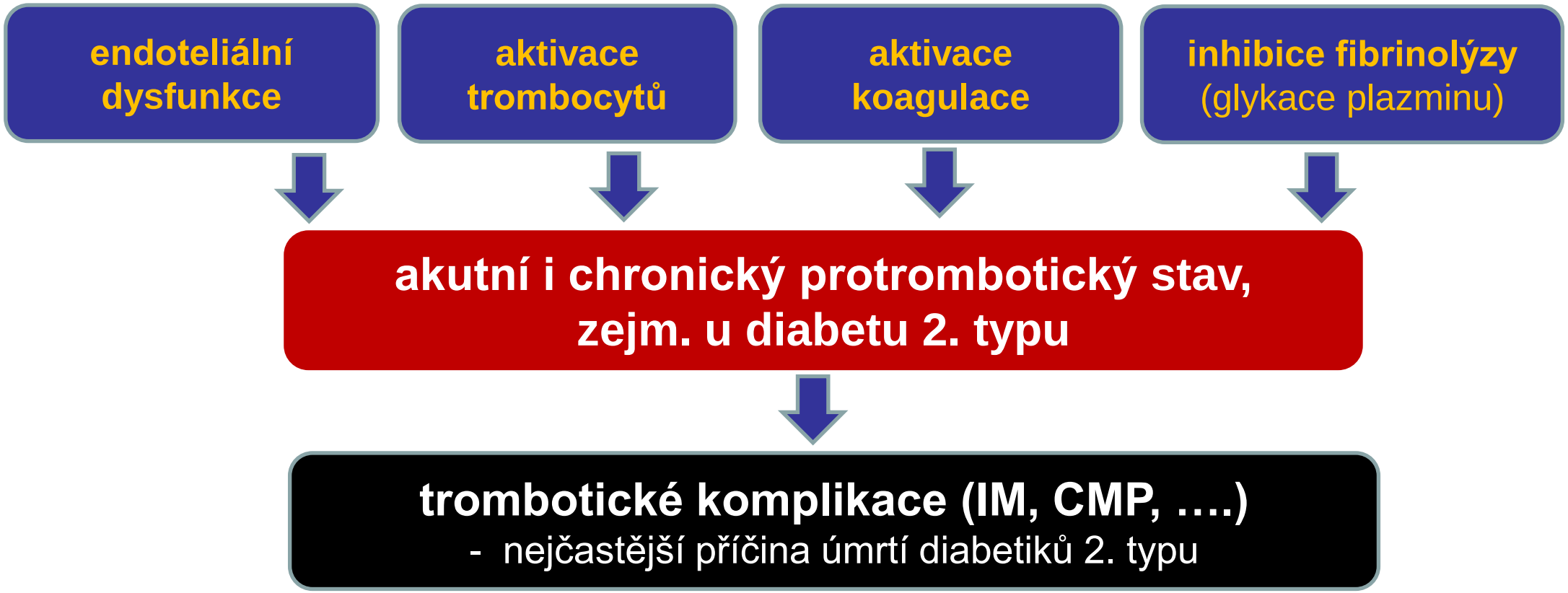
VŠEOBECNÁ FAKULTNÍ NEMOCNICE V PRAZE

1. LÉKAŘSKÁ FAKULTA Univerzita Karlova

Specifika antitrombotické terapie u diabetiků s vaskulárním postižením

Debora Karetová

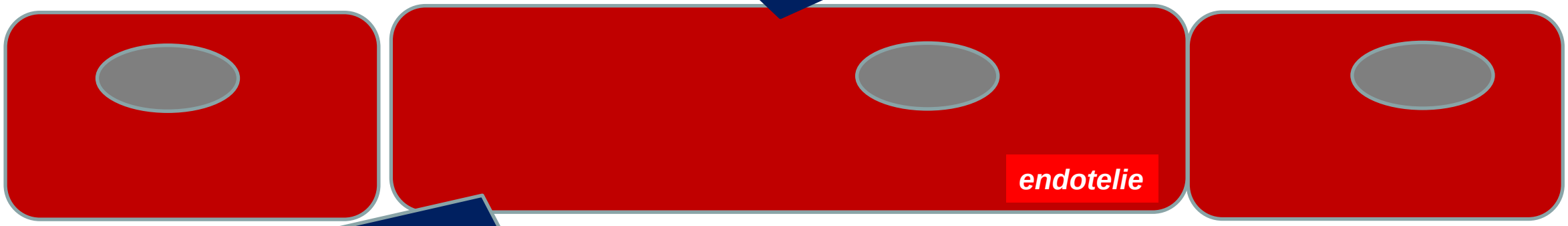
Příčiny hyperkoagulačního stavu u T2DM



Upraveno podle Ramzi A et al, European Heart Journal (2021) 42, 2235–2259 doi:10.1093/eurheartj/ehab128

Diabetes a endoteliální dysfunkce

zvýšená exprese vWF, TXA_2 – *aktivace prim. hemostázy*
zvýšená exprese PAI-1 – *inhibice trombolýzy*

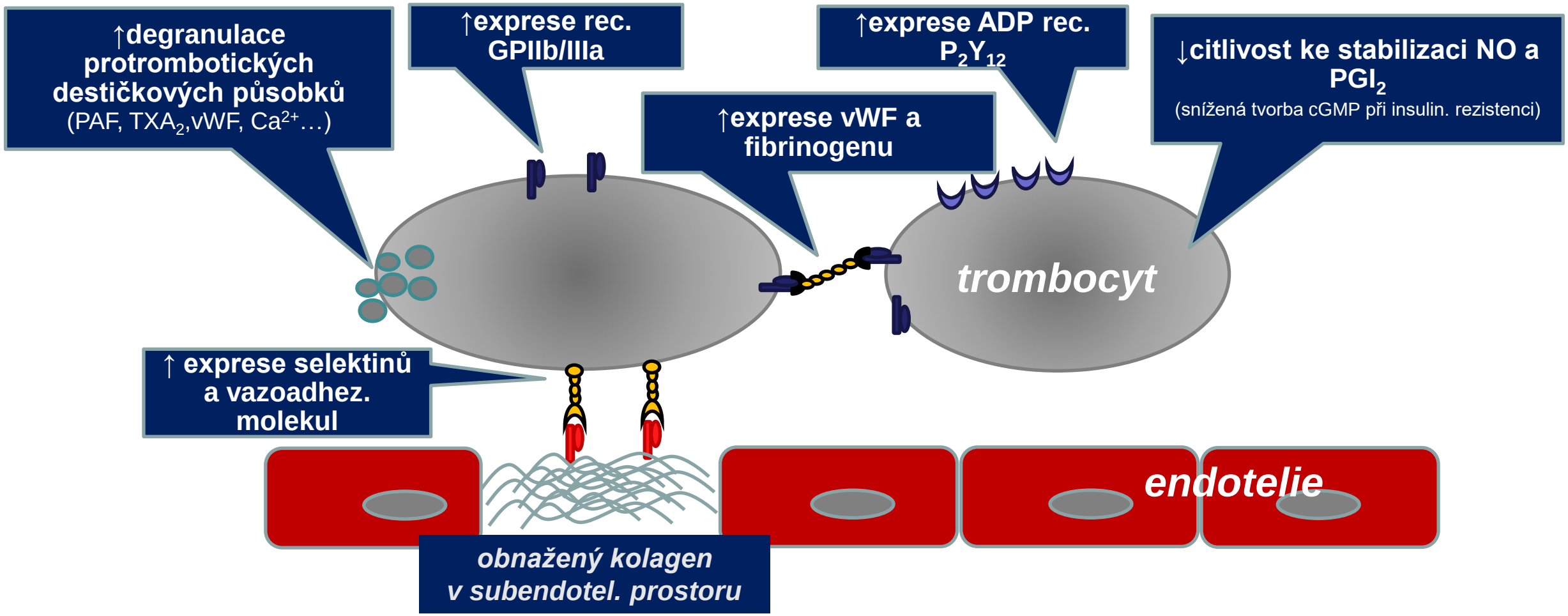


snížená exprese PGI_2 a NO – *aktivace primární hemostázy*
snížená exprese trombomodulinu – *aktivace hemokoagulace*

Upraveno podle Ramzi A et al, European Heart Journal (2021) 42, 2235–2259 doi:10.1093/eurheartj/ehab128

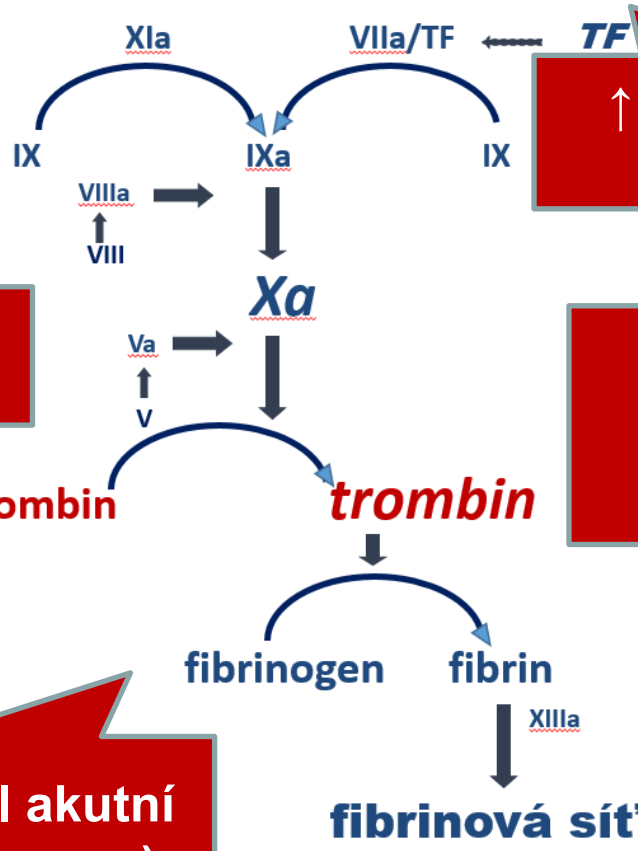
Diabetes a hyperaktivace trombocytů

→ výrazně vyšší obrat destiček (3-4 dny vs. 5-7 dnů) vede ke kratšímu efektu ASA i ADP blokátorů



upraveno podle: Rivas Rios JR et al. Diabetes and antiplatelet therapy. Cardiovasc Diagn Ther. doi: 10.21037/cdt.2018.05.09.

Diabetes a hyperkoagulační stav



↑ exprese tkáňového faktoru

↓ antitrombin - inhibující aktivaci trombinu a f.Xa

↓ exprese trombomodulinu k ukončení aktivity trombinu

↑ exprese molekul akutní fáze (zejm. fibrinogenu)

Upraveno podle Ramzi A et al, European Heart Journal (2021) 42, 2235–2259 doi:10.1093/eurheartj/ehab128

ANTITROMBOTIKA

Protidestičkové léky:

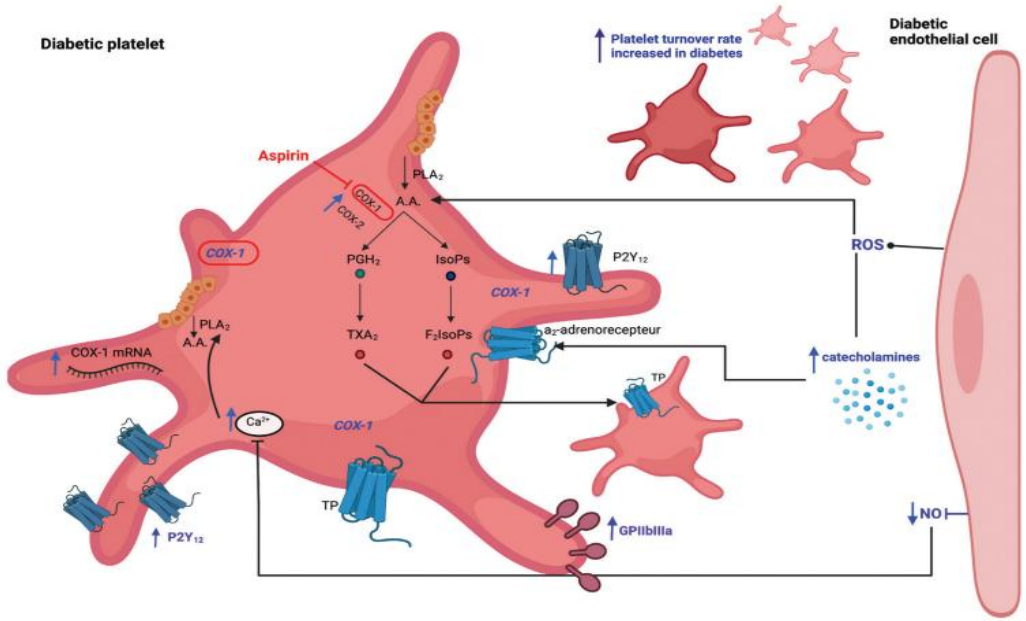
- ASA / inhibice COX-1
- klopidogrel, prasugrel, tikagrelor / blokace rec. P2Y12 pro ADP
- abciximab, eptifibatid, tirofiban / inhibice rec. GPIIb/IIIa

Antikoagulancia:

- hepariny
- přímé inhibitory trombinu
- přímé inhibitory f. Xa
- antagonisté vitamínu K

Fibrinolytika:

- altepláza, retepláza, tenekteplázа

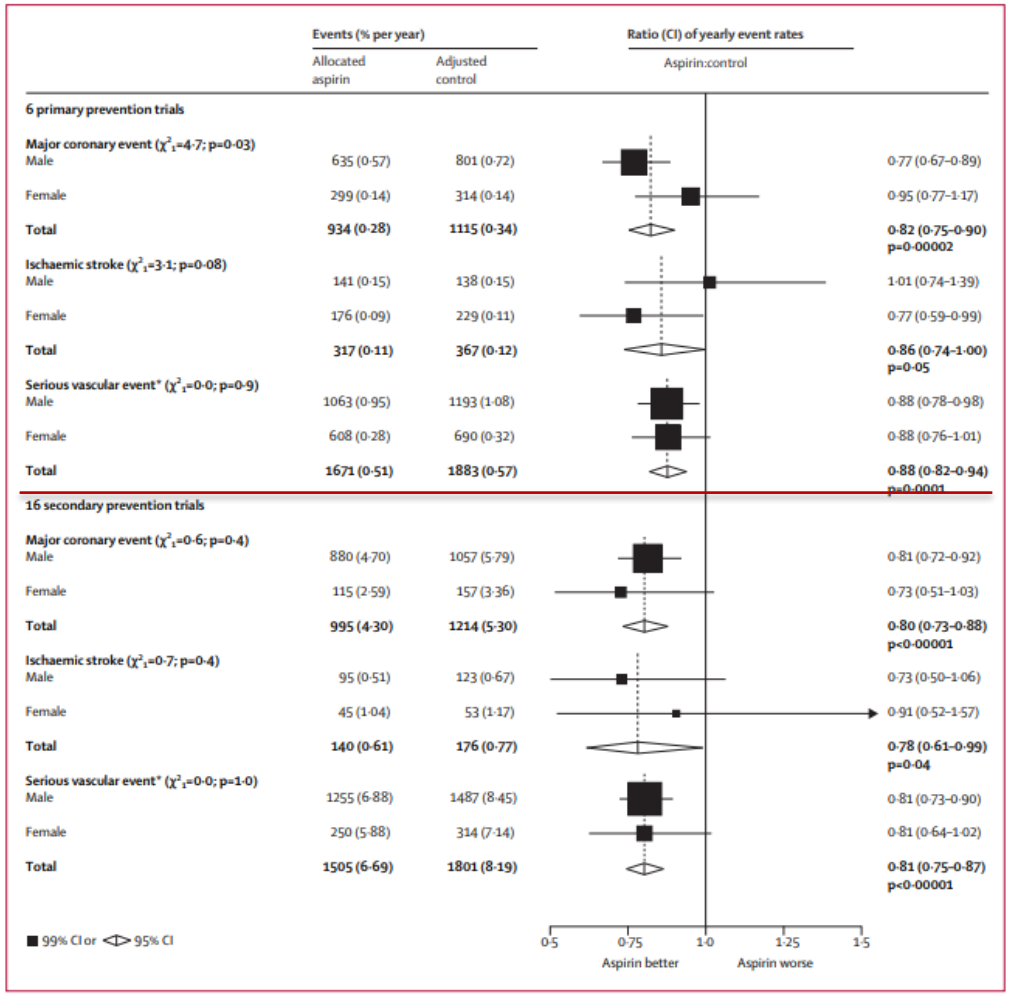


„Diabetická destička“

- Hyperglykémie → alterace COX-1, limitující ASA kapacitu k vazbě COX-1 a omezení funkce trombocytu
- TXA2 aktivace dostatečná (via TP receptor)
- endoteliální zánět → vzestup volných radikálů a aktivace přes TP, alfa-adrenoreceptory
- ……
- zvýšený obrat trombocytů
- vyšší exprese GPIIb/IIIa a ADP P2Y12 recept.
- snížení tvorby NO → vyšší uvolnění Ca^{2+} → zvýšení TXA2

Antithrombotic Trialists´Collaboration

4% diabetiků
N=3818



Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials

*Antithrombotic Trialists' (ATT) Collaboration**

Summary

Background Low-dose aspirin is of definite and substantial net benefit for many people who already have occlusive vascular disease. We have assessed the benefits and risks in primary prevention.

Methods We undertook meta-analyses of serious vascular events (myocardial infarction, stroke, or vascular death) and major bleeds in six primary prevention trials (95 000 individuals at low average risk, 660 000 person-years, 3554 serious vascular events) and 16 secondary prevention trials (17 000 individuals at high average risk, 43 000 person-years, 3306 serious vascular events) that compared long-term aspirin versus control. We report intention-to-treat analyses of first events during the scheduled treatment period.

Findings In the primary prevention trials, aspirin allocation yielded a 12% proportional reduction in serious vascular events (0·51% aspirin *vs* 0·57% control per year, p=0·0001), due mainly to a reduction of about a fifth in non-fatal myocardial infarction (0·18% *vs* 0·23% per year, p<0·0001). The net effect on stroke was not significant (0·20% *vs* 0·21% per year, p=0·4: haemorrhagic stroke 0·04% *vs* 0·03%, p=0·05; other stroke 0·16% *vs* 0·18% per year, p=0·08). Vascular mortality did not differ significantly (0·19% *vs* 0·19% per year, p=0·7). Aspirin allocation increased major gastrointestinal and extracranial bleeds (0·10% *vs* 0·07% per year, p<0·0001), and the main risk factors for coronary disease were also risk factors for bleeding. In the secondary prevention trials, aspirin allocation yielded a greater absolute reduction in serious vascular events (6·7% *vs* 8·2% per year, p<0.0001), with a non-significant increase in haemorrhagic stroke but reductions of about a fifth in total stroke (2·08% *vs* 2·54% per year, p=0·002) and in coronary events (4·3% *vs* 5·3% per year, p<0·0001). In both primary and secondary prevention trials, the proportional reductions in the aggregate of all serious vascular events seemed similar for men and women.

Interpretation In primary prevention without previous disease, aspirin is of uncertain net value as the reduction in occlusive events needs to be weighed against any increase in major bleeds. Further trials are in progress.

Lancet 2009; 373: 1849–60

ESC European Society of Cardiology
European Heart Journal (2023) 44, 4043–4140
https://doi.org/10.1093/eurheartj/ehad192

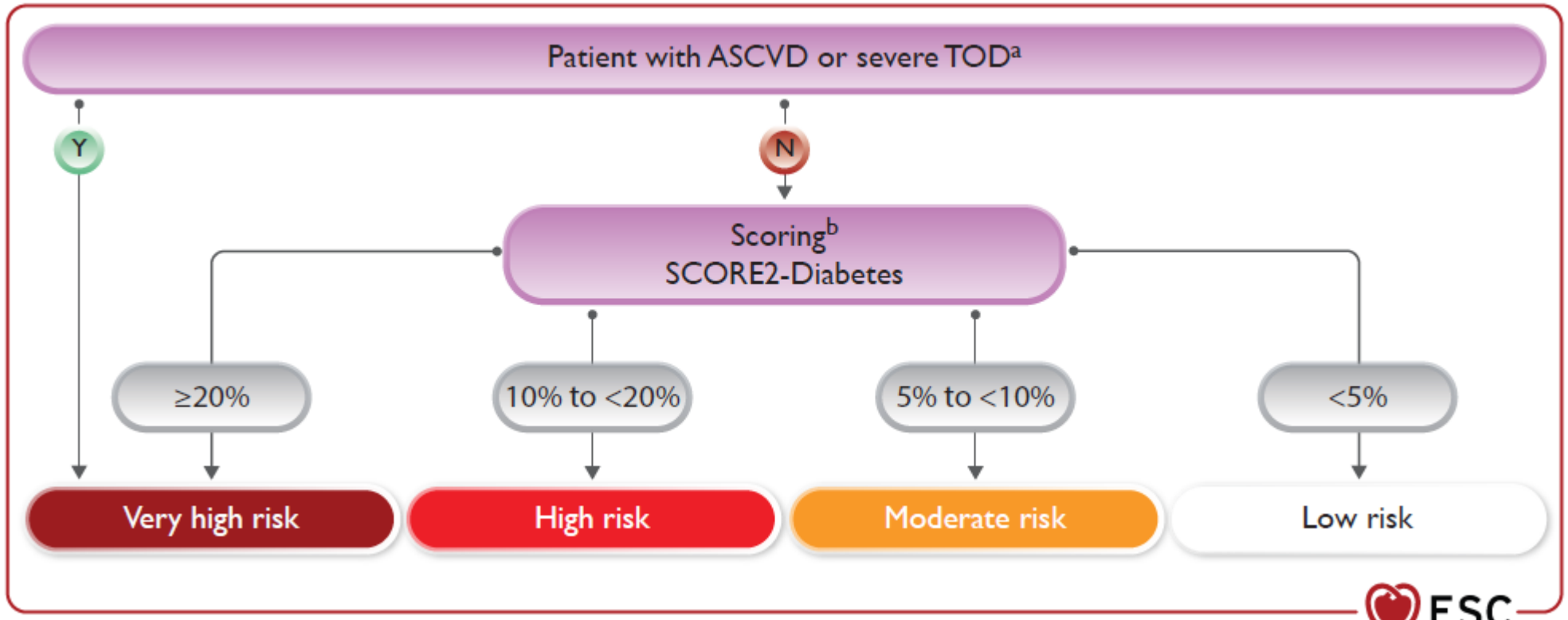
ESC GUIDELINES

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

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

Authors/Task Force Members: Nikolaus Marx *†, (Chairperson) (Germany), Massimo Federici *†, (Chairperson) (Italy), Katharina Schütt ‡, (Task Force Co-ordinator) (Germany), Dirk Müller-Wieland ‡, (Task Force Co-ordinator) (Germany), Ramzi A. Ajjan (United Kingdom), Manuel J. Antunes (Portugal), Ruxandra M. Christodorescu (Romania), Carolyn Crawford (United Kingdom), Emanuele Di Angelantonio (United Kingdom/Italy), Björn Eliasson (Sweden), Christine Espinola-Klein (Germany), Laurent Fauchier (France), Martin Halle (Germany), William G. Herrington (United Kingdom), Alexandra Kautzky-Willer (Austria), Ekaterini Lambrinou (Cyprus), Maciej Lesiak (Poland) (United States of Americ Naveed Sattar (Unite

ASCVD = vaskulární onem. na bazi aterosklerózy
TOD = orgánové poškození při DM
(mikroalbuminurie/proteinurie, renální dysfce, retinopatie, neuropatie)



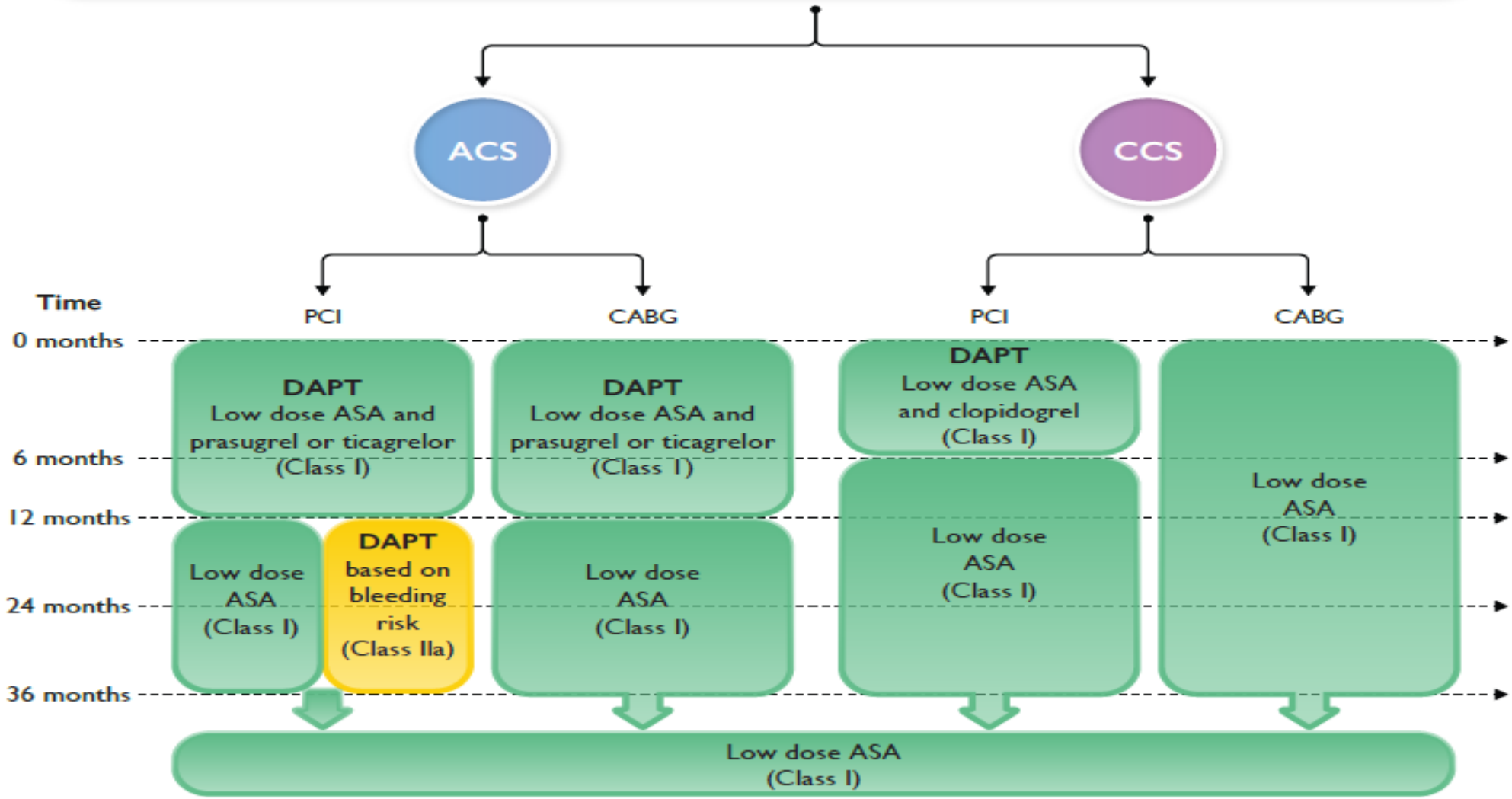
ESC Guidelines 2024 – Chronická ICHS

Recommendations for antithrombotic therapy in patients with chronic coronary syndrome (1)

Recommendations	Class	Level
Long-term antithrombotic therapy in patients with CCS and no clear indication for oral anticoagulation		
In CCS patients with a prior MI or remote PCI, aspirin 75–100 mg daily is recommended lifelong after an initial period of DAPT.	I	A
In CCS patients with a prior MI or remote PCI, clopidogrel 75 mg daily is recommended as a safe and effective alternative to aspirin monotherapy.	I	A
After CABG, aspirin 75–100 mg daily is recommended lifelong.	I	A
In patients *without* prior MI or revascularization but with evidence of significant obstructive CAD, aspirin 75–100 mg daily is recommended lifelong.	I	B
Adding a second antithrombotic agent to aspirin for extended long-term secondary prevention should be considered in patients at enhanced ischaemic risk and without high bleeding risk (options and definitions in Table 6 and in the Supplementary data online, *Tables S2* and *S3*).	IIa	A

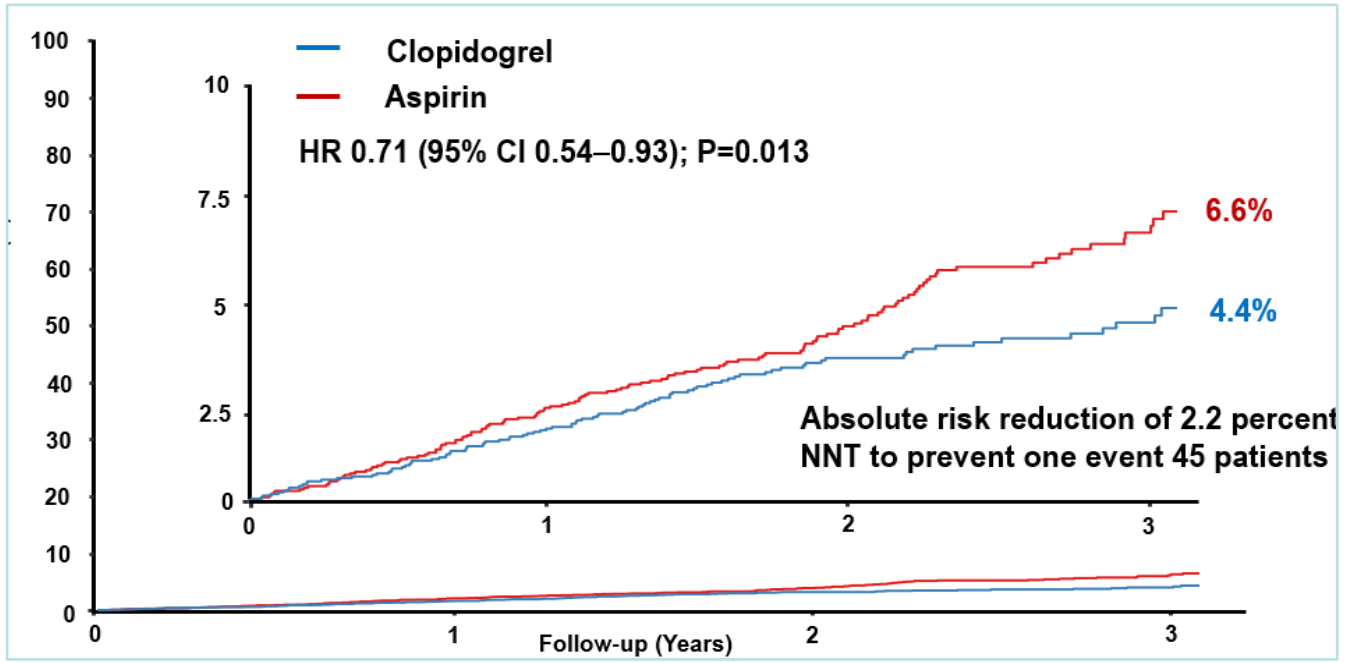
2024 ESC Guidelines for the management of chronic coronary syndromes
(European Heart Journal; 2024 – doi: 10.1093/eurheartj/ehae177)

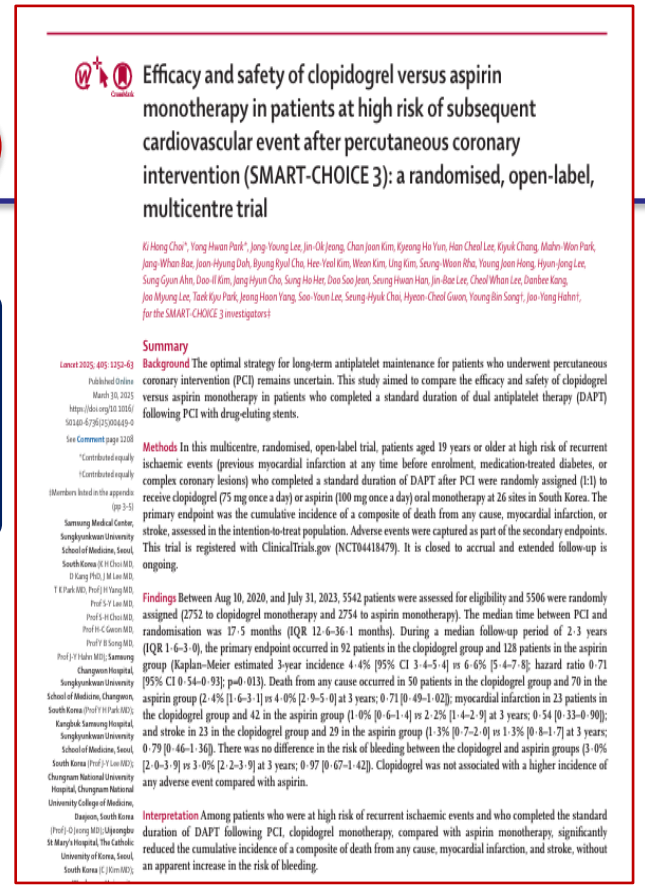
Revascularization (PCI, CABG) for ACS and CCS in patients with diabetes and no indication for anticoagulation



ESC

ASA či klopidogrel po PCI (po ukončení DAPT)





Efficacy and safety of clopidogrel versus aspirin monotherapy in patients at high risk of subsequent cardiovascular event after percutaneous coronary intervention (SMART-CHOICE 3): a randomised, open-label, multicentre trial

Ki Hong Choi*, Yong Hwan Park*, Jong-Young Lee, Jin-Ok Jeong, Chan Joon Kim, Kyeong Ho Yun, Han Cheol Lee, Kiyuk Chang, Mahn-Won Park, Jang-Whan Bae, Joon-Hyung Doh, Byung Kyul Cha, Hee-Yeol Kim, Weon Kim, Ung Kim, Seung-Woon Rha, Young Joon Hong, Hyun-Jong Lee, Sung Gyun Ahn, Doo-Il Kim, Jang Hyun Cho, Sung Ho Her, Doo Soo Jeon, Seung Hwan Han, Jin-Bae Lee, Cheol Whan Lee, Danbee Kang, Joo Myung Lee, Taek Kyu Park, Jeong Hoon Yang, Soo-Youn Lee, Seung-Hyuk Choi, Hyeon-Cheol Gwon, Young Bin Song†, Joo-Yong Hahn†, for the SMART-CHOICE 3 investigators‡

Lancet 2025; 405: 1252–63
Published Online March 30, 2025
https://doi.org/10.1016/S0140-6736(25)00449-0

See Comment page 1208

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Summary

Background The optimal strategy for long-term antiplatelet maintenance for patients who underwent percutaneous coronary intervention (PCI) remains uncertain. This study aimed to compare the efficacy and safety of clopidogrel versus aspirin monotherapy in patients who completed a standard duration of dual antiplatelet therapy (DAPT) following PCI with drug-eluting stents.

Methods In this multicentre, randomised, open-label trial, patients aged 19 years or older at high risk of recurrent ischaemic events (previous myocardial infarction at any time before enrolment, medication-treated diabetes, or complex coronary lesions) who completed a standard duration of DAPT after PCI were randomly assigned (1:1) to receive clopidogrel (75 mg once a day) or aspirin (100 mg once a day) oral monotherapy at 26 sites in South Korea. The primary endpoint was the cumulative incidence of a composite of death from any cause, myocardial infarction, or stroke, assessed in the intention-to-treat population. Adverse events were captured as part of the secondary endpoints. This trial is registered with ClinicalTrials.gov (NCT04418479). It is closed to accrual and extended follow-up is ongoing.

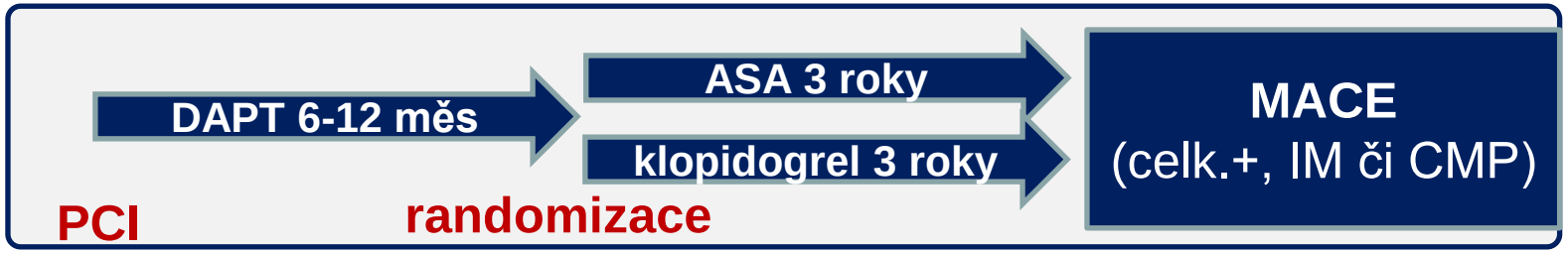
Findings Between Aug 10, 2020, and July 31, 2023, 5542 patients were assessed for eligibility and 5506 were randomly assigned (2752 to clopidogrel monotherapy and 2754 to aspirin monotherapy). The median time between PCI and randomisation was 17·5 months (IQR 12·6–36·1 months). During a median follow-up period of 2·3 years (IQR 1·6–3·0), the primary endpoint occurred in 92 patients in the clopidogrel group and 128 patients in the aspirin group (Kaplan–Meier estimated 3-year incidence 4·4% [95% CI 3·4–5·4] vs 6·6% [5·4–7·8]; hazard ratio 0·71 [95% CI 0·54–0·93]; p=0·013). Death from any cause occurred in 50 patients in the clopidogrel group and 70 in the aspirin group (2·4% [1·6–3·1] vs 4·0% [2·9–5·0] at 3 years; 0·71 [0·49–1·02]); myocardial infarction in 23 patients in the clopidogrel group and 42 in the aspirin group (1·0% [0·6–1·4] vs 2·2% [1·4–2·9] at 3 years; 0·54 [0·33–0·90]); and stroke in 23 in the clopidogrel group and 29 in the aspirin group (1·3% [0·7–2·0] vs 1·3% [0·8–1·7] at 3 years; 0·79 [0·46–1·36]). There was no difference in the risk of bleeding between the clopidogrel and aspirin groups (3·0% [2·0–3·9] vs 3·0% [2·2–3·9] at 3 years; 0·97 [0·67–1·42]). Clopidogrel was not associated with a higher incidence of any adverse event compared with aspirin.

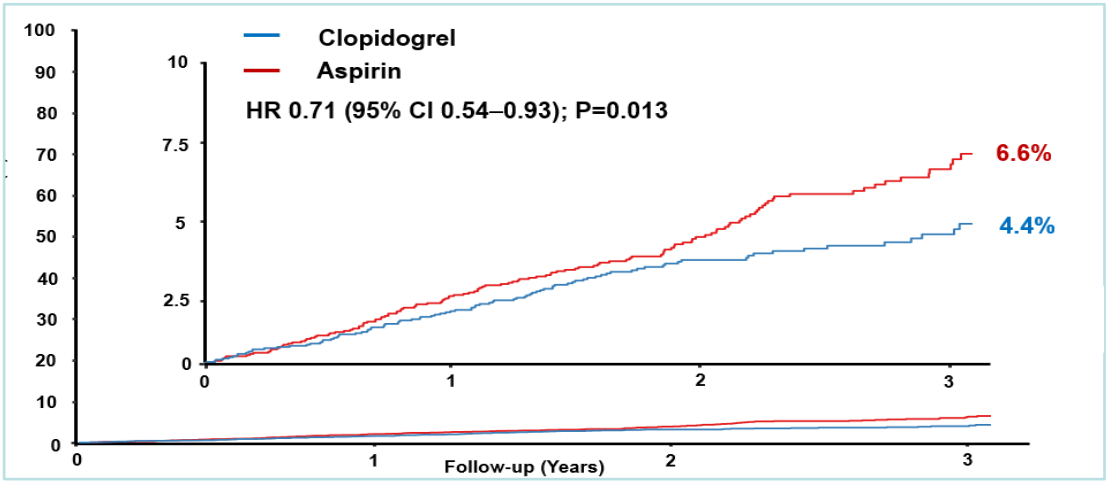
Interpretation Among patients who were at high risk of recurrent ischaemic events and who completed the standard duration of DAPT following PCI, clopidogrel monotherapy, compared with aspirin monotherapy, significantly reduced the cumulative incidence of a composite of death from any cause, myocardial infarction, and stroke, without an apparent increase in the risk of bleeding.

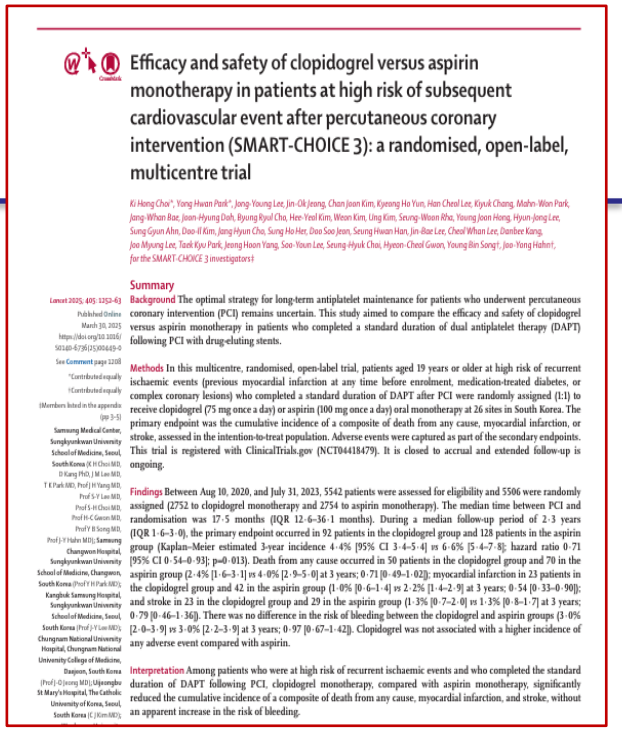
recentní data z dubna 2025
Jižní Korea

SMART CHOICE 3, Lancet 2025; 405: 1252–63

ASA či klopidogrel po PCI (po ukončení DAPT)







Efficacy and safety of clopidogrel versus aspirin monotherapy in patients at high risk of subsequent cardiovascular event after percutaneous coronary intervention (SMART-CHOICE 3): a randomised, open-label, multicentre trial

Summary

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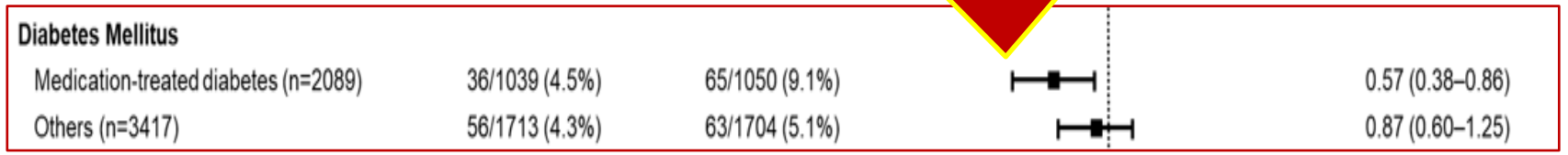
recentní data z dubna 2025, Jižní Korea

větší efekt klopidogrelu u diabetiků 2. typu



Diabetes Mellitus			
Medication-treated diabetes (n=2089)	36/1039 (4.5%)	65/1050 (9.1%)	0.57 (0.38–0.86)
Others (n=3417)	56/1713 (4.3%)	63/1704 (5.1%)	0.87 (0.60–1.25)

SMART CHOICE 3, Lancet 2025; 405: 1252–63

ESC Guidelines 2024 – Chronická ICHS

Options for extended intensified antithrombotic therapy

ESC

Drug	Dose	Clinical setting	NNT (ischaemic outcomes)	NNH (bleeding outcomes)
Co-administered with aspirin 100 mg o.d.				
Rivaroxaban (COMPASS trial; vs. placebo)	2.5 mg b.i.d.	Patients with CAD or symptomatic PAD at high risk of ischaemic events	77	84 (modified-ISTH major bleeding)
Co-administered with low-dose aspirin 75–162 mg o.d.				
Clopidogrel, (6505/9961 of DAPT trial; vs. placebo)	75 mg/day	Post MI in patients who have tolerated DAPT for 1 year (25% ACS, 22% previous MI)	63	105 (moderate and severe GUSTO bleeds, or BARC 2, 3, and 5 bleeds)
Prasugrel, (3456/9961 of DAPT trial; vs. placebo)	10 mg/day (5 mg/day if body weight <60 kg or age ≥75 years)	Post PCI for MI in patients who have tolerated DAPT for 1 year	63	105 (as above)
Ticagrelor (PEGASUS-TIMI 54; vs. placebo)	60/90 mg b.i.d.	Post-MI in patients who have tolerated DAPT for 1 year	84	81 (TIMI major bleeds)

2024 ESC Guidelines for the management of chronic coronary syndromes (European Heart Journal; 2024 – doi: 10.1093/eurheartj/ehae177)

Periferní arteriální onemocnění (PAD)

Doporučené postupy ESC pro diagnostiku a léčbu onemocnění periferních tepen, 2024.

Mazzolai L, Teixido-Tura G, Lanzi S, Boc V, Bossone E, Brodmann M, Bura-Rivière A, De Backer J, Deglise S, Della Corte A, Heiss C, Kałużna-Oleksy M, Kurpas D, McEniery CM, Mirault T, Pasquet AA, Pitcher A, Schaubroeck HAI, Schlager O, Sirnes PA, Sprynger MG, Stabile E, Steinbach F, Thielmann M, van Kimmenade RRJ, Venermo M, Rodriguez-Palomares JF, ESC Scientific Document Group

Překlad souhrnu dokumentu připravený Českou angiologickou společností ČLS JEP, 2025.

(2024 ESC Guidelines for the management of peripheral arterial and aortic diseases.

Mazzolai L, Teixido-Tura G, Lanzi S, Boc V, Bossone E, Brodmann M, Bura-Rivière A, De Backer J, Deglise S, Della Corte A, Heiss C, Kałużna-Oleksy M, Kurpas D, McEniery CM, Mirault T, Pasquet AA, Pitcher A, Schaubroeck HAI, Schlager O, Sirnes PA, Sprynger MG, Stabile E, Steinbach F, Thielmann M, van Kimmenade RRJ, Venermo M, Rodriguez-Palomares JF, ESC Scientific Document Group.

Translation of the summary of the document prepared by the Czech Society of Angiology, 2025)

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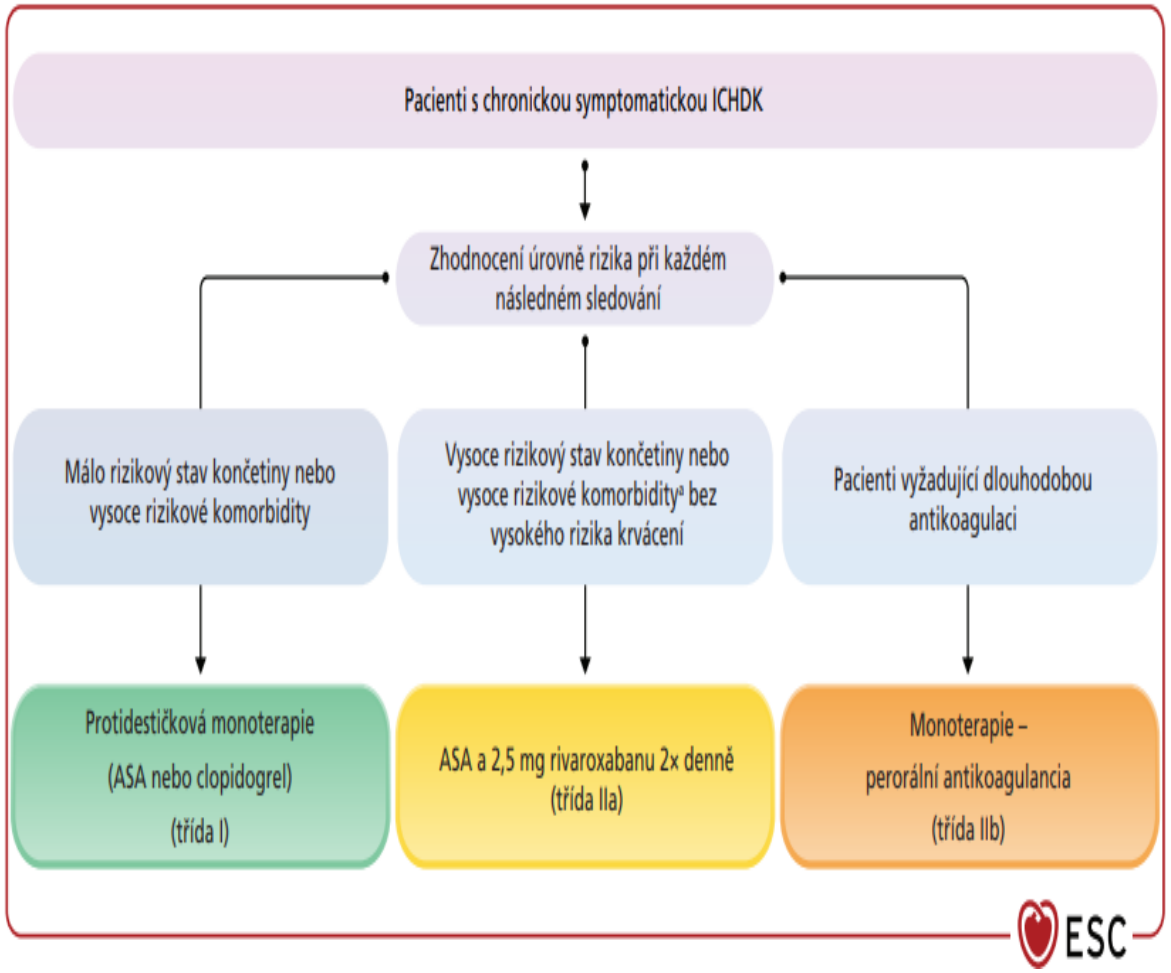
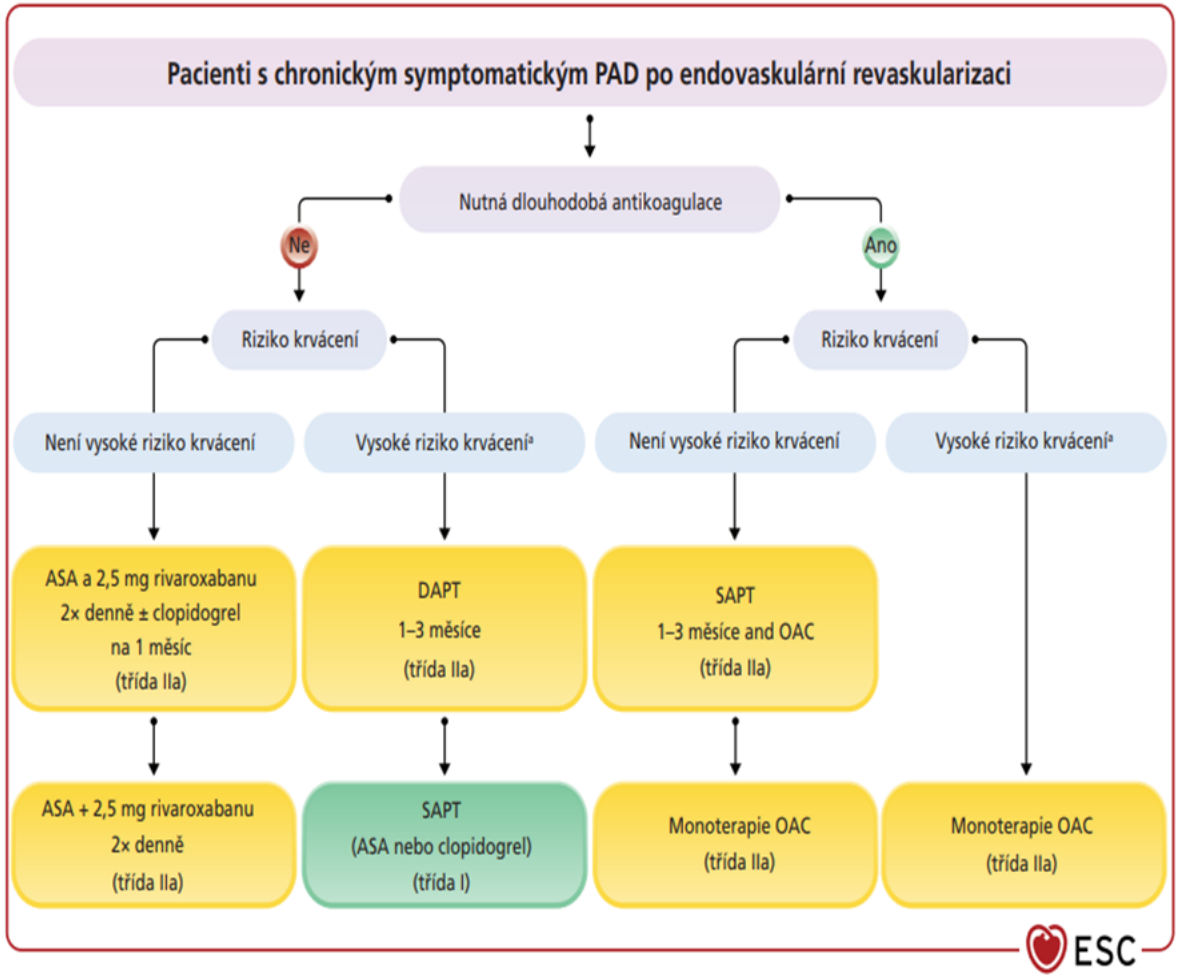
Antiotrombotika u PAD (perif. arteriální onem.)



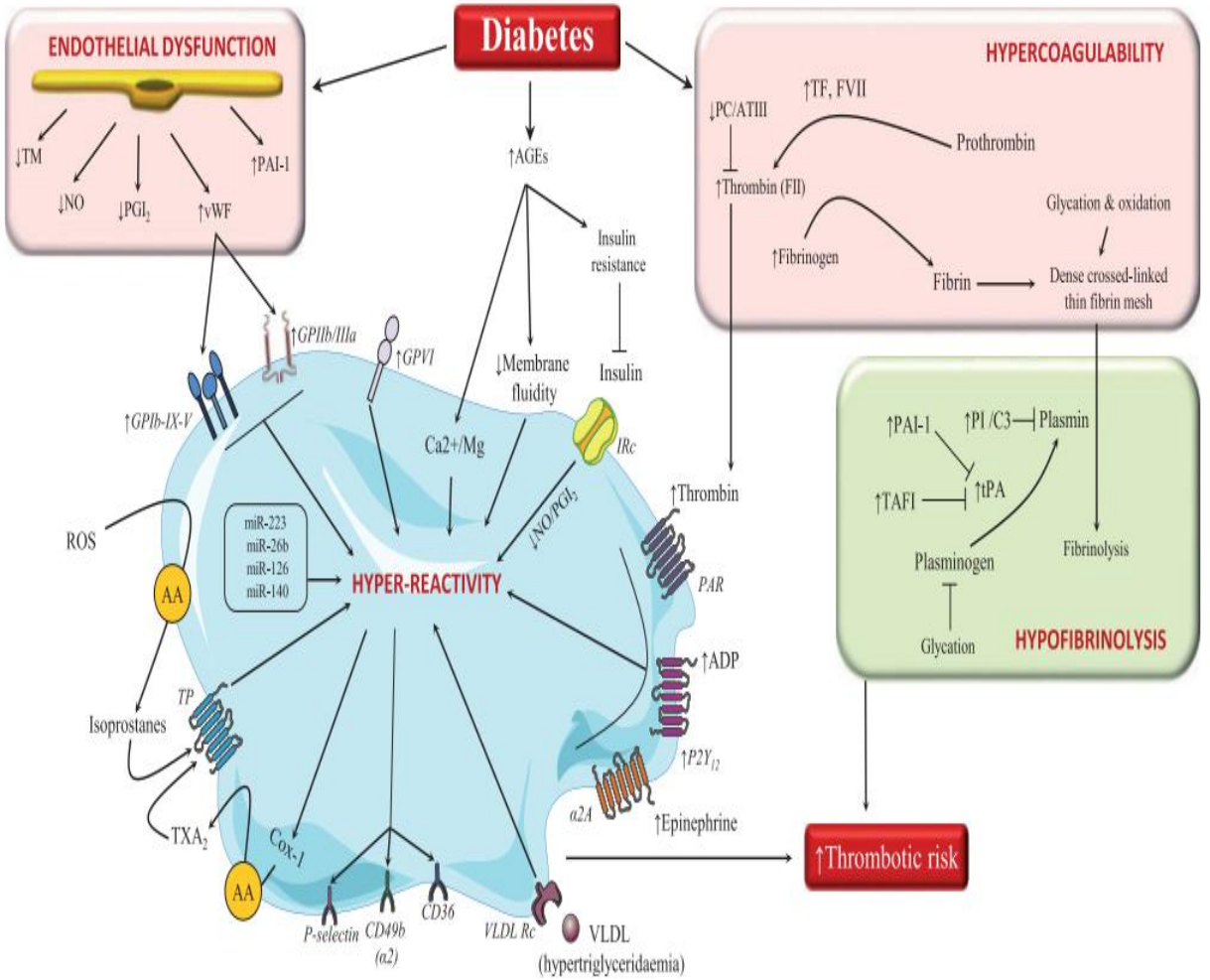


ED – pokles působků snižujících aktivaci trombocytů

Alterace funkce destiček - vyšší susceptibilita na aktivaci, vyšší obrat

Hyperkoagulace – vyšší tvorba TF, FII, Fbg … se změnou struktury fibrinové sítě

Hypofibrinolýza – více PAI-1 a TAFI, …



European Heart Journal (2021) **42**, 2235–2259
doi:10.1093/eurheartj/ehab128

Velké randomizované studie
ASA v „primární prevenci“ u diabetiků

	JPAD[6] (2008)	POPADAD[17] (2008)	ASCEND[5] (2018)	TIPS-3[19] (2021)
Country	Japan	United Kingdom	United Kingdom	International
Participants	Type 2 diabetes	Type 1 or type 2 diabetes with asymptomatic PAD	Type 1 or type 2 diabetes	Elevated INTERHEART Risk Score
Sample size	2,539	1,276	15,480	5,713 (2,095 with diabetes)
Study interventions	Low-dose aspirin (81 mg or 100 mg daily) vs. no aspirin	Aspirin 100 mg daily vs. placebo	Enteric-coated aspirin 100 mg daily vs. placebo	Enteric-coated aspirin 75 mg daily vs. placebo
Follow-up time	Median: 4.37 years	Median: 6.7 years	Median: 7.4 years	Mean: 4.6 years
Primary endpoint	Nonfatal ischemic heart disease, fatal or nonfatal stroke, or peripheral arterial disease Aspirin: 13.6 per 1,000 person-years No aspirin: 17.0 per 1,000 person-years (HR: 0.80; 95% CI: 0.58–1.10; $p = 0.16$)	Death from coronary heart disease or stroke, nonfatal myocardial infarction or stroke, or above ankle amputation for critical limb ischemia Aspirin: 18.2% Placebo: 18.3% (HR: 0.98; 95% CI: 0.76–1.26; $p = 0.86$)	Nonfatal myocardial infarction, nonfatal stroke or transient ischemic attack, or death from any vascular cause Aspirin: 8.5% Placebo: 9.6% (HR: 0.88; 95% CI: 0.79–0.97; $p = 0.01$)	Death from cardiovascular causes, myocardial infarction, or stroke Aspirin: 4.1% Placebo: 4.7% (HR: 0.86; 95% CI: 0.67–1.10) No heterogeneity of treatment according to diabetes status
Safety	No significant difference in the composite of severe GI bleeding or hemorrhagic stroke (*p*-value not available)	GI bleeding Aspirin: 4.4% Placebo: 4.9% (OR: 0.90; 95% CI: 0.53–1.52; $p = 0.69$)	Major bleeding events Aspirin: 4.1%; Placebo: 3.2% (RR: 1.29; 95% CI: 1.09–1.52; $p = 0.003$)	Similar number of patients with major bleeding (no *p*-value provided)

„underpowered“ „enteric-coated ASA“

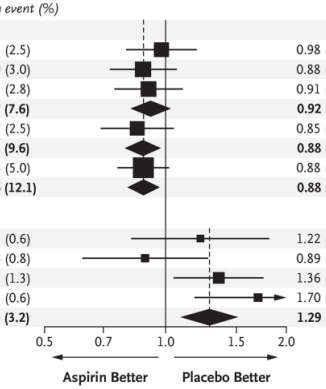
Del Bianco-Rondeau M, et al. Thromb Haemost 2022;122:1443–1453
Bowman L, et al. ASCEND Study Collaborative Group. Effects of aspirin for primary prevention in persons with diabetes mellitus. N Engl J Med 2018;379(16): 1529–153

Studie ASCEND (A Study of Cardiovascular Events iN Diabetes)

ASA vs placebo, pacienti s DMI 1. nebo DM 2. typu ***(n = 15 480)***, délka studie: 7.4 r.
bez KV onemocnění

Effect of Assignment to Aspirin Group on Components of Serious Vascular Events, the Combined Outcome of Serious Vascular Event or Revascularization, and Major Bleeding and Its Components.

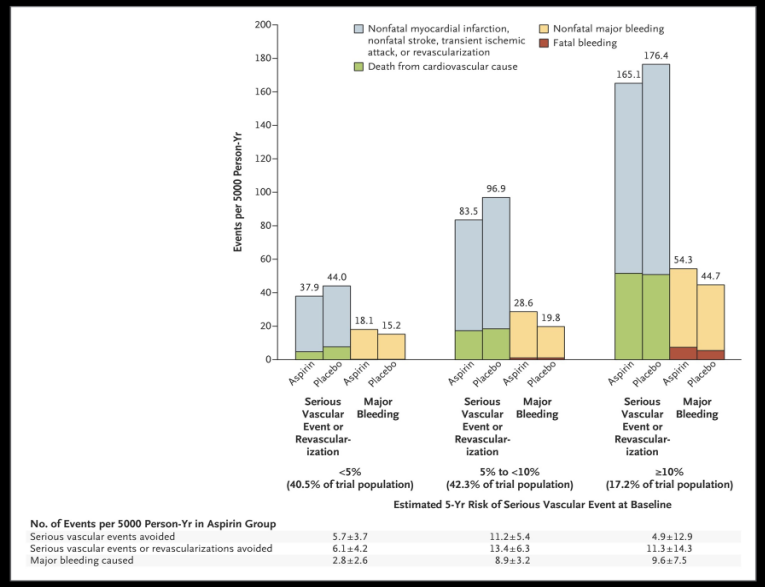
Type of Event	Aspirin (N=7740)	Placebo (N=7740)	Rate Ratio (95% CI)	P Value
	no. of participants with event (%)			
Vascular Outcomes				
Nonfatal myocardial infarction	191 (2.5)	195 (2.5)	0.98 (0.80–1.19)	
Nonfatal presumed ischemic stroke	202 (2.6)	229 (3.0)	0.88 (0.73–1.06)	
Vascular death excluding intracranial hemorrhage	197 (2.5)	217 (2.8)	0.91 (0.75–1.10)	
Any serious vascular event excluding TIA	**542 (7.0)**	**587 (7.6)**	**0.92 (0.82–1.03)**	
TIA	168 (2.2)	197 (2.5)	0.85 (0.69–1.04)	
Any serious vascular event including TIA	**658 (8.5)**	**743 (9.6)**	**0.88 (0.79–0.97)**	**0.01**
Any arterial revascularization	340 (4.4)	384 (5.0)	0.88 (0.76–1.02)	
Any serious vascular event or revascularization	**833 (10.8)**	**936 (12.1)**	**0.88 (0.80–0.97)**	
Major Bleeding				
Intracranial hemorrhage	55 (0.7)	45 (0.6)	1.22 (0.82–1.81)	
Sight-threatening bleeding in eye	57 (0.7)	64 (0.8)	0.89 (0.62–1.27)	
Serious gastrointestinal bleeding	137 (1.8)	101 (1.3)	1.36 (1.05–1.75)	
Other major bleeding	74 (1.0)	43 (0.6)	1.70 (1.18–2.44)	
Any major bleeding	**314 (4.1)**	**245 (3.2)**	**1.29 (1.09–1.52)**	**0.003**



The ASCEND Study Collaborative Group. N Engl J Med2018;379:1529-1539

The NEW ENGLAND JOURNAL of MEDICINE

Observed Absolute Effect of Assignment to Aspirin Group on Serious Vascular Events or Revascularization and on Major Bleeding, According to Vascular Risk.



No. of Events per 5000 Person-Yr in Aspirin Group			
Serious vascular events avoided	5.7±3.7	11.2±5.4	4.9±12.9
Serious vascular events or revascularizations avoided	6.1±4.2	13.4±6.3	11.3±14.3
Major bleeding caused	2.8±2.6	8.9±3.2	9.6±7.5

The ASCEND Study Collaborative Group. N Engl J Med2018;379:1529-1539

The NEW ENGLAND JOURNAL of MEDICINE

Vážné vaskulární příhody redukovány
8.5% vs. 9.6%; rr 0.88; 95% confidence interval [CI], 0.79 to 0.97; P=0.01 …… **-12% (jako meta-analýza ATT)**
vzestup krvácení: 4.1% v ASA skupině vs 3.2% v placebo sk. (rr 1.29; 95% CI, 1.09 to 1.52; P=0.003)

VŠEOBECNÁ FAKULTNÍ NEMOCNICE V PRAZE
1. LÉKAŘSKÁ FAKULTA Univerzita Karlova

Bowman L, et al. ASCEND Study Collaborative Group. Effects of aspirin for primary prevention in persons with diabetes mellitus. N Engl J Med 2018;379(16): 1529–153

ASA ve studii ASCEND / diabetici

→ **ASA signifikantně snížila MACE** (8.5% vs. 9.6%, RR 0.88; 95% CI, 0.79–0.90; *P* = 0.01; [NNT - 91].

→ **krvácení:** 4.1% vs. 3.2% resp. (RR 1.29; 95% CI, 1.09–1.52; *P* = 0.003; [NNH - 111]

NNT/NNH ratio = 0.8

- Pacienti s DM, asymptomatičtí stran ASKVO mají být „zvažováni“ k léčbě ASA (75–100 mg)
- Pacienti s DM, asymptomatičtí, ale s dokument. „atero postižením“ – tedy ve vyšším KV riziku mohou z ASA profitovat, tedy **individuálně léčbu ASA indikovat.**

Recommendation	Class[a]	Level[b]
In adults with T2DM without a history of symptomatic ASCVD or revascularization, ASA (75–100 mg o.d.) may be considered to prevent the first severe vascular event, in the absence of clear contraindications.[c,292,293]	IIb	A

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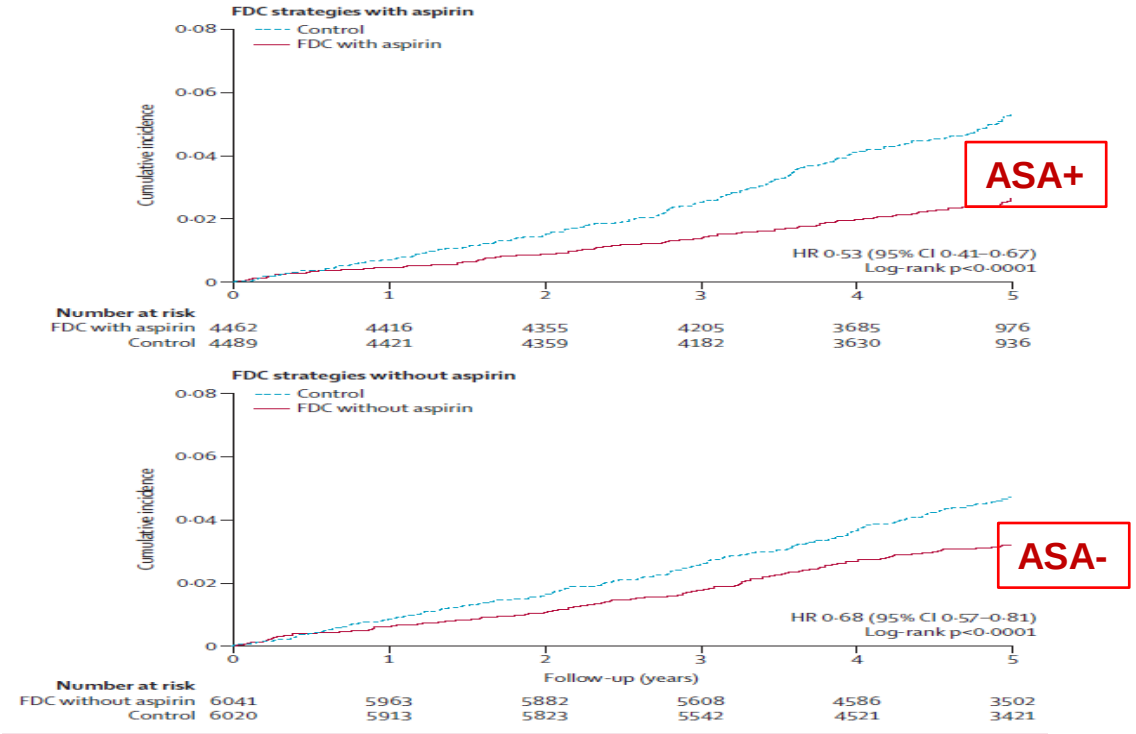
ASCEND Study Collaborative Group. Effects of aspirin for primary prevention in persons with diabetes mellitus. *N Engl J Med* 2018;**379**:1529–1539. https://doi.org/10. 1056/NEJMoa1804988

Přítomnost ASA v „polypill“ (antihypertensivum, statin ± ASA) zlepšuje KV prognózu u rizikových nemocných

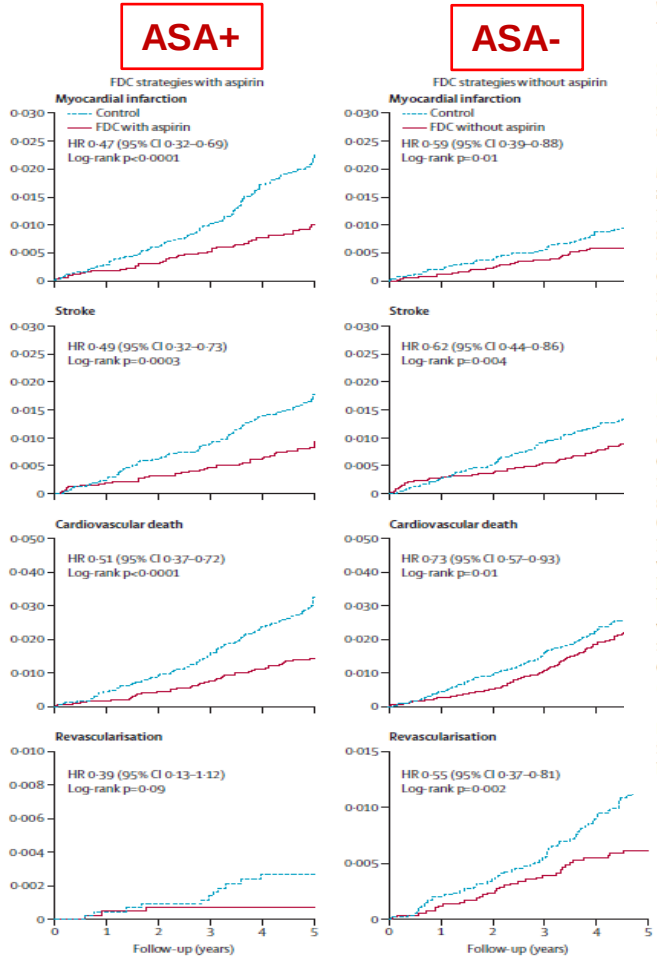
primární prevence pacientů s vysokým KV rizikem (≈20%/10let): meta-analýza 3 studií s >18 tis. probandy, FU - 5 let



ASA+

ASA-

Figure 2: **Kaplan-Meier curves for the composite primary outcome of cardiovascular death, myocardial infarction, stroke, or revascularisation**
Kaplan-Meier curves are presented up to 5 years. FDC=fixed-dose combination. HR=hazard ratio.



Fixed-dose combination therapies with and without aspirin for primary prevention of cardiovascular disease: an individual participant data meta-analysis

Philip Joseph, Gholamreza Roshandel, Peggy Gao, Prem Pais, Eva Lonn, Denis Xavier, Alvaro Avezum, Jun Zhu, Lisheng Liu, Karen Sliwa, Habib Gamra, Shrikant I Bangdiwala, Koon Teo, Rafael Diaz, Antonio Dans, Patricio Lopez-Jaramillo, Dorairaj Prabhakaran, Jose Maria Castellano, Valentin Fuster, Anthony Rodgers, Mark D Huffman, Jackie Bosch, Gilles R Dagenais, Reza Malekzadeh, Salim Yusuf, on behalf of the Polypill Trialists' Collaboration

Summary

Background In randomised controlled trials, fixed-dose combination treatments (or polypills) have been shown to reduce a composite of cardiovascular disease outcomes in primary prevention. However, whether or not aspirin should be included, effects on specific outcomes, and effects in key subgroups are unknown.

Methods We did an individual participant data meta-analysis of large randomised controlled trials (each with ≥1000 participants and ≥2 years of follow-up) of a fixed-dose combination treatment strategy versus control in a primary cardiovascular disease prevention population. We included trials that evaluated a fixed-dose combination strategy of at least two blood pressure lowering agents plus a statin (with or without aspirin), compared with a control strategy (either placebo or usual care). The primary outcome was time to first occurrence of a composite of cardiovascular death, myocardial infarction, stroke, or arterial revascularisation. Additional outcomes included individual cardiovascular outcomes and death from any cause. Outcomes were also evaluated in groups stratified by the inclusion of aspirin in the fixed-dose treatment strategy, and effect sizes were estimated in prespecified subgroups based on risk factors. Kaplan-Meier survival curves and Cox proportional hazard regression models were used to compare strategies.

Findings Three large randomised trials were included in the analysis (TIPS-3, HOPE-3, and PolyIran), with a total of 18 162 participants. Mean age was 63·0 years (SD 7·1), and 9038 (49·8%) participants were female. Estimated 10-year cardiovascular disease risk for the population was 17·7% (8·7). During a median follow-up of 5 years, the primary outcome occurred in 276 (3·0%) participants in the fixed-dose combination strategy group compared with 445 (4·9%) in the control group (hazard ratio 0·62, 95% CI 0·53–0·73, p<0·0001). Reductions were also observed for the separate components of the primary outcome: myocardial infarction (0·52, 0·38–0·70), revascularisation (0·54, 0·36–0·80), stroke (0·59, 0·45–0·78), and cardiovascular death (0·65, 0·52–0·81). Significant reductions in the primary outcome and its components were observed in the analyses of fixed-dose combination strategies with and without aspirin, with greater reductions for strategies including aspirin. Treatment effects were similar at different lipid and blood pressure levels, and in the presence or absence of diabetes, smoking, or obesity. Gastrointestinal bleeding was uncommon but slightly more frequent in the fixed-dose combination strategy with aspirin group versus control (19 [0·4%] *vs* 11 [0·2%], p=0·15). The frequencies of haemorrhagic stroke (10 [0·2%] *vs* 15 [0·3%]), fatal bleeding (two [<0·1%] *vs* four [0·1%]), and peptic ulcer disease (32 [0·7%] *vs* 34 [0·8%]) were low and did not differ significantly between groups. Dizziness was more common with fixed-dose combination treatment (1060 [11·7%] *vs* 834 [9·2%], p<0·0001).

Interpretation Fixed-dose combination treatment strategies substantially reduce cardiovascular disease, myocardial infarction, stroke, revascularisation, and cardiovascular death in primary cardiovascular disease prevention. These benefits are consistent irrespective of cardiometabolic risk factors.

Lancet 2021; 398: 1133–46
Published Online August 29, 2021 https://doi.org/10.1016/S0140-6736(21)01827-4

See Comment page 1106

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VŠEOBECNÁ FAKULTNÍ NEMOCNICE V PRAZE

1. LÉKAŘSKÁ FAKULTA Univerzita Karlova

ASA – rezistence, tolerance a dostupnost

Rezistence: **klinická a laboratorní**

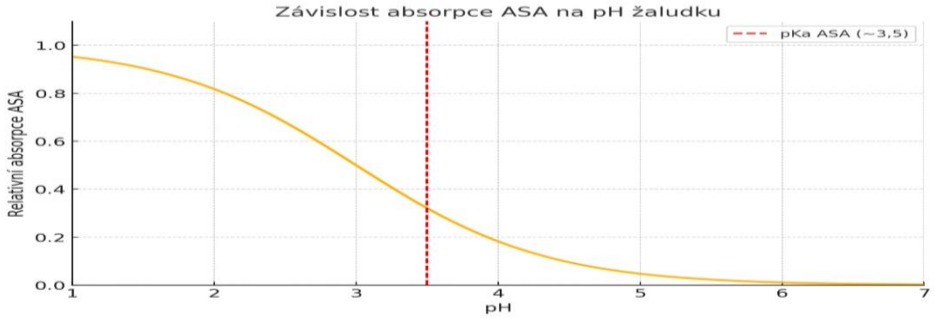
– příčiny: compliance? absorpce? abnormální aktivita COX-1? jiná cesta aktivace trombocytů? genetická?

Tolerabilita: **GI obtíže - GI krvácení, krvácivé komplikace obecně**

alergie – AERD (astma), Reyeův syndrom u dětí

Cesta zlepšení tolerance: kombinace s PPI / enterosolventní f. ASA / individualizace dávky?

- Při léčbě IPP (cca u 30% nem.) či při užití enterosolventních forem (35% léčeno „protektivními“ formami - ecASA) stoupá pH v žaludku >3,5 → klesá dostupnost ASA
- Proč? ASA je slabá kyselina s pKa ≈ 3,5, v žaludku norm. pH 1-2. ASA v nedisociované formě – lipofilní - lépe prostupuje (nejefektivnější absorpce). Je-li pH vyšší – ASA v disociované f., menší absorpce v žaludku, tím menší inaktivace trombo v portálním oběhu (presystémový kompartment, kde trombocyty exponovány 2x vyšší ASA koncentraci než v cirkulaci systémové).



Bhatt DL, Grosser T, Dong JF, et al. Enteric coating and aspirin nonresponsiveness in patients with type 2 diabetes mellitus. J Am Coll Cardiol 2017;69(06):603–612
Cox D, Maree AO, Dooley M, et al. Effect of enteric coating on antiplatelet activity of low-dose aspirin in healthy volunteers. Stroke 2006;37(08):2153–2158
Grosser T, Fries S, Lawson JA, et al. Drug resistance and pseudoresistance: consequence of enteric coating aspirin. Circulation 2013;127(03): 377–385
Lordkipanidzé M, Pharand C, Schampaert E, et al. A comparison of six major platelet function tests to determine the prevalence of aspirin resistance in patients with stable coronary artery disease. Eur Heart J 2007;28(14): 1702–1708
Santilli F, Pignatelli P, Violi F, Davì G Aspirin for primary prevention in diabetes mellitus: from the calculation of cardiovascular risk and risk/benefit profile to personalised treatment. Thromb Haemost 2017;28(14):1702–1708 37

Farmakokinetika ASA a inaktivace COX-1

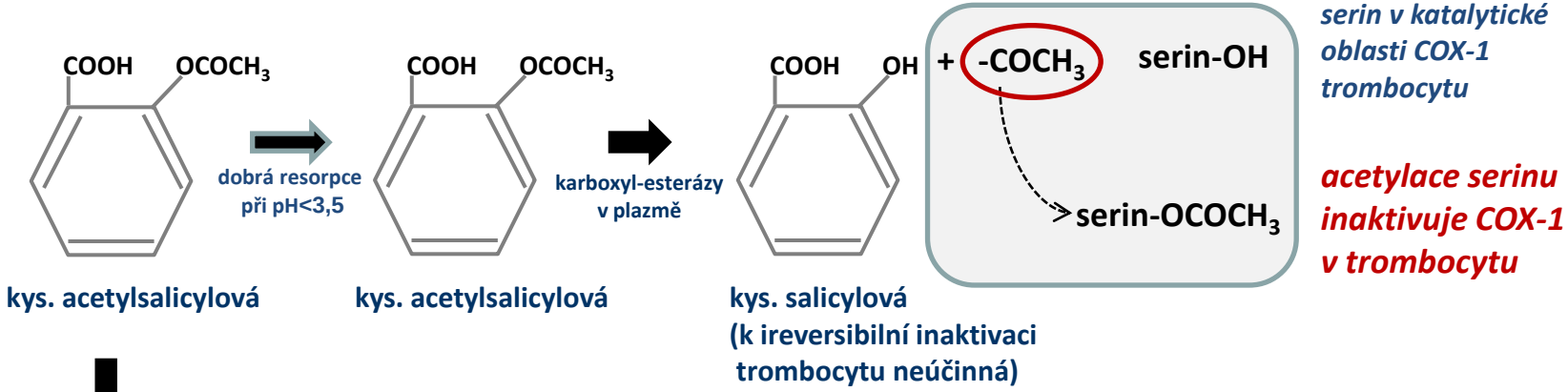
- při vzestupu pH >3,5 horší absorpce ASA, ve střevě dochází k deacetylaci na kys. salicylovou

kyselé prostředí pH<3,5

žaludek a duodenum

portální oběh

trombocyt v portálním oběhu



kys. acetylsalicylová

kys. acetylsalicylová

kys. salicylová (k ireversibilní inaktivaci trombocytu neúčinná)

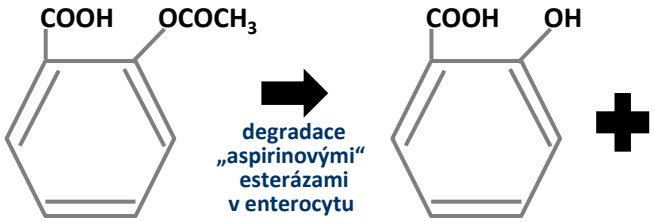
serin v katalytické oblasti COX-1 trombocytu

acetylace serinu inaktivuje COX-1 v trombocytu

nízká resorpce při pH>3,5

vzestup pH>3,5 sníží absorpci ASA, vstřebává se kys. salicylová

enterocyt



kys. acetylsalicylová

kys. salicylová (k ireversibilní inaktivaci trombocytu neúčinná)

další degradační produkty kys. acetylsalicylové

portální oběh

nedostatečná nabídka kys. acetylsalicylové k ireversibilní inaktivaci COX-1 acetylací serinu

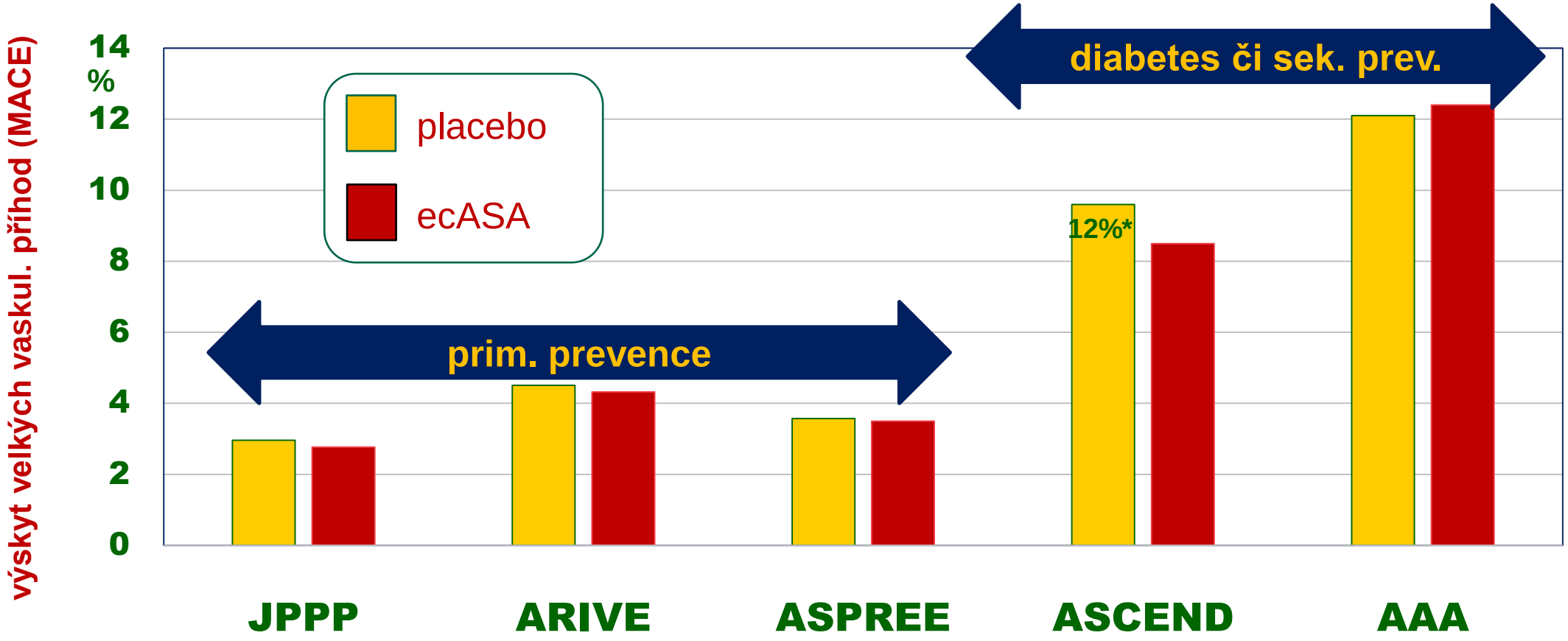
Prevence GIT krvácení v „guidelines“ / diabetici

Recommendation Table 15 — Recommendations for gastric protection in patients with diabetes taking antithrombotic drugs

Recommendations	Class[a]	Level[b]
When antithrombotic drugs are used in combination, proton pump inhibitors are recommended to prevent gastrointestinal bleeding.[337,347,348,351–353,355]	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.[338,347,348,351,352]	IIa	A
When clopidogrel is used, omeprazole and esomeprazole are not recommended for gastric protection.[356]	III	B

- PPI doporučen při kombinaci antitrombotik
- U „single“ medikace – individuálně dle rizika krvácení
- Klopidogrel nekombinovat s omeprazolem a esomeprazolem

Srovnání studií s „protektivní“ formou ASA (vs. placebo) v primární a sekundární prevenci

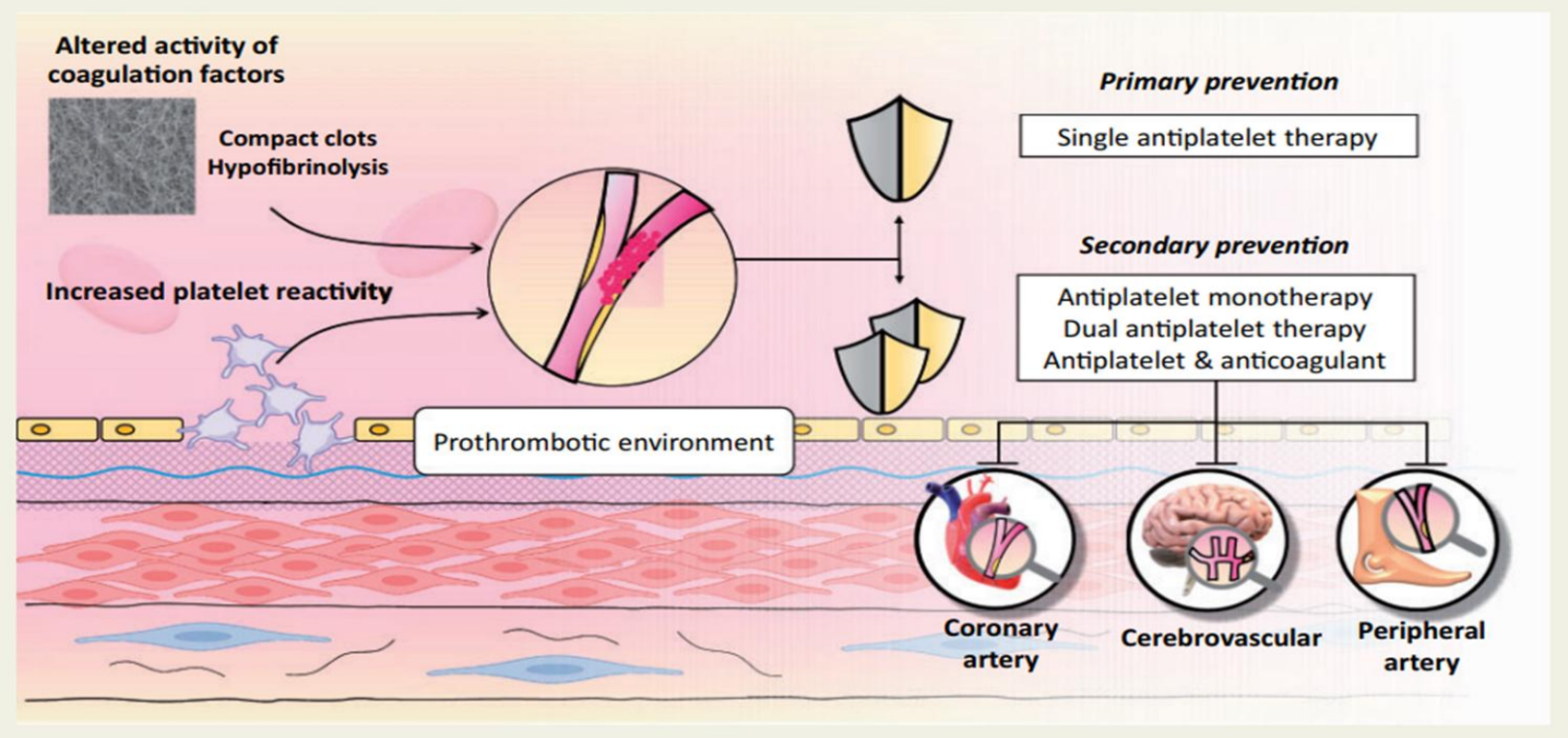


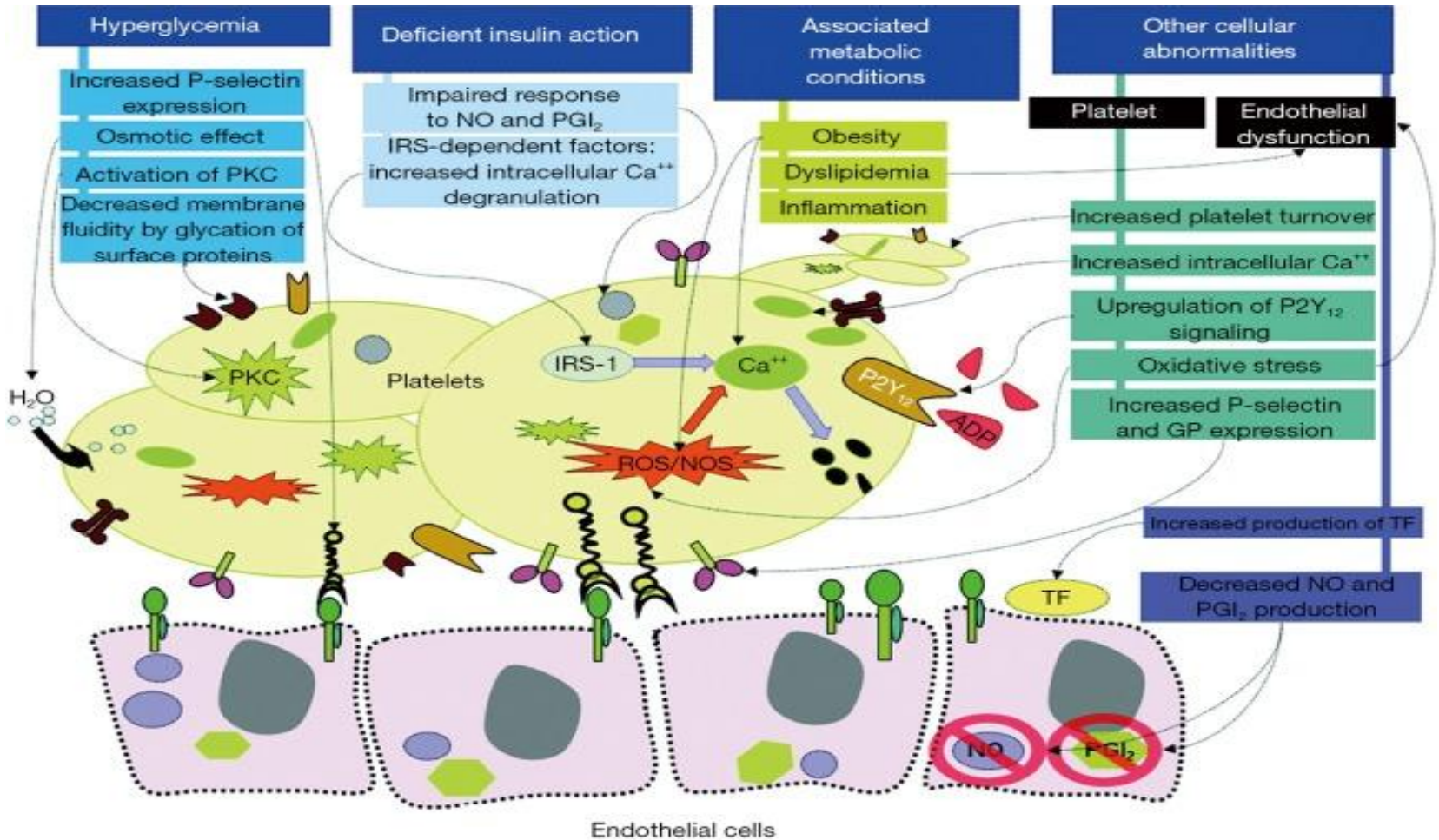
Ikeda Y, JAMA 2014; 312: 2510–2520, https://www.clinicaltrialsregister.eu/ctr-search/trial/2006-003622-29/results, https://aspree.org/aus/. Fowkes FG, J Am Med Assoc 2010; 303: 841–848, DOI: 10.1056/NEJMoa1804988

Závěry

- DM 2. typu spojen s endoteliální dysfunkcí, hyperkoagulačním stavem a poruchou fibrinolýzy, dominuje abnormální aktivace a zvýšený obrat trombocytů.
- V primární prevenci má podávání protidestičkové léčby (ASA) být zváženo u vysoce rizikových pacientů.
- V sekundární prevenci je ASA základním pilířem léčby.
- Duální antiagregační terapie podávána v souladu s „guidelines“ (např. po AKS na 6-12 měs. ASA + ADP 2Y12 inhibice).
- Diabetici s PAD – léčba u chronických stavů realizována ASA nebo klopidogrelem, duální léčba pouze dočasně po stentingu. Ke zvážení je u vysoce rizikových nem. kombinace DAT (ASA + rivaroxaban 2x2,5 mg, dle studie COMPASS, výraznější čistý benefit u diabetiků).
- Antikoagulační léčba u DM dle zvyklých doporučení.
- U diabetiků žádoucí častěji sledovat komedikaci, funkci ledvin, hmotnost, ..
- Běžné formy ASA mají lepší absorpci v žaludku, rychlý nástup účinku a vyšší dostupnost.

DIABETES MELL. & (ATERO)TROMBÓZA




Hyperglycemia
Deficient insulin action
Associated metabolic conditions
Other cellular abnormalities
Increased P-selectin expression
Osmotic effect
Activation of PKC
Decreased membrane fluidity by glycation of surface proteins
Impaired response to NO and PGI2
IRS-dependent factors: increased intracellular Ca++ degranulation
Obesity
Dyslipidemia
Inflammation
Platelet
Endothelial dysfunction
Increased platelet turnover
Increased intracellular Ca++
Upregulation of P2Y12 signaling
Oxidative stress
Increased P-selectin and GP expression
Increased production of TF
Decreased NO and PGI2 production
PKC
Platelets
IRS-1
Ca++
P2Y12
ADP
ROS/NOS
H2O
TF
NO
PGI2
Endothelial cells