Contents available at ScienceDirect

Diabetes Research and Clinical Practice

journal homepage: www.elsevier.com/locate/diabres

Proton pump inhibitors use and risk of chronic kidney disease in diabetic patients

Hsun Yang [a], Shiun-Yang Juang [c], Kuan-Fu Liao [b,d,e,*]

[a] Division of Nephrology, Department of Internal Medicine, Taichung Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, Taichung, Taiwan

[b] Division of Gastroenterology, Department of Internal Medicine, Taichung Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, Taichung, Taiwan

[c] Department of Medical Research, Taichung Tzu Chi General Hospital, Buddhist Tzu Chi Medical Foundation, Taichung, Taiwan

[d] College of Medicine, Tzu Chi University, Hualien, Taiwan

[e] Graduate Institute of Integrated Medicine, China Medical University, Taichung, Taiwan

ARTICLE INFO

Article history:
Received 31 August 2018
Received in revised form
14 November 2018
Accepted 23 November 2018
Available online 27 November 2018

Keywords:
PPIs
CKD
DM

ABSTRACT

Aims: Chronic kidney disease consumes a huge amount of medical resources and proton pump inhibitors may be a potential factor for the increasing prevalence. This population-based cohort study investigates the risk of chronic kidney disease in a diabetic population using proton pump inhibitors in Taiwan.

Methods: This study is based on a specific diabetic database obtained from the National Health Insurance Research Database. Individuals with a new diagnosis of diabetes from 2002 to 2013 were enrolled. "Exposure" to proton pump inhibitors was defined as at least one prescription and dosage over 180 DDD (defined daily dose) in one year after the index date. A multivariable Cox proportional hazard model and competing-risk regression model were applied.

Results: There were 5994 patients in the final cohort of proton pump inhibitor users and 23,976 patients in the matched controlled cohort based on 1:4 propensity score matching. Compared with no exposure users, PPIs exposure group had more anemia prevalence, anti-hypertension medication and NSAIDs prescriptions.

The multivariable Cox proportional hazard model showed that the adjusted hazard ratio of chronic kidney disease was 1.52 (95% CI 1.40–1.65) in diabetic individuals with PPIs exposure, compared with no exposure users.

Conclusions: Proton pump inhibitors use is associated with 1.52-fold increased risk of chronic kidney disease in diabetic patients when the dosage is over 180 DDD in one year in Taiwan.

* Corresponding author at: Division of Gastroenterology, Department of Internal Medicine, Taichung Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, No. 88, Sec. 1, Fengxing Rd., Tanzi Dist., Taichung City 427, Taiwan.
E-mail address: kuanfuliaog@gmail.com (K.-F. Liao).

https://doi.org/10.1016/j.diabres.2018.11.019
0168-8227/

1. Introduction

In Taiwan, the overall prevalence of chronic kidney disease (CKD) was 1.99% in 1996 and gradually increased to 9.83% by 2003 [1]. CKD is mostly an irreversible process and consumes huge amounts of medical resources. According to the United States Renal Data System (USRDS), the total spending for Medicare beneficiaries with kidney disease alone is nearly $100 billion [2]. This includes over $64 billion in spending for all Medicare beneficiaries who have CKD and another $34 billion for beneficiaries with end-stage renal disease. Hence, trends in the prevalence of chronic kidney disease and end-stage renal disease are important for health care policy and planning.

Diabetes mellitus is considered the most common cause of end-stage renal disease [3]. The increasing prevalence of CKD is partly explained by the increasing prevalence of diabetes and hypertension [4,5]. However, medication use may be a potential factor contributed to the disease process. Current possible strategies for kidney health care are reducing drug-induced nephropathy and identifying possible factors that can delay dialysis, especially in high-risk populations.

Proton pump inhibitors (PPIs) are currently one of the most popular medications for treating diseases related to gastric acid. However, it has been estimated that between 25 and 70% of the PPI prescriptions in United States have no appropriate indication [6]. Although there are several restrictions according to the National Health Insurance (NHI) regulations in Taiwan, the prescription of PPIs is gradually increasing [7]. More and more adverse outcomes of PPIs are being discovered, such as hip fracture [8] and acute kidney injury [9]. Thus, it seems that the use of these drugs in high-risk patients should be re-examined.

To date, there are no relevant warnings about CKD risk in the instructions for the use of current proton pump inhibitors, especially in diabetic populations which are priority candidates for end-stage renal disease. According to USRDS data, Taiwan has the highest annual incidence and prevalence of end-stage renal disease in the world (458 people per million population and 3138 people per million population in 2013, respectively), followed by the USA and Japan [5]. When CKD is diagnosed, potentially nephrotoxic drugs should be used very cautiously [10]. Furthermore, from the perspective of prevention, drugs that increase CKD risk during non-pathogenic stages should also be used with caution. Therefore, we conducted this population-based cohort study to investigate the risk of CKD in a diabetic population using PPIs in Taiwan.

2. Materials and methods

2.1. Data source

The present study is based on data obtained from the NHI Research Database (NHIRD). Data from the NHI program are sorted into files, including registration files and original claim data for reimbursement. These data files were de-identified by scrambling the identification codes of both patients and medical facilities. The NHI program collects almost 95% of hospitals' healthcare data, and 99% of the entire population of 23 million in Taiwan are enrolled. Diseases are defined using the International Classification of Diseases codes (Ninth Revision, Clinical Modification; ICD-9-CM). ICD-9-CM codes for CKD diagnosis were applied in this study (016.0, 042, 095.4, 189, 223, 236.9, 250.4, 271.4, 274.1, 403–404, 440.1, 442.1, 446.21, 447.3, 572.4, 580–589, 590–591, 593, 642.1, 646.2, 753, and 984). Data on diagnostic codes, medication prescriptions, and medical procedures were also included in the database. The diabetic population was sorted as a specific database for further analysis.

The study was approved by the Institutional Review Board (IRB) at Taichung Tzu Chi Hospital (IRB: REC140-30). Since the original identification numbers have been encrypted to protect patients' privacy in NHIRD, the IRB agreed that the inform consent of the patient could be waived.

2.2. Study design and population

A population-based cohort study was designed to investigate the risk of CKD associated with PPI use in diabetic patients in Taiwan. Individuals in the diabetic population database of the NHIRD with a new diagnosis of diabetes from 2002 to 2013 were enrolled. The day on which diabetes mellitus was diagnosed was defined as the index day. The analysis was done using the diagnosis codes for diabetes mellitus, CKD, hypertension, gout, cerebrovascular disease, ischemic heart disease, peripheral arterial disease, and congestive heart failure.

The study also included PPIs available in Taiwan from 2002 to 2013 (esomeprazole, lansoprazole, omeprazole, pantoprazole, and rabeprazole). "Exposure" to PPIs was defined as subjects who had at least one prescription for PPIs after the index date and dosage over 180 DDD in one year. "No exposure" to PPIs was defined as never having any prescriptions for PPIs or not exceeding 180 DDD in one year after the index date. The average daily maintenance dose for an average of 70 kg of adults against the primary indication is the definition of the basic unit of defined daily dose (DDD). DDD is just a standardized unit and does not reflect the recommended or prescribed dose. The data on drug consumption is expressed in DDD using only the estimated consumption of the population. However, DDD provides a fixed reference unit that allows researchers to assess trends in drug consumption and compare different ethnic group. Besides, we also included the prescription history of antihypertensive medications, nonsteroid anti-inflammation drugs (NSAIDs), and oral antihyperglycemic medication, and matched them with individuals.

This study selected patients with incident diabetes from 2002 to 2013 and excluded patients with CKD that occurred before the diabetes index date. Individuals with PPI prescriptions before the diabetes index date or whose follow up duration was <60 days during the study period were excluded. For matching between cases and controls by comorbidities, the propensity score with 1:4 matching was used for comparison to a group with no exposure to PPIs. A flow chart is shown in Fig. 1.

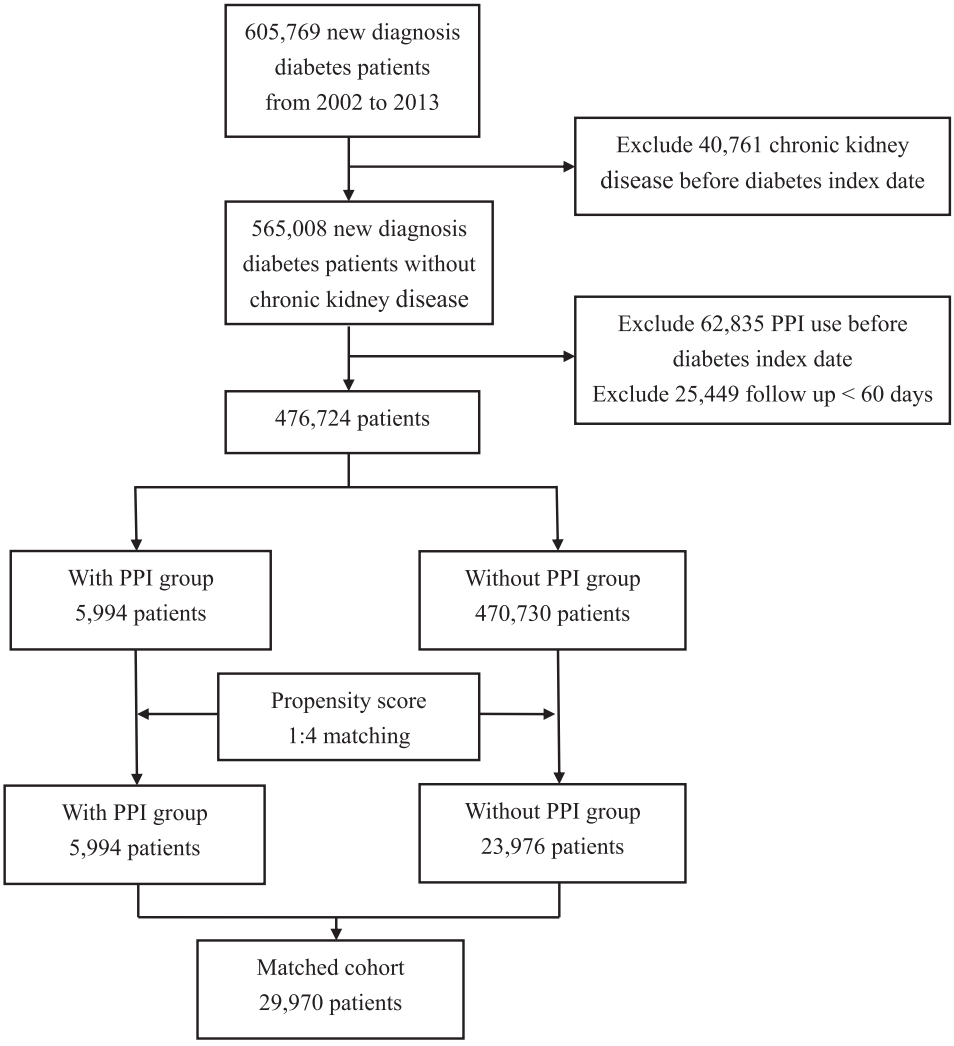

Fig. 1 – Flow chart of patient selection.

2.3. *Statistical analysis*

Qualitative variables are presented as numbers and percentages, and quantitative variables are expressed as the mean and standard deviation (SD). Pearson's χ^2 test and a *t*-test were used to examine the distributions of categorical variables and differences between continuous variables, respectively. A Cox proportional hazards regression model was used to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs) of incident CKD associated with PPI use. Multivariate analyses were used to adjust for potential confounding between comorbidities and the risk of CKD.

A multivariable adjusted competing-risk regression (CRR) model was introduced for further analysis. The most commonly used regression model for analyzing event-time data is the Cox proportional hazards model. In the presence of competing risks, however, the standard Cox model is not adequate because it treats competing risks for the event of interest as censored observations. Since the diabetic population has a higher risk of major adverse cardiac events (MACEs: cardiac death, nonfatal myocardial infarction, or a re-intervention procedure) [11], we considered death as a competing risk factor in our study.

The results of hazard ratios are presented as a forest plot. The cumulative risk of CKD was plotted as a Kaplan-Meier survival curve and stratified by PPI exposure.

SAS for Windows (version 9.3, SAS Institute Inc., Cary, NC, USA) and SPSS (version 19.0, SPSS Inc., Chicago, IL, USA) were used for the statistical analyses. The significance threshold was set at 0.05. Differences with a P-value of <0.001 were considered extremely statistically significant.

3. Results

Using the NHIRD sorted diabetic population file, we identified 605,769 patients with incident diabetes from 2002 to 2013 by ICD-9 diagnosis code, and excluded 40,761 individuals who had CKD before the diabetes index date. Therefore, 565,008 patients who had been newly diagnosed with diabetes without CKD were selected. Furthermore, to clarify the effect of PPIs during the study period, 62,835 individuals with PPI use before the diabetes index date were also excluded. In

addition, 25,449 patients were excluded for having a follow-up duration <60 days. Finally, 476,724 patients were enrolled.

A total 5994 patients who had a record of PPI use were in the PPI group, and 470,730 patients without a record of PPIs were in the no-PPI group. The PPI group was defined by having at least one PPI dosage over 180 DDD in one year. Using the propensity score with 1:4 matching, 23,976 patients were selected for the comparison cohort from the no-PPI group. The total matched cohort including the PPI cohort (5994) and no-PPI cohort (23,976) comprised 29,970 patients. A flow chart of the patient selection is presented in Fig. 1.

There were no significant differences between the exposure and no-exposure cohorts in age, gender, and comorbidities (including hypertension, gout, cerebrovascular disease, ischemic heart disease, peripheral arterial disease, and congestive heart failure). Except for anemia, the prevalence in the exposure cohort seemed slightly elevated. The exposure cohort also had more anti-hypertension medication and NSAIDs prescriptions. Almost 95% of patients in both the exposure and no-exposure cohorts had prescriptions for oral anti-hyperglycemic medication. The baseline characteristics of the subjects are listed in Table 1.

A multivariable Cox proportional hazard model was applied for the hazard ratios of CKD in diabetic patients with PPIs exposure (Table 2). Using the no-exposure as a reference, the PPI exposure group had a CKD rate of 12.6 per 100 people. Diabetic individuals using PPIs had a hazard ratio for developing CKD of 1.52 (CI 1.40–1.65, $p < 0.001$). Patients who had hypertension or gout also had hazard ratios of 1.23 (CI 1.14–1.32, $p < 0.001$) and 1.42 (CI 1.26–1.60, $p < 0.001$) for developing CKD, respectively. The cumulative CKD risk stratified by PPI exposure in diabetic patients is shown as Kaplan-Meier survival curves in Fig. 2. The results of a log rank test with $p < 0.001$ are also presented.

The results of multivariable adjusted CRR model of CKD in diabetic patients with PPI exposure are shown in Table 3. The results were obtained after adjustment for age, gender, hypertension, gout, cerebrovascular disease, ischemia heart disease, peripheral arterial disease, congestive heart failure, socioeconomic status, urbanization, and region. After adjusting and considering death as a competing risk, diabetic individuals with PPI exposure (with the no-exposure group as a reference) had a hazard ratio of 2.22 (CI 2.10–2.36, $p < 0.001$) for developing CKD. In the multivariable adjusted CRR model,

Table 1 – Baseline characteristics.

Characteristics	Exposure	No exposure	p-value
Patient no.	5994	23,976	
Age (mean ± SD)	59.1 ± 11.9	59.1 ± 11.9	0.628
Gender			0.967
Male	3565(59.5)	14,267(59.5)	
Female	2429(40.5)	9709(40.5)	
Comborbidities			
Hypertension	2127(35.5)	8546(35.6)	0.819
Gout	355(5.9)	1367(5.7)	0.511
CVA	358(6.0)	1467(6.1)	0.673
IHD	567(9.5)	2216(9.2)	0.605
PAD	87(1.5)	295(1.2)	0.172
CHF	196(3.3)	645(2.7)	0.015
Anemia	56(0.9)	144(0.6)	0.005
Drug			
Antihypertensive medications			<0.001
None-prescribed	1873(31.2)	9148(38.2)	
Prescribed	4121(68.8)	14,828(61.8)	
NSAIDs medications			<0.001
None-prescribed	409(6.8)	3840(16.0)	
Prescribed	5585(93.2)	20,136(84.0)	
OAM			<0.001
None-prescribed	46(0.8)	1268(5.3)	
Prescribed	5948(99.2)	22,708(94.7)	
SES			0.946
Low	1907(31.8)	7639(31.9)	
Moderate and high	4087(68.2)	16,337(68.1)	
Urbanization			0.361
Urban	1664(27.8)	6515(27.2)	
Un-urban	4330(72.2)	17,461(72.8)	
Geographic region			0.976
Northern/Central	3759(62.7)	15,031(62.7)	
Southern/Eastern	2235(37.3)	8945(37.3)	

Abbreviation: SES, socioeconomic status; NSAIDs, nonsteroidal anti-inflammatory drugs; OAM, oral anti-hyperglycemic medication; CVA, cerebrovascular disease; IHD, ischemic heart disease; PAD, peripheral arterial disease; CHF, congestive heart failure.
Antihypertensive medications: ACEI and ARB.
NSAIDs medications: naproxen, diclofenac, indomethacin, niflumic, mefenamic, nabumetone, tiaprofenic, tenoxicam, sulindac, celecoxib, etodolac, meloxicam, nimesulide, rofecoxib OAM: alpha-glucosidase, biguanides, DPP4, meglitinides, sulfonylureas, thiazolidnediones.

Table 2 – Multivariable cox proportional hazard model hazard ratios of CKD in diabetes patients.

Characteristics	Event, n	Rate (per 100 persons)	Multivariate HR [95% CI]	p-value
PPIs usage				
No exposure	2892/23,976	12.1	1	
Exposure	758/5994	12.6	1.52(1.40–1.65)	<0.001
Age			1.01(1.01–1.01)	<0.001
Gender				
Female	1461/12,138	12.0	1	
Male	2189/17,832	12.3	1.03(0.97–1.11)	0.344
Comborbidities				
Hypertension	1463/10,673	13.7	1.23(1.14–1.32)	<0.001
Gout	297/1722	17.2	1.42(1.26–1.60)	<0.001
CVA	207/1825	11.3	0.75(0.65–0.87)	<0.001
IHD	370/2783	13.3	0.96(0.85–1.07)	0.436
PAD	57/382	14.9	1.12(0.86–1.46)	0.384
CHF	128/841	15.2	1.11(0.93–1.34)	0.242
Anemia	24/200	12.0	1.16(0.77–1.73)	0.484
Drug				
Antihypertensive	2619/18,949	13.8	1.23(1.14–1.33)	<0.001
NSAIDs	2981/25,721	11.6	0.43(0.39–0.47)	<0.001
OAM	3363/27,024	12.4	1.30(1.15–1.47)	<0.001
SES				
Low	1214/9546	12.7	1	
Moderate and high	2436/20,424	11.9	0.91(0.85–0.98)	0.008
Urbanization				
Urban	915/8179	11.2	1	
Un-urban	2735/21,791	12.6	1.10(1.02–1.19)	0.014
Geographic region				
Northern/Central	2199/18,790	11.7	1	
Southern/Eastern	1451/11,180	13.0	1.08(1.01–1.16)	0.021

The adjusted HR was calculated after controlling for age, gender, hypertension, gout, CVA, IHD, PAD, CHF, socioeconomic status, urbanization and region.

Abbreviation: HR, hazard ratio; CI, confidence interval; CVA, cerebrovascular disease; IHD, ischemic heart disease; PAD, peripheral arterial disease; CHF, congestive heart failure.

PPIs exposure definition: over 180 DDD in one year after prescription.

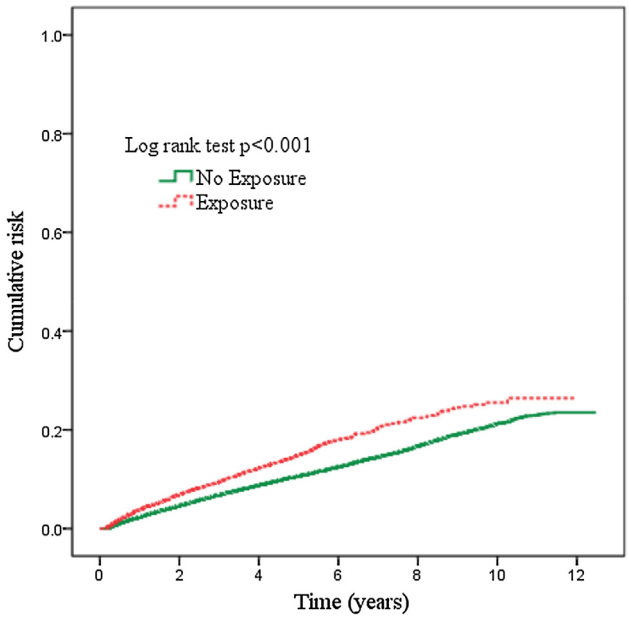

Fig. 2 – CKD cumulative risk stratified by with and without PPIs exposure.

the effect of hypertension (HR 1.17, CI 1.10–1.24, $p < 0.001$) and gout (HR 1.21, CI 1.09–1.33, $p < 0.001$) seemed weakened.

We also analyzed the effect of different types of PPIs (esomeprazole, lansoprazole, omeprazole, pantoprazole, and rabeprazole). Supplement table 1 shows the results of multivariable Cox proportional hazard model of CKD in the exposure and no-exposure group. Lansoprazole had the highest hazard ratio of 1.49 (CI 1.26–1.77, $p < 0.001$). Esomeprazole had a hazard ratio of 1.39 (CI 1.22–1.57, $p < 0.001$), while the hazard ratio of omeprazole was 1.12 but without statistical significance (CI 0.64–1.98, $p = 0.687$).

In the multivariable adjusted CRR model (supplement table 2), esomeprazole had the highest hazard ratio of 2.08 (CI 1.91–2.26, $p < 0.001$), and lansoprazole had a hazard ratio of 1.94 (CI 1.72–2.18, $p < 0.001$). The effect of pantoprazole (HR 1.58, CI 1.33–1.88) and rabeprazole (HR 1.81, CI 1.49–2.22) were also amplified in the CCR model compared to the Cox proportional hazard model. Fig. 3 shows a forest plot for comparison of the exposure factor.

4. Discussion

The results indicated that PPI use was associated with increased risk of CKD in diabetic patients in Taiwan. When

Table 3 – Multivariable adjusted competing-risk regression (CRR) model of CKD in diabetes patients.

Characteristics	Multivariate HR	95% CI	P value
PPIs usage			
No exposure	1		
Exposure	2.22	2.10–2.36	<0.001
Age	1.03	1.02–1.03	<0.001
Gender			
Female	1		
Male	1.28	1.21–1.35	<0.001
Comborbidities			
Hypertension	1.17	1.10–1.24	<0.001
Gout	1.21	1.09–1.33	<0.001
CVA	0.95	0.85–1.05	0.281
IHD	0.93	0.85–1.02	0.110
PAD	1.07	0.87–1.31	0.537
CHF	1.18	1.03–1.36	0.016
Anemia	1.63	1.25–2.11	<0.001
Drug			
Antihypertensive	1.03	0.97–1.09	0.356
NSAIDs	0.52	0.49–0.56	<0.001
OAM	1.39	1.26–1.53	<0.001
SES			
Low	1		
Moderate and high	0.83	0.79–0.88	<0.001
Urbanization			
Urban	1		
Un-urban	1.09	1.02–1.15	0.011
Geographic region			
Northern/Central	1		
Southern/Eastern	1.11	1.05–1.17	<0.001

The adjusted HR was calculated after controlling for age, gender, hypertension, gout, CVA, IHD, PAD, CHF, socioeconomic status, urbanization and region.

Abbreviation: HR, hazard ratio; CI, confidence interval; CVA, cerebrovascular disease; IHD, ischemic heart disease; PAD, peripheral arterial disease; CHF, congestive heart failure.

PPIs exposure definition: over 180 DDD in one year after prescription.

using a PPI dosage over 180 DDD in one year, CKD risk increased by almost 52% in diabetic patients. After separating the different types of PPIs, the results were still sound and statistically significant. Lansoprazole and esomepraozle had higher risk than the other PPIs. The outcome was amplified in the multivariable adjusted CRR model.

Recently, an observational US study found that PPI use is associated with a 20–50% higher risk of incident CKD [12]. The hazard ratio of baseline PPI use vs. propensity score-matched no PPI use was 1.76 (CI 1.13–2.74) in ARIC (Atherosclerosis Risk in Communities Study) cohort and 1.16 (CI 1.09–1.24) in Geisinger Health System replication cohort. The DM subgroup analysis revealed the hazard ratio for CKD remains significant. But the number of DM patients in each cohort was 14.9% of 322 patients & 10.8% of 16,900 patients in PPI users. Besides, another retrospective case–control study conducted by Arora et al. [13] has set CKD as PPI risk outcome and got an odds ratio (OR) 1.66 (CI 1.59 1.74) in DM subgroup (PPI with DM, n = 3976). However, these articles' DM study numbers are less than our study.

Furthermore, Xie et al. [14] suggested that PPI exposure associates with increased risk of incident chronic kidney disease with HR 1.28 (CI 1.23–1.34). Klatte et al. [15] addressed that initiation of PPI therapy and prolonged PPI use is associated with increased risk of CKD progression. Although the study numbers are in a large scale (PPI with DM, n = 72,309 & n = 14,319 in each study), there is neither dose effect nor PPIs difference discussed in those articles.

Hung et al. [16] claimed that the OR for CKD is 1.41 (CI 1.34, 1.48) for subjects using PPIs. Besides, the odds ratio of CKD in relation to the cumulative duration of different proton pump inhibitor is also clearly announced. Peng et al. [17] disclosed that PPIs use is associated with the risk of ESRD in patients with renal diseases. Odds ratio of ESRD associated with cumulative DDD of individual PPIs with third quartile segments were shown. But no clear cut off dose with safety is set up for clinical general practice and both are case control study essentially.

Comparing our study to previous findings, we had same conclusion that the use of PPIs is risk for chronic kidney disease. In addition, there are some differences and some new findings in our study. First, national wide relatively large scale population cohort study is achieved by NHIRD diabetic population database. Although it would be possible to analyze the association between PPIs use and CKD incidence in the overall population with subgroup analysis according to the presence or absence of diabetes, we have some considerations. Based on the database we have obtained previously (LHID 2010, NHI million people sample file), it is hard to produce a large number of DM patients which can overcome other

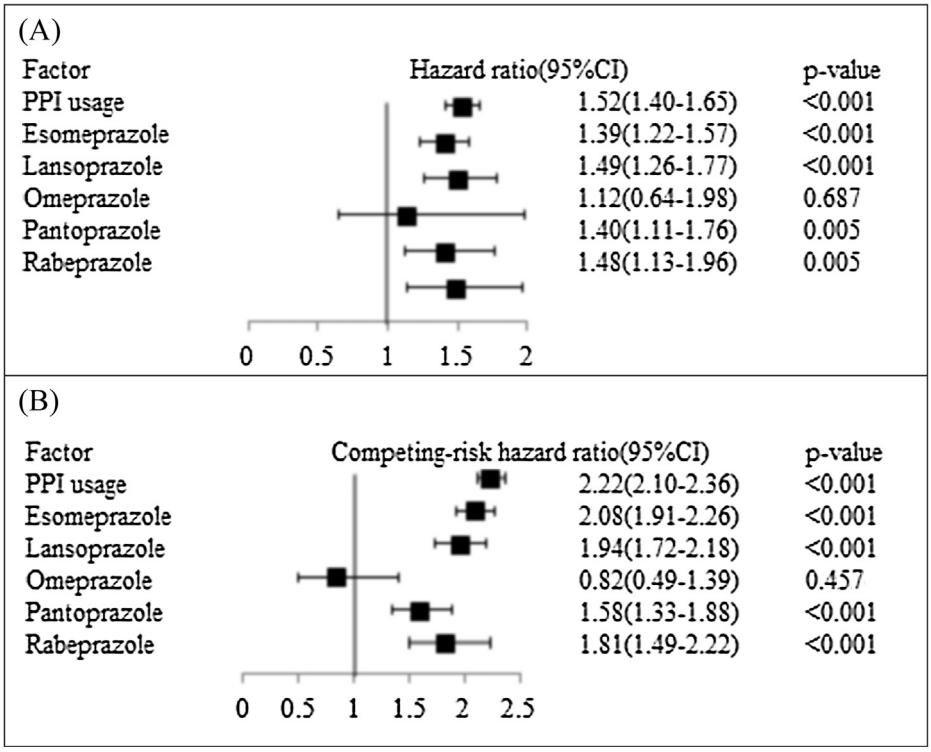

Fig. 3 – Multivariable cox proportional hazard model (A) and competing-risk model hazard ratios of CKD (B) by different PPIs exposure in diabetes patients.

studies. Therefore, we tried to use NHIRD diabetic population database to generate a confident number. Honestly speaking, it is our limitation and adaptation in database acquisition. Second, among the related topic of CKD risks with PPIs use in Taiwan NHIRD studies, Hung et al. and Peng et al. both exploited case control design. But we have followed world's trend and conducted a retrospective cohort study instead of case control study. Third, multivariable adjusted competing-risk regression (CRR) model was introduced. It is not seen in other related studies. Forth, a clear cut of 180 DDD is generally practicable in clinical. It is plausible that limiting PPI use reduces the incidence of CKD. On the other hand, it is important to use the lowest doses and shortest duration of treatment necessary for the condition being treated. We have announced the reasonable results. Instead of one or none exposure to PPIs, we have selected a practicable method under clinical indication.

To explain the possible pathogenesis and mechanisms of CKD, some studies have linked PPI use with acute interstitial nephritis [18–22] and acute kidney injury [23–27], which cause CKD and lead to end-stage renal disease. What is the cause of discrepancy between PPIs left room for discussion. Though PPIs share the core structures, their pharmacokinetics and pharmacodynamics are a little different. Area under the plasma concentration curve (AUC) and the gastric pH profile are very good indicators for evaluating PPI efficacy. Omeprazole has smaller AUC and $T_{1/2}$ (elimination half-life) than other PPIs [28], which may somehow explain the consequence of difference between PPIs in our study.

PPI usage was associated with adverse kidney outcomes; however, these findings were based on observational studies and low-quality evidence [29]. Even though the evidence power is inferior to that of randomized controlled studies, observational cohort studies are one of the best methods to study the adverse effects of medications in real-world settings. Therefore, we have followed the trends of previous investigations and further focused on diabetic individuals. Different regression model were also used to enhance the results and minimize confounders. The aim of this study is to clarify the effect of possible drug-induced risk, and although there is insufficient evidence to establish a causal relationship with certainty, there does appear to be a prevalent association.

One of the strengths in this study is that it is the first population-based observational cohort study to examine the occurrence of CKD in diabetic individuals who use PPIs in Taiwan. Although there may be some flaws (methodological limitations such as selection bias, detection bias) in the design, the results cannot be ignored. Second, we analyzed the exposure effect of different types of PPIs to give a clearer view of drug selection and comparisons. Even with the same kind of medicine, there are still different degrees of differences. Third, the results showed that the hazard ratios of PPIs seemed to be amplified after adjusting in the competing risk model. Death as a competing risk factor makes our study different than others.

Nevertheless, there were several inevitable limitations to our study. First, creatinine levels are not available, and there

is lack of laboratory examination data in the NHIRD database. However, the diagnosis of CKD was accurate. Nearly all Taiwanese patients with a principal diagnosis of CKD have received a multidisciplinary care (MDC) program since 2004 [30–32], thus reducing the probability of misdiagnosis.

Second, this study design was not a randomized clinical trial. A large-scale randomized controlled trial is impracticable in Taiwan, but well-designed observational studies can also yield comparable outcomes [33,34]. Although observational cohort studies cannot provide causative explanations, a national database such as the NHIRD can show trends and help to explore possible interventions and provide oriental results.

Third, information on the use of self paid medications and over-the-counter drugs remains unavailable in the NHIRD. The results of this study may therefore under-estimate the actual use of PPIs. A sensitivity analysis is also required. Fourth, because glycosylated hemoglobin (HbA1c) data are not available, the association between glycemic control and CKD cannot be explored.

Given the widespread use of PPIs, even a small effect on kidney outcomes could result in a large public health burden. PPIs should be used at the lowest effective dose, and inappropriate use should be avoided. Timely cessation of PPI therapy is recommended when there is no clear indication for use. We hope that such efforts might reduce the population burden of CKD in Taiwan.

5. Conclusion

PPIs increase the risk of CKD by 52% in diabetic patients when the dosage is over 180 DDD in one year in Taiwan. Lansoprazole and esomepraozle have higher risk than other PPIs.

Conflict of interest

The authors declare that they have no conflict of interest regarding the publication of this article. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diabres.2018.11.019.

REFERENCES

[1] Kuo HW, Tsai SS, Tiao MM, Yang CY. Epidemiological features of CKD in Taiwan. Am J Kidney Dis 2007;49(1):46–55. https://doi.org/10.1053/j.ajkd.2006.10.007. PubMed PMID: 17185145.

[2] Saran R, Robinson B, Abbott KC, Agodoa LYC, Bhave N, Bragg-Gresham J, et al. US Renal Data System 2017 annual data report: epidemiology of kidney disease in the United States. Am J Kidney Dis 2018;71(3S1):A7. https://doi.org/10.1053/j.ajkd.2018.01.002. PubMed PMID: 29477157.

[3] National Kidney F. KDOQI clinical practice guideline for diabetes and CKD: 2012 update. Am J Kidney Dis 2012;60 (5):850–86. https://doi.org/10.1053/j.ajkd.2012.07.005. PubMed PMID: 23067652.

[4] Coresh J, Selvin E, Stevens LA, Manzi J, Kusek JW, Eggers P, et al. Prevalence of chronic kidney disease in the United States. JAMA 2007;298(17):2038–47. https://doi.org/10.1001/jama.298.17.2038. PubMed PMID: 17986697.

[5] Jha V, Garcia-Garcia G, Iseki K, Li Z, Naicker S, Plattner B, et al. Chronic kidney disease: global dimension and perspectives. Lancet 2013;382(9888):260–72. https://doi.org/10.1016/S0140-6736(13)60687-X. PubMed PMID: 23727169.

[6] Forgacs I, Loganayagam A. Overprescribing proton pump inhibitors. BMJ 2008;336(7634):2–3. https://doi.org/10.1136/bmj.39406.449456.BE. PubMed PMID: 18174564; PubMed Central PMCID: PMC2174763.

[7] Chen TJ, Chou LF, Hwang SJ. Trends in prescribing proton pump inhibitors in Taiwan: 1997–2000. Int J Clin Pharmacol Ther 2003;41(5):207–12. PubMed PMID: 12776811.

[8] Lenihan CR, Sukumaran Nair S, Vangala C, Ramanathan V, Montez-Rath ME, Winkelmayer WC. Proton pump inhibitor use and risk of hip fracture in kidney transplant recipients. Am J Kidney Dis 2017;69(5):595–601. https://doi.org/10.1053/j.ajkd.2016.09.019. PubMed PMID: 27866965.

[9] Cho NJ, Choi CY, Park S, Park SH, Lee EY, Gil HW. Association of proton pump inhibitor use with renal outcomes in patients with coronary artery disease. Kidney Res Clin Pract 2018;37(1):59–68. https://doi.org/10.23876/j.krcp.2018.37.1.59. PubMed PMID: 29629278; PubMed Central PMCID: PMC5875577.

[10] Stevens PE, Levin A, Kidney Disease: Improving Global Outcomes Chronic Kidney Disease Guideline Development Work Group M. Evaluation and management of chronic kidney disease: synopsis of the kidney disease: improving global outcomes 2012 clinical practice guideline. Ann Intern Med 2013;158(11):825–30. https://doi.org/10.7326/0003-4819-158-11-201306040-00007. PubMed PMID: 23732715.

[11] Arampatzis CA, Goedhart D, Serruys PW, Saia F, Lemos PA, de Feyter P, et al. Fluvastatin reduces the impact of diabetes on long-term outcome after coronary intervention – a Lescol Intervention Prevention Study (LIPS) substudy. Am Heart J 2005;149(2):329–35. https://doi.org/10.1016/j.ahj.2004.03.067. PubMed PMID: 15846273.

[12] Lazarus B, Chen Y, Wilson FP, Sang Y, Chang AR, Coresh J, et al. Proton pump inhibitor use and the risk of chronic kidney disease. JAMA Intern Med 2016;176(2):238–46. https://doi.org/10.1001/jamainternmed.2015.7193. PubMed PMID: 26752337; PubMed Central PMCID: PMC4772730.

[13] Arora P, Gupta A, Golzy M, Patel N, Carter RL, Jalal K, et al. Proton pump inhibitors are associated with increased risk of development of chronic kidney disease. BMC Nephrol 2016;17(1):112. https://doi.org/10.1186/s12882-016-0325-4. PubMed PMID: 27487959; PubMed Central PMCID: PMC4973085.

[14] Xie Y, Bowe B, Li T, Xian H, Balasubramanian S, Al-Aly Z. Proton pump inhibitors and risk of incident CKD and progression to ESRD. J Am Soc Nephrol 2016;27(10):3153–63. https://doi.org/10.1681/ASN.2015121377. PubMed PMID: 27080976; PubMed Central PMCID: PMC5042677.

[15] Klatte DCF, Gasparini A, Xu H, de Deco P, Trevisan M, Johansson ALV, et al. Association between proton pump inhibitor use and risk of progression of chronic kidney disease. Gastroenterology 2017;153(3):702–10. https://doi.org/10.1053/j.gastro.2017.05.046. PubMed PMID: 28583827.

[16] Hung SC, Liao KF, Hung HC, Lin CL, Lai SW, Lee PC, et al. Using proton pump inhibitors correlates with an increased risk of chronic kidney disease: a nationwide database-derived case-controlled study. Fam Pract 2018;35(2):166–71. https://doi.org/10.1093/fampra/cmx102. PubMed PMID: 29045621.

[17] Peng YC, Lin CL, Yeh HZ, Chang CS, Wu YL, Kao CH. Association between the use of proton pump inhibitors and the risk of ESRD in renal diseases: a population-based, case-

control study. Medicine 2016;95(15). https://doi.org/10.1097/MD.0000000000003363. PubMed PMID: 27082596; PubMed Central PMCID: PMC4839840 e3363.
[18] Blank ML, Parkin L, Paul C, Herbison P. A nationwide nested case-control study indicates an increased risk of acute interstitial nephritis with proton pump inhibitor use. Kidney Int 2014;86(4):837–44. https://doi.org/10.1038/ki.2014.74. PubMed PMID: 24646856; PubMed Central PMCID: PMC4184187.
[19] Harmark L, van der Wiel HE, de Groot MC, van Grootheest AC. Proton pump inhibitor-induced acute interstitial nephritis. Br J Clin Pharmacol 2007;64(6):819–23. https://doi.org/10.1111/j.1365-2125.2007.02927.x. PubMed PMID: 17635502; PubMed Central PMCID: PMC2198775.
[20] Sierra F, Suarez M, Rey M, Vela MF. Systematic review: proton pump inhibitor-associated acute interstitial nephritis. Aliment Pharmacol Ther 2007;26(4):545–53. https://doi.org/10.1111/j.1365-2036.2007.03407.x. PubMed PMID: 17661758.
[21] Moore I, Sayer JA, Nayar A, Ahmed S, Tapson JS. Pantoprazole-induced acute interstitial nephritis. J Nephrol 2004;17(4):580–1. PubMed PMID: 15372423.
[22] Leonard CE, Freeman CP, Newcomb CW, Reese PP, Herlim M, Bilker WB, et al. Proton pump inhibitors and traditional nonsteroidal anti-inflammatory drugs and the risk of acute interstitial nephritis and acute kidney injury. Pharmacoepidemiol Drug Saf 2012;21(11):1155–72. https://doi.org/10.1002/pds.3329. PubMed PMID: 22887960.
[23] Brewster UC, Perazella MA. Acute kidney injury following proton pump inhibitor therapy. Kidney Int 2007;71(6):589–93. https://doi.org/10.1038/sj.ki.5002038. PubMed PMID: 17164832.
[24] Antoniou T, Macdonald EM, Hollands S, Gomes T, Mamdani MM, Garg AX, et al. Proton pump inhibitors and the risk of acute kidney injury in older patients: a population-based cohort study. CMAJ Open 2015;3(2):E166–71. https://doi.org/10.9778/cmajo.20140074. PubMed PMID: 26389094; PubMed Central PMCID: PMC4571830.
[25] Svanstrom H, Lund M, Melbye M, Pasternak B. Use of proton pump inhibitors and the risk of acute kidney injury among patients with rheumatoid arthritis: cohort study. Drug Saf 2018. https://doi.org/10.1007/s40264-018-0663-1. PubMed PMID: 29603109.
[26] Yang Y, George KC, Shang WF, Zeng R, Ge SW, Xu G. Proton-pump inhibitors use, and risk of acute kidney injury: a meta-analysis of observational studies. Drug Des Dev Therapy 2017;11:1291–9. 10.2147/DDDT.S130568 PubMed PMID: 28479851; PubMed Central PMCID: PMC5411168.
[27] Klepser DG, Collier DS, Cochran GL. Proton pump inhibitors and acute kidney injury: a nested case-control study. BMC Nephrol 2013;14:150. https://doi.org/10.1186/1471-2369-14-150. PubMed PMID: 23865955; PubMed Central PMCID: PMC3717286.
[28] Shin JM, Kim N. Pharmacokinetics and pharmacodynamics of the proton pump inhibitors. J Neurogastroenterol Motil 2013;19(1):25–35. https://doi.org/10.5056/jnm.2013.19.1.25. PubMed PMID: 23350044; PubMed Central PMCID: PMC3548122.
[29] Nochaiwong S, Ruengorn C, Awiphan R, Koyratkoson K, Chaisai C, Noppakun K, et al. The association between proton pump inhibitor use and the risk of adverse kidney outcomes: a systematic review and meta-analysis. Nephrol Dial Transplant 2018;33(2):331–42. https://doi.org/10.1093/ndt/gfw470. PubMed PMID: 28339835.
[30] Chen YR, Yang Y, Wang SC, Chiu PF, Chou WY, Lin CY, et al. Effectiveness of multidisciplinary care for chronic kidney disease in Taiwan: a 3-year prospective cohort study. Nephrol Dial Transplant 2013;28(3):671–82. https://doi.org/10.1093/ndt/gfs469. PubMed PMID: 23223224.
[31] Hwang SJ, Tsai JC, Chen HC. Epidemiology, impact and preventive care of chronic kidney disease in Taiwan. Nephrology. 2010;15(Suppl 2):3–9. https://doi.org/10.1111/j.1440-1797.2010.01304.x. PubMed PMID: 20586940.
[32] Yu YJ, Wu IW, Huang CY, Hsu KH, Lee CC, Sun CY, et al. Multidisciplinary predialysis education reduced the inpatient and total medical costs of the first 6 months of dialysis in incident hemodialysis patients. PLoS ONE 2014;9(11). https://doi.org/10.1371/journal.pone.0112820. PubMed PMID: 25398129; PubMed Central PMCID: PMC4232513 e112820.
[33] Concato J, Shah N, Horwitz RI. Randomized, controlled trials, observational studies, and the hierarchy of research designs. N Engl J Med 2000;342(25):1887–92. https://doi.org/10.1056/NEJM200006223422507. PubMed PMID: 10861325; PubMed Central PMCID: PMC1557642.
[34] Benson K, Hartz AJ. A comparison of observational studies and randomized, controlled trials. N Engl J Med 2000;342(25):1878–86. https://doi.org/10.1056/NEJM200006223422506. PubMed PMID: 10861324.