

Nový pohled na kardiovaskulární riziko u pacientů se syndromem diabetické nohy

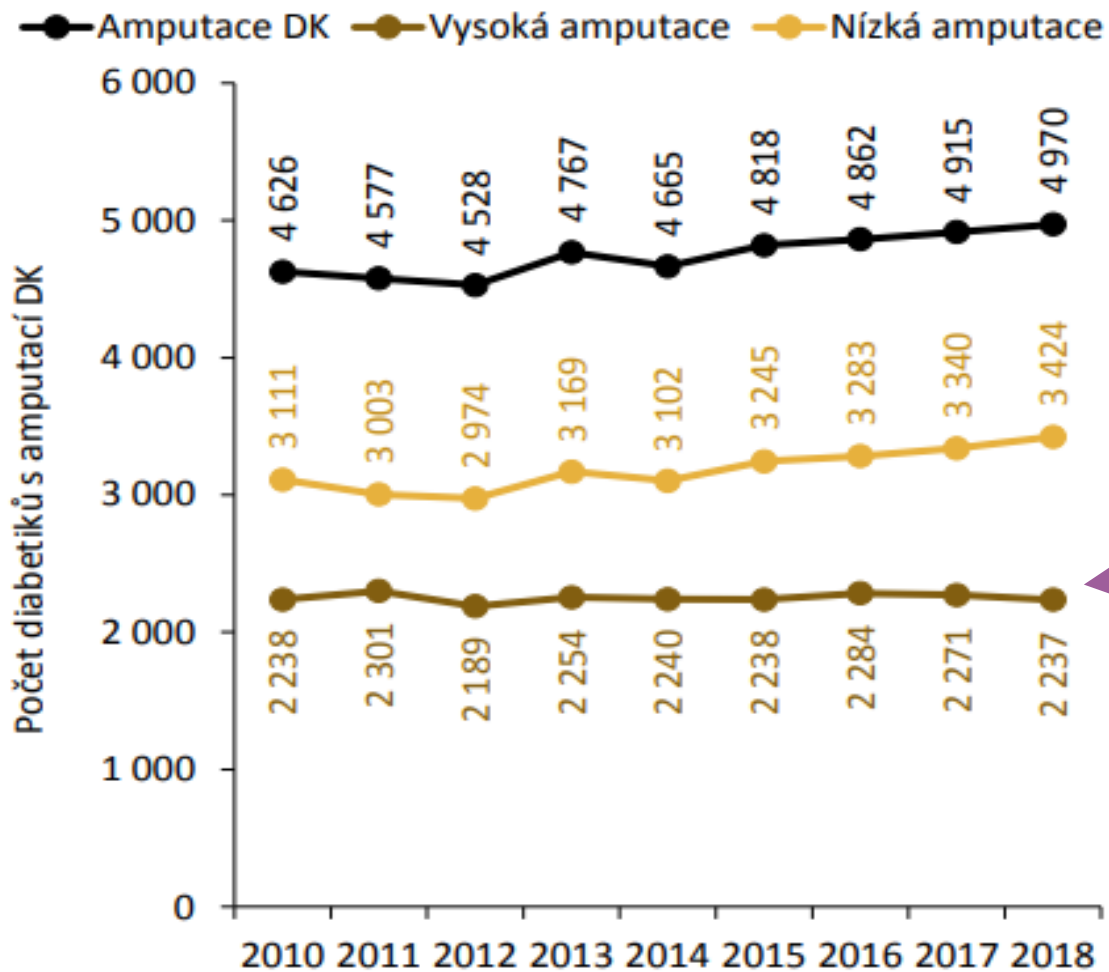
FEJFAROVÁ V.
CD IKEM, PRAHA





Epidemiologie SDN

Počet diabetiků s amputací dolní končetiny v daném roce:



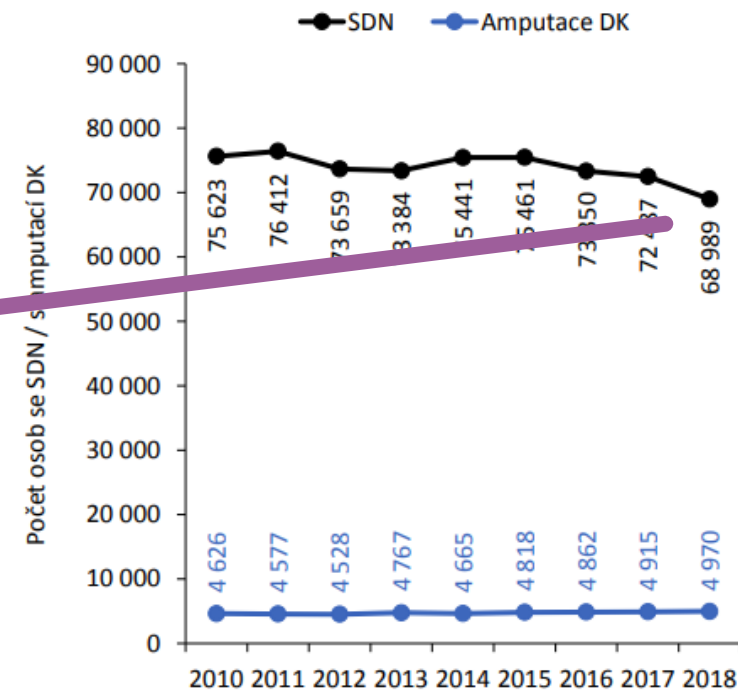
Syndrom diabetické nohy a amputace DK

Zdroj dat: NRHVS 2010–2018;

Syndrom diabetické nohy je u pacienta v daném roce definován výskazem E10.5, E11.5, E12.5, E13.5, E14.5.

Amputace dolní končetiny je u pacienta v daném roce definována výkazem 66851, 66685, 66683, 66679, 66681, 66695, 66697, 66699.

Počet diabetiků se syndromem diabetické nohy a počet diabetiků s amputací DK v daném roce:



7%

Jak vysoké je KV riziko u nemocných se syndromem diabetické nohy?



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), Maddalena Lettino (Italy), Darren K. McGuire (United States of America), Wilfried Mullens (Belgium), Bianca Rocca (Italy), Naveed Sattar (United Kingdom), and ESC Scientific Document Group

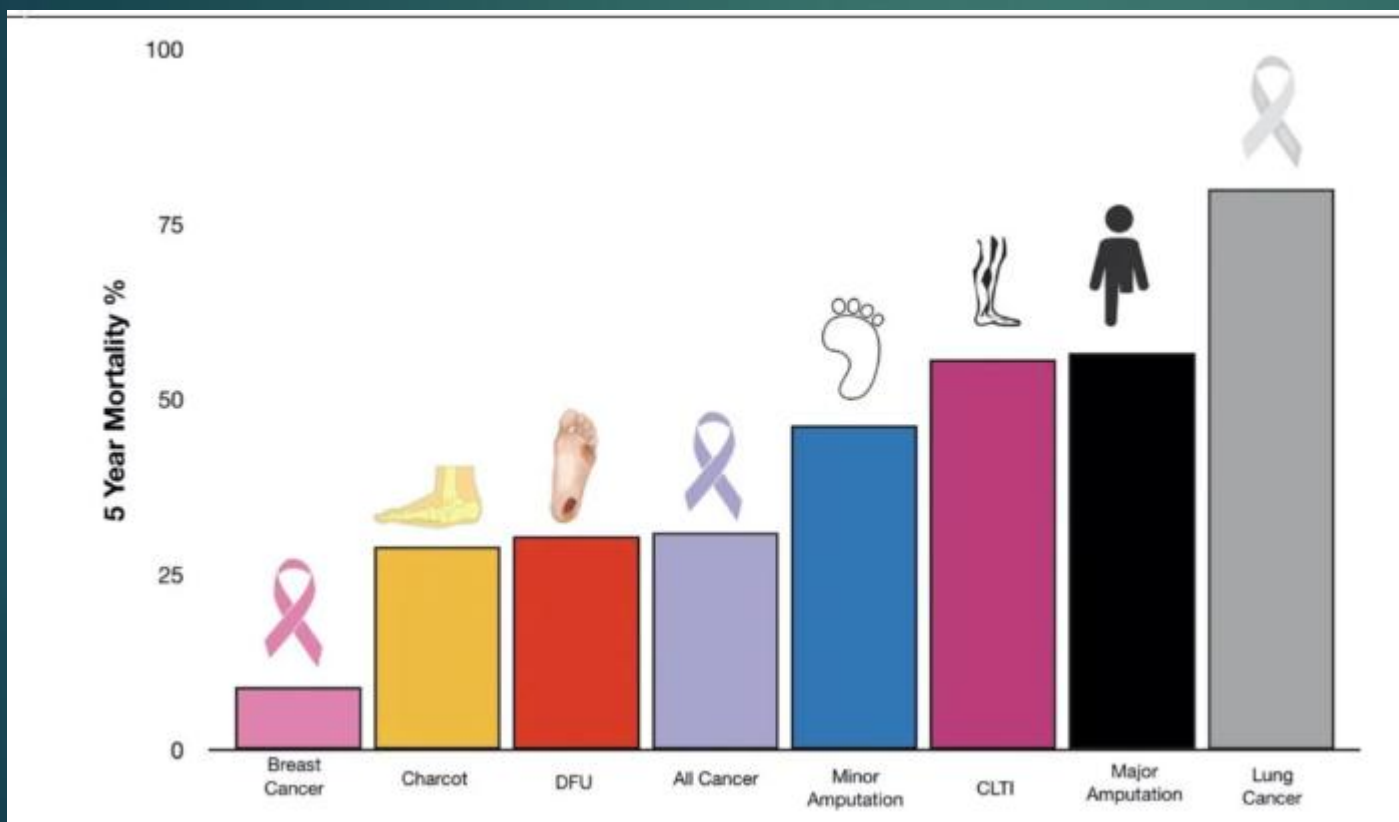
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 PAD	 Offloading	 Wound Healing	 Charcot
Intersocietal PAD guideline (2023 update) Read more	Offloading guideline (2023 update) Read more	Wound healing interventions guideline (2023 update) Read more	Charcot's neuro-osteoarthropathy (2023 update) Read more
 Methodology	 Definitions and Criteria		
Development and Methodology IWGDF 2023 update Read more	Definitions & criteria (2023 update) Read more		

Jak vysoké je KV riziko u nemocných se syndromem diabetické nohy?



Pacienti se SDN jsou dle doporučení mezinárodních organizací považováni za pacienty s velmi vysokým KV rizikem a tak by měli být i léčeni.

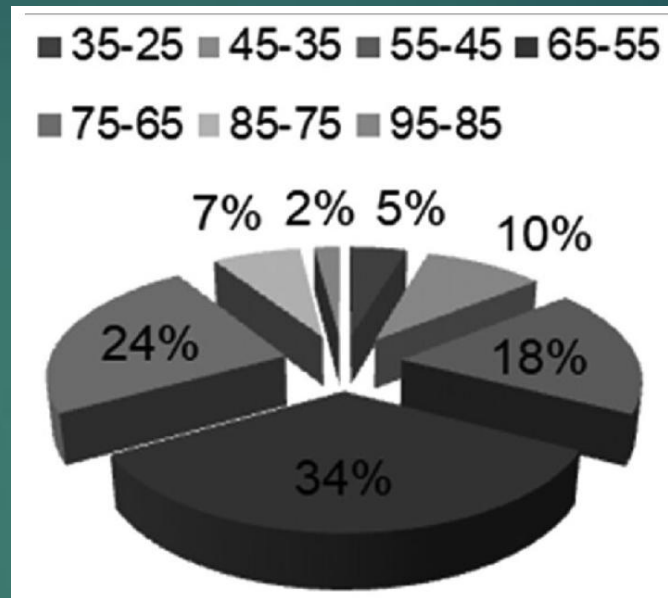
*Cave - vzhledem k neuropatii, s diabetem sdruženými dalšími komorbidity, vyššímu věku, křehkosti, socioekonomickým podmínkám je **nutno léčbu individualizovat**Nutno vzít v potaz životní prognózu nemocných, výše zmíněné faktory, očekávaný benefit, lékové interakce apod.*



Má SDN průniky s KV onemocněním?

Z hlediska rizikových faktorů:

▶ 1. Věk



- ▶ **2. Neuropatie** – periferní senzomotorická a autonomní (asymptomatické příznaky ICHS, ICHDK, AN- náhlá úmrtí, klidová tachykardie, orthostatické hypotenze, snížená variabilita srdeční frekvence)

..... Studie Elrefaia a spol. prokázala alespoň jeden typ neuropatie u 89% pacientů , příznaky autonomní neuropatie byly nalezeny u 12% nemocných se SDN

Má SDN průniky s

▶ 3. Infekce

Přibližně 50% to 60% diabetických ulcerací jsou závažně a těžce infikovaných ulcerac

Opakované infekce potencují proces aterosklerózy

Figure No.1: ORs (95% CIs) of new carotid plaques calculated for various types of chronic infections.

Variable

Chronic infection

COPD with infect exacerbation

Chronic bronchitis / sinusitis

Chronic / recurrent urinary infection

Other infections

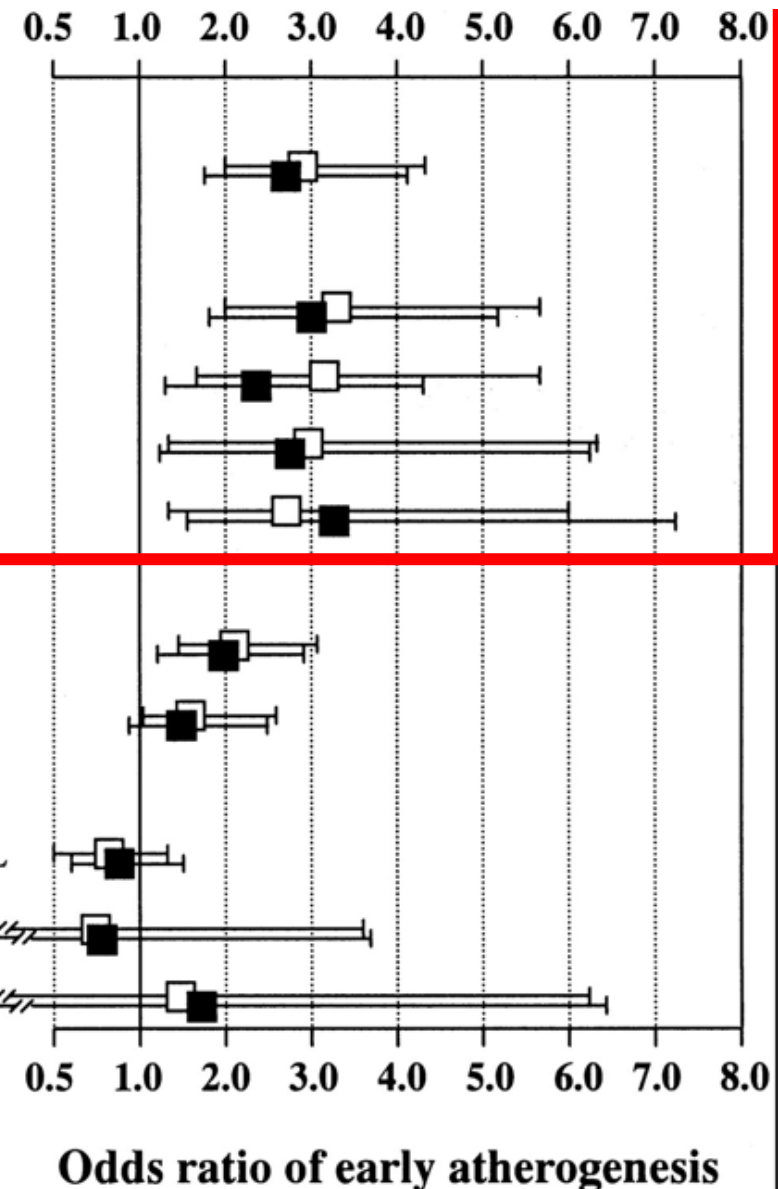
IgA antibody titer to *C pneumoniae* >16

IgG *H pylori* antibody ≥ 16 U/mL

IgG cytomegalovirus antibody ≥ 20 U/mL

Herpes zoster

Chronic active hepatitis B/C



Má SDN průniky s KV onemocněním?

▶ 4. Komorbidity – zejména CHRI

- ▶ Dle studie Bonneta a spol. více než **40% pacientů** s DM rozvine CHRI
- ▶ Studie Ndipa a spol. prokázala u **11% pacientů** s DM a CHRI/CHRS DFU.

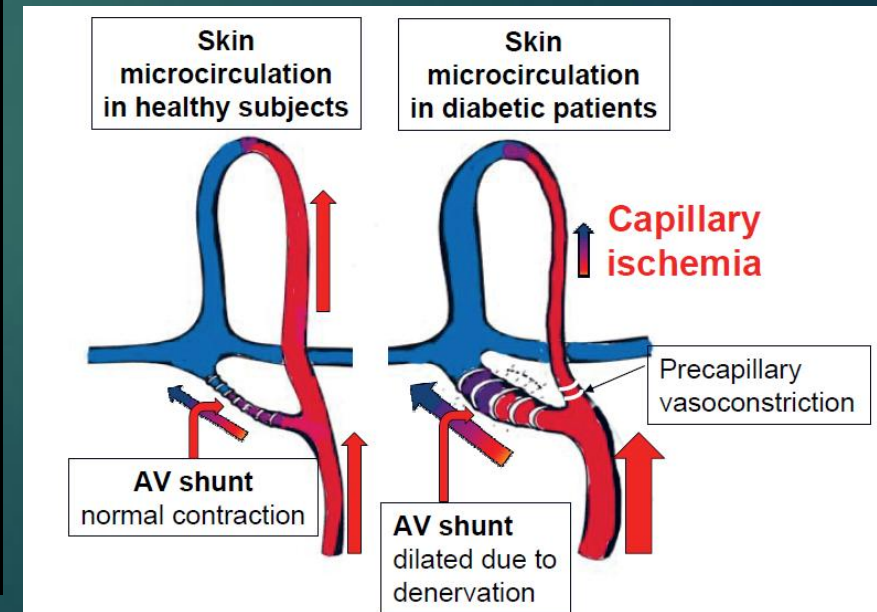
.....U HD pacientů jsou diabetické ulcerace častější oproti nemocným s CHRI/CHRS bez HD (21% vs. 5%).....měli častěji diabetickou neuropatii (79% vs. 65%), ICHDK (64% vs. 43%), předchozí amputaci (15% vs. 6.4%) a ulceraci v anamnéze (32% vs. 20%).

- ▶ **DFU a CHRI mají společné patofyziologické koreláty – ICHDK, diabetickou a uremickou neuropatii a malnutrice**
- ▶ **Jupiter ve své studii prokázal, že CHRI je nezávislým rizikovým faktorem pro vyšší mortalitu u nemocných se SDN.**



Má SDN průniky s KV onemocněním?

► 5. ICHDK



Small artery disease....lze odhadnout dle přítomnosti mediokalcinózy.....



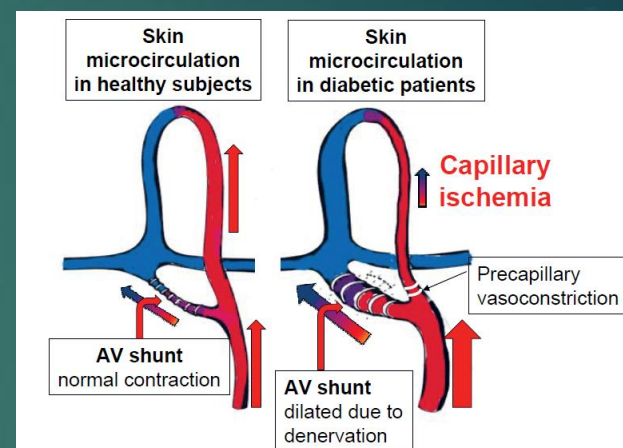
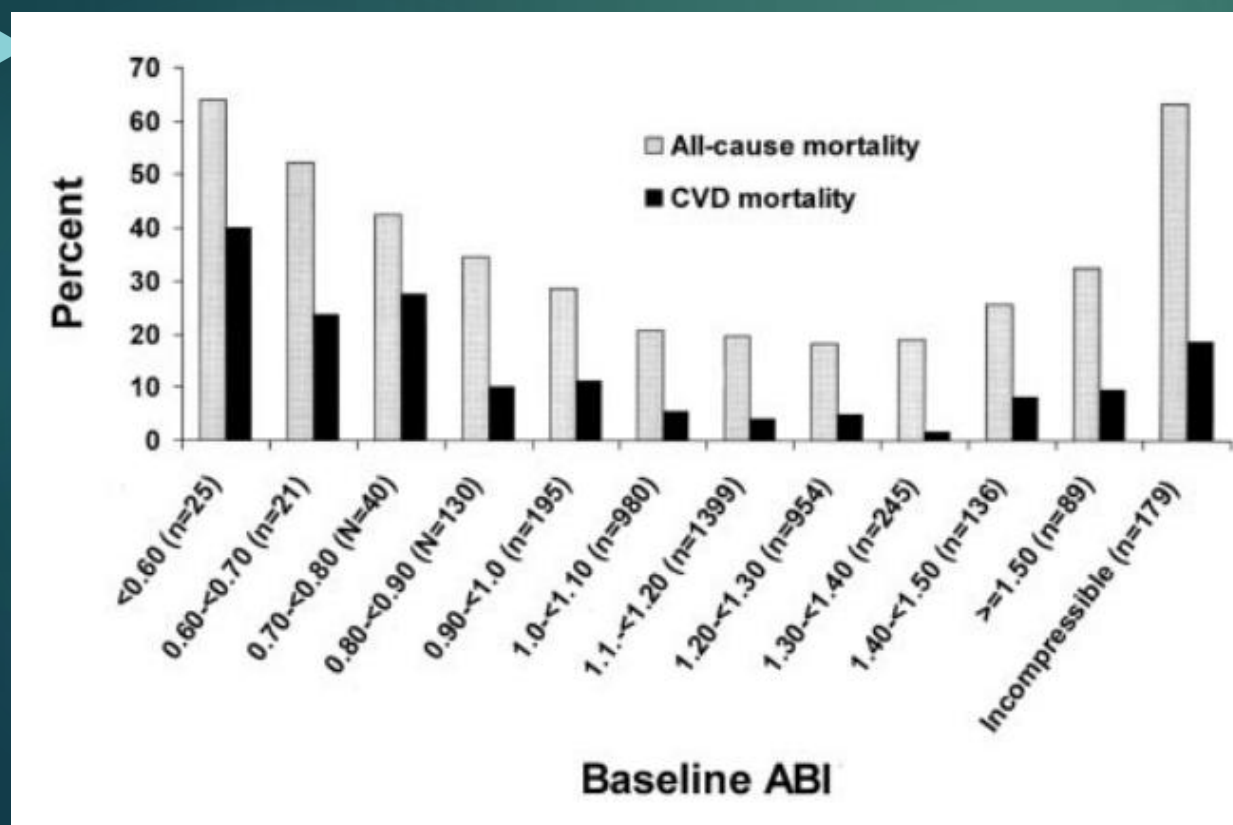
Site	Calcium length	Point	Sum all points up	MAC score
1		yes = 1 or no = 0		→
2	≥ 2 cm?	yes = 1 or no = 0	2-3 = moderate MAC	
3		yes = 1 or no = 0	4-5 = severe MAC	
4	≥ 1 cm?	yes = 1 or no = 0		
5		yes = 1 or no = 0		



- MAC / SAD skóre signifikantně koreluje s klasifikačními systémy používanými ke stratifikaci nemocných s ICHDK (GLASS, Graziani).
- Nižší MAC/SAD skóre je spojeno s dlouhodobou horší prognózou hojení ran a amputacemi dolních končetin.

ICHDK

- ▶ Vyskytuje se zhruba u 10–30% nemocných s DM, ale více než ½ nemocných je asymptomatická !!!! (dáno AN - proteplení, lokací lézí a periferní neuropatií – projevy až hodně pokročilých nálezů včetně CLTI!!!).



Podobně predikuje i vysoké amputace

Diagnostika ICHDK je klíčová pro určení pravděpodobnosti hojení, prognózy amputací, rizika rekurence a rizika pravděpodobného výskytu jiných KV onemocnění.

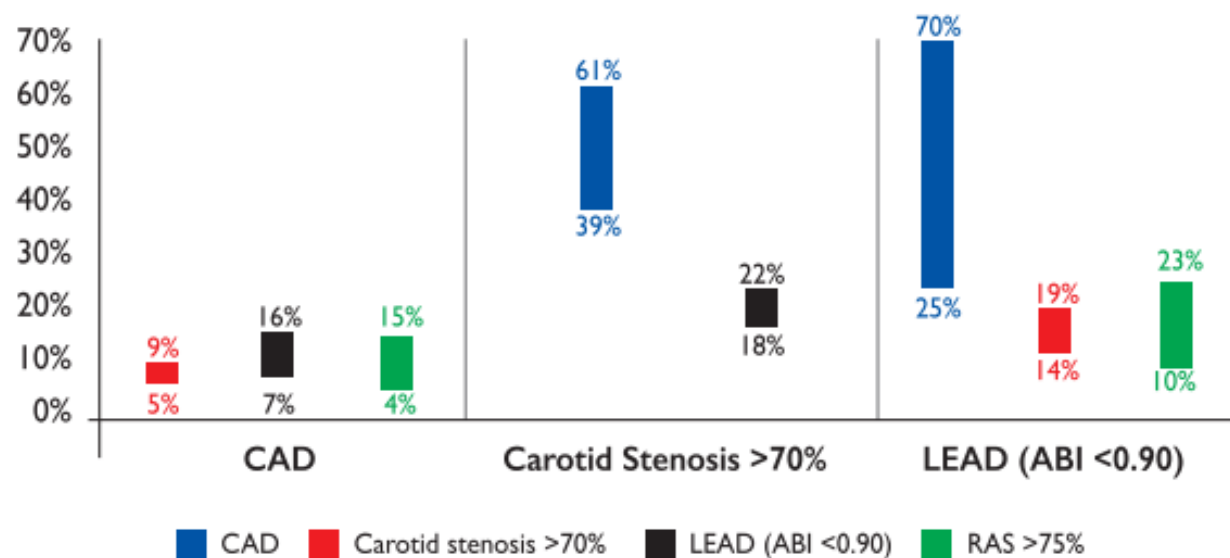
Component	Score	Description		
W (Wound)	0	No ulcer (ischaemic rest pain)		
	1	Small, shallow ulcer on distal leg or foot without gangrene		
	2	Deeper ulcer with exposed bone, joint or tendon ± gangrenous changes limited to toes		
	3	Extensive deep ulcer, full thickness heel ulcer ± calcaneal involvement ± extensive gangrene		
I (Ischaemia)		ABI	Ankle pressure (mmHg)	Toe pressure or TcPO ₂
	0	≥0.80	> 100	≥60
	1	0.60–0.79	70–100	40–59
	2	0.40–0.59	50–70	30–39
	3	<0.40	<50	<30
fl (foot Infection)	0	No symptoms/signs of infection		
	1	Local infection involving only skin and subcutaneous tissue		
	2	Local infection involving deeper than skin/subcutaneous tissue		
	3	Systemic inflammatory response syndrome		

Example: A 65-year-old male diabetic patient with gangrene of the big toe and a <2 cm rim of cellulitis at the base of the toe, without any clinical/biological sign of general infection/inflammation, whose toe pressure is at 30 mmHg would be classified as Wound 2, Ischaemia 2, foot Infection 1 (Wifl 2-2-1). The clinical stage would be 4 (high risk of amputation). The benefit of revascularization (if feasible) is high, also depending on infection control.

ABI = ankle-brachial index; TcPO₂ = transcutaneous oxygen pressure.

Abovans V., et al. *Eur Heart J*, 2018
 Mathioudakis N, et al. *J Vasc Surg* 2017
 Mills JL st., et al. *J VAsc Surg* 2014
 Armstrong DG, et al. *N Engl J Med*. 2017

	Ischaemia – 0				Ischaemia – 1				Ischaemia – 2				Ischaemia – 3			
W-0	VL	VL	L	M	VL	L	M	H	L	L	M	M	L	M	M	H
W-1	VL	VL	L	M	VL	L	M	H	L	M	H	H	M	M	H	H
W-2	L	L	M	H	M	M	H	H	M	H	H	H	H	H	H	H
W-3	M	M	H	H	H	H	H	H	H	H	H	H	H	H	H	H
	fl-0	fl-1	fl-2	fl-3	fl-0	fl-1	fl-2	fl-3	fl-0	fl-1	fl-2	fl-3	fl-0	fl-1	fl-2	fl-3



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Diagnostika ICHDK

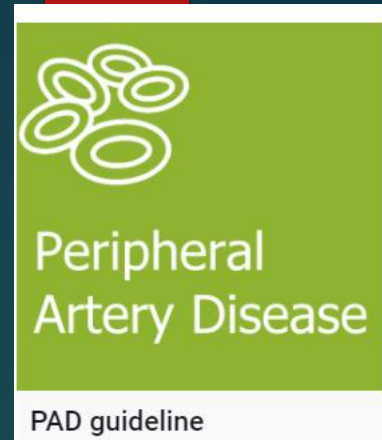
Každoročně je doporučeno vyšetřit možnou ICHDK u všech diabetiků včetně pacientů se syndromem diabetické nohy (SDN)....

-ANAMNÉZA

MAKROCIRKULACE - PALPACE PERIFERNÍCH PULSACÍ, DOPPLEROVSKÉ VYŠETŘENÍ TEPEN – ABI/SYSTOLICKÉ TLAKY, PALCOVÉ TLAKY (+ TBI) i na ostatních prstech, **DUPLEXNÍ ULTRAZVUK**

ICHDK je méně pravděpodobná , pokud je ABI 0,9–1,3, TBI \geq 0,70 a pokud je detekována trifázická/bifázická pedální dopplerovská křivka.

MIKROCIRKULACE – TRANSKULÁTNNÍ TENZE KYSLÍKU, LASER DOPPLER FLOWMETRIE



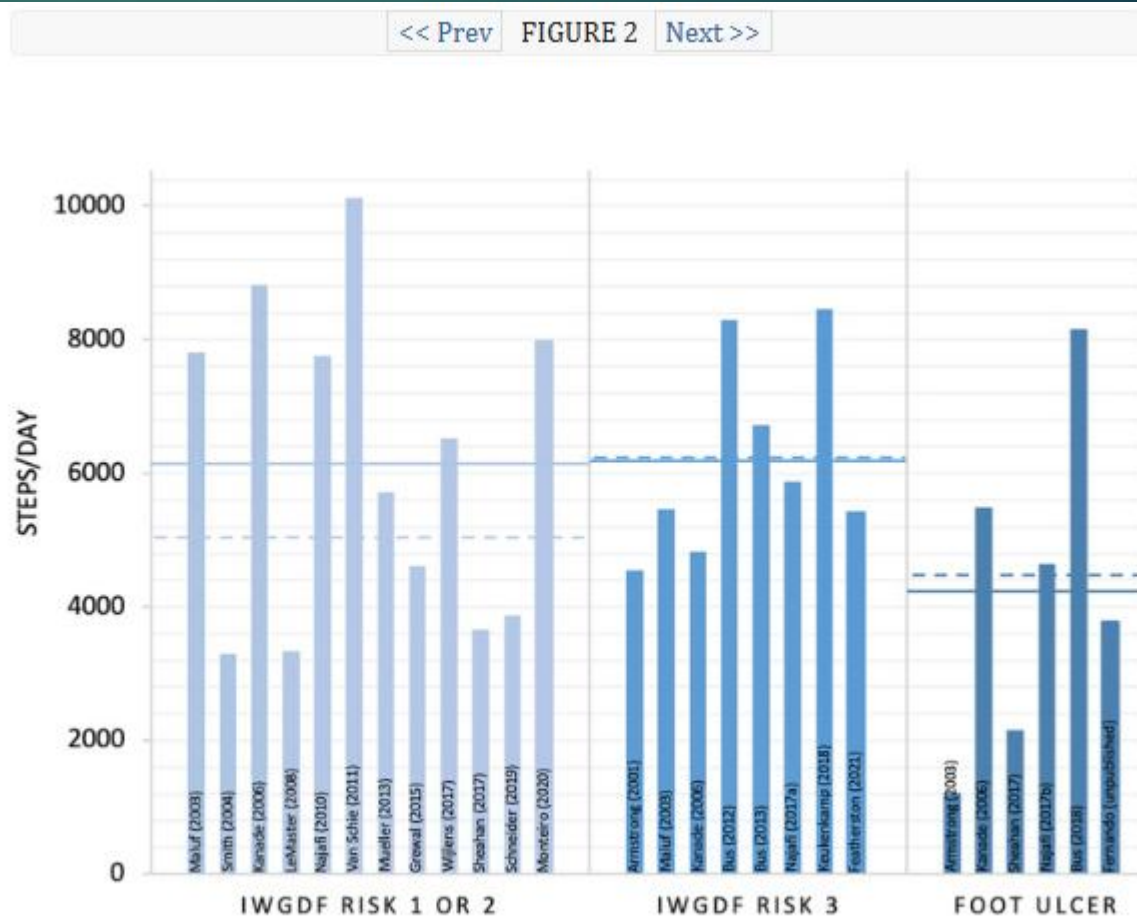
Z hlediska léčby SDN

► 6. Odlehčeníje základem terapie SDN

...snížení FA...zvýšení rizika obezity...KV rizika

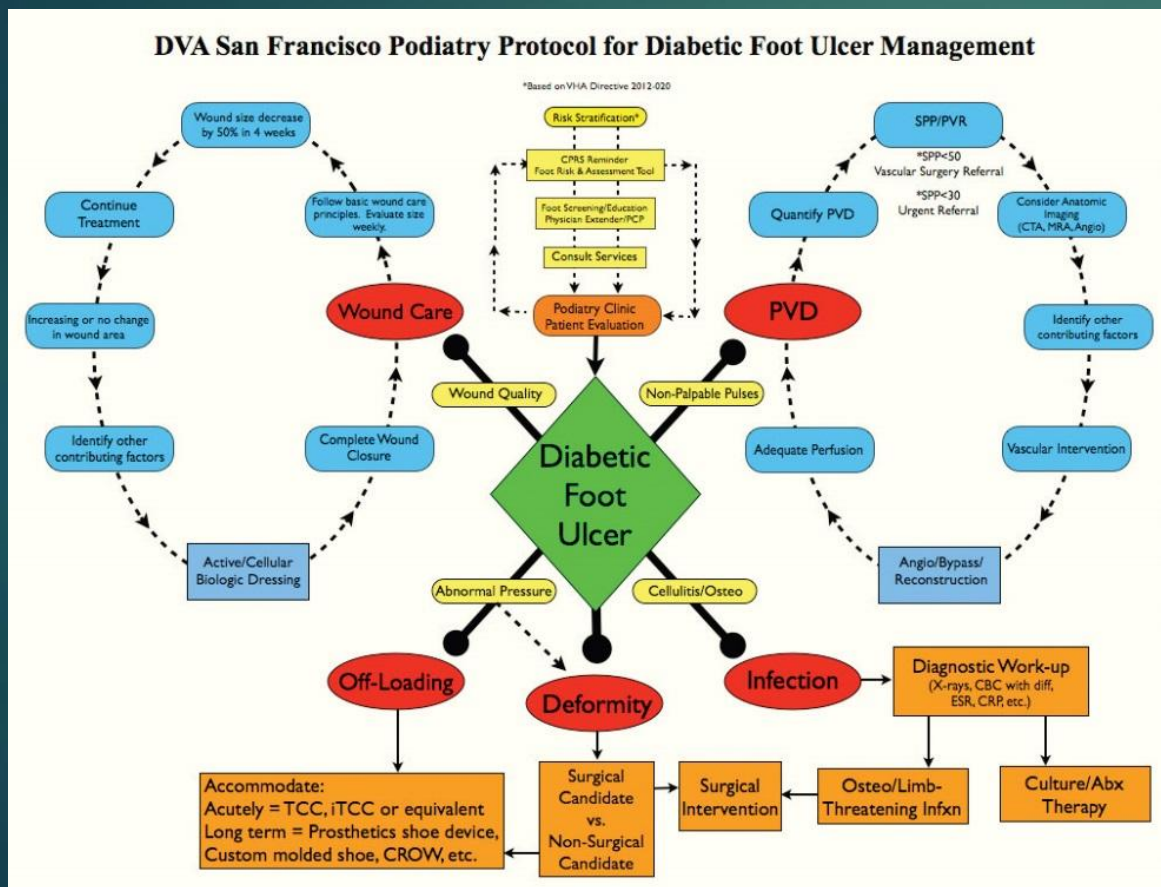
Systematické review van Nettena prokázalo na základě 27 studií signifikantní redukci fyzické aktivity dle rizika SDN a u nemocných s již rozvinutým SDN

FIGURE 2



Mean steps/day in studies in people with diabetes at risk of or with a foot ulcer. Mean (solid line) and weighted mean (dashed line) are shown per group. IWGDF, International Working Group on the Diabetic Foot

Proto je klíčový multidisciplinární přístup k léčbě SDN včetně managementu KV rizik.



- Kompenzace DM
- Kontrola KV rizik
- Léčba komorbidit
- Management malnutrice

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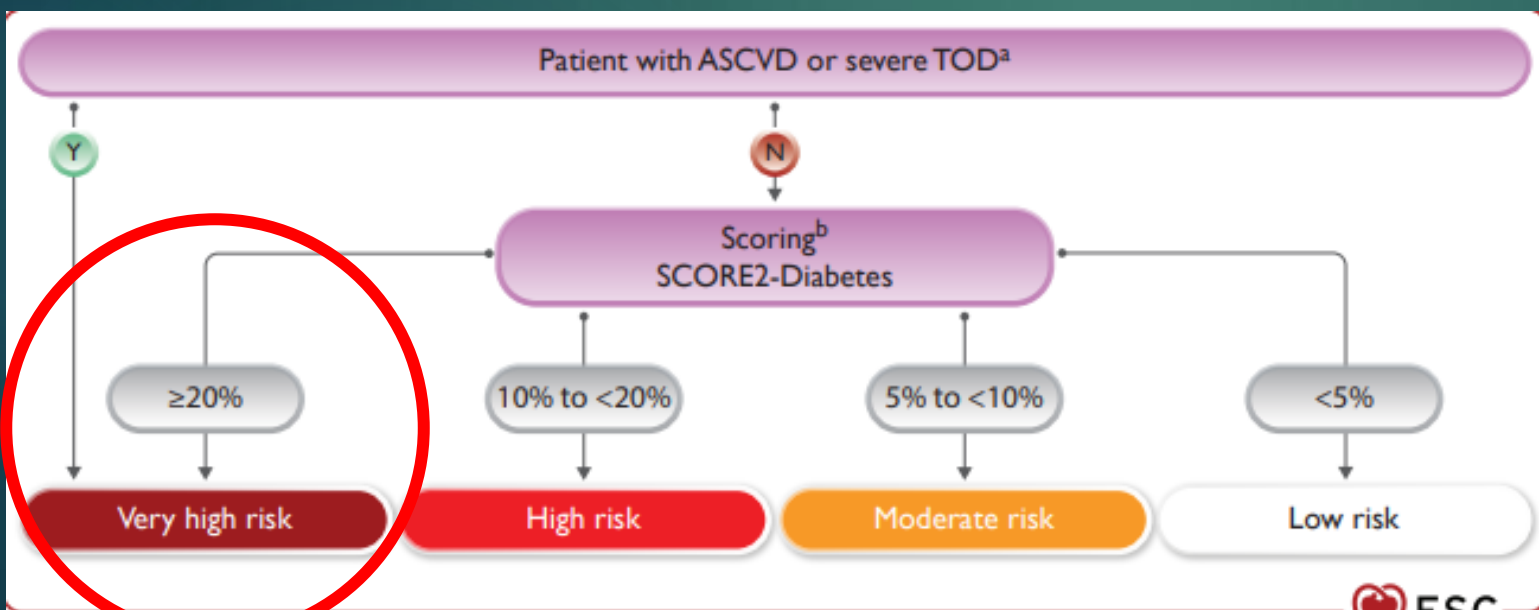
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Methodology Development and Methodology IWGDF 2023 update	Definitions and Criteria Definitions & criteria (2023 update)		

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

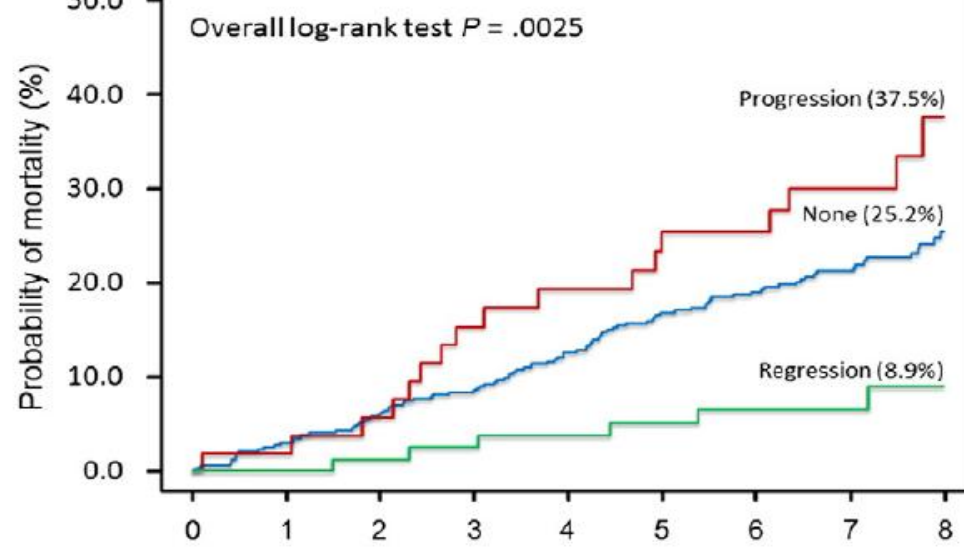
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Very high CV risk	Patients with T2DM with: <ul style="list-style-type: none"> • Clinically established ASCVD or • Severe TOD or • 10-year CVD risk $\geq 20\%$ using SCORE2-Diabetes
High CV risk	Patients with T2DM not fulfilling the very high-risk criteria and a: <ul style="list-style-type: none"> • 10-year CVD risk 10 to $<20\%$ using SCORE2-Diabetes
Moderate CV risk	Patients with T2DM not fulfilling the very high-risk criteria and a: <ul style="list-style-type: none"> • 10-year CVD risk 5 to $<10\%$ using SCORE2-Diabetes
Low CV risk	Patients with T2DM not fulfilling the very high-risk criteria and a: <ul style="list-style-type: none"> • 10-year CVD risk $<5\%$ using SCORE2-Diabetes



Recommendation Table 26 — Recommendations for patients with type 1 diabetes

Recommendation	Class ^a	Level ^b
In patients with T1DM, it is recommended that adjustment of glucose-lowering medication follows principles of patient self-management under the guidance of the diabetes healthcare multidisciplinary team.	I	C
Avoiding hypoglycaemic episodes is recommended, particularly in those with established CVD. ^{780–782}	I	C
Statins should be considered for LDL-C lowering in adults older than 40 years with T1DM without a history of CVD to reduce CV risk. ⁷⁸⁷	IIa	B
Statins should be considered for use in adults younger than 40 years with T1DM and other risk factors of CVD or microvascular end-organ damage or 10-year CVD risk $\geq 10\%$ to reduce CVD risk. ^{787,788}	IIa	B
The use of the Scottish/Swedish risk prediction model may be considered to estimate 10-year CVD risk in patients with T1DM. ⁷⁹³	IIb	B



Patients at risk	0	1	2	3	4	5	6	7	8
Progression	53	52	49	43	41	36	34	26	12
None	472	455	438	421	396	368	314	233	119
Regression	80	80	79	78	74	71	52	41	17

Kaplan-Meier curves of 8-year all-cause mortality; none indicates no progression/regression group.

Pokud mají nemocní opakované cévní příhody v posledních 2 letech, cílíme LDLcholesterolu $< 1,0$ mmol/L.(cave málo důkazů pro nemocné s DM a CLTI)

Lipids and diabetes—Section 5.5

A PCSK9 inhibitor is recommended in patients at very high CV risk, with persistently high LDL-C levels above target despite treatment with a maximum tolerated statin dose, in combination with ezetimibe, or in patients with statin intolerance.

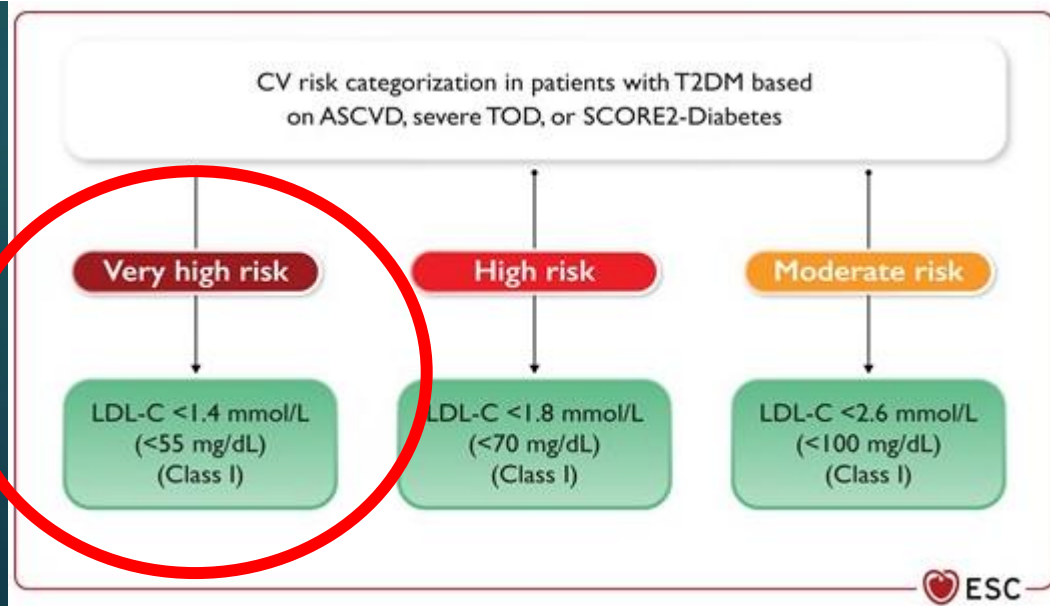
I	A
----------	----------

If a statin-based regimen is not tolerated at any dosage (even after re-challenge), a PCSK9 inhibitor added to ezetimibe should be considered.

IIa	B
------------	----------

If a statin-based regimen is not tolerated at any dosage (even after re-challenge), ezetimibe should be considered.

IIa	C
------------	----------



- ▶ **Statiny** účinně zabraňují KV příhodám a snižují KV mortalitu, mají poměrně málo nežádoucích účinků (ROSUVASTATIN, ATORVASTATIN)

U pacientů s DM - **1.volba** – intenzivní terapie založená na individualizaci

- ▶ **Ezetimib** nebo **inhibitor proprotein convertase subtilisin/kexin typu 9(PCSK9)** – (evolocumab or alirocumab) - samotně nebo do kombinace se statiny, nebo u intolerance statinů—další snížení LDL-cholesterolu u nemocných s DM....(novými alternativami inclisiran, kys bempedoová)- **2.volba**

- ▶ Fibráty (lépe ester kys.eikosapetaenové)....**3.volba**



Figure 2: Primary Endpoint

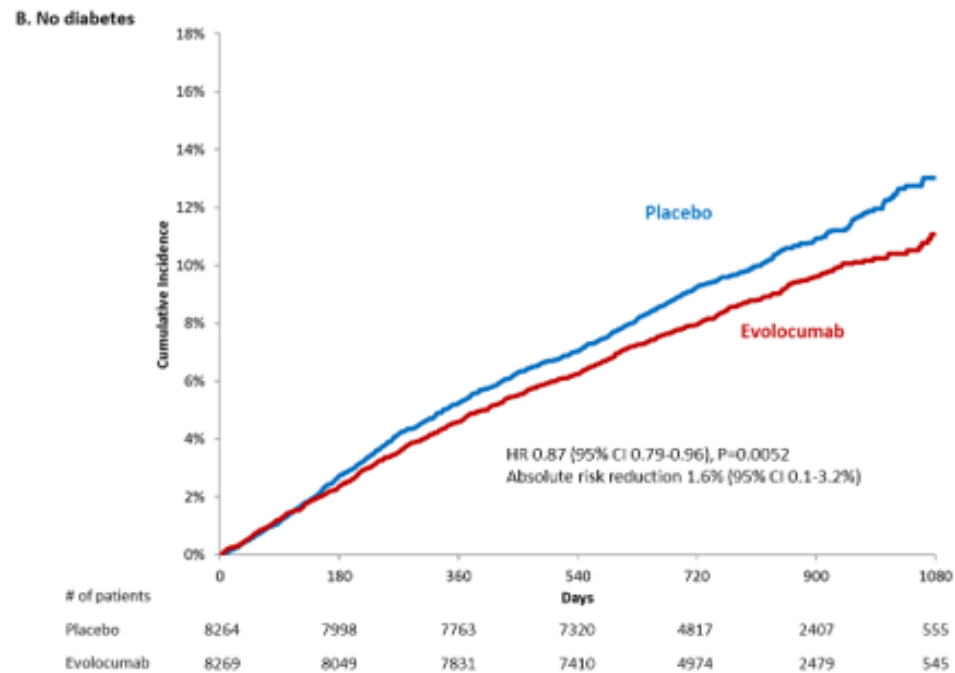
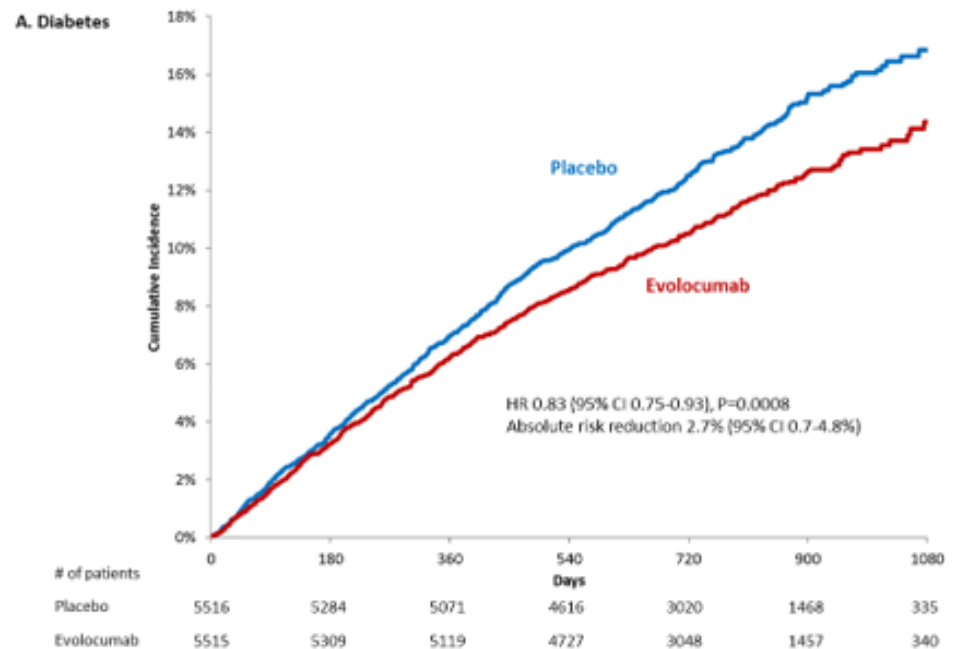
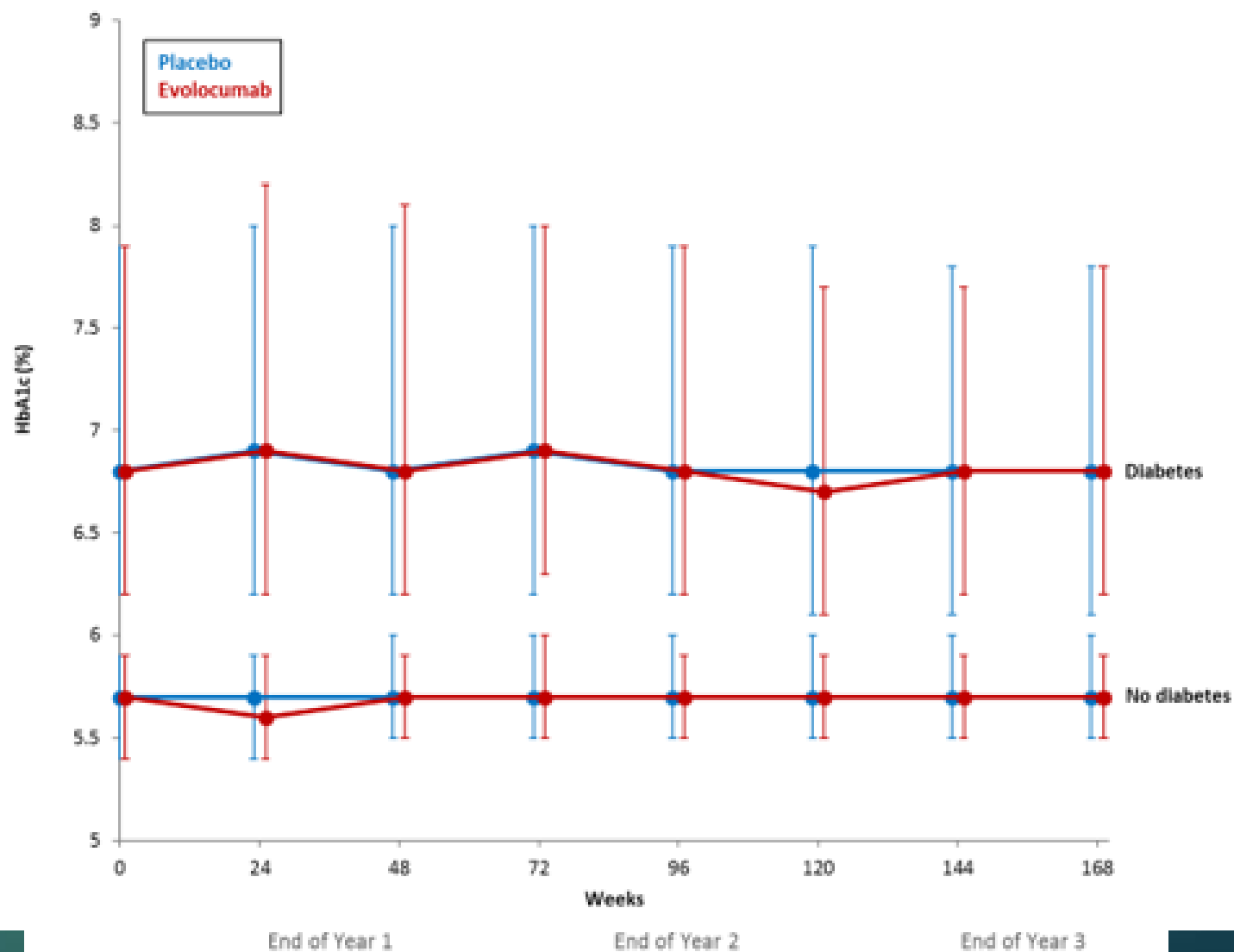


Figure 5: HbA1c over time



Kyselina bempedoová

- ▶ Kyselina bempedoová (inhibitor ATP citrát lyázy), u níž bylo prokázáno snížení LDL cholesterolu (LDL-c) o 17-28 %, ovlivňuje syntézu cholesterolu v mechanismem jako statiny.



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Lawrence A. Leiter MD , Maciej Banach MD, PhD, Alberico L. Catapano MD, PhD, P. Barton Duell MD, Antonio M. Gotto Jr MD, DPhil, Ulrich Laufs MD, PhD, G. B. John Mancini MD ... [See all authors](#)

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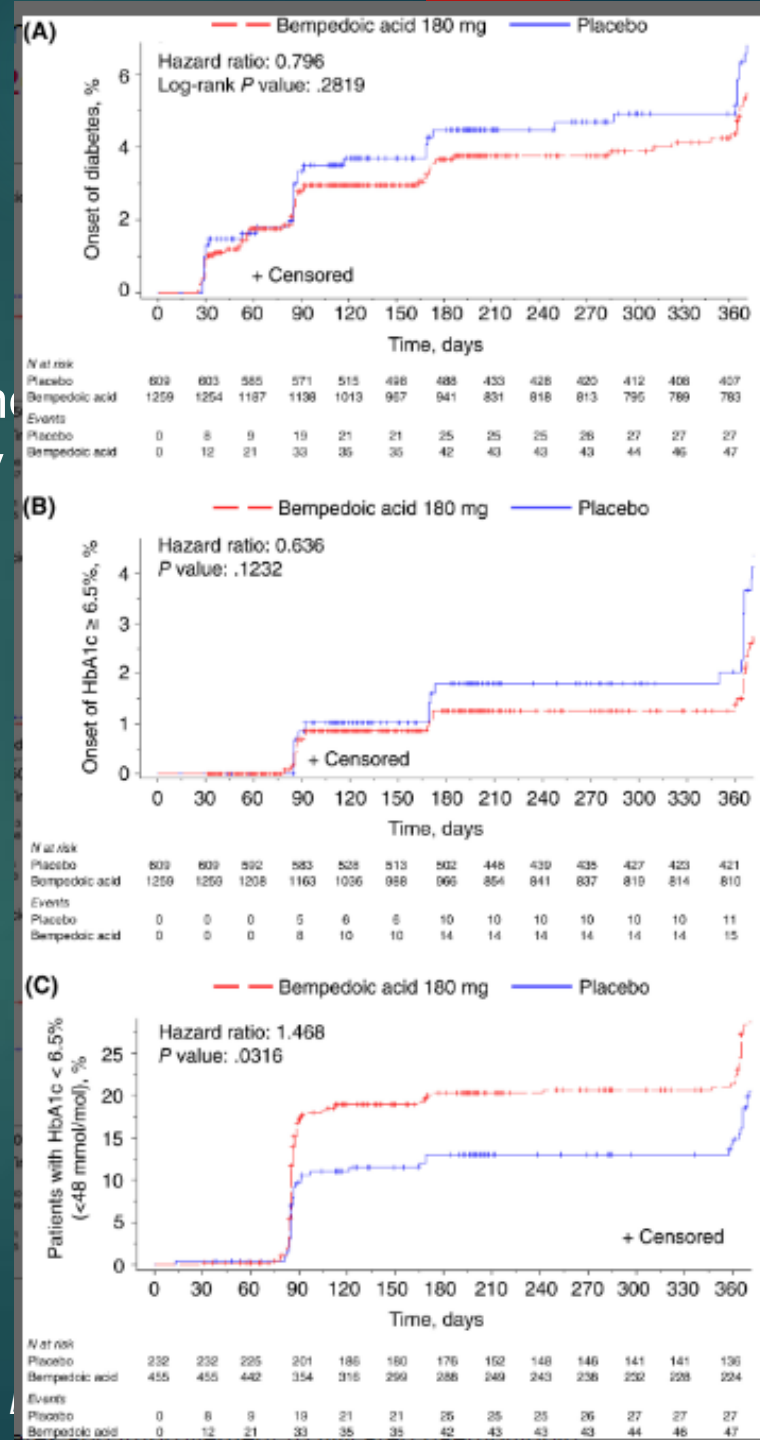
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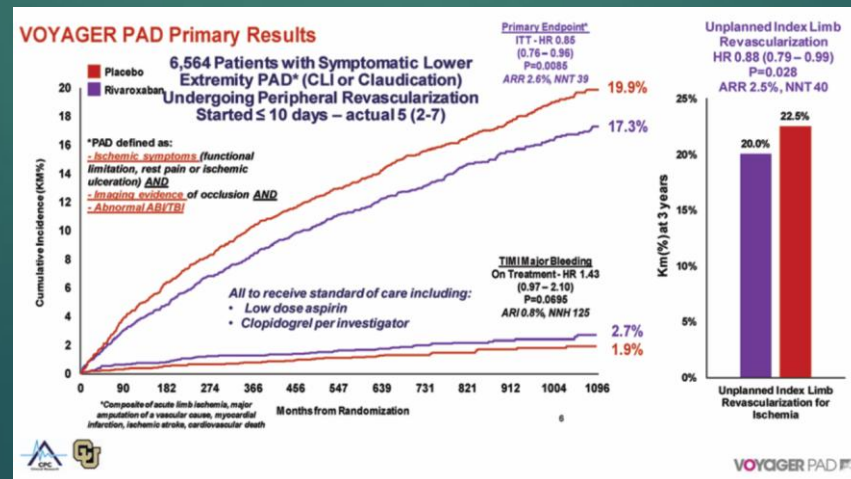
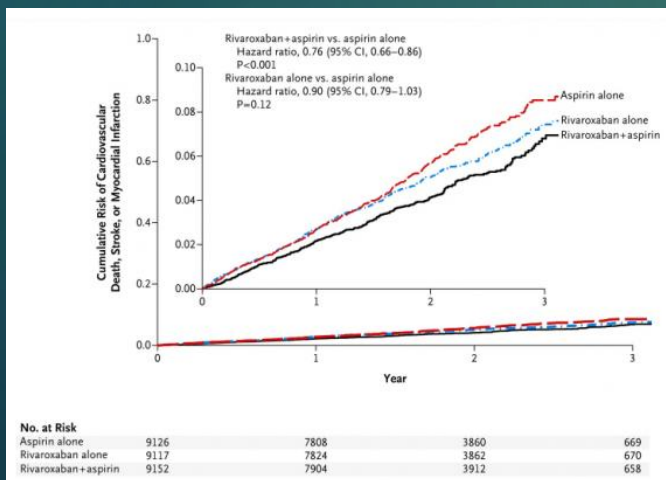
Surgery or Endovascular Therapy for Chronic Limb-Threatening Ischemia

Alik Farber, M.D., Matthew T. Menard, M.D., Michael S. Conte, M.D., John A. Kaufman, M.D., Richard J. Powell, M.D., Nitesh K. Choudhry, M.D., Ph.D., Taye H. Hamza, Ph.D., Susan F. Assmann, Ph.D., Mark A. Creager, M.D., Mark J. Cziraky, Pharm.D., Michael D. Dake, M.D., Michael R. Jaff, D.O., et al., for the BEST-CLI Investigators†



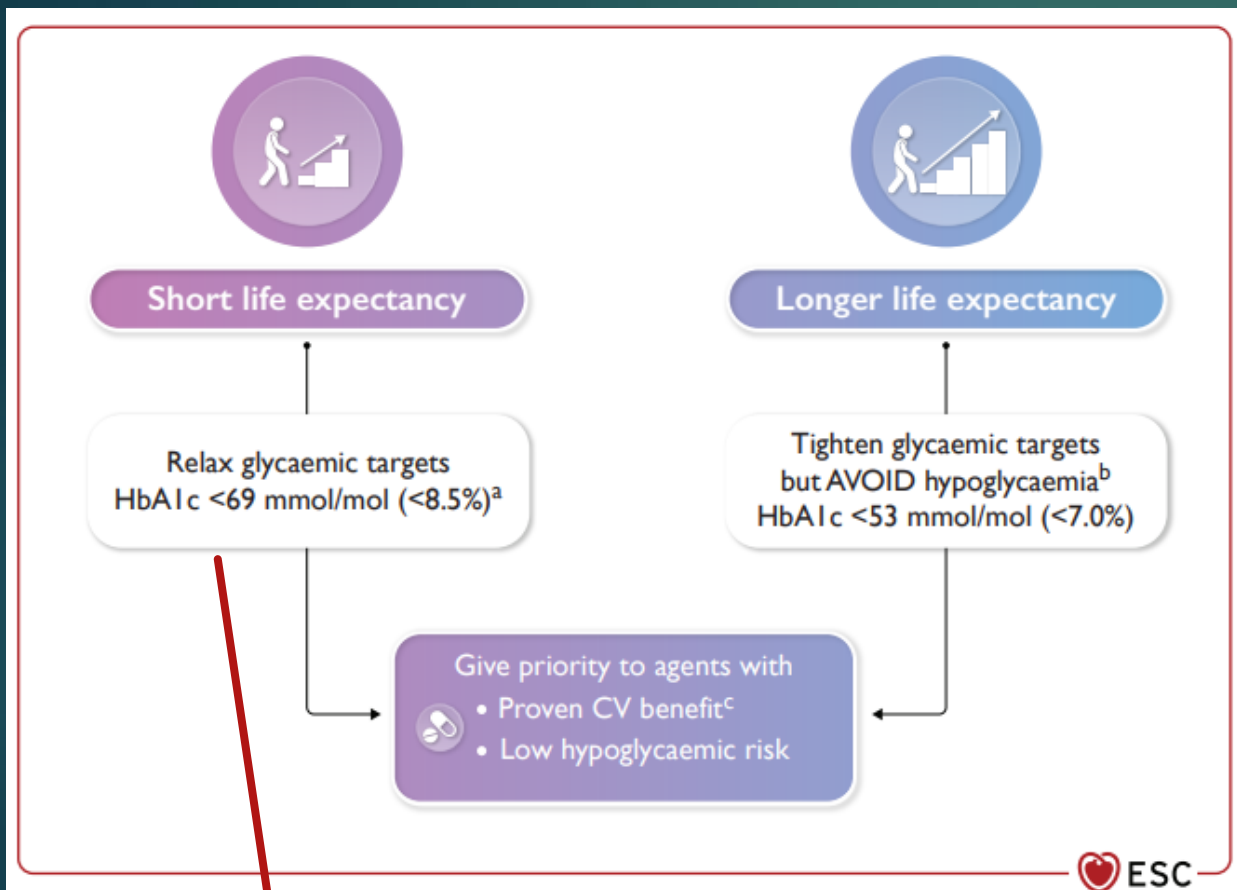
Antiagregace/antikoagulace

- **S ohledem na ICHDK - léčba ASA, lépe u DM 2.typu Clopidogrel** ((CAPRIE trial....redukce KV rizik bez významného rizika krvácivosti – cave pouze 21% mělo DM.
- Lze zvážit u nemocných s ICHDK a SDN (COMPASS) a s vysokým rizikem rekurence kardiovaskulárních příhod, bez vysokého rizika krvácení kombinaci rivaroxabanu (2x 2,5 mg denně) + ASA (100 mg)...redukce MALE i u CLTI
- (Best Practice Statement) - po revaskularizaci se má u nemocných bez vysokého rizika krvácivosti zvážit aplikace 1-6 měsíců duální antiagregace (ASA + clopidogrel) nebo rivaroxabanu (2x 2,5 mg denně) + ASA (100 mg) - VOYAGER

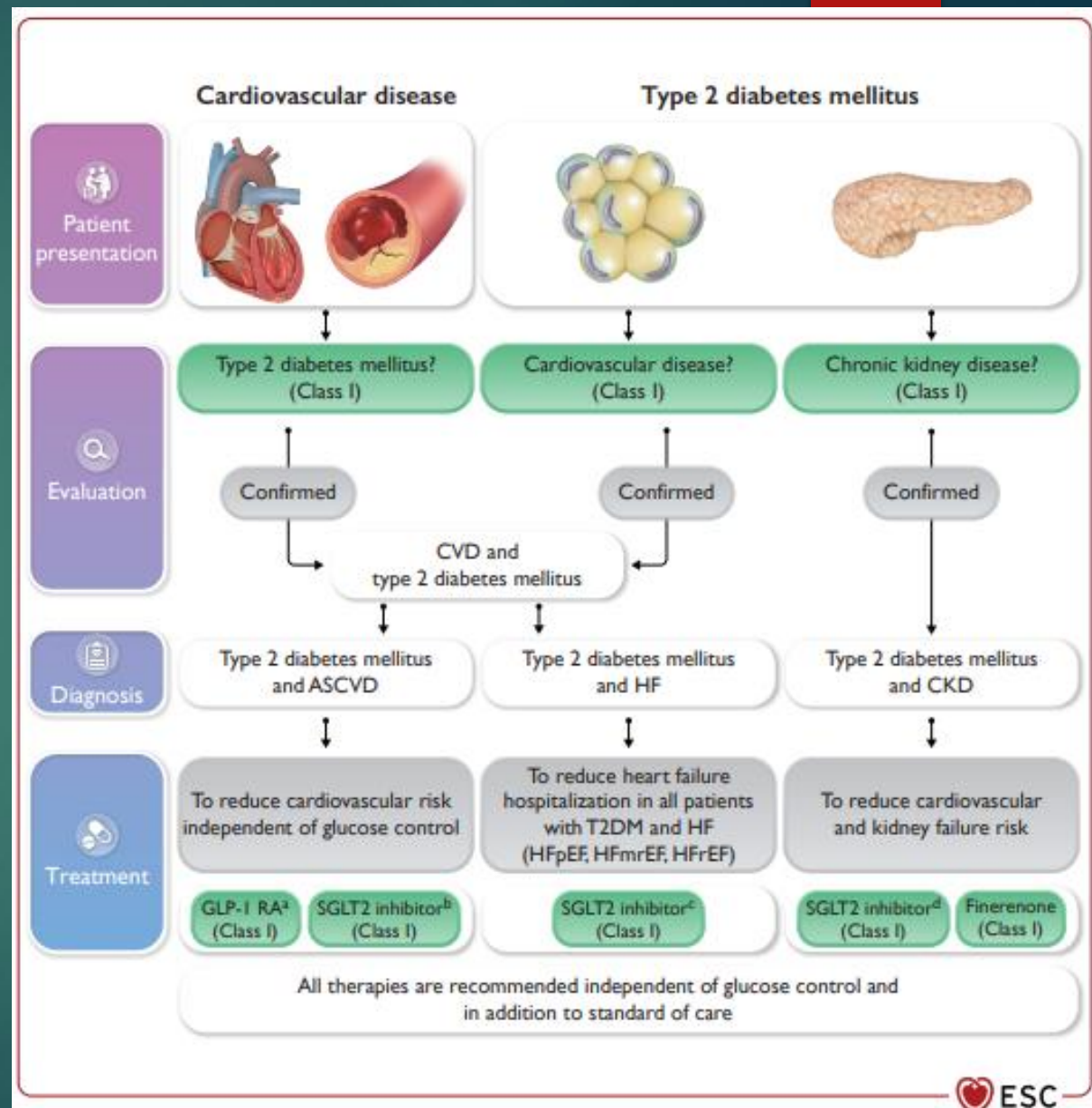


ESVM Guideline on peripheral arterial disease. *Vasa*. 2019 Sep;48(Suppl 102):1-79
S.S. Anand, F. Caron, J.W. Eikelboom, et al. *J Am Coll Cardiol*, 71 (2018), pp. 2306-2315
A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). CAPRIE Steering Committee. *Lancet*. 1996

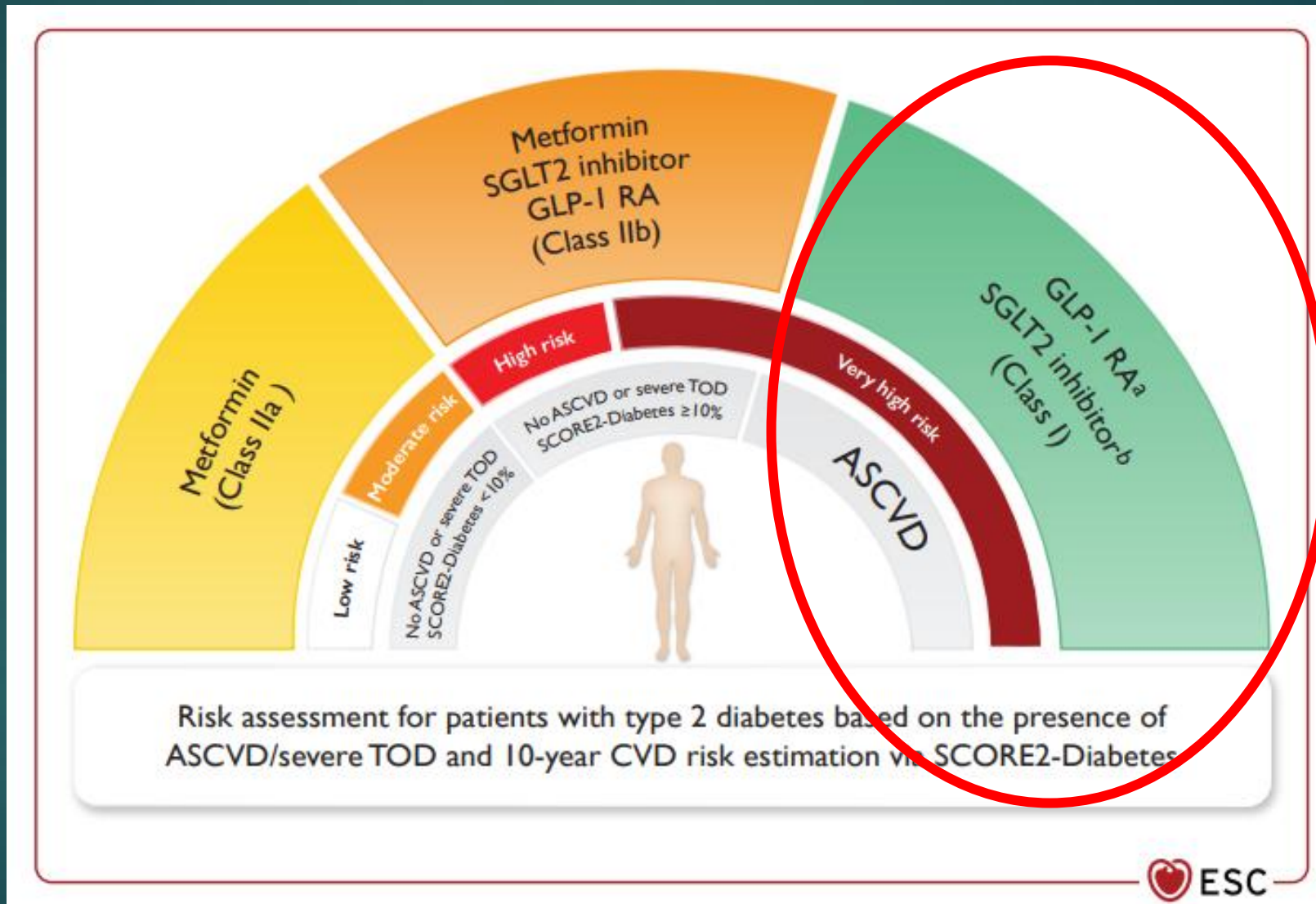
Léčba DM s ohledem na KV riziko/choroby



Cave fragilní, riziko hypoglykémii



Léčba dle KV rizika – efekt na glukóza nezávislý



- ▶ SGLT2-inhibitor canagliflozin byl spojen s vyšším rizikem vysokých amputací (RCT-CANVAS, ne v CREDENCE). Nebylo prokázáno ostatními studii včetně prospektivních.
- ▶ Ale data z reálné praxe popsala vyšší výskyt amputací– dokonce data z dánského a švédského registru prokázala, že SGLT-2 inhibitory až zdvojnásobují riziko amputací DK (2,7 vs. 1,1 na 1000 pacientů) v porovnání s analogy GLP-1 – nezávisle na přítomnosti ICHDK.
- ▶ BEST PRACTICE STATEMENT...Inhibitory SGLT-2 mají benefitní efekt na KV riziko a jsou renoprotektivní i u nemocných s ICHDK...cave pacienti s ulceracemi byli ze studie vyřazeni. Infekce a operativy mohou zvýšit riziko ketoacidóz.

▶
...proto u nemocných bez léčby by se SGLT-2 inhibitory u SDN neměly nasazovat, u těch, kteří jsou již léčeni SGLT2-i, by se měli po dobu léčby SDN dočasně vysadit .

Závěr:

- ▶ Pacienti se SDN patří vesměs do kohorty nemocných s vysokým a velmi vysokým rizikem KV onemocnění.
- ▶ Management rizikových faktorů vedoucích nejen ke KV chorobám, ale i SDN, a jejich screening by měly být agresivní již od časně diagnózy především DM 2. typu nebo déle trvajícího DM 1. typu a hlavně u všech s již manifestovanými komplikacemi diabetu.

Stop kouření

Léčba HT

Dieta a terapie malnutrice

Analoga GLP-1

Léčba HLP

Antiagregancia/antikoagulancia

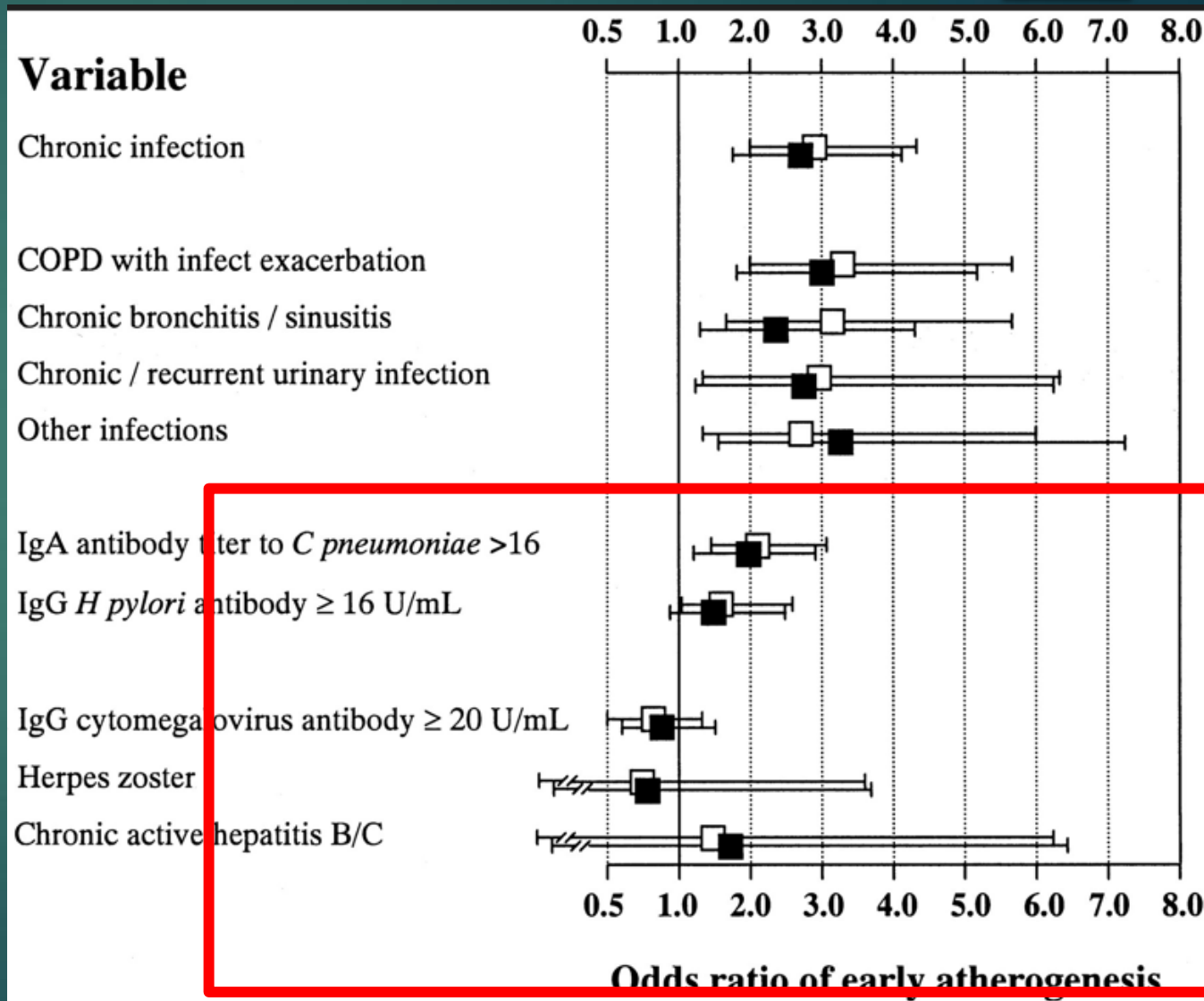
SGLT-2 inh.?

Obrázek č...ORs (95% CIs) of new carotid plaques calculated for various types of chronic infections. Adjustment, s

Infekce

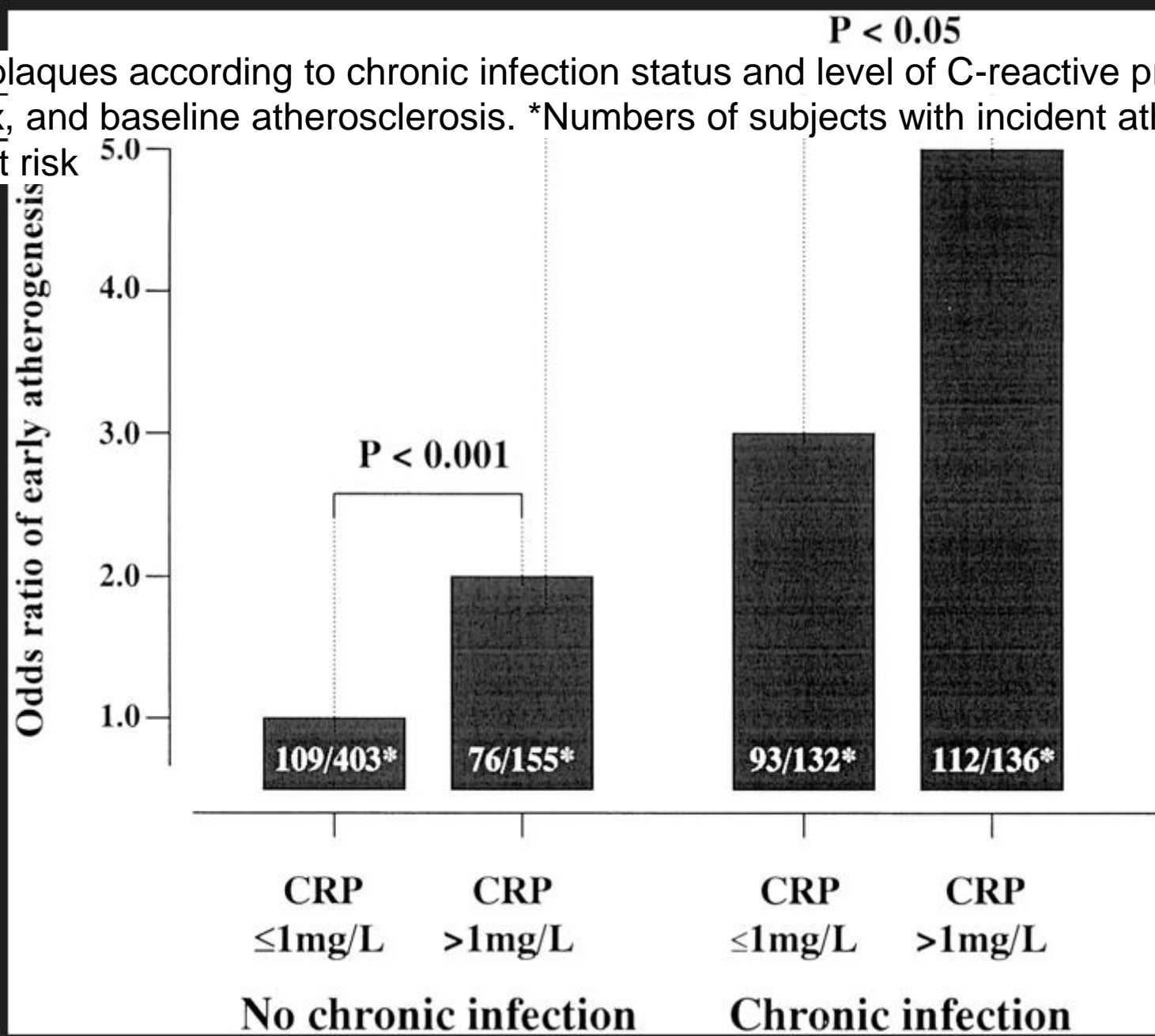
► The Bruneck Study is a prospective population-based survey on the pathogenesis of atherosclerosis. In 826 men and women 40 to 79 years old (1990 baseline), 5-year changes in carotid atherosclerosis were thoroughly assessed by high-resolution duplex scanning. The presence of chronic respiratory, urinary tract, dental, and other infections was ascertained by standard diagnostic criteria. Chronic infections amplified the risk of atherosclerosis development in the carotid arteries. The association was most pronounced in subjects free of carotid atherosclerosis at baseline (age-/sex-adjusted odds ratio [95% CI] for any chronic infection versus none, 4.08 [2.42 to 6.85]; $P < 0.0001$) and applied to all types of chronic (bacterial) infections. It remained independently significant after adjustment for classic vascular risk attributes and extended to low-risk individuals free of conventional risk factors. Among subjects with chronic infections, atherosclerosis risk was highest in those with a prominent inflammatory response. Markers of systemic inflammation, such as soluble adhesion molecules and circulating bacterial endotoxin, and levels of soluble human heat-shock protein 60 and antibodies to mycobacterial heat-shock protein 65 were elevated in subjects with chronic infections and predictive of an increased risk of atherosclerosis.

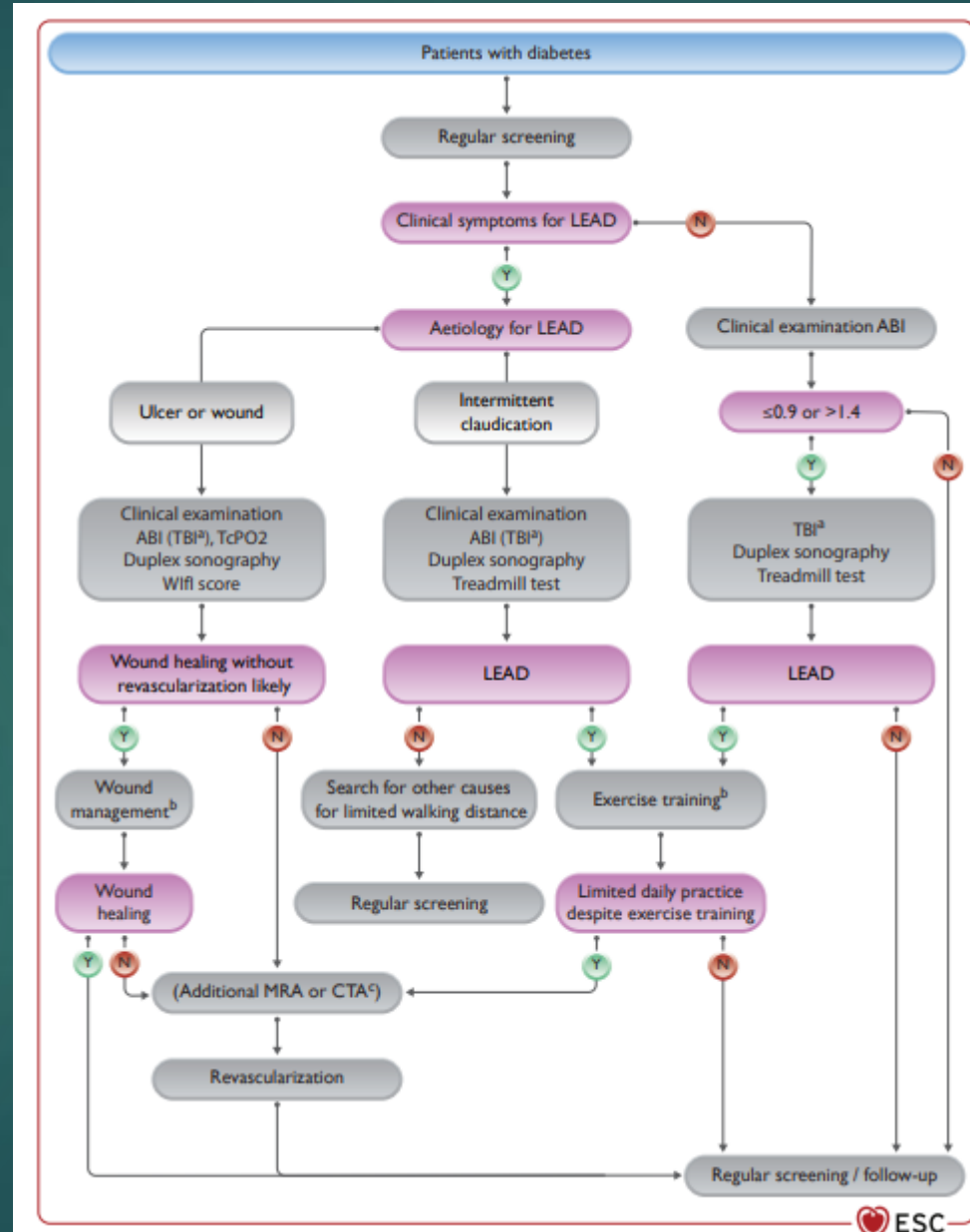
► **Conclusions:** The present study provides solid evidence for a role of common chronic infections in human atherogenesis. Induction of systemic inflammation and autoimmunity may be potential pathophysiological links.



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ORs of new carotid plaques according to chronic infection status and level of C-reactive protein. ORs were adjusted for age, sex, and baseline atherosclerosis. *Numbers of subjects with incident atherosclerosis per number of patients at risk





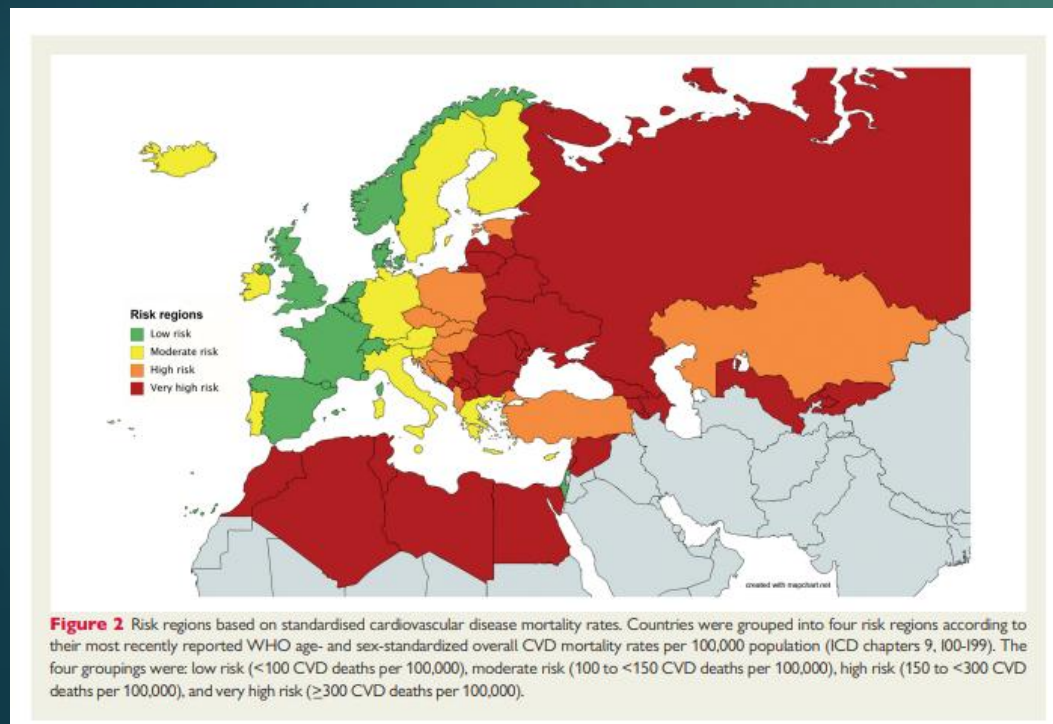


SCORE2 risk prediction algorithms: new models to estimate 10-year risk of cardiovascular disease in Europe

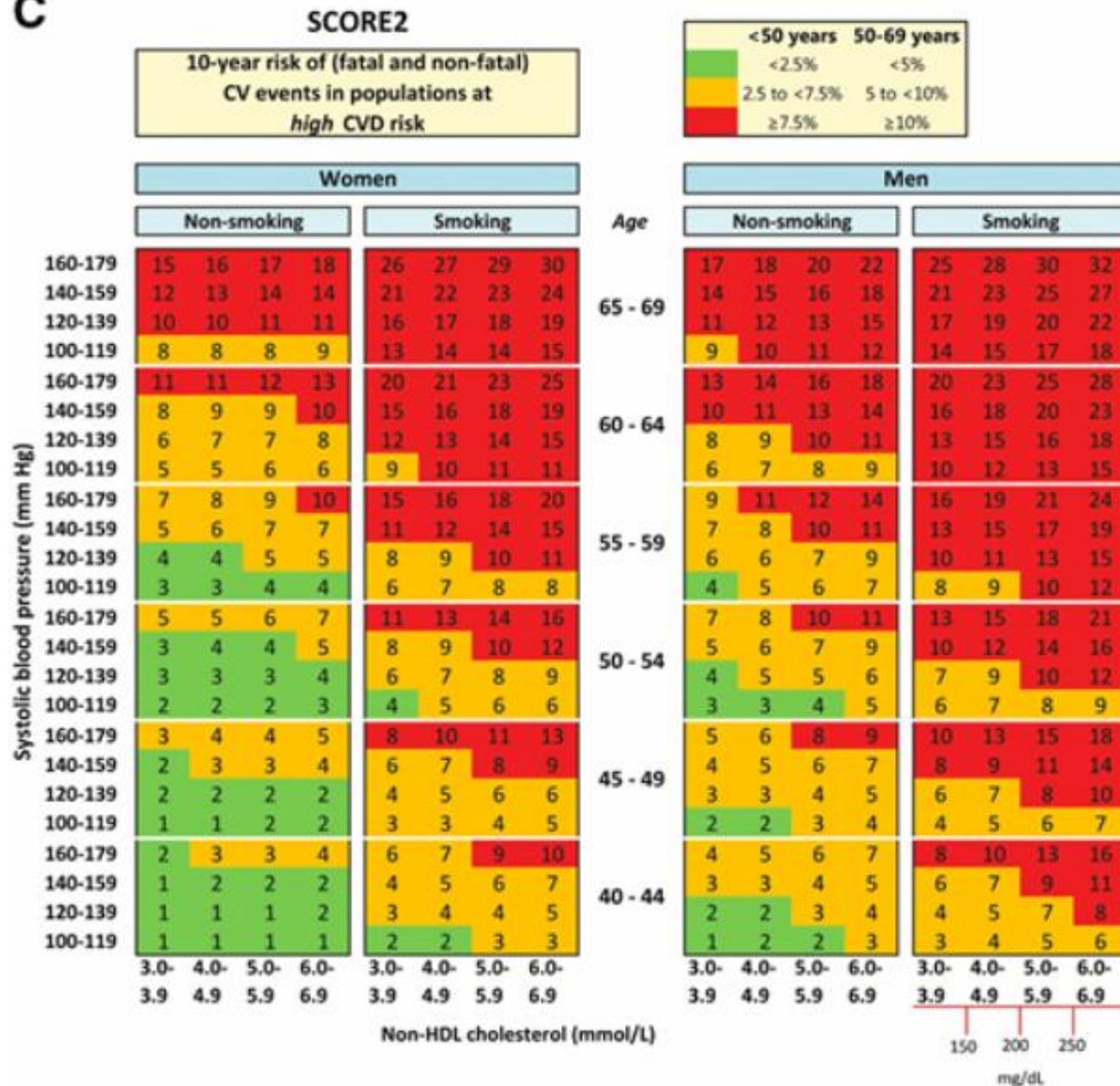
SCORE2 working group and ESC Cardiovascular risk collaboration

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See page 2468 for the editorial comment on this article (doi: 10.1093/eurheartj/ehab310)



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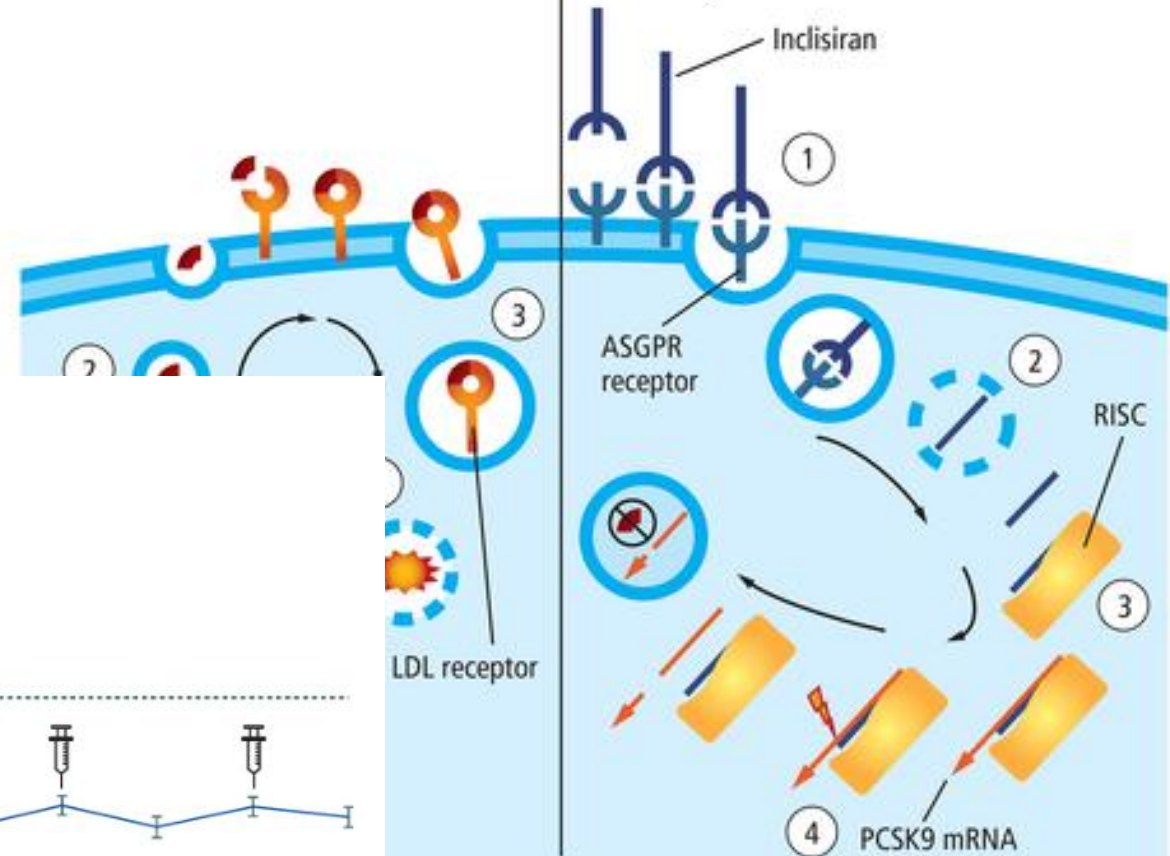
Inclisiran (Leqio)

Malé molekuly RNA (siRNA) interferující s expresí specifických genů ovlivňují hepatální produkci PCSK9.



- Action of PCSK9 protein**
1. PCSK9 is produced using mRNA
 2. PCSK9 is secreted
 3. PCSK9 binds to LDL receptor
 4. LDL receptor is degraded

- Action of inclisiran**
1. Inclisiran binds to ASGPR receptor and is endocytosed
 2. Endosome is degraded releasing siRNA
 3. siRNA loaded into RISC complex
 4. Complex binds to PCSK9 mRNA and destroys it



receptor; PCSK9 = proprotein convertase subtilisin-kexin type 9; RISC = RNA-induced silencing complex; siRNA = small interfering RNA.

