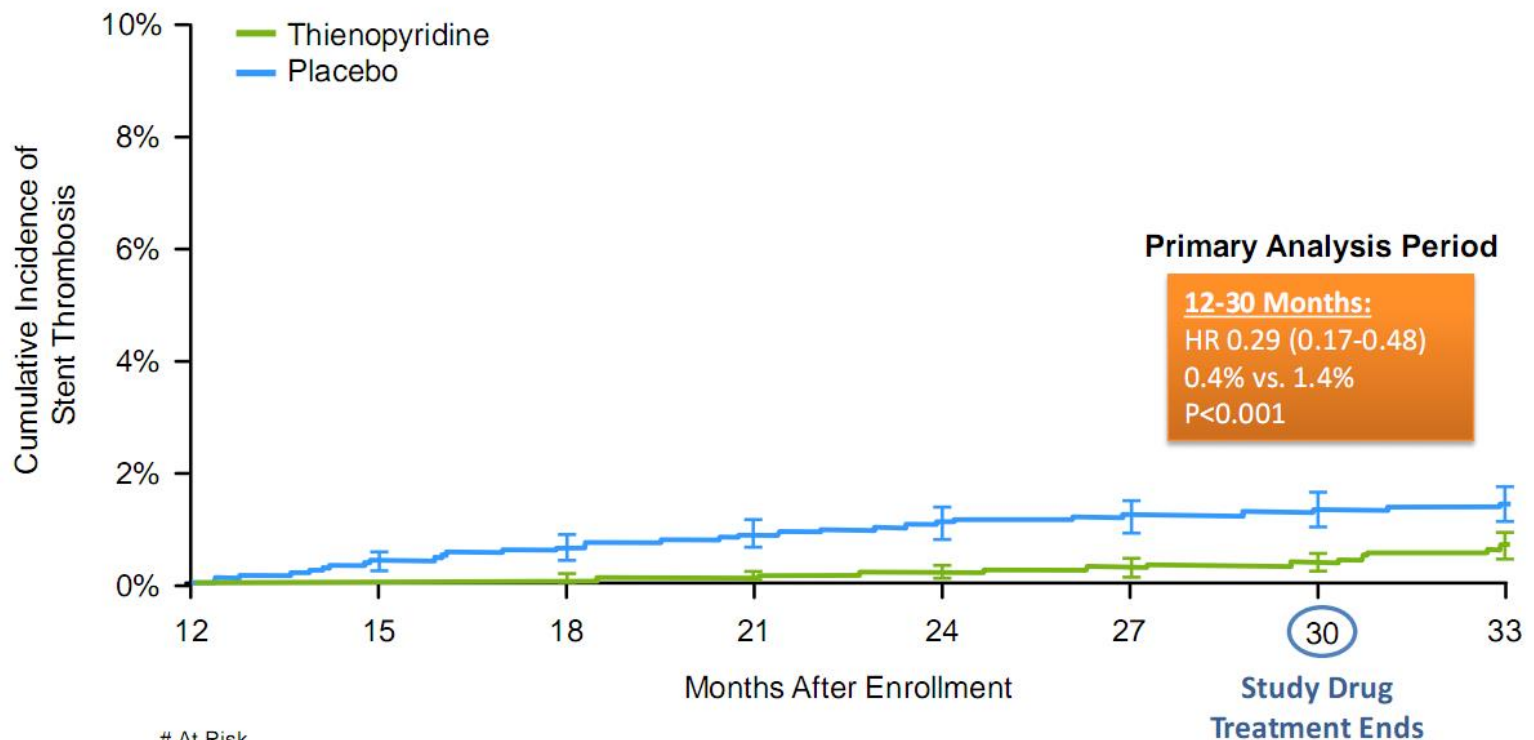
Number (%) of Major (BARC ≥ 3) Bleeding Events by DAPT Status*



*Out of 196 Bleeding events at 2 years, 131 (66.8%) occurred while patients were ON DAPT. Major Bleeding defined as BARC ≥ 3 .

DAPT (Dual Antiplatelet Therapy)

Co-Primary Effectiveness End Point Stent Thrombosis



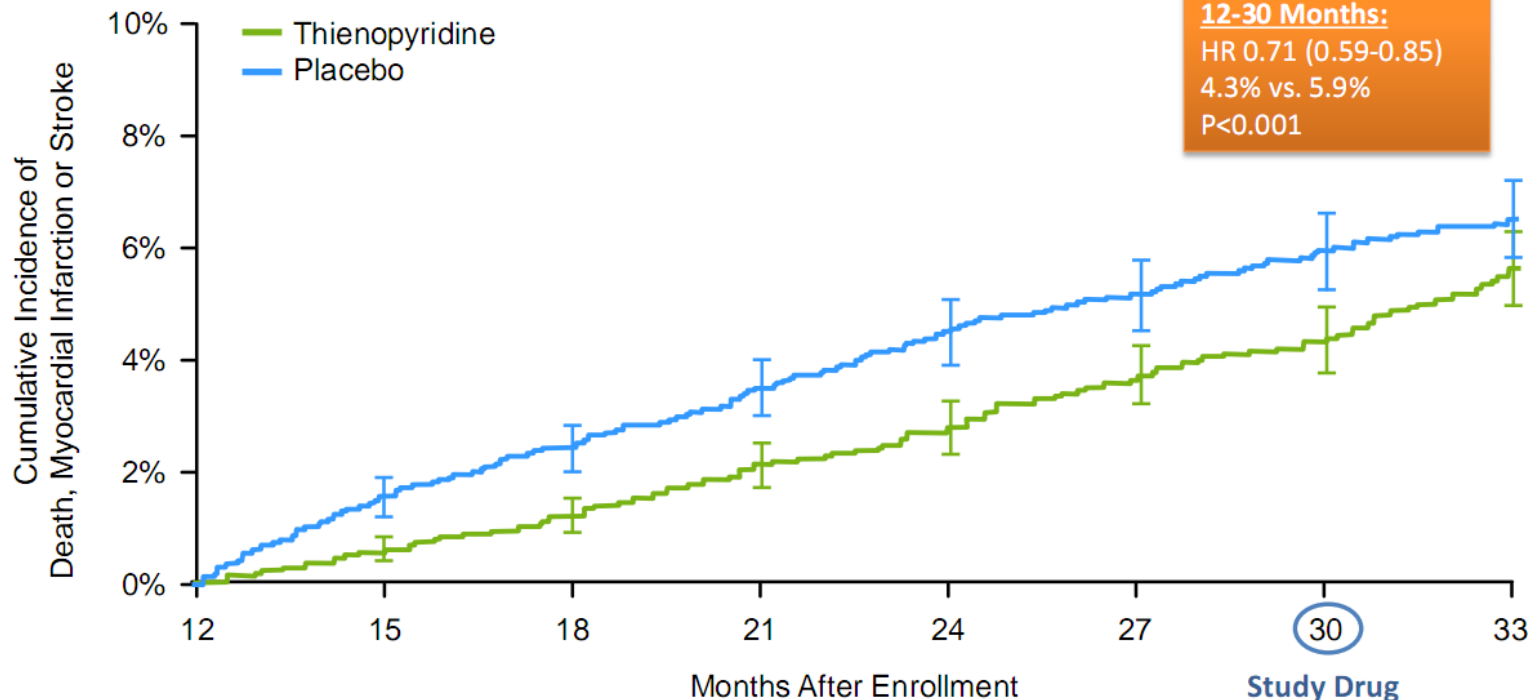
DAPT (Dual Antiplatelet Therapy)

Co-Primary Effectiveness End Point MACCE



Primary Analysis Period

12-30 Months:
HR 0.71 (0.59-0.85)
4.3% vs. 5.9%
P<0.001

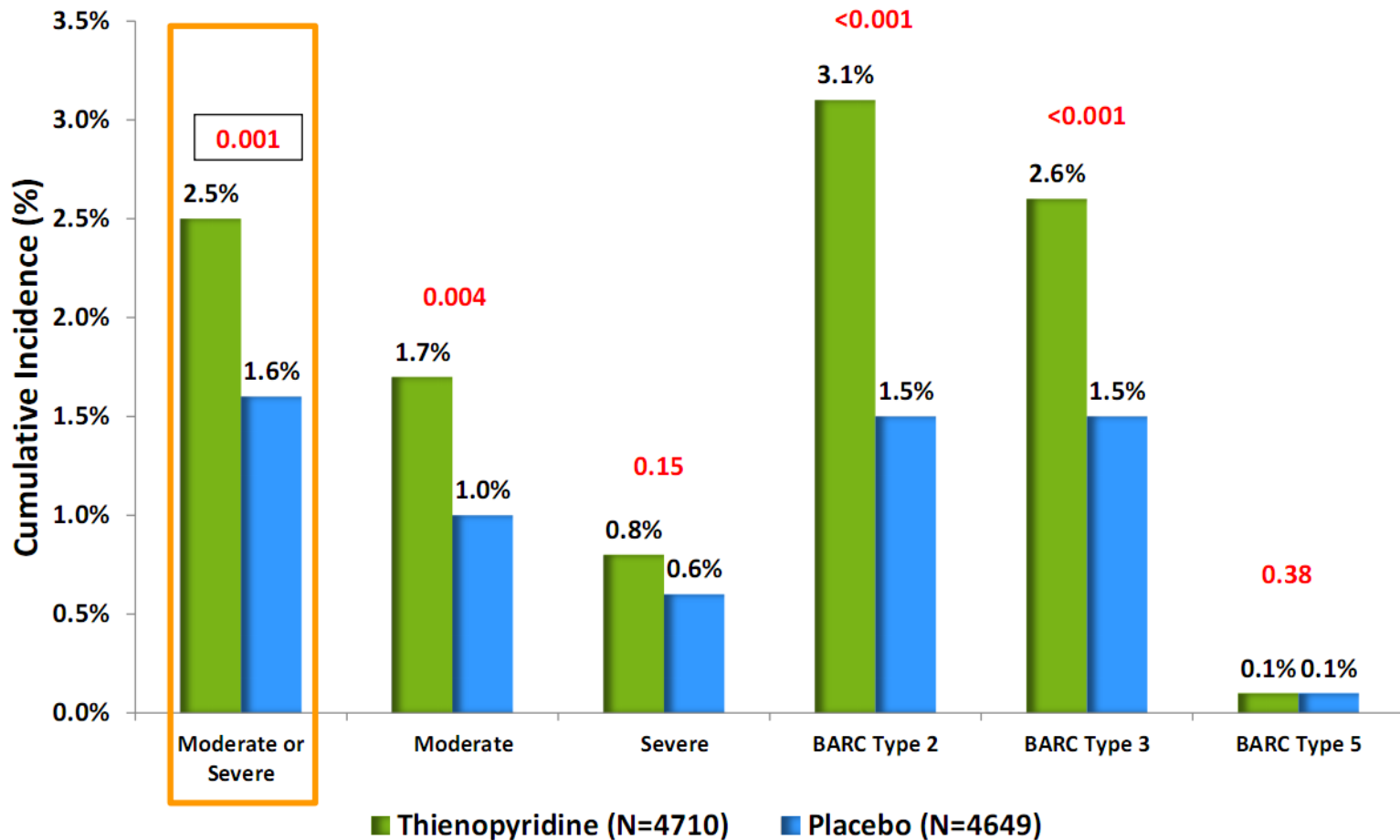


At Risk

Thienopyridine	5020	4917	4840	4778	4702	4611	4554	3029
Placebo	4941	4799	4715	4635	4542	4476	4412	2997

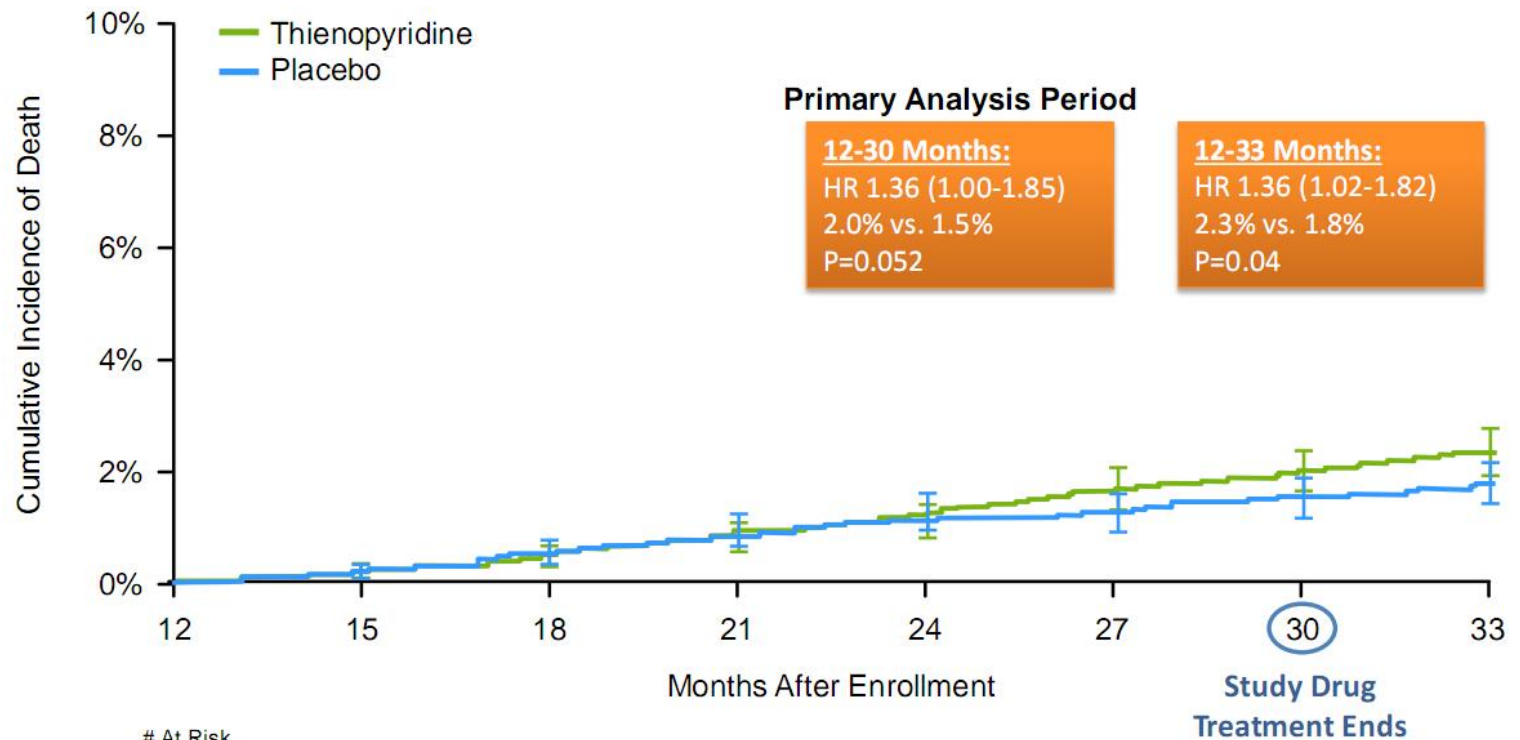
DAPT (Dual Antiplatelet Therapy)

Primary Safety End Point (Moderate or Severe Bleeding): 12-30 Months

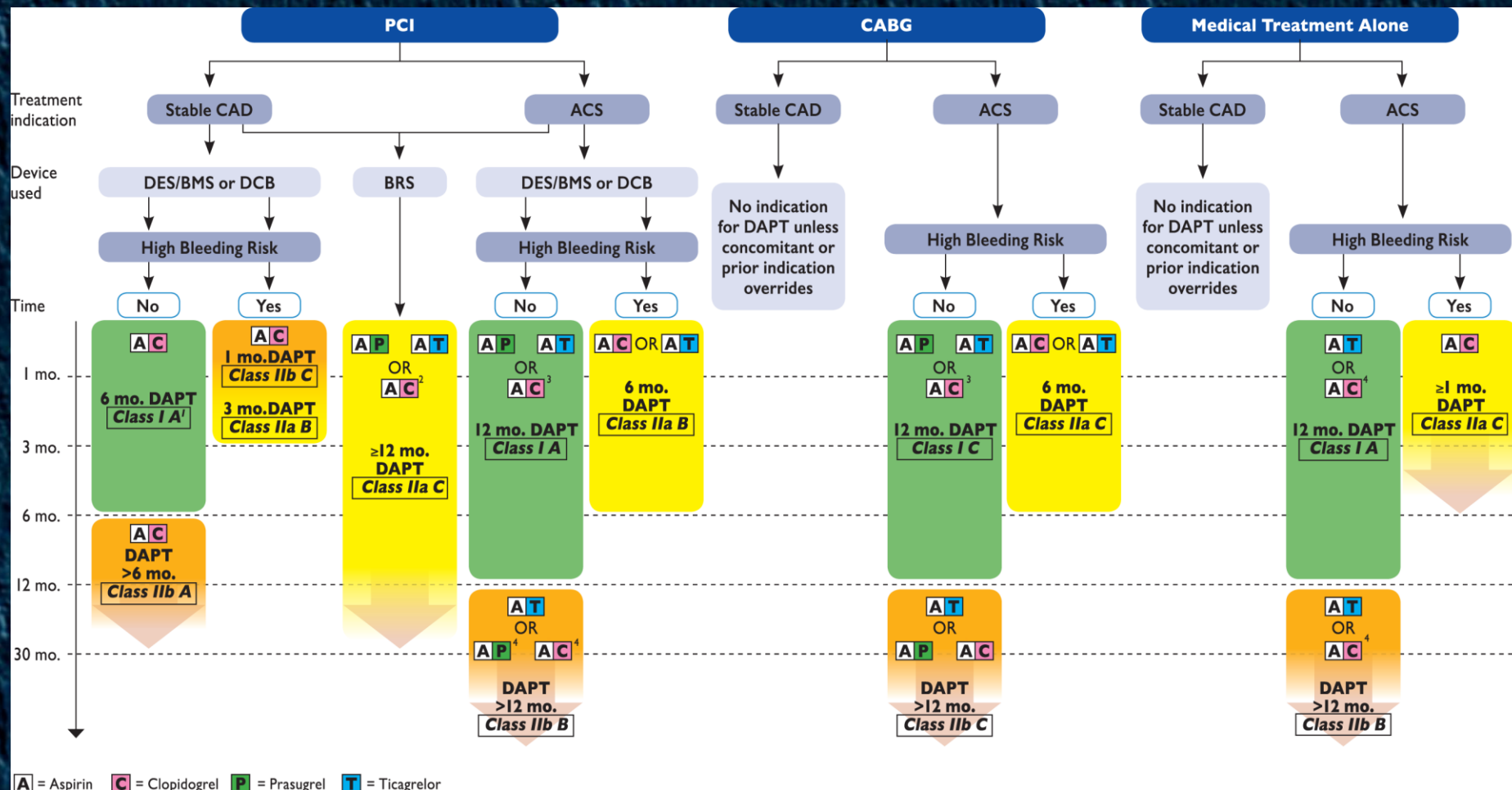


DAPT (Dual Antiplatelet Therapy)

All-Cause Mortality

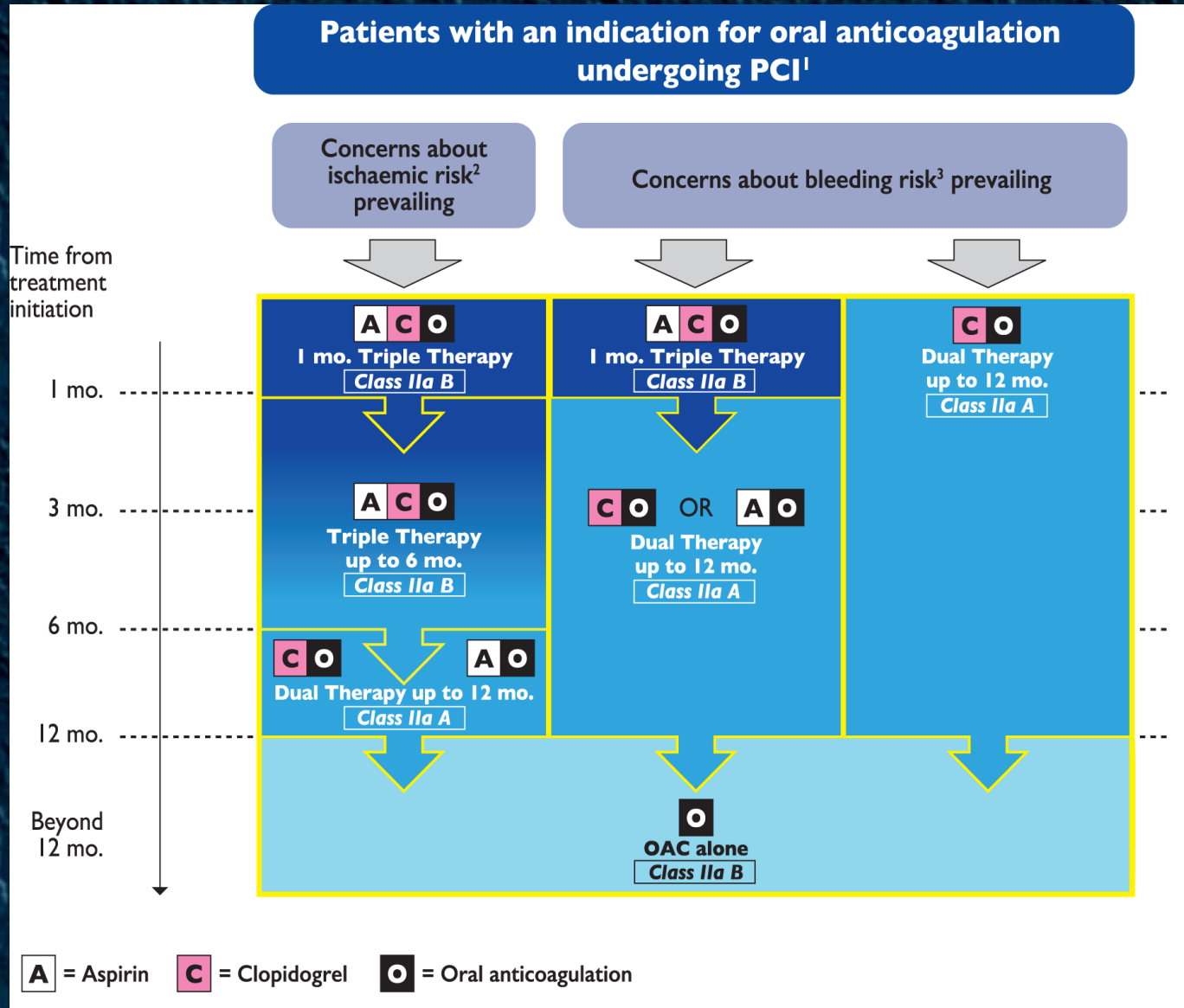


DAPT alkalmazása CAD-ben

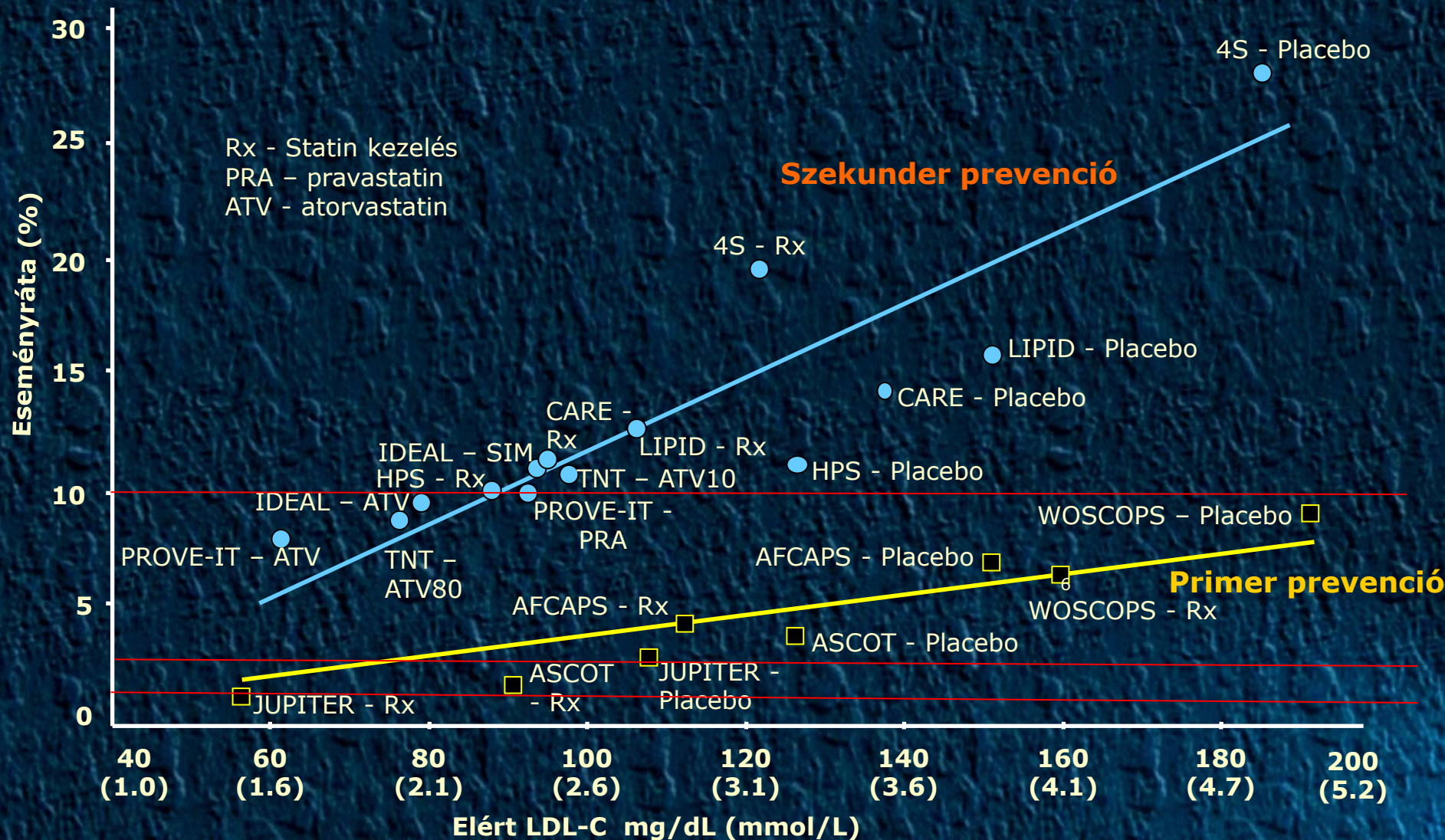


- 1: After PCI with DCB 6 months. DAPT should be considered (Class IIa B).
- 2: If patient presents with Stable CAD or, in case of ACS, is not eligible for a treatment with prasugrel or ticagrelor.
- 3: If patient is not eligible for a treatment with prasugrel or ticagrelor.
- 4: If patient is not eligible for a treatment with ticagrelor.

DAPT + OAC PCI után

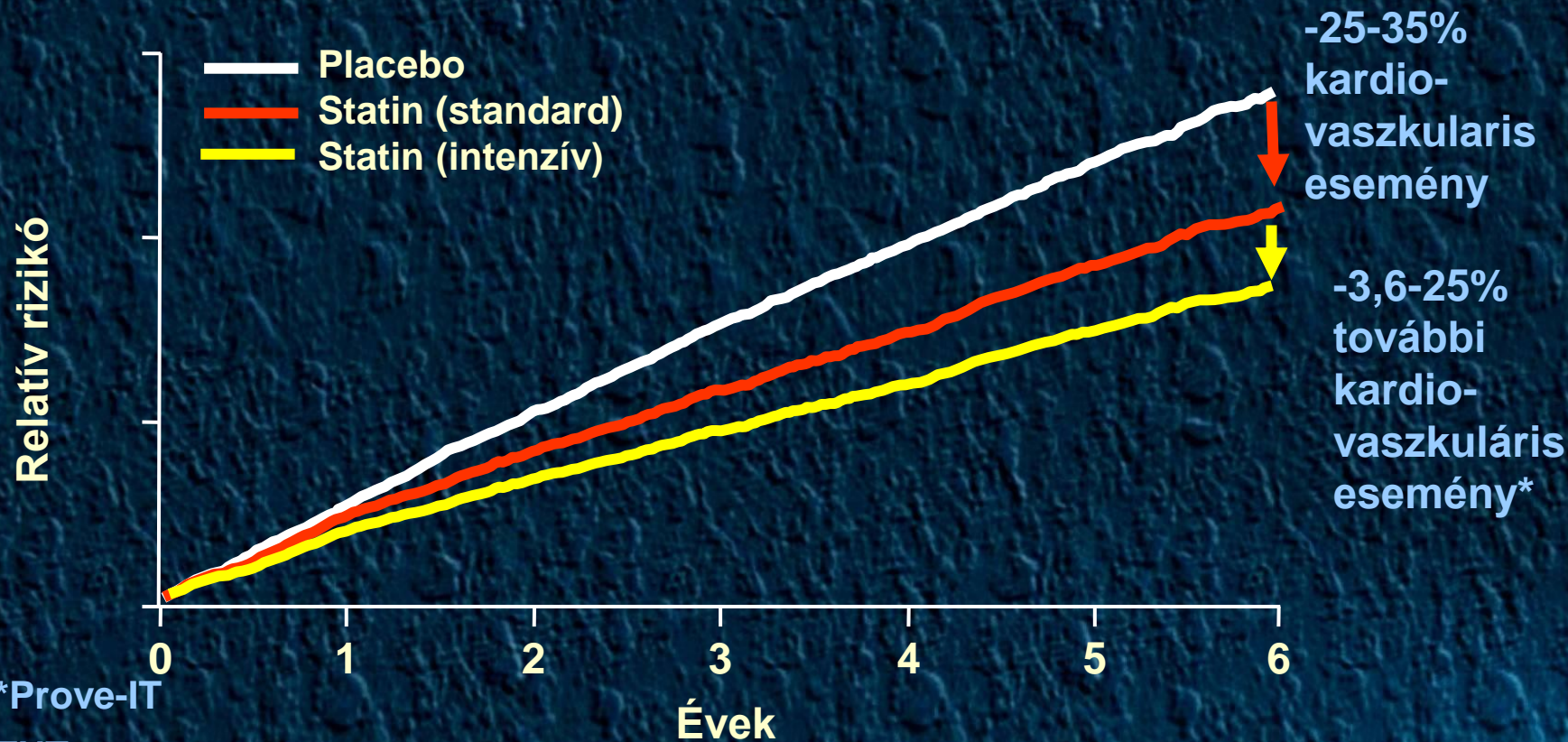


Az LDL-koleszterin és az 5 éves major koszorúér események kockázatának kapcsolata



Rosensen RS. *Exp Opin Emerg Drugs* 2004;9(2):269-, LaRosa JC et al. *N Engl J Med* 2005;352:e-version, Ridker PM, *N Engl J Med* 2008;359:2195- alapján

A statin kezelés hatása a kardiovaszkuláris eseményekre a (szekunder) prevenció során



*Prove-IT

TNT

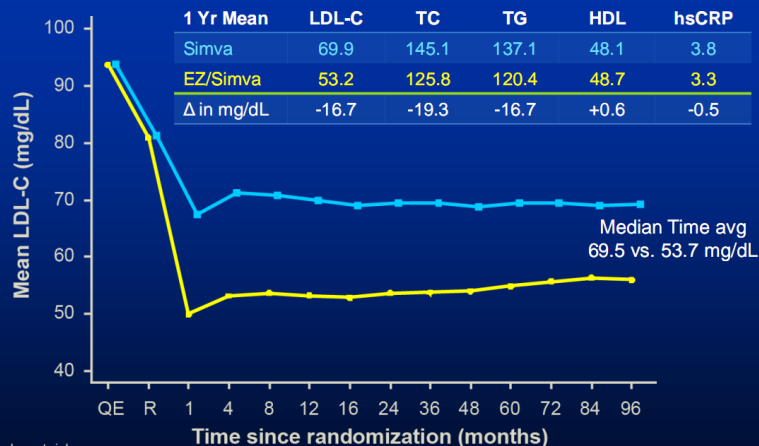
A-Z

IDEAL

SEARCH

IMPROVE-IT - HIJ-PROPER

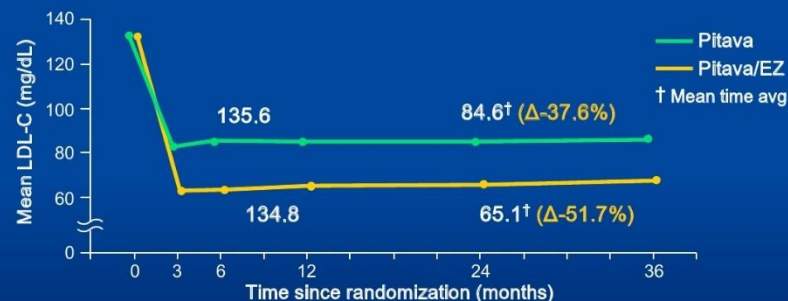
LDL-C and Lipid Changes



Number at risk:

EZ/Simva	8990	8889	8230	7701	7264	6864	6583	6256	5734	5354	4508	3484	2608	1078
Simva	9009	8921	8306	7843	7289	6939	6607	6192	5684	5267	4395	3387	2569	1068

LDL-C and Lipid Changes

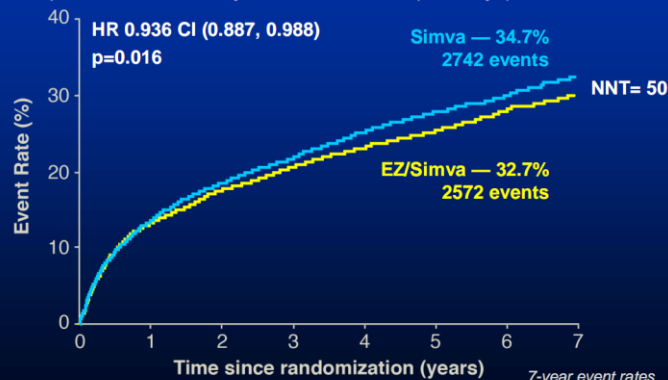


1yr mean	LDL-C	TC	TG	HDL-C	Pitava mean dose (mg/day)
Pitava, mg/dL	87.2	165.3	144.2	50.3	2.02
Pitava/EZ, mg/dL	67.5	142.7	125.2	50.9	2.36
Δ in mg/dL	-19.7*	-22.6*	-19.0*	+0.6	

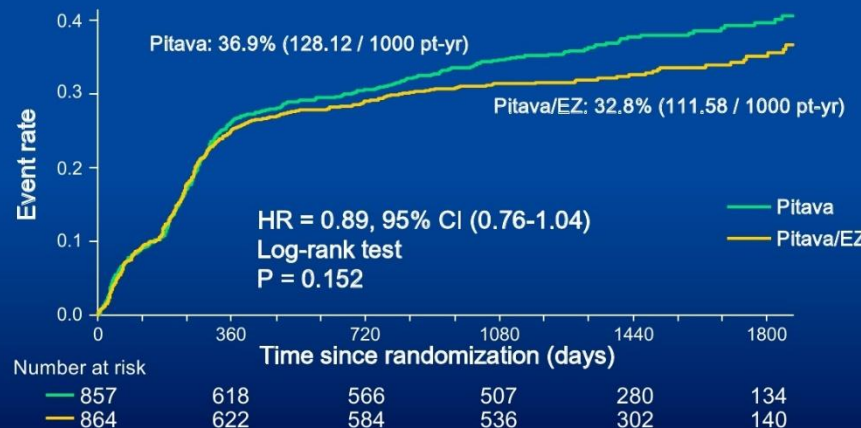
Primary Endpoint — ITT



Cardiovascular death, MI, documented unstable angina requiring rehospitalization, coronary revascularization (≥ 30 days), or stroke



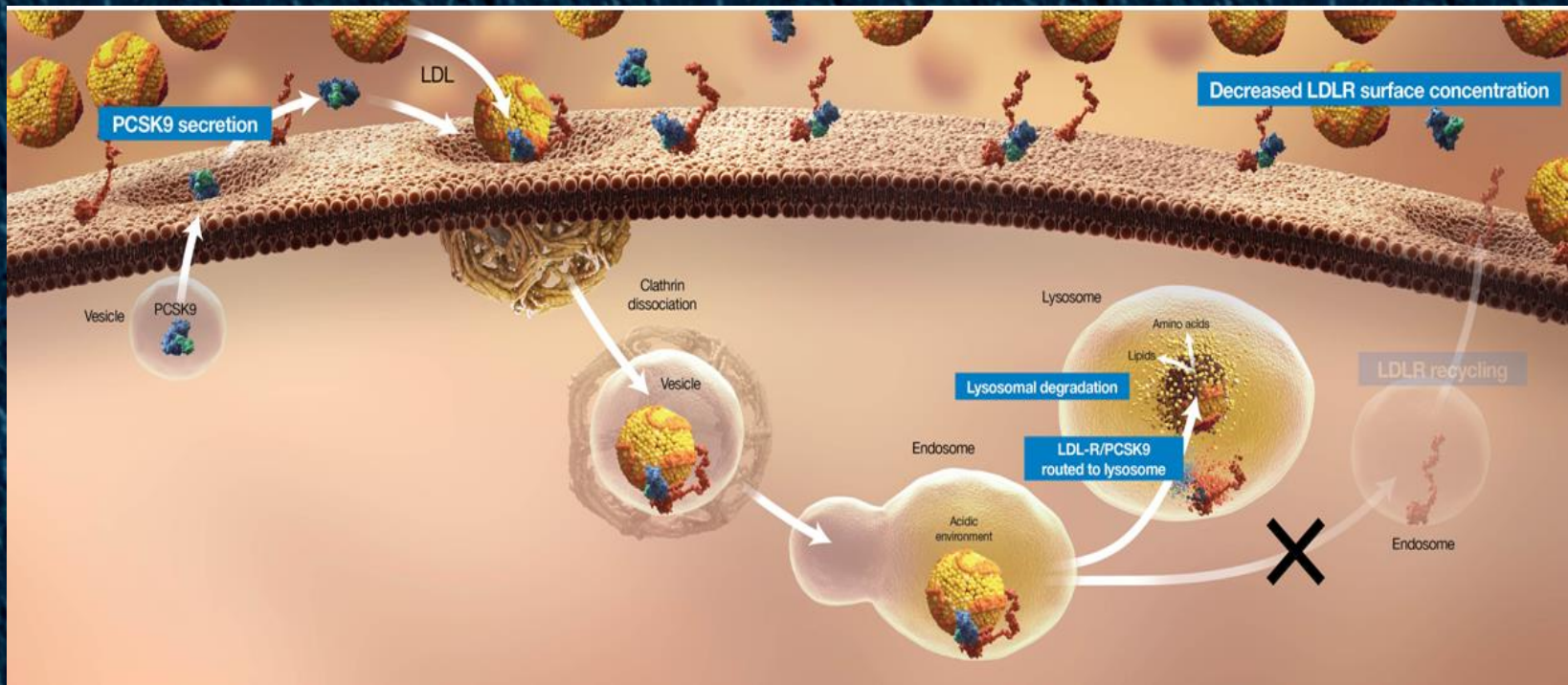
Primary Endpoint (composite)



Új terápiás lehetőségek

PCSK9 - a Key Regulator of LDL-R Recycling

- PCSK9 mediates degradation of the LDL-R by interacting with the extracellular domain and targeting the receptor for degradation¹



LDL = low-density lipoprotein.

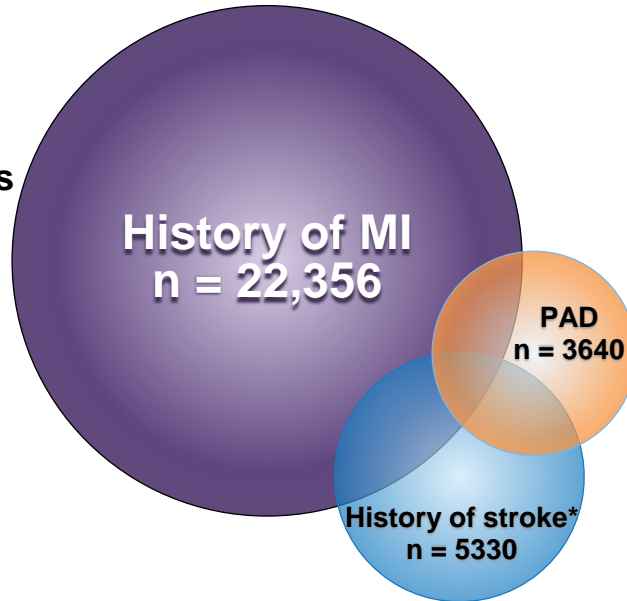
1. Horton JD, et al. *J Lipid Res.* 2009;50:S172-S177. 2. Qian YW, et al. *J Lipid Res.* 2007;48:1488-1498. 3. Zhang DW, et al. *J Biol Chem.* 2007;282:18602-18612.

PCSK9 - FOURIER és ODYSSEY tanulmányok

FOURIER¹
N = 27,564

ODYSSEY OUTCOMES²
N ~ 18,530

Median time from
the event ~ **3 years**



Median time from
the event ~ **3 months**

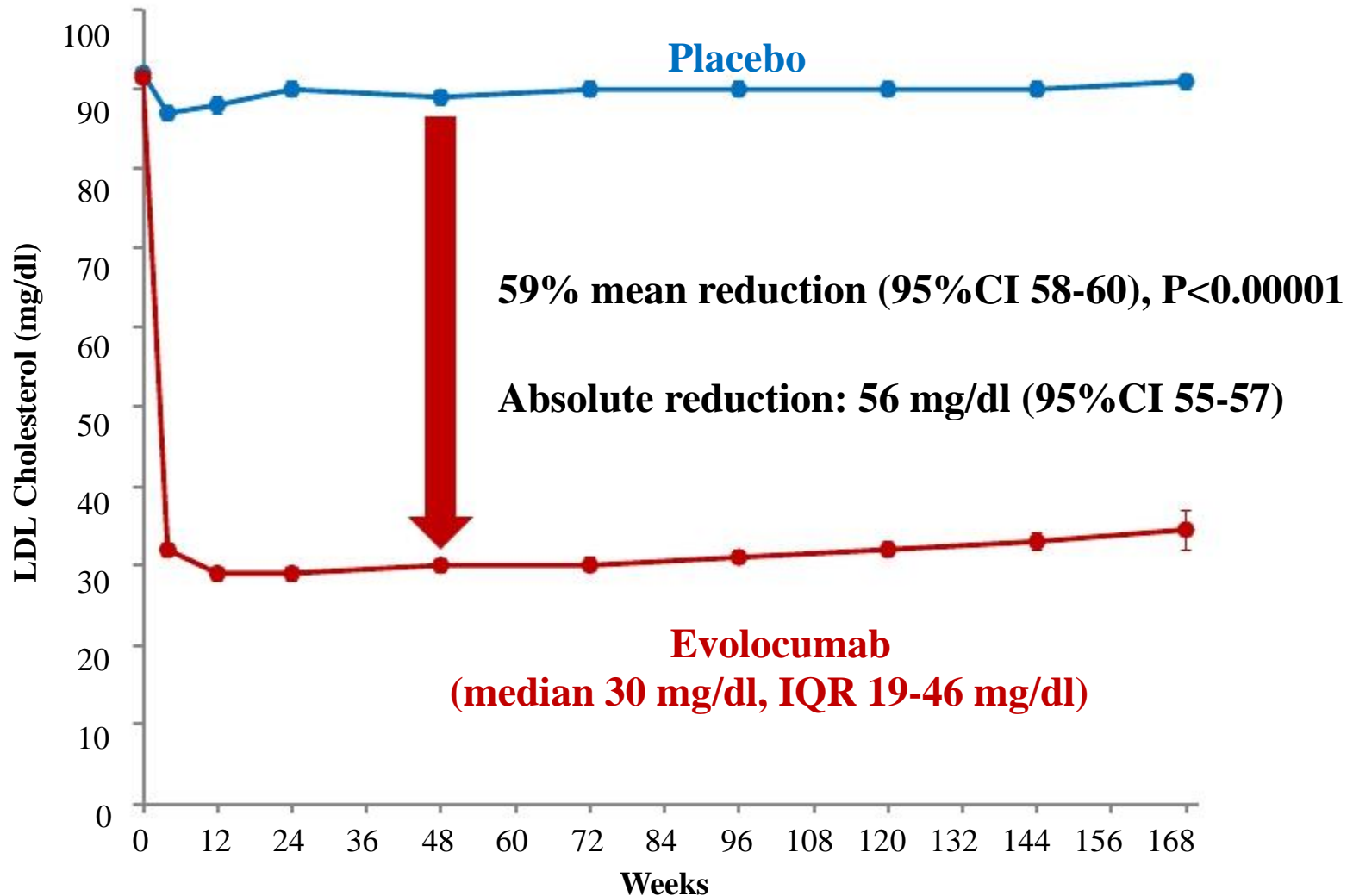


• *Non-haemorrhagic stroke.

1. Sabatine MS, et al. Am Heart J 2016;173:94–101. 2. Schwartz GG, et al. Am Heart J 2014;168:682–9.

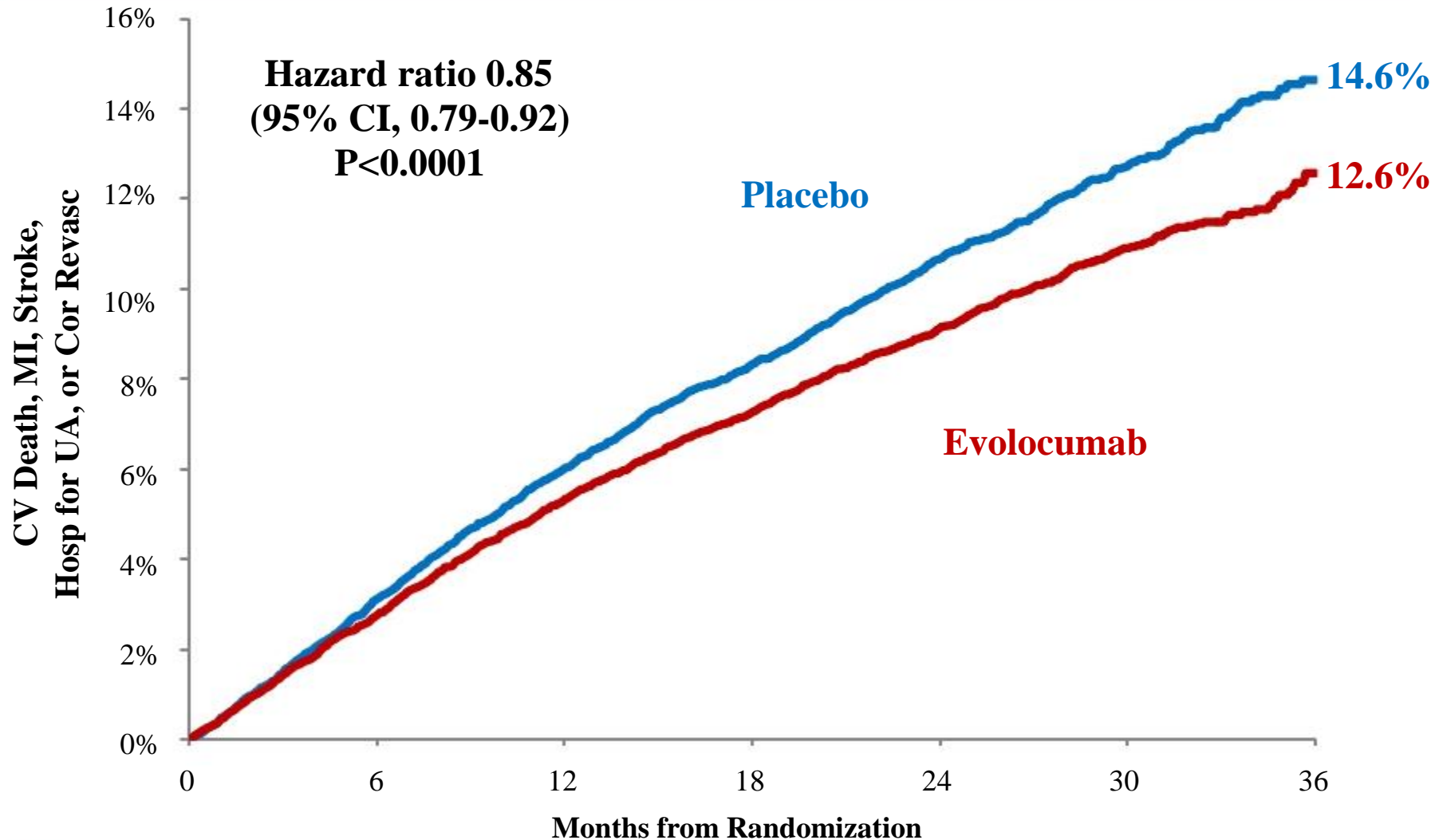


LDL Cholesterol



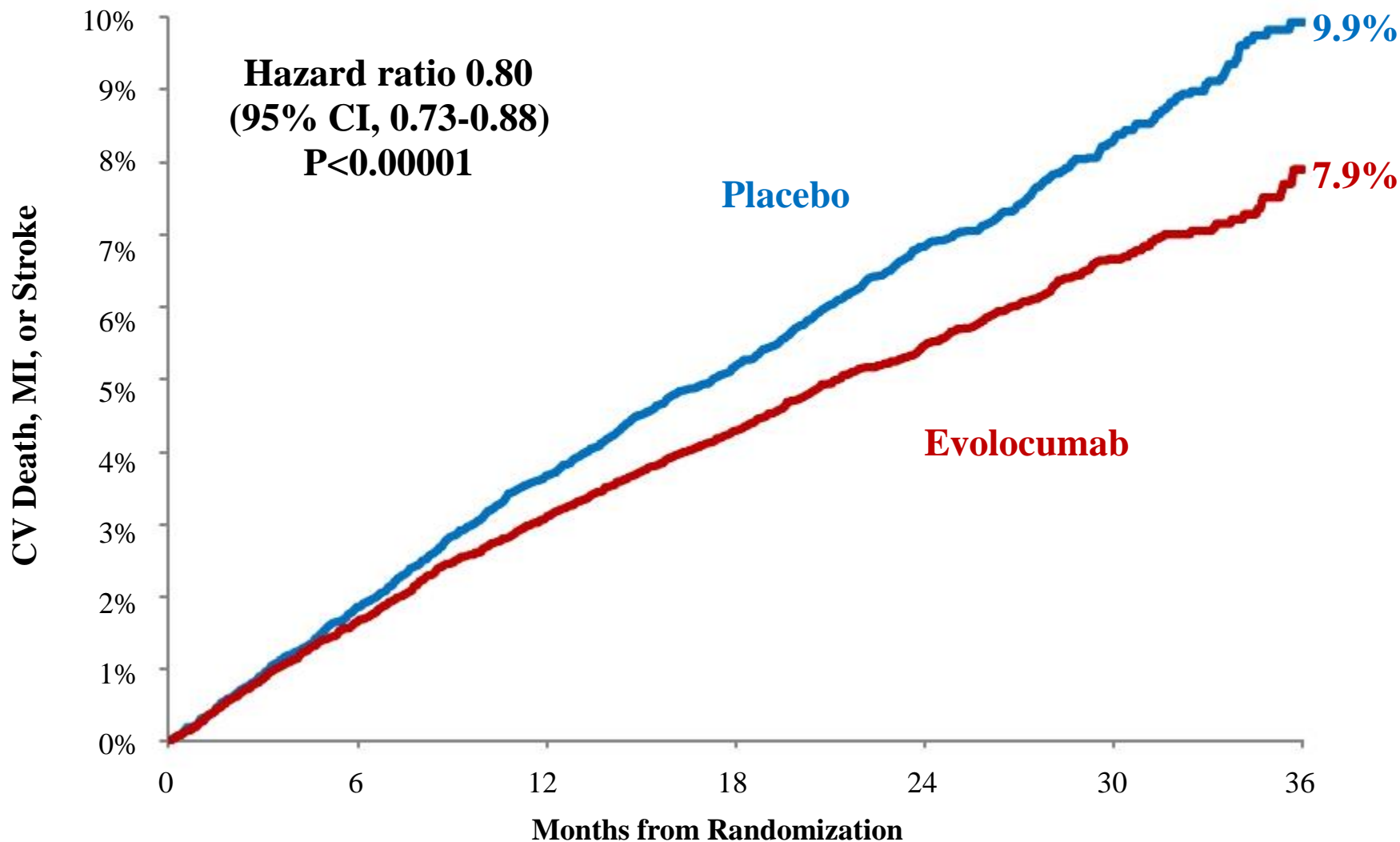


Primary Endpoint

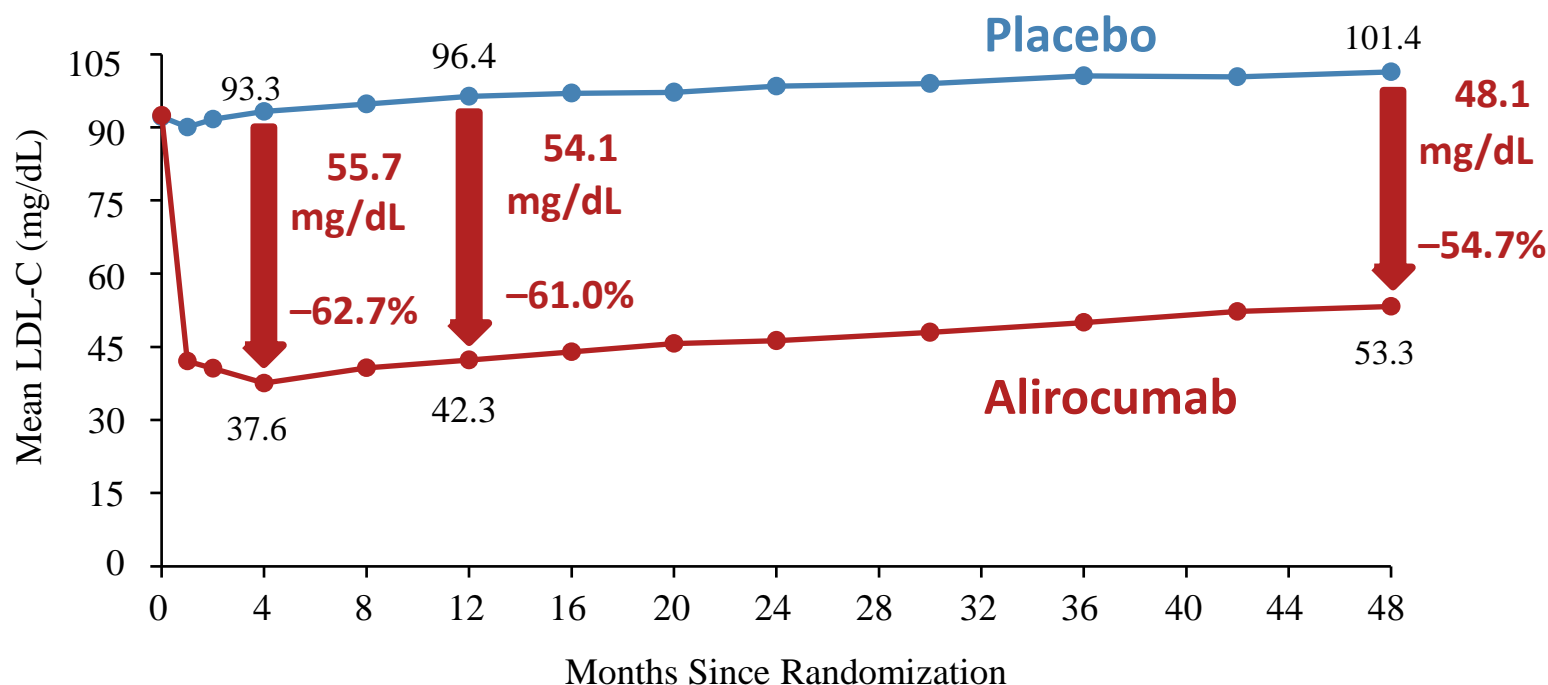




Key Secondary Endpoint



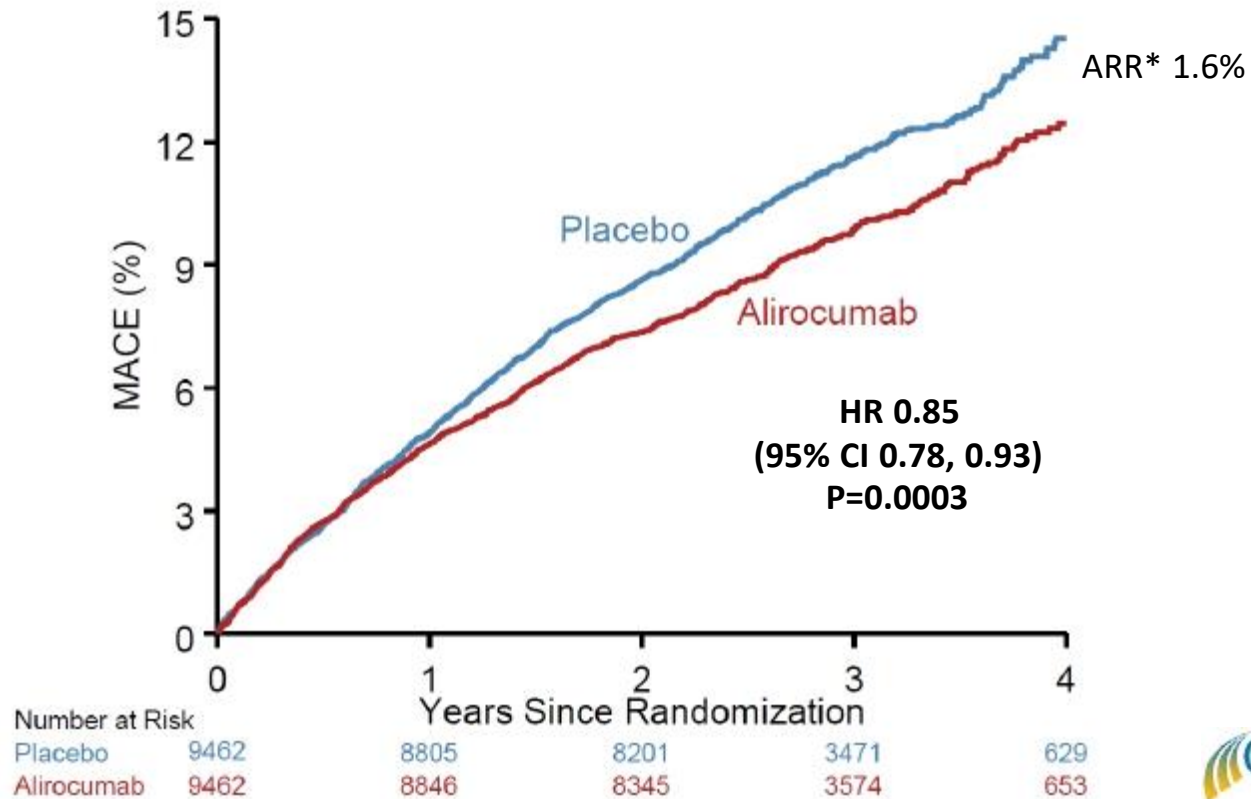
LDL-C: On-Treatment Analysis



Excludes LDL-C values after premature treatment discontinuation or blinded switch to placebo
Approximately 75% of months of active treatment were at the 75 mg dose

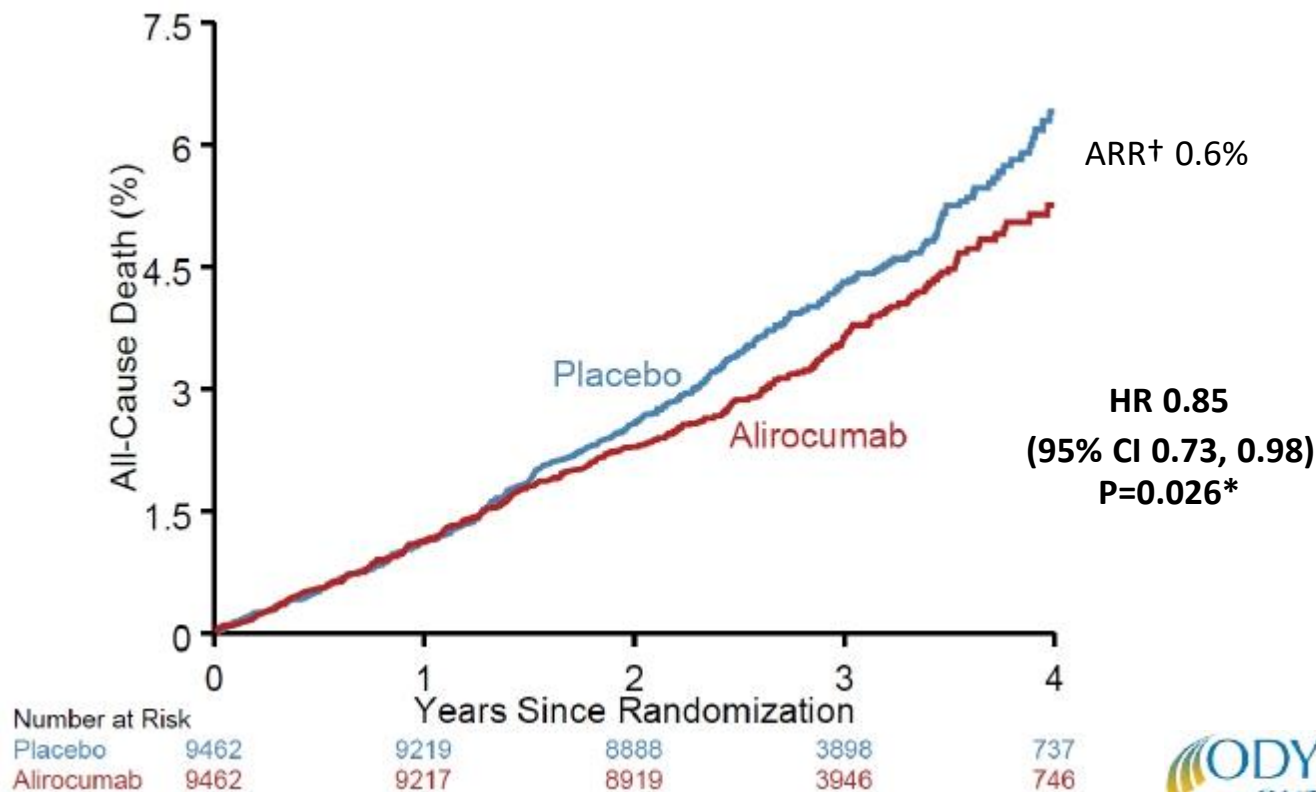


Primary Efficacy Endpoint: MACE





All-Cause Death



*Nominal P-value

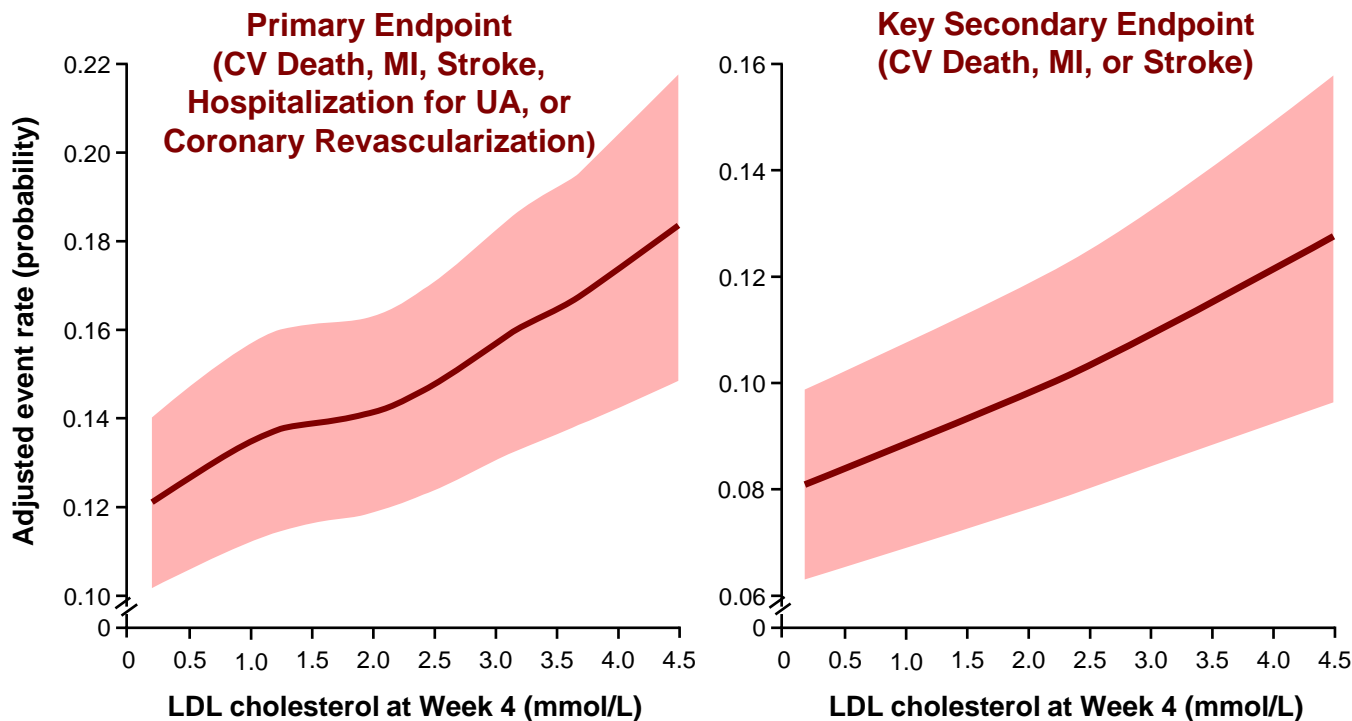
†Based on cumulative incidence



An Academic Research Organization of
Brigham and Women's Hospital and Harvard Medical School



Relationship Between Achieved LDL-C Level at Week 4 and Risk for the Primary and Key Secondary Efficacy Composite Endpoints



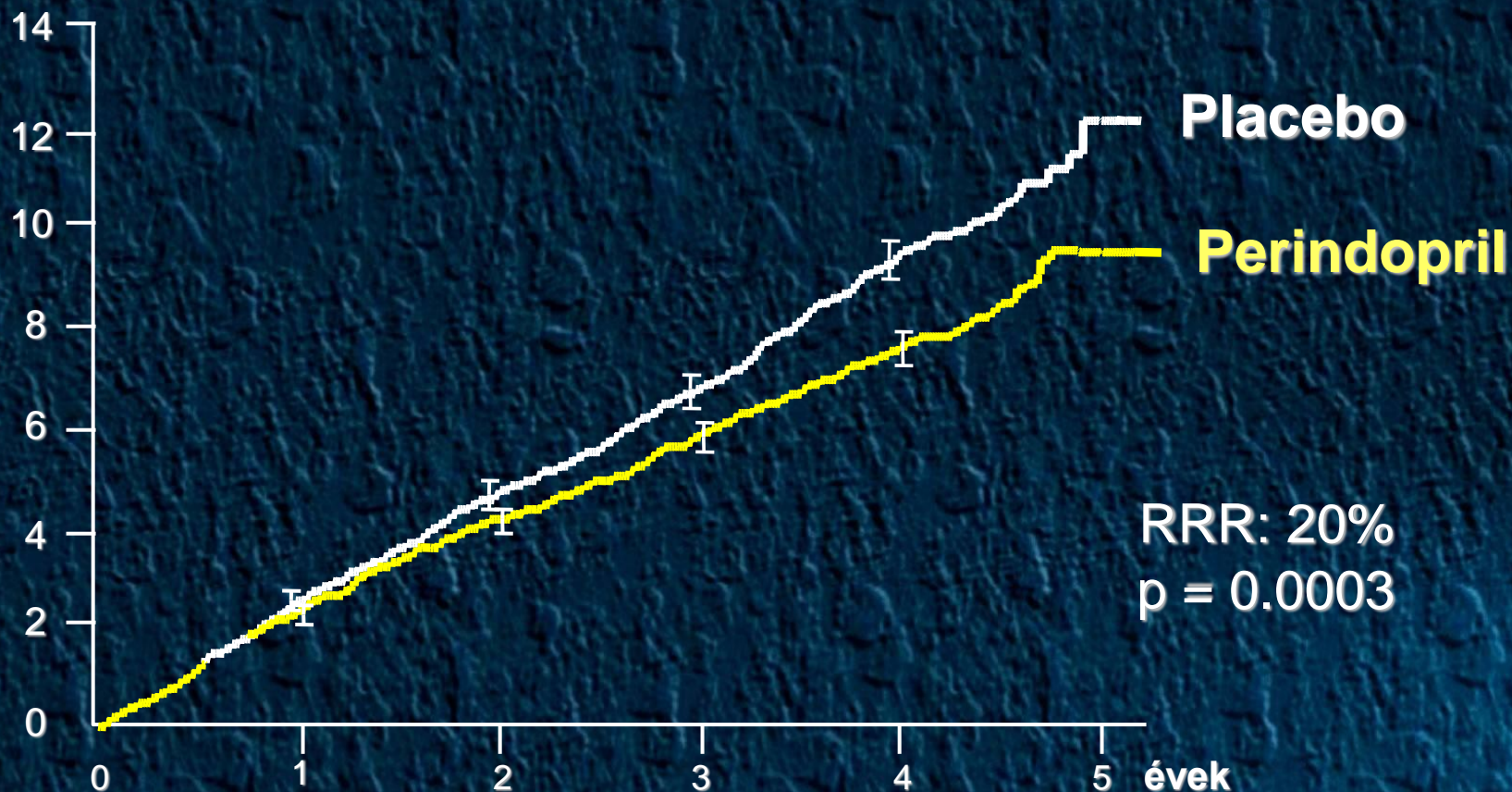
Risk of the primary and secondary composite endpoints was progressively lower as the achieved LDL-C at week 4 was reduced

For the primary endpoint $p = 0.0012$ for the β coefficient. For the secondary endpoint $p = 0.0001$ for the β coefficient.
CV = cardiovascular, MI = myocardial infarction, UA = unstable angina. The blue line represents the hazard ratio and shaded areas are the 95% CIs of the regression model estimate. Giugliano RP, et al. *Lancet*. [published online ahead of print August 28, 2017]. doi: 10.1016/S0140-6736(17)32290-0

GIUGLIANO, R., PEDERSEN, T., PARK, J., DE FERRARI, G., M., GACIONG, Z., CESKA, R., **TOTH, K.**, GOUNI-BERTHOLD, I., LOPEZ-MIRANDA, J., SCHIELE, F., MACH, F., OTT, R., KANEVSKY, E., LIRA-PINEDA, A., SOMARATNE, R., WASSERMAN, S., KEECH, A., SEVER, P., SABATINE, M. Clinical efficacy and safety of achieving very low LDL-CLDL-cholesterol concentrations with the PCSK9 inhibitor evolocumab: a prespecified secondary analysis of the FOURIER trial. *Lancet*, doi: 10.1016/S0140-6736(17)32290-0, 2017.



% CV halálozás, MI vagy szívmegállás

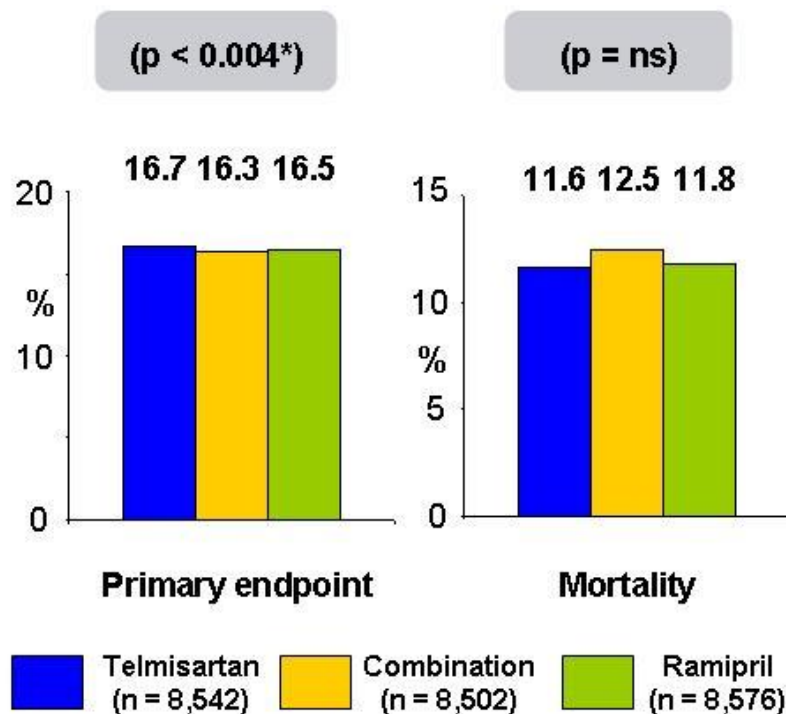


Placebo csoport, éves eseményráta: 2.4%



ONTARGET

Trial design: Patients at high risk for cardiovascular events, but without heart failure, were randomized to telmisartan, ramipril, or the combination. Patients were followed for a median of 56 months.



* Telmisartan vs. ramipril for noninferiority

Results

- Telmisartan (16.7%) noninferior; combination (16.3%) not superior to ramipril (16.5%) for primary endpoint (CV death, MI, stroke, heart failure)
- Greater incidence of hypotension in combination (4.8%) and telmisartan (2.7%) groups, compared with ramipril group (1.7%) ($p < 0.001$)

Conclusions

- Either telmisartan or ramipril, but not both, can be used in hypertensive patients at high risk for cardiovascular events
- Side effects greater with combination therapy



American Heart Association | American Stroke Association

Learn and Live.

TRANSCEND

Telmisartan Randomized Assessment Study in ACE Intolerant Subjects With CV Disease.

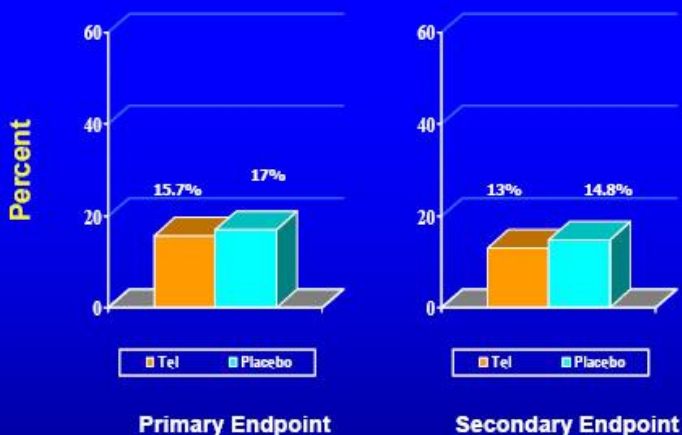
BACKGROUND: Providing alternatives to ACEI intolerant patients is important. This is a parallel study to ON-TARGET (Effectiveness & Safety of Ramipril Alone Compared With Telmisartan Alone & in Combo With Ramipril in Pts at Hi Risk for

CV Events) seeking to identify if a ARB alone can be effective in improving outcomes in hi risk CV pts.

PURPOSE: to determine if telmisartan 80mg daily vs placebo can reduce CV event outcomes.

DESIGN: Prospective, multicenter, randomized, parallel, placebo controlled study of 5,926 ACEI Intolerant pts randomized to: Telmisartan (Tel) 80mg po daily (n = 2,954) & placebo (n = 2,972). Median follow-up 56 months.

Telmisartan vs Placebo
At 56 months



Primary Endpoint:

Composite of CV death, MI, Stroke & HF hospitalization

Secondary Endpoint:

Composite of CV death, MI and Stroke

Results:

Primary: Tel (15.7%, n = 465) vs placebo (17%, n = 504)

HR .92 [95% CI (.81 – 1.05)]; p = 0.216

Secondary: Tel (13%, n = 384) vs placebo (14.8%; n = 440)

HR .87 [95% CI (.76 – 1.0)]; p = .048 unadj

Conclusions: Telmisartan is well tolerated in ACEI intolerant patients. There were no improvements in the composite primary outcomes; but there was a modest improvement with telmisartan in the composite secondary outcome when hospitalization was removed.

ARB coronaria betegségben (HIJ-CREATE)

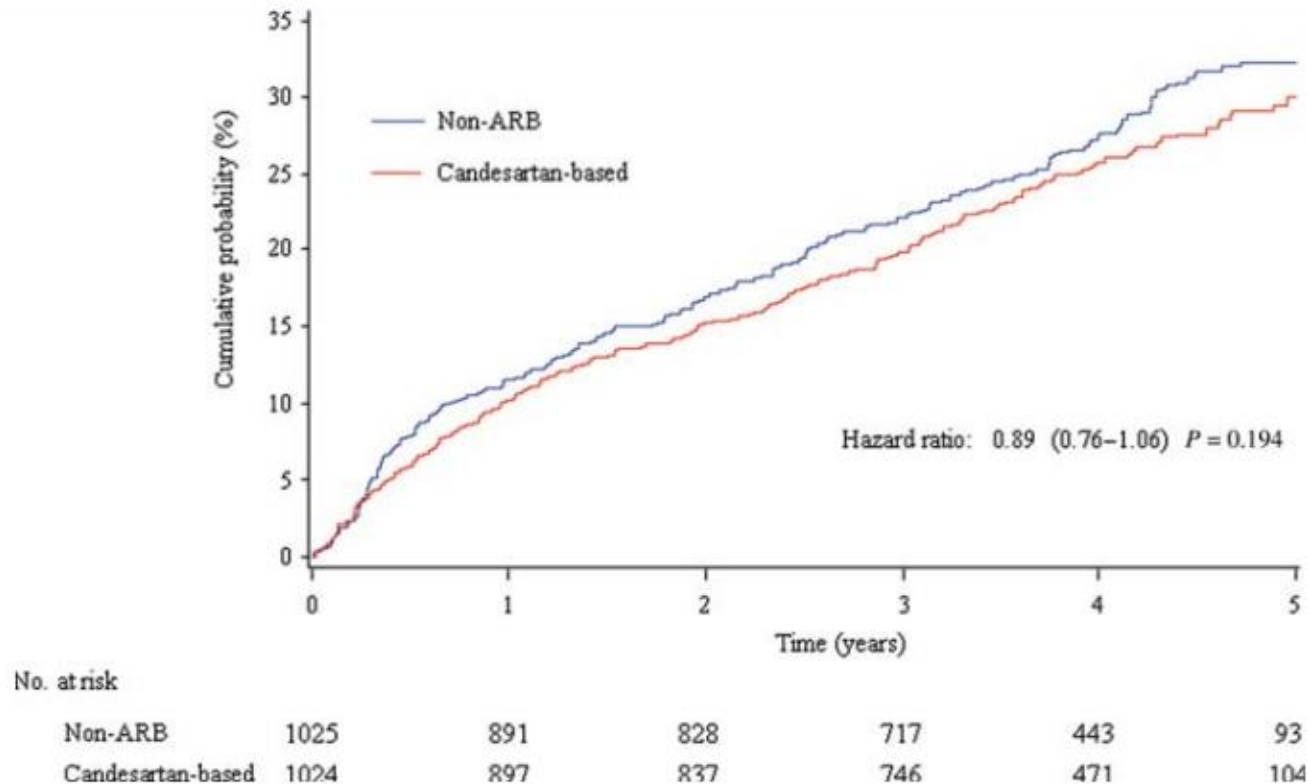


Figure 3 Kaplan–Meier curve for primary endpoint (major adverse cardiovascular event).

n = 2049

ACEI/ARB illetve statin stabil coronaria betegségekben

(REACH)

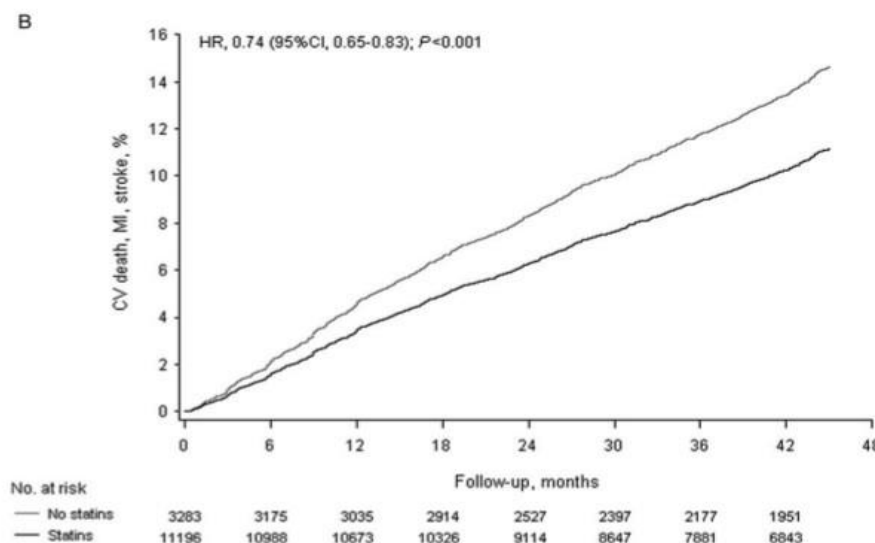
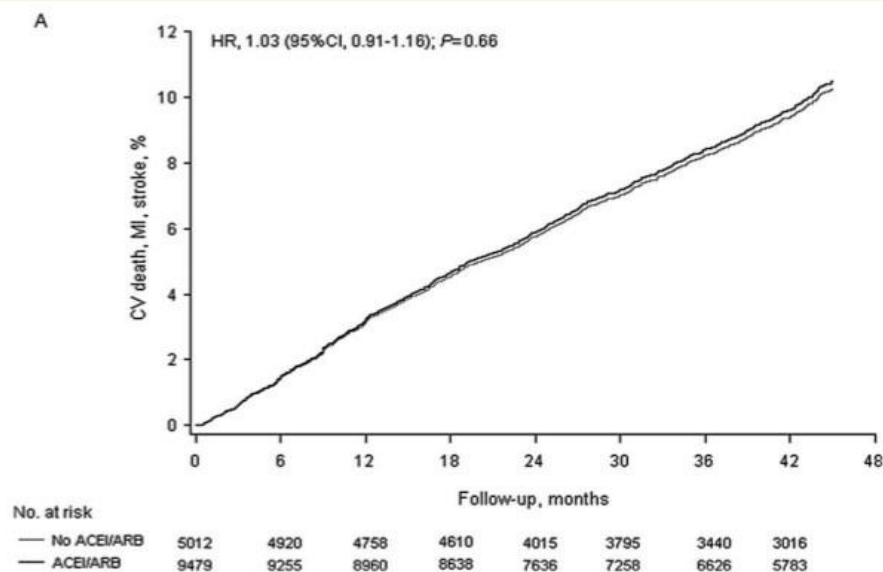


Figure 2 Cumulative incidence curve for the risk of primary outcome by ACEI/ARB use (A) and statin use (B) in propensity score-adjusted analysis. Adjusted event curves were calculated using the corrected group prognosis after categorization of propensity score into deciles.

n = 20.909,
4-yr-f.u.

Esemény megelőzés II

Lipid-lowering drugs	Class ^a	Level ^b
Statins are recommended in all patients with CCS. ^c	I	A
If a patient's goal ^c is not achieved with the maximum tolerated dose of statin, combination with ezetimibe is recommended.	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.	I	A
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
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 = angiotensin-converting enzyme; ARB = angiotensin-receptor blocker; CCS = chronic coronary syndrome; HF = heart failure; LV = left ventricular; PCSK9 = proprotein convertase subtilisin-kexin type 9; STEMI = ST-elevation myocardial infarction.

^aClass of recommendation.

^bLevel of evidence.

^cThe treatment goals are shown in the European Society of Cardiology/European Atherosclerosis Society Guidelines for the management of dyslipidaemias.

A stabil CAD gyógyszeres kezelésének algoritmus (ESC)

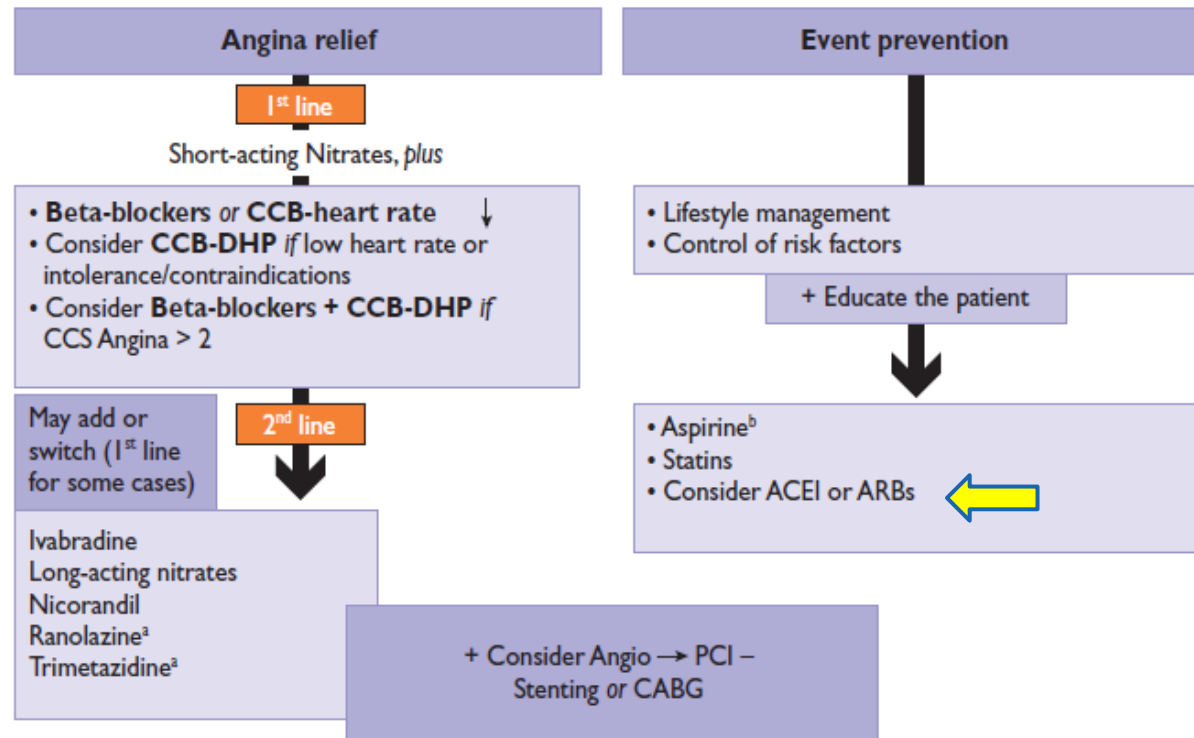
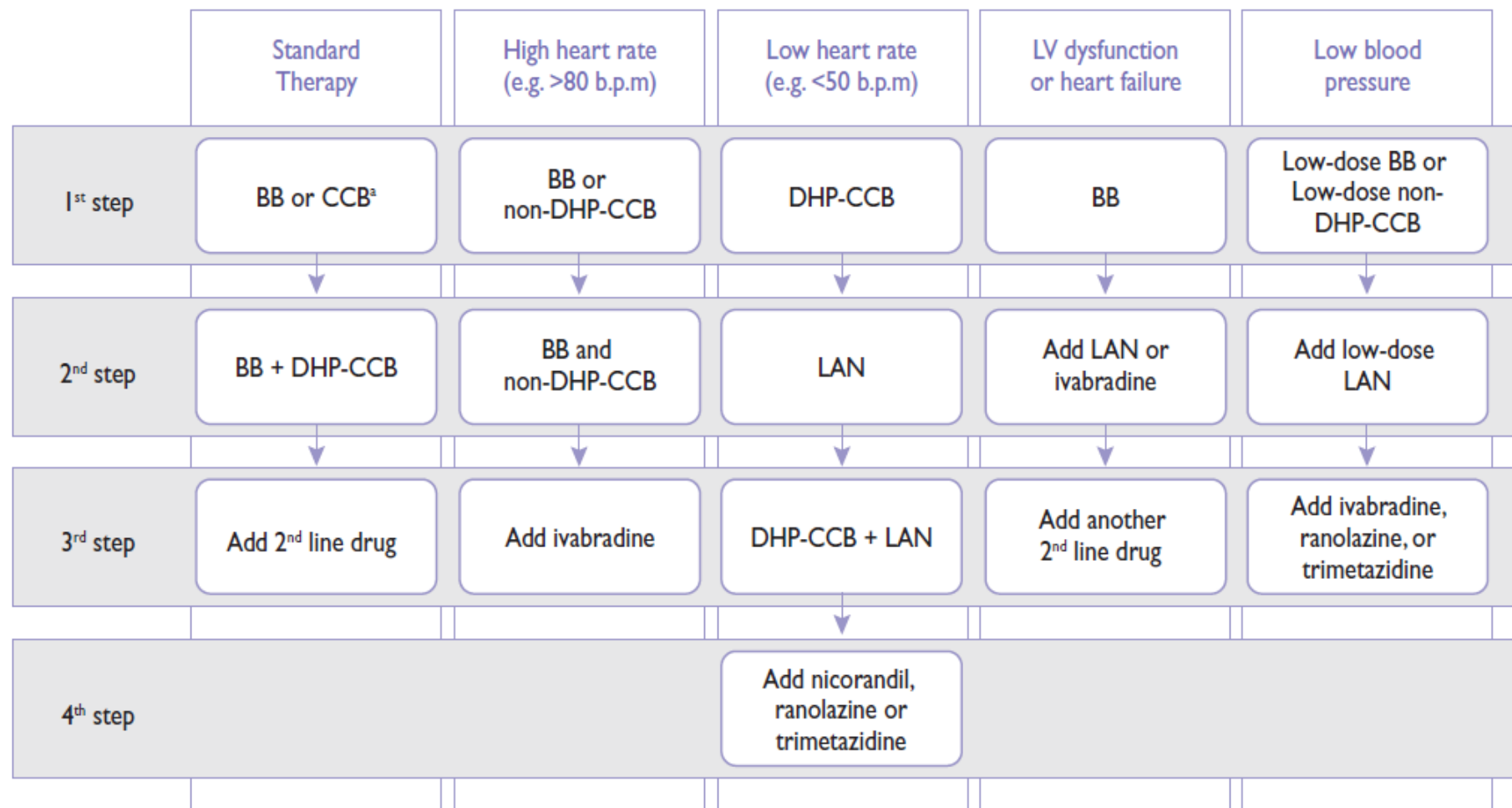


Figure 4 Medical management of patients with stable coronary artery disease. ACEI = angiotensin converting enzyme inhibitor; CABG = coronary artery bypass graft; CCB = calcium channel blockers; CCS = Canadian Cardiovascular Society; DHP = dihydropyridine; PCI = percutaneous coronary intervention.

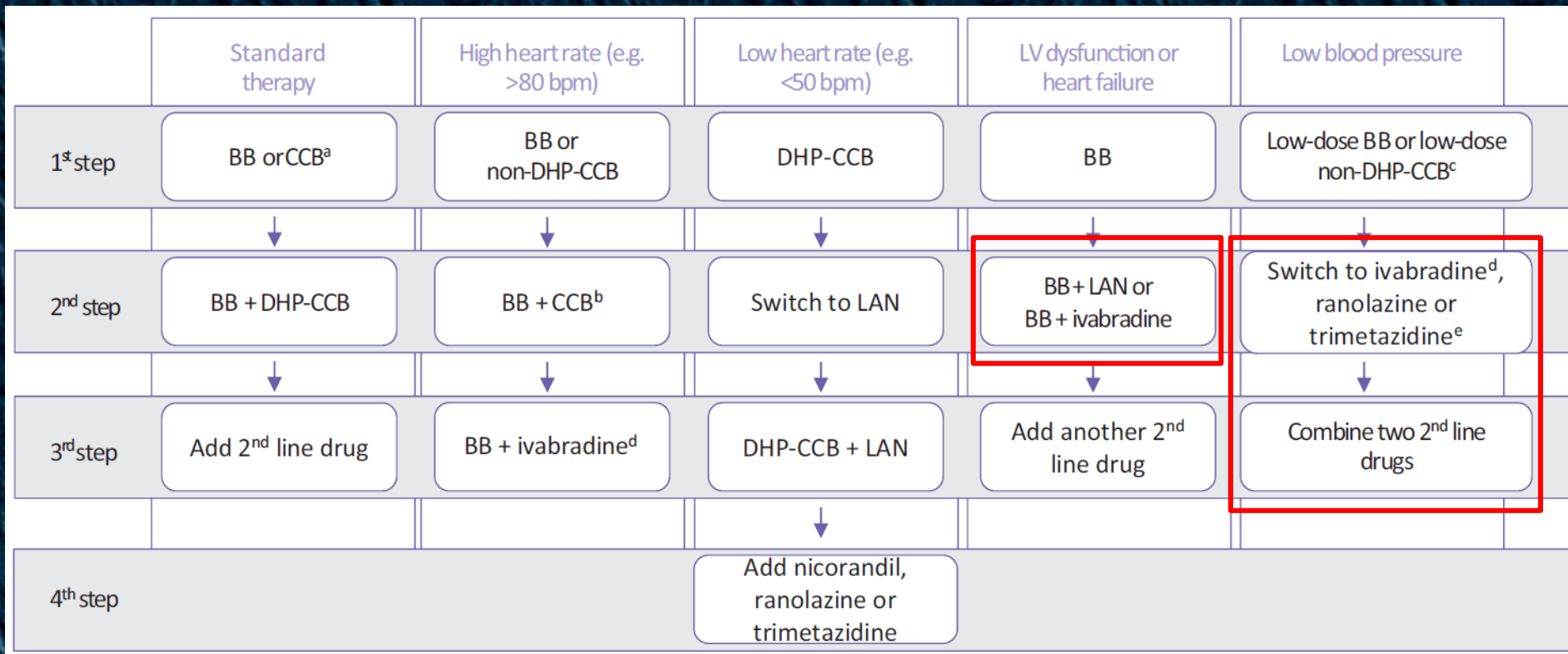
^aData for diabetics.

^bif intolerance, consider clopidogrel

Anti-ischaemiás gyógyszeres terápia CCS-ben



Anti-ischaemiás gyógyszeres terápia CCS-ben



„A stepwise strategy for anti-ischaemic drug therapy in CCS is proposed, depending on some baseline patient characteristics (Figure 8).

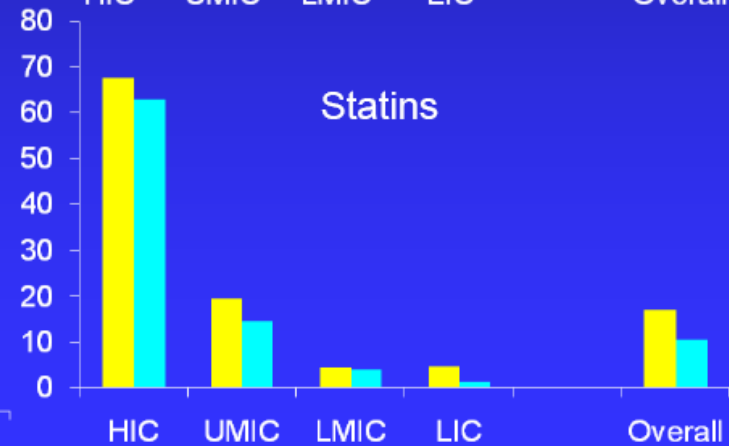
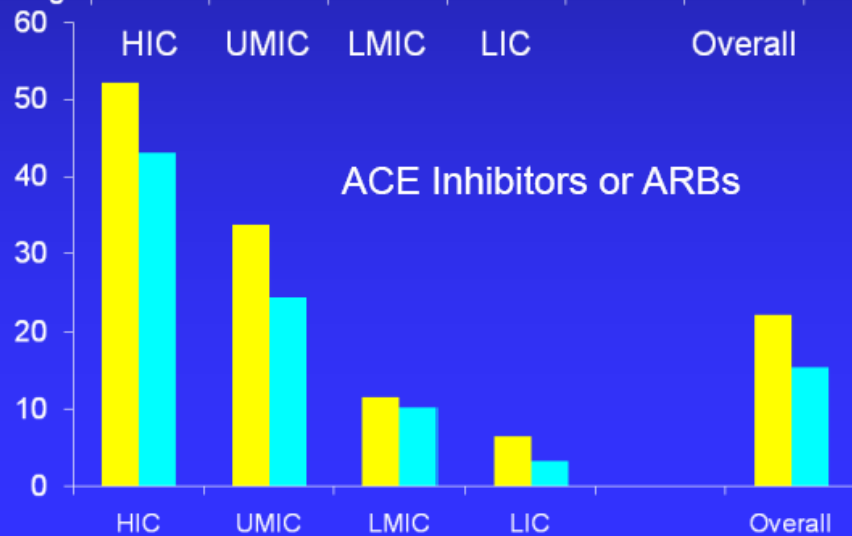
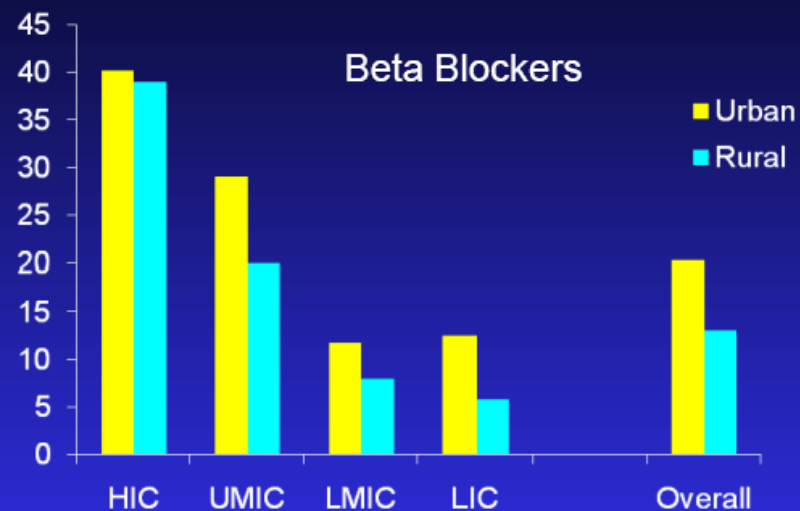
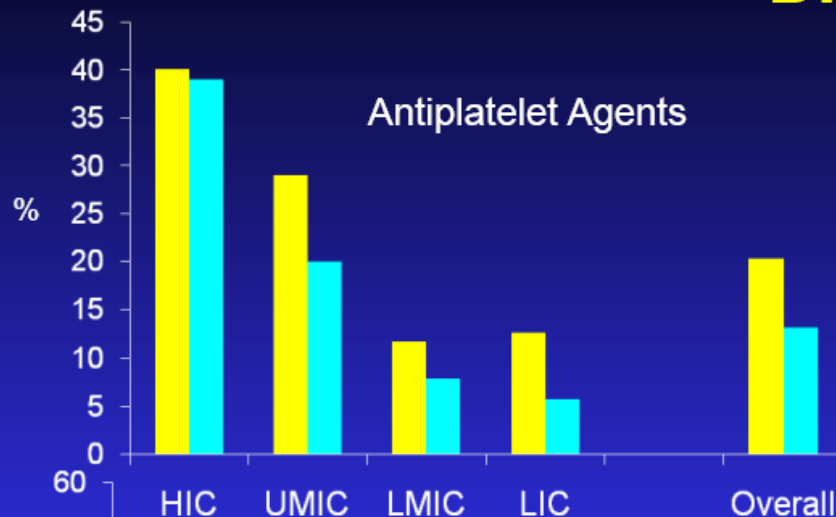
Incomplete responses or poor tolerance at each step justify moving to the next step.

The strategy must be adapted to each patient's characteristics and preferences, and does not necessarily follow the steps indicated in the figure.”

Mi van a hegyen túl?



Drugs



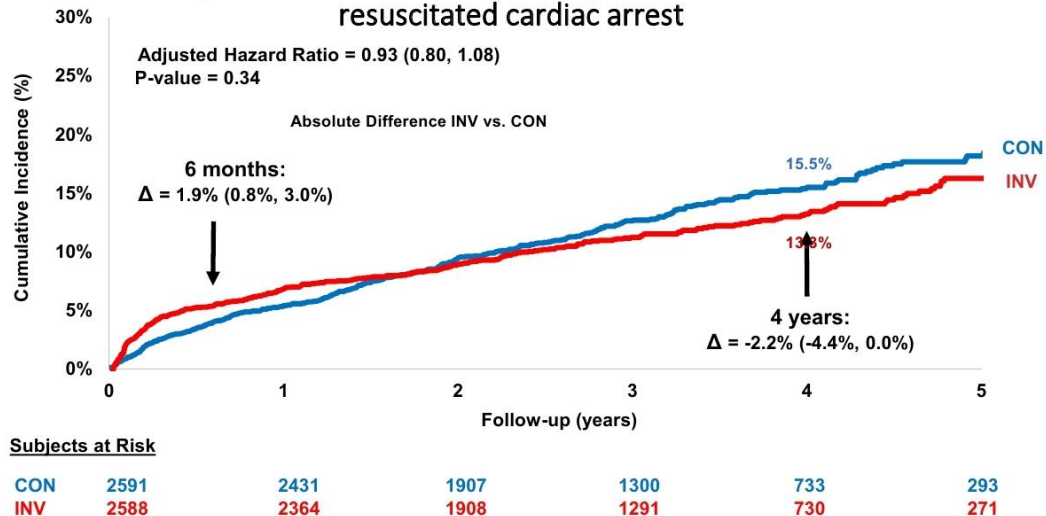
A szekunder prevenció során történő gyógyszerhasználat

Table 3 Temporal trends (2003–07) in treatment with aspirin, statins, β -blockers, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers and n-3 polyunsaturated fatty acids

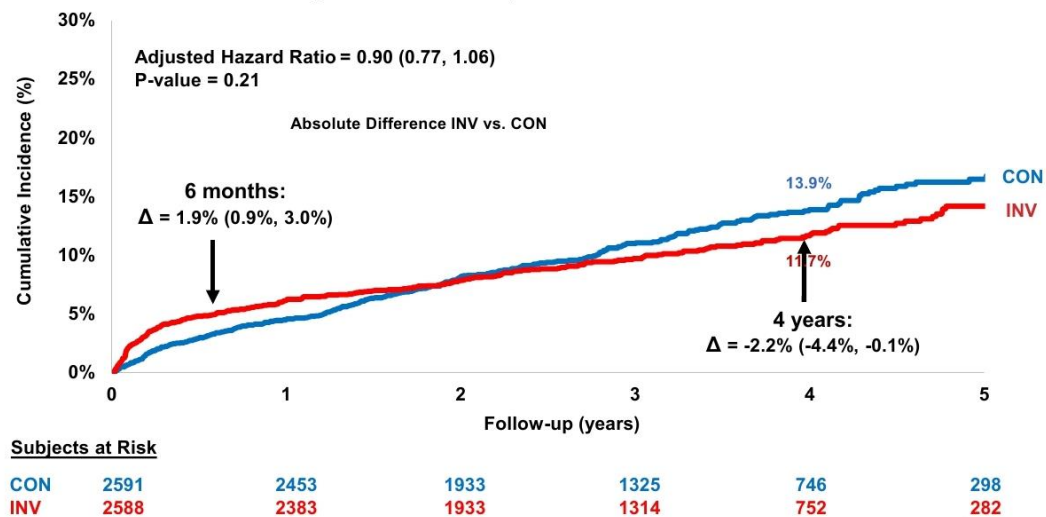
	Men ≤ 75 years ($n = 10\,980$)	Women ≤ 75 years ($n = 3266$)	Men > 75 years ($n = 3515$)	Women > 75 years ($n = 3662$)
Aspirin				
2003 (ref.)	1.00	1.00	1.00	1.00
2005	2.09 (1.82–2.39)	1.63 (1.29–2.06)	1.61 (1.31–1.98)	1.57 (1.30–1.90)
2007	2.30 (1.99–2.65)	1.43 (1.14–1.80)	1.69 (1.38–2.08)	1.52 (1.26–1.84)
Statins				
2003 (ref.)	1.00	1.00	1.00	1.00
2005	2.28 (1.99–2.61)	2.02 (1.61–2.53)	1.92 (1.60–2.30)	1.64 (1.38–1.97)
2007	2.15 (1.88–2.46)	1.74 (1.39–2.17)	2.28 (1.89–2.74)	1.94 (1.62–2.32)
β -Blockers				
2003 (ref.)	1.00	1.00	1.00	1.00
2005	1.52 (1.36–1.68)	1.65 (1.36–2.01)	1.65 (1.38–2.00)	1.60 (1.35–1.91)
2007	1.62 (1.45–1.80)	1.66 (1.36–2.02)	1.73 (1.45–2.06)	1.94 (1.63–2.31)
ACE-I/ARB				
2003 (ref.)	1.00	1.00	1.00	1.00
2005	1.67 (1.48–1.88)	1.54 (1.22–1.93)	1.66 (1.34–2.05)	1.28 (1.05–1.57)
2007	1.69 (1.50–1.90)	1.48 (1.18–1.86)	1.37 (1.11–1.69)	1.26 (1.03–1.55)
n-3 PUFA				
2003 (ref.)	1.00	1.00	1.00	1.00
2005	2.51 (2.25–2.81)	1.97 (1.58–2.45)	2.02 (1.57–2.60)	1.52 (1.15–2.00)
2007	2.62 (2.34–2.92)	2.09 (1.67–2.59)	2.00 (1.56–2.58)	1.85 (1.42–2.43)

ISCHEMIA

Primary Outcome: CV Death, MI, hospitalization for UA, HF or resuscitated cardiac arrest

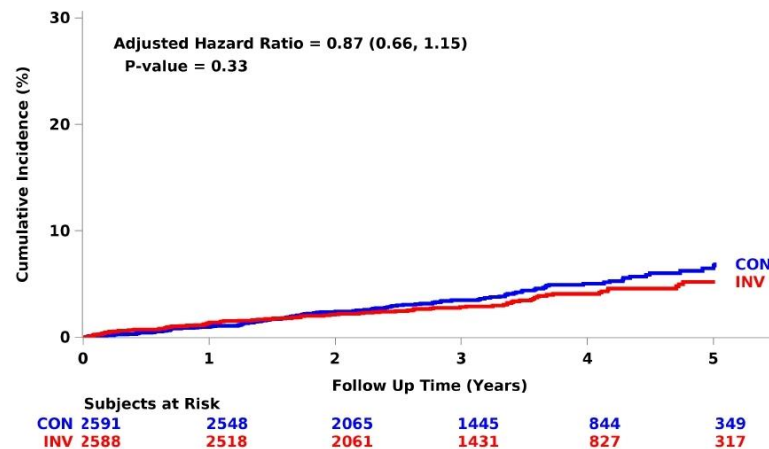


Major Secondary: CV Death or MI

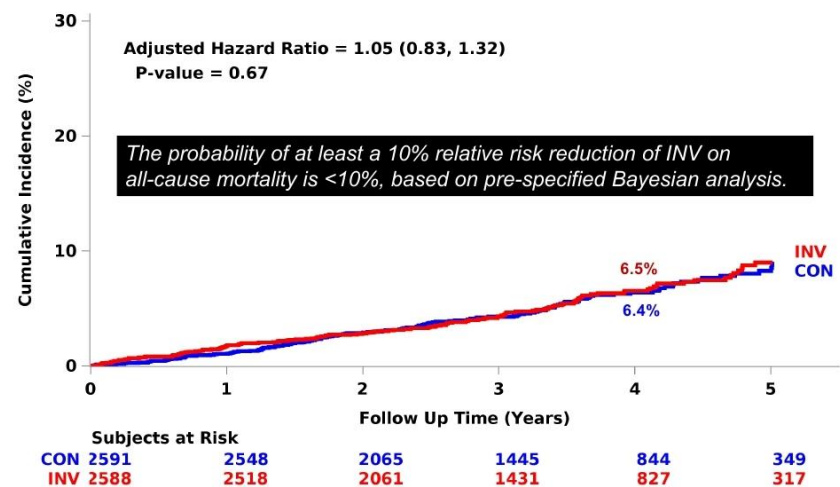


ISCHEMIA

Cardiovascular Death



All-Cause Death



Gyógyszeres vs. revasc. kezelés

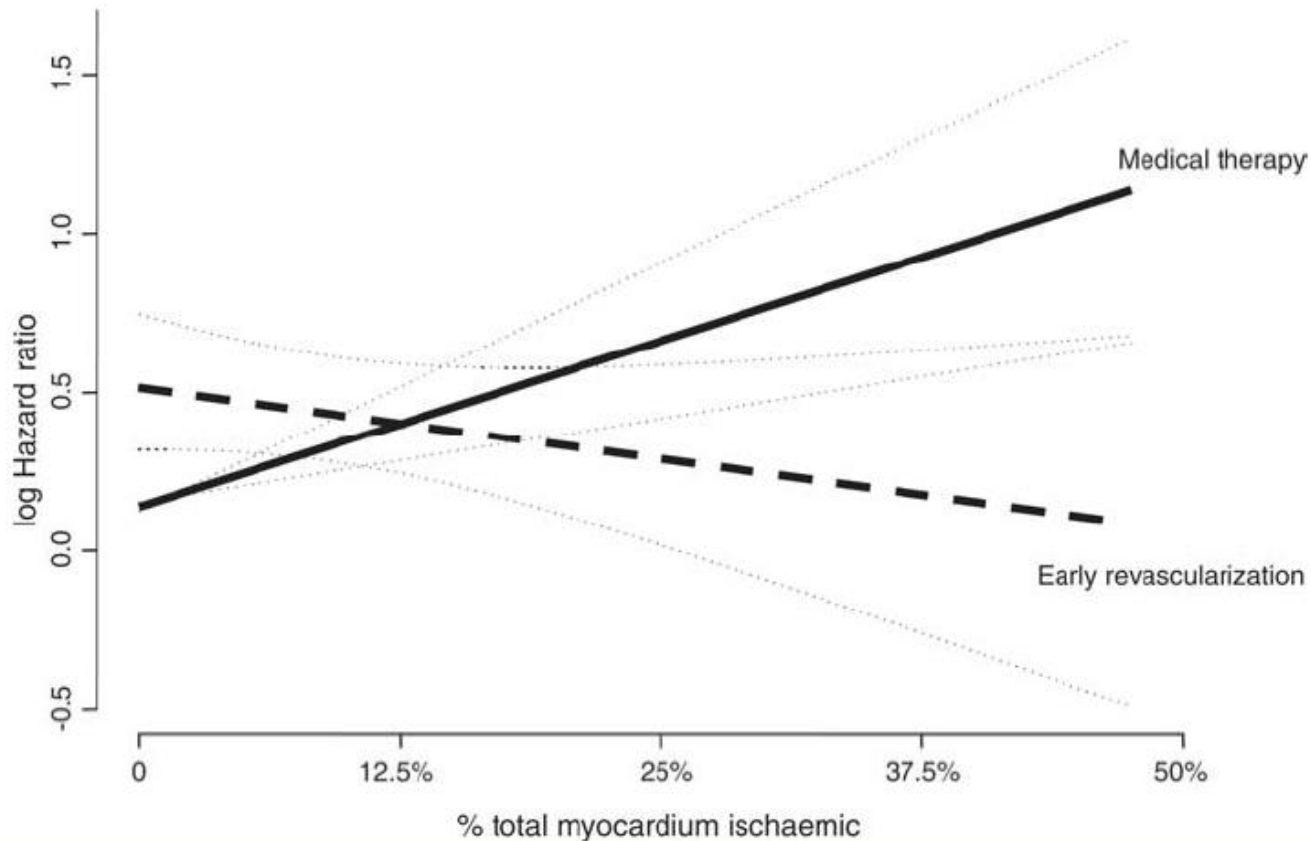


Figure 4 Log hazard ratio for revascularization vs. medical therapy as a function of %myocardium ischaemic in patients with <10% ischaemic myocardium. Graphic representation based on Cox proportional hazards model. Interaction $P < 0.001$.

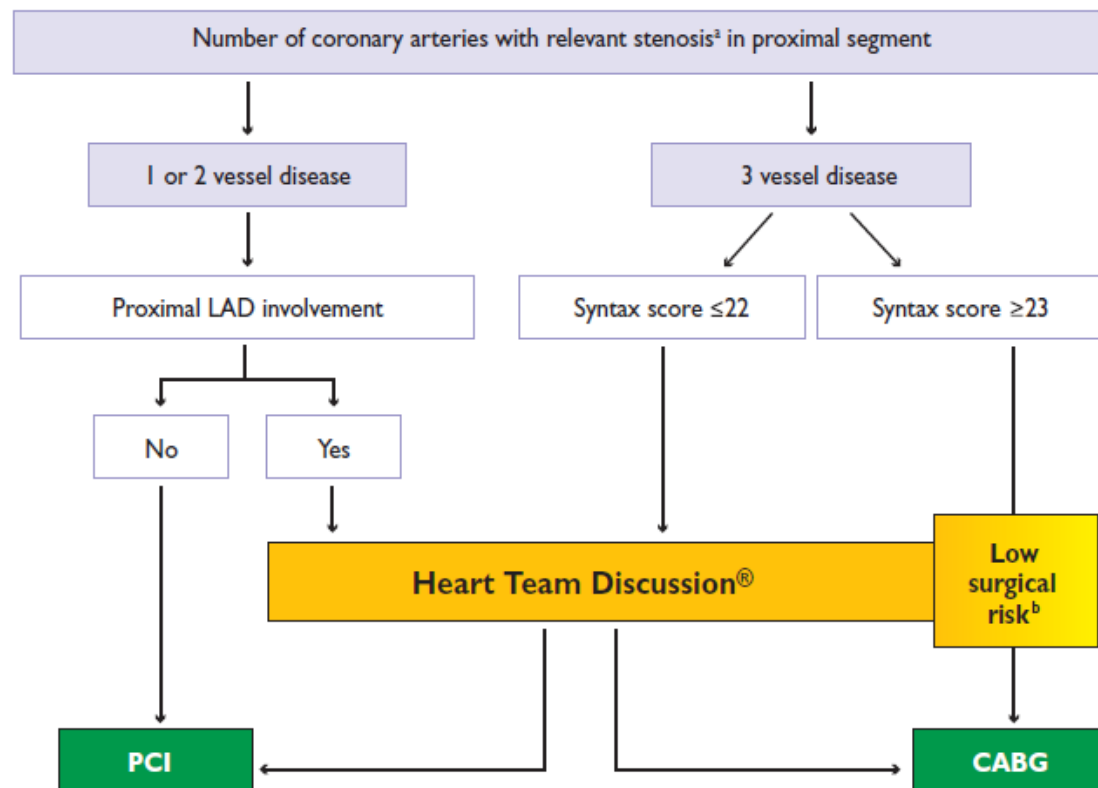
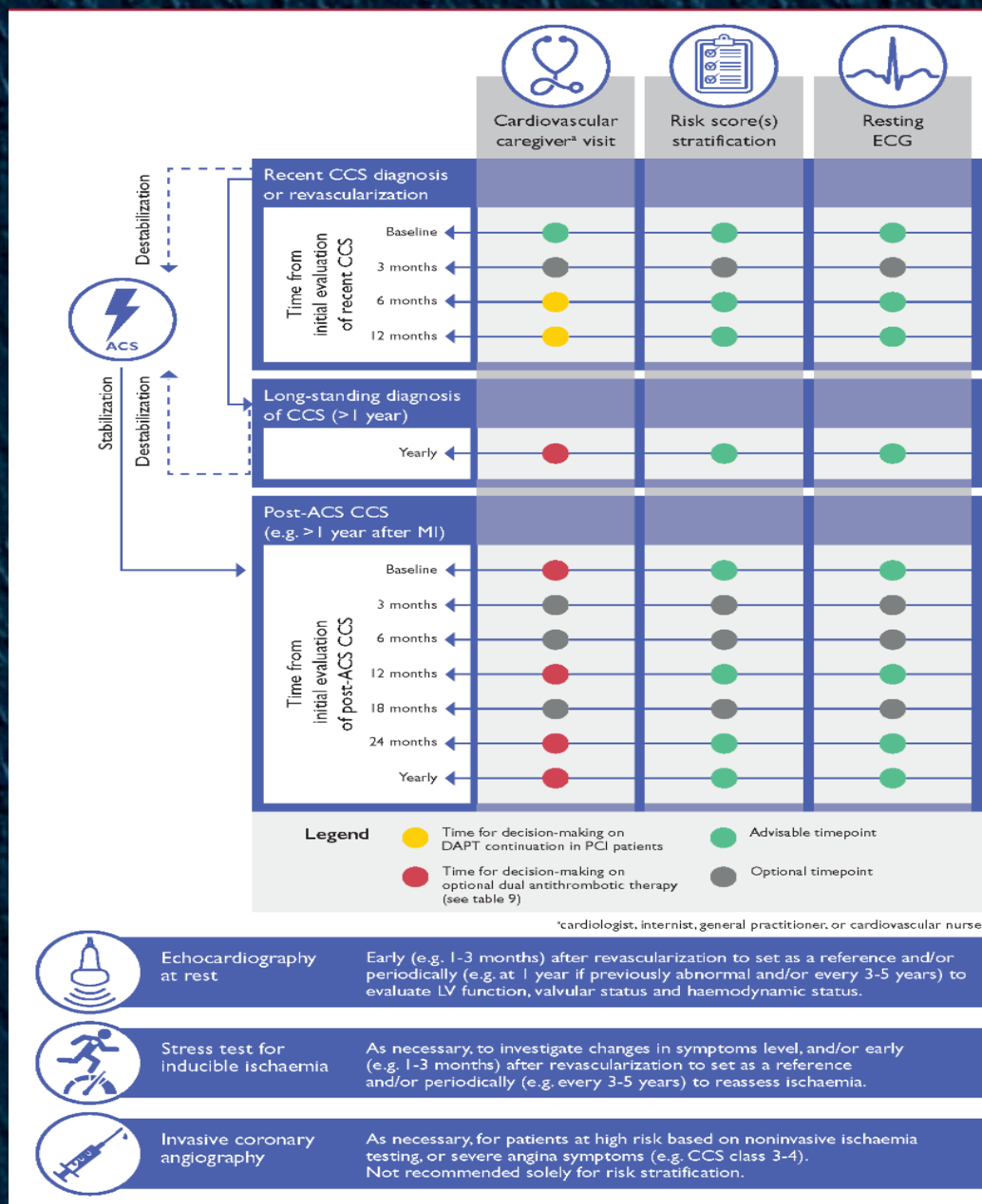


Figure 6 Percutaneous coronary intervention (PCI) or coronary artery bypass graft surgery (CABG) in stable coronary artery disease without left main coronary artery involvement. CABG = coronary artery bypass graft; LAD = left anterior descending; PCI = percutaneous coronary intervention.

^a>50% stenosis and proof of ischaemia, >90% stenosis in two angiographic views, or FFR = 0.80.

^bCABG is the preferred option in most patients unless patients co-morbidities or specificities deserve discussion by the heart team. According to local practice (time constraints, workload) direct transfer to CABG may be allowed in these low risk patients, when formal discussion in a multidisciplinary team is not required (adapted from ESC/EACTS Guidelines on Myocardial Revascularization 2010).

CCS betegek utánkövetése, gondozása



Köszönöm a figyelmet!

