Hypokretin/orexinový systém a riziko úmrtí po IM

Peter Wohlfahrt, Dominik Jenča, Dana Dlouhá, Vojtěch Melenovský, Petr Jarolím, Marek Šramko, Martin Kotrč, Michael Želízko, Jolana Mrázková, Jan Piťha, Věra Adámková, Josef Kautzner

IKEM, Praha
Brigham and Women's Hospital, Boston, USA

JAHA
Journal of the American Heart Association

OPEN ACCESS
RESEARCH ARTICLE

Attenuation of Hypocretin/Orexin Signaling Is Associated With Increased Mortality After Myocardial Infarction

Peter Wohlfahrt, Dominik Jenča, Vojtěch Melenovský, Petr Jarolím, Dana Dlouhá, Marek Šramko, Martin Kotrč, Michael Želízko, Jolana Mrázková, Jan Piťha, Věra Adámková and Josef Kautzner

Originally published 9 Mar 2023 | https://doi.org/10.1161/JAHA.122.028987 | Journal of the American Heart Association. 2023;12:e028987

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Abstract

Background

The hypocretin/orexin system has been shown to play a role in heart failure. Whether it also influences myocardial infarction (MI) outcomes is unknown. We evaluated the effect of the rs7767652 minor allele T associated with decreased transcription of the hypocretin/orexin receptor-2 and circulating orexin A concentrations on mortality risk after MI.

Methods and Results

Data from a single-center, prospectively designed registry of consecutive patients hospitalized for MI at a large tertiary cardiology center were analyzed. Patients without previous history of MI or heart failure were included. A random population sample was used to compare allele frequencies in the general population. Out of 1009 patients (aged 64±12 years, 74.6% men) after MI, 6.1% were homozygotes (TT) and 39.4% heterozygotes (CT) for minor allele. Allele frequencies in the MI group did not differ from 1953 subjects from general population ($\chi^2 P$=0.62). At index hospitalization, MI size was the same, but ventricular fibrillation and the need for cardiopulmonary resuscitation were more prevalent in the TT allele variant. Among patients with ejection fraction ≤40% at discharge, the TT variant was associated with a lower increase in left ventricular ejection fraction during follow-up (P=0.03). During the 27-month follow-up, there was a statistically significant association of the TT variant with increased mortality risk (hazard ratio [HR] 2.83; P=0.001). Higher circulating orexin A was associated with a lower mortality risk (HR 0.41; P<0.05)

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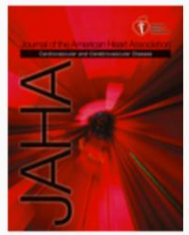
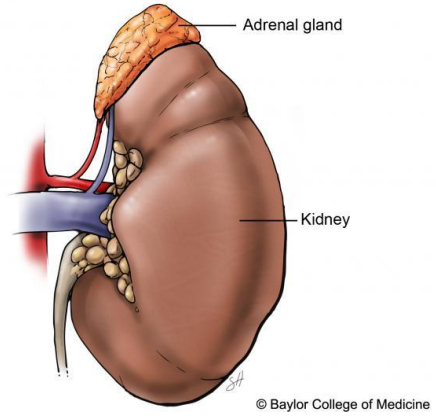


March 21, 2023
Vol 12, Issue 6

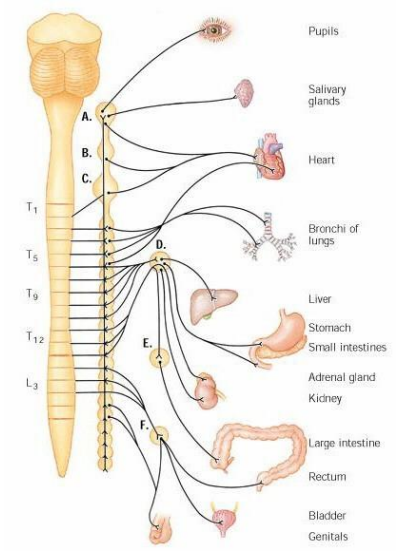
Atitrombotická terapie

Hypolipidemická terapie



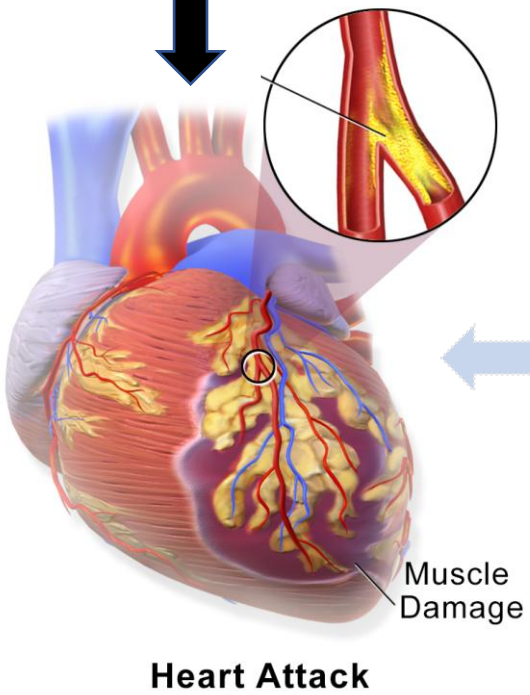
Renin-angiotensin aldosteron

ACEi, aldosterone ant.

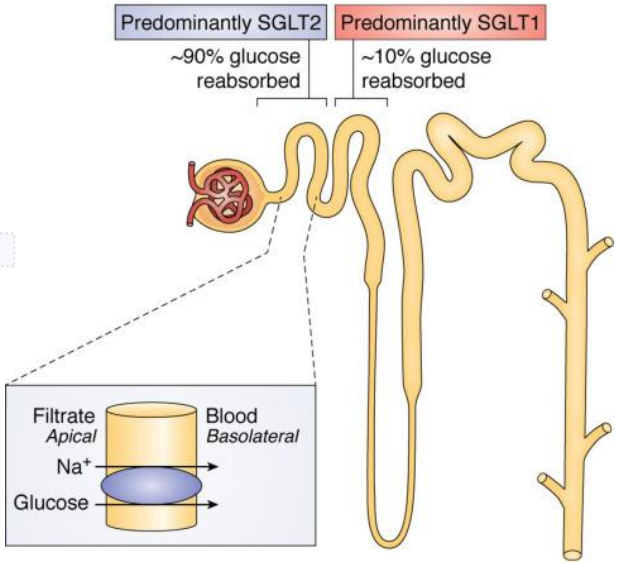


Sympathetic system

β-blockers



SGLT2i



Prognóza pacientů po STEMI

1. rok po IM

- 20-30 % srdeční selhání

- 14-23 % mortalita, 16.1 YLL

Jiné patofyziologické cesty, které ovlivňují prognózu po IM

Tsao CW et al. Circulation. 2022 Feb 22;145(8):e153-e63

Hypokretin/orexinový systém

LIFE SCIENCES BREAKTHROUGH PRIZE

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LAUREATES

Masashi Yanagisawa

University of Tsukuba

2023 Breakthrough Prize in Life Sciences

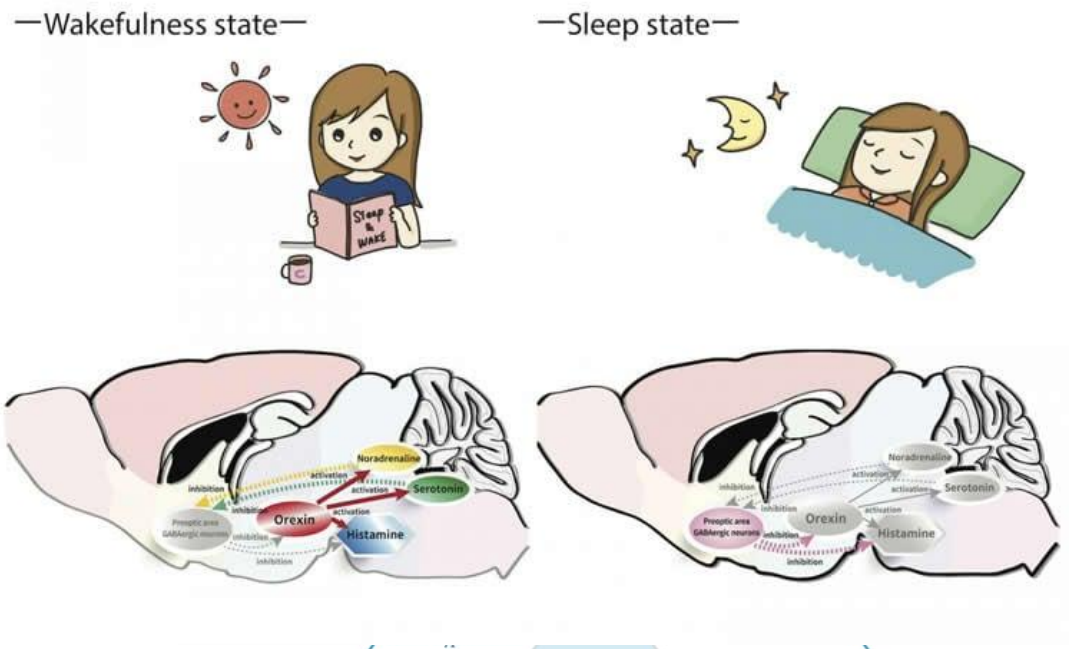
For discovering that narcolepsy is caused by the loss of a small population of brain cells that make a wake-promoting substance, paving the way for the development of new treatments for sleep disorders.

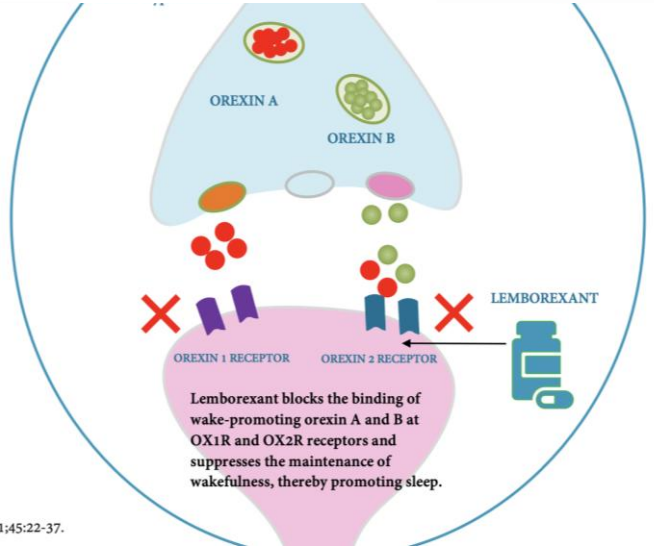
Emmanuel Mignot

Stanford University School of Medicine

2023 Breakthrough Prize in Life Sciences

For discovering that narcolepsy is caused by the loss of a small population of brain cells that make a wake-promoting substance, paving the way for the development of new treatments for sleep disorders.



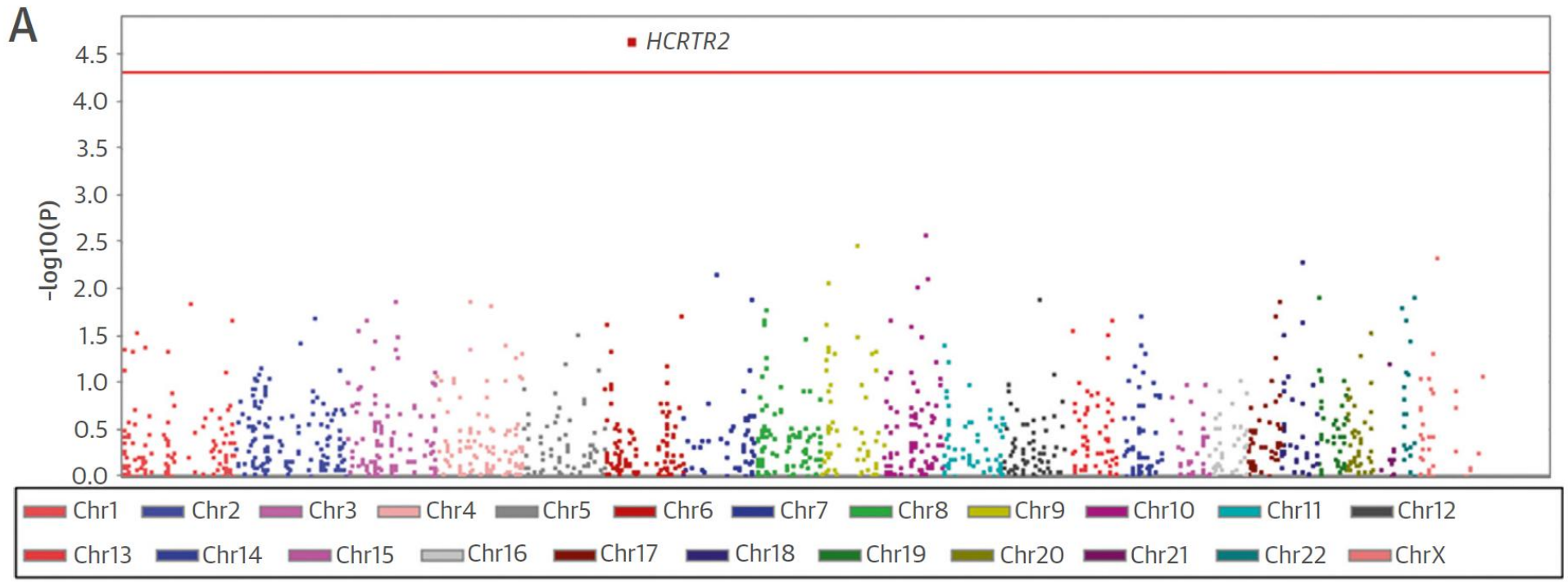


1;45:22-37.

Hypokretin/orexinový systém u HF

Genetická analýza variant spojených s odpovědí na farmakoterpaii HF

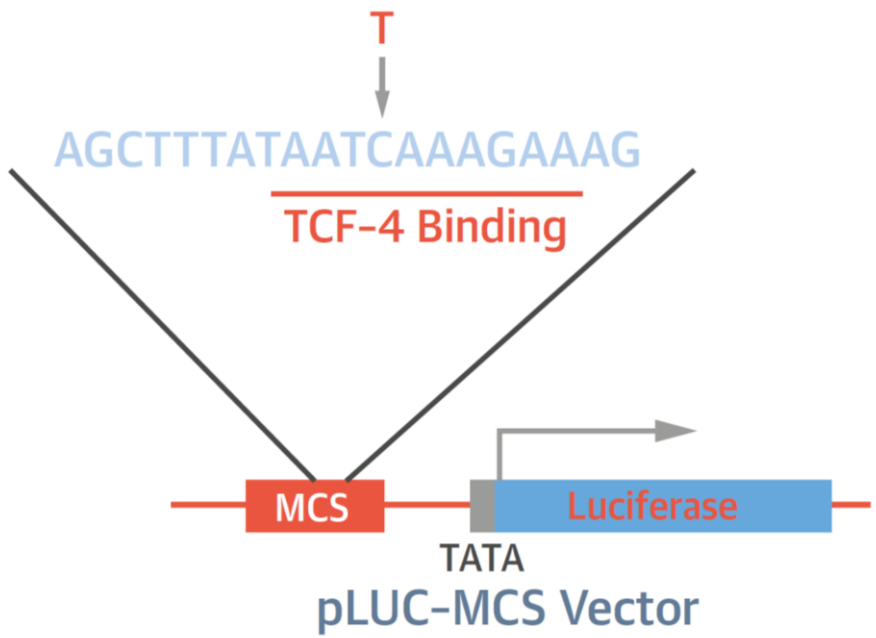
Minoritní alela T rs7767652 v regulační oblasti pro OR2 je spojena s nižší pravděpodobností zlepšení EF
odds ratio: 0.40 per minor allele; $p = 3.29 \times 10^{-5}$).



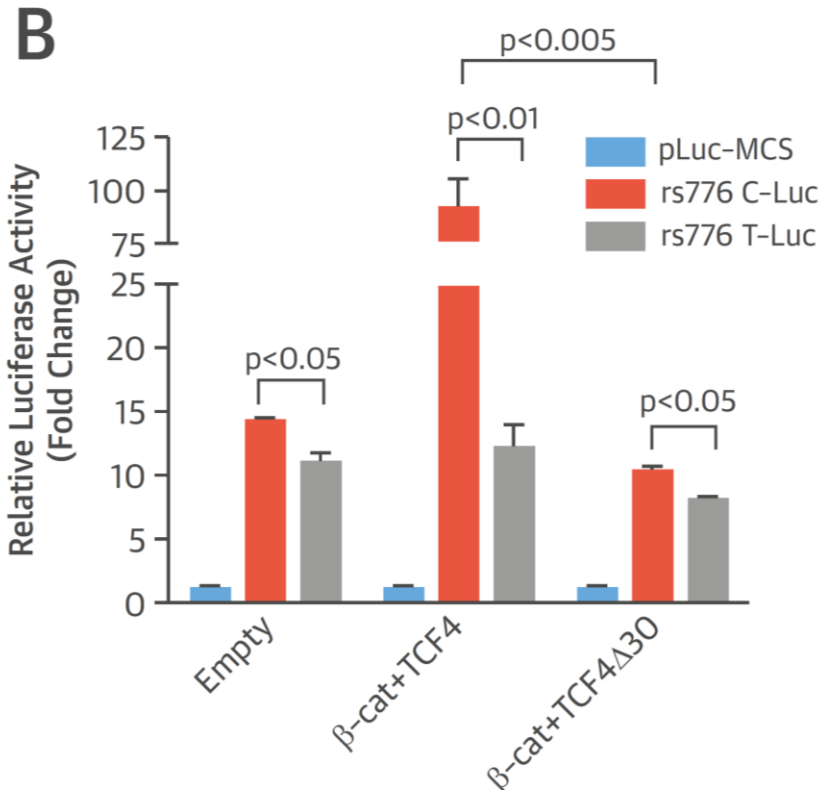
Perez MV et al., J Am Coll Cardiol. 2015 8;66(22):252

Hypokretin/orexinový systém u HF

Funkční validace rs7767652



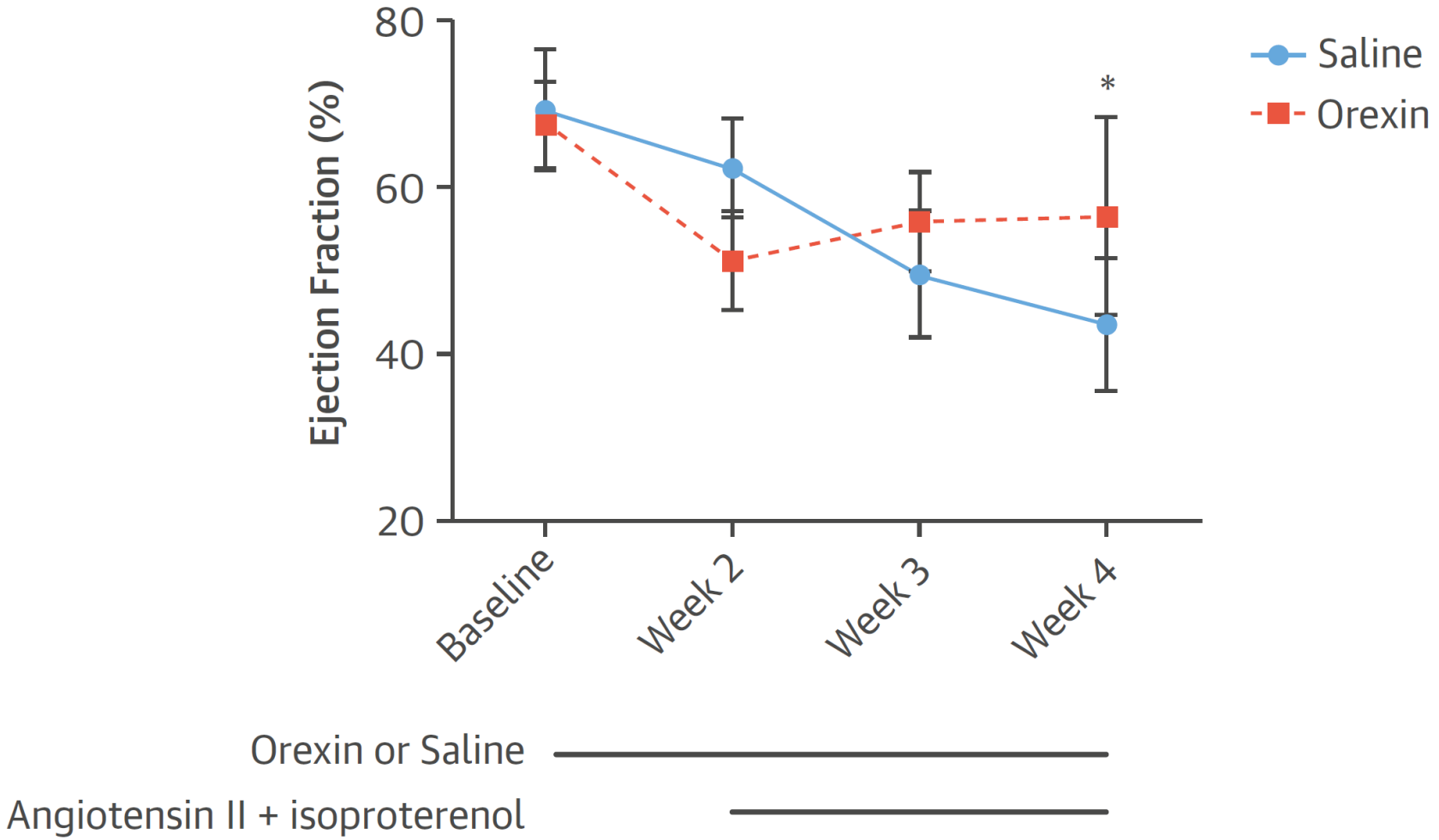
minoritní alela (T) narušuje vazební místo pro transkripční faktor 4 (TCF4)



Minoritní alela T snižuje expresi orexinového receptoru 2

Perez MV et al., J Am Coll Cardiol. 2015 8;66(22):252

Podání orexinu A zlepšuje systolickou funkci LK v animálním experimentu HF



Perez MV et al., J Am Coll Cardiol. 2015 8;66(22):252

Hypotéza

Hypocretin/orexin system ovlivňuje prognózu pacientů po IM

Cíl studie

Popsat vliv hypokretin/orexinového systému na riziko úmrtí pacientů po 1. IM

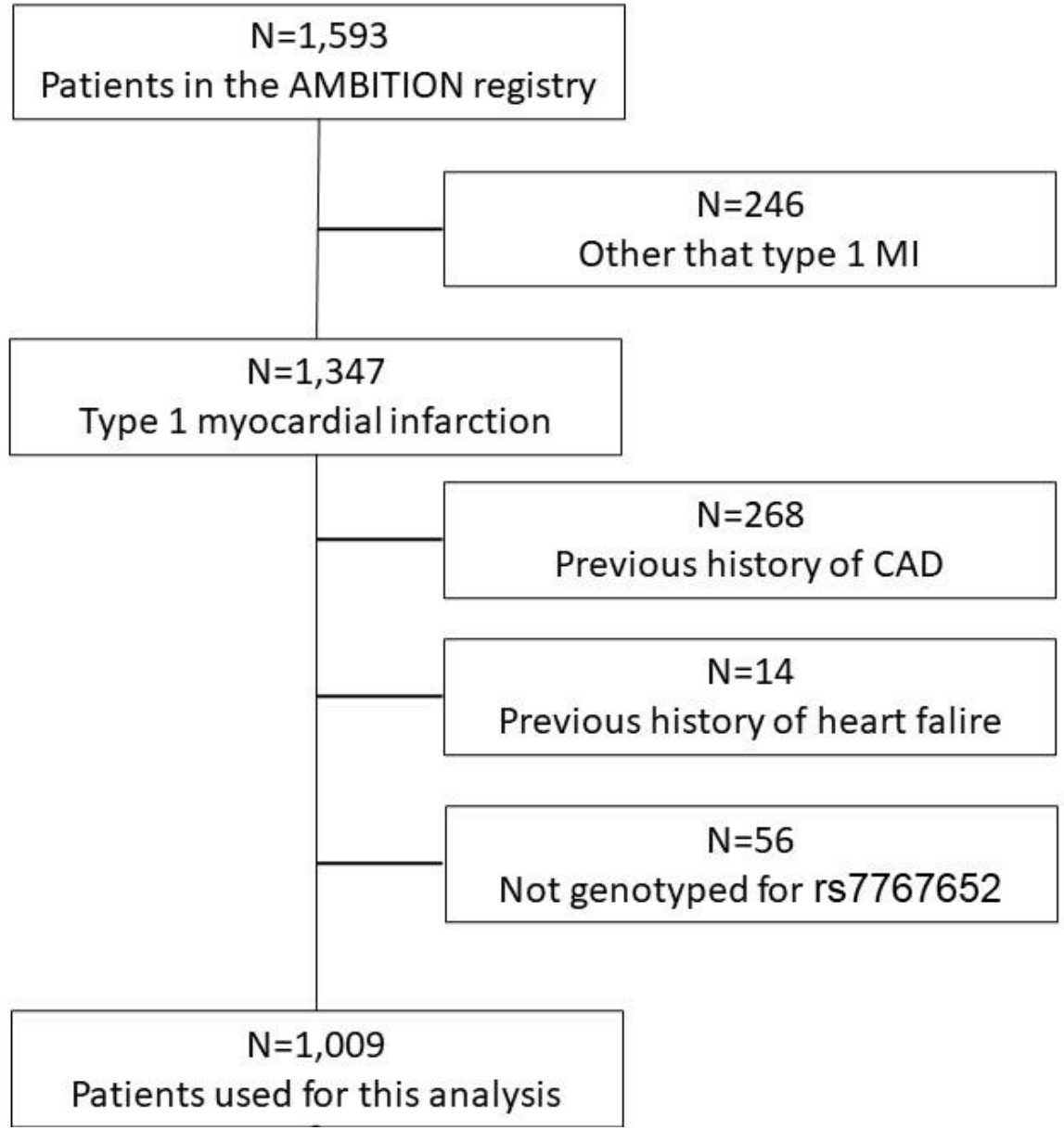
Metódy

Czech post-MONICA study (kontrolní skupina)

- 1% vzorek populace 9 okresů ČR

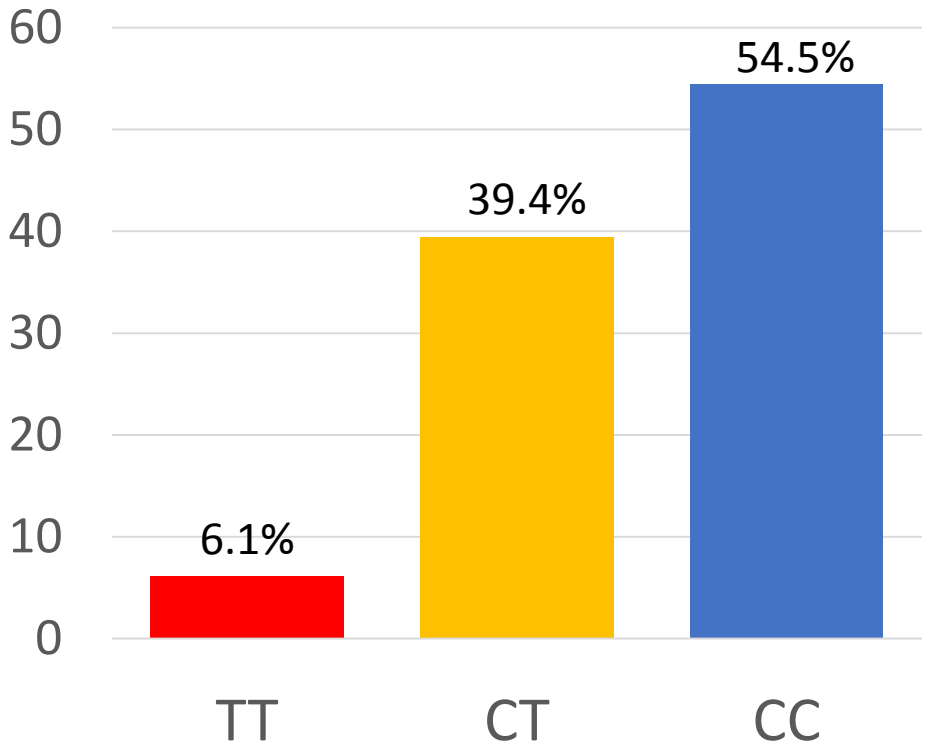
AMBITION register

- Prospektivní registr pacientů hospitalizovaných v IKEM po IM
- IM 1. typu, 1. IM
- Bez anamnézy HF

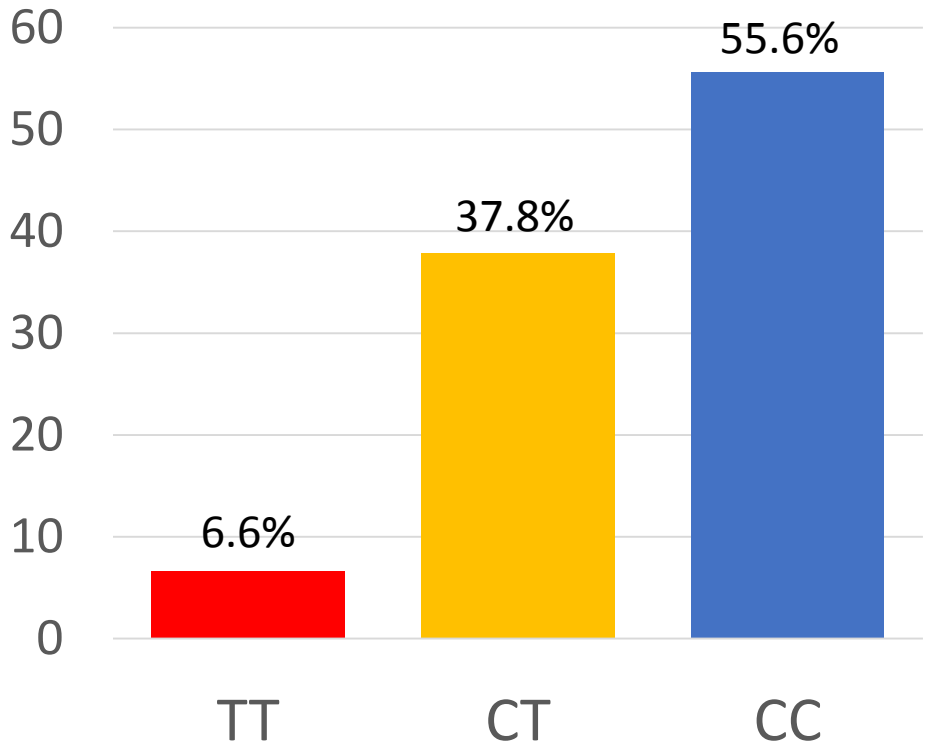

N=1,593
Patients in the AMBITION registry
N=246
Other that type 1 MI
N=1,347
Type 1 myocardial infarction
N=268
Previous history of CAD
N=14
Previous history of heart falire
N=56
Not genotyped for rs7767652
N=1,009
Patients used for this analysis

rs7767652 neovlivňuje riziko IM

AMBITION registry (after MI)
N=1,009



Czech post-MONICA (general population)
N=1,953



χ^2 p=0.62

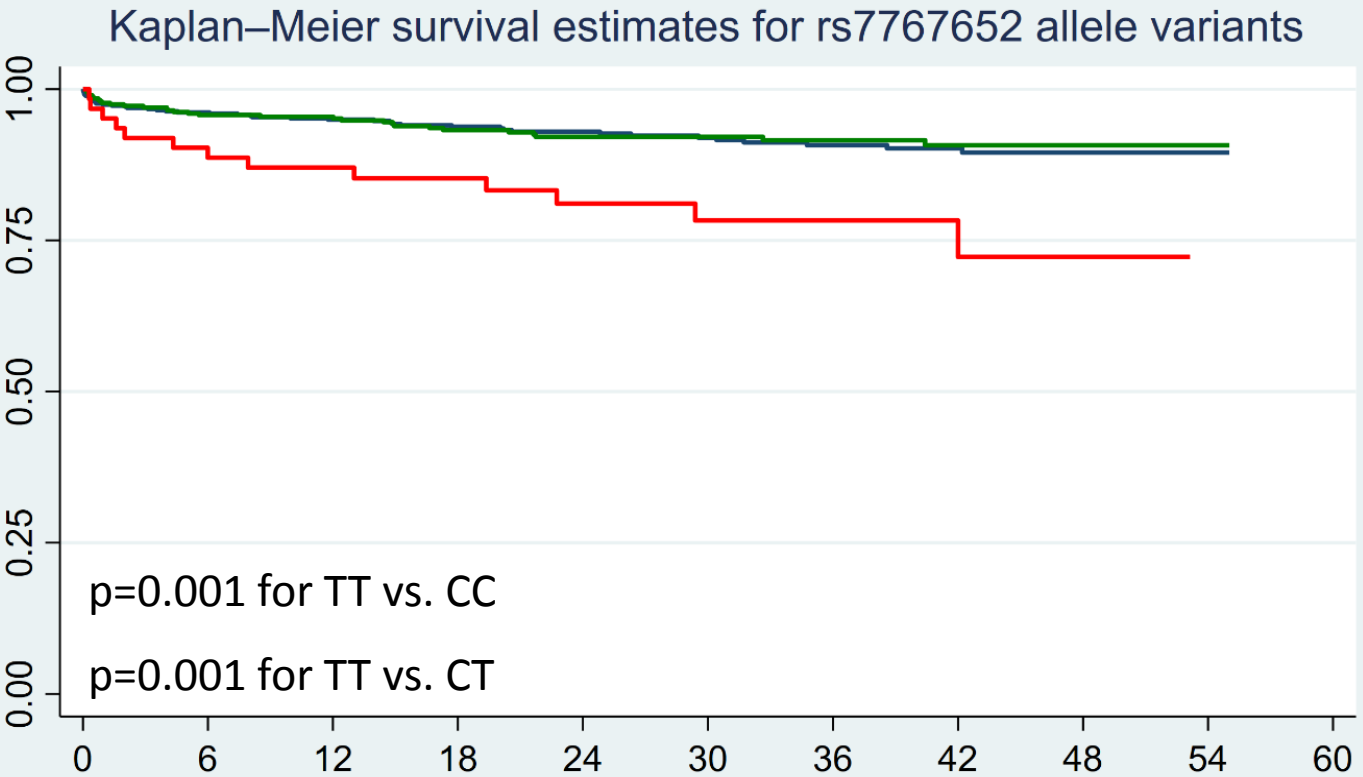
AMBITION registry (patients after MI)

Variable	CC N=549	CT N=398	TT N=62	p for linear trend
Age, years	63.6±12.6	63.5±11.7	66.5±12.0	0.078
Male gender	414 (75.4)	294 (73.9)	46 (74.2)	0.843
Risk factors				
Arterial hypertension, n(%)	309 (56.4)	236 (59.4)	44 (66.1)	0.268
Diabetes, n(%)	131 (23.9)	106 (26.6)	18 (29.0)	0.491
Current smoking, n(%)	248 (45.2)	186 (46.7)	27 (43.5)	0.799
BMI, kg/m^2	28.6±4.7	28.9±5.1	28.3±5.7	0.564

AMBITION registry (patients after MI)

Variable	CC N=549	CT N=398	TT N=62	p for linear trend
Max Troponin natural log, ng/L	7.00±1.53	7.01±1.54	6.76±1.38	0.242
CKD EPI, ml/min/1.73 m²	77.6±22.2	77.9±22.7	75.8±19.9	0.528
HbA1c, mmol/L/mol	44.5±11.6	45.8±14.5	44.9±11.8	0.852
Fasting glycemia, mmol/L	8.3±3.8	8.4±3.8	8.1±3.2	0.743
Total cholesterol, mmol/L	4.86±1.15	4.89±1.34	4.63±1.08	0.153
Triglycerides, mmol/L	1.7±1.0	1.8±1.4	1.9±1.3	0.031
LDL cholesterol, mmol/L	3.25±1.11	3.21±1.11	2.99±0.97	0.075

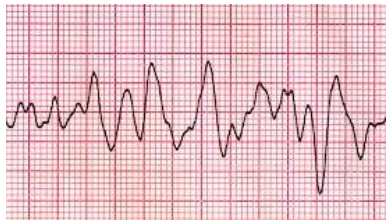
rs7767652 a riziko mortality po IM



Coxova regrese faktorů asociovaných s rizikem mortality po IM

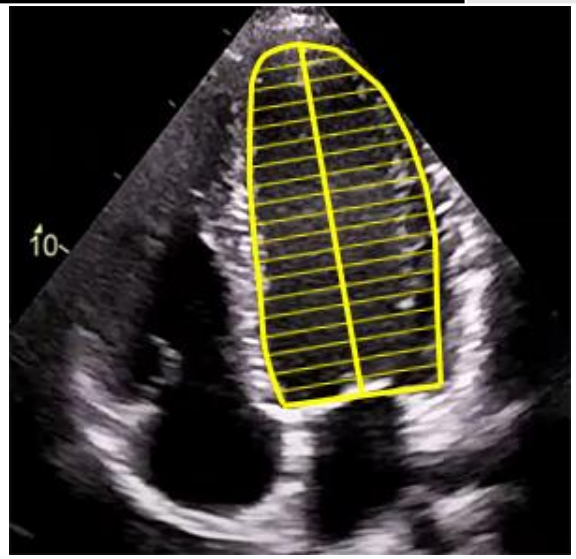
Variable	HR (95% CI)	p
Age	1.052 (1.027-1.78)	<0.001
CKD EPI	0.973 (0.962-0.984)	<0.001
Smoking	1.741 (1.080-2.807)	0.023
Left ventricular EF		0.016
EF<40% vs. EF>50%	1.628 (0.977-2.714)	0.061
EF 40-50% vs. EF>50%	0.699 (0.378-1.294)	0.254
Glycemia	1.061 (1.016-1.108)	0.008
Killip class >I	2.551 (1.562-4.166)	<0.001
rs7767652 minor allele homozygote	2.833 (1.545-5.194)	0.001

Variable	CC N=549	CT N=398	TT N=62	p for linear trend
Cardiopulmonary resustitation, n(%)	34 (6.2)	32 (8.0)	10 (16.1)	0.005
Ventricular fibrillation, n(%)	23 (4.2)	22 (5.5)	8 (12.9)	0.004
In-hospital AF, n(%)	65 (11.8)	52 (13.1)	7 (11.3)	0.890



Variable	CC N=549	CT N=398	TT N=62	p for linear trend
Discharge ejection fraction, %	44.9±10.1	45.3±10.3	46.1±10.9	0.382

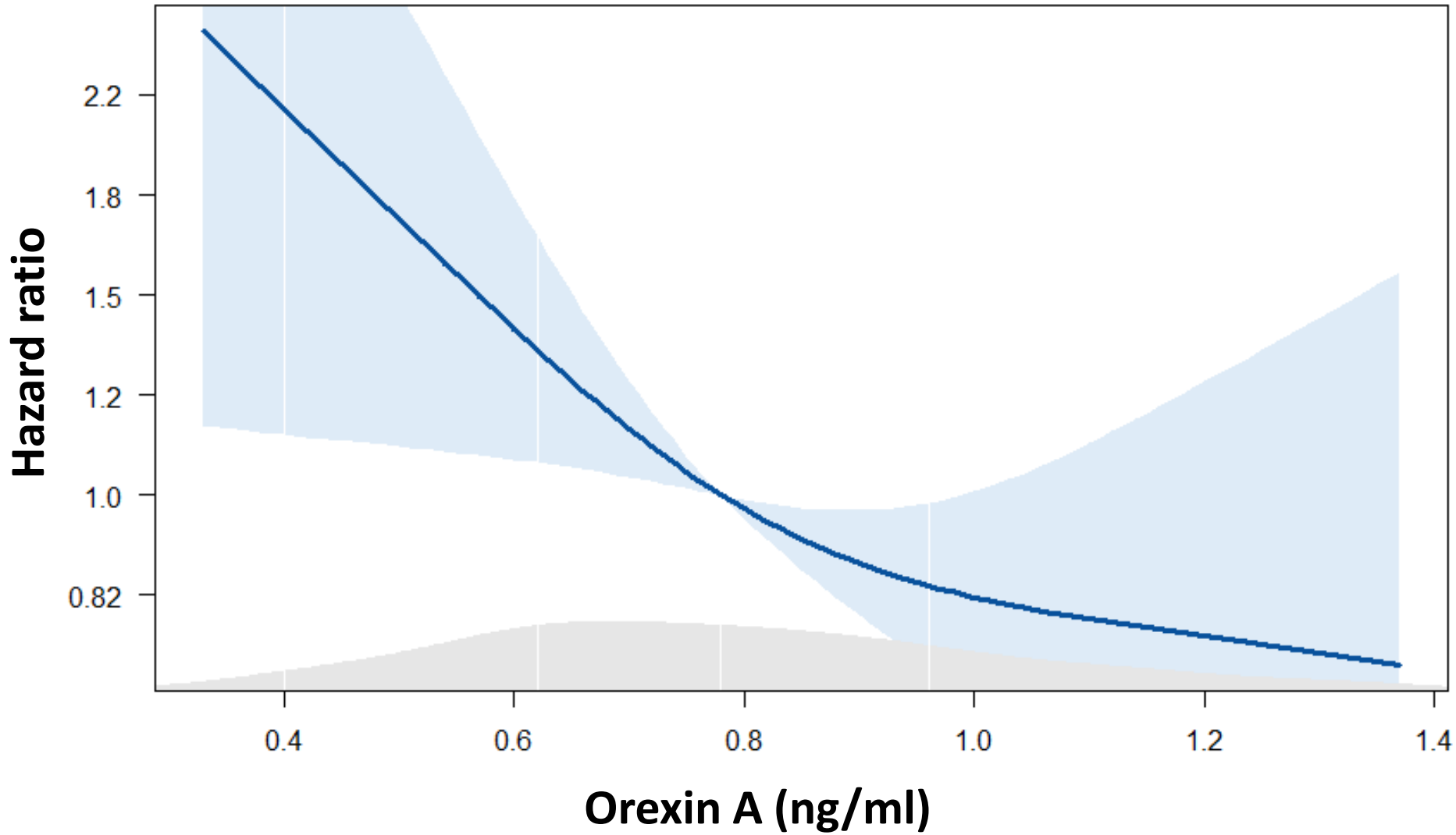
Echocardiography follow-up*	CC	CT	TT	p for linear trend
EF change, %	9.0±8.7	8.0±9.2	2.5±11.0	0.019
End-diastolic diameter change, mm	2.2±5.6	2.6±5.6	4.8±9.4	0.146



243 patients with discharge EF≤40% and available follow-up echocardiography

Circulating Orexin A concentration and mortality

245 patients with systolic dysfunction and EF≤40%



Data are adjusted for age. Gray area represents Orexin A histogram.

Increased Orexin A is associated with lower mortality

Variable	HR (95% CI)	p
Age	1.029 (1.003-1.055)	0.030
CKD EPI	0.274 (0.140-0.535)	<0.001
Admission heart rate	1.012 (1.003-1.024)	0.013
Killip class >I	2.862 (1.710-4.792)	<0.001
Orexin A ≥1.0 ng/mL	0.413 (0.186-0.914)	0.029

Závěry

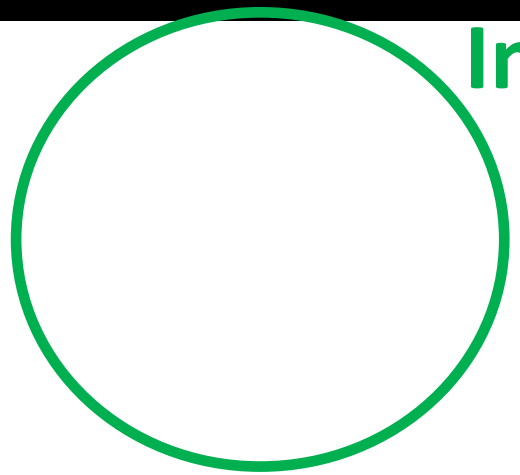
- TT varianta rs7767652, která vede k nižší expresi receptoru OX2 je spojena se zvýšeným rizikem úmrtí po IM

Vyšší mortalita

Závěry

- TT varianta rs7767652, která vede k nižší expresi receptoru OX2 je spojena se zvýšeným rizikem úmrtí po IM

- Zvýšená hladinia Orexinu A je spojena s nižším rizikem úmrtí po IM



Increase

↓

Nižší mortalita po IM

Závěry

- TT varianta rs7767652, která vede k nižší expresi receptoru OX2je spojena se zvýšeným rizikem úmrtí po IM
- Zvýšená hladinia Orexinu A je spojena s nižším rizikem úmrtí po IM
- Zvýšené arytmické riziko (FiK) a horší obnova systolické funkce levé komory po IM můžou vysvětlit zvýšené riziko mortality pacientů se sníženou aktivitou H/O systému

H/O nový terapeutický cíl po IM