



# Pioglitazone Reduces Mortality and Adverse Events in Patients With Type 2 Diabetes and With Advanced Chronic Kidney Disease: National Cohort Study

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Chieh-Li Yen,<sup>1</sup> Chao-Yi Wu,<sup>2</sup>  
Lai-Chu See,<sup>3,4,5</sup> Yi-Jung Li,<sup>1</sup>  
Min-Hua Tseng,<sup>6</sup> Wei-Sheng Peng,<sup>4</sup>  
Jia-Rou Liu,<sup>4</sup> Yung-Chang Chen,<sup>1</sup>  
Tzung-Hai Yen,<sup>1</sup> Ya-Chung Tian,<sup>1</sup>  
Chih-Wei Yang,<sup>1</sup> Gerard F. Anderson,<sup>7</sup>  
and Huang-Yu Yang<sup>1,7</sup>

Several oral hypoglycemic agents (OHA) are not recommended for patients with advanced chronic kidney disease (CKD). Early use of supplemental insulin, which can potentially increase the risk of hypoglycemia and cardiovascular events, was noted among patients with limited choices. Pioglitazone is a thiazolidinedione, which can be safely used in patients with CKD and patients with end-stage renal disease (ESRD) without dose adjustment. Previous research has indicated that pioglitazone can improve peripheral insulin sensitivity and potentially reduce cardiovascular risks (1). However, the benefit of pioglitazone in patients with type 2 diabetes (T2D) with advanced CKD has been overlooked. Using Taiwan's National Health Insurance Research Database (NHIRD), which covers ~99.8% of Taiwan's population (nearly 23.37 million) and provides comprehensive health care information, we compared the incidence of major cardiac and cerebrovascular events (MACCE) and new-onset ESRD requiring dialysis and the rate of mortality in T2D patients with advanced CKD treated with pioglitazone and the most popular OHA, dipeptidyl peptidase 4 (DPP-4) inhibitors, in this population.

DPP-4 inhibitors were known for their low risk of hypoglycemia and near-neutral effect on cardiovascular outcomes (2).

In this study, a total of 90,193 T2D patients older than the age of 20 years with advanced CKD were identified from the NHIRD between 2006 and 2016. The patients were divided into two groups, pioglitazone ( $n = 2,121$ ) or DPP-4 inhibitors (reference group [ $n = 15,325$ ]), according to the treatments they received within the 3-month period after the diagnosis of advanced CKD, defined as the date of initiation of erythropoietin-stimulating agents for the treatment of CKD. Defining the 91st date after advanced CKD diagnosis as the index date, we used the propensity score stabilized weights to simulate a randomized clinical trial by balancing the baseline characteristics between the two study groups (3). Baseline characteristics including age, sex, income level, urbanization level of residence, comorbidities (hypertension, dyslipidemia, connective tissue diseases, liver cirrhosis, peripheral artery disease, and atrial fibrillation), history of hospitalizations (related to infection, myocardial infarction, stroke, or heart failure), and medications (all kinds of OHA,

antihypertension, antiplatelet agents, non-steroid anti-inflammatory drugs, ketosteril, and diuretics) were included in the study. The values of absolute standardized mean difference of all characteristics in this study are  $\leq 0.1$ , indicating an insignificant difference in potential confounders between the two study groups. Then survival analysis (Kaplan-Meier method and log-rank test for univariate analysis and Cox proportional hazards model for multivariate analysis) was performed for comparison of the study outcomes between the pioglitazone group and the DPP-4 group.

As shown in Table 1, after propensity score stabilized weights, the pioglitazone group exhibited a lower rate (per person-years) of all-cause mortality (12.4% vs. 13.4%, HR 0.87, 95% CI 0.81–0.94), MACCE-related mortality (4.6% vs. 4.7%, HR 0.87, 95% CI 0.77–0.98), new-onset heart failure (1.67% vs. 2.64%, HR 0.75, 95% CI 0.62–0.91), and infection-related mortality (7.5% vs. 8.1%, HR 0.87, 95% CI 0.77–0.98) and a marginally lower risk of MACCE (10.9% vs. 12.4%, HR 0.92, 95% CI 0.85–1.00) compared with the reference group. The risk of new-onset ESRD requiring permanent dialysis did not differ between two.

<sup>1</sup>Kidney Research Institute, Nephrology Department, Chang Gung Memorial Hospital, College of Medicine, Chang Gung University, Taoyuan, Taiwan

<sup>2</sup>Division of Allergy, Asthma, and Rheumatology, Department of Pediatrics, Chang Gung Memorial Hospital, College of Medicine, Chang Gung University, Taoyuan, Taiwan

<sup>3</sup>Division of Rheumatology, Allergy and Immunology, Chang Gung Memorial Hospital, Taoyuan, Taiwan

<sup>4</sup>Department of Public Health, College of Medicine, Chang Gung University, Taoyuan, Taiwan

<sup>5</sup>Biostatistics Core Laboratory, Molecular Medicine Research Center, Chang Gung University, Taoyuan, Taiwan

<sup>6</sup>Division of Nephrology, Department of Pediatrics, Chang Gung Memorial Hospital, Chang Gung University, Taoyuan, Taiwan

<sup>7</sup>Department of Health Policy and Management, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD

Corresponding author: Huang-Yu Yang, [hyyang01@gmail.com](mailto:hyyang01@gmail.com)

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**Table 1—Mortality, MACCE, and ESRD among patients with T2D and advanced CKD, after propensity score stabilized weighting**

Outcome	Events (incidence, per 100 person-years)			P
	Pioglitazone (n = 1,909.5)	DPP-4 inhibitors (n = 15,281.8)	HR (95% CI)	
All-cause mortality	1,003.08 (12.44)	5,361.82 (13.44)	0.87 (0.81–0.94)	<0.001
MACCE <sup>a</sup>	700.3 (10.90)	4,102.53 (12.42)	0.92 (0.85–1.00)	0.053
Cardiogenic shock	14.54 (0.18)	47.02 (0.12)	1.55 (0.84–2.84)	0.159
New-onset heart failure	129.38 (1.67)	1,005.65 (2.64)	0.75 (0.62–0.91)	0.002
Malignant arrhythmia	49.59(0.58)	214.81 (0.48)	1.11 (0.81–1.54)	0.514
Myocardial infarction	177.6 (2.29)	1,006.98 (2.62)	0.89 (0.75–1.05)	0.157
Stroke	219.30 (2.88)	1,071.10 (2.80)	0.98 (0.84–1.14)	0.753
Revascularization with PCI	361.60 (5.07)	2,172.87 (6.02)	0.88 (0.79–0.99)	0.037
Revascularization with TT	0 (0)	0 (0)		
Revascularization with CABG	52.90 (0.67)	291.26 (0.74)	0.86 (0.63–1.17)	0.328
MACCE-related death	375.40(4.65)	1,908.79 (4.78)	0.87 (0.77–0.98)	0.022
Infection-related death	606.97 (7.53)	3,235.45 (8.11)	0.88 (0.81–0.97)	0.008
New-onset ESRD	1,046.98 (27.92)	8,021.76 (38.82)	0.97 (0.91–1.04)	0.423

For hazard ratios (HRs), pioglitazone vs. DPP-4 inhibitors and DPP-4 inhibitors was a reference group. CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention; TT, thrombolytic therapy. <sup>a</sup>Any of myocardial infarction, cardiogenic shock, new-onset heart failure, coronary revascularization, malignant arrhythmia, and cerebrovascular events.

A significant body of evidence, such as that from the PROspective pioglitAzone Clinical Trial In macroVascular Events (PROactive) and Pioglitazone Effect on Regression of Intravascular Sonographic Coronary Obstruction Prospective Evaluation (PERISCOPE) trial (4), has shown that the use of pioglitazone can reduce atherosclerosis and related cardiovascular risk. Our study further indicated that the protective effects of pioglitazone on cardiovascular events persisted even in patients with advance CKD who required dialysis. Moreover, our data also demonstrated that pioglitazone can reduce the probability of infection-related mortality, which was less evaluated in previous research. We surmised that the benefits of pioglitazone may be via the reduction of protein energy wasting, which is a common complication among patients with CKD and ESRD, causing fragility, infection, and death (5). The insulin-sensitizing and appetite-stimulating effects of pioglitazone potentially attenuate the protein energy wasting effect and further reduce the infection-related death. Finally, regarding drug safety, fluid retention is of concern when pioglitazone is prescribed. In fear of early

dialysis or heart failure, clinicians may avoid using it. In the current study, our results show that pioglitazone does not increase the risk of new-onset ESRD requiring dialysis or new-onset heart failure.

Lack of laboratory data, including sugar control and albumin level, in the NHIRD and the observational study design were inevitably the two inherent limitations in this study. However, extensive and comprehensive comparison of the outcomes of interest between pioglitazone and DPP-4 inhibitor treatment provided novel insights into the benefits of pioglitazone in a targeted population.

In conclusion, this study revealed that pioglitazone can safely reduce several adverse outcomes in T2D patients with advanced CKD.

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Y.-C.T., and C.-W.Y. contributed to critical revision. L.-C.S., W.-S.P., J.-R.L., and G.F.A. performed the statistical analysis. H.Y.Y. and L.C.S. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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