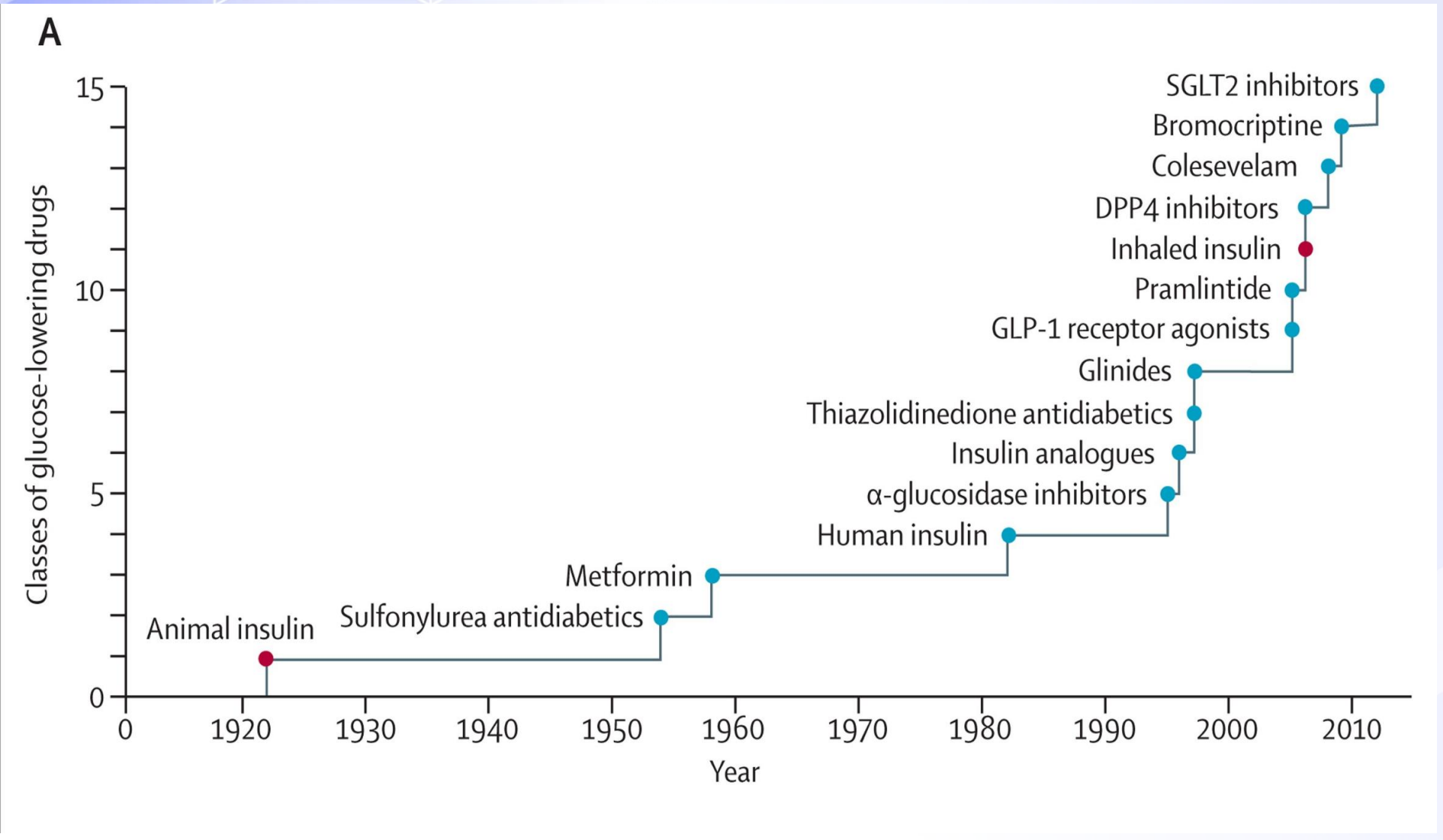
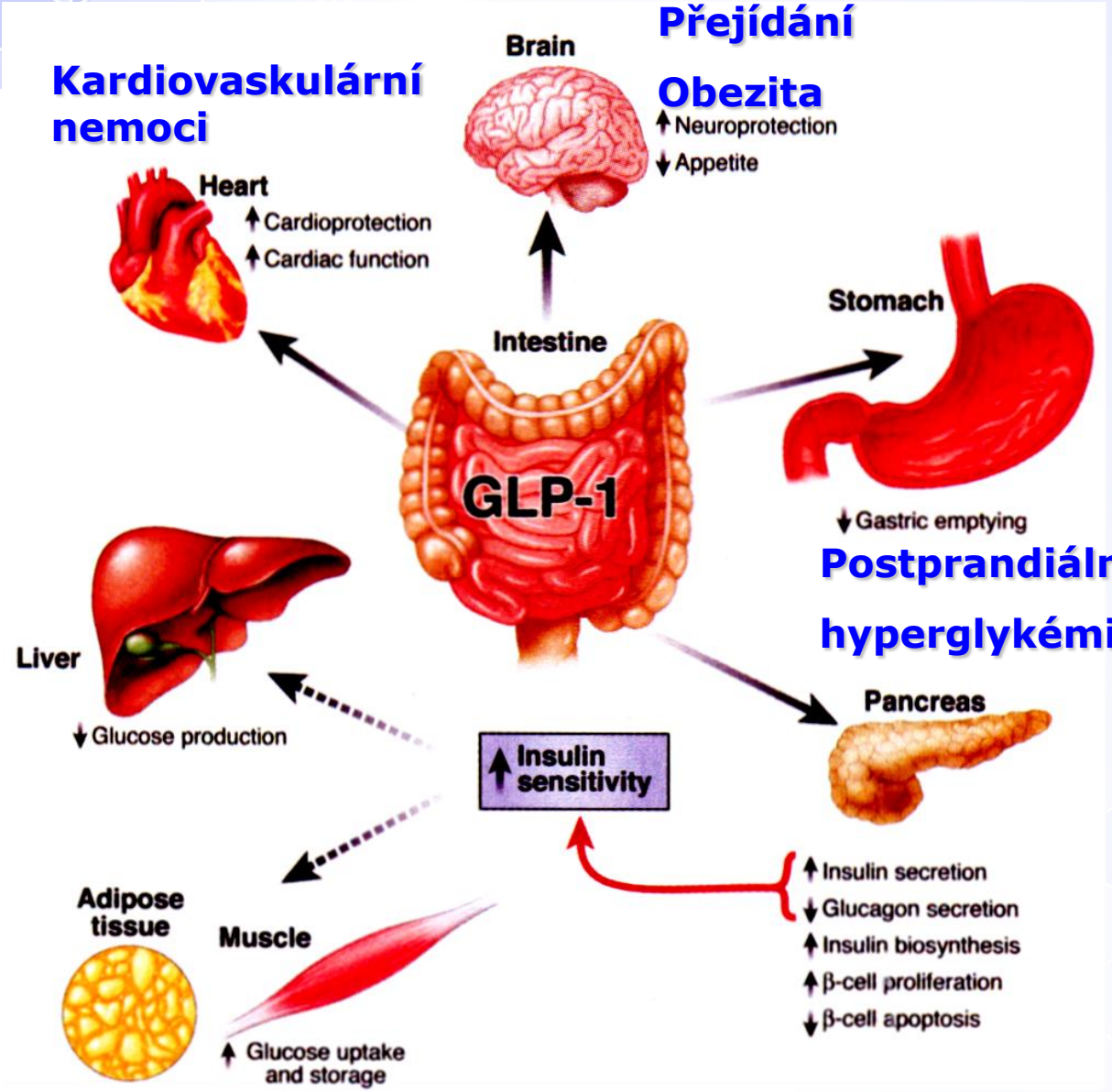
DIABETES MELLITUS
INKRETINY

L. Špinarová,
Brno

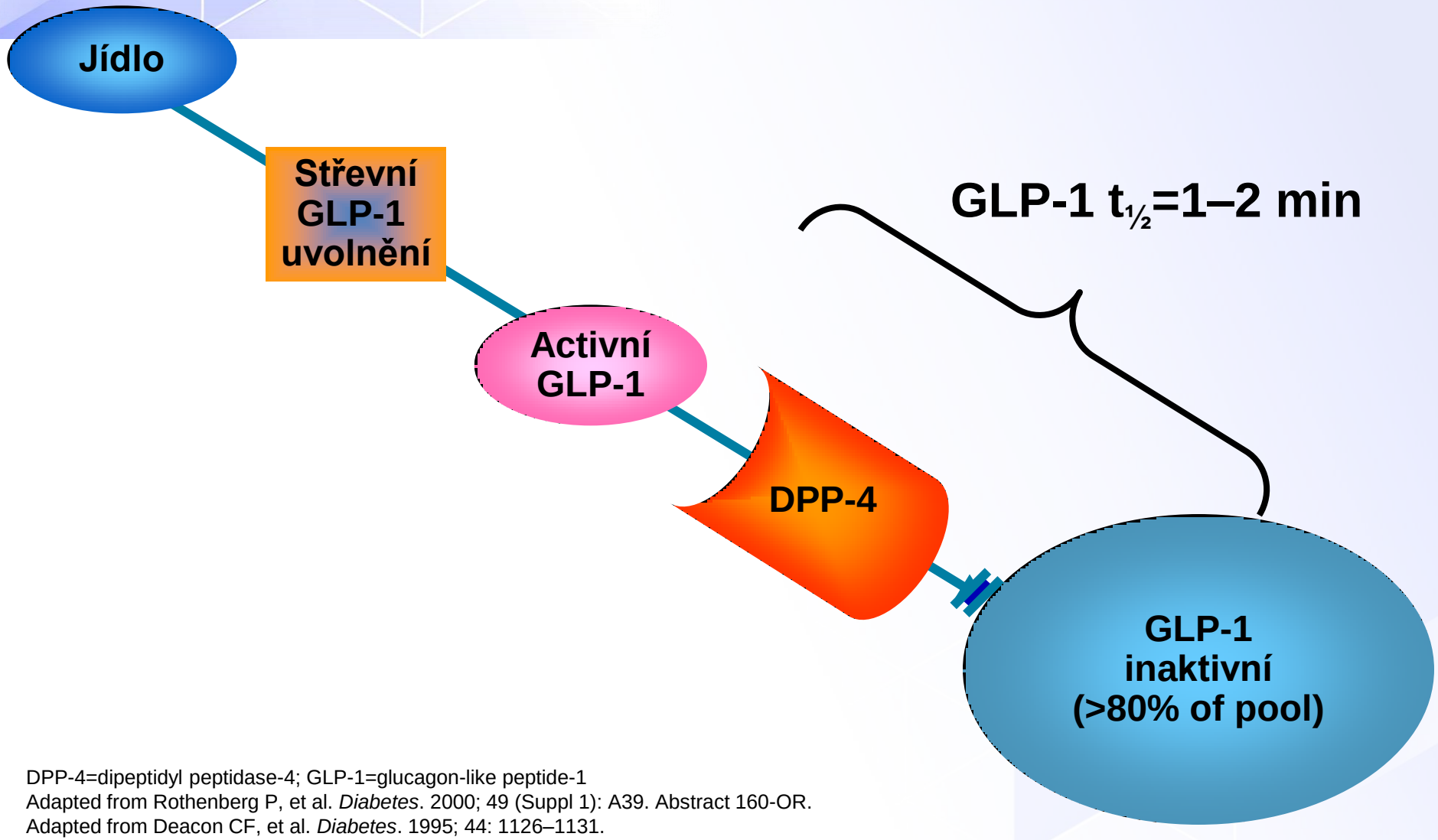
Vývoj léků snižující glukózu



GLP-1: Anti-diabetický účinek



Inhibice DPP-4 zvyšuje aktivitu GLP-1



DPP-4=dipeptidyl peptidase-4; GLP-1=glucagon-like peptide-1
Adapted from Rothenberg P, et al. *Diabetes*. 2000; 49 (Suppl 1): A39. Abstract 160-OR.
Adapted from Deacon CF, et al. *Diabetes*. 1995; 44: 1126–1131.

Farmakokinetické vlastnosti inhibitorů DPP-4[a]

	Sitagliptin (Merck)[1]	Vildagliptin (Novartis)[2]	Saxagliptin (BMS/AZ)[3]	Alogliptin (Takeda)[5]	Linagliptin (BI)[6–9]
Absorption t_{max} (median)	1–4 h	1.7 h	2 h (4 h for active metabolite)	1–2 h	1.34–1.53 h
Bioavailability	~87%	85%	>75 %[4]	N/A	29.5%
Half-life ($t_{1/2}$) at clinically relevant dose	12.4 h	~2–3 h	2.5 h (parent) 3.1 h (metabolite)	12.4–21.4 h (25–800 mg)	113–131 h (1–10 mg)
Distribution	38% protein bound	9.3% protein bound	Low protein binding	N/A	Prominent concentration-dependent protein binding: <1 nM: ~99% >100 nM: 70%–80%
Metabolism	~16% metabolized	69% metabolized mainly renal (inactive metabolite)	Hepatic (active metabolite) CYP3A4/5	<8% metabolized	~10% metabolized
Elimination	**Renal 87% (79% unchanged)**	Renal 85% (23% unchanged)	Renal 75% (24% as parent; 36% as active metabolite)	Renal (60%–71% unchanged)	Feces 81.5% (74.1% unchanged); Renal 5.4% (3.9% unchanged)

DPP-4=dipeptidyl peptidase-4.

[a]Pharmacokinetic studies were performed in different assay systems and should not be compared.

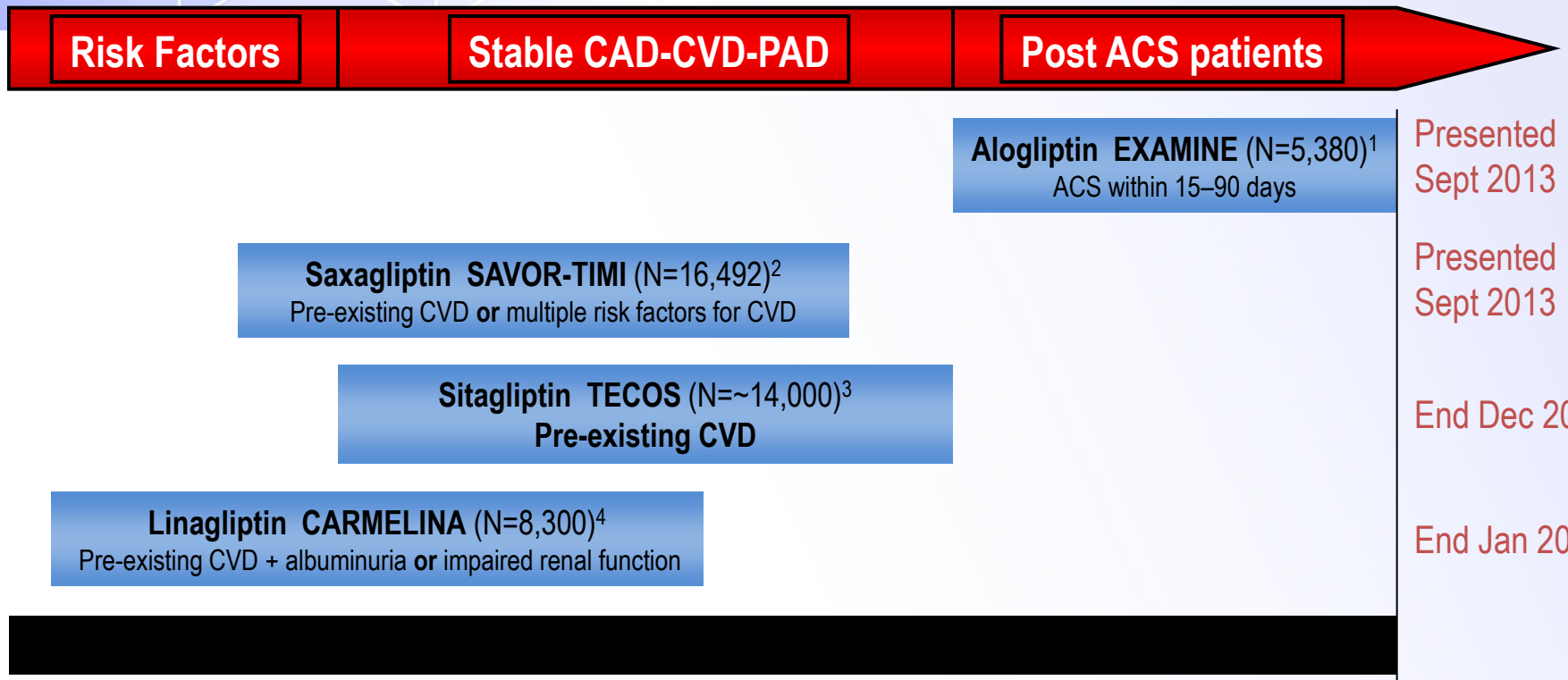
1. Data on file, MSD. **2.** EU-SPC for Galvus, 2010. **3.** EU-SPC for Onglyza, 2010. **4.** EPAR for Onglyza. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/001039/WC500044319.pdf. Accessed May 4, 2011. **5.** Christopher R et al. *Clin Ther*. 2008;30:513–527. **6.** Heise T et al. *Diabetes Obes Metab*. 2009;11:786–794. **7.** Reitlich S et al. *Clin Pharmacokinet*. 2010;49:829–840. **8.** Fuchs H et al. *J Pharm Pharmacol*. 2009;61:55–62. **9.** Blech S et al. *Drug Metab Dispos*.2010;38:667–678.

Jediná cesta, jak prokázat účinek inhibitorů DPP4 na kardiovaskulární příhody, jsou dostatečně silné, randomizované, kontrolované studie

Sitagliptin TECOS[1]	Start: Dec 2008 Projected completion: Dec 2014 N=14,000	Trial Evaluating Cardiovascular Outcomes With Sitagliptin **Primary Outcome:** Time to first confirmed occurrence of CV event , a composite defined as CV-related death, nonfatal MI, nonfatal stroke, or unstable angina requiring hospitalization
Alogliptin EXAMINE[2,5]	Start: Sept 2009 Projected completion: May 2015 N=5,400	Examination of Cardiovascular Outcomes: Alogliptin vs Standard of Care in Patients With Type 2 Diabetes Mellitus and Acute Coronary Syndrome **Primary Outcome:** Time from randomization to the occurrence of the primary major adverse cardiac events, a composite of CV death, nonfatal MI, and nonfatal stroke
Saxagliptin SAVOR[3,6]	Start: May 2010 Projected completion: June 2014 N=16,500	Saxagliptin Assessment of Vascular Outcomes Recorded in Patients With Diabetes Mellitus Trial **Primary Outcome:** The primary efficacy outcome variable of the study is defined as the composite end point of CV death, nonfatal MI, or nonfatal ischemic stroke
Linagliptin CAROLINA[4]	Start: Oct 2010 Projected completion: Sept 2018 N=6,000	Cardiovascular Outcome Study of Linagliptin vs Glimepiride in Patients With Type 2 Diabetes **Primary Outcome:** Time to first occurrence of any component of the composite end point: CV death, nonfatal MI, nonfatal stroke, and hospitalization for unstable angina pectoris
Vildagliptin	• **Vildagliptin nemá žádnou probíhající studii na CV dopady**	

Aguilar D American Heart Journal 2011; doi:10.1016/j.ahj.2011.08.016

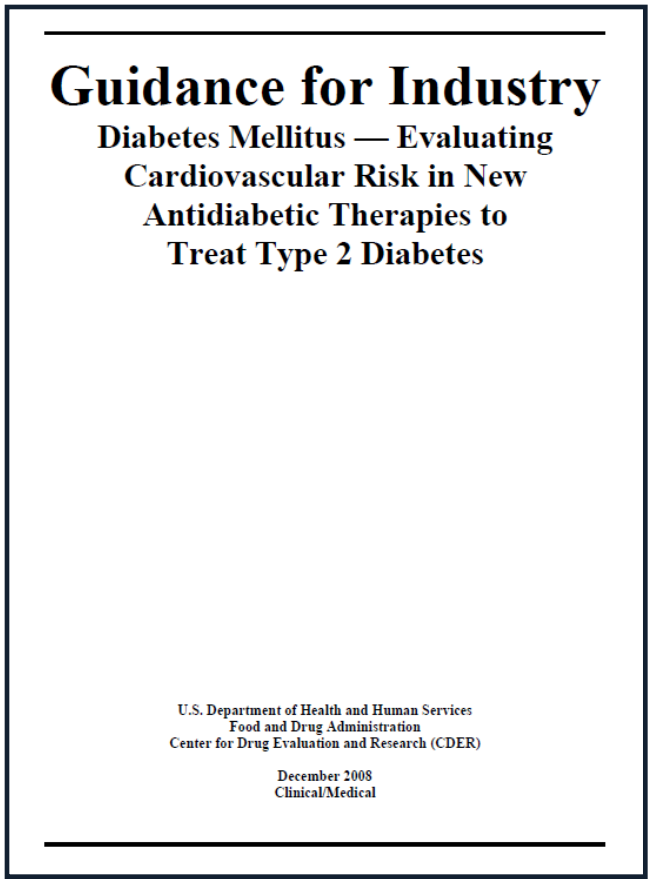
Riziko KV kardiovask. příhod ve skupinách v klinických studiích s inhibitory DPP-4



Examination of Cardiovascular Outcomes: Alogliptin vs Standard of Care in Patients With Type 2 Diabetes Mellitus and Acute Coronary Syndrome; SAVOR-TIMI = Saxagliptin Assessment of Vascular Outcomes Recorded in Patients With Diabetes Mellitus Trial-Thrombolysis in Myocardial Infarction; TECOS = Trial Evaluating Cardiovascular Outcomes With Sitagliptin; CARMELINA = Cardiovascular and Renal Microvascular Outcome Study With Linagliptin in Patients With Type 2 Diabetes Mellitus at High Vascular Risk.

1. White W et al. *N Engl J Med*. 2013;369:1327–1335. **2.** Scirica BM et al. *N Engl J Med*. 2013;369:1317–1326. **3.** Green JB et al. *Am Heart J* 2013;166:983–989.e7. **4.** CARMELINA: Cardiovascular and renal microvascular outcome study with linagliptin in patients with type 2 diabetes mellitus at high vascular risk. ClinicalTrials.gov web site. http://clinicaltrials.gov/ct2/show/NCT01703298. Accessed September 12, 2014.

FDA požadavky na kardiovaskulární cíle s novými perorálními antidiabetiky



Guidance for Industry

Diabetes Mellitus — Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes

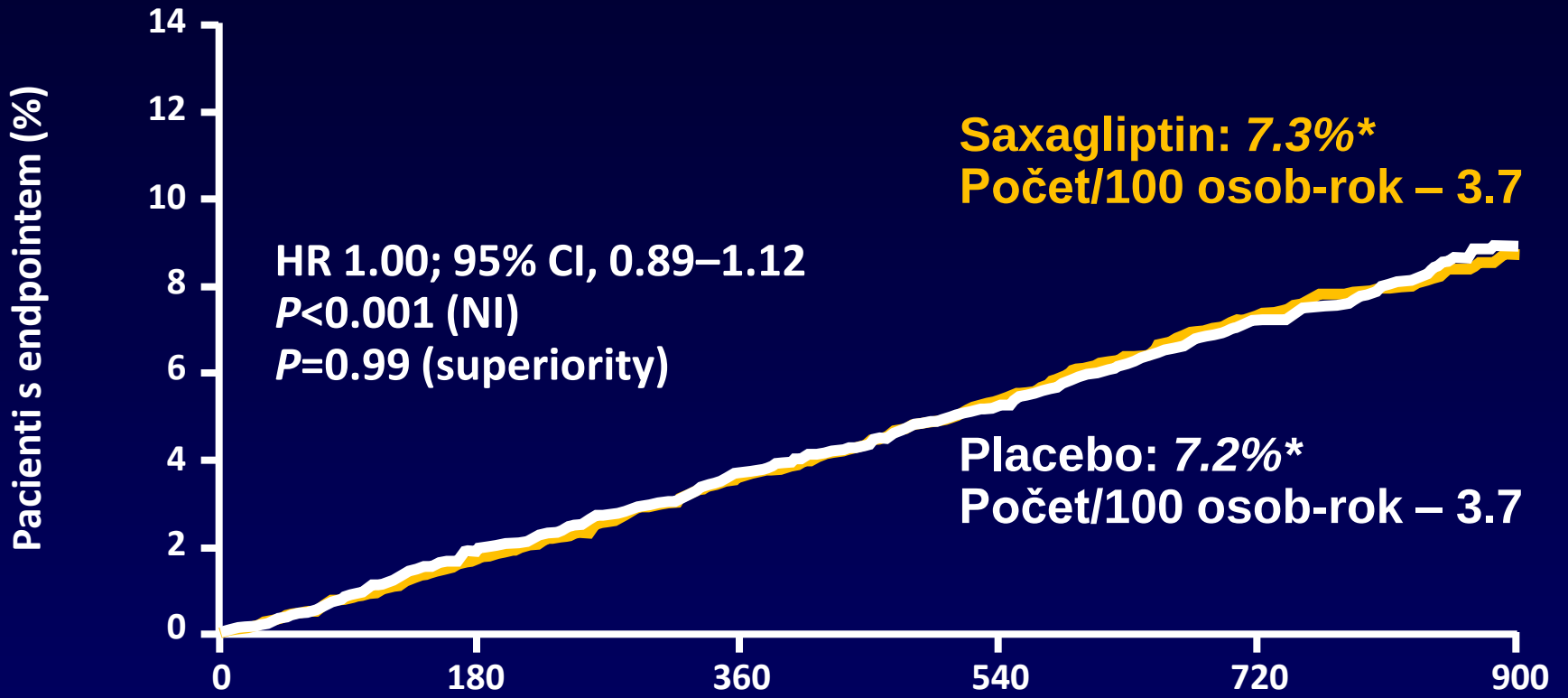
U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

December 2008
Clinical/Medical

2008 FDA doporučení pro perorální antidiabetika zdůrazňují nutnost kardiovaskulární bezpečnosti (účinnosti) před samotným snížením glykémie.

FDA Guidance for Industry. Diabetes mellitus – evaluating cardiovascular risk in new antidiabetic therapies to treat type 2 diabetes. Available from: www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071627.pdf [Accessed Jan 2014]

Primární cíl SAVOR – KV úmrtí, nefatální IM, nefatální ischemická CMP



Placebo	8212	7983	7761	7267	4855	851
Saxagliptin	8280	8071	7836	7313	4920	847

*K-M event rates are presented after 2 yrs.

HR: hazard ratio; K-M: Kaplan-Meier; Pbo: placebo; Saxa: saxagliptin

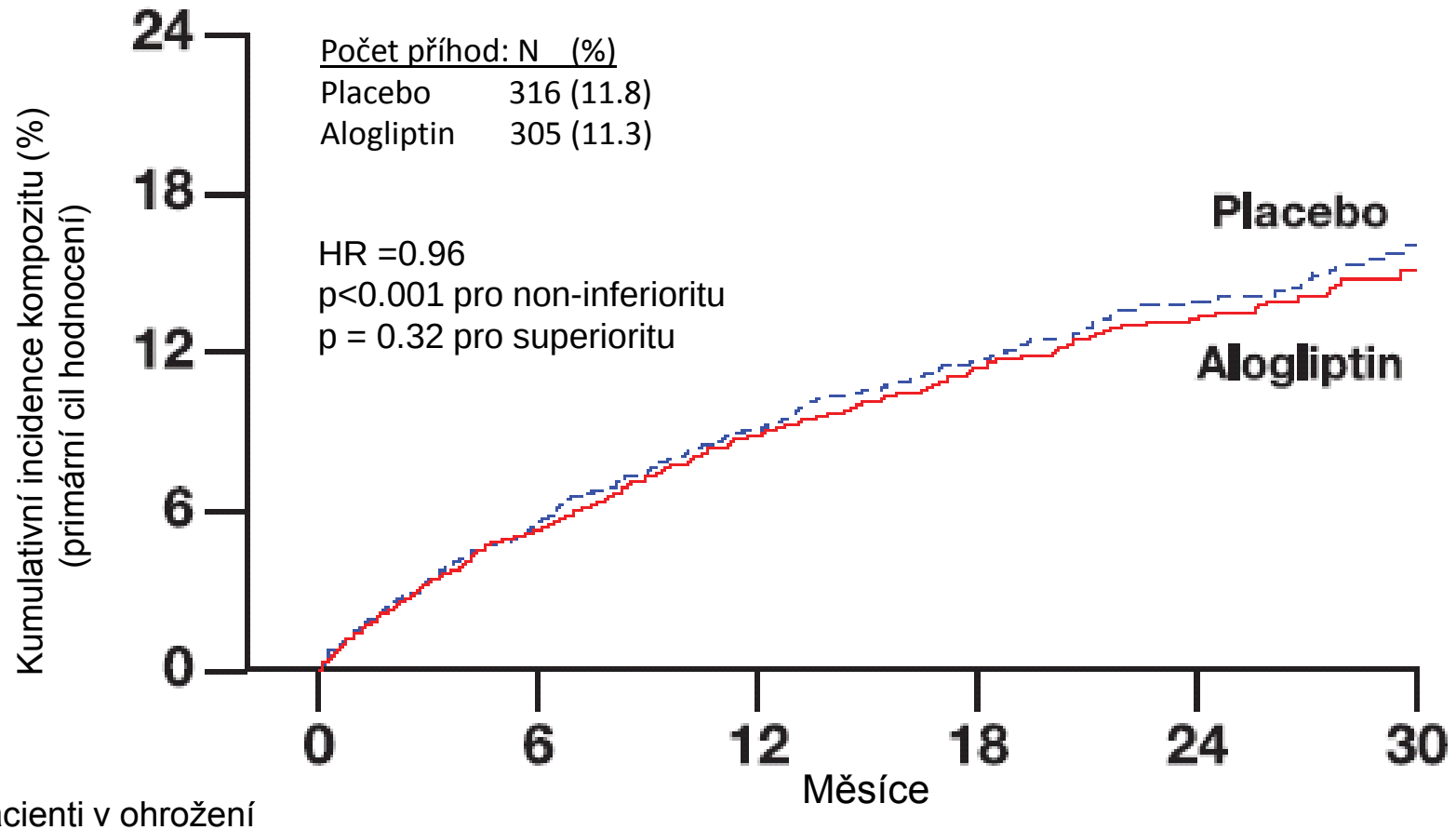
Scirica BM, et al. *N Engl J Med.* 2013.10.1056/NEJMoa1307684.

Jednotlivé součásti sekundárního cíle - SAVOR

Účinnost	Saxagliptin n (%)* (N = 8,280)	Placebo n (%)* (N = 8,212)	HR (95% CI)	*P* value
KV úmrtí	269 (3.2)	260 (2.9)	1.03 (0.87–1.22)	0.72
IM	265 (3.2)	278 (3.4)	0.95 (0.80–1.12)	0.52
Ischemická CMP	157 (1.9)	141 (1.7)	1.11 (0.88–1.39)	0.38
Hosp pro NAP	97 (1.2)	81 (1.0)	1.19 (0.89–1.60)	0.24
Hosp pro SS	289 (3.5)	228 (2.8)	1.27 (1.07–1.51)	0.007
Hosp pro koron. revasc.	423 (5.2)	459 (5.6)	0.91 (0.80–1.04)	0.18

Scirica BM, et al. *N Engl J Med.* 2013.10.1056/NEJMoa1307684.

Alogliptin + standardní léčba ve srovnání s placebem + standardní léčbou nezvyšuje výskyt MACE - EXAMINE primární cíl



Pacienti v ohrožení

Placebo (n):	2679	2299	1891	1375	805	286
Alogliptin (n):	2701	2316	1899	1394	821	296

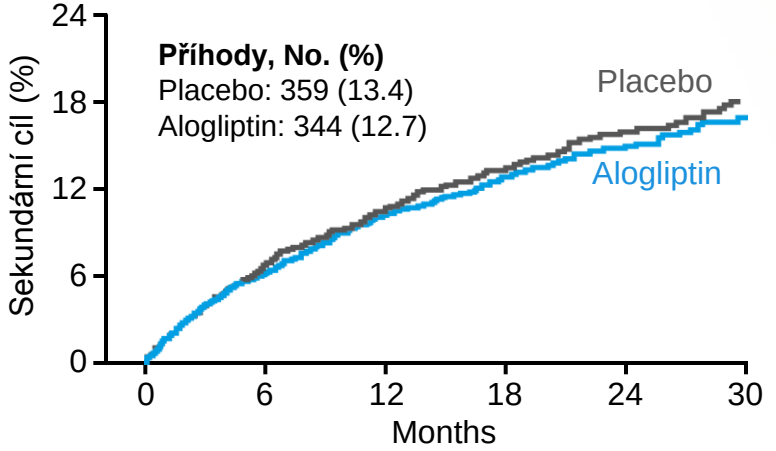
MACE: závažné kardiovaskulární příhody (CV úmrtí, nefatální infarkt myokardu, nefatální mozková mrtvice)

White WB, et al. *N Engl J Med* 2013;369:1327–1335

Sekundární cíle EXAMINE

Sekundární cíl

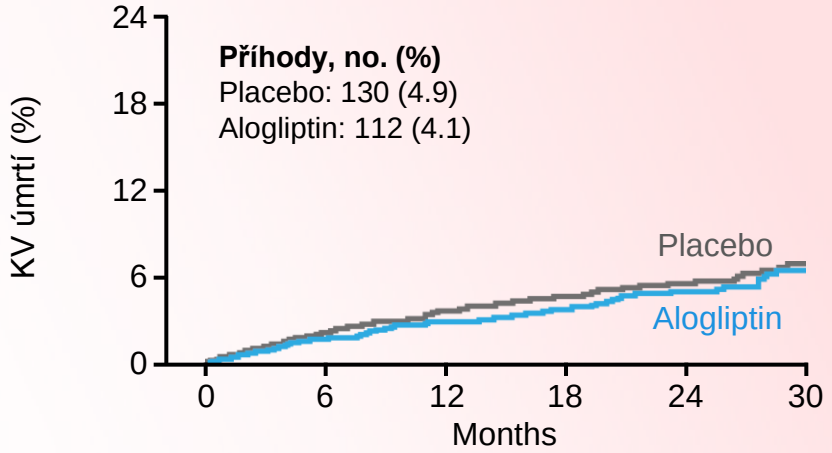
Hazard ratio, 0.95 (*one-sided repeated CI bound, 1.14)



Placebo (n):	2679	2275	1861	1345	784	278
Alogliptin (n):	2701	2297	1873	1373	806	287

KV úmrtí

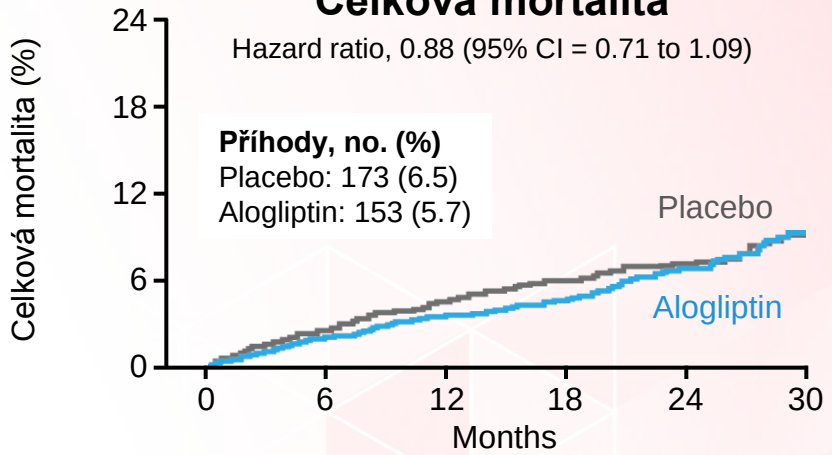
Hazard ratio, 0.85 (95% CI = 0.66 to 1.10)



Placebo (n):	2679	2384	1996	1477	889	324
Alogliptin (n):	2701	2402	2023	1504	894	320

Celková mortalita

Hazard ratio, 0.88 (95% CI = 0.71 to 1.09)



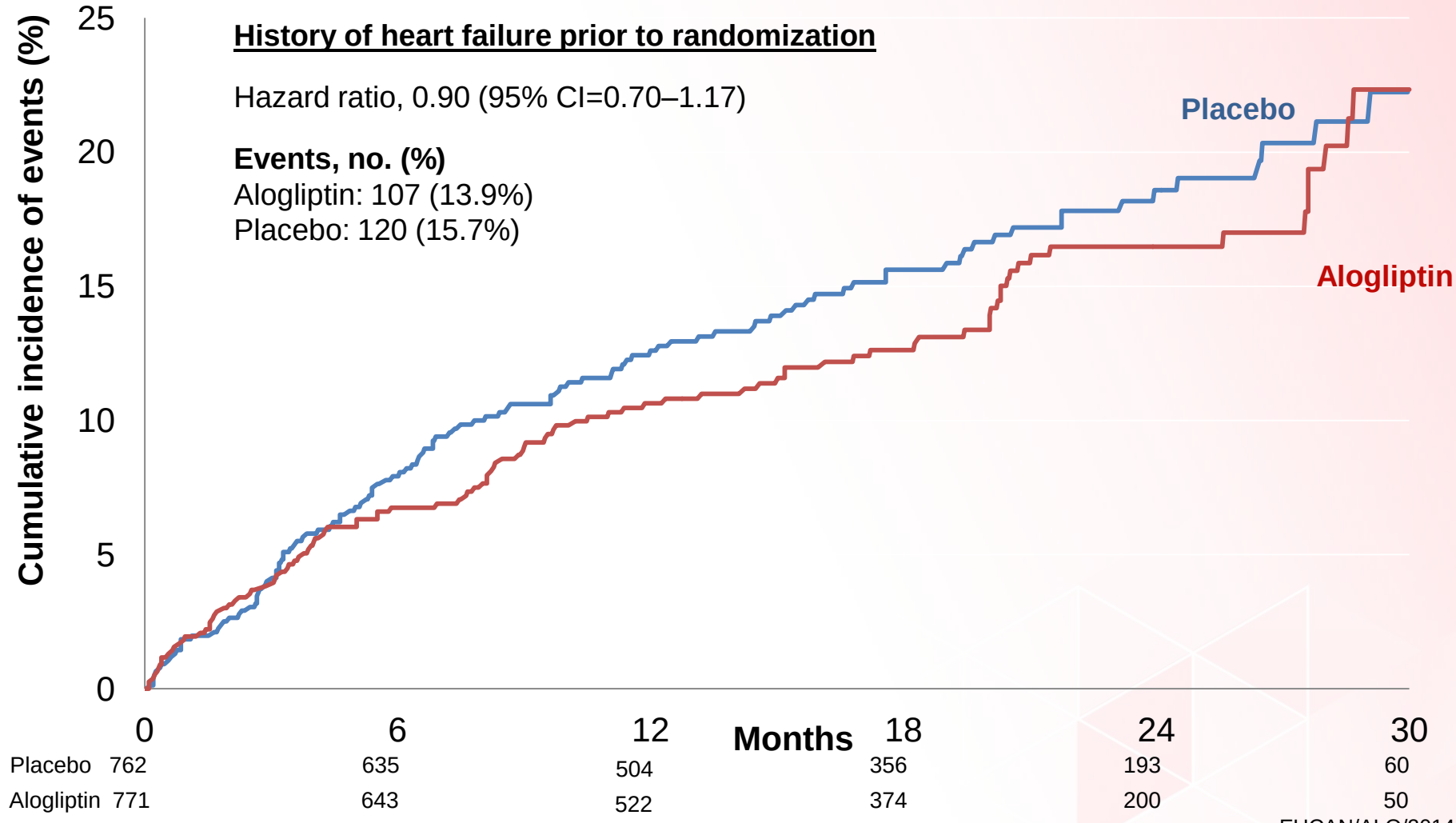
Placebo (n):	2679	2384	1996	1477	889	324
Alogliptin (n):	2701	2401	2023	1504	894	320

* Using alpha=0.01.

White WB et al. *N Engl J Med* 2013;369:1327–1335

EUCAN/ALO/2014-10030
February 2014

KV úmrtí a hospitalizace pro SS podle anamnézy SS před randomizací EXAMINE



Zannad F, et al. *Lancet.* 2015, Mar 9, [Epub ahead of print]; doi: 10.1016/S0140-6736(14)62225-X

EUCAN/ALO/2014-10030
February 2014

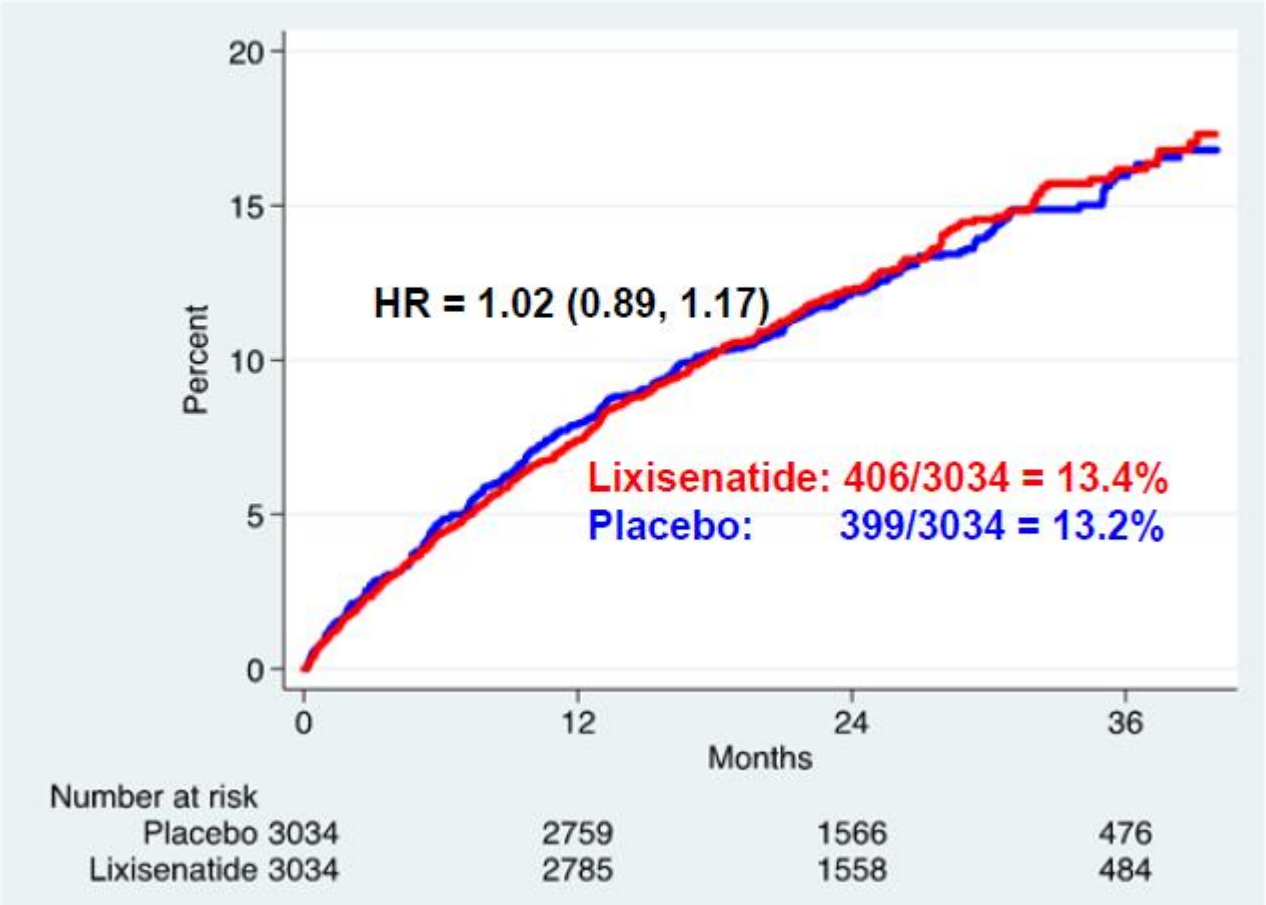
KV úmrtí nebo hospitalizace pro SS podle anamnézy SS před randomizací EXAMINE

	Všichni pac.		Anam.SS		Bez anam. SS	
	Alo 2701	Plac 2679	Alo 771	Plac 769	Alo 1930	Plac 1917
KV úmrtí	4,1%	4,9%	7,1%	7,9%	3,0%	3,2%
p	0,212		0,508		0,643	
SS hosp	3,9%	3,3%	8,2%	8,5%	2,2%	1,3%
p	0,220		0,996		**0,026**	

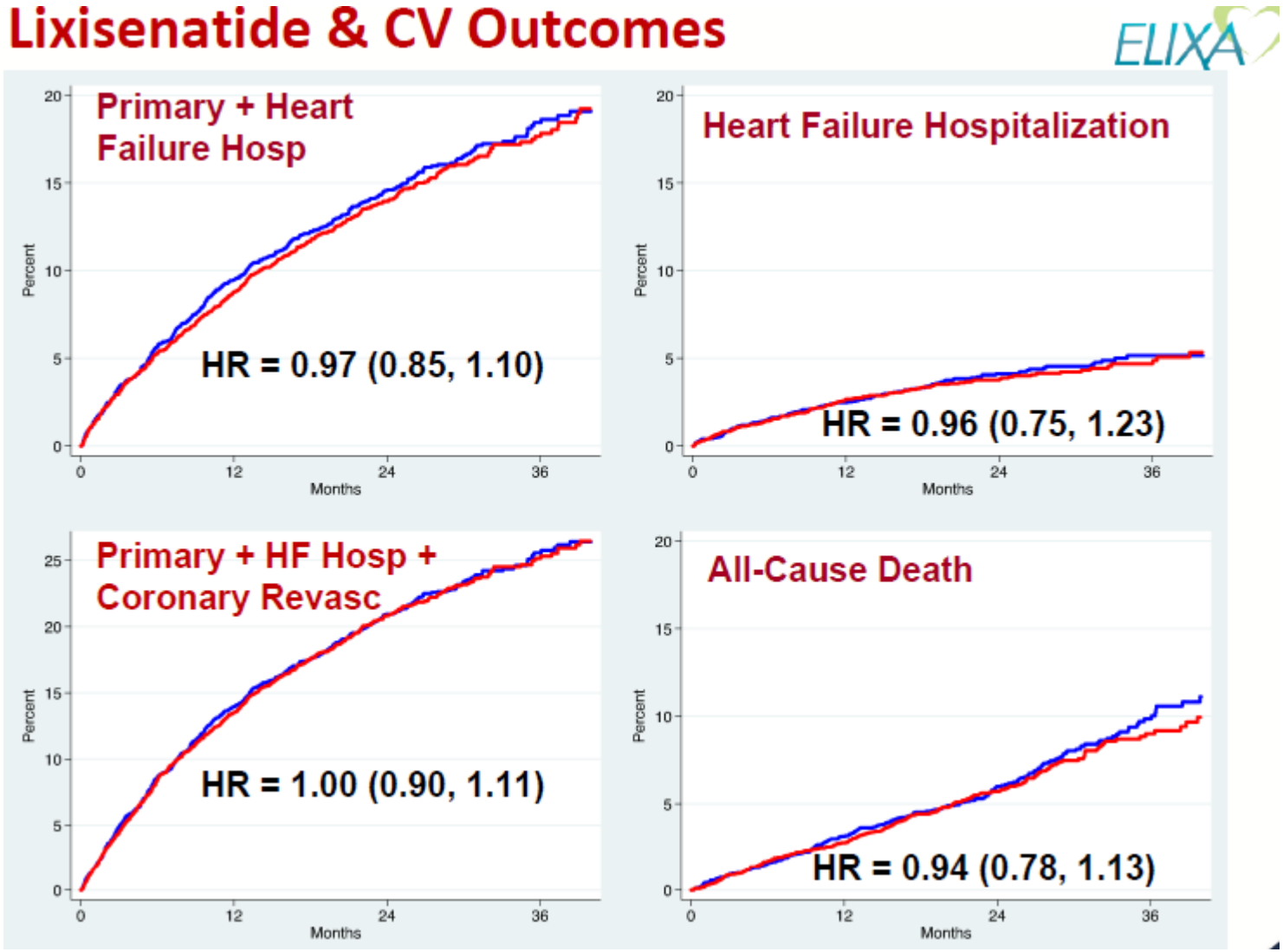
Lixisenatide + standardní léčba ve srovnání s placebem + standardní léčbou nezvyšuje výskyt MACE

1°Outcome (CV Death, MI, Stroke or UA)

ELIXA

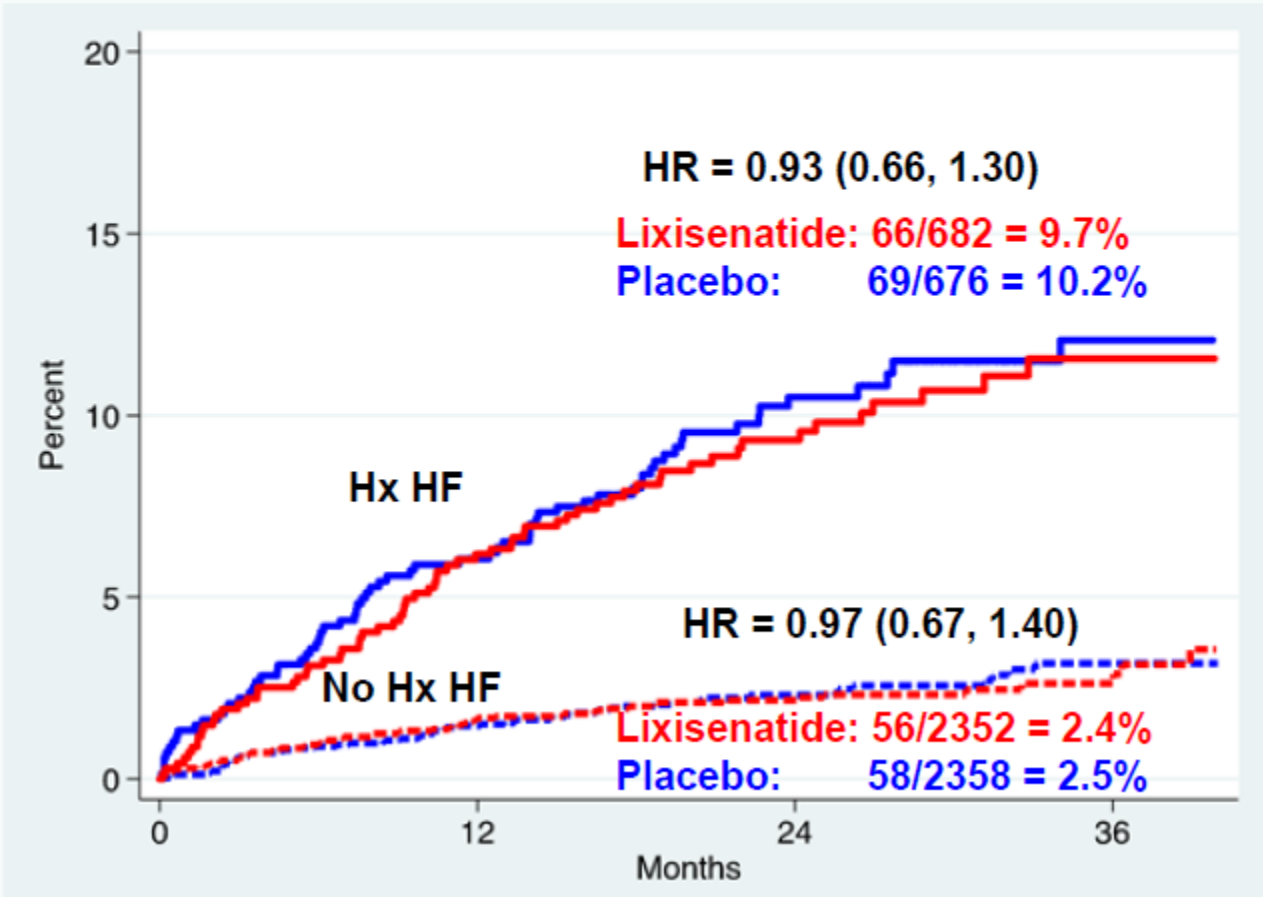


Lixisenatide + standardní léčba ve srovnání s placebem + standardní léčbou nezvyšuje výskyt MACE



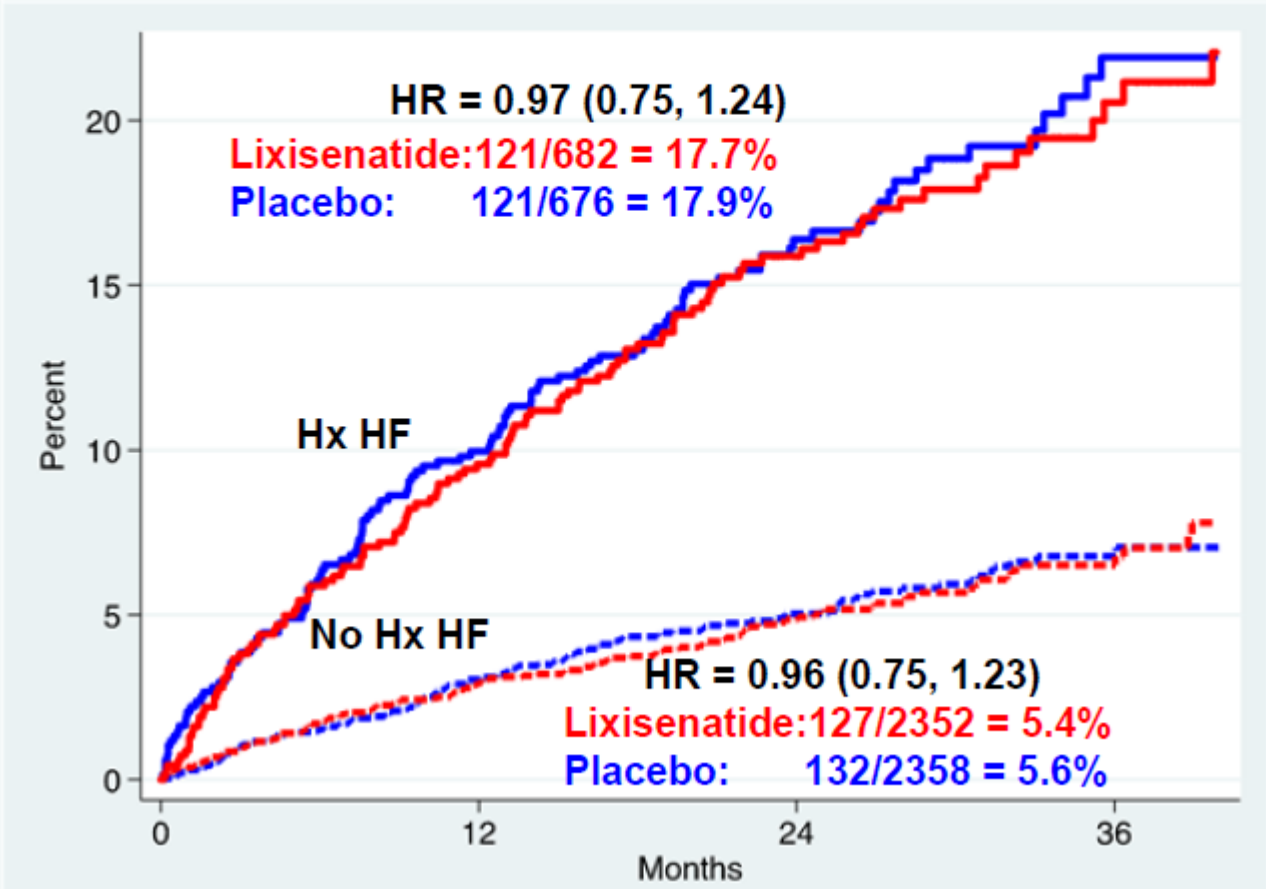
Lixisenatide + standardní léčba ve srovnání s placebem + standardní léčbou nezvyšuje hospitalizaci pro SS

Heart Failure Hospitalization (by History of HF)



Lixisenatide + standardní léčba ve srovnání s placebem + standardní léčbou nezvyšuje hospitalizaci pro SS

CV Death + Heart Failure Hospitalization (by history of HF)



Trial Evaluating Cardiovascular Outcomes With Sitagliptin (TECOS)

KV onemocnění při zařazení do studie

Characteristic	Sitagliptin n=7332	Placebo n=7339
Předchozí KV onemocnění	5397 (73.6%)	5466 (74.5%)
Infarkt myokardu	3133 (42.7%)	3122 (42.5%)
PCI	2814 (38.9%)	2900 (40.1%)
CABG	1845 (25.2%)	1819 (24.8%)
≥50% koronární stenóza	3804 (51.9%)	3883 (52.9%)
Předchozí cerebrovask.onemocnění	1806 (24.6%)	1782 (24.3%)
CMP	1297 (17.7%)	1258 (17.1%)
TIA	280 (3.8%)	286 (3.9%)
≥50% stenóza karotidy	431 (5.9%)	429 (5.8%)
Ischemická choroba DKK	1217 (16.6%)	1216 (16.6%)
Anamnéza srdečního selhání	1303 (17.8%)	1340 (18.3%)

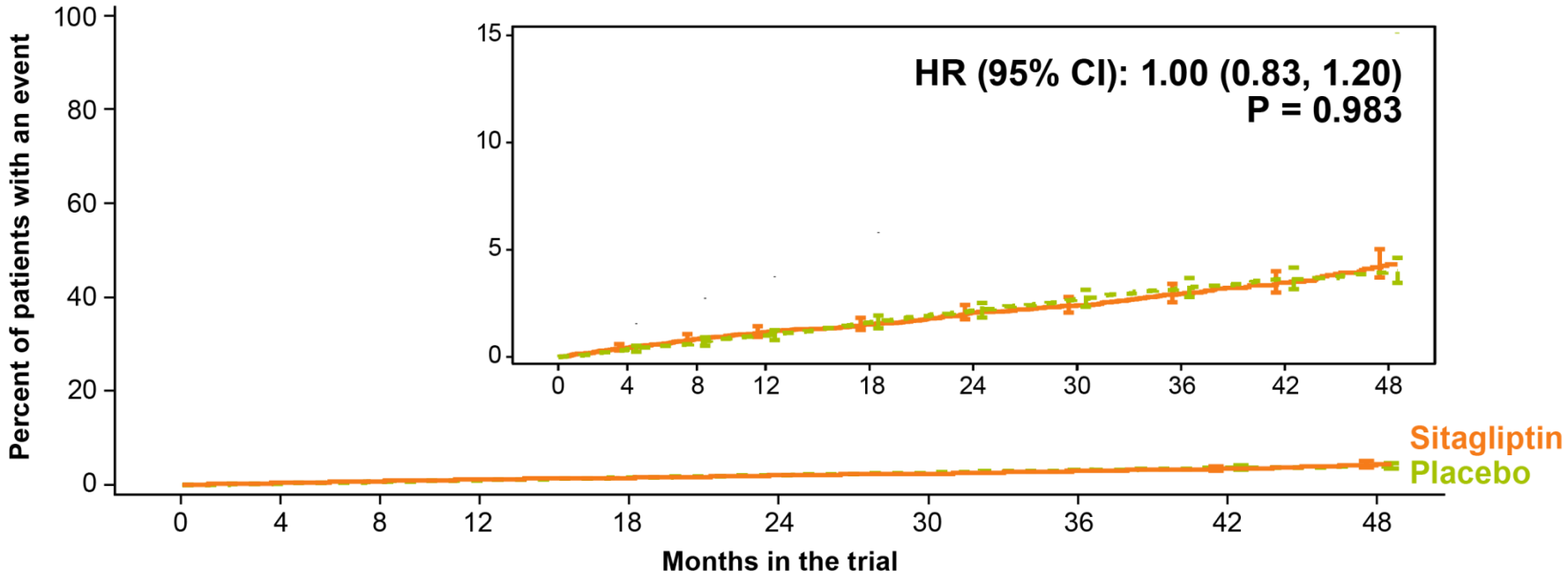
Green JB et al. NEJM 2015; DOI: 10.1056/NEJMoa1501352

Primární KV výsledky pro ITT populaci

Počet pacientů s příhodou	Sitagliptin n=7332	Placebo n=7339
Primární složený KV cíl	**839 (11.4%)**	**851 (11.6%)**
	4.06 *per* 100 pyrs	4.17 *per* 100 pyrs
	ITT HR=0.98 (0.89, 1.08), p=0.65	
Individuální komponenty		
• KV úmrtí	311 (4.2%)	291 (4.0%)
• Nefatální IM	275 (3.8%)	286 (3.9%)
• Nenfatální CMP	145 (2.0%)	157 (2.1%)
• Hospitalizace pro nestabilní anginu	108 (1.5%)	117 (1.6%)

Green JB et al. NEJM 2015; DOI: 10.1056/NEJMoa1501352

Hospitalizace pro srdeční selhání * analýza ITT



Patients at risk:										
Sitagliptin	7,332	7,189	7,036	6,917	6,780	6,619	4,728	3,515	2,175	1,324
Placebo	7,339	7,204	7,025	6,903	6,712	6,549	4,599	3,443	2,131	1,315

** Adjusted for history of heart failure at baseline*

Green JB et al. NEJM 2015; DOI: 10.1056/NEJMoa1501352

Hospitalizace pro srdeční selhání * analýza ITT

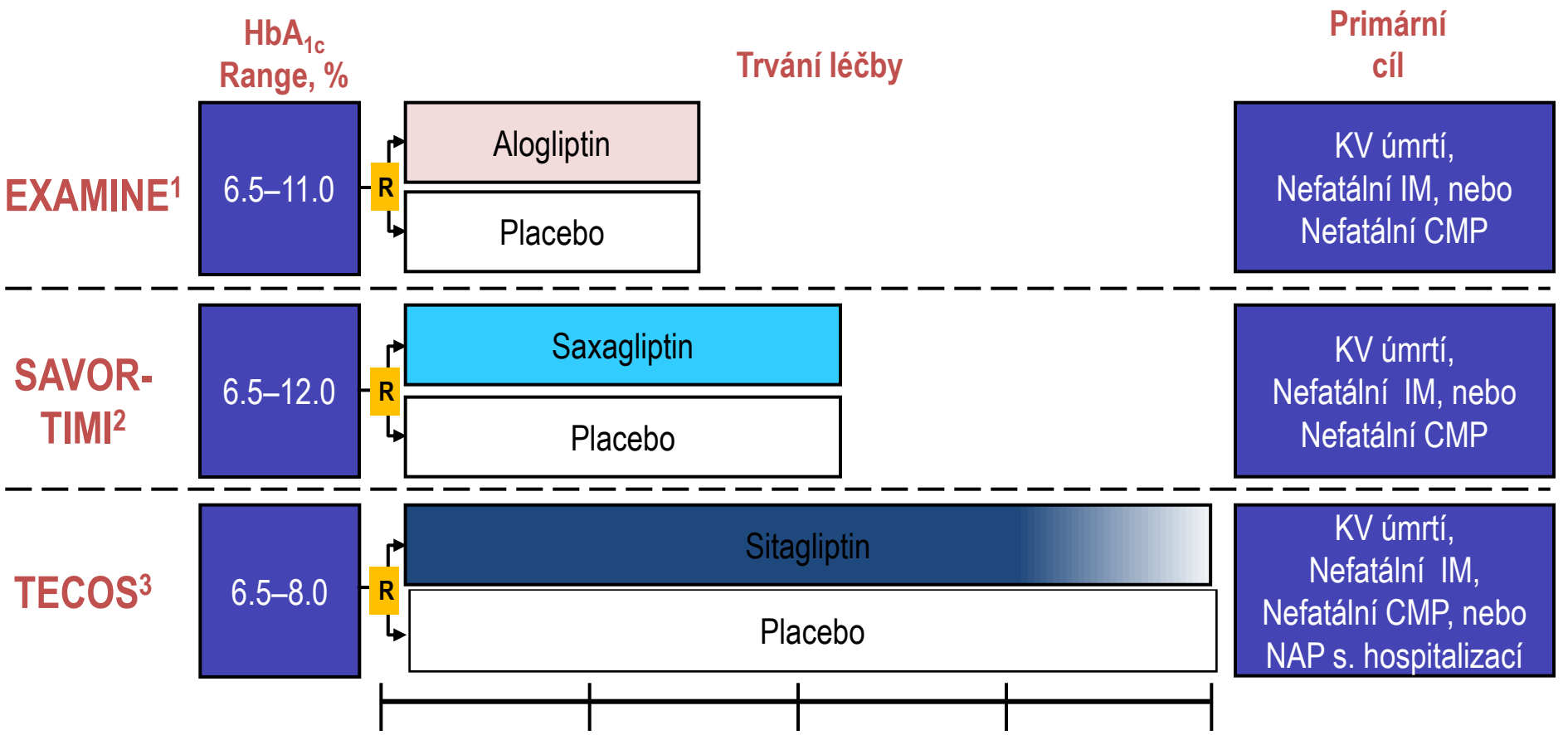
Počet pacientů s příhodou	**Sitagliptin** n=7332	**Placebo** n=7339
Hospitalizace pro srdeční selhání†	**228 (3.1%)**	**229 (3.1%)**
	1.09 *per* 100 pac.let	1.00 *per* 100 pac.let
	ITT HR=1.00 (0.83, 1.20), p=0.98	
Hospitalizace pro srdeční selhání nebo KV úmrtí †	**538 (7.3%)**	**525 (7.2%)**
	2.54 *per* 100 pac.let	2.50 *per* 100 pac.let
	ITT HR=1.02, (0.90, 1.15), p=0.74	

* *Adjusted for history of heart failure at baseline*

† *Prespecified analyses*

Green JB et al. NEJM 2015; DOI: 10.1056/NEJMoa1501352

EXAMINE, SAVOR-TIMI a TECOS srovnání

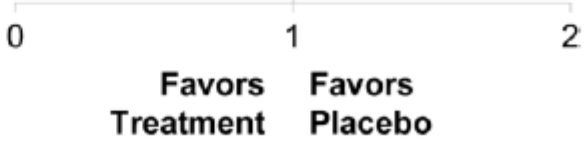


EXAMINE = Examination of Cardiovascular Outcomes: Alogliptin vs Standard of Care in Patients With Type 2 Diabetes Mellitus and Acute Coronary Syndrome;
SAVOR-TIMI = Saxagliptin Assessment of Vascular Outcomes Recorded in Patients With Diabetes Mellitus Trial-Thrombolysis in Myocardial Infarction;

2. Scirica BM et al. *N Engl J Med* 2013;369:1317–1326. Green JB et al. *Am Heart J.* 2013;166:983–989.e7.

SAVOR-TIMI 53, EXAMINE, and TECOS*: Hospitalization for Heart Failure

Trial	HR (95% CI)	P-Value
SAVOR-TIMI 53	1.27 (1.07–1.51)	0.007
EXAMINE	1.19 (0.89–1.59)	0.235
TECOS	1.00 (0.84–1.20)	1.000
SAVOR-TIMI 53 + EXAMINE + TECOS	1.14 (0.97–1.34)	0.102



Test for heterogeneity for 3 trials: p=0.16, I^2=44.9

TECOS TRIAL EVALUATING CARDIOVASCULAR

*

White WB, et al. *N Engl J Med* 2013;369:1327–1335; Mosenzon WB, et al. *Diabetes Metab Res Rev* 2013;29:417–426; Scirica BM, et al. *N Engl J* Med. 2013 Oct 3;369(14):1317–26

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Multicenter Observational Study of Incretin-based Drugs and Heart Failure

Kristian B. Filion, Ph.D., Laurent Azoulay, Ph.D., Robert W. Platt, Ph.D.,

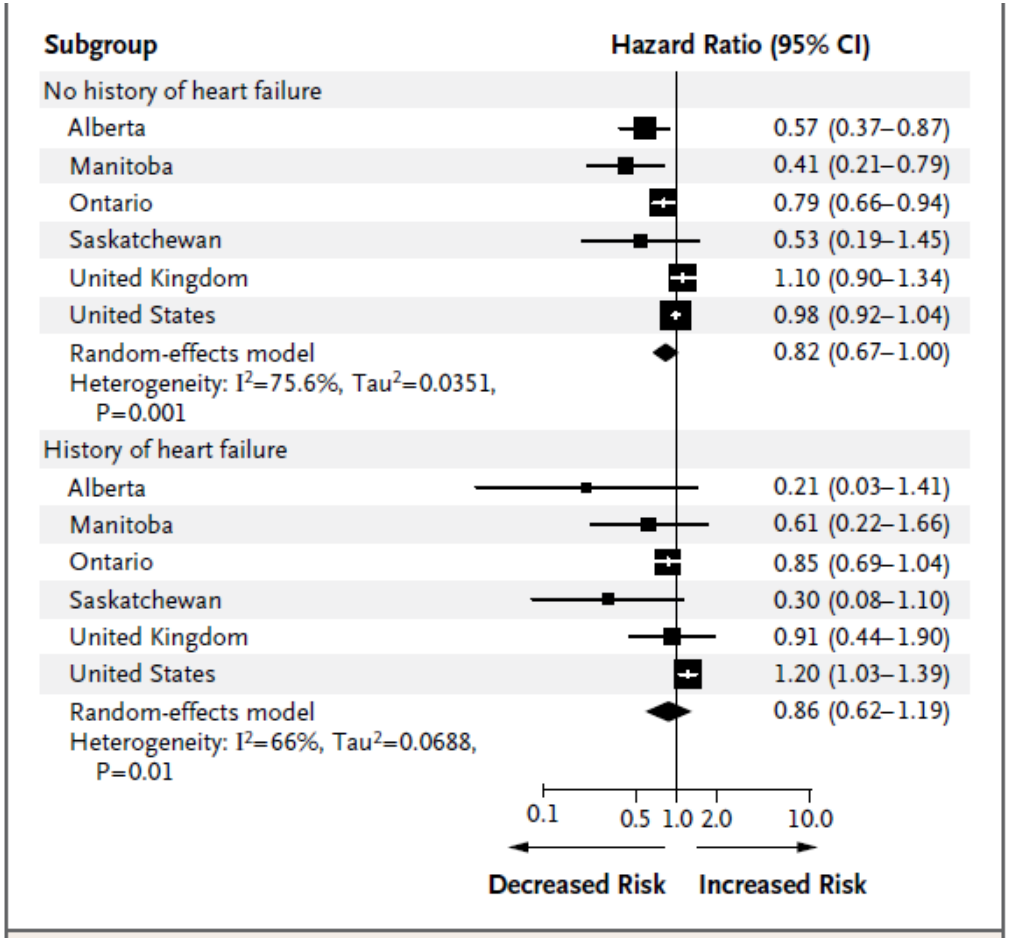


Figure 2. Association between Treatment with Incretin-based Drugs and the Risk of Hospitalization for Heart Failure among Patients with and Those without a History of Heart Failure.

n = 23 205

n = 6 536

NEJM 2016 374;12:1145-54,

Děkuji vám za pozornost