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LETTER TO THE EDITOR
Cardiovascular Disease

Tramadol use increases mortality and risk of major adverse cardiovascular events in rheumatoid arthritis patients: evidence from a population-based cohort study

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With great interest, we studied the research conducted by Dr Nalini and colleagues. With a population-based cohort, the present study evaluated a great amount of individuals and provided an important evidence about the association between long-term opiate use and cardiovascular death.[1] However, since opioid use was of high rate prescribed in patients with rheumatoid arthritis (RA) and osteoarthritis, we believe that the scope could be extended to the field of rheumatic diseases. Moreover, the association between opiate use and other related outcomes such as major adverse cardiovascular events (MACE) and overall mortality, were also worth of being evaluated.

To clarify the issue, we designed a population-based retrospective cohort study to evaluate the influence of tramadol to subsequent MACE risk and mortality in RA patients. As a weak opioid agonist, tramadol has been commonly utilized in pain management, especially in patients with chronic pain conditions. Clinically, previous study indicated that opioid use was of high rate in patients with RA, and tramadol was one of the most utilized opioid agonists (71.1%).[2] Previous studies evaluating severe adverse effect of tramadol faced strong limitation of small sample size, which could possibly cause lower evidence power.[3,4] Two clinical trials with small sample size reported tramadol users not showing significantly higher risk in myocardial injury or adverse events in cardiovascular system, comparing with non-tramadol users.[5] Large-scale study evaluating the risk of MACE and overall mortality in tramadol users with RA is currently lacking.

In this study, we utilized datasets from the Longitudinal Health Insurance Database (LHID), a subset of the National Health Insurance Research Database (NHIRD) in Taiwan. The LHID included one million randomly chosen beneficiaries and provided information regarding outpatient visits, hospitalizations, and medications.

Patients diagnosed with RA (ICD-9-CM: 714) from 2000 to 2012 were included. Index date was set as the first prescription of tramadol. We excluded patients with previous MACE (including ischaemic heart disease, congestive heart failure, acute ischaemic stroke, and intracranial haemorrhage), major depression, cancer, and those without previous related drug use (including tramadol, Panadol, and Non-Steroidal Anti-Inflammatory Drugs) before index date. Ultimately, 440 tramadol users with RA were included as study group, serving as the tramadol-using cohort. After 1:2 matching of age, sex, and year of RA diagnosis, 880 matched tramadol non-users with RA were matched and served as the comparison cohort. Utilizing Cox proportional regression model, we evaluated the adjusted hazard ratio (aHR) of developing future MACE in the tramadol user group, comparing with non-users. Kaplan–Meier methods and log-rank test was also performed to compare the difference in the cumulative incidence between the two cohorts. Each cohort was tracked 144 months with Kaplan–Meier curves.

The result of this study suggested that comparing with non-tramadol users, RA patients using tramadol was of higher risk developing subsequent MACE and the overall mortality was significantly higher. After the adjustment of potential confounders such as age and sex, the aHR of tramadol user group developing MACE was 1.715 [95% confidence interval (CI) 1.082–2.718], indicating a significantly higher risk. The incidence rate of MACE for non-tramadol cohort and tramadol cohort were 19.26 (95% CI 15.28–24.26) and 30.12 (95% CI 22.95–39.53) per 10 000 person-months, respectively. The aHR of death event for tramadol-using RA patients was 3.936-fold higher than non-users (95% CI 1.864–8.314) (*Table 1*).

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Table 1 Time to event analysis of MACE and overall mortality

	After age–sex and diagnosis year matched	
	Non-tramadol (n = 880)	Tramadol user (n = 440)
MACE		
Events	72	52
Incidence rate[a] (95% CI)	19.26 (15.28–24.26)	30.12 (22.95–39.53)
Crude HR (95% CI)	Reference	1.546 (1.082–2.210)
Adjusted HR (95% CI)	Reference	1.715 (1.082–2.718)
Mortality		
Events	22	31
Incidence rate[a] (95% CI)	5.50 (3.62–8.36)	16.06 (11.30–22.84)
Crude HR (95% CI)	Reference	2.943 (1.704–5.084)
Adjusted HR (95% CI)	Reference	3.936 (1.864–8.314)

CI, confidence interval; HR, hazard ratio; MACE, major adverse cardiovascular events.
[a]Per 10 000 person-months.

The main strength of this study was based on the utilized robust database with great amount of population. Selection bias could be addressed based on the population-based database. However, limitation of the study should be stated. First, ICD-9 CM code, as an administrative code, might not be precise enough to define diagnoses. Second, residual confounders could exist. For instance, confounders including lifestyle or cytokine levels were not adjusted in the present study since the information were not available in LHID.

As a conclusion, we report that tramadol usage could increase a 70% higher risk of developing MACE and have a 3.936-fold mortality in RA patients. Clinicians should be aware of the association in management of RA patients.

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Conflict of interest: none declared.

Statement of Ethics

This study conformed to the principles of the Declaration of Helsinki and was approved by the Institutional Review Board of Chung Shan Medical University (IRB permit number CS15134). Individual identification numbers were encrypted to protect the personal privacy of subjects. Since data in NHIRD were de-identified, patient consent was exempted.

Data availability

Datasets from the Longitudinal Health Insurance Database (LHID) 2000 were retrieved in this retrospective cohort study, and the data are available from the Taiwan National Health Insurance (NHI) Bureau. The data are not publicly available because of legal restrictions regarding the 'Personal Information Protection Act' in Taiwan. However, requests for data can be formally sent to the NHI bureau (https://dep.mohw.gov.tw/DOS/cp-2516-3591-113.html).

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