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Context. The effect of antidepressants (ATDs) use on mortality in patients with diabetes mellitus (DM) has not yet been sufficiently studied although co-morbid depression is common in this population.

Objective: To explore the impact of ATDs on mortality among DM patients.

Design: A retrospective cohort study in a national database.

Setting: This population-based study used National Health Insurance Research Database in Taiwan. Since 2000, we identified 53,412 cases of newly diagnosed patients with DM and depression. Patient cases were followed for assessing mortality until 2013.

Main outcome measure: The association between mortality and ATDs use was explored adjusting for cumulative dosing.

Result: Using the time-dependent Cox regression model, ATDs use was associated with significantly reduced mortality among patients with DM (in the highest dose group, hazard ratio [HR]= 0.65, 95% confidence interval [CI]= 0.59-0.71). Further analysis showed that differences on mortality existed across ATD categories: selective serotonin reuptake inhibitors (HR=0.63, 95% CI= 0.56-0.71), serotonin-norepinephrine reuptake inhibitors (HR=0.58, 95% CI= 0.44-0.78), norepinephrine-dopamine reuptake inhibitors (HR=0.20,95% CI= 0.07-0.63), mirtazapine (HR=0.60, 95% CI= 0.45-0.82), tricyclic/tetracyclic antidepressants (HR=0.73, 95% CI= 0.54-0.97), trazodone (HR=0.52, 95% CI= 0.29-0.91). However, reversible inhibitor of monoamine oxidase A (RIMA) was found to be associated with an increase, rather than decrease, in total mortality. (HR=1.48, 95% CI= 1.09-1.99).

Conclusion: Most ATDs but not RIMA were associated with significantly reduced mortality among population with comorbid DM and depression.

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Introduction

Diabetes mellitus (DM) is a highly prevalent chronic disease associated with increased mortality(1). DM significantly raises the incidence of mortality, ischemic attacks and heart failure in patients with established or high-risk atherosclerosis in a recent 4-year large cohort(2). A study in China analyzing mortality in DM patients (n=2654) from 2002 to 2012 also reported increased mortality largely due to cardiovascular-related events (3). The reduction of mortality in individuals with DM remains a critically important and unmet need.

The incidence of major depressive disorder amongst individuals with DM is significantly greater than the general population(4-6). Independently, depression is associated with significant excess mortality resulting from suicide, accidental or violent causes, and diseases (7). Consequently, DM and depression each independently contribute to increasing total mortality (8-11). Therefore, assessing the impact of antidepressants (ATDs) on mortality in patients with comorbid depression and DM has significant clinical relevance.

Several studies have reported an association between ATD use and increased risk of DM diagnosis(12-14). These findings suggest a deleterious effect of certain ATDs on insulin/glucose homeostasis, including tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs), and serotonin antagonist and reuptake inhibitors (SARIs). To our knowledge, the effect of the ATDs use on mortality in DM patients has not yet been sufficiently studied. In the present study, we sought to determine the effect of ATD on mortality in persons with diabetes and depression.

Methods

Cases were identified from the Taiwan National Health Insurance Research Database (NHIRD) (see figure 1 for flowchart)(15). The present study applied a specific data subset for all patients with mental disorders (ICD-9 codes 290–319) among 1998 to 2013. This subset data included patients who had at least one psychiatric admission or three psychiatric outpatient visits and the diagnosis was made by psychiatrists (16). From the dataset, newly diagnosed DM patients (ICD 9 code: 250) among 2000 to 2013, who combined a later newly diagnosis of depression, including major depressive disorder or dysthymic disorder (ICD 9 code: 296.2, 296.3, 300.4, 311), were selected in this study. Towards establishing the validity of a DM diagnosis in the NHIRD, diagnostic accuracy has been reported previously as 74.6% (17). Subjects with ATDs use prior to the diagnosis of DM were excluded. The cumulative dose of ATDs was measured during the time of follow-up.

Of the 53412 enrollees, 50,532 people using ATDs and 2,880 people not using ATDs (Table 1). There was an attempt to determine whether there were any characteristics (e.g. sociodemographic) that differentiate the two groups (i.e. those taking and not taking ATDs). Urbanization and financial status were divided into 4 levels. Four comorbid chronic diseases (heart failure, end-stage renal disease (ESRD), chronic obstructive pulmonary disease (COPD), malignancy) that was known to increase the mortality of patients with depression,

were included as possible confounding variables(18). Adapted diabetes complication severity index, indicating the severity of DM complication for each patient, was also counted in.(19)

Later, we analyzed the individual effect of these covariates on mortality (Table 2), with adjustment for multiple confounding variables including gender, age, urbanization, income, comorbidity, the severity of DM, and the total ATD dose (cumulative defined daily dose, cDDD)(20). In addition, the ATDs were further analyzed as a function of seven different classes adjusting for other covariates (i.e., SSRI; serotonin-norepinephrine reuptake inhibitor, SNRI; norepinephrine-dopamine reuptake inhibitor, NDRI; mirtazapine; trazodone; tricyclic/tetracyclic antidepressants; and reversible inhibitor of monoamine oxidase A (RIMA). Each category of antidepressants was divided into 3 groups according to cumulative dose exposure. Risk of mortality was evaluated by comparing the highest dose group (cDDD $\geqq$ 84) to the lowest dose group (cDDD < 28). All-cause mortality was analyzed using a repeated measures time-dependent Cox regression model. ATDs prescription was measured each year during the study period. Dosages of ATDs prescriptions per year served as the main exposure variable. The risk of mortality during the follow-up period was calculated through survival analysis (21). To explore the influence of time since diagnosis of diabetes and duration of ATD use, we also carried out the sensitivity analysis by time-fixed model (see the supplement tables) (22).

Results

Comparing the demographic data between the ATD use and non-ATD use groups, there were more males and elderly individuals in the non-ATD use group (p<0.05) (Table 1). The ATD use group had a younger age distribution, higher degree of urbanization, better socioeconomic state, which may be due to their greater accessibility to psychotropic medication. In the non-ATD use group, there was a higher rate of heart failure (p<0.001); no significant differences detected between groups with respect to the other three comorbid diseases. Furthermore, the non-ATD use group had higher severity of DM complications than the ATD use group, which may reflect insufficient personal healthcare or insufficient drug adherence. Duration between diagnosis of DM to death or censored was 7.4±3.4 years in death group and 10.0±3.3 years in non-death group. Duration between ATD first prescription to death or censored was 4.4±3.2 years in death group and 6.3±3.7 years in non-death group (see supplement) (22). For Time-fixed Cox regression model, the cohort was divided into three subgroups: < 28 DDDs (n =10317), 28–84 DDDs (n = 9771), and 84-364 DDDs

(n =33324) (Fig 2). The mean follow duration among different groups ranged from 9.2 years to 9.9 years. The incidence rate of death events ranged from 1113.7/ per 100000 person-years (95 %CI: 1078.4-1150.3) in highest dose group to 1963.7/ per 100000 person-years (95%CI: 1876.8-2054.7) in lowest dose group (Log-rank test, p<0.001). (Supplement table 6) (22)

After adjustment (Table 2), it was determined that as total cumulative dose increased, total mortality decreased; statistical significance was noted when cDDD was higher than 28 (HR= 0.91, CI=0.83-1.00). When cDDD >= 84, the statistical significance was greater (HR= 0.65, CI=0.59-0.71). The results from different sensitivity analysis by considering duration of diagnosis of DM or prescription of antidepressants also showed similar findings (22). Males were at greater risk for mortality compared to females (HR=1.71, CI=1.63-1.80). Compared to individuals living in rural areas, those in urban areas exhibited a lower risk of mortality (in highest urbanization group, HR=0.75, CI=0.69-0.83). Moreover, higher financial status was associated with reduced mortality (in the best economic group, HR= 0.67, CI=0.61-0.73). Four comorbid diseases (i.e. heart failure, ESRD, COPD, and malignancy) independently contributed to increased mortality (p<0.05). The greater overall severity of DM complications was associated with a higher mortality (HR=1.18, CI=1.15-1.20).

In table 3, we further analyze 7 ATDs to ascertain the effect of each respective antidepressant class/agent ATD on mortality. When cDDD < 83, there was no significant effect detected on overall mortality. When cDDD ≥84, there was a significant reduction in DM mortality: SSRI (HR= 0.63, 95% CI= 0.56-0.71), SNRI (HR=0.58, 95% CI=0.44-0.78), NDRI (HR=0.20, 95% CI= 0.07-0.63), mirtazapine (HR=0.60, 95% CI= 0.45-0.82), tricyclic/tetracyclic antidepressants (HR=0.73, 95% CI= 0.54-0.97), trazodone (HR=0.52, 95% CI= 0.29-0.91). In contrast, mortality of the RIMA group was increased in both the low dose (HR=1.91, 95% CI= 1.39-2.61) and high dose groups (HR=1.48, 95% CI= 1.09-1.99).

Discussion

To our knowledge, this is the first large population-based cohort study to identify an inverse association between ATD use and mortality among individuals diagnosed with DM and comorbid depression. Higher dose of ATD use was linked to lower mortality. The inverse effect existed across different types of antidepressants.

There are studies that have reported on the association between ATD use and mortality in other chronic disease states. For example, Qian et al. reportedthat ATD use significantly

reduced total mortality in persons with COPD (HR=0.55, CI=0.44-0.68)(23). Separate and contradictory findings were reported in person with cardiac disease. For example a single large study assessed 121,252 patients with heart failure and found that ATD use increased total mortality; with depression (n=2568, HR=1.21) and without a diagnosis of depression (n=16780, HR=1.24) (24). Another study evaluated 19411 patients surviving their first hospitalization for heart failure reporting that tricyclic antidepressants and SSRI use increased risk of both overall and cardiovascular death(25). In our study we found directionally opposite findings i.e. ATD use reduces all-cause mortality, with a dose-dependent effect.

The mediators of mortality reduction in our sample is not known but is hypothesized to be due to disparate factors including but not limited to inflammation(26). It is possible that proinflammatory cytokines could be meditational. Cytokines and their signaling pathways have multiple downstream effects that influence the metabolism (i.e., synthesis, release, reuptake) of a variety of neurotransmitters including serotonin, dopamine, and glutamate (27). In addition, alterations in the innate immuno-inflammatory system are also well documented in diabetes and have been associated with increased level of interleukin-6 and C-reactive protein(28). The foregoing observation provides the framework for hypothesizing that modulating inflammatory systems with ATD use in patients with DM could have an anti-mortality effect.

A separate non-mutually exclusive hypothesis is that ATD exerted a salutary effect on the coagulation profile in individuals with DM and depression. Carmassi Fet. al studied 40 insulin dependent DM patients, and found an impairment of the homeostatic balance, possibly a hypercoagulable state(29). As well known, SSRI and SNRI showed the ability to inhibit platelet adhesion and consequently influence coagulation and possibly atherosclerotic pathway (30).

This data provide further rationale for the screening and treating of depression in persons who have DM(31). In future research, it should be further clarified the different effect of ATDs among different diseases, as the present opposite effect found in DM and heart failure patients.

There were several limitations to our study and interpretation of our results. For instance, the specific cause of death for each individual was not known, especially unnatural deaths or cardiovascular deaths (32). Having this information may help to understand a mechanistic pathway wherein ATDs reduce mortality (a direct effect through anti-depression or a possible

indirect effect through anti-inflammation). Notwithstanding the use of specific data subsets (registry for the psychiatric illness patient database), the validity of the diagnosis of depression remains a limitation to this database study. Furthermore, we did not include comorbid conditions (e.g. smoking, obesity) that may potentially be confounding factors (33). Finally, this result may not be generalized to the population beyond DM patients in Taiwan. Further studies are warranted to explore whether the findings can be replicated among non-DM patients or in other countries with different prescription pattern of antidepressants. Notwithstanding these limitations, several strengths are noted in ours study. We used a nationwide database with a large sample size and selection bias is minimized. Moreover, the large national database makes it possible to analyze seven classes of antidepressants. We limited the assessment to these persons who had a relatively recent diagnosis of diabetes, which minimizes the influence of their DM course on the mortality. Additionally, we limited the enrollment in our sample to these with a recent diagnosis of depression, which provided opportunity to evaluate cumulative-dose calculation and the time-dependent model.

This data provides further rationale for the screening and treating of depression in persons who have DM (33). In future research, it should be further clarified the different effect of ATDs among different diseases, as the present opposite effect found in DM and heart failure patients.

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Disclosure summary:

The Institutional Review Board (IRB) of the Chang Gung Memorial Hospital approved this study (CGMH 104-7528B). All authors have fulfilled the criteria of authorship, without conflict of interest, reviewed and approved the paper, and attested to the integrity of the work submitted. The manuscript is original, is not under consideration by another journal, and has not been published previously.

Data Availability

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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Figure 1. Flowchart of the study design

Figure 2. The incidence rate of death per 100,000 person-years between three exposure subgroups (Time-fixed Model)

Table 1. The demographic and clinical characteristics of cases ATD and non-ATD user

Variables	Total		ATD user (N=50532)		Non-ATD user (N=2880)		p value
	n	%	n	%	n	%	
Gender							0.0135
Male	23903	44.75	22550	44.63	1353	46.98	
Female	29509	55.25	27982	55.37	1527	53.02	
Age (year)							<0.0001
18-44	10974	20.55	10529	20.84	445	15.45	
45-64	26243	49.13	25022	49.52	1221	42.40	
>=65	16195	30.32	14981	29.65	1214	42.15	
Urbanization level							<0.0001
1(City)	16324	30.56	15519	30.71	805	27.95	
2	24179	45.27	22944	45.40	1235	42.88	
3	8811	16.50	8268	16.36	543	18.85	
4(Villages)	4098	7.67	3801	7.52	297	10.31	
Income							0.0003
0	10327	19.33	9717	19.23	610	21.18	
1~15840	9456	17.70	8963	17.74	493	17.12	
15841~25000	23843	44.64	22518	44.56	1325	46.01	

>25000	9786	18.32	9334	18.47	452	15.69	
Comorbidities							
Heart failure	9223	17.27	8645	17.11	578	20.07	<0.0001
ESRD	1921	3.60	1813	3.59	108	3.75	0.6494
COPD	21502	40.26	20322	40.22	1180	40.97	0.4209
Malignancy	9882	18.50	9325	18.45	557	19.34	0.2333
Adapted DCSI (mean±SD)	0.45±0.90		0.45±0.90		0.53±0.99		<0.0001

ESRD=end-stage renal disease, COPD=Chronic Obstructive Pulmonary Disease, DCSI=Diabetes Complications Severity Index

Table 2. Time-dependent Cox regression analysis of mortality in patients with DM and depressive disorder

Variables	Crude HR				Adjusted HR*			
	HR	95% CI		p value	HR	95% CI		p value
Antidepressant drug use								
<28 cDDD	1.00	Reference			1.00	Reference		
28-83 cDDD	0.92	0.84	1.01	0.0818	0.91	0.83	1.00	0.0478
>=84 cDDD	0.60	0.55	0.66	<0.0001	0.65	0.59	0.71	<0.0001
Gender								
Female	1.00	Reference			1.00	Reference		
Male	1.78	1.70	1.87	<0.0001	1.71	1.63	1.80	<0.0001
Age (year)								
18-44	1.00	Reference			1.00	Reference		
45-64	1.82	1.66	2.00	<0.0001	1.58	1.44	1.74	<0.0001
>=65	5.34	4.88	5.84	<0.0001	3.44	3.13	3.78	<0.0001
Urbanization level								
1(City)	0.69	0.63	0.76	<0.0001	0.75	0.69	0.83	<0.0001
2	0.78	0.72	0.85	<0.0001	0.83	0.76	0.91	<0.0001
3	0.91	0.83	1.00	0.0536	0.90	0.82	0.99	0.0282
4(Villages)	1.00	Reference			1.00	Reference		
Income								
0	1.00	Reference			1.00	Reference		
1~15840	1.09	1.02	1.17	0.0177	1.00	0.93	1.07	0.9265
15841~25000	0.77	0.73	0.82	<0.0001	0.87	0.81	0.93	<0.0001
>25000	0.55	0.51	0.60	<0.0001	0.67	0.61	0.73	<0.0001
Comorbidities								
Heart failure	2.52	2.40	2.65	<0.0001	1.45	1.37	1.52	<0.0001
ESRD	3.26	3.02	3.51	<0.0001	2.73	2.53	2.96	<0.0001
COPD	1.75	1.67	1.84	<0.0001	1.07	1.02	1.12	0.0105
Malignancy	3.93	3.75	4.12	<0.0001	3.16	3.01	3.32	<0.0001
Adapted DCSI	1.37	1.34	1.39	<0.0001	1.18	1.15	1.20	<0.0001

ESRD=end-stage renal disease, COPD=Chronic Obstructive Pulmonary Disease, DCSI=Diabetes Complications Severity Index

*Adjustment for gender, age, urbanization, income, comorbidities, adapted DCSI

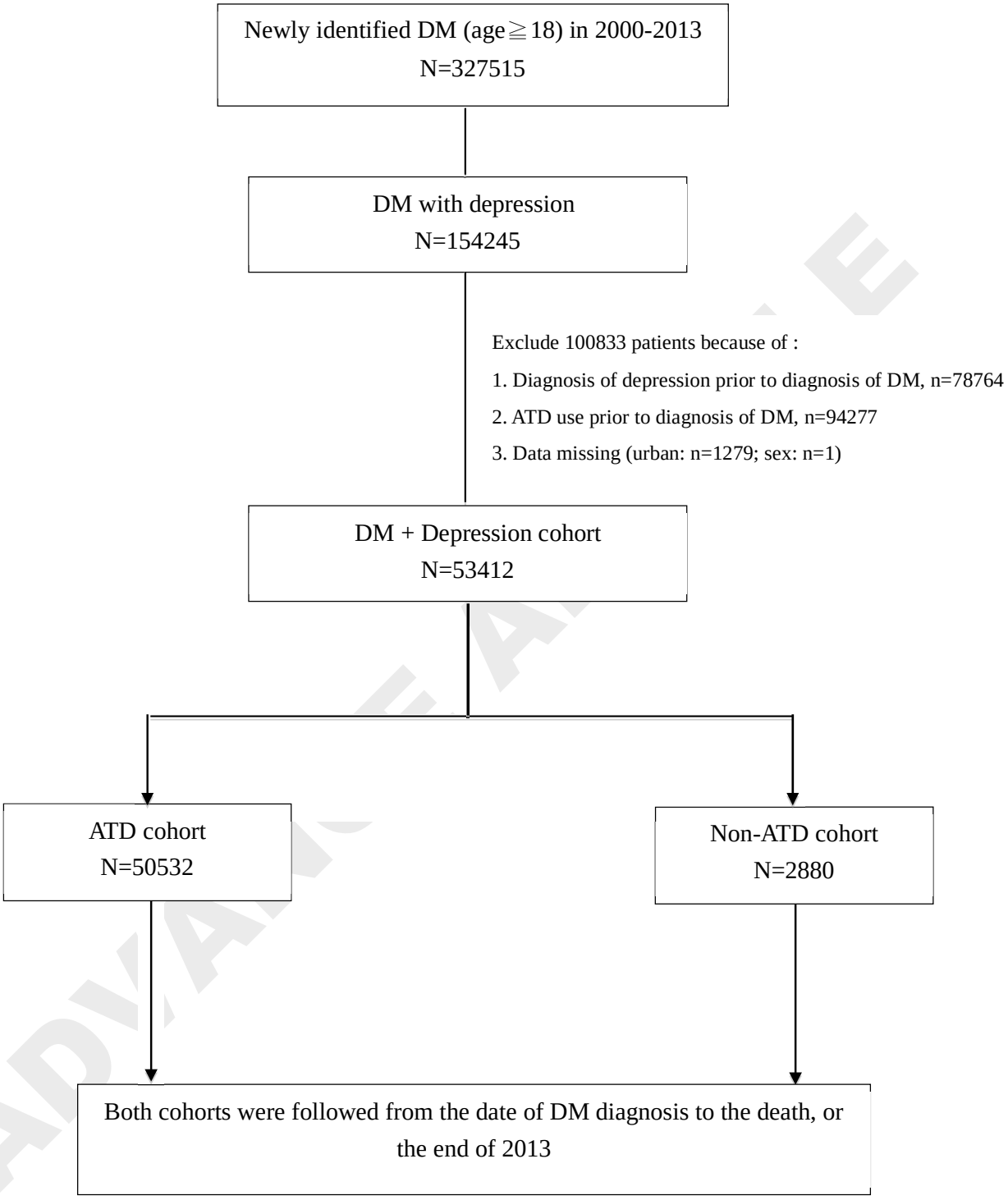
Table 3. Time-dependent Cox regression analysis of mortality in patients with DM and depressive disorder: specific antidepressant subgroup analysis

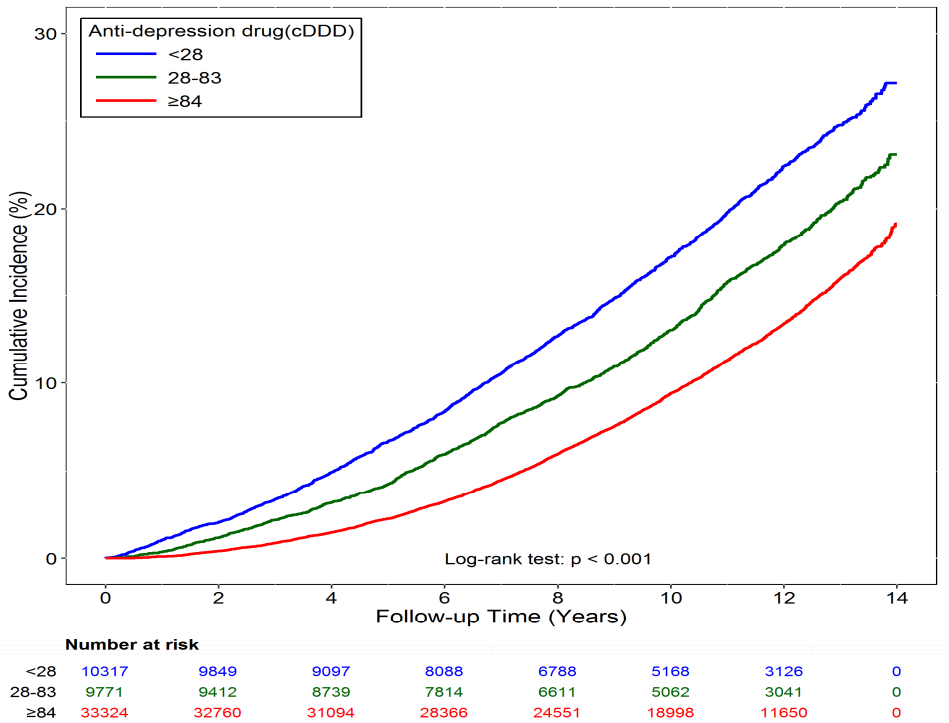
			Crude HR				Adjusted HR*			
	N	%	HR	95% CI		p value	HR	95% CI		p value
SSRI										
<28 cDDD	21923	41.05	1.00	Reference			1.00	Reference		
28-83 cDDD	8631	16.16	0.88	0.78	0.99	0.0367	0.97	0.86	1.10	0.6465
>=84 cDDD	22858	42.8	0.56	0.50	0.63	<.0001	0.64	0.57	0.71	<.0001
SNRI										
<28 cDDD	46638	87.32	1.00	Reference			1.00	Reference		
28-83 cDDD	2338	4.38	0.65	0.46	0.92	0.0138	0.81	0.57	1.14	0.2182

>=84 cDDD	4436	8.31	0.47	0.35	0.64	<.0001	0.59	0.44	0.80	0.0005
NDRI										
<28 cDDD	50894	95.29	1.00	Reference			1.00	Reference		
28-83 cDDD	1170	2.19	0.43	0.23	0.83	0.0121	0.56	0.29	1.08	0.0855
>=84 cDDD	1348	2.52	0.15	0.05	0.47	0.0011	0.20	0.07	0.63	0.0056
Mirtazapine										
<28 cDDD	47322	88.6	1.00	Reference			1.00	Reference		
28-83 cDDD	2276	4.26	0.96	0.70	1.30	0.7724	1.01	0.75	1.38	0.9282
>=84 cDDD	3814	7.14	0.59	0.44	0.80	0.0008	0.60	0.45	0.82	0.0011
Tricyclic/tetracyclic Antidepressants										
<28 cDDD	46144	86.39	1.00	Reference			1.00	Reference		
28-83 cDDD	3728	6.98	1.04	0.87	1.25	0.681	0.89	0.75	1.07	0.2314
>=84 cDDD	3540	6.63	0.78	0.58	1.04	0.0886	0.73	0.54	0.97	0.0311
SARI(Trazodon)										
<28 cDDD	45344	84.89	1.00	Reference			1.00	Reference		
28-83 cDDD	4088	7.65	0.76	0.63	0.92	0.004	0.80	0.66	0.96	0.0189
>=84 cDDD	3980	7.45	0.42	0.24	0.75	0.0029	0.52	0.29	0.91	0.0230
RIMA(Moclobemide)										
<28 cDDD	51838	97.05	1.00	Reference			1.00	Reference		
28-83 cDDD	673	1.26	2.01	1.47	2.76	<.0001	1.91	1.39	2.61	<.0001
>=84 cDDD	901	1.69	1.69	1.25	2.29	0.0006	1.48	1.09	1.99	0.0111

SSRI=selective serotonin reuptake inhibitors, SNRI=serotonin-norepinephrine reuptake inhibitors, NDRI=norepinephrine-dopamine reuptake inhibitors, RIMA=reversible inhibitor of monoamine oxidase A)

*Adjustment for 7 types of ATDs, age, gender, urbanization, income, comorbidities, adapted Diabetes Complications Severity Index.





	Death event	Total follow-up (person-year)	Incidence rate[a]	95% CI		follow-up year (mean)
<28 cDDD(n=10317)	1873	95380.2	1963.7	1876.8	2054.7	9.2
28-83 cDDD(n=9771)	1392	91858.7	1515.4	1437.8	1597.1	9.4
≥84 cDDD(n=33324)	3688	331138.4	1113.7	1078.4	1150.3	9.9

[a]Per 100000 person-years