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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 $\geq 7$ 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