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Non-adherence to cardiovascular drugs in older patients with depression: A population-based cohort study

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Abstract

Background: Depression is common among patients with cardiovascular disease and has been associated with both drug non-adherence and increased mortality. Non-adherence can occur because of non-initiation, suboptimal implementation, or non-persistence. We aimed to determine if depression increased the risk of any of these components of non-adherence among older patients prescribed cardiovascular drugs in primary care.

Methods: A longitudinal analysis of routine primary care data from the Nivel Primary Care Database was performed using data for 2011–2013. A total of 1512 patients aged ≥60 years diagnosed with depression in 2012 were compared with age- and sex-matched groups with either other psychological diagnoses (N = 1457) or mentally healthy controls (N = 1508), resulting in the inclusion of 4477 patients. Non-adherence was classified as non-initiation, suboptimal implementation, or non-persistence. Regression analyses were performed to determine the association between mental health status and non-initiation, suboptimal implementation, and non-persistence.

Results: Mixed-effects logistic regression analyses showed increased odds for suboptimal implementation of beta-blockers among depressed patients (2.18; 95% CI 1.29–3.69). For non-persistence, a clustered Cox regression analysis demonstrated that, compared with controls, there was an increased hazard ratio for depressed patients to discontinue beta-blockers (2.31; 95% CI 1.58–3.37) and calcium antagonists (1.74; 95% CI 1.23–2.46).

Conclusions: It is likely that older patients in primary care diagnosed with depression are at increased risk of non-persistence with cardiovascular drug therapy. Because non-adherence is associated with increased cardiovascular mortality, it is important that physicians ensure that older depressed patients persevere with therapy.

1. Introduction

Non-adherence to cardiovascular drug therapy has been associated with the onset [1] and outcomes of cardiovascular disease (CVD), including increased mortality [2]. While many patients experience

difficulties adhering to drug prescriptions [3], this seems especially true for patients with depression, which itself has been associated with non-adherence to antihypertensive [[4], [5], [6]], antiplatelet [7], and lipid-lowering [8] therapy. Depression is particularly relevant as a contributory factor for non-adherence to cardiovascular drug therapy because it is a common disorder that is associated with increased mortality in CVD [9]. Older adults with depression may be more prone to non-adherence because they have greater chronic somatic disease burdens and greater chronic drug use, both associated with non-adherence [10], compared with both younger adults [11,12] and other older adults without depression [13].

Adherence is a complicated process that follows a patient being prescribed drug treatment, but that has been explained by the ABC model [14]. According to this model, non-adherence can be divided into non-initiation, suboptimal implementation, and non-persistence. The first phase is the initiation of treatment and involves patients filling their prescription at a pharmacy. The second stage is treatment implementation and involves a quality assessment of how well a patient implements the prescribed dosing regimen in everyday life; that is, the extent to which a patient's actual dosing corresponds with the prescribed dosing regimen. Third, persistence refers to long-term adherence and is defined as the time between treatment initiation and the last dose taken. Finally, non-persistence occurs when no more doses are taken and the patient discontinues the prescribed drug [14].

In terms of the ABC model, previous studies have mostly focused on the implementation phase of adherence [[4], [5], [6], [7], [8]] even though it is likely that enhancing initiation and persistence require different interventions. Moreover, research has mostly been conducted in secondary settings [[5], [6], [7], [8]], despite depression and chronic somatic diseases being treated most often in primary care [15,16]. Adherence may be particularly affected in primary care because of the importance of self-reliance in that setting.

In this study, we aimed to examine whether depression in older patients in primary care was associated with an increased risk of either non-initiation of, suboptimal implementation of, or non-persistence with cardiovascular drugs. In addition, we aimed to determine whether the associations were specific to depression or could be explained by general psychological distress.

2. Methods

2.1. Design and setting

This was a population-based cohort study using data routinely collected in primary care for the years 2011–2013. The study was conducted and reported following the Checklist for Medication Compliance and Persistence Studies Using Retrospective Databases [17]. Data were obtained from three sources: the Nivel Research Primary Care Database (Nivel-PCD), the Foundation for Pharmaceutical Statistics (SFK), and Statistics Netherlands (CBS).

2.2. Databases

In the Netherlands, all individuals are registered in general practice, and the Nivel-PCD provides a nationally representative database comprising data for individuals registered in approximately 10% (N = 498) of general practices [18]. This database contains routine data from patients' electronic medical records (EMRs), including diagnostic information coded according to the International Classification of Primary Care (ICPC) [19], information on prescribed drugs, and a patient's sex and age. Pharmacy dispensing data are available in the SFK database, which provides virtually complete medication histories through a closed pharmacy system (i.e., 89% of patients have all their prescriptions filled in a single pharmacy and another 10% usually do) [20]. All medications in the Nivel-PCD and the SFK database are recorded with corresponding prescribing or dispensing dates, with coding according to the Anatomical Therapeutic Classification (ATC) [21]. Sociodemographic data are

available from the CBS, which manages data on economic and social characteristics in the Dutch population based on legal civil status and tax registers.

2.3. Study population

The Nivel-PCD records of patients aged ≥60 years were linked to individual SFK data based on sex, year of birth, four-digit postal code, ATC codes of prescribed drugs, prescription dates, and dispensing dates [22]. To ensure successful matching of individuals, at least 50% of the Nivel-PCD data had to match the SFK data within a lag period of 6 days. Only patients registered at participating practices throughout the study period and with successful data linkage were included. Among these, we identified three comparison groups based on mental health status in 2012. The first group comprised all patients with either recorded depressive symptoms (ICPC P03) or a depressive disorder (ICPC P76) (hereafter, 'depression'). The second group comprised patients individually matched to the first by age and sex, who had no recorded diagnosis of depression, but who had another psychological diagnosis recorded (any ICPC code in the 'P chapter', excluding codes P03 and P76). The third group, again matched to the first by age and sex, included control patients who had no recorded mental health problem (no ICPC code in the P chapter).

2.4. Ethical considerations

This study complies with the Declaration of Helsinki. Dutch law allows the use of electronic health records for research purposes under certain conditions. According to this legislation, neither obtaining informed consent from patients nor approval by a medical ethics committee is obligatory for observational studies containing no directly identifiable patient data (Dutch Civil Law, Article 7:458). This study has been approved by the applicable governance bodies of Nivel Primary Care Database under no. NZR00315.016.

2.5. Medication

Non-adherence was determined for six classes of chronically used cardiovascular drugs, mostly distinguished at the ATC two-digit level: diuretics (C03), beta-blocking agents (C07), calcium-channel antagonists (C08), angiotensin-converting-enzyme inhibitors/angiotensin II receptor blockers (C09), lipid-lowering drugs (C10), and thrombocyte aggregation inhibitors (ATC 4-digit level B01AC). Note that the thrombocyte aggregation inhibitors were distinguished at the four-digit ATC level because the two-digit level included vitamin K antagonists. These antagonists were excluded to reduce the influence of variable dosing, which resulted in the precise dosing regimen being absent in approximately 50% of dispenses in our database. Inclusion of these drugs would have led to unreliable estimates of non-adherence.

2.6. Outcome measures

The three components of non-adherence (i.e., non-initiation, suboptimal implementation, and non-persistence) were determined using data for 2011–2013.

2.6.1. Non-initiation

Therapy was considered non-initiated if a new prescription by the GP registered in a patient's EMR in the Nivel-PCD was not dispensed within 14 days. For this purpose, a new prescription was defined as a case where no prescription of that drug had been made in the preceding 182 days.

2.6.2. Suboptimal implementation

We assessed suboptimal implementation using the medication possession ratio (MPR) in 2012 [17] which was defined by the following formula:

$$\text{MPR} = \frac{\text{number of days for which doses were dispensed}}{\text{total number of days between first and last dispensed doses}}$$

First, we identified the start date of dispensing for the first doses in 2012. If this was in 2011, we arbitrarily set the start date to 1st January 2012. Second, we identified the end date for the last dispensing in 2012. If this was in 2013, we arbitrarily set the end date to 31st December 2012. The total number of days between the start and end dates was then used as the denominator for the MPR. Next, we summed up the total number of days for which dosages were dispensed between the start and end dates to use as the numerator. As done in previous studies [[23], [24], [25]], we dichotomized the MPR because of skewness into >80% and ≤80% for the adherent and non-adherent groups, respectively. Hypercompliant MPR values >1 were converted to 1.

2.6.3. Non-persistence

Time to non-persistence was defined as the number of days between the date of the first dispense of a drug to the theoretical end date of the last dose of that drug, if a patient would take the drug exactly as prescribed. Similar to non-initiation, a first dispense was defined as a drug that had not been dispensed in the preceding 182 days. The last dose of a drug was set as the last recorded dispensing date (i.e., no dispensing for 182 days after the last dispense) plus the number of days for which that last dispense covered. Non-persistence was calculated using data for 2011 to 2013.

2.7. Covariates

Age, sex, socioeconomic status (SES), the number of chronic somatic diseases, and the number of chronically used drugs were considered as covariates [10]. We included age and sex to allow for the fact that matching in a cohort study does not entirely eliminate confounding [26]. Age was defined as that on 1st January 2012. SES was a proxy measure based on four indicators of the neighbourhood in which patients lived (defined by 4-digit postal code), namely the proportions with low incomes, low educational levels, and unemployment, as well as the mean income [27]. Chronic somatic diseases were identified from ICPC codes based on a predefined list published by the National Institute for Public Health and Environment [28]. Chronic drug use was defined as ≥4 prescriptions for a drug in a year or use for ≥90 days [29].

2.8. Missing data

Patients were only eligible for inclusion if they were registered at the same general practice throughout the study. Only a few depressed patients could not be matched to the comparison groups of patients who had another psychological diagnosis (3.6%, N = 55) or of mentally healthy controls (0.3%, N = 4). Because of the small numbers involved, we did not impute data, and instead performed complete case analyses.

2.9. Analysis

First, we described the baseline characteristics of our population by mental health status. Differences were assessed using chi-square tests for categorical variables and Kruskal–Wallis tests for count or continuous variables (data were not normally distributed). We used the Mann–Whitney *U* test for post-hoc pairwise comparisons if the overall Kruskal–Wallis test was statistically significant. Associations between the three components of non-adherence and the three patient groups were examined by regression analyses, adjusting for age, sex, SES, number of chronic somatic diseases, and number of chronically used drugs. Mixed-effects logistic regression analyses were performed with a random intercept and an independent covariance structure, using non-initiation (1 for yes vs. 0 for no) and the dichotomized MPR (1 for ≤80% vs. 0 for >80%) as dependent variables. The mixed-effects approach was used to account for clustering (i.e., patients from the same general practice). For non-

persistence measures, we performed time-to-event (last dose dispensed) survival analyses by Cox regression, using time-to-event or 31st December 2013 (censoring date) as the dependent variable. Clustering was accounted for by robust variance estimates [30]. Log-minus-log plots confirmed that the Cox proportional hazard assumptions were met.

[Figure 1]

Finally, we performed sensitivity analyses to examine the robustness of our results. First, we repeated the mixed-effects logistic regression analyses, adjusting the dependent variables such that non-initiation was defined as a new prescription not dispensed within 30 days and that suboptimal implementation was defined as an MPR ≤ 70%. Second, we repeated all analyses using only one drug per class, as follows: hydrochlorothiazide (ATC code C03AA03), metoprolol (C07AB02), amlodipine (C08CA01), enalapril (C09AA02), simvastatin (C10AA01), and acetylsalicylic acid (B01AC06). This was because determining non-adherence to cardiovascular drug classes instead of specific drugs could underestimate non-persistence among patients using two drugs in the same ATC category at the 2-digit level (e.g., two diuretics could be taken and stopping one might not be recognized as non-persistence if the other was continued).

We present odds ratios (ORs) and hazard ratios (HR), together with their 95% confidence intervals (95% CI) and p-values, for the logistic and Cox regression analyses, respectively. Also, survival curves are presented for the persistence measures. We applied false discovery rate (FDR) correction to control for multiple comparisons [31]. All analyses were conducted with Stata SE version 14.0 (StataCorp. 2013, College Station, TX).

3. Results

3.1. Patient characteristics

In total, 80% of the data in the Nivel-PCD was successfully matched to the SFK data, corresponding to 31,693 patients. The patient flow diagram is demonstrated in Fig. 1. We analysed data for 1512 patients diagnosed with depression in 2012. These were age- and sex-matched with 1457 patients who had another psychological diagnosis and with 1508 mentally healthy controls. Thus, 4477 patients were included, and their characteristics are summarised in Table 1.

3.2. Non-initiation and suboptimal implementation

Non-initiation and suboptimal implementation (MPR ≤ 80%) were present in 1.2%–12% and 2.9%–11.6%, respectively (Table 2). Mixed-effects logistic regression showed no differences in non-initiation between the three patient groups (Table 2). Although the same applied for suboptimal implementation of most medications (Table 2), patients with depression and who were prescribed beta-blockers had higher odds of suboptimal implementation compared with mentally healthy controls (OR 2.18; 95% CI 1.29–3.69; p = 0.004).

[Table 1][Table 2]

3.3. Non-persistence

Survival curves are shown in Fig. 2. Clustered Cox regression analyses showed statistically significant differences between patients diagnosed with depression and mentally healthy controls in terms of two chronically used cardiovascular drug classes. Notably, patients diagnosed with depression had higher risks of discontinuing beta-blockers (HR 2.31; 95% CI 1.58–3.37; p < 0.001) and calcium antagonists (HR 1.74; 95% CI 1.23–2.46; p = 0.002) compared with mentally healthy controls (Table 2). No difference existed between patients diagnosed with depression and patients with other psychological diagnoses.

3.4. Sensitivity analyses

The sensitivity analyses confirmed all earlier results. Mental health status was not associated with non-initiation (no dispense within 30 days) of the six cardiovascular drug classes. Depressed patients also had higher odds of suboptimal implementation (MPR ≤ 70%) of beta-blocking agents only (OR 2.37; 95% CI 1.20–4.70; p = 0.01).

Repeating the analyses with the drugs prescribed most often per class confirmed the associations between depression and suboptimal implementation for metoprolol (OR 2.18; 95% CI 1.09–4.34; p = 0.03), and between depression and non-persistence with metoprolol (HR 1.68; 95% CI 1.03–2.76; p = 0.04) and amlodipine (HR 1.69; 95% CI 1.10–2.60; p = 0.02). Depression also affected persistence with enalapril (HR 2.53; 95% CI 1.21–5.28; p = 0.01). However, after FDR correction, these outcomes did not remain significant.

4. Discussion

4.1. Summary of main findings

Compared with mentally healthy controls, older patients diagnosed with depression were at increased risk of non-persistence with beta-blockers and calcium-channel antagonists. There were also increased odds of suboptimal beta-blocker implementation among older patients with depression when compared with mentally healthy controls, but we found no other increased risks of non-initiation or suboptimal implementation in patients with depression. By contrast, patients with other psychological diagnoses had no increased risks of non-adherence.

4.2. Comparison with the existing literature

To our knowledge, we are the first to have studied how the major components of adherence relate to the use of common cardiovascular drugs among patients with depression in the same cohort. We demonstrated that depression among older patients in primary care was particularly associated with an increased risk of non-persistence to cardiovascular drug therapy. Although previous studies have shown an association between depression and suboptimal implementation of antihypertensives [[4], [5], [6]], antiplatelets [7], and lipid-lowering drugs [8], we showed that it was persistence with cardiovascular drug therapy that was most affected by the presence of depression. It might be that persistence negatively affected implementation rates in previous studies, which would explain the impaired MPRs that were reported. Another study, in which non-adherence was measured by means of self-report among patients that were younger than in our sample, did not demonstrate an association between depression and non-adherence to antihypertensives and lipid-lowering drugs [32]. This could indicate that while patients report good adherence, they may be actually non-adherent as demonstrated by our analysis of objective dispensing data. In addition, not differentiating between drug classes might positively affect overall adherence [32], in the sense that non-adherence to certain drugs (i.e. beta-blockers and calcium antagonists) could be masked by adherence to other drugs.

Although older patients with depression were able to initiate drug treatment and implement a dosing regimen in everyday life, they were often unable to persevere with that therapy. Non-adherence has been associated with increased relative and absolute mortality risks, which can even outweigh other risk factors [2]. Given that patients with depression had especially poorer persistence, it may be that physicians in primary and secondary care need to offer prolonged monitoring for adherence. This is especially relevant because it has been suggested that the poorer CVD outcomes associated with non-adherence occur predominantly in patients who first initiated but later discontinued treatment [33]. The reasons for non-adherence in this study are not known. For example, we do not know whether discontinuation was done after consultation with a physician or whether it was because of side-effects. This is relevant because side-effects are important determinants of non-adherence [10], yet no studies

have investigated whether their presence or the perception of them results in non-adherence among depressed patients. Also dosing frequency is a determinant of non-adherence [10]. Although prescriptions of more than a single daily dose were more prevalent among patients with depression for beta-blockers and calcium antagonists, this was also observed for diuretics and angiotensin-converting-enzyme inhibitors/angiotensin II receptor blockers. Thus, prescription of more than a single daily dose is an unlikely reason why patients did not adhere to beta-blockers and calcium antagonists in particular. Depression is associated with cognitive decline [34], and cognitive decline has been associated with non-adherence as well [35,36], yet no studies have examined whether this is the driver of non-adherence in depressed patients. It is important that we understand these reasons for non-adherence, because non-adherence is known to worsen the prognosis of CVD.

As has previously been suggested, a triangular relationship may exist between depression, adherence to cardiovascular drug therapy, and CVD [9]. Depression was associated with non-adherence to cardiovascular drug therapy not only in our study but also in previous research. It is also well-established that there is an association between depression [9], as well as non-adherence [1,2], and the onset and prognosis of CVD. Future research should examine whether the onset and poorer prognosis of CVD, and the increased mortality among patients with depression, is dependent on non-persistence to cardiovascular drug therapy. If true, a next step would be to study whether treatment for depression could improve CVD outcomes and reduce mortality by improving medication adherence, as suggested by earlier research [7].

Research focusing on the association between depression and non-adherence has not distinguished between cardiovascular and antihypertensive drug classes to date [[4], [5], [6]]. We demonstrated an increased risk for non-adherence with beta-blockers among depressed patients. Another large population-based retrospective cohort showed that adherence among antihypertensive drug classes was highest for beta-blockers [37]. However, that study included patients from various ages and did not evaluate the effect of depression on non-adherence. These differences could indicate that vigilance is required when prescribing beta-blockers to older patients with depression, although reasons for these patients to beta-blockers in particular are not yet known. It could be that a drug-disease interaction between beta-blockers and depression exists, but this possible interplay cannot be disentangled using our data.

Although we selected patients from routine primary care data, our findings may be applicable to secondary care as well. In the Netherlands, all individuals are registered in general practice, even though some of their healthcare is received in secondary care. Diagnoses in secondary care are carefully recorded in a patient's EMR, which is held in general practice, thus providing the most comprehensive patient records. Moreover, although non-initiation was determined using prescription data from primary care, implementation and persistence measures were determined using data from the SFK only, which provides almost complete medication histories using prescription data from primary and secondary care. This also applied to the finding that older patients with depression were at higher risk for non-persistence with cardiovascular drug therapy.

4.3. Limitations

Some limitations need to be considered. First, we used pharmacy dispensing data as a proxy for drug use. Although dispensing data more closely reflects actual drug use than prescription data, we cannot be certain whether the dispensed drugs were taken by patients. Second, because we used routine data, unrecognized depression could have been present among patients in the comparison groups. This would most likely have led to an underestimation rather than an overestimation of the association, whereas using a validated screening instrument to diagnose depression might have led to overdiagnosis because only a fraction of older adults with a positive screen are clinically depressed [38]. By using data in which depression was diagnosed during routine clinical care, it is likely that our results more accurately reflect the true risks in patients with mental health problems diagnosed in general practice. Moreover, the Nivel-PCD is a nationally representative database, which enhances the

generalizability of our findings. However, only a minority of our study population had CVD [13], which may limit the generalizability of our findings to older patients with CVD. These latter patients could be more motivated to adhere than those who take the medication for preventative purposes. Although the SFK provides virtually complete medication histories through a closed pharmacy system, prescriptions filled at other pharmacies are not included. Finally, certain methodological issues should be considered. For example, we dichotomized the MPR to account for data skewness and converted values that were >1 to 1, both of which might have reduced the precision and statistical power of the study. Moreover, although the sensitivity analysis confirmed similar patterns to the primary analyses, they did not remain significant after FDR correction. Insufficient power may also have been relevant in this regard.

4.4. Conclusion

Older patients diagnosed with depression in primary care are likely to be at increased risk of non-persistence with cardiovascular drug therapy. Physicians must focus on ensuring that these patients adhere to their drug therapy to mitigate against the known association of non-adherence with increased CVD mortality. Future research should further elucidate the complex interplay that appears to exist between depression, non-adherence, and poor CVD prognosis.

Statement of authorship

All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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Declaration of interest

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Figure and Table

Table 1. Baseline characteristics stratified by mental health status*.

	Depression (N = 1512)	Psychological diagnosis (N = 1457)	Controls (N = 1508)	P-Value
Female	1053 (69.6)	1001 (68.7)	1052 (69.8)	0.792
Age	68 (63–75)	68 (63–75)	68 (63–75)	0.771
SES categories^				0.006
Low	345 (22.8)	307 (21.1)	362 (24.0)	
Medium	872 (57.7)	923 (63.3)	899 (59.6)	
High	295 (19.5)	227 (15.6)	247 (16.4)	
Number of chronic somatic diseases	2 (1–2)‡	1 (1–2)₸	1 (1–2)‡,₸	<0.001
Number of chronic drugs	4 (2–6)†,‡	3 (1–5)†,₸	1 (1–4)‡,₸	<0.001

*Using Chi square tests for categorical data (N [%]) and Kruskal Wallis tests for continuous or count data (median [interquartile range]). Using a Mann–Whitney U test as a post hoc analysis for the Kruskal–Wallis test. Superscript symbols refer to statistically significant differences between: †patients with depression and patients with another psychological diagnosis; ‡patients with depression and mentally healthy controls; and ₸patients with another psychological diagnoses and mentally health controls. ^Similar to previous studies [27] SES was divided into quintiles. Highest or lowest quintiles were categorized as high or low SES score, respectively. Middle three quintiles categorized as medium SES score.

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Table 2. Association between mental health status and non-adherence.

	Total number of patients with drug prescribed	Depression	Psychological Diagnosis	Controls	Depression vs controls[c]	Psychological diagnosis vs controls[c]
		Non-initiation[a]			OR (95% CI)	OR (95% CI)
Diuretics	1363	97 (21.3%)	55 (11.9%)	53 (11.9%)	0.92 (0.51–1.67)	0.81 (0.45–1.47)
Beta-blocking agents	835	50 (17.0%)	26 (8.6%)	26 (10.9%)	1.94 (0.96–3.92)	0.99 (0.48–2.05)
Calcium-antagonists	468	21 (13.4%)	12 (7.1%)	16 (11.3%)	1.21 (0.44–3.29)	0.80 (0.29–2.21)
ACE inhibitors/ARBs	926	41 (13.8%)	24 (7.0%)	24 (8.4%)	1.02 (0.48–2.15)	0.76 (0.37–1.58)
Lipid lowering drugs	1052	56 (16.1%)	32 (8.5%)	36 (11.0%)	1.27 (0.69–2.35)	0.86 (0.46–1.60)
Thrombocyte aggregation inhibitors	681	47 (20.5%)	28 (11.2%)	30 (14.9%)	1.88 (0.98–3.64)	0.97 (0.50–1.88)

	Total number of patients with drug prescribed	Depression	Psychological Diagnosis	Controls	Depression vs controls[c]	Psychological diagnosis vs controls[c]
		MPR ≤ 80%[a]			OR (95% CI)	OR (95% CI)
Diuretics	1083	38 (11.1%)	39 (10.9%)	28 (7.4%)	1.60 (0.93–2.73)	1.57 (0.94–2.64)
Beta-blocking agents	1401	45 (10.1%)	38 (7.8%)	27 (5.7%)	2.18 (1.29–3.69)	1.50 (0.89–2.55)
Calcium-antagonists	642	18 (8.8%)	14 (6.4%)	11 (5.1%)	2.82 (1.21–6.58)	1.58 (0.68–3.67)
ACE inhibitors/ARBs	507	58 (34.9%)	57 (29.8%)	45 (30.0%)	1.51 (0.93–2.45)	1.06 (0.70–1.62)
Lipid lowering drugs	1639	48 (9.1%)	60 (10.5%)	45 (8.3%)	1.31 (0.84–2.04)	1.36 (0.90–2.05)
Thrombocyte aggregation inhibitors	1028	18 (5.2%)	28 (7.9%)	18 (5.5%)	1.04 (0.51–2.12)	1.59 (0.84–2.99)

	Total number of patients with drug prescribed	Depression	Psychological Diagnosis	Controls	Depression vs controls[c]	Psychological diagnosis vs controls[c]
		Non-persistence[b]			HR (95% CI)	HR (95% CI)
Diuretics	492	80 (51.6%)	100 (54.4%)	75 (49.0%)	1.12 (0.82–1.54)	1.25 (0.90–1.74)
Beta-blocking agents	454	83 (50.0%)	76 (44.4%)	37 (31.6%)	2.31 (1.58–3.37)	1.61 (1.13–2.31)
Calcium-antagonists	331	54 (46.2%)	50 (43.1%)	36 (36.7%)	1.74 (1.23–2.46)	1.36 (0.84–2.19)
ACE inhibitors/ARBs	507	58 (34.9%)	57 (29.8%)	45 (30.0%)	1.51 (0.93–2.45)	1.06 (0.70–1.62)
Lipid lowering drugs	560	69 (35.5%)	82 (40.8%)	54 (33.1%)	1.29 (0.91–1.82)	1.31 (0.94–1.81)
Thrombocyte aggregation inhibitors	348	38 (29.5%)	44 (34.7%)	27 (29.4%)	1.19 (0.66–2.13)	1.20 (0.68–2.12)

Values are numbers (%) of patients who non-initiated drug treatment, with an MPR ≤ 80%, or with a last dosage dispensed (i.e. discontinuation) during the study period (914 days).

Abbreviations: OR, Odds Ratio; 95% CI, 95% confidence interval; ACE, angiotensin-converting-enzyme; ARBs, angiotensin II receptor blockers; HR, Hazard Ratio.

Significant ORs and HRs are printed bold and underlined.

[a] Using a mixed effects logistic regression analysis with non-initiation or MPR ≤ 80% as dependent variable.

[b] Using a clustered Cox regression analyses with time to last dosage dispensed as dependent variable.

[c] Adjusted for age, sex, SES, number of chronic diseases, and number of chronically used drugs.

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Fig. 2. Survival plots of persistence by chronically used drug classes using clustered Cox regression analysis.