HYPOLIPIDEMICKÁ LÉČBA U PACIENTA S LABORATORNÍMI ODCHYLKAMI

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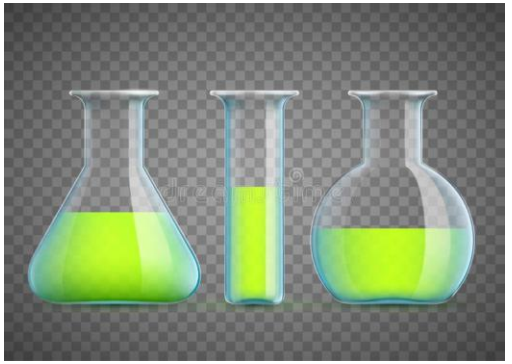
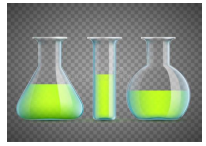
Praha

XXXI.SJEZD ČKS BRNO 14.5.2023

NEJČASTĚJŠÍ LABORATORNÍ ODCHYLKY PŘED NASAZENÍM/ V PRŮBĚHU HL

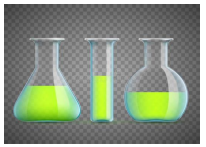
- JATERNÍ MARKERY
- RENÁLNÍ MARKERY
- GLYKÉMIE





HYPOLIPIDEMICKÁ LÉČBA
ÚČINEK NA JÁTRA

JÁTRA A STATINY
Drug Induced Liver Injury)



ALT/AST < 3x ULN

- frekvence 3/100

ALT/AST ≥ 3x ULN a bilirubin > 2x ULN

- frekvence 1/ 100 000

Akutní selhání jater:

- frekvence 1/ 1 000 000

Thapar et al.: Statins and liver injury. Gastroenterol Hepatol (NY) 2013

STATINY A JATERNÍ LÉZE

	Sweden (n=73)	Spain (n=47)	USA (n=22)
Věk (roky)	64	62	60
Muži	55%	47%	32%
Dávka (median)	–	–	20 mg
Hepatocel.léze	59%	51%	55%
Latence (median)	90 dní	57 dní	155 dní
Ikterus	35%	53%	68%
Autoantibodies	–	25%	27%
Chronicita	–	19%	18%
Atorvastatin	41%	34%	36%
Simvastatin	38%	28%	23%
Fluvastatin	15%	25%	9%
Lovastatin	–	4%	5%
Rosuvastatin	3%	–	18%
Pravastatin	3%	8%	9%

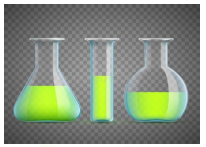
Björnsson ES, Liver International 2016

TYP STATINU A JATERNÍ LÉZE

STATIN	n	Léze po opětovném nasazení	Fatal liver injury
Simvastatin	68	+	+
Atorvastatin	65	+	+
Fluvastatin	28	+	0
Rosuvastatin	13	0	0
Lovastatin	12	0	0
Pravastatin	11	0	0

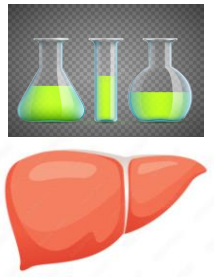
Björnsson ES, Liver International 2016

STATINY A NAFLD/NASH



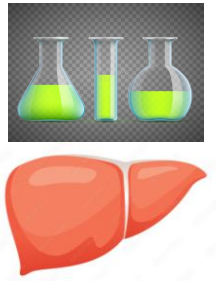
- NAFLD/NASH – významný KV rizikový faktor
- Hypolipidemická léčba doporučena
- Statiny, ezetimib, PCSK9-I, fibráty i omega-3 MK bezpečné
- Vliv na histolog. obraz zatím neprokázán

STATINY A CHRONICKÉ VIROVÉ HEPATITIDY



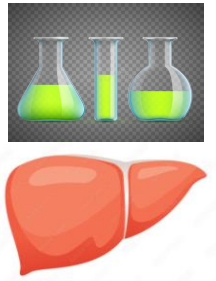
- Chron. HCV zvyšuje KV riziko
- Statiny bezpečné u chron. HCV i chron. HBV
- Možné interakce s antivirotiky (monitorace ALT)
- Po skončení léčby antivirotiky:
  léčit pacienta podle KV guidelines

STATINY A PBC



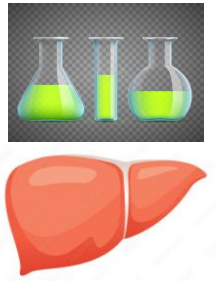
- PBC primárně KVR nezvyšuje
- Statiny (ani jiná HL) nejsou kontraindikovány u pacientů s KVR vyžadujících snížení LDL-ch
- Vysadit pouze při cirhóze Child-Pugh B a C
- Statiny neutrální vliv na průběh PBC

STATINY A CIRHÓZA JATER



- Statiny bezpečné u cirhózy Child-Pugh A

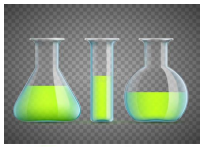
STATINY PO TX JATER



- Vysoké KVR: sekundární dyslipidémie (calcineurin, sirolimus, tacrolimus, kortikoidy)
- Statiny (i ostatní HL) bezpečné

JÁTRA A STATINY

Kontrola ALT:

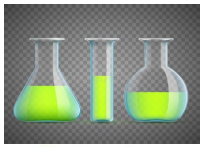


- Před nasazením léčby
- 8-12 týdnů po nasazení
- Rutinní sledování není třeba

ALT ≥ 3x ULN:

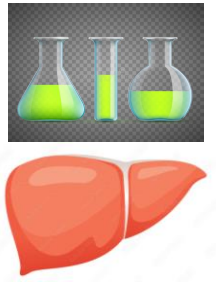
- stop
- Kontrola ALT za 4-6 týdnů
- Znovu statin – nižší dos., jiný statin až po normalizaci ALT
- Přetrvává elevace ALT – další příčiny ?

STATINY A SELHÁNÍ JATER



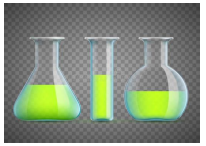
- 1/ 1 000 000
- Stop STATIN!
- Kontraindikace jakékoli statinové léčby!

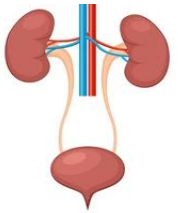
JÁTRA A FIBRÁTY



- NE u cholelitiázy
- Bezpečné u NAFLD
- Bezpečné u cholestázy – PBC, PSC

Hepatology 2015; 62(2): 635–643

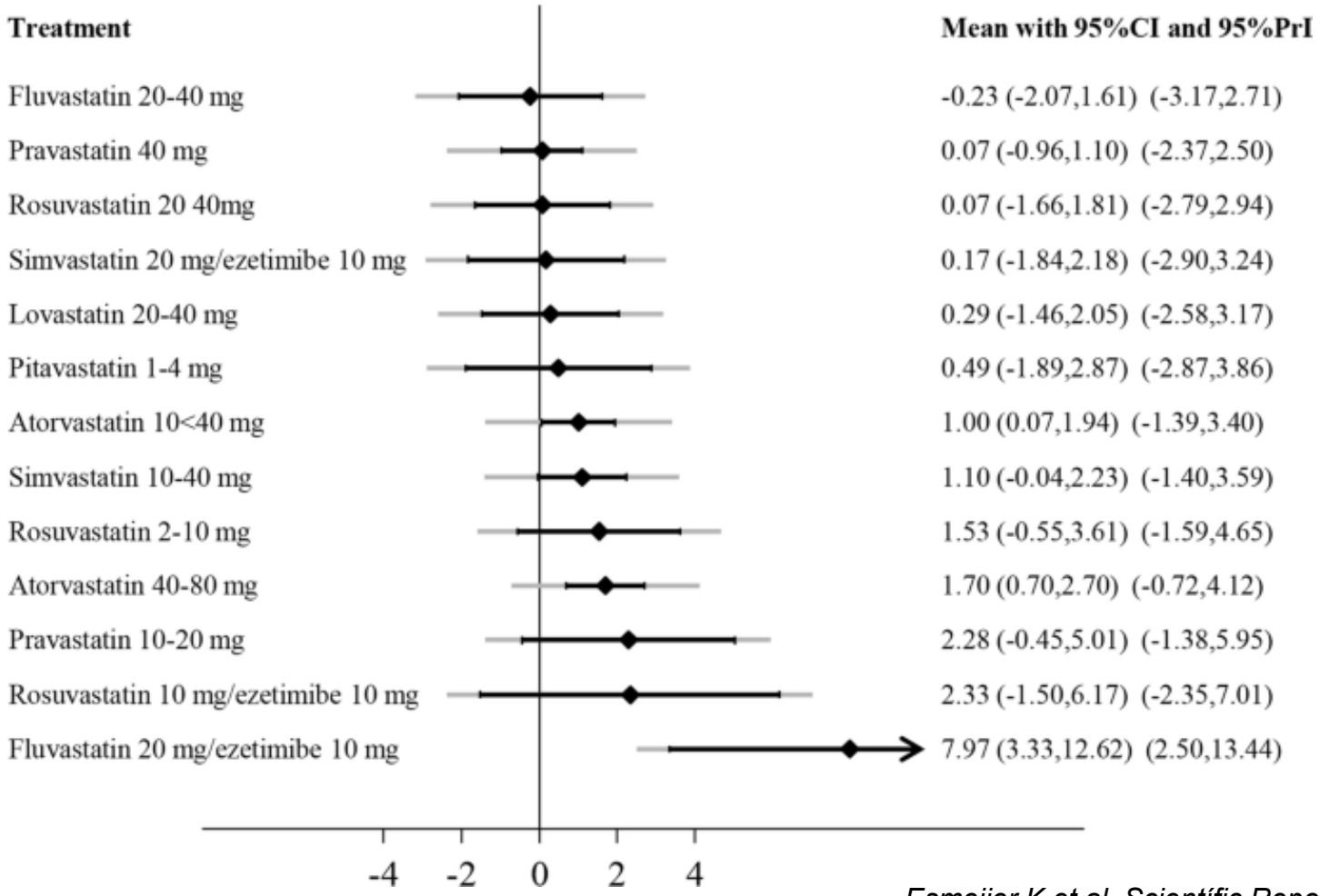




HYPOLIPIDEMICKÁ LÉČBA A RENÁLNÍ FUNKCE

STATINY - RENOPROTEKTIVNÍ EFEKT U CKD

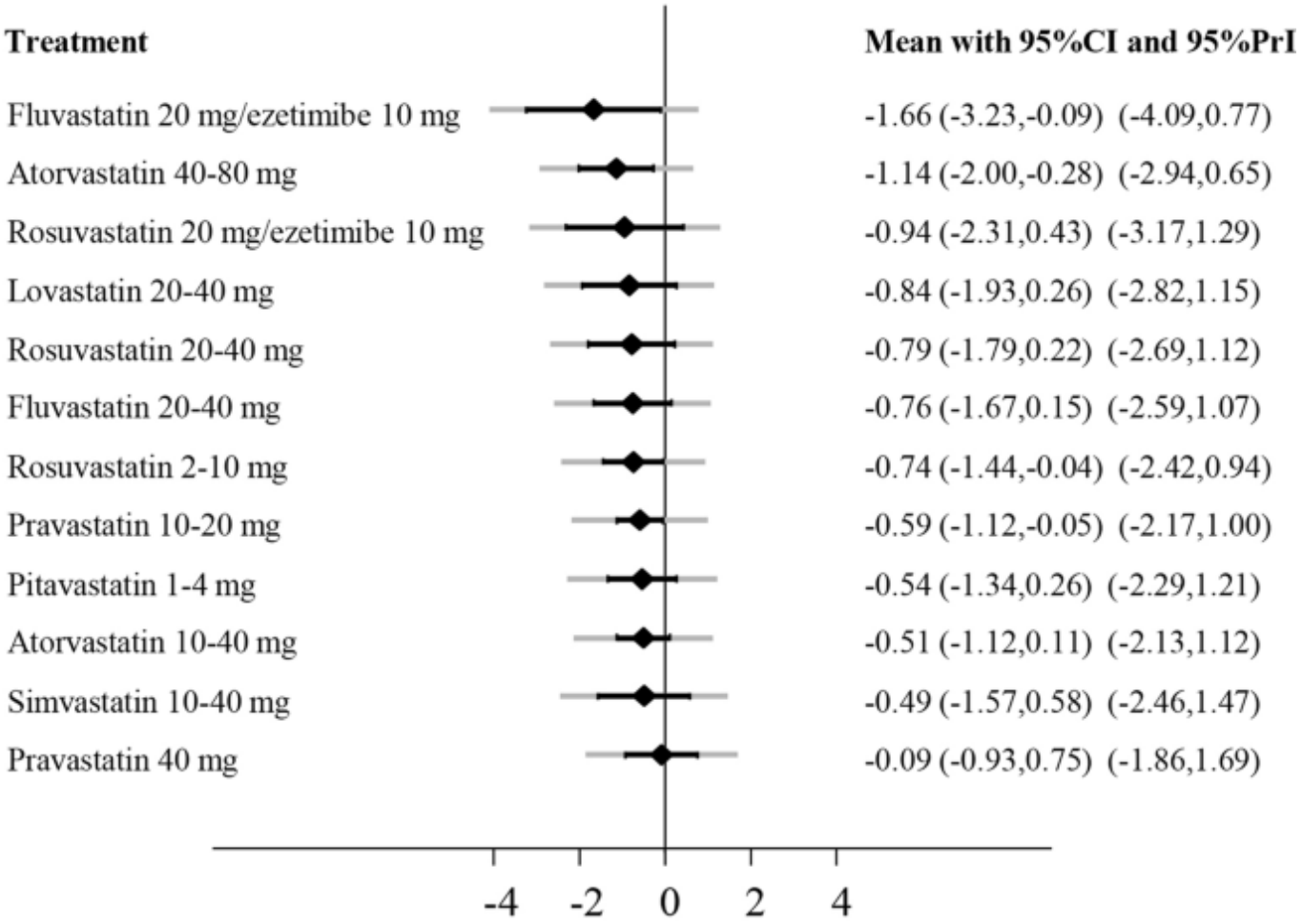
Reduction of annual eGFR decline for different statins compared to control



Esmeijer K et al. Scientific Reports 2019

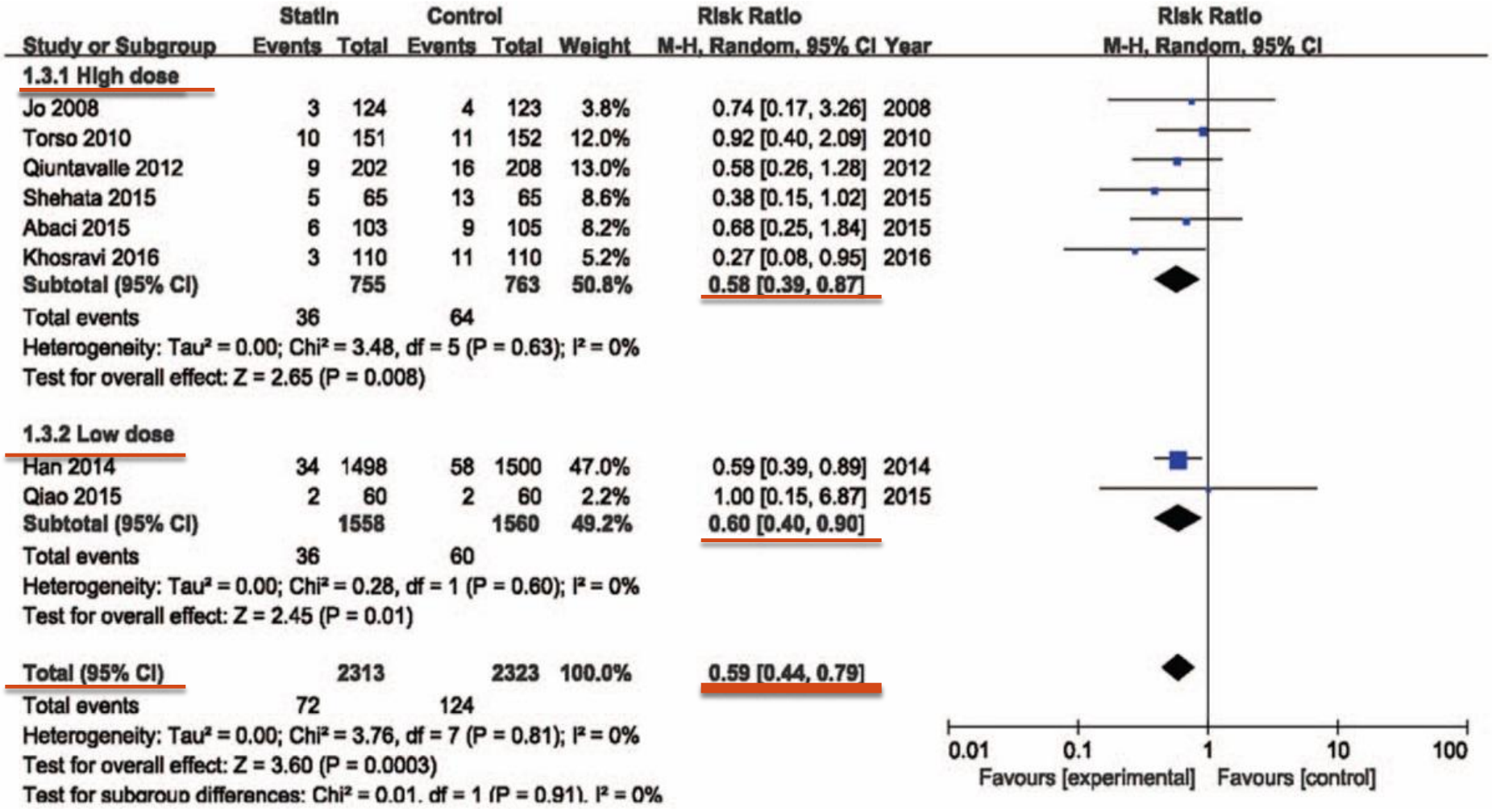
STATINY - RENOPROTEKTIVNÍ EFEKT U CKD

Annual change in proteinuria for different statins compared to control



Esmeijer K et al. Scientific Reports 2019

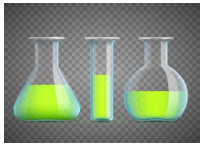
STATINY
A KONTRASTNÍ NEFROPATIE U CKD

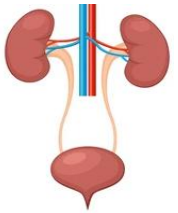


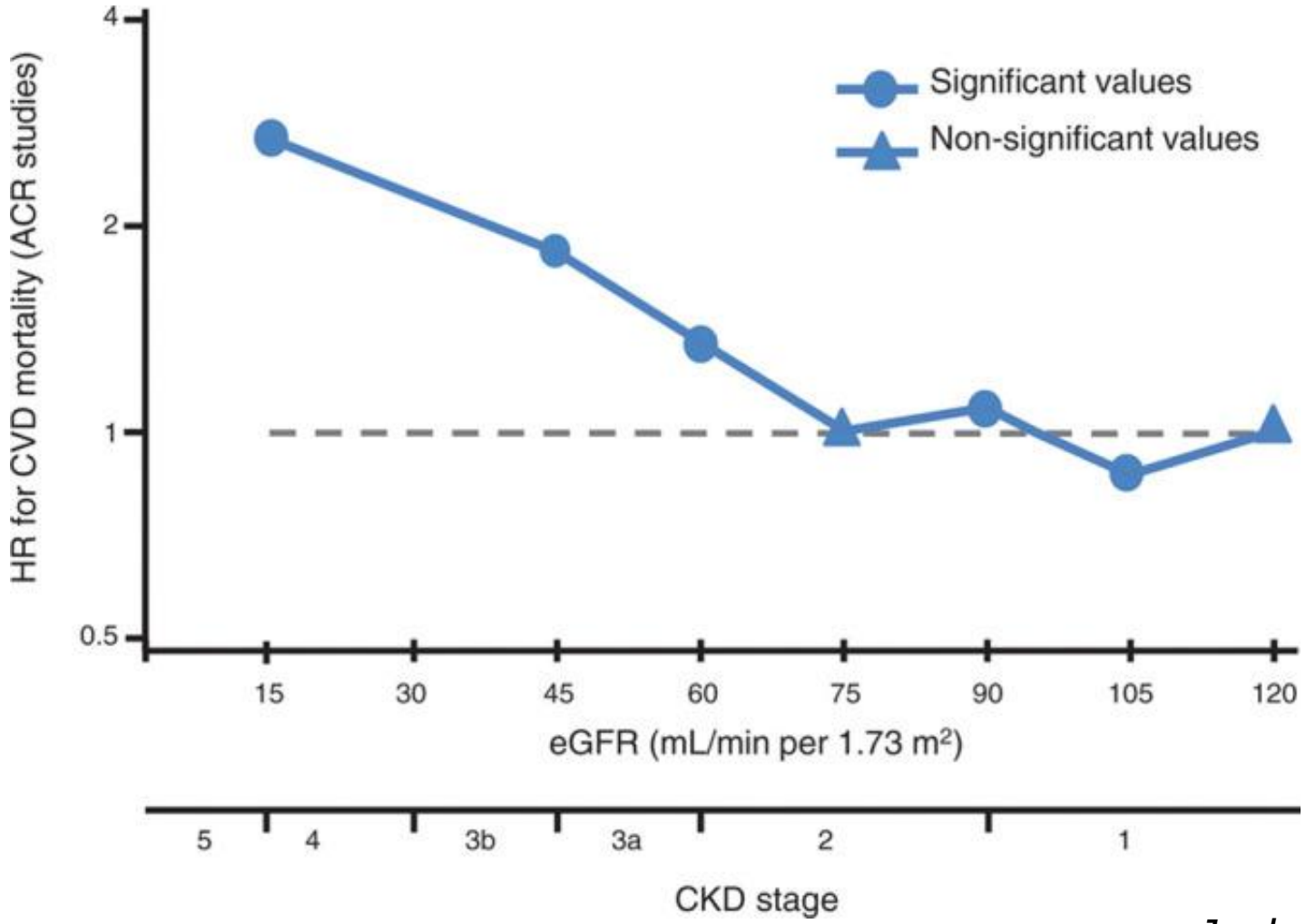
Study or Subgroup	Statin Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
1.3.1 High dose							
Jo 2008	3	124	4	123	3.8%	0.74 [0.17, 3.26]	2008
Torso 2010	10	151	11	152	12.0%	0.92 [0.40, 2.09]	2010
Qiuntavalle 2012	9	202	16	208	13.0%	0.58 [0.26, 1.28]	2012
Shehata 2015	5	65	13	65	8.6%	0.38 [0.15, 1.02]	2015
Abaci 2015	6	103	9	105	8.2%	0.68 [0.25, 1.84]	2015
Khosravi 2016	3	110	11	110	5.2%	0.27 [0.08, 0.95]	2016
Subtotal (95% CI)		**755**		**763**	**50.8%**	**0.58 [0.39, 0.87]**	
Total events	36		64				
Heterogeneity: Tau² = 0.00; Chi² = 3.48, df = 5 (P = 0.63); I² = 0%							
Test for overall effect: Z = 2.65 (P = 0.008)							
1.3.2 Low dose							
Han 2014	34	1498	58	1500	47.0%	0.59 [0.39, 0.89]	2014
Qiao 2015	2	60	2	60	2.2%	1.00 [0.15, 6.87]	2015
Subtotal (95% CI)		**1558**		**1560**	**49.2%**	**0.60 [0.40, 0.90]**	
Total events	36		60				
Heterogeneity: Tau² = 0.00; Chi² = 0.28, df = 1 (P = 0.60); I² = 0%							
Test for overall effect: Z = 2.45 (P = 0.01)							
Total (95% CI)		**2313**		**2323**	**100.0%**	**0.59 [0.44, 0.79]**	
Total events	72		124				
Heterogeneity: Tau² = 0.00; Chi² = 3.76, df = 7 (P = 0.81); I² = 0%							
Test for overall effect: Z = 3.60 (P = 0.0003)							
Test for subgroup differences: Chi² = 0.01, df = 1 (P = 0.91), I² = 0%							

Ajin C et al. Medicine 2020; 99(10): e19473

KV MORTALITA A GF

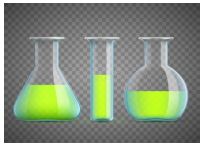


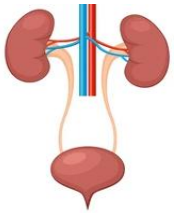




Jankowski J et al. Circulation 2021

KDIGO CLASSIFICATION CKD AND CARDIOVASC. DIS.



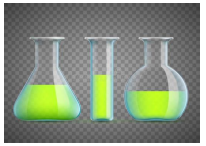


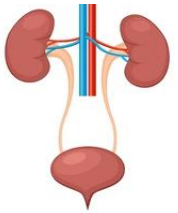
Progression of CKD by GFR and Albuminuria Categories				Albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30-299 mg/g 3-29 mg/mol	≥300 mg/g ≥30 mg/mmol
GFR categories (ml/min/1.73m²) Description and range	G1	Normal to high	≥90			
	G2	Mildly decreased	60-90			
	G3a	Mildly to moderately decreased	45-59			
	G3b	Moderately to severely decreased	30-44			
	G4	Severely decreased	15-29			
	G5	Kidney failure	15			

Green: low risk (if no other markers of kidney diseases, no CKD); Yellow: moderately increased risk; Orange: high risk; Red, very high risk

Jankowski J et al. Circulation 2021

CÍLOVÉ HODNOTY LDL-CH U CKD





KV RIZIKO	LDL-chol
HIGH RISK	< 1,8 mmol/l
VERY HIGH RISK	< 1,4 mmol/l

ESC GUIDELINES 2019: dle GFR

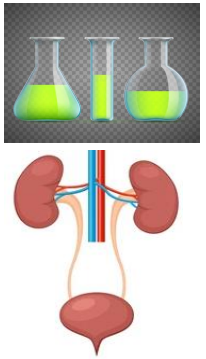
KDIGO 2012: dle GFR + albuminurie

SEKUNDÁRNÍ DYSLIPIDÉMIE U CKD

	Nefrot. syndrom	CKD st.1–2	CKD St. 3–4	HD	PD	TX
CHOL	↑↑	=	=	=/ ↓	↑	↑
LDL-ch	↑↑	=	=/ ↓	=/ ↓	↑	↑
HDL-ch	↓	↓	↓	↓	↓	=/ ↓
TAG	↑↑	↑↑	↑↑	= / ↑	↑↑	↑ / ↑↑

Pontremoli R et al. J Nephrol 2020

KVO-EFEKT STATINŮ U CKD



	MAE	MI	Total mortality
CKD 1-5 bez HD[1]	**0,72 (0,66-0,79)**	**0,55 (0,42-0,72)**	**0,62 (0,35-1,12)**
ESRD – HD[2]	0,90 (0,75-1,08)	-	-

	MAE	Cardiac death/ non-fatal MI
Renal TX[3]	**0,79 (0,63-0,99)**	**0,71 (0,55-0,72)**

1) meta-analýza 8 studií (PREVEND IT, AFCAPS/TexCAPS, JUPITER, ALLIANCE, LIPS, AURORA, 4 D SHARP)
2) SHARP
3) ALERT

Kennard A, Singer S, Austr Prescr 2017

INDIKACE LÉČBY STATIN/EZE U CKD

CKD konzervat.	HD	Renal TX
+	Nově nezahajovat	+
	Statin nasazen před HD: +	

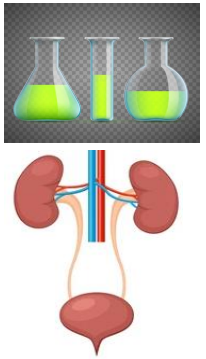
KDIGO 2013

STATINY U CKD

STATIN	DÁVKOVÁNÍ U CKD
ATORVASTATIN	CKD 1-5 **10-80 mg**
ROSUVASTATIN	CKD 1-2 **5-40 mg** CKD 3A-B **5-20 mg** CKD 4-5 **KI !!!**
SIMVASTATIN	CKD 1-3 **5-80 mg** CKD 4-5 **5-10 mg**

Vaziri et al, J Fam Pract 2016

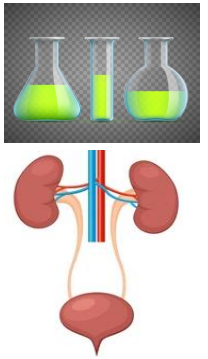
FIBRÁTY U CKD



- RELAT. BEZPEČNÉ: mladší jedinci, CKD 1-2
- Elevace kreatininu: starší muži
- Redukce KVO u CKD: NEPROKÁZÁNA
- FIELD, ACCORD: ⬇ mikrovask. komplikace
- Weinstein (2013) – FENO ad ROSUVA in CKD G3: eGFR 49 → 43 ml/s/1,73m^2/ 16 weeks
- Pokud eGFR < 45 ml/s/1,73m^2 nebo o 20 %: fibrát STOP nebo redukce dávky

ABCD THE RENAL ASSOCIATION 2021 update

PCSK9I U CKD



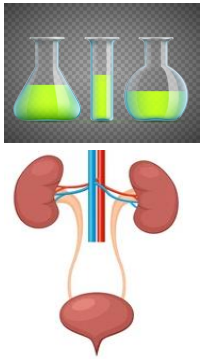
- Bezpečné

- FOURIER
  – evolocumab u CKD 1-4: stejný efekt na snížení LDL-ch
  – snížení MAE (KV úmrtí, MI, CMP) významněji u CKD 3-4

- ODYSSEY COMBO II
  – alirocumab u eGFR < 30 ml/s/1,73m^2: ⬇ LDL-ch 49%

ABCD THE RENAL ASSOCIATION 2021 update

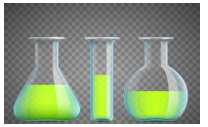
EZETIMIB U CKD



- BEZPEČNÝ

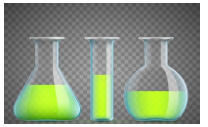
- SHARP: SIMVA 20 + EZE: ⬇ MAE o 17 %

ABCD THE RENAL ASSOCIATION 2021 update



HYPOLIPIDEMICKÁ LÉČBA A DIABETES MELLITUS

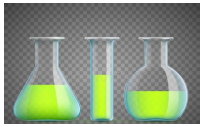
STATINY A RIZIKO DM



Monitorace glykémie a HbA1c:

- Pacienti s metabol. syndromem/prediabetem
- Starší pacienti
- Vysoká dávka statinu

Recommendations	Class[a]	Level[b]
In patients with T2DM at very-high risk[c], an LDL-C reduction of ≥50% from baseline and an LDL-C goal of <1.4 mmol/L (<55 mg/dL) is recommended.[34,418,432]	I	A
In patients with T2DM at high risk,[c] an LDL-C reduction of ≥50% from baseline and an LDL-C goal of <1.8 mmol/L (<70 mg/dL) is recommended.[418]	I	A
Statins are recommended in patients with T1DM who are at high or very-high risk.[c 427]	I	A
Intensification of statin therapy should be considered before the introduction of combination therapy.	IIa	C
If the goal is not reached, statin combination with ezetimibe should be considered.[33,299]	IIa	B
Statin therapy is not recommended in premenopausal patients with diabetes who are considering pregnancy or are not using adequate contraception.	III	C
Statin therapy may be considered in both T1DM and T2DM patients aged ≤30 years with evidence of end organ damage and/or an LDL-C level >2.5 mmol/L, as long as pregnancy is not being planned.	IIb	C



ESC guidelines 2019

Děkuji za pozornost!

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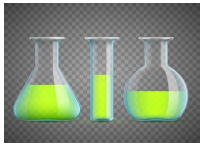
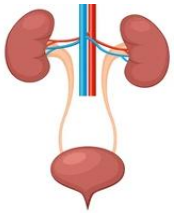
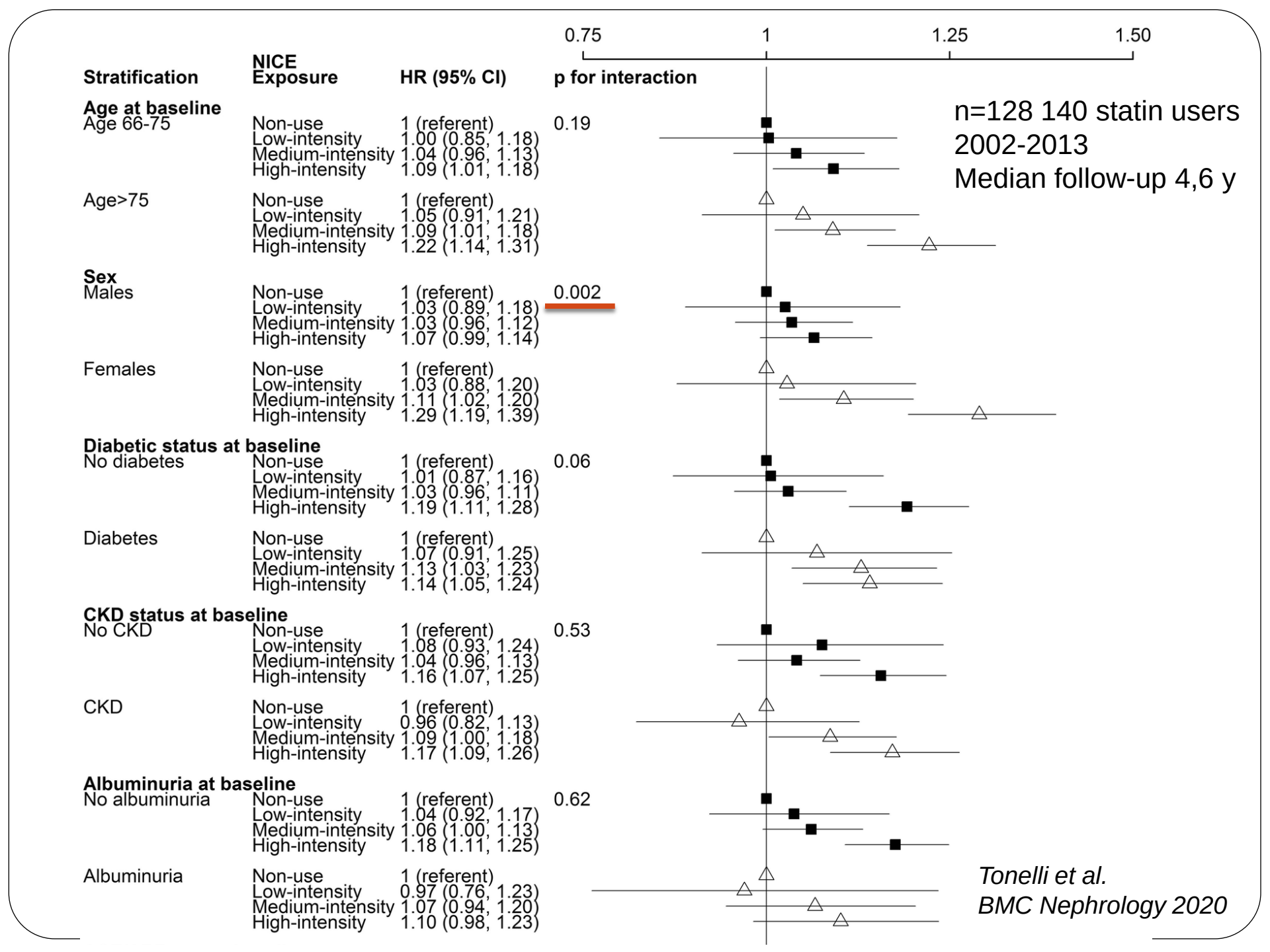
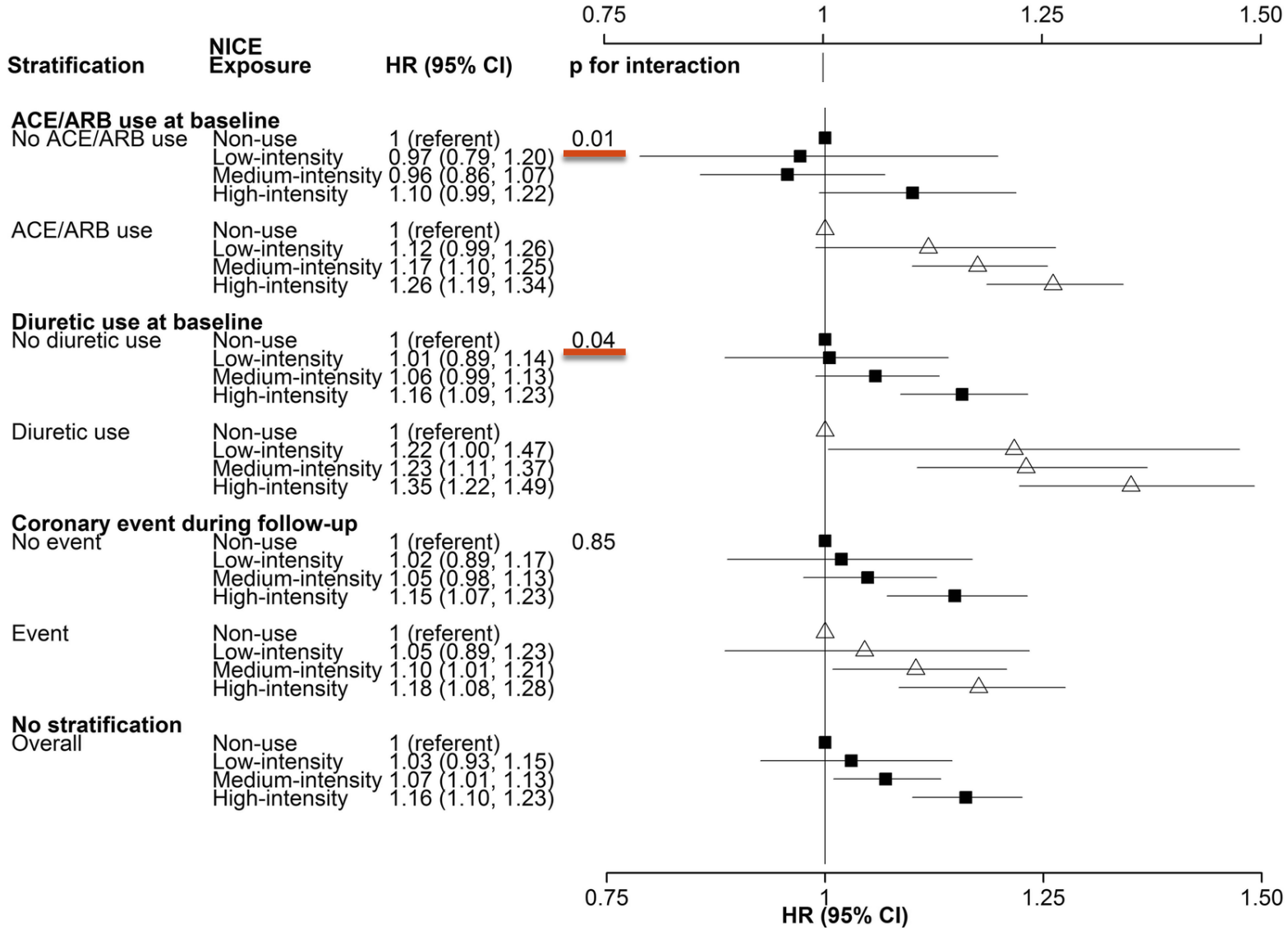




STATINY A RIZIKO AKUTNÍHO POŠKOZENÍ LEDVIN BEZ RABDOMYOLÝZY


0.75
1
1.25
1.50
Stratification
NICE Exposure
HR (95% CI)
p for interaction
Age at baseline
Age 66-75
Non-use 1 (referent)
Low-intensity 1.00 (0.85, 1.18)
Medium-intensity 1.04 (0.96, 1.13)
High-intensity 1.09 (1.01, 1.18)
0.19
Age>75
Non-use 1 (referent)
Low-intensity 1.05 (0.91, 1.21)
Medium-intensity 1.09 (1.01, 1.18)
High-intensity 1.22 (1.14, 1.31)
Sex
Males
Non-use 1 (referent)
Low-intensity 1.03 (0.89, 1.18)
Medium-intensity 1.03 (0.96, 1.12)
High-intensity 1.07 (0.99, 1.14)
0.002
Females
Non-use 1 (referent)
Low-intensity 1.03 (0.88, 1.20)
Medium-intensity 1.11 (1.02, 1.20)
High-intensity 1.29 (1.19, 1.39)
Diabetic status at baseline
No diabetes
Non-use 1 (referent)
Low-intensity 1.01 (0.87, 1.16)
Medium-intensity 1.03 (0.96, 1.11)
High-intensity 1.19 (1.11, 1.28)
0.06
Diabetes
Non-use 1 (referent)
Low-intensity 1.07 (0.91, 1.25)
Medium-intensity 1.13 (1.03, 1.23)
High-intensity 1.14 (1.05, 1.24)
CKD status at baseline
No CKD
Non-use 1 (referent)
Low-intensity 1.08 (0.93, 1.24)
Medium-intensity 1.04 (0.96, 1.13)
High-intensity 1.16 (1.07, 1.25)
0.53
CKD
Non-use 1 (referent)
Low-intensity 0.96 (0.82, 1.13)
Medium-intensity 1.09 (1.00, 1.18)
High-intensity 1.17 (1.09, 1.26)
Albuminuria at baseline
No albuminuria
Non-use 1 (referent)
Low-intensity 1.04 (0.92, 1.17)
Medium-intensity 1.06 (1.00, 1.13)
High-intensity 1.18 (1.11, 1.25)
0.62
Albuminuria
Non-use 1 (referent)
Low-intensity 0.97 (0.76, 1.23)
Medium-intensity 1.07 (0.94, 1.20)
High-intensity 1.10 (0.98, 1.23)
n=128 140 statin users
2002-2013
Median follow-up 4,6 y
Tonelli et al.
BMC Nephrology 2020



Tonelli et al.
BMC Nephrology 2020

ROSUVASTATIN VS. ATORVASTATIN

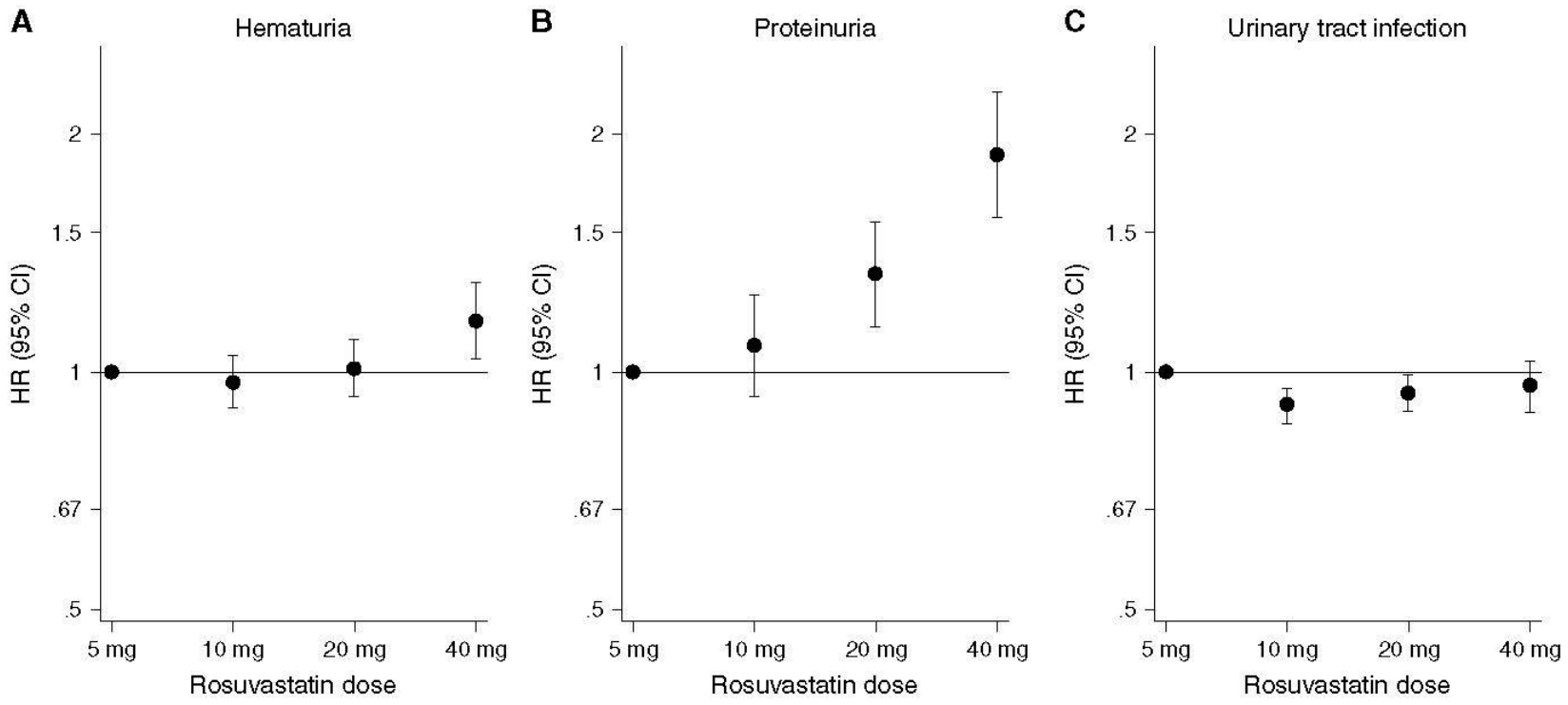
Rosuvastatin n = 152 101
Atorvastatin n = 795 799

	HR (95% CI)
Hematurie	**1,08 (1,04-1,11)**
Proteinurie	**1,17 (1,10-1,25)**
Selhání ledvin	**1,08 (1,02-1,30)**
ASKVO	1,02 (0,96-1,08)

44% pacientů s CKD 4+
rosuvastatin > 10 mg/D
(nad doporučení FDA)
- 30% 20 mg/D
- 14% 40 mg/D

Shin J et al. JASN 2022

ROSUVASTATIN - DÁVKA



Shin J et al. JASN 2022