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ORIGINAL RESEARCH

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

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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 (χ^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).

CONCLUSIONS: Attenuation of hypocretin/orexin signaling is associated with increased mortality risk after MI. This effect may be partially explained by the increased arrhythmic risk and the effect on the left ventricular systolic function recovery.

Key Words: hypocretin/orexin receptor-2 ■ hypocretin/orexin system ■ inflammation ■ mortality ■ myocardial infarction ■ outcomes ■ recovery

In the central nervous system, the hypocretin/orexin (H/O) system regulates sleep–wake cycles and metabolism. The loss of orexin-producing neurons in the hypothalamus causes narcolepsy with cataplexy (narcolepsy type I).[1] On the other hand, orexin receptor antagonists have been used for insomnia treatment.[2] Other studies suggested the role of the brain's H/O system in feeding behavior and propensity for weight gain, with orexin signaling acting through a net increase in energy expenditure.[3]

Outside of the central nervous system, the impact of the H/O system has been recently recognized in patients with heart failure (HF). In an unbiased systems-biology search, Perez et al identified the rs7767652 locus in the regulating domain of HCRTR-2 (hypocretin receptor-2) as the strongest predictor of left ventricular ejection fraction (EF) improvement in response to HF pharmacotherapy.[4] In the functional validation study, the rs7767652 minor allele T was associated with disruption of a transcription factor

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CLINICAL PERSPECTIVE

What Is New?

- In patients after myocardial infarction, attenuation of hypocretin/orexin signaling is associated with increased mortality risk.

What Are the Clinical Implications?

- Orexin receptor agonists may improve outcomes after myocardial infarction, but further research is needed.

Nonstandard Abbreviations and Acronyms

AMBITION	Institute for Clinical and Experimental Medicine Acute Myocardial Infarction Registry
HCRTR-2	hypocretin orexin receptor-2
H/O	hypocretin/orexin

4 binding site, leading to decreased transcription of HCRTR-2. Impact of the H/O system on HF was further confirmed in an animal model of HF, in which orexin administration improved left ventricular EF. In a human HF study, subjects with a higher circulating orexin A concentration (≥1.04 ng/mL) had more significant reduction in left ventricular end-diastolic and end-systolic volume and a trend toward greater improvement in left ventricular EF in response to HF therapy.[5]

Myocardial infarction (MI) is one of the most common causes of HF development and is associated with increased mortality risk.[6] Until now, no study has evaluated the effect of the H/O system on MI outcomes. The aim of the present prospective study was to describe the effect of the H/O system on total mortality among consecutive patients hospitalized for their first MI. To overcome typical biases associated with biochemical biomarker measurements that may impact results validity, we have used a genetic variant in the regulating domain of the HCRTR-2 gene, which is associated with attenuated HCRTR-2 signaling. Because of Mendelian inheritance laws, genetic variants are randomly distributed in the population. Unlike biochemical variables, genetic variants are not confounded by environmental and other factors. As a sensitivity analysis to further confirm the impact of the H/O system on survival, we have also measured circulating orexin A levels in a high-risk subgroup of patients with systolic dysfunction after MI.

METHODS

Data Availability Statement

The data that support the findings of this study are available from the corresponding author, upon reasonable request.

Population

This study used data from the prospective AMBITION (Institute for Clinical and Experimental Medicine Acute Myocardial Infarction Registry) registry,[7] which has been collecting clinical data and biospecimens from all consecutive patients hospitalized for acute coronary syndrome at a tertiary heart center since June 2017. The methods of this study were previously described.[8] During the hospital stay, all patients underwent detailed interviews, and additional information was obtained through manual chart abstraction and laboratory studies.

For this analysis, data from individuals without a previous history of HF and coronary artery disease hospitalized for type 1 MI (caused by atherosclerotic plaque rupture and thrombosis)[9] between June 2017 and November 2021 were used. The institutional review board of the Institute for Clinical and Experimental Medicine approved the study, and all participants signed informed consent. The investigation conformed to the principles outlined in the Declaration of Helsinki.

To identify the impact of rs7767652 on MI risk, we compared allele frequencies in the general population and patients after MI. As a control group, we used data from the Czech post-MONICA (Monitoring of Trends and Determinants in Cardiovascular Disease) study, which examined a 1% random population sample in 9 districts of the Czech Republic. Methods of the Czech post-MONICA study were previously reported.[10]

Definition of Comorbidities

History of diabetes was defined by oral antidiabetic drugs or insulin use at the time of hospital admission or by glycated hemoglobin ≥48 mmol/mol at the time of hospitalization. Arterial hypertension was defined as self-reported use of antihypertensive drugs at admission. Self-reported history of smoking was used. A person was considered a current smoker if smoking at least 1 cigarette per day during the past 12 months. Positive family history of cardiovascular disease was defined by MI or stroke in first-degree relatives before age 55 years in men and before age 60 years in women, respectively.

rs7767652 Genotyping

DNA was isolated from peripheral blood. The rs7767652 locus in the regulating domain of HCRTR-2 was analyzed using the TaqMan SNP assay

No.C_29161754_20. Genotyping was performed according to the manufacturer's protocol on an ABI 7300 real-time polymerase chain reaction instrument.

Orexin A Concentration Measurement

In 245 patients with systolic dysfunction and EF <40% at hospital discharge, we measured the concentration of orexin A in blood samples drawn on the first day after hospital admission using the ELISA method (Phoenix Pharmaceuticals, Burlingame, CA).

Outcomes

The primary outcome of this study was all-cause mortality. Mortality data were provided by the Institute of Health Information and Statistics, which keeps a record of all deceased individuals by law.

Statistical Analysis

Data are presented as mean±SD, median (interquartile range [IQR]), or frequency (percent). ANOVA, Kruskal-Wallis, or χ^2 tests were used to compare differences across the 3 allele variants, as appropriate. A log-rank test was used to compare survival by allele variants. A Cox proportional hazard model was used to assess factors influencing survival after MI. The proportional hazard assumption was checked and fulfilled. Follow-up was defined as the time from hospital discharge to death ascertained to January 1, 2022, without censoring for any additional events.

Statistical analyses were performed using SPSS version 25.0 (IBM, Armonk, NY), Stata version 17 (StataCorp, College Station, TX), or R software version 3.6.2 (R Foundation for Statistical Computing, Vienna, Austria). Statistical significance was set at $P<0.05$. The same threshold was used for variables to enter the multivariable analyses.

RESULTS

Of the 1593 patients in the AMBITION registry, 1347 had type 1 MI. Of these, 268 had a previous history of coronary artery disease, and another 14 had chronic heart failure and were therefore excluded. Of the 1065 eligible patients, rs7767652 allele variants were available in 1009 patients. The study flowchart is shown in Figure 1. The main study findings are summarized in Figure 2.

rs7767652 Allele Variants in MI and the General Population

In 1009 patients from the MI population, 6.1% patients were homozygotes (TT) and 39.4% heterozygotes (CT) for the hypofunctional rs7767652 minor T allele. Similarly, in 1953 subjects from the general population of the Czech post-MONICA study, 6.6% were homozygotes and 37.8% were heterozygotes for the rs7767652 minor allele. Allele frequencies in the MI and general population were not statistically different (χ^2 P=0.62), suggesting that rs7767652 does no increase MI risk.

Traditional Risk Factors and MI Complications by rs7767652 Allele Variants

Demographic characteristics by allele variants are shown in Table 1. There were no statistically significant differences in traditional risk factors such as diabetes, body mass index, glycemia or low-density lipoprotein cholesterol by the rs7767652 allele variants. Similarly, there was no statistically significant difference in MI size as assessed by maximal troponin level or discharge EF. However, subjects with the TT variant more often experienced ventricular fibrillation (12.9% versus 4.8%, P=0.01) and more often required cardiopulmonary resuscitation (16.1% versus 7.0%, P=0.02), as compared with the CT and CC variants combined. Among the 243 patients with EF ≤40% at hospital discharge and available follow-up EF measured on a median of 128 days (IQR, 98–395 days) after the baseline EF measurement, minor allele homozygotes had a lower increase in EF during the follow-up (2.5±11.0% versus 8.4±9.4%, P=0.04, for TT versus CT and CC combined).

rs7767652 Allele Variants and Total Mortality

During the median follow-up of 27 months (IQR, 13–41 months), the total mortality rate was 8.4% (n=83). Homozygotes for the rs7767652 minor and hypofunctional allele had a higher mortality risk as compared with heterozygotes (P=0.001) and homozygotes for the major allele (P=0.001), with no statistically significant difference between heterozygotes and major allele homozygotes (P=0.836) (Figure 3). After multivariable adjustment, minor allele homozygotes remained at increased mortality risk (hazard ratio, 2.83 [95% CI, 1.55–5.19]) (Table 2).

Orexin A Concentration and Mortality

To further confirm the effect of the H/O system on mortality after MI, we measured orexin A levels in 245 patients with systolic dysfunction and EF ≤40% at hospital discharge. At baseline, patients with the rs7767652 TT allele variant had no statistically significant difference in orexin A concentrations from those with the CT (0.76±0.26 versus 0.80±0.28 ng/mL, P=0.82) and CC (0.76±0.26 versus 0.84±0.29 ng/mL, P=0.48) variants, respectively. In the analysis adjusted for age, mortality risk was lowest in subjects with orexin concentration ≥1.0 ng/mL (Figure 4). After multivariable adjustment,

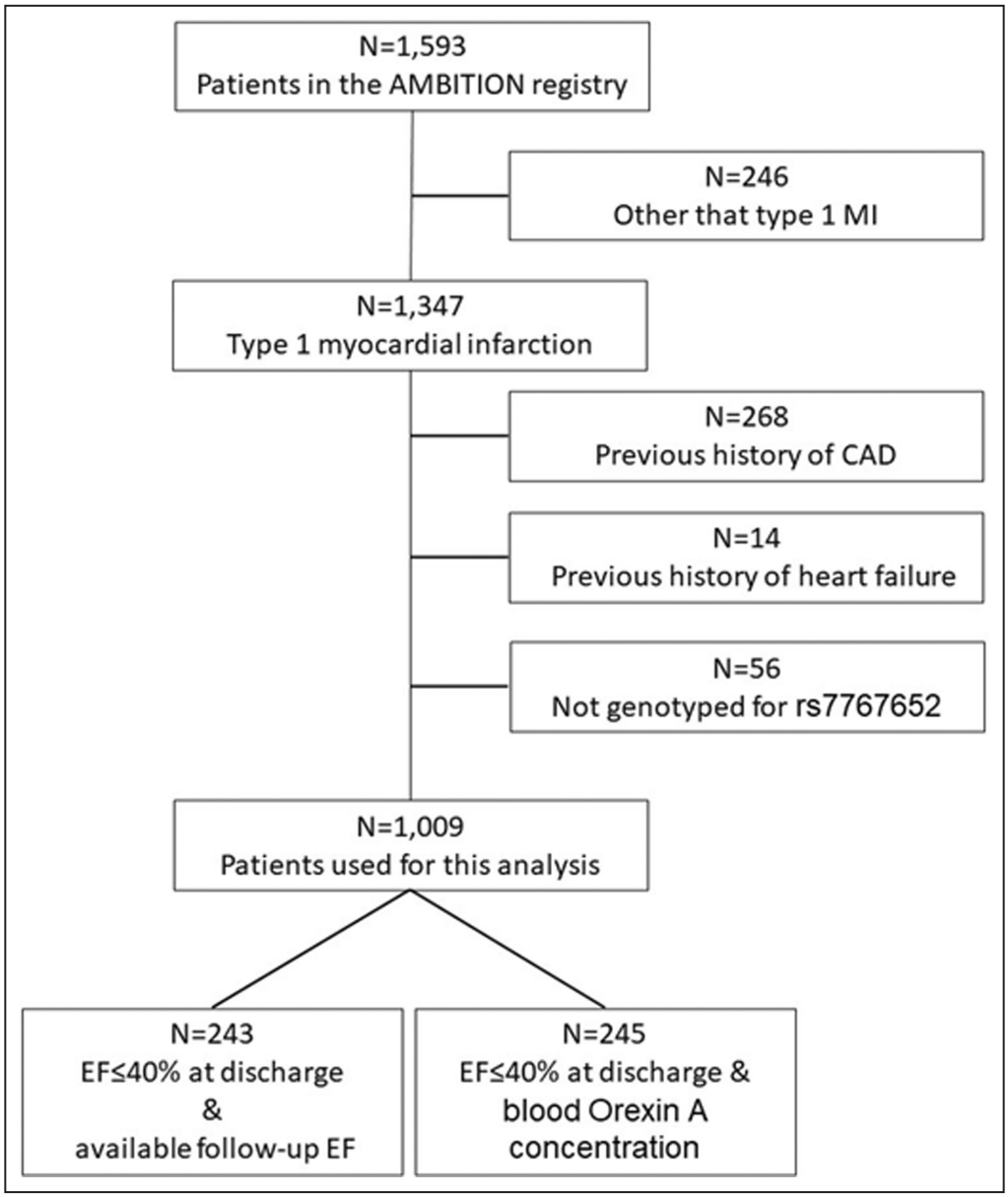

Figure 1. Study flowchart.
AMBITION indicates Institute for Clinical and Experimental Medicine Acute Myocardial Infarction Registry; CAD, coronary artery disease; EF, ejection fraction; and MI, myocardial infarction.

the mortality risk among patients with orexin A concentration ≥1.0 ng/mL was 59% lower than in patients with orexin <1.0 ng/mL (Table 3).

DISCUSSION

This is the first study to describe the influence of the H/O system on the prognosis of patients after the first MI. We have shown that the rs7767652 minor allele, which is associated with attenuated H/O signaling, does not increase MI risk and is not associated with traditional risk factors. Although MI size was similar, the long-term outcome differed by rs7767652 allele variants. Minor allele homozygous, which confers with lower HCRTR-2 transcription,[4] and subjects with lower circulating orexin A level were at increased total mortality risk. This effect of the H/O system on mortality may be partially explained by the increased arrhythmic risk and the impact on the left ventricular systolic function recovery.

The H/O system was first described almost 25 years ago by 2 independent groups searching for a possible treatment for obesity. De Lecea et al named discovered proteins hypocretins because of their location in the hypothalamus and amino acid similarities with a gut hormone secretin.[11] Sakurai et al named peptides

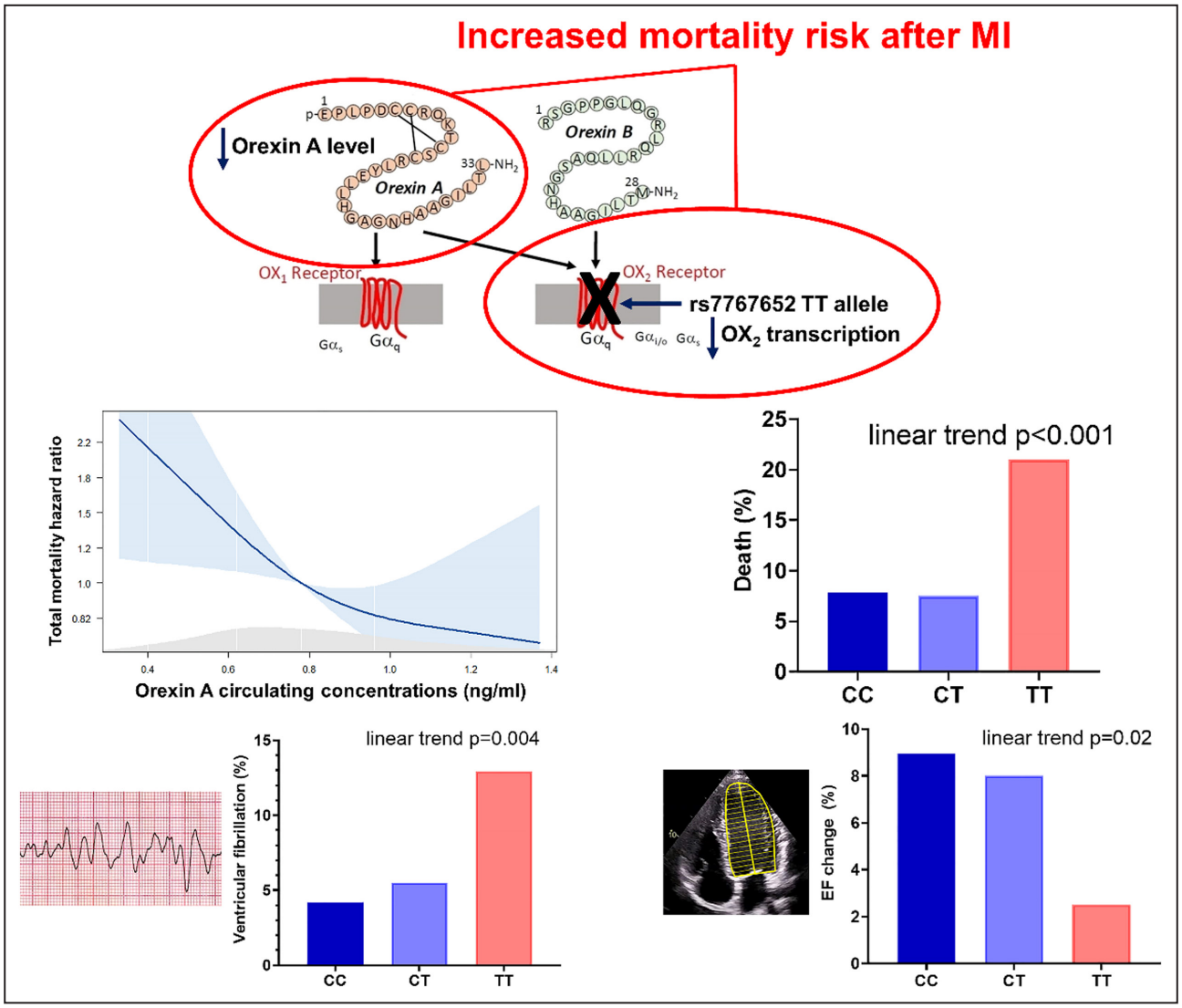

Figure 2. Main study findings.
EF indicates ejection fraction; and MI, myocardial infarction.

orexins after the Greek word for appetite, because their application induced feeding in rats.[12] It was discovered that the proteins identified by these groups were identical.

In the following years, the research on the central nervous system described involvement of the H/O system in maintaining wakefulness,[13] food intake, energy homeostasis, reward-seeking, stress, motivation, and drug addictions.[14] Outside the central nervous system, the H/O system may influence the risk of digestive tract cancer, inflammatory bowel syndrome, and glucose metabolism.[15] In humans, orexin deficiency is associated with glucose intolerance and insulin resistance.[16] In rodents, orexin overexpression protects from diet-induced obesity and improves glucose control.[17] This is related to orexin-induced increase in GLUT4 (glucose transporter type 4) expression in the liver and increased insulin secretion.[18,19]

The involvement of the H/O system in heart disease has been recognized only recently among patients with HF.[4,5,20] We added to this evidence by showing for the first time that the H/O system also influences prognosis after MI.

Several possible mechanisms may mediate the influence of the H/O system on mortality after MI. First, this effect may be caused by long-term exposure to classical risk factors. Association of the H/O system with metabolic syndrome and insulin sensitivity was described in previous studies,[15,16] both of which influence outcomes after MI.[21] However, we did not find any difference in diabetes, glucose, or body mass index by the rs7767652 allele variants in the present study. Although the H/O system influences drug addiction, including smoking,[14] there was no difference in the proportion of smokers by allele

Table 1. Demographic Characteristics by rs7767652 Allele Variants (N=1009)

Variable	CC, N=549	CT, N=398	TT, N=62	*P* for linear trend
Age, y	63.6±12.6	63.5±11.7	66.5±12.0	0.078
Male sex	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
Statin use before admission, n (%)	91 (16.6)	72 (18.1)	14 (22.6)	0.242
Family history of CVD, n (%)	145 (26.4)	117 (29.4)	13 (21.0)	0.348
AF history, n (%)	24 (4.4)	20 (5.0)	4 (6.5)	0.470
Index event				
Cardiopulmonary resuscitation, 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
STEMI, n (%)	361 (65.8)	262 (65.8)	38 (61.3)	0.481
Subacute MI, n (%)	78 (14.2)	54 (13.6)	10 (16.1)	0.674
Killip class >1, n (%)	108 (19.7)	78 (19.6)	14 (22.6)	0.584
Selective coronarography, n (%)	546 (99.5)	393 (98.7)	61 (98.4)	0.410
PCI, n (%)	460 (83.8)	346 (86.9)	53 (85.5)	0.744
CABG, n (%)	54 (9.8)	31 (7.8)	5 (8.1)	0.659
Pericarditis, n (%)	11 (2.0)	9 (2.3)	5 (8.1)	0.004
Intravenous diuretics, n (%)	130 (23.7)	91 (22.9)	15 (24.2)	0.922
Anterior MI, n (%)	241 (43.4)	173 (43.5)	26 (41.9)	0.769
Admission systolic BP, mm Hg	143.6±26.2	142.4±26.6	142.2±29.8	0.697
Admission diastolic BP, mm Hg	80.0±14.0	78.6±13.5	77.6±14.6	0.193
Admission heart rate, min^{-1}	77.9±19.2	76.9±17.0	77.4±16.2	0.851
Maximum troponin natural log, ng/L	7.00±1.53	7.01±1.54	6.76±1.38	0.242
Discharge EF, %	44.9±10.1	45.3±10.3	46.1±10.9	0.382
CKD EPI, mL/min per 1.73 m^2	77.6±22.2	77.9±22.7	75.8±19.9	0.528
BMI, kg/m^2	28.6±4.7	28.9±5.1	28.3±5.7	0.564
HbA1c, mmol/L per 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
HDL cholesterol, mmol/L	1.14±0.34	1.12±0.31	1.06±0.27	0.047
LDL cholesterol, mmol/L	3.25±1.11	3.21±1.11	2.99±0.97	0.075
Leukocytes, 10^9/L	11.37±3.97	11.37±4.04	10.73±3.64	0.234
Hemoglobin, g/L	142.7±15.6	141.4±16.1	142.0±15.9	0.759
Discharge medication				
ACEi/ARB, n (%)	397 (73.7)	309 (78.2)	49 (81.7)	0.177
β-Blocker, n (%)	436 (80.9)	327 (82.8)	49 (81.7)	0.894
Furosemide, n (%)	106 (22.3)	67 (19.3)	13 (23.6)	0.792
Spironolactone, n (%)	100 (21.0)	67 (19.3)	13 (23.6)	0.634
Statin, n (%)	520 (96.5)	377 (95.4)	58 (96.7)	0.929
Echocardiography follow-up*				
EF change, %	9.0±8.7	8.0±9.2	2.5±11.0	0.019

(*Continued*)

Table 1. Continued

Variable	CC, N=549	CT, N=398	TT, N=62	*P* for linear trend
End-diastolic diameter change, mm	2.2±5.6	2.6±5.6	4.8±9.4	0.146
Outcome				
30-d mortality	14 (2.6)	9 (2.3)	3 (4.8)	0.276
Death, n (%)	43 (7.8)	30 (7.5)	13 (21.0)	<0.001

ACEi/ARB indicates angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; AF, atrial fibrillation; BMI, body mass index; BP, blood pressure; CABG, coronary bypass grafting; CKD EPI, Chronic Kidney Disease Epidemiology Collaboration; CVD, cardiovascular disease; EF, ejection fraction; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MI, myocardial infarction; PCI, percutaneous coronary intervention; and STEMI, ST-segment–elevation myocardial infarction.

*Analyzed in 243 patients with discharge EF ≤40% and available follow-up echocardiography.

variants. Second, infarct size, assessed by EF, troponin release, or medication use, was not affected by the rs7767652 polymorphism, indicating that infarct size per se does not explain the difference in survival. Third, the orexin system effected arrhythmia risk. We found a higher prevalence of ventricular fibrillation in rs7767652 minor allele homozygotes. Minor allele homozygotes had also higher triglyceride levels at the time of MI, which may reflect increased lipolysis in subcutaneous and epicardial adipose with release of nonesterified fatty acids and adipokines that promote arrhythmogenesis.[22] Fourth, on the effect on inflammation, we found that pericarditis was more prevalent in minor allele homozygotes despite a similar MI size, suggesting a higher inflammatory response to MI. This may be explained by an immunomodulatory effect of the orexin system.[23] Several recent studies have described the effect of the inflammatory response on outcomes after MI.[24] Fifth, we found that the H/O system affects EF recovery after MI, which is associated with improved survival.[25] Previously, variation in rs7767652 identified superresponders to pharmacotherapy, who had improved EF because of reverse remodeling.[4] In the present study among patients with EF ≤40% at hospital discharge, rs7767652 minor allele homozygotes had a lower increase in EF during follow-up. This is also supported by the fact that 30-day mortality did not differ by allele variants, whereas

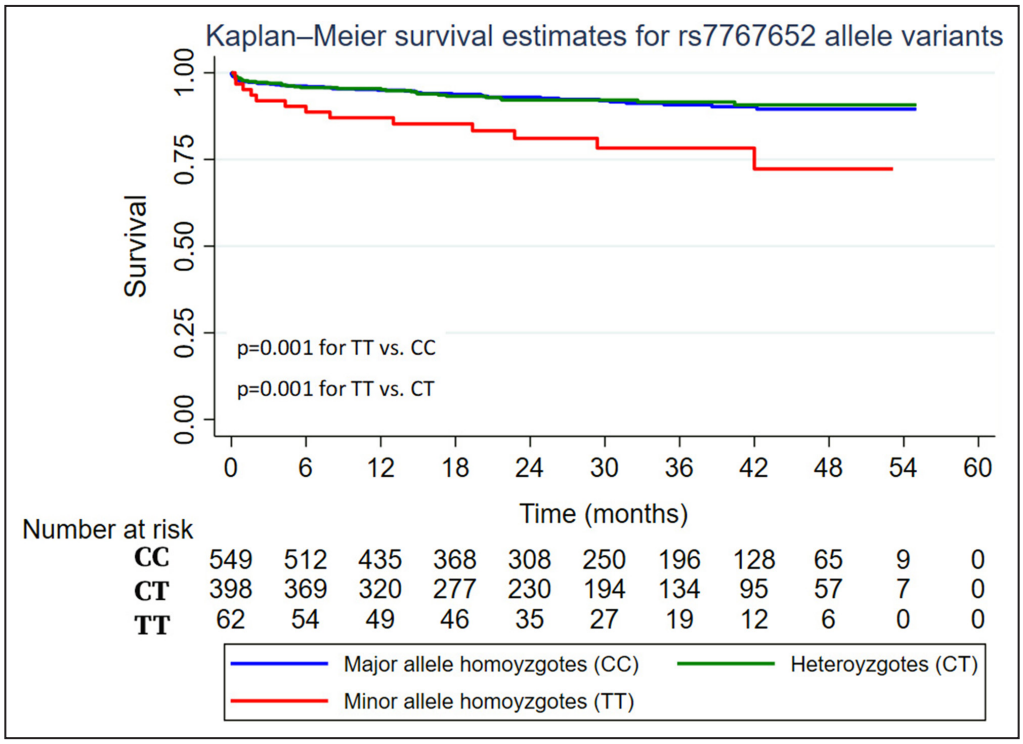

Figure 3. Kaplan-Meier survival estimates for rs7767652 allele variants.
Patients with the rs7767652 TT allele combination (red line) are at higher mortality risk as compared with those with the CC (blue line) and CT (green line) allele combination (both log-rank *P*<0.001).

Table 2. Factors Associated With Mortality Risk After Myocardial Infarction (N=1009)

Variable	HR (95% CI)	*P* value
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

CKD EPI indicates Chronic Kidney Disease Epidemiology Collaboration; EF, ejection fraction; and HR, hazard ratio.

Table 3. Factors Associated With Mortality Risk in Patients With Systolic Dysfunction at Hospital Discharge (n=245)

Variable	HR (95% CI)	*P* value
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 ≥1.0 ng/mL	0.413 (0.186–0.914)	0.029

CKD EPI indicates Chronic Kidney Disease Epidemiology Collaboration; and HR, hazard ratio.

there was a difference in long-term mortality. The variety of mechanistic links connecting orexin signaling with increased mortality risk in our study may seem tricky at first. However, a multitude of downstream orexin signaling that involves SGK-1 (serum and glucocorticoid-regulated kinase-1)[26]; HIF-1 (hypoxia-inducible factor-1)[26]; phospholipase A2, C, and D; diacylglycerol lipase; Ca2+; and adenylyl cyclase cascades[23] may explain this variety of orexin signaling effects. In a recent study by Patel et al, orexin B but not orexin A had a direct cardioprotective effect in human heart samples that was mediated by the ERK1/2 (extracellular signal-regulated kinase 1 and 2) phosphorylation.[20] ERK1/2 phosphorylation is involved in the activation of contractile responses through direct phosphorylation of the Ca2+/calmodulin-dependent MLC (myosin light chain) kinase.[27]

Our findings have several clinical implications. Orexin receptor antagonists are widely used for insomnia treatment and in patients with MI. Whether their use may influence outcomes after MI needs to be examined. In addition, targeting the H/O system and increasing its activity by oral receptor antagonists, currently developed for treatment of narcolepsy, may be a novel therapeutic pathway to decrease the mortality risk and improve myocardial recovery after MI.

Study Limitations

Although this is an observational study, the use of a genetic instrumental variable with natural randomization of individuals under the Mendel law of segregation and independent assortment excludes the effect of confounding factors on our results. Although our

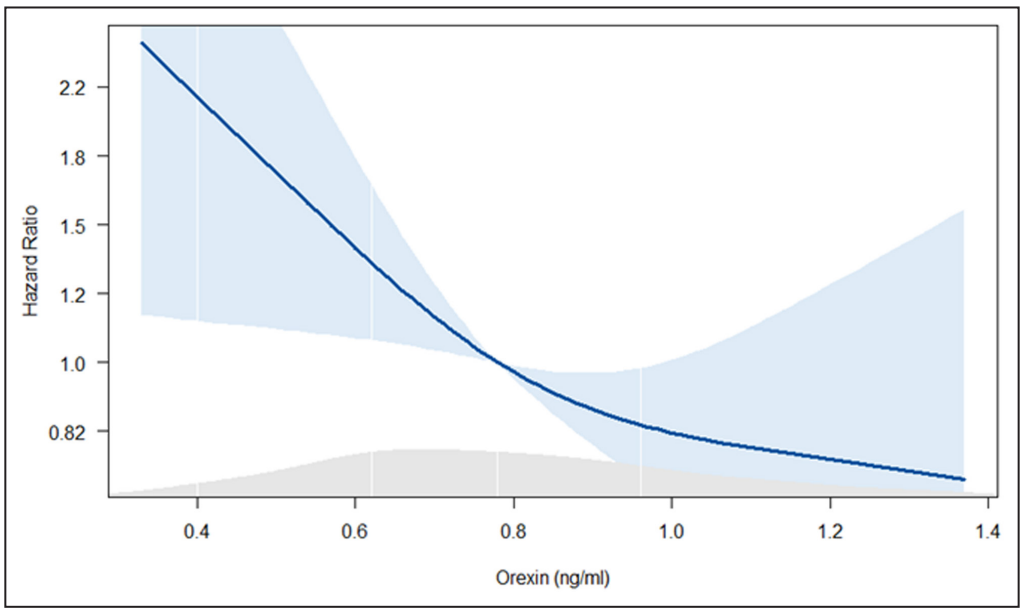

Figure 4. Circulating orexin A concentrations and mortality risk after myocardial infarction.
The relationship between circulating orexin A concentration assessed at the time of myocardial infarction and total mortality hazard ratio. Data are adjusted for age. The gray area represents orexin A histogram, and the light blue area is the 95% CI.

study is relatively small by genetic standards and uses only a single nucleotide polymorphism, the effect of this polymorphism on survival is substantial, thus requiring a lower sample size. As a sensitivity analysis, we have confirmed the impact of the H/O system on survival using circulating orexin A concentrations. Our results are consistent with those observed in patients with HF.

CONCLUSIONS

The present study shows for the first time the effect of the attenuation of H/O signaling on increased mortality risk after myocardial infarction. Several mechanisms may mediate this association, of which the effect on left ventricular systolic function recovery and ventricular fibrillation risk seems promising. Future studies will have to address potential relevance of the H/O axis pharmacomodulation on post-MI remodeling and survival.

ARTICLE INFORMATION

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J.M., P.W., M.Š., M.Ž., and M.K. collected the clinical data. P.J. and D.D. analyzed blood specimens. P.W. and D.J. wrote the draft of the article. V.M., J.K., V.A., and J.P. critically revised the article. All authors read and approved the final version of the article.

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Disclosures

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