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ORIGINAL ARTICLE

Antidepressants and heart-rate variability in older adults: a population-based study

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Background. Tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs) may be associated with lower heart rate variability (HRV), a condition associated with increased mortality risk. We aimed to investigate the association between TCAs, SSRIs and HRV in a population-based study.

Method. In the prospective Rotterdam Study cohort, up to five electrocardiograms (ECGs) per participant were recorded (1991–2012). Two HRV variables were studied based on 10-s ECG recordings: standard deviation of normal-to-normal RR intervals (SDNN) and root mean square of successive RR interval differences (RMSSD). We compared the HRV on ECGs recorded during use of antidepressants with the HRV on ECGs recorded during non-use of any antidepressant. Additionally, we analysed the change in HRV on consecutive ECGs. Those who started or stopped using antidepressants before the second ECG were compared with non-users on two ECGs.

Results. We included 23 647 ECGs from 11 729 participants (59% women, mean age 64.6 years at baseline). Compared to ECGs recorded during non-use of antidepressants ($n = 22\,971$), SDNN and RMSSD were lower in ECGs recorded during use of TCAs ($n = 296$) and SSRIs ($n = 380$). Participants who started using TCAs before the second ECG had a decrease in HRV and those who stopped had an increase in HRV compared to consistent non-users ($p < 0.001$). Starting or stopping SSRIs was not associated with HRV changes.

Conclusion. TCAs were associated with a lower HRV in all analyses, indicating a real drug effect. For SSRIs the results are mixed, indicating a weaker association, possibly due to other factors.

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Key words: Antidepressive agents, electrocardiography, epidemiology, heart-rate variability, population surveillance.

Introduction

Heart-rate variability (HRV) refers to the beat-to-beat variability in heart rate. HRV is influenced by the parasympathetic and sympathetic autonomous nervous system. HRV is lowered when parasympathetic nerve activity is decreased or when sympathetic nerve activity is increased (Pomeranz *et al.* 1985; Bigger *et al.* 1988; Rajendra Acharya *et al.* 2006). A relatively low HRV is associated with an increased risk of all-cause mortality (Kleiger *et al.* 1987; Fei *et al.* 1996; de Bruyne *et al.* 1999; Stein *et al.* 2005; Erdogan *et al.* 2008; Huikuri *et al.* 2009), cardiac mortality (La Rovere *et al.* 1998; Huikuri *et al.* 2009), and sudden cardiac death (Makikallio *et al.* 2005).

Use of antidepressants has been associated with a lower HRV in a number of studies (Khaykin *et al.* 1998; Lederbogen *et al.* 2001; Davidson *et al.* 2005; Licht *et al.* 2008, 2010; Kemp *et al.* 2010; O'Regan *et al.* 2014). Two studies on the relationship between antidepressants and HRV (Licht *et al.* 2008; O'Regan *et al.* 2014) reported that use of tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs) is associated with a lower HRV. In both studies, the effect of the TCAs on HRV was more pronounced than that of SSRIs (Licht *et al.* 2008; O'Regan *et al.* 2015). This is possibly caused by the anticholinergic effects of TCAs (Snyder & Yamamura, 1977). Nevertheless, there is also considerable disagreement in the literature on the potential decrease in HRV by antidepressants. A meta-analysis reported that

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depression itself – and not antidepressant use – is associated with a lower HRV (Kemp *et al.* 2010), while two other studies suggested that the association between depression and HRV was found to be predominantly driven by the use of antidepressants (Licht *et al.* 2008, 2015).

To date, one population-based cohort study has addressed the association between TCAs, SSRIs and HRV (O'Regan *et al.* 2015). However, this study neither investigated longitudinal effects of antidepressant use on HRV nor a possible dose-response relationship of antidepressants on HRV. Longitudinal effects and dose-response relationships have, however, been investigated in different studies in a population of patients with depression or anxiety and healthy controls (Licht *et al.* 2008, 2010). Moreover, they addressed the association between individual antidepressants and HRV (Licht *et al.* 2008), while most other studies considered class effects only. Both studies concluded that the association between depression and HRV was mainly driven by the use of antidepressants.

By using longitudinal analyses, analyses of dose-response relationships, and analyses of individual drugs in a population-based cohort study, we might be able to distinguish if there is a true drug effect of antidepressants on HRV or whether the effect is observed due to residual confounding by depressive symptoms. Therefore, in order to address these issues, our objective was to investigate the association between TCA use, SSRI use, and HRV in a population-based cohort of older adults.

Method

Study setting

This study is part of the Rotterdam Study, a prospective population-based cohort study, which was designed to investigate the incidence of age-related diseases and risk factors for age-related diseases. The design and rationale of the Rotterdam Study have been described in more detail elsewhere (Hofman *et al.* 1991, 2013). In short, from 1990 to 1993, all inhabitants aged $\geqslant$55 years from the Ommoord district in Rotterdam, The Netherlands, were invited to participate in the initial cohort. A total of 7983 individuals agreed to participate (response rate 78%). In 2000, the cohort was extended by including all inhabitants from the same district who became $\geqslant$55 years, or who had moved into the district after the start of the initial cohort. In this extension of the cohort, 3011 individuals agreed to participate (response rate 67%). The cohort was additionally extended in 2006 by inviting inhabitants of the same district aged $\geqslant$45 years. In total, 3932 individuals agreed to participate (response rate 65%). Electrocardiograms (ECGs) were also recorded during follow-up examinations, which were conducted approximately every 4–5 years after the baseline examination, with a maximum of five centre visits per participant. The Rotterdam Study has been approved by the medical ethics committee according to the Wet Bevolkingsonderzoek ERGO (Population Study Act Rotterdam Study), executed by the Ministry of Health, Welfare and Sport of The Netherlands. Written informed consent was obtained from all study participants.

Study population and selection of ECGs

We included in the present study ECGs of participants of the Rotterdam Study recorded during the examination rounds that took place between 1 January 1991 and 31 December 2012. ECGs recorded before 1 January 1991 were excluded because pharmacy dispensing records were not available. We also excluded ECGs with less than five normal heartbeats and ECGs on which the following pathology was detected: left or right bundle branch block, second-degree or third-degree atrioventricular block, ventricular hypertrophy according to Sokolow–Lyon criteria, atrial fibrillation. ECGs recorded with a pacemaker rhythm or recorded during the use of monoamine oxidase inhibitors (ATC code: N06AF/AG) and other antidepressants (ATC code: N06AX) were excluded, because of the low number of prescriptions and heterogeneous pharmacodynamics.

Antidepressant exposure assessment

At study entry, more than 95% of the participants had their drug prescriptions dispensed at one of the seven fully computerized regional pharmacies, which use one common computer network. Dispensing data was available on a day-to-day basis, which included the anatomical therapeutic chemical (ATC) code, the dispensing date, the total amount of tablets/capsules per dispensation, the prescribed daily number of tablets/capsules, and the product name of the drug. Dispensing episodes were calculated by dividing the total number of dispensed tablets/capsules by the daily prescribed number. If the date of an ECG recording fell within a dispensing episode of TCAs (ATC code: N06AA) or SSRIs (ATC code: N06AB), the participant was considered as being exposed during that ECG recording. We allowed a carry-over period of 7 days to define current users. For individual antidepressants, the complete, 7-digit ATC code was used. The dosage was defined as the ratio between the prescribed daily dosage by the defined daily dosage (PDD/DDD ratio), as determined by the World Health

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Organization (WHO Collaborating Centre for Drug Statistics Methodology, 2015).

Assessment of RR interval and HRV

A standard 10-s, 12-lead resting ECG was recorded with an ACTA Gnosis electrocardiograph (Esaote Biomedica, Italy) at a sampling frequency of 500 Hz and stored digitally. ECGs were processed by the standardized modular ECG analysis system (MEANS), which has been described previously and has been validated and applied extensively (Willems *et al.* 1987, 1991; van Bemmel *et al.* 1990; de Bruyne *et al.* 1997; Darpo *et al.* 2006).

HRV was calculated based on RR intervals between normal heart beats: RR intervals were excluded if they immediately preceded or followed premature ventricular complexes or premature supraventricular complexes (Kors & van Herpen, 2009). We selected two of the most commonly used HRV variables; the standard deviation of normal-to-normal RR intervals (SDNN) and the root mean square of successive RR interval differences (RMSSD) (Malik *et al.* 1996; Malik, 1997).

Depression score

A Dutch version of the Center for Epidemiological Studies Depression (CES-D) scale was used to screen for depressive symptoms. The outcome of this questionnaire is a score ranging between 0 and 60. A higher score indicates more depressed feelings (Radloff, 1977; Beekman *et al.* 1997). The CES-D questionnaire was administered by research assistants during a home interview before every research centre visit from 1993 onwards.

Covariables

The following covariables were considered: age, sex, smoking status, highest reached level of education, body mass index (BMI), RR interval, hypertension, prevalent coronary heart disease, prevalent diabetes mellitus, heart failure, use of beta-blockers, use of verapamil and use of diltiazem. All covariables were determined at the date of ECG recording. Smoking status (current smoker or non-smoker) was determined by home interview. Four categories of education were defined: 'basic' equals primary education; 'low' equals lower vocational, lower and intermediate general, 'medium' equals intermediate vocational and higher general education; 'high' equals higher vocational and university. These categories are similar to the UNESCO classification, and have previously been described for the Rotterdam Study (UNESCO, 1976). BMI was calculated by dividing weight by the squared height (kg/m^2), which were both measured at the study centre. Heart rate was taken into account in the form of the RR interval as recorded on the ECG (heart rate equals 60 000/RR interval) because both HRV measures are also based on the RR interval, and HRV and RR interval are both associated with sympathetic and parasympathetic nervous activity. Blood pressure was measured twice in sitting position using the upper right arm. The average of these measurements was used. Hypertension was defined as a systolic blood pressure of $\geqslant$140 mmHg, a diastolic blood pressure of $\geqslant$90 mmHg, or the use of blood pressure lowering medication for the indication hypertension. Coronary heart disease was defined as a prevalent myocardial infarction or as a history of coronary artery bypass graft surgery (CABG) or percutaneous coronary intervention (PCI). Myocardial infarction was adjudicated based on a combination of symptoms, ECG measurements, and enzyme markers indicative for the presence of myocardial infarction (Leening *et al.* 2012). Diabetes mellitus was defined by the use of blood-glucose lowering drugs, a non-fasting glucose level of >11.0 mmol/l, or a fasting glucose level of >6.9 mmol/L (American Diabetes Association, 2010). The diagnosis of heart failure was based on typical signs and symptoms confirmed by objective cardiac dysfunction (Leening *et al.* 2012). Use of heart-rate-affecting drugs (beta-blockers, verapamil, diltiazem) at the date of ECG recording was based on pharmacy dispensing records.

Statistical analyses

Baseline characteristics were assessed at the first eligible ECG recording for each participant. We log-transformed the HRV measures for all analyses, but results are presented back-transformed to the geometric scale.

We used linear mixed models to take into account the within-person correlation between multiple visits. We fitted models with different covariance matrices and selected the model that had the lowest Akaike's Information Criterion (AIC). All statistical models were adjusted for age, sex, RR interval, and heart-rate-affecting drugs (beta-blockers, verapamil, diltiazem). In a second model, we tested whether the association was modified by age and included all other available covariables.

In the first set of analyses, we compared the HRV and heart rate recorded during TCA use and SSRI use with the HRV recorded during non-use of antidepressants. We repeated these analyses for the individual antidepressants if more than 10 exposed ECGs were available. For paroxetine and amitriptyline, the most frequently prescribed drugs in the Rotterdam Study cohort (Aarts *et al.* 2014), we additionally analysed a possible dose-response relationship.

In the subsample for which CES-D scores were available, we analysed the association of the CES-D score

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Table 1. *Baseline characteristics of the study population*

Characteristic	Non-user of antidepressants (*N* = 11 328)	Users of TCAs (*N* = 139)	Users of SSRIs (*N* = 204)
Age, years, mean (S.D.)	64.7 (9.5)	65.2 (9.0)	61.2 (8.4)
Age, years, range	45.6–106.2	48.9–95.9	47.4–98.9
Women, *n* (%)	6594 (58.2)	107 (77.0)	156 (76.5)
Body mass index, kg/m^2, mean (S.D.)	26.9 (4.1)	27.6 (4.5)	28.8 (5.8)
Highest reached level of education			
Low, *n* (%)	4494 (39.7)	63 (45.3)	105 (51.5)
Medium, *n* (%)	4558 (40.2)	48 (34.5)	62 (30.4)
High, *n* (%)	323 (2.9)	1 (0.7)	3 (1.5)
CES-D score, median (IQR)	3 (1–8)	7 (2–13.5)	8.7 (3–18.8)
RR interval, ms (S.D.)	881 (140)	806 (131.1)	896 (135)
Heart rate, beats per minute, mean (S.D.)	69.8 (11.3)	76.4 (12.1)	68.4 (10.4)
Beta-blocker use, *n* (%)	1389 (12.3)	35 (25.2)	34 (16.7)
Verapamil use, *n* (%)	61 (0.5)	4 (2.9)	2 (1.0)
Diltiazem use, *n* (%)	130(1.1)	0 (0.0)	4 (2.0)
Current smoking, *n* (%)	2351 (20.8)	41 (29.5)	51 (25.0)
Coronary heart disease, *n* (%)	659 (5.8)	9 (6.5)	5 (2.5)
Heart failure, *n* (%)	172 (1.5)	2 (1.4)	4 (2.0)
Hypertension, *n* (%)	5848 (51.6)	81 (58.3)	101 (49.5)
Diabetes mellitus, *n* (%)	821 (7.2)	11 (7.9)	10 (4.9)

TCA, Tricyclic antidepressant; SSRI, selective serotonin reuptake inhibitor; CES-D, Center of Epidemiological Studies Depression Scale; IQR, interquartile range; S.D., standard deviation.

with heart rate and HRV. We also adjusted all previously mentioned analyses for the CES-D score. With this adjustment, we aimed to determine if the association between the antidepressants and HRV is confounded by depressive symptoms.

In the second set of analyses, we compared the change in HRV of those who started or stopped using TCAs or SSRIs by the time of the second visits with the HRV of non-users on two consecutive visits. Because the HRV variables were log-transformed and because $\log(a) - \log(b) = \log(a/b)$, the difference between two log-transformed measurements is presented as the fold change in HRV of the back-transformed measurement. We also performed all aforementioned analyses with RR interval as outcome.

We used IBM SPSS Statistics version 21.0 (IBM Corp., USA) for all analyses. Two-sided *p* values <0.05 were considered statistically significant.

Results

Study characteristics

In total, 27 833ECGs were recorded. We excluded 3004 (10.8%) ECGs because cardiac pathologies had been detected. An additional 1072 (3.9%) ECGs were excluded because they had less than five normal heartbeats. In total, 110 ECGs were excluded because they were recorded during use of antidepressants other than TCAs and SSRIs. In the final selection, 23 647 ECGs from 11 729 participants were used. Overall, 59% of the total study population were women, and the mean age was 64.6 years with a standard deviation (S.D.) of 9.5 years. Baseline characteristics of the final study population are shown stratified on antidepressant drug use in Table 1. Participants who used a TCA or SSRI at baseline were more frequently women, were lower educated, had a higher median CES-D score, and were more frequently current smokers than non-users of antidepressants at baseline.

Antidepressant use and HRV

The lowest AIC was achieved with the 'first-order autoregressive covariance structure with heterogeneous variances'. This covariance structure was therefore used in all analyses. Table 2 presents the geometric estimated means of SDNN and RMSSD for ECGs made during non-use of antidepressants and during use of TCAs and use of SSRIs. Of all 23 647 included ECGs, 296 were recorded during TCA use and 380 ECGs were recorded during SSRI use.

Compared with ECGs recorded during non-use of antidepressants, ECGs recorded during TCA use had a significantly (*p* values < 0.05) 82 ms shorter RR interval (952 ms for non-use, and 870 ms for TCAs), a 2.7 ms

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Table 2. *Heart-rate variability recorded during non-use and use of antidepressants*

	ECG, *n*	Median PDD/DDD	RR interval (ms) $Mean_{adj}$ (95% CI)	SDNN (ms) $Mean_{adj}$ (95% CI)	RMSSD (ms) $Mean_{adj}$ (95% CI)
Non-use of antidepressants (ref.)	22 971	N.A.	952 (939–965)	18.3 (17.0–19.7)	19.8 (18.4–21.4)
TCA use	296	0.33	870 (851–889)***	15.6 (14.0–17.4)***	16.7 (15.0–18.7)***
Imipramine	16	0.50	848 (786–910)***	15.9 (11.3–22.5)	19.3 (13.6–27.4)
Clomipramine	27	0.50	905 (860–951)**	10.9 (8.3–14.4)***	11.4 (8.6–15.0)***
Amitriptyline	185	0.33	870 (848–892)***	16.3 (14.4–18.5)	17.3 (15.2–19.7)*
Nortriptyline	13	0.67	810 (745–875)***	10.3 (6.8–15.5)**	11.3 (7.4–17.2)**
Maprotiline	48	0.50	863 (825–900)***	15.5 (12.5–19.3)	17.0 (13.6–21.1)
SSRI use	380	1.00	966 (948–984)**	15.4 (14.0–17.0)***	17.1 (15.4–19.0)***
Fluoxetine	35	1.00	982 (941–1023)	12.5 (9.8–15.8)**	14.1 (11.1–18.0)**
Citalopram	28	1.00	960 (913–1008)	16.8 (13.0–21.8)	18.0 (13.9–23.3)
Paroxetine	237	1.00	959 (938–979)	15.2 (13.5–17.0)***	16.9 (15.0–19.0)**
Sertraline	37	1.00	1001 (959–1042)**	15.8 (12.4–20.0)	16.8 (13.2–21.5)
Fluvoxamine	39	1.00	971 (930–1013)	17.6 (14.0–22.2)	19.6 (15.5–24.7)

ECG, Electrocardiogram; PDD, prescribed daily dosage; DDD, defined daily dosage; $Mean_{adj}$, geometric mean adjusted for covariables; CI, confidence interval; SDNN, standard deviation of normal-to-normal RR interval; RMSSD, root mean square of successive differences; ref., reference; N.A., not applicable; TCA, tricyclic antidepressant; SSRI, selective serotonin reuptake inhibitor.

Only individual antidepressants prescribed during more than 10 ECG recordings were analyzed. Analyses were adjusted for age, sex, RR interval (excluded from all analyses with RR interval as outcome), use of beta-blockers, verapamil and diltiazem.

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$ compared with non-use of antidepressants.

lower SDNN (18.3 ms for non-use, and 15.6 ms for TCAs) and a 3.1 ms lower RMSSD (19.8 ms for non-use and 16.7 ms for TCAs). ECGs recorded during SSRI use had a significantly 2.9 ms lower SDNN (18.3 ms for non-use and 15.4 ms for SSRI use) and a 2.7 ms lower RMSSD (19.8 ms for non-use and 17.1 ms for SSRI use) than ECGs recorded during non-use. Of the individual antidepressants, ECGs recorded during use of clomipramine ($n = 27$), amitriptyline ($n = 185$), nortriptyline ($n = 13$), fluoxetine ($n = 35$) and paroxetine ($n = 237$) showed significantly lower HRV measures than ECGs recorded during non-use of antidepressants. A dose-response relationship was analyzed for amitriptyline and paroxetine, which were the most frequently prescribed antidepressants. A higher prescribed dosage of both amitriptyline (Fig. 1*a*) and paroxetine (Fig. 1*b*) was associated with a statistically significant trend toward a lower SDNN. Results were similar for RMSSD (results not shown).

Similar results were observed when adjusted for all considered covariables in this study, and we observed no effect modification by age (results not shown).

Analyses for possible confounding by depressive symptoms

A total of 14 693 ECGs from 9194 participants were recorded during visit rounds when information of depressive symptoms was available. Of those ECGs, 180 were recorded during use of TCAs and 318 ECGSs were recorded during use of SSRIs. In the non-users of antidepressants in this subgroup, no association was observed between the CES-D score and SDNN and RMSSD ($p = 0.97$ and 0.33, respectively). However, a higher CES-D score was associated with a shorter RR interval ($p = 0.002$). In the subcohort with CES-D data available, the associations of TCAs and SSRIs with heart rate and the HRV measures were similar to those observed in the total cohort. Additional adjustment for CES-D score did not materially change these results (Supplementary Tables S1–S3).

Longitudinal analysis of antidepressant use and HRV

Table 3 shows the ECGs made on two consecutive visits, and the estimated mean fold-change in SDNN and RMSSD between two visits. Median time interval between ECG recordings was 4.1 years (interquartile range 2.4–5.0). The results show that HRV is reduced and heart rate is increased when TCA use is started, and that HRV is increased and heart rate is reduced when TCA use is stopped. For SSRIs the same pattern of SDNN and RMSSD change was observed with regard to HRV, but with a smaller effect size and no statistically significant difference with consistent

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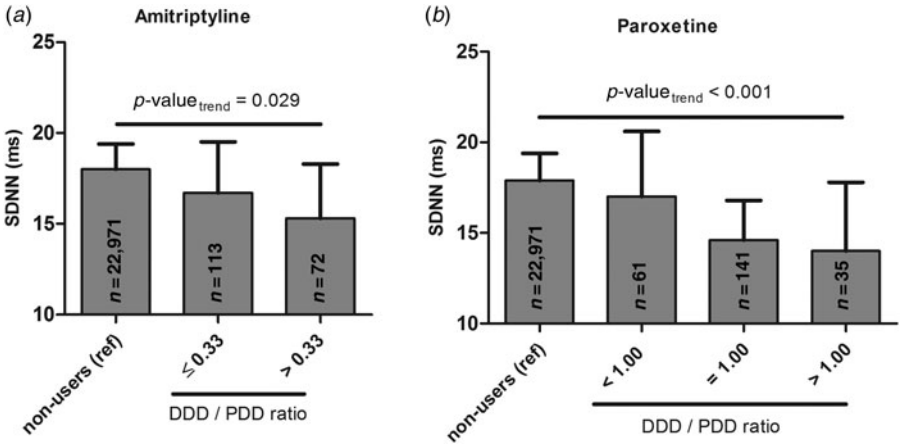

Fig. 1. Association of amitriptyline and paroxetine dosages with heart-rate variability. DDD, Defined daily dosage; PDD, prescribed daily dosage; SDNN, standard deviation of normal-to-normal RR intervals. The bars represent mean SDNN, the whiskers are the upper limit of the 95% confidence interval. p value$_{trend}$ indicates the level of statistical significance across strata. Analyses were adjusted for age, sex, RR interval, use of beta-blockers, verapamil and diltiazem.

Table 3. *Antidepressant use and fold-change in heart-rate variability between two consecutive visits*

Use on first visit	Use on second visit	ECG, n	Mean$_{adj}$ change in RR interval (95% CI)	Mean$_{adj}$ fold-change (95%CI)	
				SDNN	RMSSD
None	None	11 006	29.9 (14.5 to 45.4)	1.06 (0.96–1.18)	1.08 (0.97–1.20)
None	TCA	81	−45.8 (−74.7 to −16.8)**	0.76 (0.62–0.94)**	0.75 (0.61–0.93)**
None	SSRI	92	37.7 (9.7 to 65.7)	0.90 (0.74–1.10)	0.98 (0.80–1.20)
TCA	None	64	102 (69.4 to 134)**	1.49 (1.18–1.87)**	1.64 (130–2.08)**
SSRI	None	61	−0.1 (−33.3 to −33.0)	1.10 (0.87–1.39)	1.10 (0.87–1.40)
TCA	TCA	64	0.5 (−29.2 to −30.2)*	1.11 (0.90–1.39)	1.17 (0.95–1.45)
SSRI	SSRI	62	29.5 (−1.2 to −60.2)	1.02 (0.82–1.26)	0.97 (0.78–1.21)

ECG, Electrocardiogram; Mean$_{adj}$, geometric mean adjusted for covariables; CI, confidence interval; SDNN, standard deviation of normal-to-normal RR intervals; RMSSD, root mean square of successive differences; TCA, tricyclic antidepressant; SSRI, selective serotonin reuptake inhibitor.

Analyses were adjusted for age, sex, RR interval, use of beta-blockers, verapamil and diltiazem.

*$p < 0.05$, **$p < 0.001$ compared with non-use of antidepressants during both ECGs.

non-users. No significant change in RR interval was observed after starting or stopping SSRI use. There was no effect of consistent use of TCAs and SSRIs on HRV, and only consistent use of TCAs showed a smaller increase in RR interval compared to consistent non-users.

Discussion

In this population-based study in older adults, use of TCAs and SSRIs was associated with a lower HRV, which was independent of the effects of TCAs and SSRIs on the RR interval. In addition, the individual antidepressants clomipramine, amitriptyline, nortriptyline, fluoxetine and paroxetine were significantly associated with a lower HRV and a dose-response relationship of amitriptyline and paroxetine with HRV was observed. In the longitudinal analysis, the start of TCA use, and not SSRI use, was associated with significant changes in HRV. Additional adjustment for CES-D score did not materially change the results.

To our knowledge, only one study to date has analyzed the effect of antidepressant use on HRV in the general older population (O'Regan *et al.* 2015). This study reported a lower HRV in users of TCAs and SSRIs, which is in line with the results of our study. However, we additionally investigated the effect of individual antidepressants on HRV: most previous studies considered only antidepressant classes. We observed a lower HRV for all individual TCAs, but the difference with non-use of antidepressants

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was largest for clomipramine and nortriptyline. Imipramine and maprotiline showed much smaller differences in HRV compared with non-use, while the prescribed daily dosages were similar. For amitriptyline, the smaller effect on HRV can be explained by the fact that it was prescribed at a lower median daily dosage than the other TCAs. This is supported by the fact that we found a significant trend towards a lower HRV with higher amitriptyline dosages. For individual SSRIs, the results were difficult to interpret. Users of fluoxetine had a notably lower HRV than users of the other SSRIs while the median daily dosage of all individual SSRIs was the same. Although HRV was somewhat lower during the use of all individual SSRIs, the difference for these individual SSRIs was not statistically significant, which could be due to a low number of users. Therefore, we were not able to exclude the possibility that HRV is dependent on the use of only certain SSRIs. Nevertheless, we observed a significant dose-response relationship for paroxetine, which was not statistically significant in the overall analysis. For this reason, these analyses should be repeated in other studies.

Additional adjustment for depressive score did not materially change the results. This finding contradicts the meta-analysis (Kemp *et al.* 2010), but is in line with both a recent case-control study and a cohort study (Licht *et al.* 2008, 2015). These two studies found that the association of depression with HRV was predominantly driven by the use of antidepressants. The case-control study (Licht *et al.* 2008) also suggested depression was not associated with cardiac autonomic control, which is in line with our findings, that the CES-D score is not associated with HRV.

The previously mentioned population-based study (O'Regan *et al.* 2014) had only one measurement per participant and could not assess longitudinal changes over time. One study did assess longitudinal changes in HRV with respect to starting and stopping of TCA treatment and SSRI treatment (Licht *et al.* 2010). They found that starting TCA treatment or starting SSRI treatment was associated with a reduction in HRV. However, starting SSRI treatment was associated with less reduction in HRV than starting TCAs (Licht *et al.* 2010). In our study, we observed no significant decrease in HRV after starting SSRIs, and no significant increase after stopping SSRIs. The inconsistent results for SSRIs for the cross-sectional and longitudinal analyses might suggest that other, unexamined, factors than the drug itself lead to a lower HRV, but additional research is required to support this suggestion.

The relatively low HRV in users of TCAs might have clinical consequences for an individual patient, as a relatively low HRV has been associated with an increased risk of all-cause mortality (Kleiger *et al.* 1987; Fei *et al.* 1996; de Bruyne *et al.* 1999; Stein *et al.* 2005; Erdogan *et al.* 2008; Huikuri *et al.* 2009), cardiac mortality (La Rovere *et al.* 1998; Huikuri *et al.* 2009), and sudden cardiac death (Makikallio *et al.* 2005). TCAs have also been associated with an increased risk of cardiac mortality (Hamer *et al.* 2011). Whether this increased risk is due to a low HRV should be determined in subsequent studies.

This study has a number of strengths and limitations. Major strengths were the availability of detailed pharmacy dispensing data and the availability of multiple ECG recordings for most participants. The population-based (cohort) study design enhanced the generalizability (Szklo, 1998), and the ECG recordings were collected prospectively and irrespective of the hypothesis of the present study. Further, RR intervals and HRV were systematically and automatically calculated using MEANS, which enhances measurement precision and prevents bias (Willems *et al.* 1991; de Bruyne *et al.* 1997). Information bias for drug use was limited as pharmacy dispensing data was collected prospectively and irrespective of disease state. The analysis using the calculated within-person changes of HRV between two consecutive visit rounds is less subjected to confounding than our cross-sectional analysis and the results are complementary. Finally, we added a variable for depressive symptoms which did not change the results, and no association was observed between depressive symptoms and HRV. Information regarding anxiety disorder in our study population was not available. Misclassification was probably limited, however, because a previous study showed that anxiety accounted only for a minor proportion of the indications for antidepressants (Noordam *et al.* 2015). There are also some limitations to address. First, some of the individual antidepressants were dispensed in low numbers. Second, the median time interval between two ECG recordings was 4.1 years, which limits the interpretation of a change in HRV between visits, as other confounding factors may occur in the long time period. Third, we used standard 10-s ECG recordings, while the major studies in the literature are based on $\geqslant$5-min ECGs. It is likely that measurement error is larger when HRV is assessed on a 10-s ECG, and this increased measurement error might be the reason why no association was observed between depressive symptoms and HRV. However, HRV derived from 10-s ECGs was also predictive for cardiovascular disease and mortality (Dekker *et al.* 1997; de Bruyne *et al.* 1999), and the results of the first set of analyses in this paper are in line with that of previous studies (Licht *et al.* 2010; O'Regan *et al.* 2014). Finally, the CES-D score is probably less sensitive in assessing depressive symptoms than a formal diagnosis.

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Nevertheless, a higher CES-D score was associated with a lower RR interval (i.e. faster heart rate).

In conclusion, the results indicate that TCAs are associated with a lower HRV independent of the lower RR interval in older adults, a condition associated with an increased risk of mortality. For SSRIs this is less clear, although we observed an association between SSRIs and HRV and a dose-response relationship of paroxetine with HRV.

Supplementary material

For supplementary material accompanying this paper visit http://dx.doi.org/10.1017/S0033291715002779.

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