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Original Article

Antidepressant prescription in acute myocardial infarction is associated with increased mortality 1 year after discharge

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ABSTRACT

Aims: To assess the impact of antidepressant (AD) prescription at discharge on 1-year outcome of patients presenting with acute myocardial infarction (AMI) in Switzerland.
Methods: We used data from the AMIS Plus registry including patients admitted between March 2005 and August 2016 with AMI to a Swiss hospital who were followed up by telephone, 12 months after discharge. We compared patients who received AD medication at discharge with those who did not, with regard to baseline characteristics and outcomes in 1-year follow-ups using logistic regression. Outcome endpoints included mortality, re-hospitalisation, cerebrovascular events, re-infarction, percutaneous coronary intervention (PCI), coronary artery bypass graft as well as pacemaker and/or cardioverter-defibrillator implantations. Additionally, work and daily life conditions were compared between the groups.
Results: Among 8911 AMI patients, 565 (6.3%) received AD at discharge. These patients were predominantly female, older, experienced more often non-ST-segment elevation myocardial infarction, were in higher Killip classes, and had more frequently hypertension, diabetes, dyslipidaemia, obesity and comorbidities. They underwent less frequently PCI, and stayed in hospital longer. The AD-receiving group had higher crude all-cause mortality at 1-year follow-up than the non-receiving group (7.4% vs 3.4%; $p < .001$) and AD prescription was an independent predictor for mortality (OR 1.67; CI: 1.17 to 2.40).
Conclusion: AD medication at discharge was associated with poorer prognosis in AMI patients at 1-year follow-up. However, this study has limited data on depression diagnosis and drug classes. Further research is needed to pinpoint the causes and underlying pathomechanisms for the higher mortality observed in this patient group.

1. Introduction

Cardiovascular disease is still the leading cause of overall mortality in Switzerland [1] even though advances in medical technologies and health care have led to a decrease in mortality rates in recent years [2].

Age, obesity, smoking, dyslipidaemia, diabetes, hypertension, genetics and stress are well known risk factors for cardiovascular disease [3]. Studies have also shown depression to be a significant risk factor for acute myocardial infarction (AMI) and cardiac death [4,5]. Furthermore, anxiety has been shown to be a relevant and independent risk factor for cardiovascular disease [6].

Depressive disorders are common in Switzerland. On average, 5.8% of men and 7.1% of women suffer from major depression [7]. A depressed mood and loss of interest are the main symptoms of depressive disorders but often other symptoms are associated with major depression, such as fatigue, sleeping problems, weight loss and a diminished ability to think or concentrate [8]. Depression's burden of disease goes further than psychological issues and daily life functioning. This illness also impacts on somatic health. Patients with depression tend to live an unhealthier lifestyle than the non-depressed population [9]. They are more likely to be smokers, excessive alcohol users, unhealthy eaters, have lower treatment compliance and lower socioeconomic status [9]. In addition, depression increases the relative risk for somatic health issues that are known to increase the probability of developing cardiovascular disease such as diabetes type 2 [10], obesity [11] and hypertension [12]. However, cardiovascular disease itself leads to a higher prevalence of major depressive disease [13].

Previous studies have shown a link between depression and cardiovascular disease [14–17].

The aim of our study was to evaluate the impact of antidepressants

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(AD) on 1-year outcome in Swiss AMI patients and compare the group characteristics of AD-receiving patients with non-AD-receiving patients and analyse the differences.

2. Material and methods

2.1. Setting

AMIS Plus (Acute Myocardial Infarction in Switzerland) is an open-ended nationwide registry existing since 1997. Of 106 Swiss hospitals treating AMI, 83 voluntary participated and either temporarily enrolled or are still enrolling anonymised data of patients in the AMIS Plus registry. Participating institutions range from small regional hospitals to large, highly specialised clinics. All patients presenting with acute coronary syndrome (ACS): ST-elevation myocardial infarction (STEMI), non-ST elevation myocardial infarction (NSTEMI) and unstable angina (UA) were included. Since 2005, patients were asked to participate in a telephonically performed 1-year follow-up [18]. Upon acceptance, they were required to sign an informed consent form. AMIS Plus was approved by all cantonal ethics commissions, supra-regional ethics committee for clinical studies and the Swiss board for data security.

In-hospital data are collected on age, gender, health insurance, clinical presentation, regular medication at admission, blood test results, comorbidities (assessed using the Charlson comorbidity index (CCI)) [19] (1), risk factors (previous cardiac events, family history, hypertension, dyslipidaemia, diabetes, smoking habits, alcohol consumption, other drugs), immediate therapy, interventions, discharge destination, diagnosis and discharge medication. Anonymised data are entered on paper or internet questionnaires centralised at the AMIS Plus data centre, where they are controlled for plausibility and consistency. Incomplete questionnaires are returned to the enrolling hospital for completion. The design of the AMIS Plus registry has been described previously in other publications [20,21].

In the 1-year follow-up, primary and secondary endpoints are collected telephonically using a standardised questionnaire. Patients are asked questions on rehospitalisation, further interventions, complications with medication, work life before and after AMI and daily life conditions before and after AMI.

2.2. Study cohort

For this analysis, all patients with a diagnosis of STEMI or non-STEMI and available data on regular medication at discharge who also agreed to participate in the 1-year follow-up were included. Patients with UA were excluded. STEMI is defined as a syndrome that has characteristic symptoms of myocardial ischaemia with coexisting persistent electrocardiographic ST-segment elevation and a subsequent rise in biomarkers for myocardial necrosis such as cardiac specific troponins I or T, or creatinine kinase (CK-MB) [22]. NSTEMI is defined as ischaemia severe enough to cause myocardial cell death also leading to the release of biomarkers of myocardial necrosis into the circulation, but with no ST elevation on the ECG [23].

One year all-cause mortality was the primary endpoint of this study. Further endpoints included: any cardiac intervention (coronary angiography, percutaneous coronary intervention (PCI), pacemaker, cardioverter defibrillator (ICD) implantation and coronary artery bypass surgery (CABG)), rehospitalisation of at least 1 night due to cardiovascular disease (including adverse reactions to medication at discharge, bleeding, persistent angina pectoris, cardiac syncope and arrhythmias).

Patients' medical history delivers information on cardiovascular risk factors. Hypertension, diabetes and dyslipidaemia were considered if the patient had either previously been treated for the condition or had received this diagnosis by a physician. A patient was defined as obese if the body mass index was a minimum of 30 kg/m^2 and a smoker if the patient was a current smoker at the time of the AMI. Comorbidity severity was evaluated using CCI [19], which includes among others, diabetes, liver and renal disease. Each additional disease is weighted from one to six for severity and mortality risk and summarised in the total CCI weighted score [19,24]. Re-infarction was defined as a clinical presentation with new ECG changes indicating cardiac ischaemia and re-rising of myocardial necrosis biomarkers any time after the first myocardial infarction. A stroke was defined as any cerebral event caused by ischaemia or haemorrhagic disturbance.

The patients who had AD on their discharge medication list were analysed regardless of the particular AD prescribed: selective serotonin reuptake inhibitors (SSRI), atypical AD with noradrenergic and specific serotonergic activity (NaSSA), reversible inhibitor of monoamine oxidase A (RIMA) or tricyclic AD (TCA).

2.3. Statistical analysis

Statistical analysis was performed using SPSS for Windows (version 23.0). Results with $p < .05$ were considered statistically significant. The tests were performed two sided. To test for differences between groups, we used the Pearson chi-square test or Fisher's exact test for categorical variables, and the Mann-Whitney Test was used for continuous variables. Normal distributed data are presented as means ± standard deviation (SD). Continuous, non-normally distributed variables are presented as median and interquartile ranges (IQRs). First, baseline characteristics and group differences were analysed as described above. Secondly, a binary logistic analysis was performed. AD at discharge was used as a dependent variable and backwards logistic regression was performed to determine the most significant factors for AD prescription. Thirdly, mortality within the 1-year follow-up was used as a dependent variable while gender, age per additional year, Killip-Class > 2 at event, STEMI/NSTEMI, complications during hospitalisation and performed PCI were used as covariates to show the impact each factor independently had on mortality after 1 year. We performed a 1:1 propensity score matching to analyse differences in baseline characteristics. One-year cumulative survival was described using the Kaplan Meier Curve.

3. Results

Data from March 2005 to August 2016 of 8911 patients who suffered AMI were included.

Clinical characteristics and demographics of the dataset are shown in Table 1. Patients prescribed AD at discharge differed significantly from those who were not. They were predominantly female, older, had more often cardiovascular risk factors such as hypertension, diabetes, dyslipidaemia and/or obesity. There was no significant difference in smoking prevalence. Patients who were prescribed AD more frequently had pre-existing coronary artery disease. They also more often had one or several comorbidities as well as a higher CCI score.

There were also significant differences in clinical presentation at admission. The AD group had significantly less often typical symptoms, more often dyspnoea and significantly higher Killip classes.

Statistically significant differences were also found in the immediate therapy of patients who were prescribed AD at discharge. The AD group underwent significantly less frequently PCI (76.8% versus 85.0%; $p < .001$). They also differed from the non-AD group in terms of discharge medication. At discharge they received significantly more often statins (93.9% versus 89.2%; $p < .001$) but less frequently P2Y12 blockers (clopidogrel, prasugrel or ticagrelor) (82.9% versus 88.7%; $p < .001$), whereas prescription of beta blockers (82.1% versus 80.7%; $p = .47$) and ACE inhibitors or angiotensin II receptor blockers (68.1% versus 70.9%; $p = .18$) were similar.

The complications during hospitalisation, which included cardiogenic shock, re-infarction, cerebrovascular events, acute renal failure and new heart failure, altogether occurred significantly more often in patients with AD (22.1% versus 14.1%; $p < .001$).

Table 1
Baseline characteristics of acute myocardial infarction patients according to prescription of antidepressant medication at discharge.

	AD Yes	AD No	P-Value
Number of patients	N = 565	N = 8346	
Sex male (%)	327/565 (57.9%)	6295/8346 (75.4%)	< 0.001
Age in years, mean (± SD)	67.6 (13.1)	64.9 (12.7)	< 0.001
Median symptom onset to hospitalisation (IQR) in min	210(110;556)	210(102;645)	0.745
Resuscitation prior to admission (%)	15/565 (2.7%)	245/8346 (2.9%)	0.797
Symptoms at admission			
Typical (%)	463/561 (82.5%)	7303/8281 (88.2%)	< 0.001
Pain (%)	493/558 (88.4%)	7564/8252 (91.7%)	0.010
Dyspnoea (%)	194/521 (37.2%)	2296/7711 (29.8%)	< 0.001
Diagnosis			
STEMI (%)	292/565 (51.7%)	4937/8346 (59.2%)	0.001
NSTEMI (%)	273/565 (48.3%)	3409/8346 (40.8%)	0.001
Killip class > 2	38/565 (6.7%)	287/8323 (3.4%)	< 0.001
Risk factors			
Hypertension (%)	395/547 (72.2%)	4687/7982 (58.7%)	< 0.001
Diabetes (%)	140/552 (25.4%)	1418/8091 (17.5%)	< 0.001
Dyslipidaemia (%)	316/503 (62.8%)	4151/7317 (56.7%)	0.008
Obesity (BMI > 30) (%)	137/508 (27.0%)	1586/7628 (20.8%)	0.001
Smoking (%)	197/512 (38.5%)	2935/7850 (37.4%)	0.842
Coronary artery disease (%)	155/401 (38.7%)	1822/5874 (31.0%)	0.002
Comorbidities			
Heart failure (%)	24/557 (4.3%)	166/8232 (2.0%)	0.001
Cerebrovascular disease (%)	51/557 (9.2%)	379/8232 (4.6%)	< 0.001
Haemiplegia (%)	10/557 (1.8%)	34/8232 (0.4%)	< 0.001
Dementia (%)	14/557 (2.5%)	49/8232 (0.6%)	< 0.001
Chronic lung disease (%)	57/557 (10.2%)	415/8232 (5.0%)	< 0.001
Moderate to severe renal disease (%)	65/557 (11.7%)	413/8232 (5.0%)	< 0.001
Cancer disease (%)	26/557 (4.7%)	330/8232 (4.0%)	0.436
Charlson Score > 1	192/565 (34.0%)	1582/8346 (19.0%)	< 0.001

Table 2
Independent predictors for antidepressant prescription at discharge in acute myocardial infarction patients (N = 8779).

	OR	95% CI		p-Value
		Lower	Upper	
Female	2.089	1.738	2.510	< 0.001
Age	0.998	0.991	1.006	0.658
Killip > 2	1.535	1.064	2.214	0.022
Comorbidity according to CCI*	2.022	1.680	2.435	< 0.001
NSTEMI*	1.272	1.067	1.516	0.007
Complications during hospitalisation	1.499	1.206	1.864	< 0.001

* CCI = Charlson comorbidity index, NSTEMI = non-ST elevation myocardial infarction.

The most important predictors for receiving AD at discharge were female sex, comorbidities and complications during hospitalisation (Table 2).

Patients who received AD at discharge had a longer hospital stay compared to those who did not (8 days (IQR 5, 12) versus 6 days (IQR 4, 9) p < .001).

3.1. Outcome at 1 year after discharge

Patients were followed up at a median of 392 (IQR: 368; 468) days after discharge. There was no significant difference in the time to follow up between the two groups.

Outcome at 1-year follow-up is described in Table 3. Among 8911 patients, 323 (3.6%) died, and from these, 42 were from the AD-prescribed group comprised of 565 patients (7.4%). No significant differences in the AD and non-AD groups were found in terms of re-hospitalisation, cerebrovascular events, re-infarction, interventions and daily life. Notable differences were found in the work life before and after AMI. AD-receiving patients were significantly more often not working before and after the AMI, particularly patients younger than 65 (men) and 64 (women) years of age. In patients working before the AMI, the AD group significantly more frequently reduced or stopped working after the AMI compared to the non-AD group.

The difference between AD groups in crude all-cause mortality at 1-year follow-up was statistically significant (p < .001). After adjusting for gender, age, Killip Class > 2, any comorbidity according to CCI, STEMI/NSTEMI, complications and performed PCI, the AD and non-AD groups still differed significantly in terms of mortality at 1-year follow up (Table 4; Fig. 1). In addition, we applied propensity score matching (1:1). Patients were matched for age, gender, diagnosis and Charlson Index. Even after matching for differences in baseline characteristics, this analysis also showed that mortality 1 year after myocardial infarction was still significantly higher in the AD receiving group.

4. Discussion

This study shows that there is an association between AD prescription after AMI and mortality 1 year after discharge. Patients receiving AD at discharge had significantly higher all-cause mortality after 1 year. The analysis was adjusted for important confounding factors and group heterogeneity was minimized, but a marked difference in mortality remained between the two groups.

We also found that AD-receiving patients differed from the non-AD group in terms of treatment and length of hospital stay. AD patients also experienced more frequently complications, underwent less frequently PCI and subsequently received less frequently P2Y12 blockers. These patients also received less frequently statins at discharge.

To our knowledge, this is the first large Swiss population-based study to examine 1-year outcomes of AMI patients who were prescribed AD at discharge. This analysis showed that AD at discharge after AMI was a significant negative predictor of 1-year survival. Mathur et al. performed a prospective cohort study examining the risk of incident AMI and stroke between March 2005 and March 2015 in 524,952 patients aged 30 and over from the east London primary care database for patients with anxiety or depression. They found a statistically significant association of incident AMI in both these groups of patients. Correcting for established cardiovascular risk factors, patients with

Table 3
Outcome within 1 year of acute myocardial infarction according to prescription of antidepressant medication at discharge.

	AD Yes	AD No	P-value
Number of patients	N = 565	N = 8346	
Mortality (%)	42/565 (7.4%)	281/8346 (3.4%)	< 0.001
Rehospitalisation (%)	122/519 (23.5%)	1830/8063 (22.7%)	0.386
Stroke/TIA/cerebral haemorrhage (%)	5/507 (1.0%)	49/7955 (0.6%)	0.256
Re-infarction (%)	20/510 (3.9%)	272/7969 (3.4%)	0.530
Any intervention (%)	64/513 (12.5%)	1121/7998 (14.0%)	0.357
CABG (%)	10/461 (2.2%)	127/7221 (1.8%)	0.468
Pacemaker (%)	5/438 (1.1%)	54/6777 (0.8%)	0.406
ICD (%)	2/438 (0.5%)	67/6775 (1.0%)	0.441
Work status before AMI (%)			< 0.001
Not working	330/446 (74.0%)	3744/6772 (55.3%)	
Working full time	74/446 (16.6%)	2568/6772 (37.9%)	
Working part time	42/446 (9.4%)	460/6772 (6.8%)	
Working at 1-year FU (%)			< 0.001
Not working	351/444 (79.1%)	4159/6776 (61.4%)	
Working full time	41/444 (9.2%)	1934/6776 (28.5%)	
Working part time	52/444 (11.7%)	683/6776 (10.1%)	
Not working before AMI and younger than 65(men) or 64(women) years at discharge	93/204 (45.6%)	627/3478 (18.0%)	< 0.001
Not working after AMI and younger than 65(men) or 64(women) years at discharge	114/202 (56.4%)	989/3480 (28.4%)	< 0.001
Daily condition 1-year after AMI (%)			0.072
Worse	199/506 (39.3%)	2665/7934 (33.6%)	
Same	198/506 (39.1%)	3533/7934 (44.5%)	
Better	109/506 (21.5%)	1736/7934 (21.9%)	

TIA = transient ischaemic attack, CABG = coronary artery bypass graft, ICD = implantable cardioverter defibrillator.

Table 4
Independent predictors of mortality within 1 year after discharge in acute myocardial infarction patients (N = 8512).

	OR	95% CI		P-value
		Lower	Upper	
Antidepressants	1.664	1.156	2.395	0.006
Female	0.588	0.446	0.775	< 0.001
Age	1.065	1.051	1.078	< 0.001
Killip > 2	1.484	0.956	2.305	0.079
Comorbidity according to CC* I	3.349	2.491	4.503	< 0.001
NSTEM* I	0.801	0.626	1.025	0.078
Complication during hospitalisation	1.787	1.358	2.350	< 0.001
PCI performed	0.424	0.322	0.559	< 0.001

* CCI = Charlson comorbidity index, NSTEMI = non-ST elevation myocardial infarction, PCI = percutaneous coronary intervention.

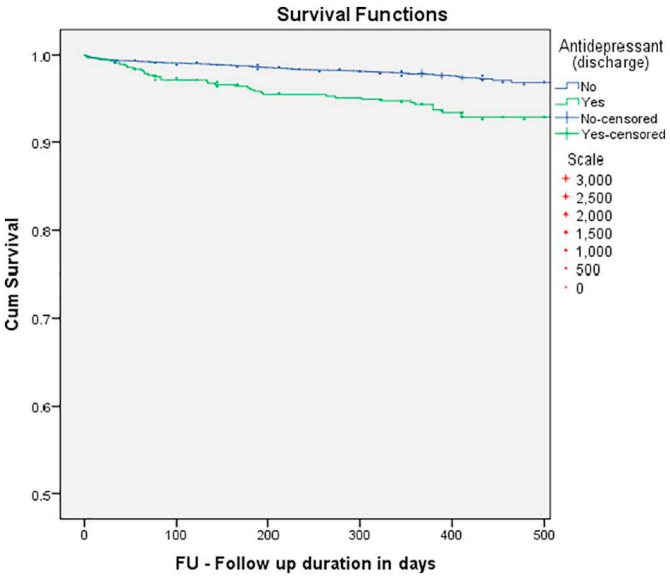

Fig. 1. Kaplan Meier Curve.

anxiety had the same risk for AMI as non-anxiety patients, whereas depressed patients still had an elevated risk for developing AMI [25].

In contrast, the US TRIUMPH study [26] showed a beneficial effect in treating depressed AMI patients. They found no significant differences in survival of treated depressed AMI patients compared to non-depressed patients but there was an increase in 1-year mortality in depressed patients who did not receive any further treatment for depression. The TRIUMPH study patients were screened for depression. One fifth of the patients with AMI had depressive symptoms and one third of these were treated in routine clinical care. In 2005, the Enhancing Recovery in Coronary Heart Disease clinical trial (ENRICHD) [27], showed a positive effect of AD (SSRI only) use in depressed patients, leading to lower recurrent myocardial infarction and death rates in 29 months of follow-up time.

The results of these studies are in contrast to ours. Direct comparison with other clinical studies is difficult as our study lacked data on the AD class and the underlying condition leading to AD prescription. Our analysis showed that the AD group had lower survival rates than patients who were not treated with AD. However, these survival rates could possibly improve if depressed patients only were compared.

Our study is in accordance with others showing that there is a correlation between depression and worse outcome after AMI [17,28]. The patient population suffering from depression is most likely a more vulnerable group that should receive special attention in post myocardial infarction treatment. A study performed at the Ayub teaching hospital in Pakistan that included patients aged between 48 and 65, screened AMI patients 3 days after the event for depression using the HADS-D score and found depression to be present in 27% of the study population [29], while the US TRIUMPH study classified 19% of their post AMI patients as depressed using the PHQ-9 score [26]. In our study, only 6% of the population was treated with antidepressants, which could be due to the differences in the study population. Perhaps routine depression screening should be introduced for AMI patients in Switzerland as recommended by the American Heart Association, even though it is controversially discussed in several reviews [30,31].

Pathomechanisms for increased mortality in depressed AMI patients are still not fully understood. It has been shown that depressive mood and emotions can lead to abnormalities in the neurocardiac reflex system, which is a possible explanation for worse outcome in depressed patients [32]. Another pathomechanism is found in elevated platelet

adenosine diphosphate aggregation and higher concentrations of inflammatory endothelial biomarkers in depressed ACS patients compared to non-depressed ACS patients [33]. Since we have no precise data on AD prescription practice in our population, TCA might have had an impact on the lower survival rate in the AD group [34]. Cohen et al. showed that tricyclic antidepressant agents do not only increase the risk of cardiac arrhythmias but also the risk for myocardial infarction. The relative risk was 2.2 compared with participants who did not take AD medication. On the other hand, patients taking SSRI had a lower relative risk for myocardial infarction of 0.8. However, this study only included patients aged between 25 and 65 years of age [35].

As our study showed that AMI patients are relatively frequently treated with AD (6.3%), research on prescription practice and post AMI care of this patient group should be performed to find causes for the significant difference in 1-year survival compared to non-AD treated patients. The question whether AD treatment leads to better 1-year outcome in depressed AMI patients in Switzerland is still open. Further research on treated and non-treated depressed AMI patients should be carried out since other studies show that treatment had a beneficial effect. In future studies, more factors concerning depression and treatment, e.g. the date of diagnosis, previous treatments, actual treatment, medication compliance and non-pharmacological treatment should be assessed.

4.1. Limitations of the study

Limitations in this analysis are those often found in studies utilising registry data. The registry was not specifically designed for this research question. Treated and non-treated depressive patients could not be compared since we lacked data on depression diagnosis. AD are a heterogeneous group of active pharmaceutical ingredients and we lacked the data on which AD group was prescribed to each patient. These medications differ not only in their mechanisms of action but also in the adverse effects. SSRI are preferred in patients with cardiac disease since they have been proven safe and efficacious in this population [36,37]. They have also been shown to have a beneficial effect on endothelial function and an inhibitory effect on collagen and serotonin-mediated platelet aggregation [38–40]. On the other hand, TCA are known to have a cardio toxic effect leading to an increased risk of arrhythmias [41]. We were limited in the information on whether the patients first received the prescription in hospital or whether they were already on this medication before the AMI. We did not know whether the medication was prescribed for depression since AD can be prescribed for other conditions such as irritable bowel syndrome [42], sleeping problems [43], somatic syndromes [44] or chronic pain [45,46]. We lacked data on patient compliance to AD, dosage or on how long they were supposed to take this medication. The higher all-cause mortality could also be explained by the underlying disease that was treated with the AD.

However, the data on over 8000 patients in a real-world situation allows us to show significant differences between the examined groups. Previously published studies had very strict inclusion and exclusion criteria, which did not necessarily represent the broad spectrum of patients presenting with AMI. As we used patient data from across Switzerland, this study also revealed how often AMI patients are treated with AD medication on a national level.

5. Conclusions

This study showed that > 6% of patients admitted for AMI received AD at discharge. These patients were older, predominantly women, had more NSTEMI, more atypical symptoms, more often cardiovascular risk factors and comorbidities compared to AMI patients without AD at discharge. The prescription of AD at discharge was associated with higher crude all-cause mortality and was an independent predictor of mortality 1 year after AMI.

These findings might have implications for future treatment and management of patients presenting with ACS who either have a history of AD use or are showing depressive symptoms that lead to AD prescription at discharge. However, our study does have limitations in terms of data on depression diagnosis, type of medication and patient compliance. Nonetheless, further research is needed to determine how AD prescription at discharge leads to increased mortality.

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Conflicts of interest

None.

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