The Effect of Strict Adherence on The Association between Concurrent Utilization of **Metformin and Fracture Risk among Type 2 Diabetes Patients**

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Prior studies showed that metformin (MET) use positively affected bone mineral density among diabetic patients; however, as a chronic disease, the patients may be non-adherent to metformin. Few researchers have discussed the flexibility of the adherence issue. This study aims to examine whether strict adherence to concurrent utilization of metformin has a lower fracture risk among type 2 diabetes mellitus (T2DM) patients.



A retrospective cohort study design utilizing data from the National Health Insurance Database (NHIRD) from 2014 to 2020. The study population includes T2DM patients aged 50 or above who concurrently maintained the use of MET and second-line oral diabetes drugs and had no previous history of fractures. A medication possession ratio (MPR) exceeding 40% within a one-year period was defined as "MET adherence," while completely discontinued individuals were categorized as "MET non-adherence." A 90-day and 45-day gap scenarios were set to examine adherence flexibility. Diagnosis codes from outpatient and inpatient settings were used to identify fracture occurrence. A propensity score matching (PSM) technique was used to balance covariates and minimize potential biases. A Cox proportional hazard model was applied to calculate the hazard ratio between the two groups in two scenarios, evaluating the impact of strict adherence to MET on fracture risk. This study protocol was approved by the Institutional Review Board (IRB) of Taipei Hospital, Ministry of Health and Welfare (TH-IRB-0023-0016).





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RESULTS

A total of 38,011 and 30,983 patients were presented in a 90-day gap and a 45-day gap scenario, respectively. In both scenarios, approximately 55% of patients are male, and 67% are aged 50-64. The adjusted subdistribution hazard ratio (aSHR) of all fractures was 0.76 under the 90-day gap scenario; however, under the 45-day scenario, the aforementioned aSHR was 0.82. (both p<.0001)

	After PSM						
	Persistence		Non-persistence				
	N	(%)	N	(%)	SMD		
amle Size	38,011		38,011				
Лаle	21,009	(55.3)	21,009	(55.3)	< 0.001		
Age, y							
Mean (SD)	61.82	(7.84)	61.83	(7.85)	< 0.001		
50-64	25,251	(66.4)	25,286	(66.5)	0.002		
65-74	9,860	(25.9)	9,817	(25.8)	0.003		
75+	2,900	(7.6)	2,908	(7.7)	0.001		
DSCI (adapted diabetes d	complications severit	y index)					
Mean (SD)	1.41	(2.18)	1.42	(2.12)	0.006		
0	20,414	(53.7)	19,243	(50.6)	0.062		
1	6,905	(18.2)	7,544	(19.8)	0.043		
2	3,825	(10.1)	4,404	(11.6)	0.049		
3+	6.867	(18.1)	6.820	(17.9)	0.003		

The hazard risk of fracture outcomes in MET persistent T2DM patients on second-line OAD therapy

Fracture Type	Incidence (per 1,0000 person-years, 95% CI)			
A11	6.10 (5.54-6.71)			<u> </u>
Hip, vertebral, radius	4.50 (4.02-5.02)			\vdash
Hip	0.46 (0.32-0.65)	F		
/ertebral	1.78 (1.49-2.12)			
Radius	2.38 (2.03-2.76)			H
		0.4	0.6	

CONCLUSION

According to our result, it may have some flexibility in the adherence criteria. Adhering strictly to concurrent metformin use is associated with a decreased risk of fractures in patients with T2DM.





