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Serotonin and norepinephrine reuptake inhibitors antidepressant use is related to lower baroreflex sensitivity independently of the severity of depressive symptoms. A community-study of 9213 participants from the Paris Prospective Study III

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ABSTRACT

Background and aims: We assess the respective relationship of high depressive symptoms and antidepressant use (ATD) with baroreflex sensitivity (BRS) in subjects from the community who enrolled the Paris Prospective Study III.

Methods: Recruitment took place in a large health preventive centre in Paris (France), between May 2008 and June 2012. BRS was investigated by spectral analysis of the spontaneous carotid distension rate and RR intervals using non-invasive high-resolution ultrasound carotid-echotracking. A total score ≥7 on a 13-item standardized questionnaire defined the presence of high depressive symptoms. Information on ATD use was obtained on a face-to-face interview with a medical doctor who checked the most recent medical prescriptions and/or medical package.

Results: There were 9213 participants aged 50–75 years (38.6% of women), including 5.6% with high-depressive symptoms and 5.2% on ATD. High depressive symptoms were not associated with low BRS (below the median) even in unadjusted logistic regression analysis (OR = 1.09; 95%CI: 0.91–1.30). Instead, ATD use was related to low BRS in multivariate logistic regression analysis (OR = 1.27; 95% CI: 1.04–1.54). This association remains after adjusting for and matching on propensity score of receiving ATD. A specific association with serotonin and norepinephrine reuptake inhibitors was observed (OR = 1.94; 95% CI: 1.16–3.22).

Conclusions: ATD use and serotonin and norepinephrine reuptake inhibitors in particular, but not high depressive symptoms, is associated with low BRS. If confirmed, these results may bring novel insights into the mechanisms linking depressive symptoms and/or ATD use with cardiovascular disease onset.

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1. Introduction

Depression and high depressive symptoms are very common in the population and are expected to rise given the aging of the population [1]. Likewise, antidepressants (ATD) are now one of the most prescribed medications worldwide [2]. A large body of evidence indicates that depression and high depressive symptoms are related to the onset of cardiovascular disease (CVD) and particularly sudden cardiac death (SCD) [3–5]. Regarding ATD use, the pro-arrhythmic effect of tricyclics and their association with SCD has been already reported; some selective serotonin reuptake inhibitors (SSRI) could be linked with an increased risk of SCD as well [6,7]. So far however, the disease processes by which depressive symptoms and/or ATD use might be related to CVD onset including SCD remain to be further investigated. Poor lifestyle risk factors, lack of adherence to medical treatment, increased platelet aggregation or chronic low-grade inflammation, have been proposed as possible explanations, but with mixed evidence [8–10]. We hypothesize that autonomic dysfunction and impairment in the baroreceptor reflex sensitivity (BRS) in particular could represent one relevant disease process to investigate. The BRS is a fundamental key process for the homeostasis of blood pressure and heart rate variability (HRV), and is one of the strongest risk factor for SCD in post myocardial infarction patients [11]. The extent to which depression and/or ATD use is associated with impaired BRS per se has been addressed by only a few studies that although contributing, suffer from the following limitations. They were of very limited sample size ($n < 100$), mostly conducted in patients with coronary artery disease (CAD) or elderly participants and only a few addressed the influence of ATD use [12–15]. Several population based studies have reported higher resting heart rate and decreased HRV- that are strong predictors of CVD mortality and SCD- [16–18] in ATD users and possibly subjects with depressive symptoms [19–24]. However, heart rate markers and HRV parameters only represent the efferent loop of the BRS.

We therefore aimed to study the respective association of high depressive symptoms and ATD use with BRS in more than nine thousands unselected participants who enrolled the Paris Prospective Study III [25].

2. Materials and methods

2.1. The Paris Prospective Study 3

The design and main objectives of the PPSIII have been previously published [25]. It is an ongoing prospective observational cohort on the novel determinants of the onset of main phenotypes of CVD in initially mostly healthy subjects. Our study is registered in the World Health Organization International Trial Registry Platform (NCT00741728 since 25/08/2008). The study-protocol was approved by the Ethics Committee of the Cochin Hospital (Paris). Between May, 2008 and June, 2012, 10,157 men and women aged 50–75 years were recruited in a large preventive medical centre, the Centre d'Investigations Préventives et Cliniques (IPC), in Paris (France) after signing an informed consent form. The IPC is a preventive medical centre that is subsidized by the French National Insurance System for Salaried Workers (Sécurité Sociale-CNAMTS), which offers to all working and retired employees and their families living in the Paris area, a free medical examination every five years. The standard health check-up includes a complete clinical examination, coupled with standard biological tests after an overnight fasting. A self-administered questionnaire provides information related to professional activity, lifestyle (tobacco and alcohol consumption, physical activity, diet, etc.), personal and family medical history, current health status and medication consumption [26].

2.2. Depressive symptoms

Since the late 80s, all preventive health centres subsidized by the French National Insurance System for Salaried Workers in France use the 13-item Questionnaire of Depression 2nd version, Abridged (QD2A) [27] to screen individuals from the community who are at high risk of depression. This questionnaire was initially based on 151 items selected from 4 self-rating scales or inventories of depression used in clinical settings: the Beck Depression Inventory [28], the Zung Self-Rating Depression Scale [29], the D Scale of Depression of the Minnesota Multiphasic Personality Inventory (MMPI) [30], and the Hopkins Symptoms Check list [31]. After principal component analysis, 52 items were retained; a subsequent factorial analysis demonstrates that an abridged version with 13 items summarized satisfactorily the severity of depressive symptoms. This 13-item questionnaire has been validated against clinically diagnosed depression [32]. In particular these 13-items cover 2 dimensions, motivation and depressive mood. Participants had to give a yes/no answer to each of the 13-item regarding their *current* emotional state (e.g. "I am disappointed and disgusted with myself", "I am sad these days", "I feel hopeless about the future"). The number of yes answers is summed to provide a total score with high internal consistency ($\alpha = 0.91$). A total score ≥ 7 indicates a high probability for major depression (sensitivity: 81%, specificity: 96%) and will be referred to as "high depressive symptoms" in the following sections [27]. The 13-item questionnaire is reported in the Supplementary file.

2.3. Medications

On a standardized questionnaire, participants reported up to 15 medications they were currently taking, together with a series of chronic conditions including depression for which they were currently prescribed medications. To reduce under reporting, participants were asked to come at the IPC with either their most recent medical prescriptions and/or with their medical package. Medications were checked by a medical doctor from the IPC during a face to face interview with the study participant. Medications were coded using the World Health Organization (WHO) Anatomical Therapeutic Chemical (ATC) classification. For the present analysis, ATD were classified as SSRI, serotonin and norepinephrine reuptake inhibitors (SNRI), tricyclic antidepressants (TCAs), and other antidepressant drugs.

2.4. Echotracking-derived neural baroreflex sensitivity

Because baroreceptors are more sensitive to arterial stretch (i.e. deformation) than pressure per se, BRS can be investigated by the spectral analysis of the spontaneous carotid distension fluctuations (input signal) and RR intervals (output signal) using non-invasive high-resolution ultrasound carotid-echotracking [33–35]. With this technique, the *neural* component of the BRS is estimated, while controlling for its *vascular* (i.e. *mechanical*) component, i.e. the stiffness of the artery [34–36]. This method has been shown to be highly consistent with other noninvasive BRS assessment methods [37]. A detailed description of the measures is given in the supplementary materials. Briefly, measurements were performed at the right common carotid artery (CCA) 1 cm proximal to the carotid bulb bifurcation using the ArtLab® (Esaote, Italy) high-resolution echotracking technology after 10′ of rest in a supine position. A 5-min continuous recording of carotid diameter and distension was performed: cross spectral analysis of distension rate and heart rate was performed, extracting low frequency (LF) and high frequency

(HF) variability of distension waveform and heart rate [33,34]. The transfer function magnitude between input (carotid distension rate) and output (R-R interval) within the frequency band of 0.04–0.15 Hz defined the LF gain and corresponds to the neural BRS (nBRS) [38,39]. In the absence of any published thresholds, we defined low nBRS as a value below the median, which was calculated in the entire participant population.

2.5. Study population

Among the 10157 subjects examined at baseline, 832 had incomplete nBRS measures, 70 had missing values on ATD intake and 50 on depressive symptoms score. Excluded subjects were older, more frequently women, had a significantly higher burden of cardiovascular risk factors (all *p values* < *0.05*) and tended to be prescribed ATD more frequently ($p = 0.06$) than the finally investigated 9213 subjects (Supplementary Table 1).

2.6. Statistical analysis

Characteristics between subjects with and without high depressive symptoms, with and without ATD use or with and without low nBRS (log transformed times 100) were compared using Pearson chi-square and *t*-test for categorical and continuous variables respectively. In the following analyses, nBRS was used as the outcome and high depressive symptoms or ATD use as the main exposure variables. Separate logistic regression analysis was employed to quantify the association between high depressive symptoms or ATD use with low nBRS. Analyses were adjusted for established confounding factors including age, sex, past history of CVD, education, single status, smoking status, hypertension, diabetes, body mass index, resting heart rate, and physical activity. Subsequent analyses focused on ATD use for which significant associations were observed. Associations between ATD use and low nBRS, were stratified by sex, age group (according to median age), hypertension, high depressive symptoms, personal history of CVD and resting heart rate levels (according to median value); interactions across strata were evaluated using a *p* value of <0.10 as potentially relevant. Given the observational nature of the study, and to minimize for indication bias for ATD prescription, the association between ATD use and low nBRS was further conducted using propensity score analysis [40]. The propensity of receiving ATD of any class was estimated by logistic regression analysis using age, sex, education, single status, prevalent CVD, smoking status, hypertension, diabetes, body mass index, resting heart rate, physical activity and high depressive symptoms as covariates on an a priori basis. Then, the association between ATD use and low nBRS was repeated after adjustment for the propensity score and after propensity score matching. [40] For the latter, 1 subject under ATD was matched with up to 4 controls using a difference in the probability of receiving ATD of less than 0.001, resulting in a study sample size of 2098 subjects after matching. Sensitivity analyses were conducted to assess the robustness of our findings on ATD use and nBRS. First, nBRS was considered as a continuous outcome (log transformed) and its association with ATD use was carried out in multivariable linear regression analyses after adjustment for the same above mentioned confounding factors. Second, nBRS was considered in quartiles and its association with ATD use was carried out in multivariable multinomial ordinal logistic regression analysis. In exploratory analysis, the association between low nBRS and ATD class - available in 71.6% of the ATD users - including SSRIs, SNRIs, TCAs and other antidepressants was quantified in separate multivariable logistic regression analyses using those not under ATD as the reference category. To minimize the impact of missing information on ATD class, a dummy variable indicator for missing information for ATD class was included in each model. All tests were two-sided and were performed using SAS software release 9.4 (Statistical Analysis System, Cary, NC, USA).

3. Results

3.1. Baseline characteristics

The mean age (standard deviation SD) of the population was 59.5 (6.30), 38.6% were women and 2% reported a past history of CVD. 5.6% of the participants had high-depressive symptoms and 5.2% were on ATD. The characteristics of the population by depressive symptoms status and by ATD use are reported in Table 1. As expected, women were more often depressed and more often prescribed ATD than men; subjects with high depressive symptoms were prescribed ATD five times more frequently than subjects without depressive symptoms, and subjects under ATD were five times more often depressed than non-users. Furthermore, subjects with high depressive symptoms and subjects on ATD had significantly worse characteristics than their respective comparison group. ATD users had significantly lower nBRS and higher CCA-IMT compared to non-users, whereas these 2 parameters did not differ between subjects with and without high depressive symptoms.

Among ATD users, 57.7% were on SSRI, 22.7% on SNRI, 15.6% on TCAs, and the remaining on other ATDs. The distribution of the baseline characteristics by ATD class is reported in Supplementary Table 2 and shows in particular that SNRI users had higher systolic blood pressure, higher CCA-IMT, higher resting heart rate and were less physically active than ATD users of other class.

Table 2 shows the baseline characteristics between subjects with low (below the median) and high nBRS (above the median). Subjects with low nBRS were older, more frequently women, less educated, more often with a personal history of CVD, more frequently diabetics or hypertensive, had higher BMI, higher resting heart rate, and were more often on ATD, especially SNRI, compared to subjects with higher nBRS. Interestingly, the prevalence of high depressive symptoms did not differ between subjects with high and low nBRS.

3.2. Odds ratios of high depressive symptoms for low nBRS

As illustrated in Fig. 1 there was no significant association between high depressive symptoms and low nBRS. This was observed even in unadjusted analysis (OR = 1.09; 95%CI: 0.91–1.30) and when the population was restricted to those not on ATD (OR = 1.01; 95% CI: 0.82–1.25).

3.3. Odds ratio of antidepressant use for low nBRS

3.3.1. Classical analysis

As shown in Fig. 1, there was a statistically significant association between ATD use and low nBRS (OR = 1.34; 95% CI: 1.11–1.62) in unadjusted analysis, which was virtually unchanged after adjustment for confounding factors (OR = 1.27; 95% CI: 1.05–1.55). Further adjustment for high depressive symptoms slightly attenuated the association with ATD (OR = 1.27; 95% CI: 1.04–1.54). As shown in Table 3, the magnitude of the association between ATD use and low nBRS was comparable to that with hypertension or diabetes and was equivalent to the effect of 8 years of ageing. As shown in Fig. 2, the multivariate-adjusted association, between ATD use and low nBRS was consistent across strata defined by age, sex, personal history of CVD, level of resting heart rate and high depressive symptoms status. However, this association existed in the absence of hypertension only (*p* for

Table 1
Baseline characteristics by depressive symptoms status and by antidepressants intake.

	Depressive symptoms score		p[a]	Antidepressants intake		p[a]
	<7 (N = 8699)	≥7 (N = 514)		No (N = 8737)	Yes (N = 476)	
Age (years)	59.57 (6.29)	59.08 (6.07)	0.083	59.52 (6.28)	60.06 (6.22)	0.065
Men	5464 (62.81)	190 (36.96)	<0.0001	5487 (62.80)	167 (35.08)	<0.0001
Marital status (single)	2144 (24.71)	243 (47.46)	<0.0001	2198 (25.22)	189 (39.79)	<0.0001
Education (Degree, master and +)	3482 (40.36)	132 (26.24)	<0.0001	3446 (39.79)	168 (35.74)	0.081
Personal history of cardiovascular disease	161 (1.85)	21 (4.10)	0.0004	167 (1.92)	15 (3.15)	0.06
Depressive symptoms score ≥7	–	–	–	403 (4.61)	111 (23.32)	<0.0001
Antidepressants intake	365 (4.20)	111 (21.60)	<0.0001			
SSRI[b]	138 (1.61)	50 (10.31)	<0.0001	0	188 (57.67)	<0.0001
SNRI[b]	54 (0.63)	20 (4.12)	<0.0001	0	74 (22.70)	<0.0001
Tricyclic antidepressants[b]	41 (0.48)	10 (2.06)	0.0003	0	51 (15.64)	<0.0001
Other[b]	23 (0.27)	5 (1.03)	0.015	0	28 (8.59)	<0.0001
Physically active	6925 (79.61)	361 (70.23)	<0.0001	6917 (79.17)	369 (77.52)	0.389
Current smoker	1236 (14.22)	116 (22.57)	<0.0001	1251 (14.32)	101 (21.22)	<0.0001
Body mass index (kg/m^2)	25.12 (3.60)	25.18 (4.21)	0.729	25.13 (3.60)	25.06 (4.20)	0.723
High density lipoprotein (mg/dL)	58.35 (15.14)	59.42 (16.58)	0.157	58.26 (15.17)	61.24 (16.04)	<0.0001
Total cholesterol (mg/dL)	221.27 (36.01)	221.01 (36.86)	0.874	221.02 (35.99)	225.71 (37.02)	0.006
Lipid lowering drugs	1081 (12.43)	66 (12.84)	0.784	1061 (12.15)	86 (18.07)	0.0001
Impaired fasting glycemia or diabetes	334 (3.85)	25 (4.87)	0.244	342 (3.92)	17 (3.57)	0.699
Systolic blood pressure, mmHg	130.97 (16.26)	130.37 (16.93)	0.418	131.00 (16.32)	129.86 (15.97)	0.138
Diastolic blood pressure, mmHg	75.78 (9.55)	74.84 (9.49)	0.031	75.78 (9.56)	74.68 (9.20)	0.015
Blood pressure lowering drugs	1176 (13.55)	95 (18.48)	0.002	1180 (13.54)	91 (19.12)	0.001
Heart rate (beats/min)	61.64 (8.85)	63.40 (10.34)	0.0002	61.66 (8.92)	63.10 (9.40)	0.0007
CCA-IMT[c] (μm)	639.61 (116.68)	641.01 (108.40)	0.777	639.13 (116.32)	649.91 (114.09)	0.049
High neural baroreflex sensitivity[d]	4360 (50.12)	247 (48.05)	0.363	4402 (50.38)	205 (43.07)	0.002

Data are reported as n (%) and mean (standard deviation) where appropriate.
SSRI: selective serotonin reuptake inhibitors; SNRI: serotonin and norepinephrine antidepressants.
[a] Person Chi-square test (or fisher exact test) and Student test where appropriate.
[b] Information on ATD class could be retrieved in only 71.6% of ATD users.
[c] Common carotid artery intima media thickness.
[d] Neural baroreflex above the median value.

Table 2
Baseline characteristics in subjects with low (below the median) and high (greater or equal to the median) neural baroreflex sensitivity.

	Low neural BRS (N = 4606)	High neural BRS (N = 4607)	p[a]
Age (years)	60.20 (6.43)	58.89 (6.06)	<0.0001
Men	2763 (59.99)	2891 (62.75)	0.006
Marital status: single	1237 (26.92)	1150 (25.03)	0.039
Education level (Degree, ≥master)	1759 (38.48)	1855 (40.69)	0.031
Personal history of cardiovascular disease	110 (2.39)	72 (1.57)	0.004
Depressive symptoms score ≥7	267 (5.80)	247 (5.36)	0.363
Antidepressants	271 (5.88)	205 (4.45)	0.002
SSRI[b]	103 (2.28)	85 (1.87)	0.174
SNRI[b]	49 (1.08)	25 (0.55)	0.005
Tricyclic antidepressants[b]	28 (0.62)	23 (0.51)	0.472
Other[b]	13 (0.29)	15 (0.33)	0.714
Physically active	3634 (78.90)	3652 (79.27)	0.659
Current smoker	703 (15.27)	649 (14.09)	0.109
Body mass index (kg/m^2)	25.31 (3.78)	24.94 (3.48)	<0.0001
High density lipoprotein (mg/dL)	58.73 (15.36)	58.09 (15.08)	0.045
Total cholesterol (mg/dL)	221.74 (36.39)	220.77 (35.72)	0.197
Lipid lowering drugs	664 (14.42)	483 (10.49)	<0.0001
Impaired fasting glycemia or diabetes	217 (4.72)	142 (3.09)	<0.0001
Systolic blood pressure, mmHg	132.66 (16.55)	129.22 (15.86)	<0.0001
Diastolic blood pressure, mmHg	75.83 (9.67)	75.61 (9.42)	0.275
Blood pressure lowering drugs	735 (15.96)	536 (11.63)	<0.0001
Heart rate (beats/min)	62.38 (9.09)	61.09 (8.76)	<0.0001
CCA-IMT[c] (μm)	651.95 (116.69)	627.42 (114.46)	<0.0001

Data are reported as n (%) and mean (standard deviation) where appropriate.
BRS: baroreflex sensitivity; SSRI: selective serotonin reuptake inhibitors; SNRI: serotonin and norepinephrine antidepressants.
[a] Person Chi-square test (or fisher exact test) and Student test where appropriate.
[b] Information on ATD class could be retrieved in only 71.6% of the users.
[c] Common carotid artery intima media thickness.

interaction = 0.07).

3.3.2. Propensity score analysis

To limit indication bias associated with ATD prescription, we have repeated the analysis using propensity score analysis. As reported on Fig. 3 and compared to the classical analysis reported above, the associations between ATD use and low nBRS remained unchanged after adjusting for (OR = 1.28; 95% CI: 1.05–1.55) or matching on (OR = 1.32; 95%CI: 1.07–1.63) propensity score respectively.

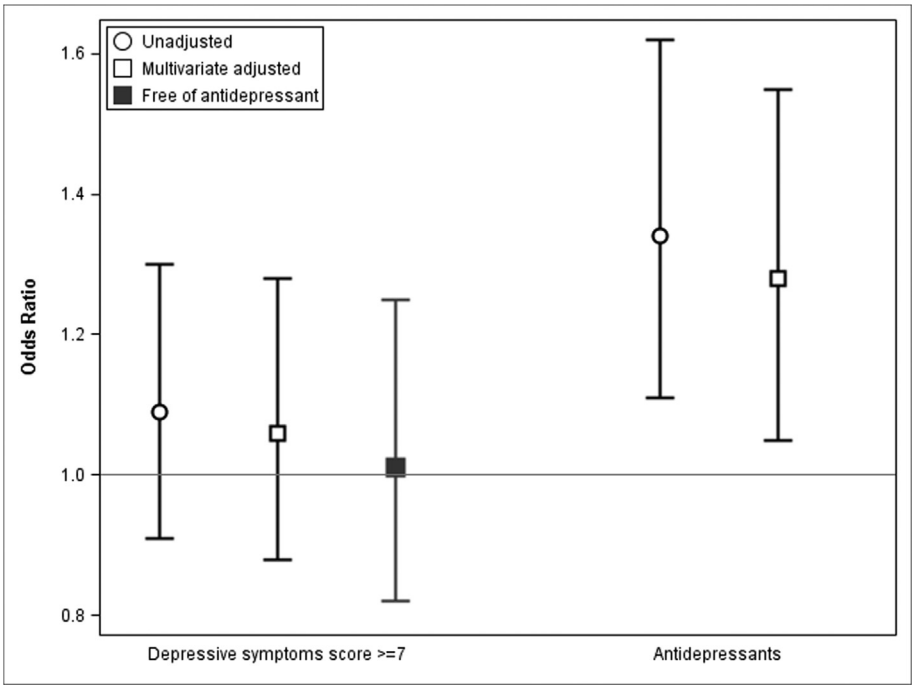

Fig. 1. Odds ratios of low neural baroreflex sensitivity for high depressive symptoms and antidepressant use. Separate logistic regression analysis adjusted for age, sex, education, single status, body mass index, resting heart rate, past history of cardiovascular disease, hypertension, diabetes, high depressive symptoms (where appropriate) and antidepressants (where appropriate).

Table 3
Risk factors associated with low neural baroreflex sensitivity in multivariate logistic regression analysis.

	OR	95% CI	*p* values
Age (/1 year)	1.03	1.02–1.04	<0.0001
Women vs. men	1.11	1.01–1.22	0.028
Single	1.05	0.95–1.16	0.366
School education[a]	0.98	0.90–1.07	0.715
Never smokers	1 (ref)		
Ex-smokers	1.09	0.99–1.20	0.074
Current smokers	1.22	1.08–1.39	0.002
Physically active	1.02	0.92–1.14	0.680
BMI (/1 kg/m^2)	1.02	1.01–1.03	0.0009
Heart rate (/10 bpm)	1.14	1.09–1.20	<0.0001
Past history of CVD	1.26	0.93–1.71	0.143
Hypertension	1.25	1.14–1.38	<0.0001
Diabetes	1.29	1.03–1.61	0.025
High depressive symptoms	1.02	0.84–1.23	0.870
Antidepressants intake	1.27	1.04–1.54	0.018

Single logistic regression analysis adjusted for all covariates present in the Table. Low neural baroreflex sensitivity is defined by a baroreflex value lower than the median.
bpm: beat per minutes; CVD: cardiovascular disease; BMI: body mass index.
[a] Degree or more.

3.4. Sensitivity analyses

In separate multivariable linear regression analysis, ATD use (regression coefficient = −0.079, *p* value = 0.007) remained associated with nBRS (log-transformed variable). Furthermore, multinomial logistic regression indicates that ATD users were more often observed in lower quartiles of nBRS as shown by odds ratios of 0.94 (0.70–1.25), 1.12 (0.85–1.48) and 1.34 (1.03–1.76) respectively for the third, second and first quartile of nBRS. Likewise, the odds ratio of ATD use for the first versus the last three quartiles of nBRS was 1.31 (1.07–1.62; $p = 0.01$).

3.5. Exploratory analysis by ATD class

Multivariable analysis by ATD class suggests a statistically significant association with SNRI (OR = 1.94; 95% CI: 1.16–3.22) only. Among SNRI users (n = 74 users), 64 were on Venlafaxine, 7 on Duloxetine and 3 on Milnacipran; association was observed with venlafaxine (OR = 1.67; 95% CI:0.99–2.82; $p = 0.056$) in fully-adjusted analysis. Associations with other ATD were as follows: SSRI: OR = 1.20 (95% CI = 0.89–1.62); TCA: OR = 1.08 (95% CI = 0.61–1.94); other ATD: OR = 0.80 (95% CI = 0.37–1.70) respectively. In neither of these analyses, depressive symptoms demonstrated any significant associations with nBRS (not shown).

4. Discussion

In 9213 men and women from the community aged 50–75 years and who were offered a free extended clinical examination in a large preventive health centre, antidepressant use was associated with impaired (neural) baroreflex sensitivity as measured by carotid echotracking. These findings were independent of depressive symptoms severity and several confounding factors and were consistent after controlling for indication bias using propensity score analyses. The effect size (OR = 1.34) was comparable to that of hypertension, diabetes and was equivalent to the effect of 8 years of ageing. Exploratory analysis further suggests a particularly strong and significant association with SNRI (OR = 1.94). Instead, there was no significant association between high depressive symptoms and lower (neural) baroreflex sensitivity.

4.1. Prior studies on depression and BRS

Only a few prior studies have investigated BRS in depressed individuals and all were of very small sample size (n < 100). The first was performed in 30 stable CAD patients and reported impaired BRS in those with depressive symptoms [12]. However,

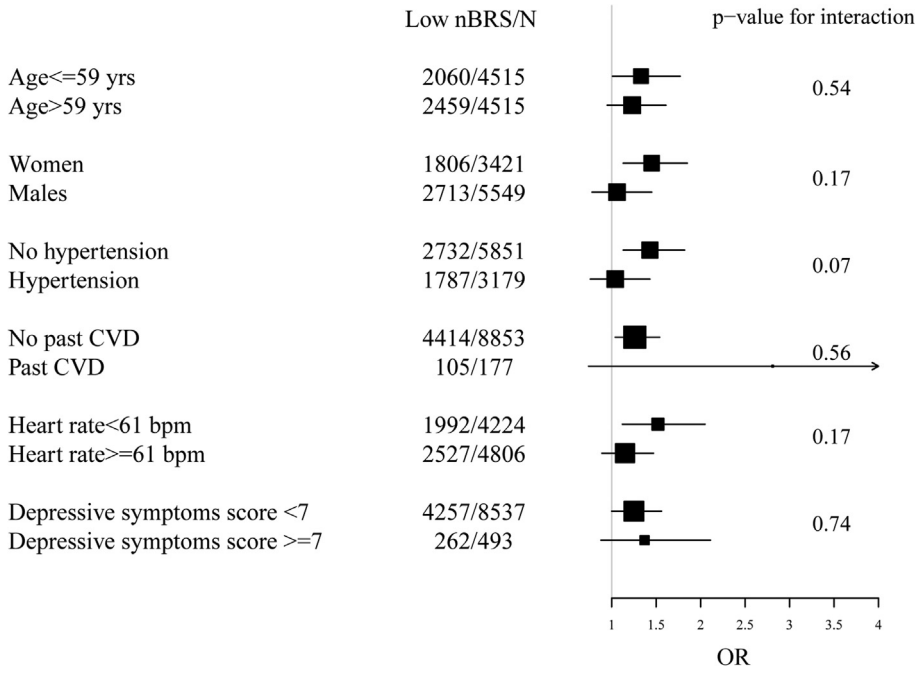

Fig. 2. Odds ratios of low neural baroreflex sensitivity for antidepressant use: stratified analysis. Low nBRS: neural baroreflex sensitivity below the median value. The strata for age and heart rate were defined a priori according to the respective median value. Logistic regression analysis was adjusted for age (where appropriate), sex (where appropriate), education, single status, smoking status, physical activity, body mass index, resting heart rate (where appropriate), past history of cardiovascular disease (where appropriate), hypertension (where appropriate), diabetes, high depressive symptoms (where appropriate).

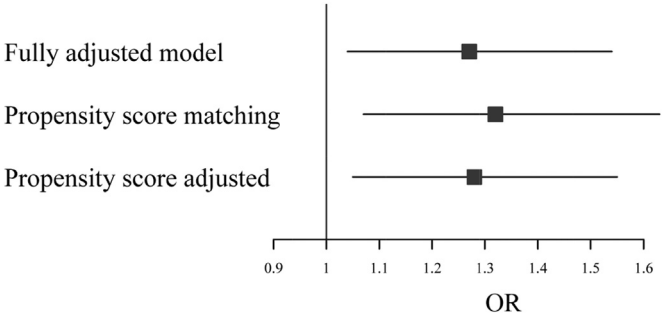

Fig. 3. Odds ratios of low neural baroreflex sensitivity for antidepressant use: propensity score analysis. The propensity score of receiving ATD of any class was estimated using logistic regression analysis and included age, sex, education, single status, smoking status, physical activity, body mass index, resting heart rate, past history of cardiovascular disease, hypertension, diabetes, high depressive symptoms as predictors. For the propensity matching analysis, 1 subject under ATD was matched with up to 4 controls using a difference in the probability of receiving ATD of less than 0.001, resulting in a study sample size of 2098 subjects. Low nBRS: neural baroreflex sensitivity below the median value.

the impact of CAD per se on BRS impairment could not be completely ruled out and, except age, other confounding factors were not adjusted for. A second small study (n = 62) reported impaired BRS in patients with remitted depression as compared to controls [13]. However this was a very selected population of remitted depression patients with no risk factors. More recently, 2 population-based studies conducted in elderly subjects reported impaired BRS in those with either major depression or high depressive symptoms. In these 2 studies however, the contribution of ATD use was not evaluated [14,15].

4.2. BRS assessment

All these previous studies used non-invasive BRS assessment methods that relate spontaneous peripheral blood pressure change with change in heart rate. Although widely used, this method is highly influenced by the stiffness of the vascular wall: for the same variation in blood pressure, the stiffer the artery, the smaller the stretch, the smaller the signal applied on the baroreceptors and the response in R-R interval, which will reduce the capacity to buffer the pressure. This may have been a critical issue in the present study that includes subjects aged 50–75 years, as the vascular wall becomes stiffer with age [34]. This is the main reason why in the present study, we preferred measuring BRS employing spontaneous carotid stretch change rather than peripheral blood pressure change as the input signal using high precision carotid echotracking. With this technique, it is possible to study specifically the neural component of the BRS, while controlling for the stiffness of the carotid wall (i.e. the vascular or mechanical component of the BRS) [33–36]. While the clinical relevance of a low BRS regarding risk stratification has been essentially shown with BRS measured with invasive methods (infusion of vasoactive medications) [11,41], recent preliminary results support that BRS as measured by carotid echotracking might discriminate post MI patients at high risk for arrhythmic events better than other noninvasive BRS methods [42]. Still, we recognize that the data acquisition required particular skill, and the analysis remained complex. Like other non-invasive BRS methods, we assessed only one aspect of baroreflex regulation, the baroreflex heart rate regulation, but not the baroreflex regulation of vascular tone.

4.3. Interpretation of the current findings

To the best of our knowledge, PPS3 is the first large study conducted in the community and addressing simultaneously the relation between depressive symptomatology, ATD use and BRS. We found that ATD use and not depressive symptoms, was associated with impaired nBRS. The lack of association between

depressive symptoms and impaired BRS does not preclude that an association may exist with clinical depression, but the latter was not measured in PPS3. There might be several explanations by which ATD use is related to low nBRS in the current study. First, ATD users may suffer from more severe depressive symptoms although our study results were observed after adjustment for and stratification on depressive symptoms severity. Second, our findings may reflect differences in the characteristics between ATD users and non-users, and to underlying factors leading to the prescription of ATD. However, we observed very consistent results after adjustment for the baseline characteristics that differed between ATD users and non-users, and after propensity score analyses that control for indication bias of receiving ATD. Third and from a pathophysiological view-point, association with BRS might reflect an association with carotid stiffness, as CCA-IMT was significantly higher in ATD users compared to non-users in our study. As mentioned previously, the method used to assess nBRS already controls for the vascular component of the BRS (i.e. for arterial stiffness) making this issue unlikely. Also, analysis stratified by CCA-IMT level did not modify our study results (not shown). Still, residual confounding cannot be excluded. For instance, anxiety usually coexists with depressive symptoms and has been related to impaired BRS in some studies, but anxiety was not collected at baseline examination [43]. Also, depressed patients lack of adherence to medications [44] so that our findings on ATD use might reflect the lack of compliance to ATD rather than the effect of ATD per se, but information on compliance to medication is hardly available in such a large observational study conducted in the community.

Our exploratory analysis suggests that the relationship between ATD use and impaired BRS was essentially driven by SNRI use, and venlafaxine in particular. This is consistent with the results of a recent study showing that in patients with major depressive disorder randomly assigned to SSRI or SNRI, impaired BRS was noted with SNRI only [45]. Elevated blood pressure, a frequent adverse effect induced by SNRI drugs [46], and possibly reflecting an alteration of the neural control of blood pressure, may contribute to explain the lower nBRS in SNRI users as reported in the present study. Coherently, Supplementary Table 2 points out higher systolic blood pressure in SNRI (133 mmHg) than in SSRI (129 mmHg) and TCA (129 mmHg) users; SNRI users were also taking more blood pressure lowering drugs (26%) than SSRI (18%) or TCA (18%) users.

4.4. Implications and perspectives

In the current study, the effect size of the association between ATD use and low nBRS was comparable to that with hypertension or diabetes and was equivalent to the effect of 8 years of ageing, making a chance finding unlikely, and suggesting the potential clinical relevance of the study results. In particular, antidepressant use should be considered carefully by physicians, particularly in those patients with underlying cardiac disease. At present, our findings may help clinicians to either adapt (for patients already under a given ATD) or initiate the most appropriate ATD treatment for their patients. Furthermore and from an intervention perspective, our study results reemphasized the role of physical activity as a large body of evidence indicates its beneficial effect on BRS and possibly on depression [47,48]. However, as a first study on nBRS, depressive symptoms and ATD use in the community, the current results need external validation. Prospective studies with repeated evaluations of nBRS, depressive symptoms and ATD use will also permit to test the temporality of these associations. In addition, these prospective studies will allow testing our initial hypothesis, i.e. that BRS alteration might mediate the association between depression, ATD use and CVD onset. The PPS3 should be able to address some of these challenging issues in the coming years after the completion of the follow-up and the validation of a sufficient numbers of CVD events including SCD.

4.5. Strengths and limitations

The large sample size, the use of very high precision echotracking measure to assess BRS, the availability of several important confounding factors, and the possibility to simultaneously investigate depressive symptomatology and ATD use represent important strengths. However, we acknowledge the following limitations. The cross-sectional and observational nature of the analysis precludes studying any temporal and causal relationship between high depressive symptoms, ATD use and altered nBRS. Despite the high concordance between high depressive symptoms as measured by the 13-item questionnaire and clinical depression [27,32], clinical diagnosed depression per se was not investigated here. We had no information on the duration of depressive symptoms and on ATD use precluding us to study dose-response relationships. We also had no information on responsiveness to ATD.

To conclude, in a sample of 9213 men and women aged 50 to 75, ATD use and SNRI use in particular but not high depressive symptoms was associated with low neural baroreflex sensitivity as estimated by carotid echotracking. If confirmed, these results may bring novel insights in the putative mechanisms linking depressive symptoms and/or ATD use with the onset of cardiovascular disease and particularly SCD in the population.

Conflict of interest

Cédric Lemogne has received advisory panels or lecture fees from AstraZeneca, Bristol-Myers Squibb, Lundbeck, Pfizer, Pierre Fabre, Sanofi and Servier.

Other authors have no conflicts of interest to declare.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://

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