Revmatologický ústav

„Kardiorevmatologie“ aneb současný pohled na kardiovaskulární riziko u revmatických onemocnění

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Revmatická horečka „klouby líže a srdce hryže“

DISEASES OF DOUBTFUL OR UNKNOWN ORIGIN

RHEUMATIC FEVER

(*Acute Rheumatic Fever, Acute Articular Rheumatism, Acute Rheumatism, Polyarthritis Rheumatica*)

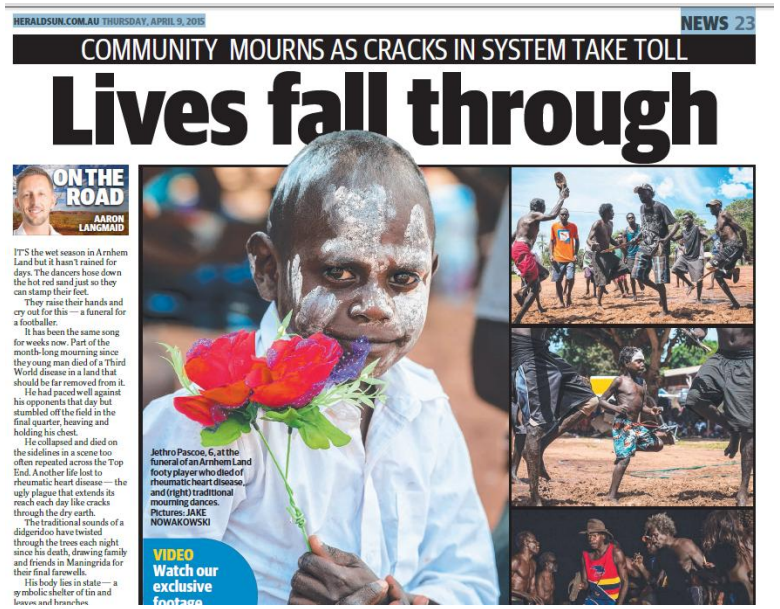
Definition.—Rheumatic fever is a disease, infectious in nature, closely associated with invasion of the body by Group A hemolytic streptococci; it is characterized by febrile and toxic states, by the presence in various parts of the cardiovascular system and joints of multiple disseminated focal inflammatory lesions and at times by serofibrinous inflammation of some of the great mesothelial-lined body cavities and joints; it is further characterized by a tendency for the febrile, toxic and arthritic signs to disappear following the exhibition of certain antipyretic drugs in sufficient doses.

Incidence.—Neither rheumatic fever nor rheumatic heart disease are reportable; hence the incidence must be estimated indirectly. Heart disease is among the first three causes of death in the first four decades of life in New York State. There are probably between 30,000 and 60,000 deaths from rheumatic heart disease per year in the United States, and at an estimated rate of 1500 to 2000 new cases per million population, there would be between 200,000 and 260,000 cases of rheumatic fever per year. There is considerable evidence of a falling incidence and death rate from decade to decade.

the characteristic rheumatic granuloma cells. These have basophilic cytoplasm, large vesicular nuclei, frequently multiple, often containing masses of dense staining chromatin. McEwen showed that they probably arise from undifferentiated mesenchymal elements of connective tissue. Granulocytes may persist and a few lymphocytes and plasma cells appear; usually the granuloma cells gradually elongate and assume the appearance of fibroblasts, until finally a scar is formed.

The myocardial Aschoff body is the most typical rheumatic granuloma; comparable lesions elsewhere are modified by the structure of the tissue involved. Thus, subcutaneous nodules are probably conglomerations of submiliary granulomata occurring in structures capable of responding more vigorously to local tissue injury than is the myocardium. Similar submiliary foci are seen in the periarticular tissues and synovial membranes, but there is, in addition, a marked increase in viscid synovial fluid containing fibrin, clasmatocytes and wandering cells; and the periarticular tissues are diffusely edematous. Under the influence of certain antipyretic drugs the exudative components quickly disappear, but the proliferative phenomena are more persistent.

In rheumatic pericarditis and pleurisy the exudate is serofibrinous; in the former the fibrinous characteristics may be very marked, and the normal endothelial cover-



HERALDSUN.COM.AU THURSDAY, APRIL 9, 2015 NEWS 23

COMMUNITY MOURNS AS CRACKS IN SYSTEM TAKE TOLL

Lives fall through

ON THE ROAD

AARON LANGMAID

IT'S the wet season in Arnhem Land but it hasn't rained for days. The dancers hose down the hot red sand just so they can stamp their feet.

They raise their hands and cry out for this — a funeral for a footballer.

It has been the same song for weeks now. Part of the month-long mourning since the young man died of a Third World disease in a land that should be far removed from it.

He had paced well against his opponents that day but stumbled off the field in the final quarter, heaving and holding his chest.

He collapsed and died on the sidelines in a scene too often repeated across the Top End. Another life lost to rheumatic heart disease — the ugly plague that extends its reach each day like cracks through the dry earth.

The traditional sounds of a didgeridoo have twisted through the trees each night since his death, drawing family and friends in Maningrida for their final farewells.

His body lies in state — a symbolic shelter of tin and

Jethro Pascoe, 6, at the funeral of an Arnhem Land footy player who died of rheumatic heart disease, and (right) traditional mourning dances. Pictures: JAKE NOWAKOWSKI

VIDEO Watch our exclusive

Přehled sdělení

- Postižení srdce u revmatických onemocnění
- (Ne)tradiční rizikové faktory KVO
- Morbidita/mortalita a KVO u revmatických pacientů
- Antirevmatické léky a riziko KVO
- Léčba a skórovací systémy KVO u revmatických pacientů

Postižení srdce u revmatických chorob

Cardiovascular disease	Inflammatory joint disease		
	Rheumatoid arthritis	**Ankylosing spondylitis**	**Systemic lupus erythematosus**
Atherosclerotic cardiovascular disease	Increased risk of myocardial infarction, cerebrovascular accident	Increased risk of myocardial infarction, cerebrovascular accident	Risk is mainly increased in young women
Pericarditis	Increased prevalence, usually of no clinical significance	Rare	Common, often asymptomatic
Myocarditis	Rare, associated with active disease	Rare	High prevalence in autopsy studies, often subclinical
Heart failure	Common, mostly diastolic heart failure	Unknown	Increased risk, mainly in young women
Valvular heart disease	Rare, mostly not clinically significant	Aortic root disease and aortic regurgitation, rare nowadays	Rare, possible association with antiphospholipid antibodies
Conduction abnormalities	Uncommon, mostly atrioventricular block or RBBB	Common, association with HLA-B27	Uncommon, mostly sinus tachycardia

Cardiac manifestations that can occur during the course of rheumatic disease. Increase in risk is relative to the general population. Abbreviation: RBBB, right bundle branch block.

Nurmohamed, M. T. et al. Nat. Rev. Rheumatol. 2015

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Tradiční KV rizikové faktory u RA

Rizikový faktor	**Prevalence u RA**	**Vztah k aktivitě nemoci**
Insulinová resistence	zvýšená	koreluje s aktivitou a lepší se léčbou nemoci
Dyslipidémie	není hyperlipidémie, ↓HDL-c	zlepšení HDL-c a AI léčbou
Hypertenze	zvýšená	není evidence o vztahu
Kouření	zvýšená	může oslabit účinek léčby
Metabolický syndrom (MetS)	zvýšená, navozen zvýšením obvodu pasu	zlepšení jednotlivých komponent, ale málo účinku o ovlivnění MetS

Skeoch, S. & Bruce, I. N. Nat. Rev. Rheumatol. 2015

Sdílené a specifické rizikové faktory KVO u RA

Genetické rizikové faktory

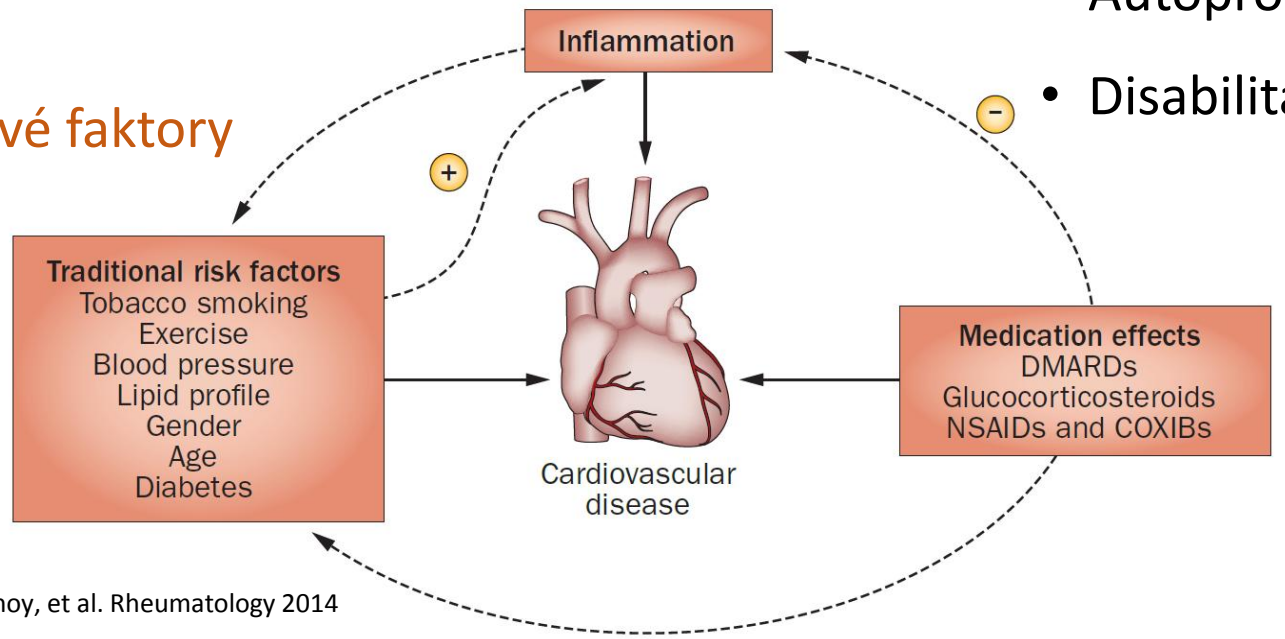
- HLA-DRB1 polymorfismus
- Polymorfismus NFκB
- MHC2TA polymorfismus
- Polymorfismus IFR5 promoteru IFN

Potenciální nové rizikové faktory

- Paradentóza

Faktory asociované s RA

- Délka onemocnění
- Vstupní a kumulativní CRP
- Extraartikulární projevy
- Autoprotilátky (RF a ACPA)
- Disabilita (HAQ)



Skeoch, S. & Bruce, I. N. Nat. Rev. Rheumatol. 2015; Choy, et al. Rheumatology 2014

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Zvýšená KV mortalita u RA pacientů

LENGTH OF LIFE AND CAUSE OF DEATH IN RHEUMATOID ARTHRITIS*

SIDNEY COBB, M.D., M.P.H.,† FLORENCE ANDERSON, A.B.,‡ and WALTER BAUER, M.D.§

BOSTON

IT has often been said that the way to live a long life is to acquire rheumatism. The present investigation was designed to test this piece of folklore. More specifically, it is concerned with the shortened life expectancy and major causes of death

The material for this study consists of observations on 583 patients with rheumatoid arthritis[1] who were hospitalized at the Massachusetts General Hospital and were subsequently followed for an average of nine and six-tenths years. It is important

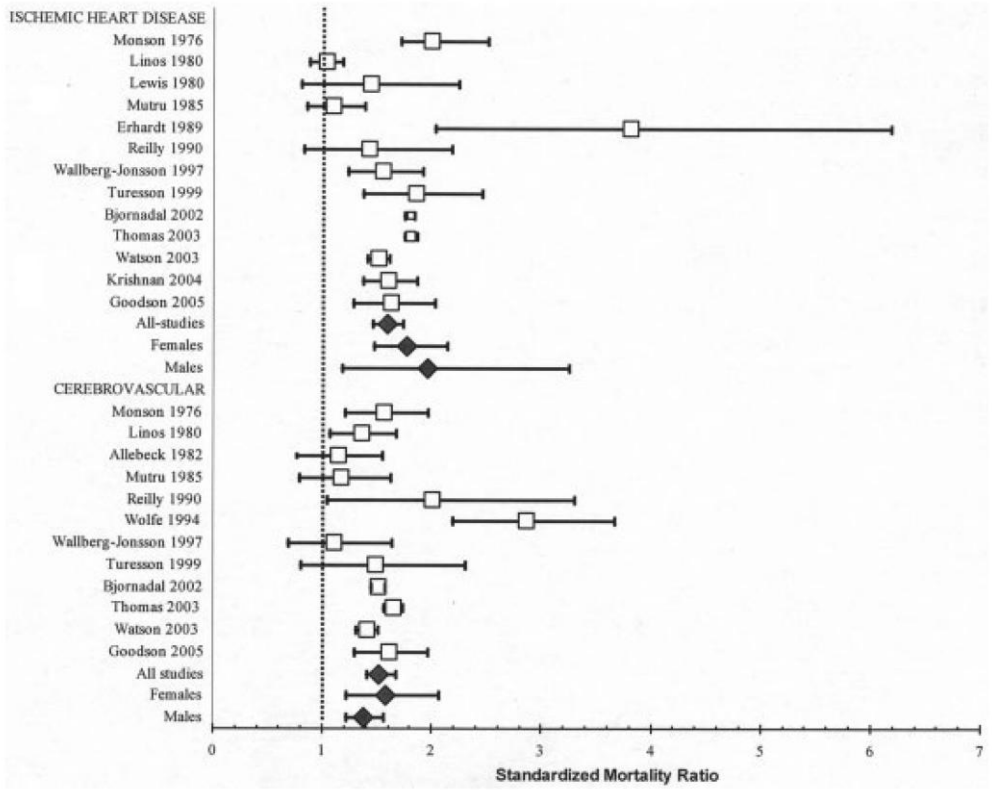
TABLE 1. *Deaths and Death Rates per 1000 Patient Years of Observation by Sex and Age Compared to Expected Values Based on Massachusetts Death Rates for White Persons, 1939–1941.*

Life-Table Age*	Male Patients		Female Patients		Expected Value for Male Patients		Expected Value for Female Patients	
	Deaths	Rate	Deaths	Rate	Deaths	Rate	Deaths	Rate
yr.								
<50	33	20.6	20	10.7	7.2	3.9	6.0	2.9
50+	25	38.4	59	39.7	30.6	47.1	61.8	41.6
Over-All.....	58	25.7	79	23.6	37.8	16.4	67.8	20.0

*Life-table age represents the accumulated experience of all the patient years observed in the specified age group.

- První data o mortalitě pacientů s RA.

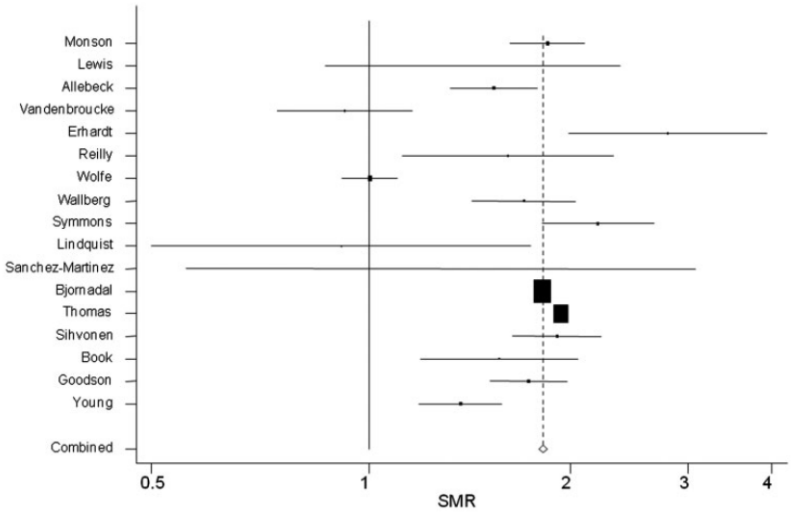
- Riziko úmrtí hospitalizovaných pacientů s RA o 29% vyšší proti hospitalizovaným pacientům bez RA.

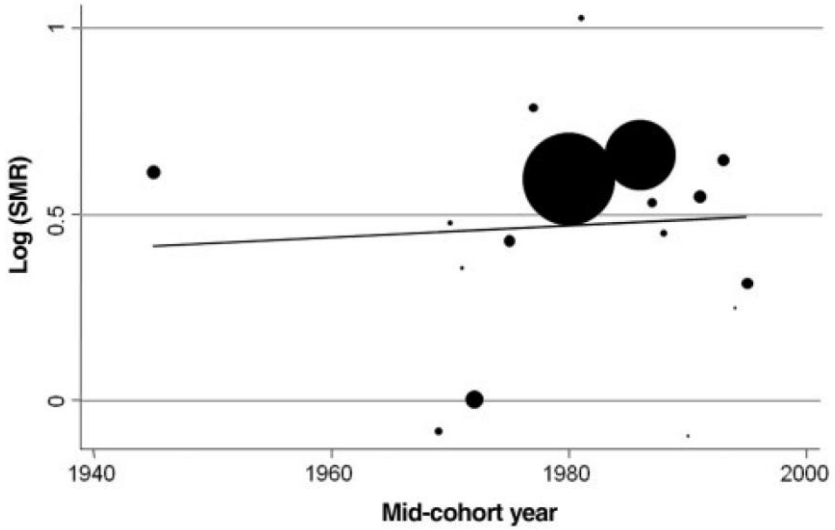


Cobb S, et al. Lancet. 1953

Avina-Zubieta JA, et al. Arthritis Rheum. 2008

Stagnace zvýšené KV mortality u pacientů s RA





- Metaanalýza 17 studií, 91 916 pacientů, 1945 – 1995.
- Riziko úmrtí: 1.6 (95% CI 1.5, 1.8; I^2=93%; P(het)<0.0001).
- Nebyl trend k poklesu úmrtí na KVO v průběhu času.

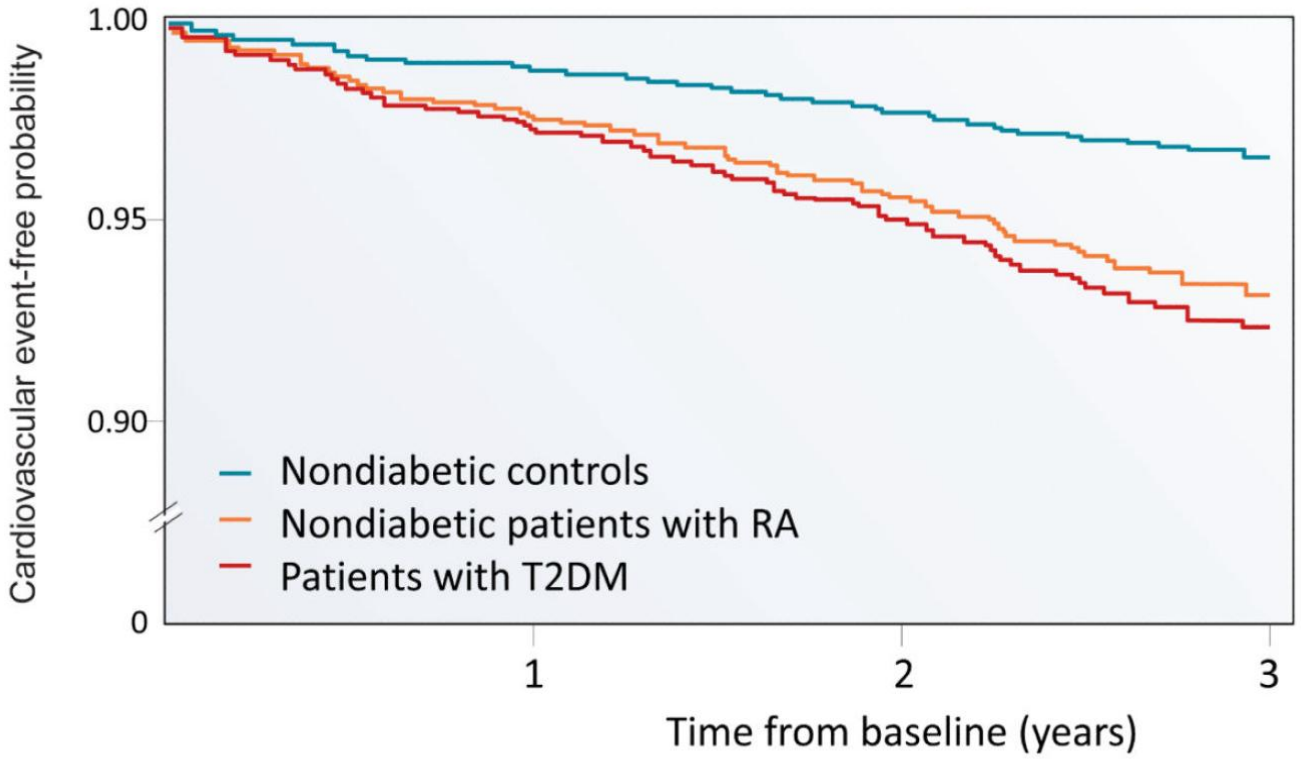
Meune Ch, et al. Rheumatology 2009

Rizikové faktory KV mortality u RA

- Zánětlivá aktivita
- HLA-DRB1*0404
- Autoprotilátky
- Glukokortikoidy

Jagpal and Navarro-Millán. BMC Rheumatology. 2018

Zvýšené KV riziko u pacientů s RA

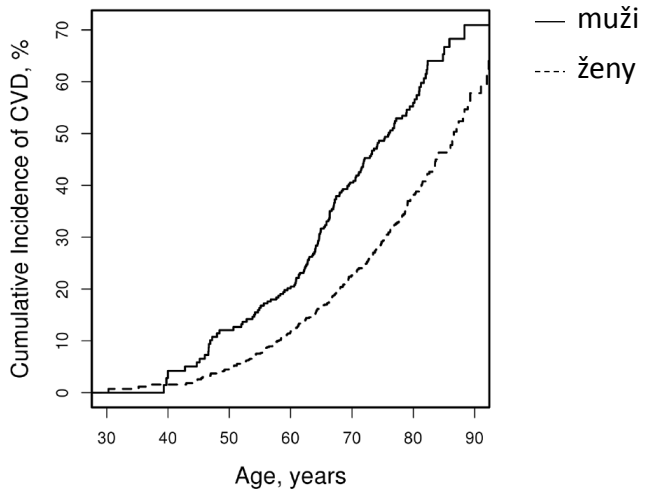


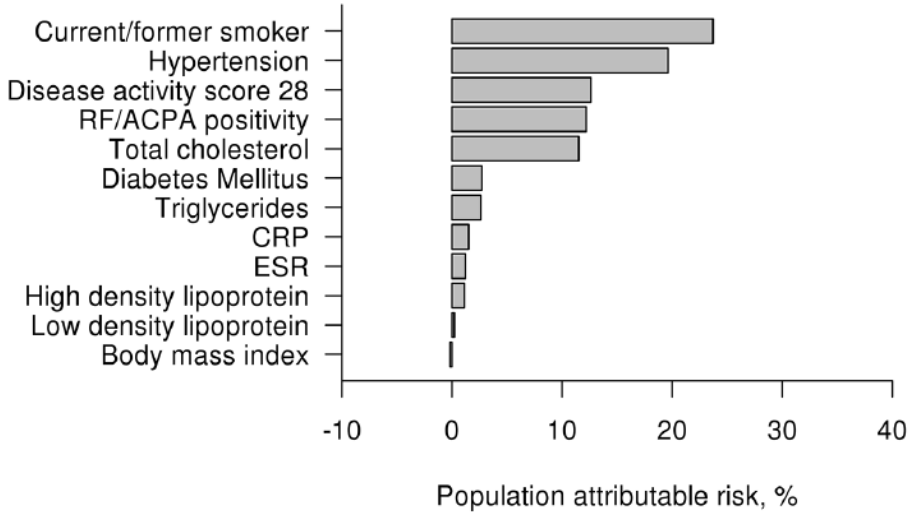
- 2x zvýšené riziko KV onemocnění.
- 2x častěji „němý“ infarkt u RA proti běžné populaci.

Choy, et al. Rheumatology. 2014; Peters, MJ. et al. Arthritis Rheum. 2009

Kumulativní incidence KVO u RA pacientů

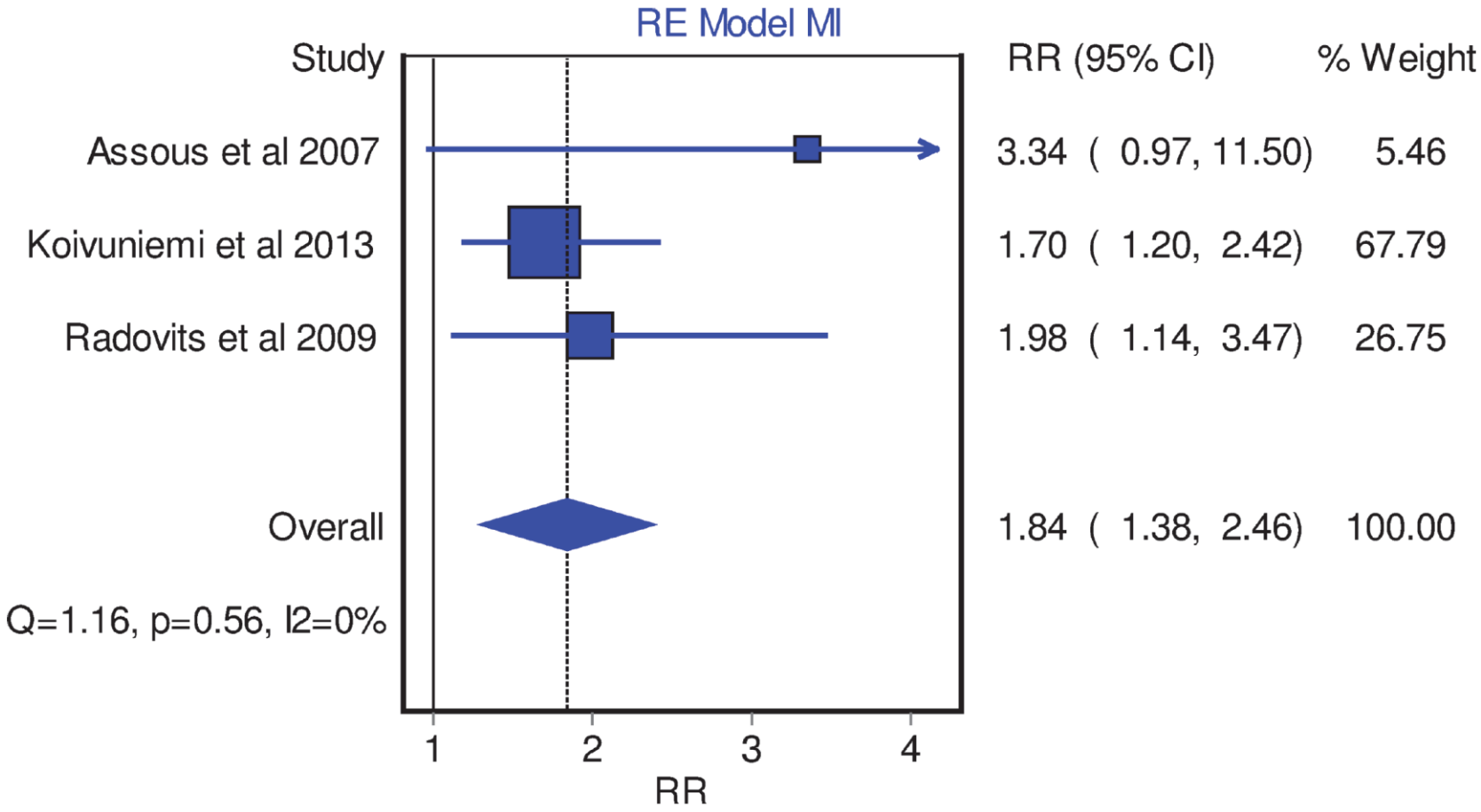
- 5 638 pacientů s RA bez předchozího KVO
- Věk 55 let, 76% žen
- Průměrné sledování 5.8 roků
- KVO: 241 žen a 148 mužů
- 10-letá kumulativní incidence 11 a 21%
- Kouření a hypertenze – největší váhu
- Aktivita nemoci a protilátky
- RA faktory – 30% váhu





Crowson CS, et al. Ann Rheum Dis. 2018

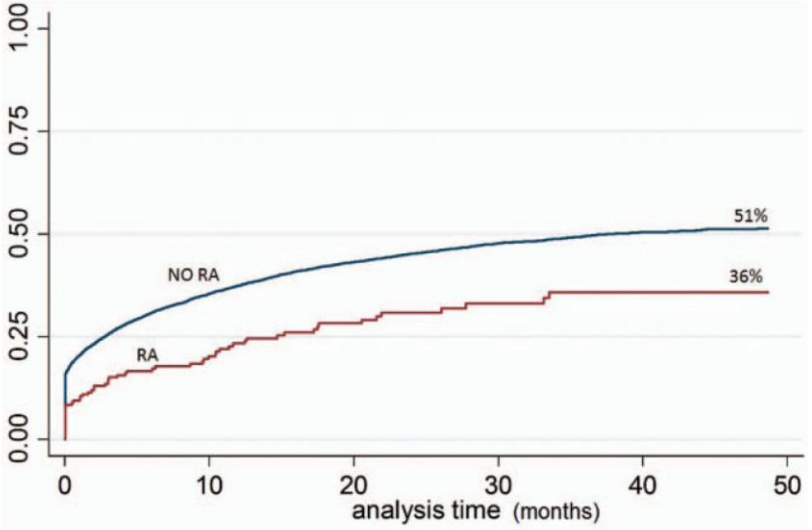
Hypertenze zvyšuje riziko IM u pacientů s RA



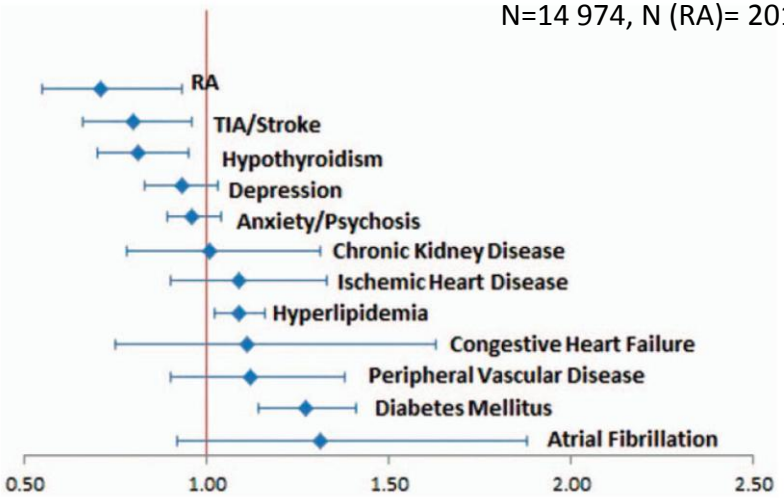
Baghdadi LR, et al. PlosOne. 2015

Suboptimální diagnostika hypertenze u pacientů s RA

- Hypertenze není často diagnostikována a pokud ano, tak je nedostatečně léčena.
- Méně než 1/3 revmatologů zahajuje antihypertenzní léčbu.

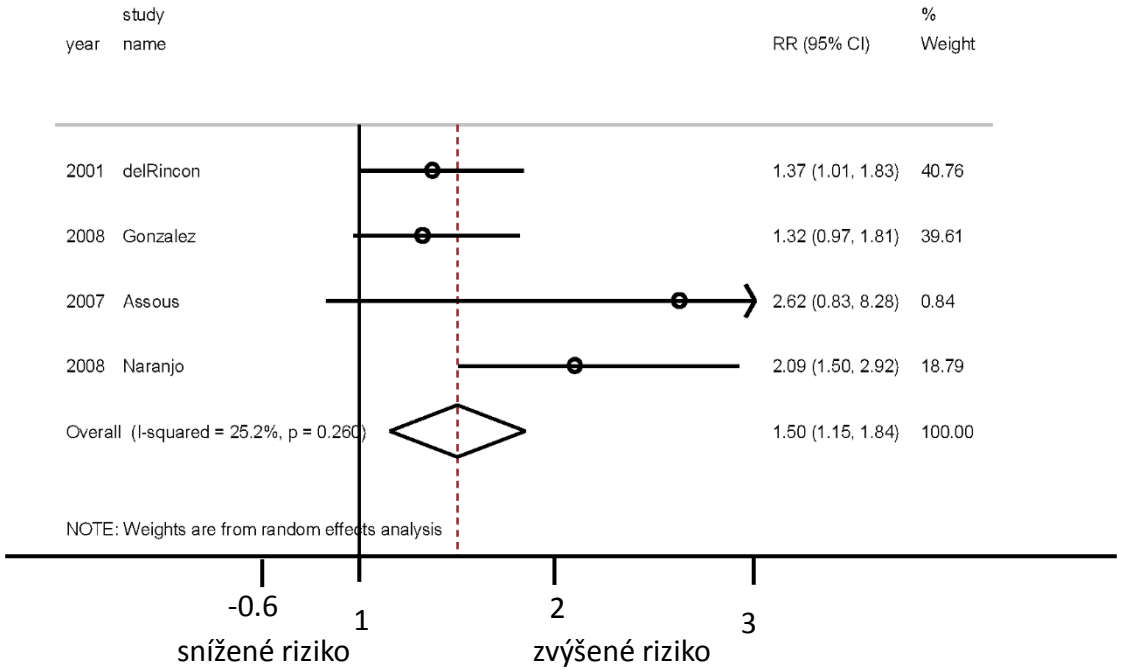


N=14 974, N (RA)= 201)



Bartels CM, et al. Arthritis Care Res (Hoboken). 2014; Jagpal and Navarro-Millán. BMC Rheumatology. 2018

Kouření a KV riziko u RA



- Prevalence kouření je častější u pacientů s RA (OR 1.6).
- Kouření cigaret je spojeno s tvorbou protilátek, závažností nemoci a špatnou odpovědí na léčbu.
- Metaanalýza potvrzuje o 50% zvýšené riziko KVO u pacientů kuřáků s RA.

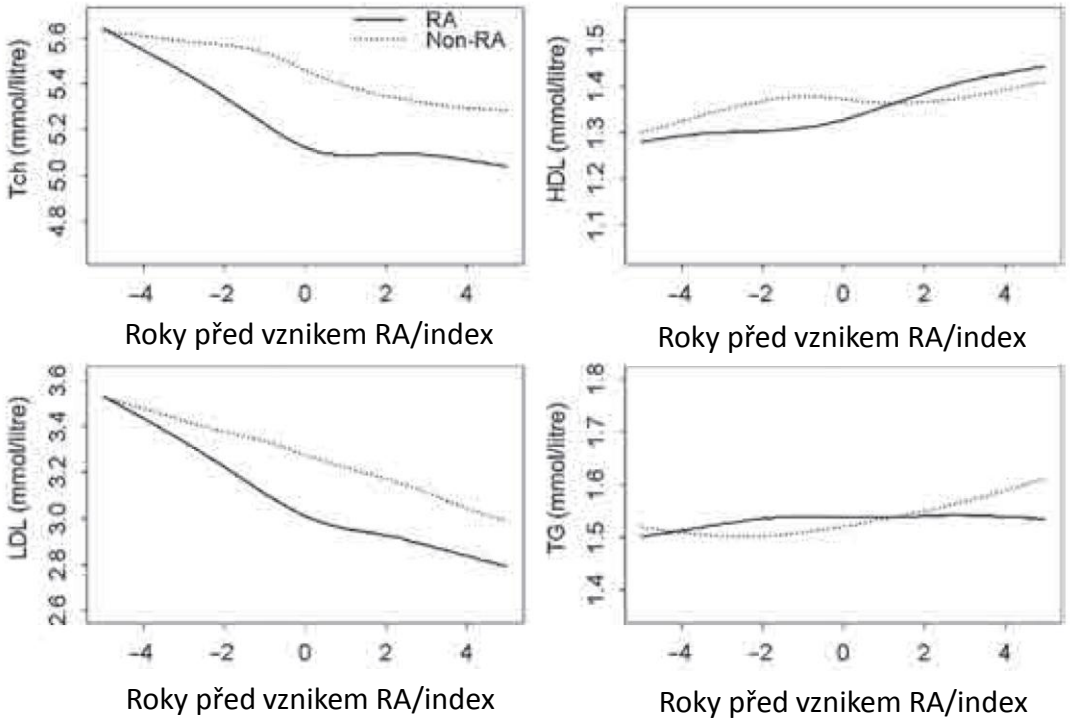
Baghdadi LR, et al. PlosOne. 2015; Jagpal and Navarro-Millán. BMC Rheumatology. 2018

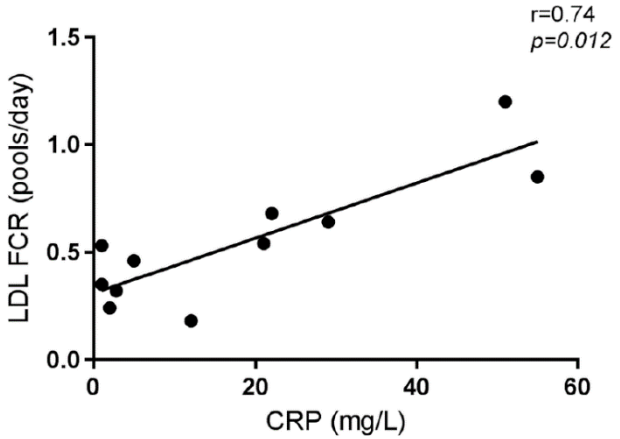
Riziko hospitalizace pro první KV příhodu je u pacientů s RA zvýšené v závislosti na kouření

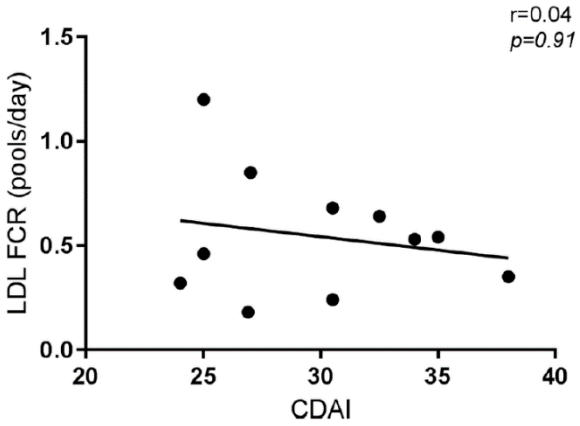
	Unadjusted, HR (95% CI)	Age-adjusted and sex-adjusted, HR (95% CI)	Fully adjusted*, HR (95% CI)
Smoking status			
Current vs never	1.64 (1.1 to 2.44)	2.19 (1.44 to 3.31)	2.23 (1.46 to 3.40)
Current vs former	0.81 (0.57 to 1.15)	1.35 (0.94 to 1.93)	1.51 (1.04 to 2.19)
Former vs never	2.02 (1.44 to 2.83)	1.62 (1.15 to 2.29)	1.47 (1.04 to 2.08)
Smoking cessation			
Per year since cessation, light smoker	0.80 (0.69 to 0.92)	0.76 (0.66 to 0.88)	0.77 (0.66 to 0.91)
Per year since cessation, heavy smoker	0.78 (0.67 to 0.91)	0.74 (0.63 to 0.86)	0.73 (0.62 to 0.87)
Heavy vs light smoker†	1.31 (0.65 to 2.65)	1.68 (0.82 to 3.45)	1.80 (0.79 to 4.10)
Interaction‡	0.98 (0.84 to 1.13)	0.97 (0.83 to 1.12)	0.95 (0.80 to 1.12)

Joseph RM, et al. RMD Open 2017

Nízké hladiny celkového cholesterolu a LDL-c u RA



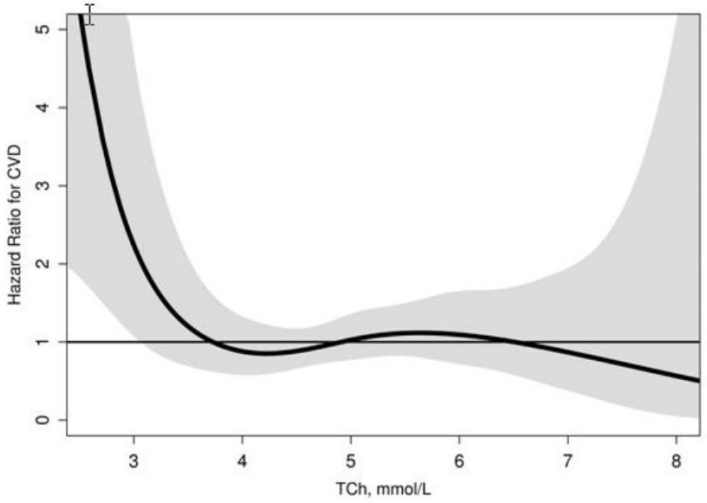


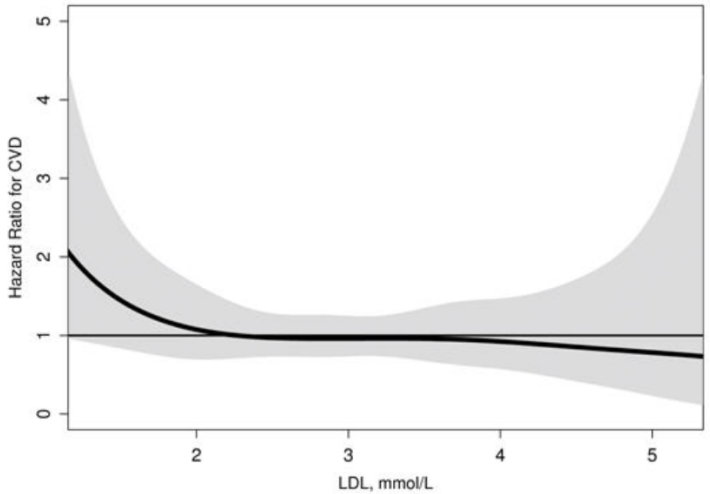


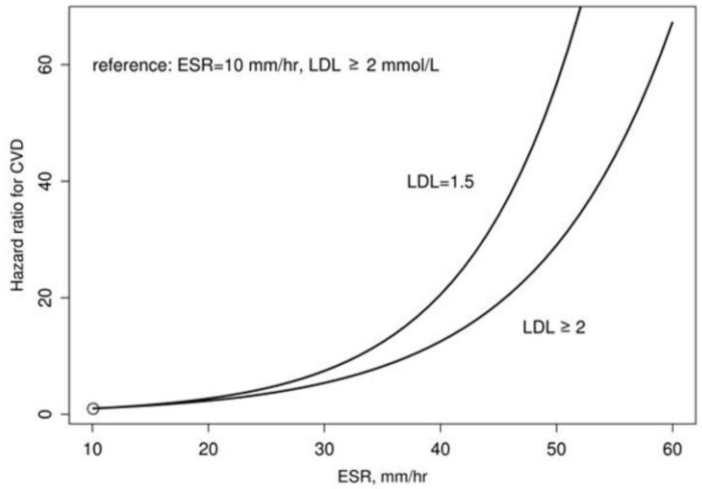
- pokles LDL-c u aktivní RA je dán hyperkatabolismem LDL částic
- po léčbě anti-IL-6 se zvyšují hladiny LDL-c (cca o 20%)
- hyperkatabolismus LDL částic se snižuje na úroveň zdravých jedinců

Myasoedova et al. Ann Rheum Dis. 2010; Robertson et al. Ann Rheum Dis. 2017

Lipidový paradox u RA







- Pacienti s celkovým cholesterolem <4 mmol/L mají 3.3 (95%CI 1.5, 7.2) násobně zvýšené riziko KV onemocnění.
- Zvýšené hladiny cholesterolu a LDL-c nemají vztah ke KV riziku.
- Zvýšené KV riziko u RA závisí na systémovém zánětu.

Myasoedova et al. Ann Rheum Dis. 2011

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Antirevmatické léky a KV riziko

Lék	Účinek na KV rizikové ukazatele
Glukokortikoidy	↑HTN, ↑TG, ↑Glu, ↓CRP
NSAID/koxiby	↑HTN, ↑trombocyty, ↓renální funkce
MTX	↓CRP, ↑adenosin
Hydroxychlorochin	↓ LDL, ↓ trombóza
Anti-TNF	↓CRP, ↑LDL , ↑TG
Anti-IL-6	↓CRP, ↑LDL , ↑TG
Deplece B-lymfocytů	dlouhodobá léčba může ↓LDL

Mason JC, et al. European Heart Journal 2015

THERAPY

Cardiovascular safety of celecoxib, naproxen and ibuprofen

Michael T. Nurmohamed

The PRECISION trial demonstrates that celecoxib is noninferior to ibuprofen and naproxen in regard to cardiovascular safety. Do these findings mark the end of the debate on this issue, or do aspects of the trial mean the implications for clinical practice are not clear-cut?

Refers to Nissen, S. E. *et al.* Cardiovascular safety of celecoxib, naproxen, or ibuprofen for arthritis. *N. Engl J. Med.* 375, 2519–2529 (2016)

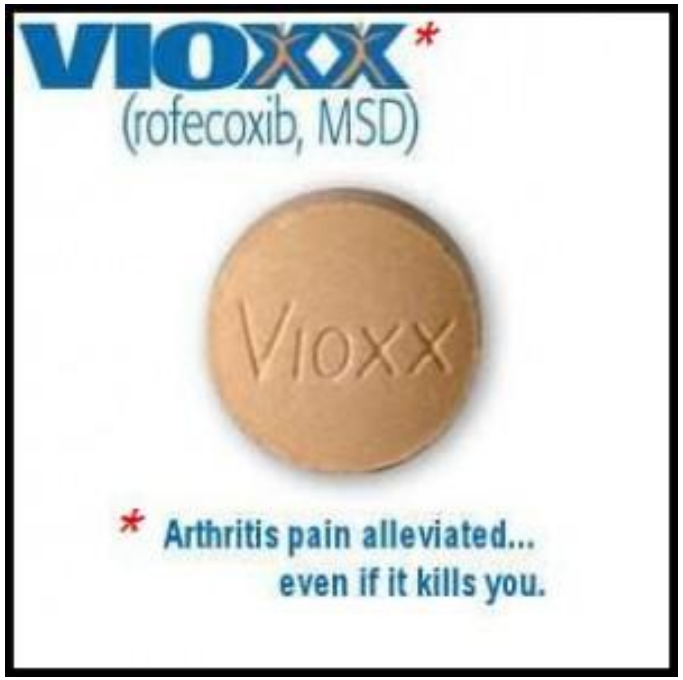
Nowadays, cyclooxygenase (COX, also known as prostaglandin G/H synthase) inhibitors are well known to be associated with increased cardiovascular risk. This increased risk also holds true for most NSAIDs, with the probable exception of naproxen[1]. The newly published results of the landmark PRECISION study seemingly refute the widely held idea that naproxen treatment is associated with fewer cardiovascular events than other NSAIDs, including the COX inhibitor celecoxib[2]. However, aspects of the study related to dosage and the study population could mean the results will be difficult to translate into clinical practice.

The first indication that COX inhibitors might be associated with increased cardio- approved for use in the USA) in this category of patients, but also extended this advice to apply to NSAIDs. The FDA also requested a cardiovascular safety trial comparing celecoxib to ibuprofen and naproxen; thus, the Prospective Randomized Evaluation of Celecoxib Integrated Safety versus Ibuprofen or Naproxen (PRECISION) trial was designed in consultation with the FDA[2].

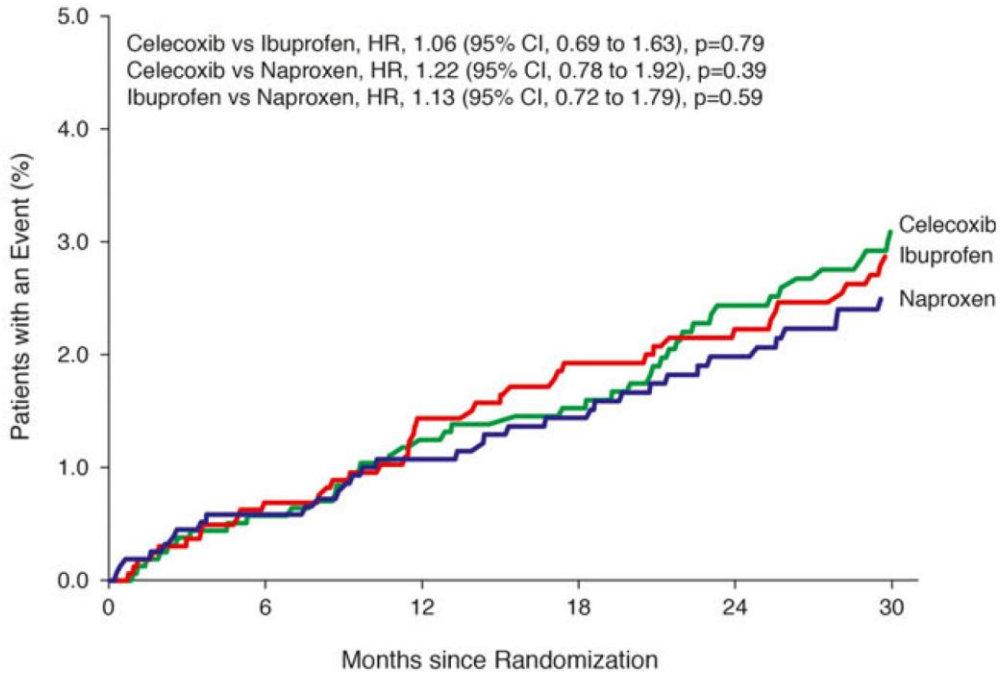
> The APPROVE trial findings… led to the worldwide withdrawal of rofecoxib from the market in 2004

During this 10-year trial the mean duration of treatment was 20.3 months and the mean follow-up was 34.1 months. The primary outcome was the occurrence of an adverse event that met Antiplatelet Trialists Collaboration (APTC) criteria; this composite endpoint included death from cardiovascular causes[2]. In the intention-to-treat analysis this APTC endpoint was met in 188 celecoxib-treated patients (2.3%), 201 naproxen-treated patients (2.5%) and 218 ibuprofen-treated patients (2.7%); the hazard ratio for celecoxib versus naproxen was 0.93 (95% CI 0.76–1.13) and for celecoxib versus ibuprofen was 0.85 (95% CI 0.70–1.04), demonstrating celecoxib to be non-inferior to both naproxen and ibuprofen with respect to cardiovascular safety. Furthermore, the rates of hospitalization for hypertension and renal adverse events were lower in the celecoxib group compared with the ibuprofen and naproxen groups, albeit the latter comparison did not reach statistical significance. As expected, composite rates of gastrointestinal adverse effects were significantly lower in the celecoxib-treated patients compared with the other two groups, but this difference was mainly attributable to iron-deficiency of gastrointestinal origin, of which the clinical relevance is unknown.

To what extent are the results of this mega-trial generalizable to clinical practice? The rate at which patients discontinued treatment (69%) and follow-up (27%) in the PRECISION trial resembles that seen in clinical practice. However, between-group differences in loss



KV bezpečnost celecoxibu není horší než naproxenu nebo ibuprofenu



No. at Risk

Ibuprofen	832	756	710	674	619	572
Naproxen	791	725	685	652	594	528
Celecoxib	813	752	710	677	608	565

- Celekoxib: snížená mortalita proti naproxenu (HR 0.47, 95% CI 0.25-0.88)

Solomon DH, et al. Arthritis Rheumatol. 2018

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Nadřazená doporučení k léčbě KVO (rizika) u pacientů s RA

- Lékaři by si měli být vědomi **vyššího rizika KVO** u pacientů s RA ve srovnání s běžnou populací.
- **Revmatolog je zodpovědný za vedení léčby** KV rizikových faktorů u pacientů s RA a dalšími revmatickými chorobami.
- **Použití NSAID a glukokortikoidů** by mělo být v souladu s doporučeními specifickými pro léčbu (EULAR a ASAS).

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Specifická doporučení k léčbě KVO (rizika) u pacientů s RA

1. Optimální kontrola aktivita nemoci → ↓riziko KVO.
2. Posouzení rizika KVO nejméně jednou za 5 let.
3. Odhad rizika KVO v souladu s národními doporučeními.
4. Lipidové spektrum hodnotit pokud je onemocnění stabilizované.
5. Predikční model rizika KVO upraven o multiplikační faktor 1,5.
6. Screening asymptomatických AT plátů - ultrazvuk karotických arterií.
7. Zdůrazňovat přínosy zdravé výživy, pravidelného cvičení a odvykání kouření.
8. Antihypertenziva a statiny jako u běžné populace.
9. Podávání NSAID opatrné, zejména při KVO nebo přítomnosti KV rizika.
10. Dávkování glukokortikoidů omezit na minimum.

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Závěr

- Zánětlivá revmatická onemocnění zvyšují riziko KV onemocnění.
- Pečlivý screening a léčba tradičních KV rizikových faktorů u revmatických pacientů.
- Nutnost optimální kontroly revmatického onemocnění (remise nebo nízká aktivita).
- Opatrnost a dodržování léčebných postupů při podávání NSA a glukokortikoidů.