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Antoine Cremer

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Par Antoine Cremer

**Déterminants et conséquences de  
l'hypotension orthostatique  
en population générale et hypertendue**

Sous la direction de : Professeur Christophe Tzourio  
(co-directeur : Docteur Philippe Gosse)

Soutenue le 11 Mai 2020

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**Titre :**

**Résumé :** L'hypotension orthostatique correspond à une baisse de la pression artérielle lors du passage à la position debout. Ce paramètre est associé à un sur-risque d'accident vasculaire cérébral, d'infarctus du myocarde, d'insuffisance cardiaque et de mortalité totale. Il est de ce point de vu proche des marqueurs de variabilité tensionnelle conventionnels qui sont la variabilité tensionnelle inter-visite, la variabilité de moyen terme mesurée en auto-mesure tensionnelle et la variabilité de court terme mesurée en holter tensionnel. Cependant, contrairement à ces marqueurs conventionnels, l'association avec la démence n'a pas été démontrée. D'autre part, les relations entre l'hypotension orthostatique et ces autres marqueurs de variabilités ne sont pas connus. Enfin, si le diagnostic de l'hypotension orthostatique est relativement simple, la généralisation du dépistage en consultation n'est pas réalisée faute de temps. Objectifs : Nous proposons dans ce travail de mesurer l'association entre la présence d'une hypotension orthostatique et la survenue d'une démence. Nous réaliserons une étude mécanistique des déterminants de l'hypotension orthostatique à travers ses relations avec deux paramètres particuliers qui sont la variabilité tensionnelle en auto-mesure et la rigidité artérielle. Enfin, nous proposerons une méthode diagnostic par l'usage de l'auto-mesure tensionnelle. Matériel et méthode : Ces travaux sont réalisés à partir de la cohorte des 3 Cités qui est une cohorte de population générale de sujets de plus de 65ans recrutés sur trois centres : Bordeaux, Dijon et Montpellier. Une première étude longitudinale étudiera l'association entre la présence d'une hypotension orthostatique à l'inclusion dans la cohorte et la survenue d'une démence dans le suivi à 12 ans à travers des analyses de survie. Une deuxième étude transversale, utilisera un échantillon des sujets de Dijon autour du suivi à 10 ans qui ont bénéficié à la fois d'un dépistage de l'hypotension orthostatique, de la mesure de la rigidité artérielle et de la réalisation d'une série d'auto-mesure tensionnelle. Enfin, le dernier travail proposera une étude de faisabilité en soins courant de dépistage de l'hypotension orthostatique à travers un protocole d'auto-mesure tensionnelle adapté. Résultats : 7425 sujets ont été suivis sur une période de 12ans. La prévalence de l'hypotension orthostatique était de 13%. Le nombre de cas incidents de démence était de 512 cas. Les analyses de survie ont montré que l'hypotension orthostatique était associée à un sur-risque de démence de l'ordre de 25% dans des modèles ajustés en particulier sur le niveau de pression artérielle. Dans le deuxième travail une analyse transversale chez 1150 sujets a montré que l'hypotension orthostatique était associée de manière indépendante à la fois à la variabilité tensionnelle en auto-mesure et à la rigidité artérielle. La variabilité tensionnelle et la rigidité artérielle ne sont pas associés. Dans le troisième travail, plus de 500 séries d'auto-mesure tensionnelle furent réalisées avec mesure de la pression artérielle en position debout sans altérer la qualité de l'auto-mesure tensionnelle classique. Conclusion : L'hypotension orthostatique est un paramètre hémodynamique riche qui reflète à la fois un vieillissement vasculaire marquée et un défaut de régulation de la pression artérielle immédiate. Elle est associée de manière indépendante au risque de démence. Une amélioration du diagnostic est possible par l'auto-mesure tensionnelle qui permet de multiplier les mesures en position debout et qui améliore le taux de dépistage.

**Mots clés :** hypotension orthostatique, variabilité tensionnelle, rigidité artérielle, démence

**Title :**

**Abstract :** Orthostatic hypotension is a blood pressure drop when moving to standing position. It is associated with an over-risk of stroke, myocardial infarction, heart failure and total mortality. From this point of view, it is close to the conventional markers of blood pressure variability which are the inter-visit blood pressure variability, the mid-term variability measured by home blood pressure and the short-term variability measured by an ambulatory blood pressure monitoring. However, unlike these conventional markers, the association with dementia has not been demonstrated. In addition, the relationships between orthostatic hypotension and these other markers of variability are not known. Finally, although the diagnosis of orthostatic hypotension is relatively simple, the generalization of screening in consultation is not achieved. Objectives: In this work, we propose to measure the association of the orthostatic hypotension and the occurrence of dementia. In addition, we will carry out a mechanistic study of the determinants of orthostatic hypotension through its relations with two particular parameters : mid term variability and arterial stiffness. Finally, we will propose a diagnostic method using home blood pressure measurement. Material and methods: This work is based on the "3 Cities" cohort which is a general population cohort of subjects over 65 years old recruited from three centres: Bordeaux, Dijon and Montpellier. We will first study the association between orthostatic hypotension at baseline cohort and the occurrence of dementia in the 12-year follow-up through survival analyses. A second cross-sectional study will use a sample of Dijon subjects around the 10-year follow-up who were screened for orthostatic hypotension, pulse wave velocity measurement and performed a series of home blood pressure measurement. Finally, the last work will propose a feasibility study on the routine care of screening for orthostatic hypotension using an adapted blood pressure self-measurement protocol. Results: 7425 subjects were followed over a 12-year period. The prevalence of orthostatic hypotension was 13%. The number of incident cases of dementia was 512. Survival analyses showed that orthostatic hypotension was associated with an over-risk of dementia in the order of 25% adjusted with blood pressure level. In the second work, a cross-sectional analysis in 1000 subjects showed that orthostatic hypotension was independently associated with both mid-term blood pressure variability and arterial stiffness. Pressure variability and arterial stiffness were not associated. In the third work, we performed 500 series of home blood pressure with a BP measurement in the standing position without altering the quality of the classical report. Conclusion: Orthostatic hypotension is a rich hemodynamic parameter that reflects both a marked vascular ageing and a defect of immediate blood pressure regulation. It is independently associated with the risk of dementia. An improvement in diagnosis is possible through self-measurement of blood pressure, which allows more measurements to be taken in the standing position and improves the screening rate.

**Keywords :** orthostatic hypotension, blood pressure variability, arterial stiffness, dementia

**Unité de Recherche :** Bordeaux Population Health Center, Inserm 1219, Université de Bordeaux

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## Préambule

Ce travail de thèse est le fruit de 4 années de réflexion autour de la problématique de la variabilité tensionnelle et de ces conséquences en population générale.

Une mesure de la variabilité a eu notre plus grande attention. Il s'agit de l'hypotension orthostatique (HO).

L'HO est une situation clinique bien connue et facilement appréhendable. C'est ce qui en fait sa richesse, l'intérêt de son étude mais le sujet est plus complexe qu'il n'y paraît. En effet, l'HO touche de très nombreuses disciplines parmi lesquelles la gériatrie avec le risque de chute, la neurologie avec la dysautonomie chez les sujets Parkinsonien en particulier, la diabétologie avec la dysautonomie diabétique, la psychiatrie avec le risque identifié de longue date d'HO dû aux traitements psychotropes et enfin la cardiologie avec la prise en charge des syncopes et de l'hypertension. L'ensemble de ces disciplines a produit une littérature riche et abondante sur le sujet mais chacune avec un point d'entrée guidé par sa discipline initiale et donc dans des populations très différentes. Cela complique largement le travail de synthèse réalisé toujours de manière partielle par plusieurs dizaines de revues de la littérature.

Dans ce travail de recherche, l'HO est vue à travers l'œil d'un cardiologue hypertensiologue et épidémiologiste. Elle est étudiée dans une population générale ou hypertendue à faible risque cardiovasculaire. Ce travail se concentre donc sur l'HO dite idiopathique c'est-à-dire essentiellement liée au vieillissement et très peu sur les formes caricaturales d'HO rencontrées dans les pathologies neurodégénératives (Parkinson) ou dysautonomiques pures (hypotension orthostatique neurogène).

Quels sont les déterminants de l'HO? Est-elle simplement un marqueur de variabilité tensionnel comme les autres ou apporte-t-elle des informations complémentaires ?

Quels sont les mécanismes reliant l'HO aux comorbidités associées ? Existe-t-il une causalité entre l'HO et ces comorbidités ?

C'est autour de ces interrogations que s'est construit ce travail de thèse. Nous souhaitons par cette recherche apporter quelques éléments nouveaux de compréhension et de prise en charge à cette situation particulière et fréquente qu'est le défaut de régulation de la pression artérielle en position debout.

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## 1. INTRODUCTION

### 1.1. PRESSION ARTERIELLE MOYENNE ET PRONOSTIC CARDIOVASCULAIRE EN POPULATION

#### 1.1.1. DE L'ÉVALUATION CLINIQUE COURT TERME AU PRONOSTIC DE LONG TERME

La pression artérielle (PA) est un paramètre hémodynamique fondamental dont l'importance est connue depuis toujours de manière empirique. La palpation du pouls permet facilement d'apprécier l'état de santé immédiat du patient en fonction de son intensité et de la fréquence cardiaque<sup>1</sup>. Ce paramètre est recueilli dans les observations médicales comme une constante vitale au même titre que la température ou la fréquence respiratoire. Elle permet d'évaluer, d'un simple geste, le pronostic vital sur le très court terme.

Historiquement, il faut attendre les premiers enregistrements de PA et les premières études épidémiologiques pour commencer à apprécier l'intérêt de la mesure de la PA sur le pronostic cardiovasculaire à long terme. Ainsi, dès le début du XXe siècle, alors qu'aucun traitement antihypertenseur n'était disponible, les assureurs américains préconisaient de ne pas assurer les personnes avec des PA systoliques supérieures à 142 mm Hg mesurée par le sphygmographe de Riva-Rocci<sup>2</sup>.

#### 1.1.2. LA COHORTE DE FRAMINGHAM

La première étude de cohorte moderne d'envergure est réalisée dans la ville de Framingham après la 2e guerre mondiale<sup>3</sup>. L'étude des associations entre la survenue d'accidents cardiovasculaires (infarctus du myocarde<sup>4</sup> et accident vasculaire cérébral en particulier<sup>5</sup>) et les caractéristiques initiales des sujets, mesurées à l'inclusion dans l'étude, permet d'identifier les principaux marqueurs de risque cardiovasculaire. L'hypertension artérielle (HTA) est alors définie par une PA supérieure à 160 mm Hg pour la systolique et 95 mm Hg pour la diastolique. Ce niveau de PA est en effet associé à un sur-risque de coronaropathie multiplié par 4 dans cette cohorte<sup>4</sup>.

#### 1.1.3. RESULTATS DES ETUDES INTERVENTIONNELLES SUR LA BAISSÉ DE PRESSION ARTERIELLE

Il faut attendre le développement de la pharmacopée et des premiers traitements hypotenseurs pour permettre d'agir sur cet excès de PA.

Des essais contrôlés randomisés ont permis de démontrer l'intérêt d'une baisse de PA sur le pronostic cardiovasculaire du sujet et de mettre en évidence la causalité



entre PA et pronostic cardiovasculaire. Il a ainsi été montré qu'une baisse de PA de 10 mm Hg, quelque soit le point de départ tensionnel, permet une réduction de<sup>6</sup>:

- 13% de la mortalité totale,
- 17% l'incidence d'évènement coronaire aigu,
- 27% les AVC
- 28% l'insuffisance cardiaque.

**L'hypertension artérielle reste à ce jour le principal facteur de risque cardiovasculaire c'est-à-dire la principale cause de morbi-mortalité toutes causes confondues dans les pays occidentaux<sup>7, 8</sup>.**

#### 1.1.4. LA PRESSION ARTERIELLE COMME CRITERE INTERMEDIAIRE

Si la baisse tensionnelle est associée à un meilleur pronostic cardiovasculaire globalement, les approches thérapeutiques utilisées pour réduire la charge tensionnelle ne sont pas équivalentes. Ainsi, 2 études majeures ont modifié les pratiques.

##### 1.1.4.1. L'ETUDE ASCOT ET L'ETUDE ACCOMPLISH

- ASCOT<sup>9</sup> :

Cette étude interventionnelle remet en cause les anciennes recommandations de traitement de l'HTA : traitement diurétique thiazidique en première intention<sup>10</sup>.

En effet, à la fin des années 90, si l'effet protecteur tensionnel était évident vis-à-vis de l'évènement AVC, les résultats étaient moins probants sur la coronaropathie. Parallèlement, les bloqueurs du système rénine angiotensine (IEC) et les inhibiteurs calciques, classes pharmacologiques plus récentes, montraient eux quelques résultats encourageants<sup>11</sup> pour la réduction du risque coronaire.

L'objectif était donc de comparer l'effet de l'association d'aténolol avec un thiazidique par rapport à l'amlodipine avec le perindopril, chez des sujets hypertendus à haut risque cardiovasculaire, sur l'infarctus du myocarde non fatal et la coronaropathie fatale.

Il s'agit d'un essai multicentrique, prospectif, contrôlé et randomisé chez 19257 patients hypertendus, âgés de 40 à 79 ans, présentant au moins trois autres facteurs de risque cardiovasculaire. Les patients ont reçu soit de l'amlodipine 5–10 mg avec du périndopril 4–8 mg selon les besoins (schéma à base d'amlodipine; n = 9639), soit de l'aténolol 50–100 mg avec du bendrofluméthiazide 1,25–2 ,5 mg (schéma à base d'aténolol; n = 9618).

Le critère d'évaluation principal était l'infarctus du myocarde non fatal et la coronaropathie fatale. L'analyse a été faite en intention de traiter.

L'étude a été arrêtée prématurément après un suivi médian de 5.5 ans bien que le critère principal n'ait pas été atteint (429 vs 474; RR non ajustée à 0.90 ; IC 95% 0.79–1.02,  $p = 0.1052$ ). Les investigateurs ont considéré qu'il n'était pas éthique de poursuivre car d'autres critères durs avaient été atteints.

Ainsi les individus traités par le schéma à base d'amlodipine avaient moins d'accidents vasculaires cérébraux mortels et non mortels (327 vs 422; RR=0.77 ; IC à 95% : 0.66–0.89 ;  $p = 0.0003$ ), moins d'événements et de procédures cardiovasculaires (1362 vs 1602; RR=0.84 ; IC à 95% : 0.78 –0.90 ;  $p < 0.0001$ ) et moins de mortalité toutes causes confondues (738 vs 820; IC à 95% : 0.89 ; 0.81–0.99 ;  $p = 0.025$ ).

Enfin, le schéma à base d'amlodipine a induit moins de diabète que le schéma à base d'aténolol (567 vs 799; RR= 0.70 ; IC à 95% : 0.63–0.78 ;  $p < 0.0001$ ).

- ACCOMPLISH<sup>12</sup> :

Dans cette étude, l'objectif est de voir si l'utilisation combinée d'un IEC et d'un inhibiteur calcique dihydropyridine en première intention améliore le pronostic cardiovasculaire par rapport à une stratégie diurétique thiazidique et IEC. Pour ce faire, un protocole d'étude interventionnelle en double aveugle et en intention de traiter est proposé. Pour obtenir la puissance nécessaire propre à démontrer une différence, 11506 sujets hypertendus à haut risque cardiovasculaire sont randomisés en double aveugle soit dans le bras IEC/Inhibiteur calcique soit dans le bras IEC/diurétique. Le critère primaire d'évaluation est un critère composite de mort de cause cardiovasculaire, d'infarctus du myocarde non fatal, d'AVC non fatal, d'hospitalisation pour angine de poitrine, d'arrêt cardiaque récupéré et de revascularisation coronaire. L'essai thérapeutique, prévu pour durer 5 ans, fut interrompu prématurément au bout de 3 ans suite à une analyse intermédiaire faisant apparaître une différence d'incidence d'évènements primaires trop importante entre les deux bras. Le niveau de pression artérielle en fin d'étude était le même dans les deux groupes (131.6/73.3 mm Hg dans le groupe benazepril–amlodipine et 132.5/74.4 mm Hg dans le groupe benazepril–hydrochlorothiazide). Il y avait dans le groupe benazepril–amlodipine une réduction du risque d'évènement absolu de 2.2% soit une baisse de 19.6% du risque relatif (RR 0.80, IC à 95% :0.72 to 0.90;  $P < 0.001$ ).

L'association benazepril–amlodipine avait une efficacité supérieure à la stratégie benazepril–hydrochlorothiazide pour réduire la survenue du critère primaire.

- Synthèse :

Ces deux essais thérapeutiques ont démontré que **les inhibiteurs calciques et les bloqueurs du SRAA améliorent le pronostic cardiovasculaire** des patients hypertendus par rapport aux bêtabloqueurs et aux diurétiques thiazidiques malgré une baisse de PA identique selon les stratégies thérapeutiques envisagées.

#### 1.1.4.2. AU DE-LA DE LA BAISSSE DE PA

Dans ces deux études ASCOT et ACCOMPLISH, la différence de protection cardiovasculaire ne passe pas par la baisse de pression artérielle périphérique mesurée en consultation. Comment alors expliquer ces différences de pronostic ?

Plusieurs explications ont été proposées qui tiennent aux modifications hémodynamiques induites par les traitements utilisés, en particulier la pression artérielle centrale et la variabilité tensionnelle.

Ainsi, l'étude CAFE a mesuré, dans un sous échantillon de l'étude ASCOT, la PA centrale par tonométrie de l'artère radiale. Il a ainsi été montré qu'il y avait une baisse de PA centrale supplémentaire significative de 4.5 mm Hg ( $p < 0.0001$ )<sup>13</sup> dans le bras traité par IEC/Inhibiteur Calcique pour une même baisse de PA périphérique.

Cette baisse supplémentaire de PA centrale s'expliquerait par la modification des propriétés mécaniques des artères et de l'aorte par les traitements vasodilatateurs (IEC et Inhibiteur Calcique) limitant ainsi le retour précoce des ondes de pression de réflexion. Ces familles de traitement semblent en effet être capables de réduire la rigidité artérielle dans certaines études même si les données sont encore limitées<sup>14</sup>.

De plus, toujours dans ASCOT, il a été montré une variabilité tensionnelle plus importante dans le groupe bêtabloqueur par rapport au groupe inhibiteur calcique. Cette différence expliquerait également une partie de la différence de pronostic entre les 2 stratégies médicamenteuses<sup>15</sup>. Une méta-analyse portant sur 389 essais thérapeutiques montre bien que les inhibiteurs calciques dihydropyridines sont la classe de traitement qui limite le plus la variabilité inter-visite de la PA systolique<sup>16</sup>.

Ainsi, dans la population d'HTA à haut risque cardiovasculaire d'ASCOT, la rigidité artérielle et la PA centrale d'une part et la variabilité tensionnelle d'autre part, apportent des éléments complémentaires pour comprendre la différence de risque cardiovasculaire entre les deux stratégies de traitement antihypertensive.

**La PA périphérique n'est donc pas un critère intermédiaire absolu** même si la baisse de PA est systématiquement associée à une amélioration du pronostic cardiovasculaire. **La variabilité tensionnelle est présentée comme un paramètre complémentaire** qui améliore la compréhension de la survenue des événements cardiovasculaire et donc aide à identifier les patients en sur-risque cardiovasculaire.

## 1.2 LA VARIABILITE TENSIONNELLE ET RISQUE CARDIOVASCULAIRE

### 1.2.1 DEFINITION

La variabilité tensionnelle est présente à différentes échelles de temps. Dans le temps long, la PA varie chez tout le monde. Elle est un marqueur du vieillissement vasculaire<sup>17</sup>. Ainsi, la PA systolique va augmenter tout au long de la vie alors que la PA diastolique augmente initialement puis va présenter une cassure vers 50 ans et diminuer dans la deuxième moitié de vie<sup>18</sup> surtout si le sujet présente des facteurs de risques cardiovasculaires associés (tabac, dyslipidémie et diabète).

Mais ce qui est mesuré dans l'étude de la variabilité, ce n'est pas la tendance moyenne dans le temps long mais au contraire la distribution des valeurs de pression autour de ces valeurs moyennes<sup>19</sup>. C'est ce que l'on appelle l'écart type ou la déviation standard. Cette variabilité est observationnelle, elle est à distinguer de la variabilité tensionnelle provoquée par le changement de position ou lors d'un effort physique par exemple.

La variabilité inter-visite, dite de long terme mesure, au cours des consultations dans le cadre du suivi d'un patient, la distribution des valeurs de PA autour de la valeur moyenne de ces PA.

La variabilité de moyen terme mesure la distribution des PA autour de la mesure de PA réalisée par auto-mesure tensionnelle. On sort donc du cadre de la mesure en milieu médical et la répétition des mesures se fait sur quelques jours (3 jours pour les auto-mesures françaises<sup>20</sup>).

La variabilité de court terme mesure la distribution de la PA autour de la valeur moyenne mesurée pendant 24H. L'outil de mesure est le holter tensionnel (ou MAPA).

Chacune de ces formes de variabilité ont été étudiées afin de déterminer si elles permettraient d'améliorer l'appréciation du niveau de risque cardiovasculaire d'un sujet au-delà des informations apportées par la PA moyenne mais également des autres facteurs de risque cardiovasculaires.

## 1.2.2 VARIABILITE TENSIONNELLE ET PRONOSTIC CARDIOVASCULAIRE

### 1.2.2.1 LA VARIABILITE INTER-VISITE

Cette analyse de la variabilité inter-visite est la plus documentée mais elle est aussi la plus hétérogène d'un point de vue méthodologique<sup>21</sup>. En effet, toutes les études de cohorte ont des protocoles de mesure de la PA différents, sur des intervalles de temps différents de quelques semaines à plusieurs années, et sur un nombre de mesures utilisées pour estimer la variabilité là encore différent. Ces limites méthodologiques importantes réduisent la pertinence des comparaisons des résultats des études entre elles<sup>19</sup>.

Ceci étant, il existe un consensus autour des travaux publiés pour dire que la variabilité inter-visite augmente le risque de survenue d'un AVC<sup>22, 23</sup>, d'un accident coronaire aigu<sup>24</sup>, d'une hospitalisation pour insuffisance cardiaque<sup>25, 26</sup>, d'un diagnostic de démence<sup>27</sup> et de mortalité cardiovasculaire<sup>28</sup>, indépendamment du niveau de PA et du niveau de risque cardiovasculaire<sup>29, 30</sup>.

### 1.2.2.2 LA VARIABILITE DE MOYEN TERME

Les données cliniques sur ce type de mesure de variabilité sont moins nombreuses que pour la variabilité inter-visite. Cependant, les mêmes signaux de sur-risque global sont visibles.

Ainsi, on retrouve un sur-risque de mortalité cardiovasculaire, d'AVC, de coronaropathie<sup>31, 32</sup> et de démence<sup>33</sup> indépendamment du niveau de PA.

### 1.2.2.3 LA VARIABILITE DE COURT TERME

Les données sont anciennes et relativement solides pour l'analyse des enregistrements de PA invasive<sup>34, 35</sup>.

Sur les enregistrements de données non invasives utilisées en pratique courante, dans la population japonaise Ohasama<sup>36</sup>, il a été montré une association entre la variabilité court terme et la mortalité cardiovasculaire. En Italie, il a été montré l'association de la variabilité tensionnelle nocturne avec la survenue des événements cardiovasculaire (infarctus du myocarde, AVC et insuffisance cardiaque)<sup>37</sup>. Enfin, très récemment, un registre espagnol de plus de 60.000 enregistrements sur 24 heures a montré que la variabilité tensionnelle de court terme était associée à un sur-risque d'évènements cardiovasculaires. En particulier, une déviation standard nocturne supérieure à 12 mm de Hg est associée à une augmentation du risque relatif de 21% de la mortalité cardiovasculaire<sup>38</sup>.

Concernant l'association variabilité tensionnelle de court terme avec les cas incidents de démence, il n'existe pas d'étude longitudinale. En revanche, il a été montré dans plusieurs études transversales, une association entre une altération de différents tests cognitifs et la variabilité tensionnelle en holter tensionnel<sup>39, 40</sup>.

### 1.2.3 SYNTHÈSE ET LIMITE DE LA VARIABILITÉ TENSIONNELLE

L'augmentation de la variabilité tensionnelle témoigne de l'éloignement des valeurs de PA autour de la PA moyenne. Plus l'on s'éloigne de cette valeur moyenne et d'un modèle idéal de perfusion continue pour nos organes, plus l'on s'expose à la survenue d'un événement cardiovasculaire. De ce point de vue, les différentes méthodes et les différents temps de mesure de la variabilité tensionnelle partagent le même type de sur-risque cardiovasculaire et cognitif. Il s'agit donc d'une manière nouvelle et complémentaire d'appréhender la problématique de la relation de la PA avec l'atteinte d'organes cibles par rapport à la vision traditionnelle de la PA moyenne.

Cependant, quelques travaux ont mesuré les corrélations entre les différents types de variabilité. Ces corrélations sont faibles de l'ordre de 10%. **Ces différentes mesures de variabilité ne mesurent donc pas les mêmes choses**<sup>41-43</sup>. Si les déterminants des variabilités tensionnelles ne sont pas vraiment identifiés, ils ont en commun de favoriser la pulsatilité de notre réseau artériel. La perte de la compliance aortique pour la variabilité de long terme<sup>44</sup> et la perte de la régulation de la PA immédiate pour la régulation de court terme<sup>45</sup> sont des hypothèses plausibles mais qui restent à vérifier.

### 1.3 SYNTHÈSE PRESSION ARTERIELLE ET RISQUE CARDIOVASCULAIRE

L'HTA est une élévation constante du niveau de PA au-delà des valeurs de référence et qui peut être illustrée par le niveau de PA moyenne<sup>46</sup>. Ainsi, les méthodes de mesures répétées de la PA, au premier rang desquels le holter tensionnel, ont montré qu'en lissant les variabilités et en réduisant les biais de mesure de la PA de consultation, elles amélioreraient la prédiction des événements cardiovasculaires<sup>47-49</sup>. Cependant, la PA seule n'est pas un critère intermédiaire absolu. La manière dont les PA se distribuent autour de cette moyenne sous l'influence des paramètres propres du sujet (génétique, régulation de la PA etc...) mais aussi du choix du traitement utilisé, participe également au pronostic cardiovasculaire du sujet<sup>50</sup>.

D'autre part, des hypothèses ont été proposées pour relier la PA à sa variabilité. La rigidité artérielle pourrait être un déterminant commun<sup>51,52</sup>. L'idée sous-jacente est de dire que la PA moyenne va d'abord s'élever avec en conséquence une accélération du vieillissement vasculaire et de la rigidité artérielle. Ce vieillissement vasculaire va

dans un deuxième temps s'accompagner d'une majoration de la variabilité tensionnelle. Cette variabilité va finir d'altérer la qualité de la perfusion artérielle en particulier de la micro-circulation. Cette temporalité a été en particulier proposée dans le cadre de la démence où il a été montré que la PA était associée aux cas incidents de démence chez le sujet jeune (<sup>53-55</sup>). Cette association disparaît chez le sujet âgé alors que la variabilité tensionnelle devient un marqueur de risque indépendant<sup>27</sup>.

La mesure simple de la variabilité tensionnelle est donc un enjeu important pour estimer le niveau de risque cardiovasculaire. Aujourd'hui, la mise en œuvre du calcul pour décrire les différents estimateurs de la variabilité est souvent complexe. D'autre part, ces marqueurs de variabilité tensionnelle ont pour particularité d'être mesurés a posteriori à partir du recueil de l'ensemble des mesures de PA ce qui est particulièrement vrai pour la variabilité inter-visite. Enfin il n'existe aujourd'hui aucun seuil interventionnel ce qui limite largement son usage clinique.

L'étude de la variabilité tensionnelle reste donc encore aujourd'hui une démarche de recherche clinique.

**L'hypotension orthostatique qui est une mesure de variabilité tensionnelle induite par le changement de position a un diagnostic immédiat et pourrait être une véritable alternative** à condition qu'elle apporte les mêmes informations que les marqueurs conventionnels de variabilités tensionnelles vus précédemment.

#### 1.4 L'HYPOTENSION ORTHOSTATIQUE : MARQUEUR DE VARIABILITE TENSIONNELLE

##### 1.4.1 DEFINITION GENERALE

L'hypotension orthostatique est une baisse de PA provoquée par le changement de position. Elle teste donc les capacités de régulation de la PA immédiate médiée par le baroréflexe soit par dysfonction de ses barorécepteurs soit par dysfonction de sa commande centrale<sup>56</sup>.

Son diagnostic repose sur un protocole de mesure de PA standardisé en position assise ou allongée puis en position debout.

##### 1.4.2 COMPLEXITE DU DIAGNOSTIC DE L'HYPOTENSION ORTHOSTATIQUE

###### 1.4.2.1 MESURE DE LA PRESSION ARTERIELLE AVANT LE PASSAGE EN ORTHOSTATISME :

Le choix de la position pour la mesure initiale de la PA peut sembler être un point critique. Toutefois, la position du corps influence modestement le niveau de PA. Ainsi, dans les différentes études qui ont mesuré l'influence de la position du corps sur les

valeurs de pression, on retrouve de manière systématique une PA diastolique plus élevée en position assise qu'allongée de l'ordre de 1 mm Hg. Cette différence ne semble pas cliniquement pertinente. En revanche les résultats sont discordants si l'on regarde la différence de PA systolique. Une étude montre une PA systolique assise supérieure à la PA allongée (+2 mm Hg)<sup>57</sup> quand d'autres montrent plutôt une PA systolique assise plus basse<sup>58, 59</sup>. Les écarts restent cependant tout à fait modestes là-encore.

Les recommandations sur la mesure de la PA dans le cadre du dépistage et de la prise en charge de l'HTA préconisent la mesure de la PA en position assise<sup>60</sup>. En effet, les essais thérapeutiques sur la prise en charge de l'HTA ont mesuré la PA en consultation en position assise (24/36) et seul deux essais ont mesuré la PA en position allongée exclusive<sup>61</sup>.

Ceci étant, l'effort demandé et la stimulation sympathique induite ne sont pas les mêmes lors du passage de la position allongée à la position debout que de la position assise à la position debout. Une équipe a essayé de préciser les seuils diagnostiques selon ces deux positions initiales, en faisant des dépistages d'HO chez 831 sujets d'abord en partant de la position allongée puis depuis la position assise, dans cet ordre, pour tous les sujets. Ce travail a montré qu'il faut réduire le seuil diagnostique lorsque le test est fait en position assise par rapport à la position couché, à 15 mm Hg pour la PA systolique et 7 mm Hg pour la PA diastolique<sup>62</sup>. Cependant, les auteurs notent qu'ils pouvaient avoir induit des biais de mesure (en particulier un biais d'apprentissage) en ayant systématiquement débuté leur protocole par les mesures de PA en position allongée. A noter, ce travail reste isolé et la question de l'influence de la position pour la mesure initiale n'a pas été jusqu'à ce jour réellement prise en compte.

A ce stade, les sociétés savantes conseillent le protocole suivant : 3 mesures de PA espacées d'une minute. En cas de différence supérieure à 10 mm Hg pour la PA systolique entre la première et la deuxième mesure, il est recommandé de répéter une série de 3 mesures. Seules les deux dernières sont moyennées et représentent la valeur finale retenue (ESH/ESC 2018)<sup>60</sup>.



#### 1.4.2.2 MESURE DE LA PRESSION ARTERIELLE EN POSITION DEBOUT

Le passage à l'orthostatisme implique un stress physique qui éloigne le sujet d'un état équilibre.

La particularité de la mesure de la PA en position debout est sa répétition dans le temps. Dans le cas d'une HO, la baisse de PA apparait généralement dès la première minute. Cela est corroboré par plusieurs études dont notre analyse des données de la cohorte 3C (81% des HO dès la première minute)<sup>63</sup>.

Il semble que ce soit la baisse de PA à la première minute qui soit la plus associée à la survenue des évènements<sup>64</sup>. Il n'en reste pas moins que les HO peuvent apparaitre retardées ou même très retardées. Ainsi, il a été montré que les HO retardées après 3 minutes étaient associées également à une surmortalité et que ces tableaux cliniques retardés évoluaient pour la moitié d'entre eux vers d'authentiques HO précoces dans les 10 ans<sup>65</sup>. Le moment de la dernière mesure en position debout reste donc à définir.

#### 1.4.2.3 COMPOSANTE SYSTOLIQUE ET DIASTOLIQUE DE LA BAISSSE DE PRESSION ARTERIELLE

La chute de PA systolique est plus fréquente chez le sujet âgé<sup>63</sup> et l'HO diastolique pure est rare (5%). La mesure de la baisse de PA systolique est suffisante pour faire le diagnostic d'une HO chez le sujet âgé. Cela semble moins vrai chez le sujet jeune où la répartition d'HO systolique et diastolique est comparable<sup>62</sup>. Cependant, les composantes systolique et diastolique restent associées au sur-risque cardiovasculaire de manière indépendante<sup>66</sup>.

Finalement, dans les études épidémiologiques, l'HO est décrite le plus souvent comme **une variable qualitative** binaire ce qui permet de tenir compte des deux niveaux de chute de PA. D'ailleurs les détails sur la valeur prédictive de chaque phénotype de chute de PA (systolique ou diastolique) ne sont que très exceptionnellement signalés dans les publications scientifiques et peuvent donner des résultats différents selon la population étudiée.

#### 1.4.2.4 DEFINITION CONSENSUELLE:

Au vu de l'ensemble des difficultés énumérées précédemment pour qualifier clairement l'HO, un consensus a été proposé en 1996<sup>67</sup>.

**Ainsi, l'hypotension orthostatique est définie comme une baisse de pression artérielle systolique supérieure d'au moins 20 mm Hg ou de pression artérielle diastolique d'au moins 10 mm Hg dans les 3 minutes après le passage en position debout.**

C'est cette définition qui est utilisée comme référence dans les études.

#### 1.4.2.5 APPLICATION A LA PRATIQUE CLINIQUE :

La mesure de la PA en consultation pour le dépistage et le suivi de l'HTA est recommandée en position assise, comme il a été indiqué précédemment. L'importance de la mesure de la PA dans le cadre de l'HTA dépasse l'intérêt de la mesure de la PA pour le dépistage de l'HO. Il semble ainsi logique de privilégier cette recommandation de position assise.

Il est donc accepté de faire du dépistage d'HO à partir de la position assise<sup>68</sup>.

#### 1.4.2.6 LIMITES DE LA MESURE DE LA PRESSION ARTERIELLE EN POSITION DEBOUT AU CABINET MEDICAL

Le protocole de dépistage de l'HO prend en consultation 5 minutes de repos plus 3 mesures espacées d'une minute en position assise et 3 nouvelles mesures espacées d'une minute en position debout soit un total de 11 minutes. Il est bien évident que la réalisation du protocole complet est difficilement réalisable en cabinet.

De plus, la reproductibilité de la chute de PA à l'orthostatisme est faible<sup>69</sup>. Le risque d'HO est majoré à certains moments de la journée. En particulier après la prise des médicaments hypotenseurs<sup>70</sup> ou dans le post prandial<sup>71</sup>. Le contact médical avec un sujet à risque d'HO ne se fera pas forcément au moment de plus grande fragilité du sujet concernant le risque d'HO.

Par exemple, 3000 sujets en Italie ont bénéficié d'une mesure de la PA en position allongée et debout à une semaine d'intervalle. Si la prévalence globale de l'HO d'une semaine à l'autre reste la même, seuls 25.7% des sujets qui avaient une HO à la première visite avaient un diagnostic confirmé à la visite suivante. Ce chiffre monte à 45% si on étudie les sujets avec des symptômes d'HO permettant alors d'être plus spécifique<sup>72</sup>.

#### 1.4.2.7 AUTRES METHODES DIAGNOSTICS DE L'HYPOTENSION ORTHOSTATIQUE

Il existe quelques données sur la chute de PA en MAPA sur les PA diurnes<sup>73</sup>. Cependant, il s'agit d'avoir un matériel adapté avec, en particulier, des capteurs de position pour connaître la position du sujet. Il a été montré chez 376 sujets hypertendus de plus de 70 ans et suivis pendant 8.5 ans en moyenne, que la valeur pronostic de l'HO était supérieure à celle de la variabilité tensionnelle nocturne<sup>74</sup> qui est pourtant reconnue pour être très fortement associée au pronostic cardiovasculaire<sup>37</sup>.

En revanche, la littérature est riche sur les associations entre le profil tensionnel selon le nyctémère et le pronostic cardiovasculaire. Ainsi, il a été bien montré que c'est le niveau de PA nocturne qui est le plus associé à la survenue d'un événement cardiovasculaire fatal ou non et plus particulièrement le profil dit « reverse dipper » (PA nocturnes supérieures aux PA diurnes)<sup>75</sup>. Les explications de ce profil tensionnel particulier sont multiples. Certains ont proposé le rôle des apnées du sommeil mais l'HO est une situation qui explique simplement ce profil tensionnel<sup>76</sup>.

#### 1.4.3 EPIDEMIOLOGIE DE L'HYPOTENSION ORTHOSTATIQUE

##### 1.4.3.1 PRESENTATION DES PRINCIPALES ETUDES DE COHORTES

L'HO est un paramètre hémodynamique étudié depuis de très nombreuses années. Il a été identifié initialement comme une cause fréquente de syncope ou de malaise lipothymique<sup>77</sup>. C'est plus récemment que des études de cohorte de population générale ont commencé à étudier ce paramètre de manière plus globale pour mettre en évidence des associations épidémiologiques entre la survenue d'une chute de PA à l'orthostatisme et la survenue d'évènements cardiovasculaires en particulier.

3 programmes épidémiologiques principaux ont étudié plusieurs aspects de l'HO, dont leurs associations aux évènements cliniques mais également certains de leurs déterminants.

- *The Malmö Preventive Project*

Il s'agit d'un programme à grande échelle de dépistage des facteurs de risque cardiovasculaire et de la consommation d'alcool, débuté dans les années 1970. Les résidents de Malmö en Suède qui avaient entre 35 et 70 ans étaient invités à participer. Ils bénéficiaient d'un examen clinique complet, d'un bilan sanguin et d'un questionnaire.

La première période, de 1974 à 1991, a inclus 33347 sujets. 70% des sujets contactés ont répondu favorablement.

Une deuxième vague d'inclusion a eu lieu de 2002 à 2006. 17284 sujets ont été inclus avec un taux de réponse de 67%.

De très nombreuses publications ont été tirées de cette étude. Plus de 20 publications concernent la problématique de l'HO. Le diagnostic de l'HO était réalisé selon le consensus de 1996.

- *ARIC study*

L'étude de cohorte ARIC est une étude américaine de population générale, montée en 1987 et qui est toujours active. L'objectif initial de cette étude est d'explorer les causes de la maladie athéromateuse et ses conséquences cliniques c'est-à-dire la survenue d'évènements cardiovasculaires : infarctus du myocarde, insuffisance cardiaque, accident vasculaire cérébral et mortalité cardiovasculaire.

Dans 4 communautés de 4 états américains différents (Est des Etats-Unis du nord au sud), 15792 sujets (soit 4000 par centre) dont l'âge d'inclusion devait être compris entre 45 et 65 ans, ont bénéficié d'exploration à visée cardiovasculaire avec en particulier la mesure de la PA en position assise, allongée et debout, la réalisation d'un ECG, d'une échographie cardiaque, carotidienne, d'une mesure la vitesse de l'onde de pouls etc...

7 visites ont eu lieu depuis le début de l'étude. A la 6<sup>ème</sup> visite, 30 ans après l'inclusion, il restait 4003 sujets. La 7<sup>ème</sup> visite est actuellement en cours.

2181 publications à ce jour ont été publiées à partir de cette cohorte. 10 publications sont centrées sur la problématique de l'HO. La partie liée à l'HO est donc un chapitre parmi d'autres mais cette cohorte est un contributeur majeur à l'état des connaissances sur l'HO dans une population générale américaine relativement jeune (<65ans à l'inclusion).

Le diagnostic de l'HO dans cette étude est réalisé selon le consensus de 1996.

- *Rotterdam Study*

L'étude de cohorte Rotterdam est une étude hollandaise en population générale débutée en 1989. Une première phase conclue en 1993, a permis de recruter 7983 participants. Plusieurs phases de recrutement ont été ajoutées avec des recrutements en 2000, 2006 et 2016. Finalement 18926 sujets ont été recrutés.

Pour être inclus, le sujet devait avoir plus de 40 ans et habité dans le quartier Ommord à Rotterdam. Ils sont suivis par un nouvel examen tous les 2 à 3 ans.

Les objectifs de ce programme sont ambitieux et multiples. 4 appareils sont étudiés : l'appareil cardiovasculaire, neurocognitif, locomoteur et oculaire.

Concernant l'appareil cardiovasculaire, les objectifs de l'étude sont de comprendre les déterminants de la progression de la maladie athéromateuse. Pour l'aspect neurocognitif, les objectifs sont d'étudier les déterminants de la maladie de Parkinson et des différentes formes de démences.

6 publications ont été réalisés sur le thème de l'HO.

Le diagnostic d'HO reposait sur les critères du consensus de 1996.

#### 1.4.3.2 PREVALENCE DE L'HO

Les chiffres de prévalences obtenus diffèrent selon les populations étudiées.

Ainsi, en population générale, c'est essentiellement l'âge qui va être le principal facteur déterminant de la prévalence de l'HO. Ainsi, par décade, la prévalence de l'HO est estimée de l'ordre de 5% chez les sujets de 50-59 ans jusqu'à environ 18.5% chez les sujets de plus de 80 ans<sup>78</sup>.

Ces prévalences vont significativement augmenter dans des populations plus spécifiques et très dysautonomiques. Elle va ainsi concerner 1/3 des sujets diabétiques<sup>79</sup>, 1/3 des sujets parkinsoniens<sup>80</sup>, 2/3 des patients âgés fragiles en institutions<sup>81</sup> et jusqu'à 100% des sujets avec une maladie dysautonomique pure<sup>82</sup>.

#### 1.4.3.3 PRINCIPALES CONDITIONS ASSOCIEES A L'HYPOTENSION ORTHOSTATIQUE

L'HO est décrite classiquement comme le résultat d'un dysfonctionnement du baroréflexe. Le baroréflexe est constitué de structures vasculaires : les barorécepteurs et de structures nerveuses périphériques mais aussi centrales : le tronc cérébral et la moelle épinière. On distinguera, selon cette description, les HO dites non-neurogéniques en rapport avec l'atteinte vasculaire du baroréflexe et des HO dites neurogéniques en rapport avec une atteinte des structures nerveuses centrales<sup>83</sup>.

#### 1.4.3.3.1 LES MARQUEURS D'ATTEINTE VASCULAIRE ORIENTANT VERS UNE OH NON NEUROGENIQUE

- L'âge

Il est le déterminant majeur du vieillissement naturellement. Il est associé à une diminution de la sensibilité du baroréflexe<sup>84</sup>.

D'autre part la déshydratation, la prise de traitements favorisant sont autant d'éléments qui font que l'âge est le principal facteur de risque d'HO en dehors des situations des maladies neurodégénératives<sup>85</sup>.

- La rigidité artérielle

La rigidité artérielle est associée à l'HO<sup>86</sup>. Cela est d'autant plus vrai qu'il y a en même temps une atteinte centrale dysautonomique du baroréflexe<sup>87,88</sup>.

Il a été montré dans la cohorte de population générale de Rotterdam que la rigidité artérielle était associée à la fois à une dysfonction du baroréflexe et à la prévalence de l'HO sans doute par altération de la structure vasculaire des barorécepteurs en particulier carotidiens<sup>89</sup>. Ainsi en pratique clinique, on observe que les situations associées à une augmentation du vieillissement vasculaire et à une rigidité artérielle marquée sont des situations à haut risque d'HO<sup>90</sup>. C'est particulièrement vrai chez les sujets polyvasculaires avec un arbre aortique très calcifié même si cela n'a pas été d'avantage étudié.

- Les traitements anti-hypertenseurs et l'HTA

L'action anti-hypertensive des traitements peut induire ou majorer des HO. C'est particulièrement vrai pour les classes de traitement qui ont pour cible pharmacologique le système sympathique c'est-à-dire les bêtabloqueurs et les alpha-bloqueurs<sup>85</sup>. Les diurétiques en aggravant ou en induisant une déshydratation peuvent également participer à une HO<sup>91</sup>.

- Le diabète

Le diabète est une cause majeure de dysautonomie<sup>92</sup>. C'est également un facteur de risque cardiovasculaire par atteinte de la micro et de la macro-circulation. En cela, le diabète est également associé à un vieillissement vasculaire marqué qui participe vraisemblablement à la survenue de la dysfonction du baroréflexe et donc de l'HO<sup>93</sup>.

#### 1.4.3.3.2 LES MARQUEURS D'ATTEINTES CENTRALES ORIENTANT VERS UNE HO NEUROGENIQUE

- Les traitements psychotropes

Toutes les classes de traitements psychotropes (neuroleptiques, anti-dépresseurs, régulateurs de l'humeur, anxiolytiques, hypnotiques) sont associées à un sur-risque d'HO<sup>94, 95</sup>. Ce risque semble majoré lorsqu'il existe une association avec les traitements anti-hypertenseurs en particulier les bêtabloqueurs, les alphabloqueurs et les IEC<sup>96</sup>.

Les mécanismes par lesquels ces traitements induisent de l'HO ne sont pas vraiment élucidés mais seraient dus à leur action sur la libération des neurotransmetteurs centraux : dopamine, sérotonine et noradrénaline.

- Le diabète

La dysautonomie diabétique est liée pour partie à la dénervation sympathique cardiaque due à la neuropathie diabétique (appelé la Cardiac autonomic neuropathy dans la littérature)<sup>97</sup>. L'HO est une des formes de cette dysautonomie et en tout cas la manifestation la plus évidente cliniquement<sup>98</sup>.

- Maladie Parkinson et traitement dopaminergique.

La maladie de Parkinson se traduit par un défaut de production de dopamine. Mais la cause principale de l'HO serait due à un défaut de production de noradrénaline secondaire à la dégénérescence des neurones du locus coeruleus et des ganglions sympathiques<sup>99</sup>. Ce défaut adrénergique initial est aggravé par une dénervation sympathique et parasympathique du cœur<sup>100</sup>.

D'autre part, les traitements dopaminergiques sont associés à l'HO par une altération de la fonction effectrice du baroréflexe également<sup>101</sup>. La levodopa entraîne une baisse de la PA, de la contraction cardiaque et du volume d'éjection systolique<sup>102</sup>.

- Autres maladies neuro-dégénératives

La plupart des maladies neuro-dégénératives peuvent s'accompagner d'HO sévère par altération centrale du baroréflexe. L'HO peut être la première manifestation d'une maladie complexe dont le diagnostic ne sera porté que de nombreuses années plus tard. En attendant elle sera classée dans les syndromes de dysautonomie pure<sup>103</sup>.

#### 1.4.3.4 HO ET ASSOCIATION AVEC DES EVENEMENTS CARDIOVASCULAIRE

Dans la cohorte de Malmö, 33346 habitants d'âge moyen 45.6 ans (26-61 ans), avec une majorité d'homme (67.3%) la prévalence de l'HO, définie selon le consensus, est de 6.1% (N=1991). Durant la période de suivi de 21 ans en moyenne, 1293 sujets ont été hospitalisés pour un premier épisode d'insuffisance cardiaque. Le fait d'avoir une HO lors de l'inclusion dans l'étude augmentait d'environ 50% le risque relatif d'une hospitalisation pour insuffisance cardiaque<sup>104</sup>.

Dans cette même cohorte, il a pu être montré une augmentation de l'ordre de 60% de la mortalité et des événements coronariens pour des chutes de PA systolique supérieures à 30 mm Hg ou de 15 mm Hg pour la PA diastolique<sup>105</sup>. Enfin, il a été mis en évidence dans cette population, une augmentation de l'ordre de 30%<sup>106</sup> d'incidence de fibrillation auriculaire chez les sujets avec HO.

Dans l'étude de Rotterdam, 5064 sujets de 68 ans en moyenne, à majorité féminine (62%) ont été suivi pendant 7.8 ( $\pm$ 3.8) ans. L'HO est associée à un sur-risque de mortalité totale de 22%, d'insuffisance cardiaque de 21%, de coronaropathie de 30% mais pas d'AVC<sup>107</sup>.

Dans l'étude ARIC, 11174 sujets de 4 communes du Sud des Etats-Unis (30% de sujets noirs) de 55 ans en moyenne ont bénéficié d'un dépistage de l'HO à l'inclusion. Le suivi moyen est de l'ordre de 5 ans. La prévalence est de 5.1% et 178 AVC ont été recensés. Il a été montré un doublement du risque d'AVC chez les sujets avec une HO à l'inclusion<sup>108</sup>. Dans cette même cohorte, le risque de coronaropathie est augmenté de 85% en cas d'HO<sup>109</sup> et le risque de mortalité toute cause a doublé<sup>110</sup>. On retrouve le même type d'association pour la mortalité cardiovasculaire, en revanche, il n'existe pas d'association pour la mortalité par cancer<sup>110</sup>.

L'ensemble de ces résultats sont confirmés par d'autres cohortes moins importantes. Ainsi, dans la cohorte d'Honolulu, 3522 sujets américains d'origine Japonaise de 74 ans en moyenne (71-93 ans) ont été suivis sur 4 ans avec 4 mesures de PA. La prévalence de l'HO est de 7%. L'HO est associée à une augmentation de 64% de la mortalité toutes causes (décès=52). Il semble qu'il existe une réponse effet-dose dans les limites d'un nombre d'évènements qui reste modeste<sup>111</sup>.

Dans une cohorte finlandaise, 792 sujets âgés de plus de 70 ans sont suivis pendant 3.58 ans en moyenne après une mesure de PA debout. 90 présentent un Infarctus du Myocarde. La chute de 8 mm Hg de la PA diastolique est associée à une



multiplication par 2.2 du risque d'infarctus du myocarde<sup>112</sup> mais pas la chute de PA systolique.

Enfin, tous ces résultats ont été regroupés dans le cadre d'une méta-analyse de 13 études pour une population totale de 121 913 sujets<sup>113</sup>. Le suivi médian était de 6 ans. La présence d'une HO est associée à une augmentation du risque de mortalité totale (RR 1.50; IC à 95% 1.24-1.81), de coronaropathie (RR 1.41; IC à 95% 1.22-1.63), d'insuffisance cardiaque (RR 2.25; IC à 95% 1.52-3.33) et d'AVC (RR 1.64; IC à 95% 1.13-2.37). Le sur-risque est surtout présent chez les sujets de moins de 65 ans avec un risque relatif de mortalité toutes causes 1.78 (IC à 95% 1.25-2.52) vs 1.26 (IC à 95% 0.99-1.62) chez les sujets de plus de 65 ans (Figure 1).

Cette méta-analyse a été renforcée depuis par d'autres résultats d'études qui les confirment un peu plus que ce soit sur l'insuffisance cardiaque, la coronaropathie, la fibrillation auriculaire<sup>114</sup>, le risque d'AVC<sup>115</sup> ou la mortalité<sup>116</sup>.

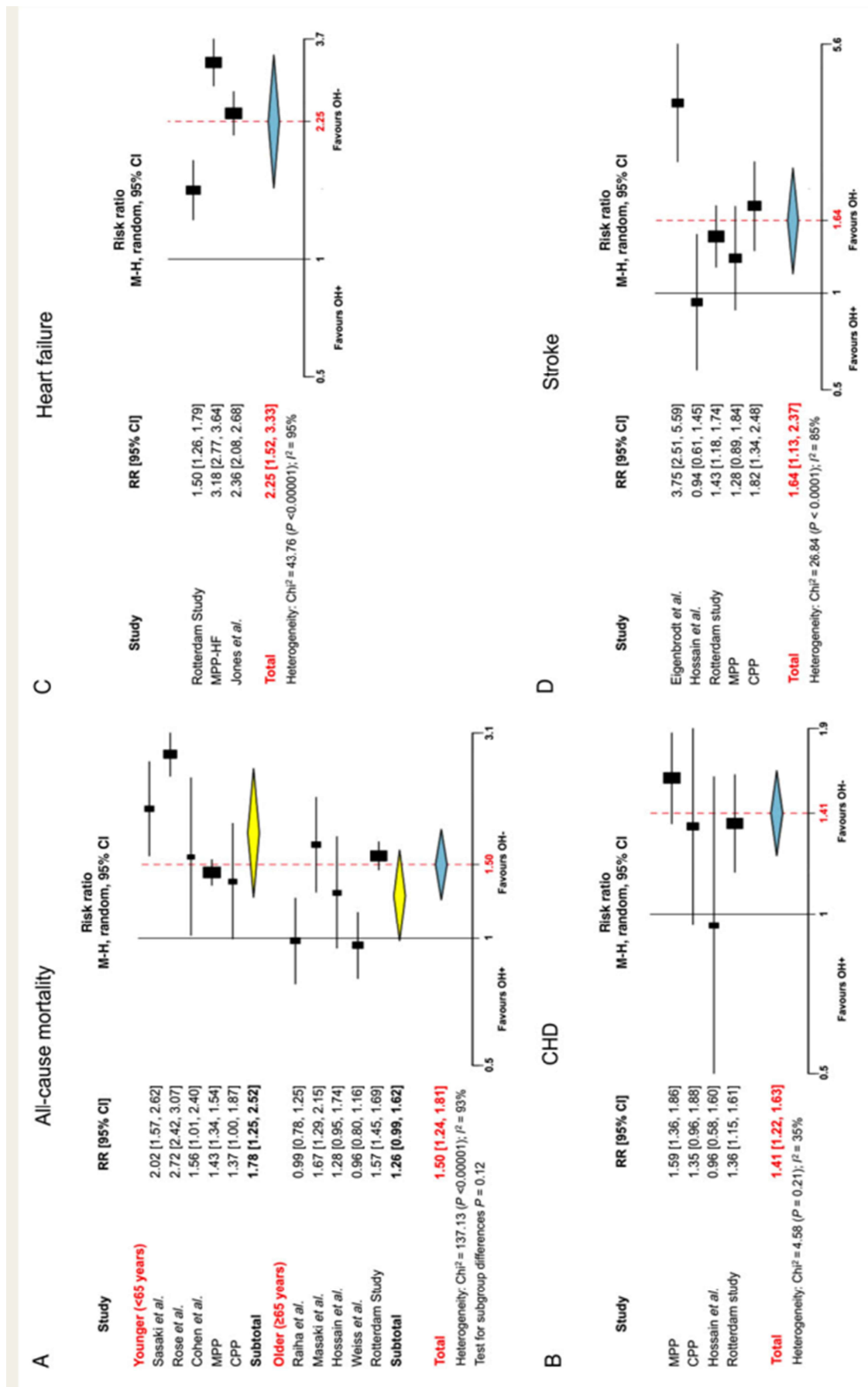


Figure 1 : Pronostic de l'hypotension orthostatique dans les études longitudinales. D'après Ricci *et al.*, EHJ 2015.

#### 1.4.4.5 HYPOTENSION ORTHOSTATIQUE ET TROUBLES DES FONCTIONS SUPERIEURES

Peu de travaux ont exploré les liens entre HO et démence au moment de l'élaboration de ce travail de thèse. Ils sont très récents et ont un manque de puissance important en raison d'effectifs ou de suivis insuffisants. La première observation est qu'il existe une augmentation de la prévalence de l'HO chez les sujets déments<sup>117</sup>.

Dans une cohorte de 211 Irlandais<sup>118</sup> avec troubles cognitifs légers ou « mild cognitive impairment » (MCI) suivis sur 3 ans, il est mis en évidence une augmentation du risque relatif de conversion vers la démence de 2.77 (IC à 95% =1.02-7.50) chez les sujets avec une chute de PA systolique après 30 secondes en position debout par rapport à la PA systolique couchée.

Dans une autre petite cohorte norvégienne<sup>119</sup>, 225 sujets avec démence légère sont suivis annuellement sur 4 ans. La prévalence de l'HO dans cette population à chaque visite est de 30 à 40%. Dans cette analyse longitudinale, le fait d'être un sujet avec HO permanente (HO mise en évidence à chaque visite) a été comparé aux autres sujets. L'analyse finale ne concerne que 86 sujets dont 29 avec HO permanente. Il n'apparaît pas d'association entre un statut HO permanent et le devenir cognitif dans cette population particulière de démence légère (p=0.5). Ceci dit, les limites de cette étude sont importantes avec un effectif particulièrement faible et des interrogations sur la pertinence du choix de suivre les HO permanentes car le caractère peu reproductible de cette mesure fait partie de ses caractéristiques intrinsèques.

Une autre étude plus ancienne<sup>120</sup> suit sur 2,5 ans, 1159 sujets de plus de 70 ans vivant à leur domicile ou en institution. Des marqueurs de risque de démence et d'altération cognitive sont recherchés. Avec une prévalence de l'HO proche de 30%, l'HO n'est pas associée au déclin cognitif (défini par une baisse du score de MMS). Cependant, là encore les limites sont nombreuses avec tout d'abord un suivi trop court pour qu'un processus démentiel franc soit mis en évidence. Ensuite sur les 1159 sujets inclus, seuls 651 ont eu une réévaluation clinique de leur statut cognitif soit à peine 50% de l'effectif initial.

La cohorte suédoise en population générale (GAS-SNAC study) de 2931 sujets de plus de 60 ans a été suivie sur 6 ans. 1099 sujets ont été perdus de vue et après avoir retiré les sujets avec MCI ou démence à l'inclusion, il reste 1480 sujets. Dans cet échantillon la prévalence de l'HO selon les critères consensuels est de 19%. Il a été montré que l'HO était associée à un sur-risque de dégradation des fonctions cognitives évaluées sur un critère combiné des cas de démence incidente mais aussi

des MCI<sup>121</sup>. Ici encore, le suivi et la taille de l'échantillon sont sans doute les deux principales limites de l'étude pour mettre en évidence une association avec la démence incidente.

Une cohorte de Singapour a été constituée<sup>122</sup> avec 2321 sujets de plus de 55 ans sans aucun antécédent cardiovasculaire. 1485 sujets avec un âge moyen de 65 ans ont été revus à 2 ans. Dans ce travail la prévalence de l'HO est de 16%. Il n'est pas mis en évidence d'association significative entre le statut HO et le déclin cognitif défini par une baisse du score de MMS à 2 ans. En revanche, il est montré une association significative chez les sujets qui présentent à la fois une HO et un statut hypotendu (PAS<120 mm Hg ou PAD<70 mm Hg). Cependant cela concerne 16% de l'échantillon revu soit seulement 237 sujets.

La cohorte américaine ARIC, a étudié également cette relation<sup>123</sup> en évaluant le statut cognitif sur presque 13000 sujets de 53 ans en moyenne, suivis sur 10 ans. Une association est démontrée entre la présence d'une HO à l'inclusion et la dégradation des résultats aux tests cognitifs en particulier du Digit Symbol Substitution Test (DSTT) avec un rapport de cote de 1.34 (IC à 95%=1.12-1.62). Le statut démentiel n'est pas évalué. Ceci dit, cette association s'explique essentiellement par le fait que les sujets présentant une HO à l'inclusion avaient déjà un statut cognitif moins bon que ceux qui n'en avaient pas. Après ajustement cette relation disparaît.

Au moment du début du travail de cette thèse, les résultats sur l'association éventuelle entre HO et démence incidente sont donc encore limités. Certains travaux tendent à penser qu'une association peut exister mais aucun des travaux réalisés n'avaient la puissance requise pour la mettre en évidence.

#### 1.4.4.6 HYPOTHESES PHYSIOPATHOLOGIQUES ET LIENS DE CAUSALITE

L'ensemble de ces travaux épidémiologiques décrivent des associations entre la présence d'une HO et de la survenue d'évènements cliniques. Ils ne répondent pas à la question des mécanismes sous-jacents et encore moins à la question de la causalité entre l'HO et l'évènement. Les conclusions des études épidémiologiques sont toujours extrêmement prudentes.

Quelques hypothèses sont proposées cependant.

Dans le programme SYSTEMA de Malmö, une étude est conduite sur des biomarqueurs<sup>124</sup>. Ils montrent que les sujets avec une HO ont une expression plus

importante de Thrombomoduline ce qui suggère un mécanisme compensatoire contre un état pro-coagulant associé au développement de l'athérosclérose<sup>125</sup>. Il existe également une sur-expression de MMP-7 qui est un biomarqueur associé à l'athérosclérose et à un sur-risque cardiovasculaire<sup>126</sup>.

L'HO est donc associée à des biomarqueurs qui ont une signature pro-inflammatoire et athérogène. Cela renforce les données épidémiologiques précédentes.

#### 1.4.4 TRAITEMENT DE L'HYPOTENSION ORTHOSTATIQUE

L'objectif du traitement est de réduire les co-morbidités secondaires à la survenue d'une hypotension orthostatique. A l'heure actuelle, les seuls événements immédiatement associés à l'HO sont le malaise lipothymique bénin : sensation brève d'étourdissement lors de la mise en position debout. Ce malaise bénin ne bénéficie pas de traitement et n'a jamais été le sujet d'un essai thérapeutique.

Les malaises plus profonds pouvant s'accompagner d'une perte de connaissance ou d'une impossibilité de maintenir la position debout sont le plus souvent en rapport avec les formes d'HO neurogénique profonde et peuvent nécessiter un traitement symptomatique c'est-à-dire de traitement qui augmente la pression artérielle globalement<sup>127</sup>. Ainsi, lors du passage à l'orthostatisme, la chute de PA reste présente mais le niveau de PA globale étant plus élevée, la PA en position debout reste supérieure à la valeur en dessous de laquelle les symptômes apparaissent.

Cependant, il n'existe pas aujourd'hui de preuve de la réduction des événements cardiovasculaires et cognitifs qui sont associés à l'HO. La causalité de l'HO dans la survenue des événements cardiovasculaires et cognitifs n'est donc pas démontrée.

Ceci étant un certain nombre de stratégies peuvent être envisagées pour améliorer les symptômes des sujets avec lipothymies induites par l'HO. Il s'agit simplement de corriger les facteurs modifiables d'hypovolémie (hydratation et consommation sodée) et d'adapter l'ordonnance chez le sujet polymédiqué.

- Traitement anti-hypertenseur

Le niveau de PA et l'HTA ainsi que ses traitements sont associés à une augmentation de la prévalence de l'HO. L'attitude vis-à-vis de la mise en place ou du retrait d'un traitement anti-hypertenseur chez des sujets avec HO est donc difficile à établir.

Ainsi, dans l'étude ACCORD qui compare dans une population de 4233 sujets diabétiques et hypertendus, deux stratégies anti-hypertensives différentes (bras conventionnel et bras intensif), il n'apparaît pas de majoration de l'incidence de l'HO dans le bras intensif<sup>128</sup>.

Ce résultat est renforcé par un autre travail plus récent sur la cohorte de l'étude SPRINT qui est cette fois une population hypertendue mais non diabétique. Il est ainsi montré que une prévalence de l'HO de 5.7% dans le groupe standard et de 5.0% dans le groupe intensif<sup>129</sup>.

De plus dans l'étude PARTHAGE, chez 994 sujets de 88 ans en moyenne, les sujets traités par anti-HTA ont une prévalence d'HO moins importantes que les sujets sans traitement<sup>99</sup>. En revanche, le choix de la classe du traitement semble influencer la fréquence de l'HO. Ainsi, il a été montré une association entre la prise de traitement bêtabloqueur et la présence d'une HO<sup>77</sup>. De la même manière, ce sur-risque d'HO est également associé à la présence du traitement par alpha-bloqueur de manière encore plus évidente cliniquement<sup>129</sup> chez l'homme avec une hypertrophie de prostate mais également chez la femme traitée par alpha-bloqueur comme traitement anti-HTA<sup>130</sup>. Il s'agit de deux classes qui bloquent les récepteurs adrénergiques.

- Traitement psychotrope

L'ensemble des classes de traitement psychotrope favorisent la survenue d'HO de manière semblable<sup>131</sup>. Il est conseillé de dépister l'HO avant chaque titration de dose de traitement<sup>96</sup>. Il est également conseillé de limiter les associations avec les traitement anti-hypertenseurs de la famille des bêtabloqueurs, des alpha-bloqueurs et des bloqueurs du système rénine angiotensine<sup>132</sup>.

Les données de la littérature montre donc que l'HO apporte des informations sur le sur-risque cardiovasculaire en particulier pour les évènements suivants : l'AVC, l'infarctus du myocarde et la mortalité. De ce point de vu, l'HO semble donc pouvoir se substituer aux autres marqueurs de variabilité tensionnelle conventionnels.

De plus l'insuffisance du baroréflexe est également un déterminant commun. En effet, il a été montré dans des modèles animaux que la défaillance du baroréflexe était un déterminant important de la variabilité tensionnelle de court terme<sup>51</sup>. Indirectement, la défaillance du baroréflexe a été démontrée chez des sujets hypertendus pour lesquels les variabilités de la PA étaient plus importantes chez les sujets non dipper que chez les sujets dipper<sup>133</sup>. De plus, l'usage de bêtabloqueurs qui altère la réponse du baroréflexe semble aggraver la variabilité tensionnelle inter-visite<sup>22</sup>.

En revanche l'HO se distingue de la variabilité tensionnelle conventionnelle par le fait qu'elle est provoquée par la mise en position debout. La redistribution du volume sanguin provoquée par le passage à l'orthostatisme sollicite également le réseau vasculaire et en particulier artériel. Ainsi, il a été montré que la qualité de diffusion des ondes de pression est associée de manière indépendante à la baisse de PA en orthostatisme<sup>134</sup>.

**Pour rapprocher l'HO des autres marqueurs conventionnels de variabilité tensionnelle nous avons donc voulu vérifier plusieurs points :**

- Les marqueurs de variabilité tensionnelle ont démontré une association avec les cas incidents de démences. L'HO est-elle également un marqueur indépendant de risque de démence ?
- La qualité du réseau vasculaire, artériel en particulier, semble être un élément important d'une bonne adaptation tensionnelle via la transmission des ondes de pression<sup>163</sup>. Auquel cas, le baroréflexe ne serait plus l'unique déterminant de l'HO. D'autre part quelles sont les relations de l'HO avec les autres marqueurs de variabilité. Si ces paramètres mesurent la même chose, ils doivent être étroitement associés. Nous essaierons donc dans un deuxième travail mécanistique d'étudier les relations entre l'HO, la rigidité artérielle et les marqueurs de variabilité tensionnelle.
- Enfin, si le dépistage de l'HO est plus simple que le calcul d'une variabilité en holter tensionnel, en auto-mesure tensionnelle et en inter-visite, la faible

reproductibilité de la mesure en consultation réduit un peu l'intérêt de ce dépistage. Une méthode diagnostique qui multiplie les mesures de PA en position debout est sans doute un bon moyen de réduire cette limite diagnostic.

Ce travail de thèse souhaite apporter des éléments de réponse sur ces trois points à travers trois travaux originaux qui exploreront respectivement :

- l'association de l'HO avec les cas incidents de démence,
- les déterminants de l'HO au regard de la variabilité tensionnelle en auto-mesure,
- une méthode diagnostic de l'HO travers l'utilisation de l'auto-mesure tensionnelle.



### 3 MATERIEL

La majorité des travaux de cette thèse ont été réalisés à partir de la cohorte des 3 Cités, cohorte de sujets âgés de plus de 65 ans en population générale, recrutés dans 3 villes françaises : Bordeaux, Dijon et Montpellier.

#### 3.1 LA COHORTE DES 3 CITES

##### 3.1.1 OBJECTIFS INITIAUX DE LA COHORTE

La cohorte des 3 Cités est une étude de population générale qui a pour objectif de mettre en évidence des associations épidémiologiques et des facteurs de risque de survenue de démence.

Cette étude prolonge 2 études épidémiologiques françaises, PAQUID<sup>135</sup> et EVA, de moins grande taille qui ont apporté les bases de ce projet ambitieux.

EVA a identifié entre autres des liens entre déclin cognitif et niveau de PA<sup>136</sup>. Ces résultats épidémiologiques ont été confortés par un essai randomisé SYS-EUR<sup>137</sup> qui montre que le traitement de l'HTA systolique isolée du sujet âgé (>60 ans) par un inhibiteur calcique en première intention diminue de manière significative l'incidence de la démence.

C'est dans ce questionnement scientifique et pour répondre à la question du rôle des facteurs de risque cardiovasculaire sur la démence que la cohorte des 3 Cités est mise en place en 1999.

Elle doit être suffisamment dimensionnée pour répondre aux objectifs principaux suivants<sup>138</sup> :

- estimer le risque de démence attribuable aux facteurs de risque et aux pathologies vasculaires
- mesurer l'effet de la réduction du risque vasculaire (par la prévention ou le traitement) sur l'incidence et la prévalence de la démence.

##### 3.1.2 CONSTITUTION DE LA COHORTE

###### 3.1.2.1 CARACTERISTIQUES INITIALES DE LA POPULATION TOTALE

La population totale de la cohorte des 3 Cités comprend 9294 sujets répartis sur trois centres : 2104 sujets sur Bordeaux, 4931 sujets sur Dijon et 2259 sujets sur Montpellier<sup>139</sup>. Elle est composée d'une majorité de femme (≈60%) d'un âge moyen de 74 ans. 1745 sujets n'ont pas bénéficié d'une mesure de la PA en position debout

à l'inclusion. Ces sujets sont significativement plus âgés ( $p < 0.0001$ ), plus hypertendus (46% vs 41% ;  $p = 0.005$ ), plus diabétique (10% vs 7% ;  $p = 0.011$ ).

### 3.1.2.2 MESURE DE LA PRESSION ARTERIELLE EN POSITION DEBOUT ET HYPOTENSION ORTHOSTATIQUE

#### 3.1.2.2.1 PROTOCOLE DE MESURE

Il existe en réalité plusieurs protocoles de mesure de la PA en position debout.

Lors de la visite d'inclusion, il a été proposé à l'ensemble des sujets des 3 centres de bénéficier d'une mesure unique de la PA en position debout juste après une mesure unique de la PA en position allongée. Il ne s'agit donc pas du protocole diagnostic consensuel. Ce protocole de mesure n'a été réalisé qu'une seule fois à l'inclusion dans l'étude.

En revanche dans le centre de Dijon, qui est le premier centre recruteur en nombre de sujets, un dépistage de l'HO a été réalisé de manière systématique à chaque suivi. Dans ce cas, le protocole de mesure repose sur le consensus de 1996. Ainsi, 3 mesures de PA seront réalisées après 1 mn, 2 mn et 3 mn d'orthostatisme.

#### 3.1.2.2.2 PREVALENCE DE L'HO DANS 3C

La prévalence de l'HO mesurée à l'inclusion dans la cohorte des 3 Cités est de 13%. Elle est relativement plus faible que dans les autres cohortes de populations générales malgré des sujets âgés > 65 ans. Il apparaît que les sujets recrutés dans cette étude bien qu'ils soient tirés au sort au départ, participent ensuite de manière volontaire aux protocoles proposés dans le cadre de cette étude (taux de participation de 37%). Dans ce contexte on retrouve un échantillon non représentatif de la population française puisqu'à tranche d'âge égal, les sujets recrutés ont un niveau socio-économique supérieur.

#### 3.1.2.2.3 DISTRIBUTION DE LA BAISSSE DE PA SYSTOLIQUE A L'ORTHOSTATISME

La chute de PA systolique a été mesurée chez 7425 sujets à l'inclusion. Cette variable quantitative suit une distribution normale (Figure 2).

La différence de PA mesurée est de 0.5 mm Hg, l'écart type est de 15.5 mm Hg. L'amplitude des mesures couvre des baisses de PA jusqu'à 119 mm Hg et des ascensions de PA jusqu'à 87 mm Hg.

3480 sujets ont une chute de PA de plus de 1 mm Hg. Dans cet échantillon, la chute de PA moyenne est de 12 mm Hg  $\pm$  10 mm Hg. L'âge ( $p < 0.0001$ ), la PA ( $p < 0.0001$ ), le

statut hypertendu ( $p < 0.0001$ ), la prise de traitement anti-hypertenseur ( $p < 0.0001$ ) et de médicaments psychotropes ( $p = 0.024$ ) sont associés à une aggravation de la chute de la PA systolique lorsqu'elle est regardée en quartiles. Ni le diabète ( $p = 0.089$ ) ni la fréquence cardiaque ( $p = 0.993$ ) ne sont en revanche associées à la baisse de la PA systolique.

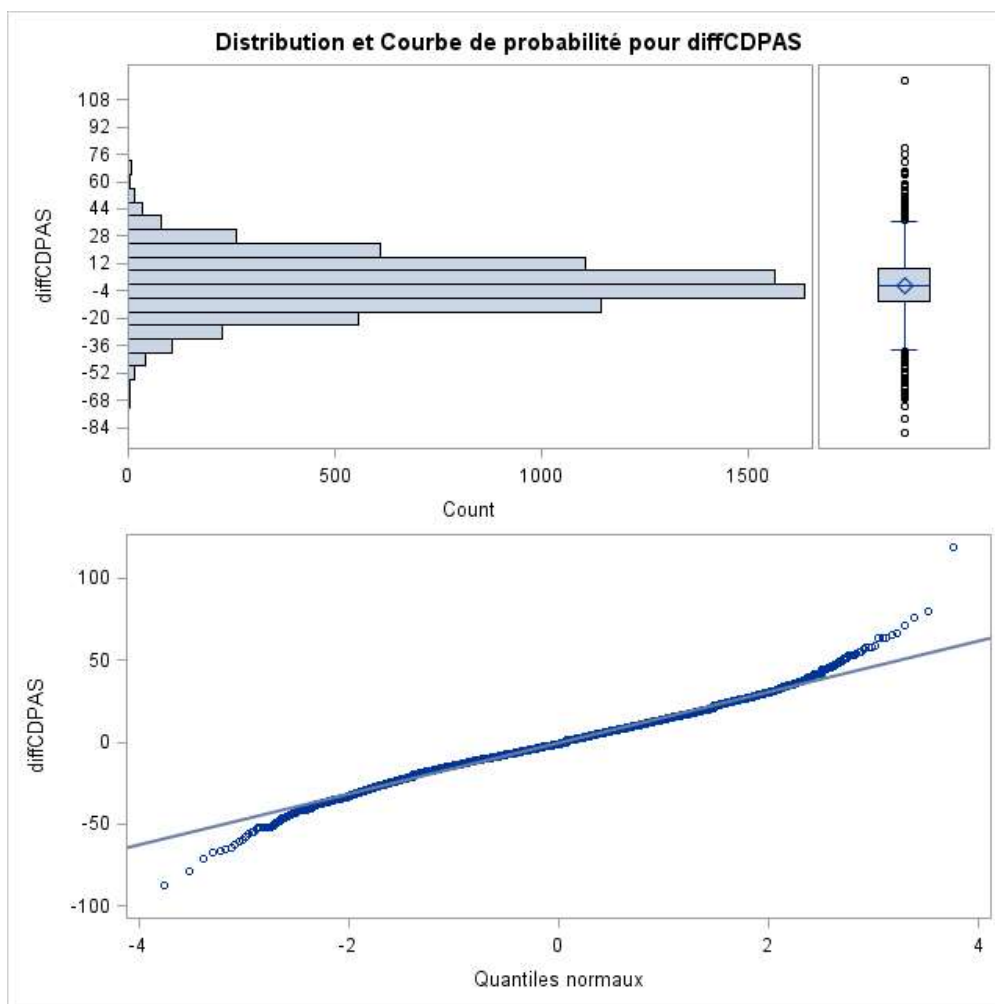


Figure 2 : Distribution de la chute de Pression Artérielle Systolique chez les 7425 sujets de la cohorte des 3 Cités

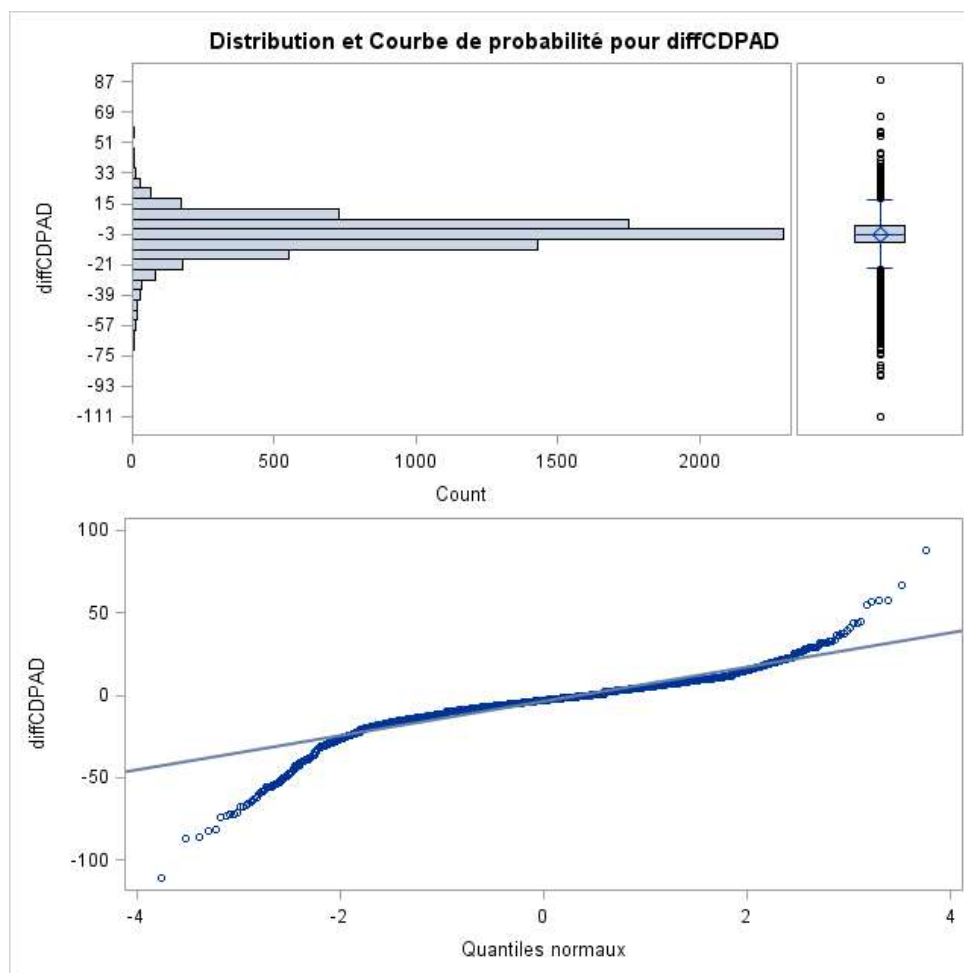
#### 3.1.2.2.4 DISTRIBUTION DE LA BAISSSE DE PA DIASTOLIQUE A L'ORTHOSTATISME

La baisse de PA diastolique est mesurée chez 7425 sujets à l'inclusion. Cette variable quantitative suit une distribution normale (Figure 3).

La différence de PA mesurée est de -3.5 mm Hg, l'écart type est de 10.5 mm Hg. L'amplitude des mesures couvre des chutes de PA jusqu'à 88 mm Hg et des ascensions de PA jusqu'à +20 mm Hg.

2397 sujets ont une baisse de PA diastolique supérieur à 1 mm Hg. Comme pour la baisse de PA systolique, on retrouve les variables classiquement associées à la chute

de PA : l'âge ( $p < 0.0001$ ), le statut hypertendu ( $p = 0.05$ ), le niveau de PA systolique ( $p < 0.0001$ ) et diastolique ( $p < 0.0001$ ) et les antécédents cardiovasculaires ( $p = 0.002$ ). Ici, le diabète ( $p = 0.948$ ) et la FC ( $p = 0.139$ ) ne sont pas non plus associés à la chute de PA diastolique. En revanche, contrairement à la baisse de PA systolique, la prise de traitement psychotrope n'est pas associée à la baisse de PA diastolique ( $p = 0.009$ )



*Figure 3 : Distribution de la chute de pression artérielle diastolique chez les 7425 sujets de la cohorte des 3 Cités*

### 3.1.2.2.5 RELATION ENTRE CHUTE DE PA SYSTOLIQUE ET DIASTOLIQUE

652 sujets ont une HO systolique et 473 sujets ont une HO diastolique. Au total, 978 sujets ont une HO selon la définition consensuelle soit une prévalence de 13% de l'échantillon étudié. Cela signifie que 87% des sujets ont une HO qui est soit diastolique soit systolique dans cette cohorte. La proportion d'HTA systolique reste prédominante mais pas dans les proportions décrites par Fedorowski<sup>63</sup>. D'ailleurs dans la cohorte des 3 Cités, la corrélation entre la mesure de la chute de la PA systolique et diastolique est significative mais reste modérée avec un coefficient de

corrélation de Pearson de 0,37. Cela montre bien la relative indépendance entre ces deux chutes de PA dans une population pourtant très homogène.

Les caractéristiques des sujets avec une HO sont cohérentes avec les données de la littérature. Les sujets avec une HO sont significativement plus âgés ( $p < 0.0001$ ), ont des niveaux de PA significativement plus importants ( $p < 0.0001$ ) associés à une fréquence plus importante d'HTA ( $< 0.0001$ ) et une consommation de médicaments hypotenseurs ( $p < 0.0001$ ). Ils ont également une plus grande fréquence d'antécédents cardiovasculaires ( $p = 0.025$ ). En revanche il n'existe pas de différence de distribution du diabète ( $p = 0.106$ ), du tabagisme ( $p = 0.105$ ) et de la dyslipidémie ( $p = 0.065$ ). La population avec HO est malgré tout à plus haut risque cardiovasculaire (âge, antécédent cardiovasculaire et HTA).

### 3.2 PRESENTATION GENERALE DES 3 ETUDES PUBLIEES

Deux des études ont été réalisées dans le cadre de la cohorte des 3 Cités, la 3ème concerne une étude de terrain.

La première recherche est **une analyse longitudinale de l'ensemble de la cohorte des 3 Cités**. L'objectif est d'étudier au cours d'analyses de survie, l'association entre la présence d'une HO à l'inclusion dans l'étude et la survenue d'une démence au cours du suivi.

Le deuxième travail est une **analyse transversale concernant uniquement l'échantillon de population du centre de Dijon**. En effet, dans ce centre des explorations hémodynamiques complémentaires ont été réalisées. Ainsi, un millier de sujets environ ont bénéficié à la fois d'un dépistage de l'HO, d'une mesure de la rigidité artérielle et d'une mesure de la variabilité tensionnelle en automesure. Cet échantillon permet donc une analyse mécanistique unique de ces trois variables d'intérêt.

Le dernier travail publié est **une étude diagnostic de terrain**. L'objectif est de vérifier que le dépistage de l'HO au cours de l'automesure tensionnelle n'altère pas la qualité du recueil de l'automesure tensionnelle classique qui doit statuer sur l'équilibre tensionnel global. Ce travail a été réalisé en dehors de la cohorte des 3 Cités. Les sujets inclus étaient les patients de consultation de l'unité d'HTA du CHU de Bordeaux et d'un cabinet de médecine général du Gers, France.

## 4 EXPLORATION DE L'ASSOCIATION ENTRE L'HYPOTENSION ORTHOSTATIQUE ET LES CAS INCIDENTS DE DEMENCE

### 4.1 PRESENTATION DE L'ARTICLE

Ce travail a été pensé afin d'explorer les liens entre l'HO et les cas de démences incidentes. Au moment de la réalisation de ce travail, il existe des données sur l'association entre variabilité tensionnelle inter-visite et démence et quelques données sur la cognition et l'HO mais dans des études de petites tailles (voir chapitre 1.4.4.5).

Grâce à la mesure de la PA en position assise et debout chez plus de 7000 sujets suivis plus de 12 ans, la cohorte des 3 Cités offre la possibilité de vérifier cette hypothèse.

L'article a été publié en Juillet 2017 dans le journal HYPERTENSION (revue de rang A, impact factor des 5 dernières années : 6.786).

## **Orthostatic hypotension and risk of incident dementia :**

### **Results from a 12-year follow-up of the Three-City study cohort**

Running Title: Orthostatic Hypotension is associated with incident dementia

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#### **Abstract:**

Several studies indicate a potential link between orthostatic hypotension (OH) and incident dementia, but without substantial evidence to date. Our objective is to study the association between OH and dementia in a cohort of elderly individuals. To do so, baseline lying and standing blood pressure measurements were taken from 7425 subjects in the Three-City study. These subjects were then followed-up over 12 years. Cox proportional hazard models, adjusted for potential confounders, were used to estimate the risk of incident dementia according to OH status. Sensitivity analysis was performed using the so-called illness-death model, a specific statistical method which takes into account competitive risk with death. OH frequency was found to be around 13%, and 760 cases of dementia were diagnosed during follow-up. We observed significant associations between the presence of OH at baseline and the occurrence of dementia during the follow-up, with an increased risk of at least 25% observed regardless of the OH threshold and the statistical method used. In conclusion, there is an association between OH and dementia. Considering that OH is a common condition and is easy to measure, OH measurements could help to identify subjects with higher risk of dementia. Moreover, reducing OH could be a step to prevent conversion to dementia.

Key words: orthostatic hypotension- dementia-blood pressure variability- vascular ageing-community based cohort

## **Introduction:**

In clinical practice, orthostatic hypotension (OH), a blood pressure drop in standing position, is a common condition affecting at least 6% of the population<sup>140</sup>. OH has been consistently associated with increased mortality and risk of cardiovascular events<sup>113</sup>. This leads us to question if cerebral perfusion variations induced by OH could contribute to an increased risk of dementia. An increase in the prevalence of OH in patients with dementia<sup>117</sup>, as well as increased risk of conversion to dementia, have been shown among patients with mild cognitive impairment (MCI) and OH<sup>118</sup>. In general population, relationships between OH and cognitive impairments are highlighted<sup>120-123</sup> but without drawing substantive conclusions given the too short duration of the follow-up and insufficient number of subjects, or as a result of an unequal distribution of the Mini-mental State Examination (MMSE) score according to OH status. Given these results, there is currently no significant evidence to support the prospective relationship between OH and the risk of dementia.

The Three-City study, a community-based cohort of 9294 individuals above the age of 65 with a follow-up of 12 years<sup>139</sup>, thus appears to be an adequate resource to attempt to make progress on this research topic.

## **Methods:**

### Study population

The principal objective of the Three-City study was to examine the vascular determining factors of incident dementia<sup>139</sup>. The study participants, aged 65 years and over, non-institutionalized, were recruited from 1999 to 2001 (inclusive), on a voluntary basis using the electoral rolls in three French cities: Bordeaux, Dijon and Montpellier. There was a 37% acceptance rate among the contacted subjects. After excluding those who refused to participate in the medical interview (n=392), the sample comprised 9294 participants (Bordeaux, n= 2104; Montpellier, n= 2259; Dijon, n= 4931). The initial interview took place either in a health center or at the subject's home, and consisted of a face-to-face interview with a trained investigator in order to collect data related to background information, lifestyle and medical history. In addition, a fasting blood sample was taken, and physical and cognitive assessments were performed. During the 12-year follow-up period, five follow-up visits took place every two or three years.



The working sample of this study consisted of subjects without prevalent dementia and who had their blood pressure measured whilst sitting and standing at baseline.

### Diagnosis of dementia

Diagnosis of dementia was based on a three-step procedure at each follow-up screening, as described elsewhere<sup>141</sup>.

First, at baseline and at each follow-up visit, trained psychologists assessed cognitive function and dementia was actively screened. Depending on the score obtained in the MMSE and Isaac test, subjects could be identified as at-risk for dementia<sup>142</sup>. On the Bordeaux and Montpellier sites, a neurologist evaluated all subjects. However and because of a large number of subjects, only at-risk subjects were evaluated by the neurologist on the Dijon site. Finally, after this examination based on clinical evaluation, the final diagnosis of dementia was made by an independent panel of neurologists and geriatricians with a strong expertise in dementia. They used the information available from the 3C examination and all exams performed by the patients' physicians who could include, but not systematically, neuroimaging exams. The diagnosis of dementia was established on the basis of the Diagnosis and Statistical Manual of Mental Disorders DSM-IV from the American Psychiatric Association. Alzheimer's disease was classified as possible or probable, using the criteria of the National Institute of Neurological and Communication Disorders and Stroke and of the Alzheimer's Disease and Related Disorders Association (*NINCDS-ADRDA* criteria<sup>143</sup>).

### Blood pressure measurement and diagnosis of orthostatic hypotension

The protocol for blood pressure measurement has been described previously<sup>139</sup>.

*For orthostatic hypotension diagnosis*, participants had to first lie down and relax for at least five minutes. Then an appropriate size cuff was placed on the right arm, close to the level of the heart. The measuring devices used consisted of automatic oscillometric devices developed by OMRON ® CP750 (Japan) rated A/A by the British Hypertension Society<sup>144</sup>. Blood pressure was measured once in lying position. Following this measurement in lying position and without removing the cuff, the participant had to stand up and then another one blood pressure measurement was immediately performed in standing position without delay. SBP and DBP values and heart rate were also recorded in the database. No data on symptoms that could

potentially indicate a drop in BP were recorded. Standing blood pressures were not measured during the follow-up.

The diagnosis of OH is based on a consensus and there are several diagnostic thresholds defined in the literature. We conducted analysis with the most consensual threshold (a reduction in SBP of at least 20 mm Hg or DBP of at least 10 mm Hg<sup>67</sup>) but also with two other thresholds commonly referred to as mild OH (reduction in SBP of at least 10 mm Hg or DBP of at least 5 mm Hg)<sup>145</sup> and severe OH (reduction in SBP of at least 30 mm Hg or DBP of at least 15 mm Hg)<sup>146</sup>.

For hypertension diagnosis, two series of blood pressure measurements were conducted, first at the beginning of the interview, and the second after the ECG to diagnose OH for the Bordeaux and Dijon centers. In Montpellier, only one series of blood pressure measurements was carried out after the ECG, which was therefore the same measurement used to diagnose OH and hypertension.

Hypertension was defined as a systolic blood pressure (SBP)  $\geq$  140 mm Hg, a diastolic pressure (DBP)  $\geq$  90mm Hg or taking antihypertensive drugs.

### **Clinical events and death during follow-up**

During follow-up, participants were asked to declare their cardiovascular history (interview or questionnaire). This included information on previous coronary events (acute coronary syndrome, myocardial revascularization), and stroke, regardless of the etiology. If the subject answered affirmatively, the potential case was further documented by medical data obtained from general practitioners, specialists, and hospitals records where possible and were reviewed by two panels of experts, one for coronary events and one for stroke.

Mortality was ascertained from the civil registry by systematic request for all subjects not included in follow-up visits. The date of death was defined as the date of event and the date of the last follow-up or phone contact for the 10-year follow-up as the date of censoring.

### **Other variables**

The level of education was divided into four categories from no school or only primary schooling to participants with studies in higher education.

The MMSE score was used to determine cognitive state. If the score was greater than or equal to 24/30, we considered the subject's cognitive state as normal<sup>147</sup>. Scores below this threshold was used to define a cognitive impairment.

Diabetic status was defined by a level of fasting blood glucose greater than 7mmol/l or the intake of anti-diabetic treatment (oral treatment or insulin).

Smoking status accounted for non-smokers, and former and active smokers. Former smokers were defined as having had quit smoking for at least six months.

Subjects were considered dyslipidemic if their total cholesterol level was greater than 5.2 mmol/l or if they were under hypolipidemic treatment.

Hypotensive medication was defined by the taken of medication which decrease the blood pressure whatever the indication: hypertension or other cardiovascular condition.

Psychotropic medication was defined by the taken of a chronic treatment for psychiatric disorder.

The diagnosis of depression was established on the basis of the score obtained on the depression scale established by the Center for Epidemiology Studies- Depression (CESD). Depression in a subject was defined by a score of >16 for men and >23 for women<sup>148</sup>.

### **Statistical Analysis**

Participants who did not have their blood pressure measured in standing position were removed from the analysis but were compared to the cohort whose blood pressure was measured whilst standing in order to determine if these values were missing at random. Comparative statistical tests adapted to independent data series were conducted to analyze subjects with OH and subjects without OH (variance analysis and chi-squared test).

We used a Cox proportional hazard model with delayed entry to study the risk of incident dementia in relation to OH. As it is difficult to define the date of onset of the dementing process, which is generally insidious, the age of diagnosis of dementia was defined as the age at the midpoint of the interval between the date of diagnosis and the date of the previous visit without dementia. The selected time axis is the age of subject, with delayed entry and left truncation. Participants without dementia were right-censored at the end of their last visit or in the event of death. The principal explanatory variable was OH status. Model 1 was a univariate model, uniquely adjusted for the variable center. Model 2 was adjusted for the variables known to be associated with dementia or with OH –ApoE4 status<sup>149</sup>, cognitive state, depression<sup>150</sup>, education level<sup>151</sup>, diabetes, high blood pressure, cardiovascular history, and center, which were selected during a step-by-step manual procedure, in descending order, using a cohort without missing data in order to ensure a constant sample size.

A sensitivity analysis was carried out using an illness-death model taking into account the competing risk by death and interval censoring<sup>152</sup>. The illness-death model is a semi-parametric multi-state model which has been designed to take into account properly the competitive risk with death induced by the interval censoring and thus avoids bias<sup>153</sup>. Therefore it incorporates the different transition states applicable to this study<sup>154</sup>. The first transition (baseline to dementia) is adjusted for the center, using only univariate analysis, and for the adjustment variables from model 2 of the principal multivariate analysis. The second transition (baseline to death) is adjusted in “univariate analysis” for sex and center. In the multivariate analysis, the cardiovascular risk factors are introduced into the model. The third transition (dementia to death) is adjusted by default for the variables used in the first transition.

In a second analysis, we explored the potential association of the OH to the two main different causes of dementia which are Alzheimer disease and vascular dementia. Cox proportional hazard models with delayed entry were performed with Alzheimer disease and then vascular dementia as primary outcome. The adjustment variables were taken from Model 2 of our primary analysis.

All analyses were performed using SAS v9.4 (SAS Institute, Inc., Cary, NC) except those concerning the illness-death model that used R<sup>®</sup>'s smooth-hazard package. A two-tailed p-value  $\leq 0.05$  was considered to be statistically significant.

## **Results**

The initial sample of the Three-City study was composed of 9294 subjects. However, 1745 of the subjects did not have their blood pressure measured in standing position rendering the diagnosis of OH impossible, and 214 subjects had already been diagnosed with dementia at the start of the study. Our final study sample therefore consisted of 7425 participants (Figure 4). Subjects who had not undergone a standing blood pressure measurement represented about 20% of the total cohort. These subjects were equally represented between the three centers. In comparing the general characteristics of these participants with those in the study sample, we observe that the former are a significantly older population group ( $p < 0.0001$ ) with an accumulation of cardiovascular risk factors (Annex1).

Using the conventional significance threshold to diagnose OH, we observe an overall OH in 978 participants (13% of the working sample). With the second definition proposed, numbers are different: mild OH was present in 2411 participants (32%), and severe OH in 330 participants (4.5%).

Participants with OH had an increased cardiovascular risk compared to participants without OH, were older ( $p=0.0016$ ), had a higher proportion of cardiovascular history ( $p<0.0001$ ) and higher SBP ( $p<0.0001$ ). Distribution of ApoE4+ state, cognitive state and level of education were comparable in the two groups (Table 1).

During a mean follow-up of 7.5 years representing 55 539 person-years, 760 cases of dementia were diagnosed. Among these, 304 died during the course of follow-up. The average period between diagnosis of dementia and death was 4.96 years ( $\pm 2.26$ ). We recorded 1962 deaths during the study. An association between the OH status and death was observed ( $p<0.0001$ ) (Annex 2). OH was associated with an increased risk of about 20% of incident dementia for conventional and mild OH thresholds (Table 2). This association appeared stronger using the severe OH threshold with an increased risk of incident dementia of 54% and 57% in the univariate and multivariate analyses respectively. Most of these associations were found to be statistically significant.

In the sensitive analysis using the illness-death model the relative risks of developing dementia were of the same order of magnitude as in the Cox proportional hazard model (Table 2), regardless of the definition of OH.

In our second analysis, according dementia etiology (Alzheimer or Vascular), we noted 512 incident Alzheimer cases and 151 incident vascular dementia represented 87% of the overall incident dementia. The cox regression analysis after adjustment didn't show a significant association between OH and Alzheimer disease (HR=1.19, 95%CI: 0.91-1.57,  $p=0.212$ ) and between OH and vascular dementia (HR=1.42; 95%CI: 0.92-2.15,  $p=0.111$ ) respectively.

## **DISCUSSION**

In the Three-City study, OH at baseline was associated with an increased risk of incident dementia during the 12 years of follow-up. This association is not explained by the initial differences in the distribution of risk factors of dementia, as no significant differences were observed between the populations with and without OH, in terms of cognitive state ( $p=0.42$ ), depression score ( $p=0.10$ ), education level ( $p=0.90$ ), and ApoE4+ status ( $p=0.31$ ).

Atrial fibrillation (AF) is another factor which has been described as associated to dementia<sup>155</sup>. However, in our study sample, if we noticed a slightly significant higher frequency of AF in subject with OH (3.46% vs 2.30%;  $p=0.0372$ ), AF was not associated to incident dementia (HR=1.18; CI 95% (0.71-1.895);  $p=0.503$ ).

Furthermore, the higher the prominence of OH, the stronger the association, with an increased risk of dementia of 50% observed for severe OH. Similar results were found in the sensitivity analysis with a dedicated method<sup>153</sup> which reinforces the strength of the association.

Blood pressure drop in standing position is a marker of autonomic dysfunction and may lead to increased BP variability. Blood pressure variability has been studied through several markers: visit-to-visit variability, variability over 24H, and home blood pressure variability. The association of all of these markers with the increased incidence of cardiovascular events has been proven<sup>156</sup>. To date, visit-to-visit variability is the only marker able to predict incident dementia as a long-term marker of variability<sup>27</sup>. OH, which is a short-term marker of variability, offers additional evidence of the link between blood pressure variability and dementia.

This work thus provides new insight on the relationship between blood pressure and dementia. In mid-life adults, high blood pressure is associated with an increased risk of dementia<sup>53-55</sup>. High blood pressure and different cardiovascular risk factors result in accelerated vascular aging, structurally modifying both large and small arteries. Regarding the large arteries (the aorta in particular), the wall loses its elastic properties and grows stiffer. This arterial stiffness is accompanied by poorer blood pressure regulation, with an increase in blood pressure variability and prevalence of OH<sup>157</sup>. In elderly individuals, we have now evidences<sup>27</sup> that it is the blood pressure variability not the blood pressure level which is associated with increased risk of dementia, leading to blood pressure surges accompanied by impaired cerebral microcirculation, most likely responsible for repeated episodes of ischemia.

However, contrary to other markers of blood pressure variability, OH has many causes. OH can be related to an insufficiency of the central regulation system of blood pressure as is the case for neurodegenerative diseases<sup>158</sup> (in particular, Parkinson's disease and diabetes) or to an inadequacy of the peripheral baroreceptors as is the case for vascular aging. Given this complexity, it is difficult to identify if OH is a pure marker of vascular aging or if it is an early marker of an ongoing neurodegenerative dementia process. Despite that OH is not more strongly associated to vascular dementia than Alzheimer disease in our second analysis, OH as a vascular ageing marker lead appears to be the most likely for several reasons. First, in our cohort, subjects with OH are significantly older ( $p < 0.0001$ ), hypertensive ( $p < 0.0001$ ) and have a greater proportion of cardiovascular events ( $p = 0.0250$ ) than those without OH (Table 1). So, this population with OH has a higher cardiovascular risk than those without.

Furthermore, as afore mentioned, many studies have shown that OH is a risk factor of cardiovascular events (coronary artery disease, heart failure and stroke)<sup>113, 159</sup>. Otherwise, and subjects in the 3C centers are screened during each visit to allow early diagnosis of dementia. Therefore, the possibility that OH remains over the years as the only sign of an on-going dementia process is quite unlikely. Moreover, OH of central origin is generally associated with other dysautonomic signs such as abnormal heart rate regulation. However, in our study we did not observe any association between heart rate variability (defined as the difference between lying and standing heart rate) and incident dementia (RR=1.00; 95%CI (0.990-1.008; p=0.783). Finally, diabetes mellitus is a frequent cause of dysautonomia and OH. However, in our study, there is no significant difference of diabetes distribution according to OH status (p=0.1060) (Table 1).

### **Limitations**

About 20% of the population did not have their blood pressure measured in standing position. This group does not have the same characteristics as the study sample (Table 1); in particular, the former is significantly older with a higher cardiovascular risk, thus with increased risk of dementia and OH. The reasons why some subjects in the study did not have their blood pressure measured in standing position have not been specified in the database but the proportion of missing data is somewhat similar in each of the three cities. This suggests that the reasons behind the lack of blood pressure measurements in standing position by investigators were similar and associated with the condition of patients (subject tiredness and clinical weakness appear evident here).

Our study incorporated a unique way of measuring orthostatism, which did not follow the general consensus on repeating the orthostatism measurements over 3 minutes, which in turn, undeniably reduced the initial prevalence recorded in our study. Moreover, symptoms induced by OH were not collected at the start of the study. Indeed, symptomatic OH reflects the reality of cerebral hypoperfusion and could be better correlated to the clinical outcome. However, recent data suggest that symptomatic hypotension makes up less than 10% of OH and does not have a stronger association with occurrence of cardiovascular event than asymptomatic OH<sup>93</sup>.

These limitations could partially explain the relatively weak prevalence of OH of about 13% compared to other studies. However, this does not question the strength of the

association between OH and dementia, which is probably underestimated as a result of these limitations.

An important limitation of the current results is the lack of representativeness of the 3C sample. As the participation rate was about 37%<sup>139</sup>, our sample was therefore not representative of the general population and the association observed might not be true in the general population.

### **Conclusion and perspectives**

Orthostatic hypotension, a simple marker of blood pressure variability is associated with an increased risk of developing dementia of about at least 25%. Thus, it could help to identify subjects with high risk of dementia.

Moreover, it raises the question of the need to take into account blood pressure variability and in particular OH among subjects with high risk of dementia and to test if reducing OH could reduce the incidence of dementia.

**Disclosures:** None

### **Novelty and significance:**

What is new?

- Orthostatic hypotension is strongly associated with incident dementia.
- This work highlights the particular relationship between blood pressure and brain ageing according the age of the subject.

What is relevant?

- Two different statistical methods and different OH thresholds were used in a large cohort of subject with an important follow-up and therefore confirmed the strength of the association.
- OH is a very common situation, in particular in old subject, and thus could help to identify subjects with a high risk of dementia



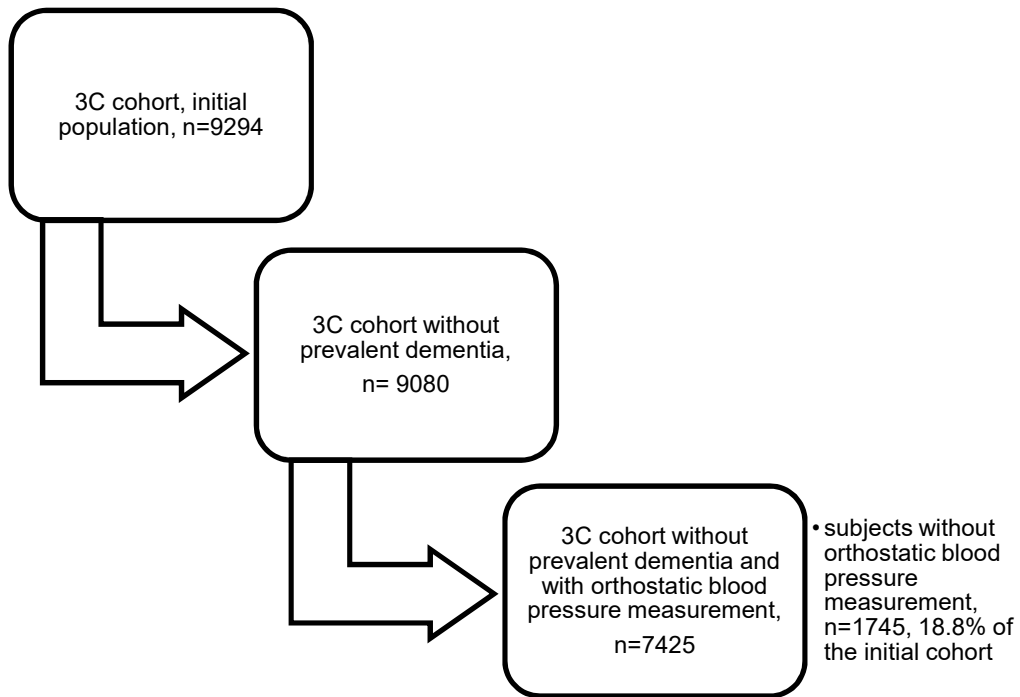


Figure 4 : Flow chart

**Table 1:** Comparison of the 3C subjects according their OH status at baseline, n=7425

Variables	N	Subjects without OH (n=6447)	Subjects with OH (n=978)	P value
<b>Age (m et SD)</b>	7425	73.39 ( $\pm$ 4.9)	74.27 ( $\pm$ 5)	<0.0001
<b>Sex (%M)</b>	7425	39.46	42.84	0.0440
<b>BMI (m et SD)</b>	7414	25.74 ( $\pm$ 4)	25.32 ( $\pm$ 4)	0.0023
<b>SBP (m et SD)</b>	7425	140.00 ( $\pm$ 20)	150.00 ( $\pm$ 22)	<0.0001
<b>DBP (m et SD)</b>	7425	80.00 ( $\pm$ 10)	85.00 ( $\pm$ 13)	<0.0001
<b>HR (m et SD)</b>	7410	67.00 ( $\pm$ 10)	67.50 ( $\pm$ 11)	0.3850
<b>Cardiovascularhistory (%)</b>	7424	8.56	10.73	0.0250
<b>Diabetesmellitus (%)</b>	7391	7.40	8.80	0.1060
<b>Hypertension (%)</b>	7378	39.70	47.44	<0.0001
<b>Active smoker (%)</b>	7379	35.53	32.82	0.1050
<b>Dyslipidemia (%)</b>	7315	33.45	39.33	0.0650
<b>Psychotropicmedication (%)</b>	7425	25.56	26.07	0.7300
<b>Hypotensive medication (%)</b>	7425	48.14	59.30	<0.0001
<b>ApoE4 (%)</b>	7234	20.32	21.72	0.3166
<b>Cognitive status (%)</b>	7341	4.69	4.11	0.4210
<b>Depression (%)</b>	7396	13.02	14.92	0.1040
<b>Education (%)</b>	7412	24/36/20/20	24/35/22/19	0.9015

% : proportion ; **M** : male ; **Age** : in years ; **m** : mean ; **SD** : standard deviation ; **BMI** : body mass index ; **SBP** : systolic blood pressure in mm of mercury ; **DBP** : diastolic blood pressure in mm of mercury ; **HR**: heart rate per minute ; **Cardiovascular history**: acute coronary syndrome, myocardial revascularization and stroke; **Diabetic status** was defined by a level of fasting blood glucose greater than 7mmol/l or the intake of anti-diabetic treatment (oral treatment or insulin), **Dyslipidemia** was defined by a cholesterol level greater than 5.2mmol/l or a hypolipidemic treatment ; **Depression** was defined by a CESD score of >16 for men and >23 for women

**Table 2:** Results from the univariate and multivariate analyses of the risk of incident dementia at 12 years of follow-up. **Cox analysis compared to Illness-Death model** of the 3C cohort, n=7425.

Variable of interest		Model 1 (n=7129)			Model2 (n=6773)		
		HR	CI95%	p-value	HR	CI95%	p-value
<b>OH</b> (*:n=117)	Cox	1.19	0.98-1.46	0.0783	1.23	1.01-1.51	0.0457
	ID-model	1.26	1.03-1.53	0.0244	1.24	1.02;1.52	0.0412
<b>Mild OH</b> (*:n=278)	Cox	1.20	1.04-1.40	0.0149	1.23	1.05-1.43	0.0086
	ID-model	1.23	1.06-1.43	0.0074	1.23	1.05;1.43	0.0086
<b>Severe OH</b> (*:n=46)	Cox	1.54	1.15-2.08	0.0043	1.57	1.15-2.14	0.0043
	ID-model	1.51	1.11-2.04	0.0077	1.51	1.12;2.04	0.0077

**For Cox analysis: Model 1:** adjusted for center; **Model 2:** adjusted for center, diabetes mellitus, cardiovascular history, hypertension, APOE4+ status, education, depression, cognitive status; **For Illness- Death Model (ID-model): Model 1 :** transition 0-1 (baseline to dementia) adjusted for center; transition 0-2 (baseline to death) adjusted for sex and center ; **Model 2 :** transition 0-1 adjusted for center, diabetes mellitus, cardiovascular history, hypertension, APOE4+ status, education, depression, cognitive status)

**OH:** drop of more than 20 mm Hg for SBP or more than 10 mm Hg for DBP; **mild OH:** drop of more than 10 mm Hg for SBP or more than 5 mm Hg for DBP; **severe OH:** drop of more than 30 mm Hg for SBP or more than 15 mm Hg for DBP

\*: incident dementia with OH

**Table S1:** Comparison of subjects according to orthostatic blood pressure measure in 3C cohort, n=9294.

Variables	Subjects with orthostatic blood pressure measure (n=7425)		Subjects without orthostatic blood pressure measure (n=1745)		p-value
	N		N		
<b>Sex (% M)</b>	7425	39.91	1745	35.76	0.0016
<b>Age (m et SD)</b>	7425	73.51 ( $\pm$ 4.9)	1745	77.50 ( $\pm$ 5.3)	<.0001
<b>BMI (m et SD)</b>	7414	25.69 ( $\pm$ 4)	1646	25.54 ( $\pm$ 4)	0.3040
<b>SBP (m et SD)</b>	7425	146 ( $\pm$ 21)	1719	151( $\pm$ 22)	<0.0001
<b>DBP (m et SD)</b>	7425	82 ( $\pm$ 12)	1719	82 ( $\pm$ 12)	0.2730
<b>Cardiovascular history (%)</b>	7424	8.85	1726	12.07	<.0001
<b>Hypertension (%)</b>	7378	40.99	1731	45.68	0.0005
<b>Hypotensive medication (%)</b>	7425	49.62	1745	57.70	0.0402
<b>Diabetes Mellitus (%)</b>	7391	7.64	1719	9.51	0.0116
<b>Dyslipidemia (%)</b>	7315	33.45	1731	39.33	0.0650
<b>Psychotropic medication (%)</b>	7425	25.63	1722	33.47	<.0001

% : proportion ; **M** : male ; **Age** : in years ; m : mean ; **SD** : standard deviation ; **BMI** : body mass index ; **SBP** : systolic blood pressure in mm of mercury ; **DBP** : diastolic blood pressure in mm of mercury ; Diabetic status was defined by a level of fasting blood glucose greater than 7mmol/l or the intake of anti-diabetic treatment (oral treatment or insulin), considered dyslipidemic if their total cholesterol level greater than 2g/l or if they had a hypolipidemic treatment

## 4.2 DISCUSSION

### 4.2.1 REVUE DE LA LITTÉRATURE DEPUIS LA PUBLICATION DE L'ARTICLE

- Une dynamique de recherche collective

En effet, 4 études ont été publiées en l'espace de 2 ans avec des résultats qui confirment les nôtres. 2 d'entre elles concernent une population âgée proche de notre étude. Les 2 autres s'intéressent à une population plus jeune et apportent donc un éclairage différent sur la chronologie des évènements.

Ainsi, 6204 sujets de 68 ans en moyenne de la cohorte de Rotterdam furent suivis pendant 15 ans en moyenne. 1176 sujets ont développé une démence. L'HO définie selon les seuils consensuels montre un sur-risque de démence de l'ordre de 15%<sup>160</sup>.

3121 sujets de 84 ans en moyenne de l'étude HYVET furent suivis pendant 2 ans<sup>161</sup>. 538 présentaient une HO soit une prévalence de l'ordre de 17%. Le seuil diagnostique n'était pas consensuel. Le diagnostic était posé pour une chute de PAS de 15 mm Hg et de 7 mm Hg pour la diastolique. 241 démences furent diagnostiquées. La présence d'une HO augmente le risque de démence de l'ordre de 34%.

Dans la cohorte de Malmö, 18240 sujets âgés en moyenne de 45 ans<sup>162</sup> sont suivis sur 23 ans, 428 cas de démence furent diagnostiqués. Ils montrent que le risque de démence augmente de 22% pour chaque chute de 10 mm Hg de PA diastolique. Aucune relation n'a été mise en évidence pour la PA systolique.

Enfin dernièrement, dans l'étude ARIC, 11709 sujets âgés en moyenne de 54.5 ans ont été suivis pendant 25 ans<sup>115</sup>. 1068 démences furent diagnostiquées. Il a été montré un sur-risque de 54% de développer une démence chez les sujets avec HO à l'inclusion.

**L'ensemble de ces travaux confirment l'association que nous avons décrite** dans la cohorte des 3C et ont été synthétisés dans une méta-analyse qui montre une augmentation du risque relatif de démence de 22% chez les sujets avec HO<sup>163</sup>. L'étude des 3C et l'étude de Rotterdam sont deux cohortes assez proches en termes d'échantillons de population, d'âge et de suivi. Ces deux études retrouvent le même ordre de grandeur de sur-risque de démence (15% pour Rotterdam et 25% pour 3C). D'autre part, un « effet dose » est décrit dans la cohorte de Rotterdam avec une majoration du risque de démence pour des baisses de PA plus importantes. Nous avons également retrouvé des associations différentes selon les seuils choisis même si nous ne l'avons pas publié dans l'article. Ainsi de manière intéressante, nous

avons pu montrer que si la baisse de PA était supérieure à 30 mm Hg pour la PA systolique et supérieure à 15 mm Hg pour la PA diastolique, l'HO était associée à la démence d'Alzheimer quand pour les baisses de l'ordre de 10mmHg pour la PA systolique et 5mmHg pour la PA diastolique, c'était la démence vasculaire qui était associée à l'HO (Tableau 3). Cela évoque d'un côté une « HO vasculaire » surtout témoin d'un vieillissement vasculaire et de l'autre une « HO centrale » surtout témoin d'un défaut de la commande centrale dans la régulation de la PA.

Tableau 3 : Résultats de l'analyse multivarié de Cox du risque incidents de démence de suivi à 12 ans selon l'étiologie de la démence et le seuil d'hypotension orthostatique : n=7425.

	Modèle 1 avec HO légère				Modèle 1 avec HO sévère			
	cas	RR	IC à 95%	p-value	cas	RR	IC à 95%	p-value
<b>démence Alzheimer (n=512)</b>	74	1.217	(0.951-1.557)	0.1185	31	1.706	1.186-2.453	0.0040
<b>démence Vasculaire (n=151)</b>	27	1.559	1.028-2.365	0.0366	8	1.475	0.723-3.006	0.2853

**HO légère** : pour chute de PA systolique > 10 mm hg ou chute de PA diastolique > 5 mm hg ;

**HO sévère** : pour chute de PA systolique > 30 mm hg ou chute de PA diastolique > 15 mm hg

#### 4.2.2 L'HO EST ASSOCIEE A LA DEMENCE COMME LES AUTRES MARQUEURS DE VARIABILITE

La variabilité tensionnelle quelle que soit la manière dont elle est mesurée semble donc être associée aux cas incidents de démence.

C'est vrai pour l'HO comme pour la variabilité tensionnelle en inter-visite<sup>27</sup> ou en auto-mesure<sup>33</sup> qui sont donc 3 temporalités différentes de variabilités de la PA.

Jusqu'à présent, on associait le niveau de PA moyen à la démence<sup>53</sup> dans la première moitié de vie, tandis que chez le sujet âgé, cette association disparaît et c'est la variabilité tensionnelle qui devient le marqueur de risque.

Cette vision vasculaire d'un processus long qui prend en compte les modifications structurelles des vaisseaux induites d'abord par la PA moyenne favorisant par la suite la variabilité tensionnelle est remise en cause par des études américaines et suédoise

en population jeune. Dans la cohorte de Malmö, avec une population de 45 ans d'âge moyen, c'est en effet la baisse de PA diastolique qui est associée au risque cognitif indépendamment du niveau de PA. Comme si, on retrouvait là des schémas que l'on connaît aussi pour l'HTA à savoir un niveau de PA diastolique plus associé au risque chez le sujet jeune et un niveau de PA systolique plus associé au risque chez le sujet âgé<sup>164</sup>.

Ces études montrent aussi que la variabilité tensionnelle (mesurée ici par l'HO) est un paramètre présent à des âges jeunes indépendamment de la PA moyenne. Un autre travail récent montre également que la variabilité inter-visite présente chez des adultes jeunes de 35 ans en moyenne est associée à un sur-risque relatif cette fois de mortalité de 25% indépendamment du niveau de PA moyenne<sup>165</sup>.

Ces résultats confirment que la variabilité tensionnelle et l'HO sont présents très tôt dans la vie et donc sans doute avant l'apparition d'une rigidité artérielle marquée remettant en cause l'histoire du continuum vasculaire depuis l'élévation de la PA puis l'apparition de la variabilité tensionnelle médiée par la rigidité artérielle.

#### 4.2.3 SYNTHÈSE HYPOTENSION ORTHOSTATIQUE ET DÉMENCE :

**L'HO est donc un marqueur de variabilité tensionnelle qui est associée à un sur-risque de démence de l'ordre de 25%. Elle rejoint de ce point de vue les autres marqueurs de variabilité.**

Cependant, le fait que des seuils différents orientent vers des mécanismes de démences différents (vasculaire vs Alzheimer) interroge sur les déterminants de l'HO. Cette double étiologie de démence qui connaît une physiopathologie différente laisse entendre une double composante de l'HO : une composante mécanique vasculaire et une composante neurologique. Ces deux composants n'ont pas été étudiés jusqu'à présent.

## 5 DETERMINANTS DE L'HYPOTENSION ORTHOSTATIQUE :

### 5.1 PRESENTATION DE L'ARTICLE :

Le baroréflexe est décrit jusqu'à présent comme le principal déterminant de l'HO<sup>83</sup>. Le baroréflexe est une structure particulièrement complexe avec une composante vasculaire (les barorécepteurs) et une composante neurologique (périphérique et centrale). Brièvement, les barorécepteurs sont des structures internes dans la paroi des vaisseaux, qui sont sensibles à l'état de distension de la paroi artérielle qui dépend directement de la pression résidant dans les artères. L'emplacement de ces barorécepteurs est stratégique puisqu'ils sont situés juste à la sortie du cœur au niveau de l'aorte et sur les artères carotides. Ainsi, les barorécepteurs reçoivent et transmettent des informations du niveau de PA pour les organes cibles fondamentaux : le cerveau et le cœur via les voies nerveuses afférentes et efférentes. Le baroréflexe a donc une double composante : vasculaire (les barorécepteurs) et neurologique (périphériques et centraux). Cette distinction est proposée pour classer les HO selon leur origine : neurogène ou non-neurogène. D'après ce point de vu, le baroréflexe est donc l'unique déterminant de l'HO.

Cependant, la rigidité artérielle est un autre paramètre hémodynamique qui revient régulièrement lors de l'étude de l'HO<sup>90</sup> et qui pourrait expliquer une partie du sur-risque cardiovasculaire. Dans l'hypothèse où l'HO est un marqueur semblable aux autres marqueurs de variabilité tensionnelle, la rigidité artérielle devrait être un déterminant commun.

Ce sont ces observations qui ont amené à s'intéresser à **une étude plus mécanistique** à travers l'étude des relations entre l'HO et un marqueur de la rigidité artérielle (la vitesse d'onde de pouls carotido-fémoral) ainsi qu'un marqueur de la variabilité tensionnelle (variabilité tensionnelle de moyen terme).

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Il s'agit d'une revue de rang B, l'impact factor des 5 dernières années est de 4.43.



## ***Orthostatic Hypotension:***

### ***A marker of Blood Pressure Variability and Arterial Stiffness***

#### ***A cross-sectional study on an elderly population: the 3-City study***

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**Abstract:** Orthostatic hypotension (OH), blood pressure variability, and arterial stiffness are three markers of cardiovascular risk beyond the average blood pressure. However, the relationships between these three parameters are not well known. **Aim:** To examine the relationships between orthostatic hypotension, blood pressure variability, and arterial stiffness. **Methods and results:** In the 3-City study, a sample of 1151 elderly participants (mean age =80±3 years) was screened for OH, undertook a home blood pressure and pulse wave velocity measurements. We performed logistic regression analyses to look at the associations between OH and both day-to-day blood pressure variability quartiles and pulse wave velocity quartiles. OH was detected in 210 subjects who were more likely to be hypertensive, exhibit higher blood pressure variability and have increased arterial stiffness. In the multivariate logistic regression analysis, the frequency of OH increased by 20% with every quartile of day-to-day systolic blood pressure variability and by 20% with every quartile of pulse wave velocity. Pulse wave velocity and day-to-day blood pressure variability were not associated. In stratified analysis, the use of beta-blocker changes these relationships : OH was not associated to pulse wave velocity anymore but its association with day-to-day systolic blood pressure variability was apparently stronger. **Conclusion:** In this large sample of elderly individuals, OH was independently associated with both blood pressure variability and pulse wave velocity. Blood pressure variability being more indicative of a baroreflex dysfunction and pulse wave velocity being a marker of vascular ageing, these two components would participate to the OH mechanisms.

**Keywords:** orthostatic hypotension, blood pressure variability, arterial stiffness, baroreflex impairment, beta-blocker

Orthostatic hypotension (OH) defined as a drop in blood pressure (BP) on standing up, is associated with increased risk of mortality<sup>105, 110</sup>, occurrence of cardiovascular events<sup>113</sup> and dementia<sup>115, 160, 166</sup> in the general population. Day-to-day (D-to-D) BP variability shares the same kind of risk for cardiovascular diseases<sup>31, 32</sup> and dementia<sup>33</sup>. Moreover, OH and D-to-D BP variability seem to have a common physiopathology via the baroreflex function<sup>167, 168</sup>. Thus, an association has been found between OH and D-to-D BP variability which reinforces its physiopathology hypothesis<sup>169</sup>.

Arterial stiffness has also proven its association with cardiovascular disease<sup>170, 171</sup> and cognitive decline<sup>172</sup>. Vascular ageing decreases arterial elasticity and could possibly decrease the carotid baroreceptor sensitivity to BP changes<sup>173</sup>. Indeed arterial stiffness and baroreflex sensitivity have demonstrated their association in different populations<sup>89, 174</sup> as well as arterial stiffness with short-term BP variability<sup>52</sup>. However, this explanation is not fully convincing. The baroreceptors are reset every minute to allow a quick adaptation of BP<sup>175</sup> which contrasts with a very stable parameter which is arterial stiffness. Moreover, it has been suggested recently, that the link from arterial stiffness to OH may be due to a loss of the cushioning effect of the ascending aorta and to an early return of pressure waves<sup>176</sup>.

In the 3-City study, a study from the French general population, a sample from the Dijon study was screened for OH and also undertook home blood pressure and pulse wave velocity (PWV) measurements.

This population sample give us a unique opportunity to determine the relationships between OH, BP variability and arterial stiffness in a cross-sectional study to clarify the relationship between three major markers of cardiovascular risk.

## **Materials and Methods:**

### *Study Population:*

The 3-City study is a study from the French general population, comprising 9294 individuals, over the age of 65 years, randomly selected from the electoral lists of Bordeaux, Dijon, and Montpellier, recruited between 1999 and 2001<sup>139</sup>.

Around visit 5 (10 years after inclusion in the study) subjects from the Dijon centre were invited to beneficiate from several additional measurements, including pulse wave velocity assessment and home BP measurements. These two sets of analyses were carried out at different times than visit 5 but within the same year.

### Measurement of BP and Heart Rate in sitting and standing position

At visit 5, BP measurements were performed on the subjects from the Dijon centre according to the following protocol: first; subjects were in sitting position, and left to rest in this position for 5 minutes, with a cuff placed on the right arm, adjusted to the arm circumference. The cuff was connected to an Omron M4 (Kyoto, Japan), an oscillometric validated automatic BP device and 3 consecutive BP measurements were taken. The mean value of the last two BP measurements was retained for the analysis. For each BP measurement, heart rate was measured by the automatic pressure device in sitting position and averaged.

OH was then detected according to guidelines<sup>67</sup>. BP was measured at 1, 2 and 3 min after standing up. OH was defined as a drop of systolic BP greater than 20mmHg or a drop in diastolic BP greater than 10mmHg between sitting and standing BP after 1, 2 or 3 minutes of standing<sup>67</sup>. Heart rate was measured for each series of BP measurements at 1, 2 and 3 minutes after standing up.

### Home blood pressure measurement protocol and day-to-day blood pressure variability

The participants of Dijon were invited in a nested interventional study investigating the role of home BP measurement on dementia<sup>177</sup>. The home BP measurement was performed with the same device following the recommendations of the French Hypertension Society with 3 measurements in the morning before taking any treatment and 3 measurements in the evening after dinner over 3 consecutive days thus producing 18 measurements used for calculation of mean home BP. Day-to-day (D-to-D) BP variability was estimated by the standard deviation (SD) and coefficient of variation (CV) for systolic and diastolic BP based on the 18 BP measurements. SD and CV are the two established approaches and are the most suitable for studying D-to-D BP variability<sup>156</sup>. Quartiles of D-to-D BP variability were used in the main analysis.

### Pulse wave velocity measurements:

Carotid-femoral PWV measurements were performed on subjects from the Dijon centre. After measuring the brachial BP following the same method as at follow-up 5, the distance  $d$  between the two tonometric sites (carotid and femoral) relative to the sternal notch was measured using a tape measure. The carotid and femoral pressure waves were then detected using tonometry. It is thus possible to measure the time delay  $dt$  between these two recordings. The speed at which the pressure wave travels from the carotid to the femoral artery is therefore equal to  $0.8 \times d/dt$  and is estimated in

m/sec<sup>178, 179</sup>. The measurements were performed with the SphygmoCor® tonometer (AtCor Medical, Sydney, Australia). Quartiles of PWV were used for the analysis.

#### Factors associated with the occurrence of OH:

Age: Despite subjects were seen at three different times during the various BP measurements protocols but within the same year, the age at visit 5 was used for the statistical analysis.

Hypotensive treatment: Use of hypotensive treatment for indicated arterial hypertension and other cardiovascular indications (coronary artery disease, arrhythmias, and heart failure.)

Beta-blockers: including the use of acebutolol, bisoprolol, atenolol, celiprolol, nebivolol, propranolol, sotalol or metoprolol.

Hypertensive status is defined by systolic BP > 140 mmHg or diastolic BP > 90mmHg or the use of anti-hypertensive treatment at the time of consultation during visit 5.

Diabetic status was defined by a level of fasting blood glucose greater than 7mmol/l or the use of anti-diabetic treatment at visit 5.

History of stroke (ischemic or haemorrhagic), myocardial infarction and heart failure were reported during the visit-5 interview.

#### Other factors:

Dyslipidaemia was defined by the use of hypolipidemic treatment or by total cholesterol level > 5.2 mmol/l at visit 5.

The status of an active smoker was defined by active smoking or having quit smoking for less than 6 months at the time of visit 5.

#### Statistical Analyses:

The analysis was carried out on the population sample who had BP measurements in standing position, home BP and PWV measurements. The sample was described by OH status according to the consensus definition, using the chi-square test for the qualitative variables and the student test for the quantitative variables. Continuous variables were presented by mean value with its standard deviation. They were tested for normality. Qualitative variables were presented by a proportion.

Logistic regressions analyses were used to explain the occurrence of OH as it seems more illustrative to apprehend these variables in quartiles. Log-linearity was tested for both d-to-d BP variability and PWV.

We first looked at the univariate analysis with both D-to-D BP variability quartiles and PWV quartiles. We then performed multivariate regression analyses using the backward stepwise technique. We thus included all the variables associated with OH in the initial model. The variables not statistically associated with OH were then removed one at a time, starting with the variable with the largest p-value. We repeated this procedure until all the remaining variables retained in the model were associated with OH with a significance threshold  $p < 0.05$ .

Two multivariate models were therefore constructed to capture the maximum of information linked to the BP and hypertensive status and to avoid over correlation with D-to-D BP variability and PWV.

**Model 1** is based on mean home systolic BP (which is assumed to be the most associated with cardiovascular prognosis compare to office BP) and the use of hypotensive treatment.

**Model 2** is based on hypertensive status at visit 5 which also takes into account BP during the consultation and the use of hypotensive treatment.

We investigated interactions among the principal variables, particularly between D-to-D BP variability, PWV, and sex.

We then plot through a 3D bar graph of the relations between the systolic SD quartile, the PWV quartile, and the OH proportion.

In a secondary analysis, we stratified the main analysis according to the presence of a beta-blocker to explore further the role of the baroreflex loop and its association with the D-to-D BP variability and PWV.

Finally, we explored the association between D-to-D BP variability and PWV quartiles via a logistic regression analysis according to the same methodology of the main analysis. Logistic regression was chosen for being close to the main analysis but linear regression with continuous variables showed the same results.

We performed analyses with SAS 9.4 (California, USA) and Excel 2010 (Microsoft, USA). The threshold of significance  $p < 0.05$  was used.

## Results:

Out of the 4920 subjects included in the baseline Dijon study, 2283 showed up for visit 5, 1733 followed the home BP measurement protocol and 1561 had measurements of PWV. The entire series of blood pressure and hemodynamic measurements were performed on 1151 subjects in total.

The sample comprises elderly people (mean age =  $80 \pm 3$  years) and is predominantly female (60%). Included subjects were comparable with non-included subjects except for age, (80.06 vs 81.40 years,  $p < 0.0001$ ).

Using the consensus definition<sup>67</sup>, OH was detected in 210 subjects, representing 18% of the sample. During the BP measurements in standing position, from the first set of measurements, 81% of the total subjects were diagnosed with OH ( $n=146/210$ ). It is during this first measurement that we observed the greatest drop in systolic BP (-21.75mmHg vs 13.91mmHg in the following measurement). The systolic BP values, regardless of the method and time of measurement (office during visit 5, during PWV measurement or home BP measurement) are all significantly associated with OH. This is not the case for diastolic BP (Table 4) apart from the initial measurement taken just prior to standing up at visit 5. Subjects with OH were more likely to be hypertensive ( $p = 0.013$ ), have increased arterial stiffness (PWV: 15.5 vs 14.5 m/s  $p < 0.0001$ ) and exhibit higher D-to-D BP variability (systolic SD: 11.84 vs 10.85 mmHg ( $p=0.001$ )) (Table 4). Only 119 subjects of the whole study showed an HR decrease in response to orthostatism with no statistical difference according to OH status.

Among the other factors usually associated with OH, only the use of hypotensive drugs was associated with OH and in particular the use of a beta-blocker ( $p=0.039$ ). Subjects under beta-blocker are more likely diabetic ( $p=0.002$ ) and associated with heart failure ( $p < 0.0001$ ) (Annex 3).

In the multivariate logistic regression analysis, the prevalence of OH increased by 20% with every quartile of D-to-D BP variability and by 20% with every quartile of PWV, regardless of the measurement considered (Table 5) and independently of BP level. This main result is illustrated by Figure 5 which shows that the prevalence of OH increases for each quartile of systolic SD D-to-D BP and PWV separately and the increase is steeper when both systolic SD D-to-D BP and PWV are increasing.

In the secondary analysis, the intake of beta-blocker influences the association between our variables of interest. In the subgroup with beta-blocker intake, the

association of PWV with OH disappears but the association with systolic SD D-to-D BP is stronger. In the absence of a beta-blocker, we observed the opposite (Table 6). These results are not explained by the different prevalence of diabetes mellitus or heart failure between these two subgroups. Indeed these two variables are not associated with OH in each of the subgroups (with or without beta-blocker) and do not change the results of the multivariate analysis when they are forced into the models.

Finally, we did not find any association between PWV and systolic SD D-to-D BP (Annex 4).

### **Discussion:**

The main finding of this study is that OH is associated with both systolic D-to-D BP variability and PWV in a large elderly population-based sample.

The sample is rather homogenous with a mean age above 80 years and presenting marked arterial stiffness (mean PWV=14.71±3.25) as expected. The responses of HR to the standing position show a large majority of acceleration of the HR (90% of the sample). In essence, this population is in good health without major cardiovascular comorbidities or neurodegenerative disorders. Thus, OH characteristics are consistent with idiopathic OH<sup>180</sup>. The causes of these types of OH are unknown and vascular ageing is the likely hypothesis. It may, therefore, be surprising to find no association between age and OH. However, this is explained by the very homogenous age distribution as subjects are 80 ±3 years old, which masks the effect of age.

In our main analysis, OH was independently associated to both PWV and D-to-D BP variability. These two parameters have already been described as being associated with OH but have never been studied simultaneously. The results from this analysis help to better understand the relationships between these different hemodynamic markers. Indeed in our models, OH is associated with both D-to-D BP variability and PWV but PWV is not associated with D-to-D BP variability (Annex 4). D-to-D BP variability and PWV, therefore, do not measure the same phenomenon and OH is associated with both.

In the case of stiff arteries, the early return of the pressure waves to the heart and the loss of compliance of the aorta during diastole may contribute to the drop in blood pressure. This explanation has been proposed by Sung et al<sup>176</sup> based on the association they found between PWV and OH in a general population. But the hypothesis that arterial stiffness alters the quality of baroreceptors, particularly the

carotid baroreceptor, resulting in an increase in BP variability is therefore called into question<sup>181</sup>.

On standing up, the sympathetic nervous system is immediately activated, mainly by mechanoreceptors in the heart and the aorta. The latter contribute to an acceleration of the HR, an increase of myocardial inotropism and peripheral resistance to restore the initial level of BP<sup>182</sup>. Therefore, in the case of autonomic system dysfunction, we can observe large short term BP variability and OH<sup>45</sup>. Indeed, in our stratified analysis, the intake of beta-blockers by reducing the adrenergic response to the standing position induces an increase of BP variability (Table 6). This is consistent with the analysis of Coats et al which showed that a more stable HR that results from an ineffective baroreflex is associated with a more variable systolic BP<sup>183</sup>. At the opposite, in the absence of beta-blockers and with a more effective baroreflex loop, arterial stiffness is the most predominant component of OH in our study (Table 6).

This interpretation of the data is supported by several studies. First, in the Paris Prospective study III, Sharman et al showed that impaired baroreflex sensitivity but not carotid stiffness is independently associated with exaggerated exercise BP which is basically another way to measure BP variability<sup>184</sup>. The results from DENER-HTN trial showed that short-term night-time BP variability is associated with the BP response to renal denervation and therefore of the adrenergic tone<sup>185</sup>. In addition it has been shown that beta-blockers increased the risk of both OH<sup>70, 186</sup> and BP variability<sup>15, 187</sup>, thus strengthening our hypothesis. BP variability seems to be therefore a better marker of sympathetic activity than arterial stiffness.

However, the links between short term BP variability and arterial stiffness have been demonstrated in hypertensive patients (with or without treatment) previously<sup>52</sup>. But we can note some critical differences with our study. First, with a mean age of 49 years old and a larger distribution ( $\pm 11$ ), this population is much younger than our study sample (mean age 80 years old). Second, the compliance of the aorta is considered normal with a mean PWV value around 9.3m/sec, while in our study, mean PWV is around 15m/sec which indicates very stiff arteries (even if these values are expected in such range of age<sup>188</sup>). Moreover, authors admitted that contribution of BP variability to aortic stiffness was of limited size and that mechanisms which linked one to the other were unsolved. We could assume that this association has been found because they both provide evidence for global individual ageing with parallel trajectories<sup>189</sup>. This relation probably disappears in our elderly population because of the small age range



which gave us a unique opportunity to show this double component of the OH fully and truly adjusted over calendar age.

A potential interpretation of our results is therefore that OH would have a mechanic part (approached by arterial stiffness) and an adrenergic part (BP variability) (Fig 6).

### **Limitations:**

This study is cross-sectional with intrinsic limitations. It could help in understanding the relationships between three major markers of cardiovascular risk there is no possible cause-consequence conclusion between them.

Because, the participants of this study are volunteers from the general population, there is a potential self-participation bias. Thus, the sample is not representative of the population and the results of these analyses cannot be generalized.

The protocol for diagnosing OH is rigorous and difficult to implement in clinical practice. Indeed, after 5 minutes of rest in lying position, the subject must stand up and undertake 3 measurements at 1, 2 and 3 minutes intervals in standing position. In this study, the initial measurement is made in a sitting position. However, in clinical practice, OH is more often detected from measurements in sitting position and this is how we show the association of OH with the occurrence of dementia in this sample<sup>27</sup>. Furthermore, the medical community agrees that a single measurement in a sitting position and a single measurement in standing position are acceptable<sup>68</sup> even though the diagnostic thresholds may need to be revisited<sup>62</sup>. Based on these points, we can consider the screening of OH in this study acceptable.

The different hemodynamic parameters are measured at different times. This is particularly true for PWV which is measured, on average, 6 months after visit 5. However, although the age difference is statistically significant between visit 5 and when the PWV measurement took place, this difference is not clinically relevant (6 months) in view of the age of the subjects and the relative stability of PWV at these advanced ages<sup>190</sup>. The same applies to the series of home measurements, even if it is not possible to be 100% sure that there was no medical intervention between visit 5 and the Home BP measurement.

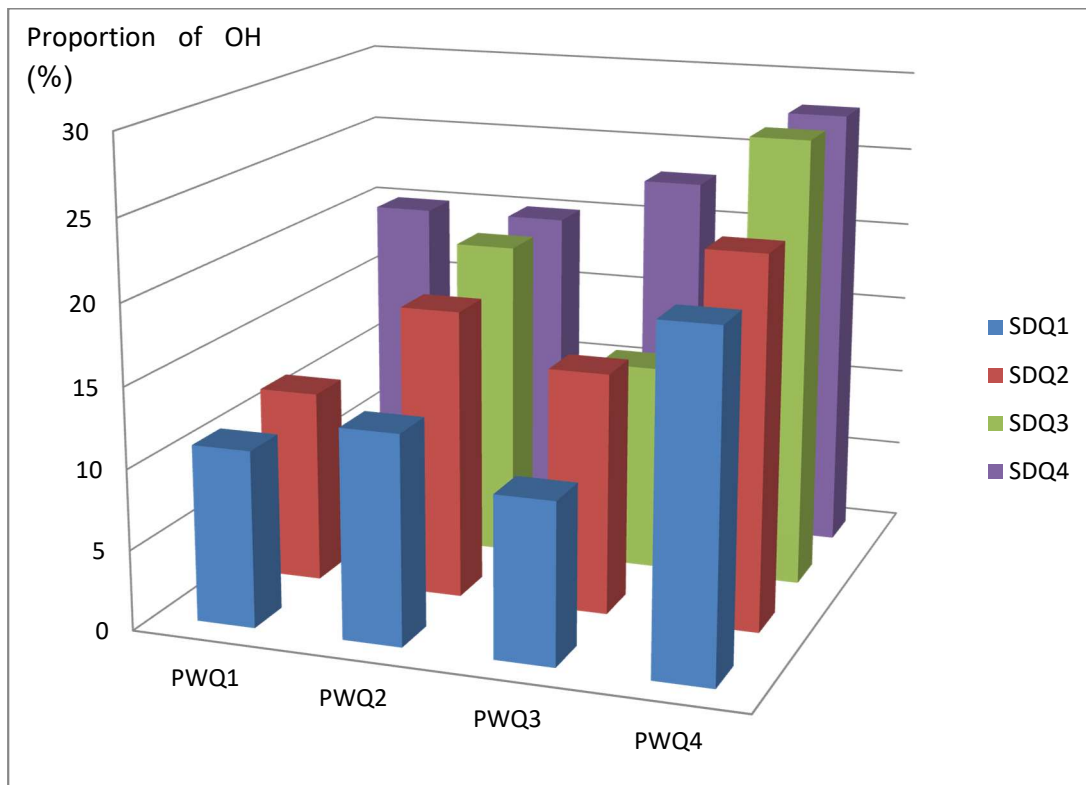
## **Conclusion**

OH is a major cardiovascular risk marker that takes into accounts two well-known cardiovascular risk factors: day-to-day blood pressure variability and arterial stiffness.

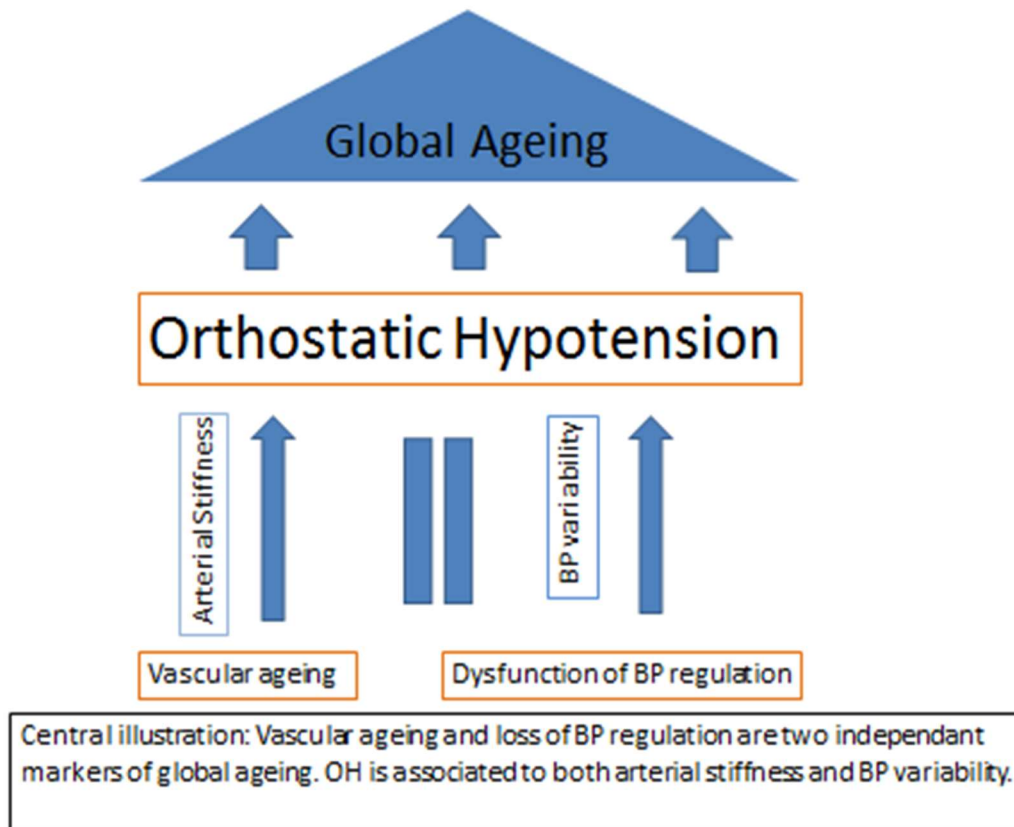
BP variability is more likely informative of a baroreflex impairment while PWV is a marker of vascular ageing which are two independent components of the OH mechanisms.

Beta-blockers are more likely to induce an OH via a less effective baroreflex which can be approached by a wider day-to-day BP variability. Therefore this class should be avoid in patients with high risk of OH.

Finally, screening for OH should be done more systematically to improve cardiovascular risk assessment.



**Figure 5 :** Proportion of OH according quartiles of PWV (PWVQ) and quartiles of systolic SD D-to-D blood pressure (SDQ)



**Figure 6:** Illustration and key message

**Table 4:** Description of the population according the occurrence of an orthostatic hypotension

	<b>N</b>	<b>OH+ (N=210)</b>	<b>OH-(N=942)</b>	<b>P-value</b>
<b>Age (SD)</b>	1151	80.28(3.79)	80.01(3.81)	0.354
<b>% Male</b>	1151	49.48	37.82	0.003
<b>BMI (SD)</b>	1151	25.87(3.68)	25.94(3.80)	0.808
<b>% Diabetes M</b>	1130	10.58	9.26	0.556
<b>%Dyslipidaemia</b>	1148	41.29	39.85	0.705
<b>% Active Smoker</b>	1150	5.71	2.87	0.178
<b>% Hypertensive</b>	1146	65.85	55.14	0.005
<b>% Stroke (n)</b>	1151	0.48 (1)	1.28 (12)	0.585
<b>% MI (n)</b>	1151	1.42 (3)	0.00 (0)	0.508
<b>% Heart Failure (n)</b>	1151	1.42 (3)	2.66 (25)	0.323
<b>% Cancer (n)</b>	1151	11.90 (25)	10.00 (94)	0.412
<b>SBP V5 (SD)</b>	1151	153.09 (18.52)	138.86 (17.64)	<0.0001
<b>DBP V5 (SD)</b>	1151	77.27 (9.82)	73.09 (9.60)	<0.0001
<b>HR V5 (SD)</b>	1037	68.04 (11.55)	69.80 (10.95)	0.043
<b>SBP-Home BP (SD)</b>	1146	144.80 (16.86)	141.00(16.52)	0.003
<b>DBP-HomeBP (SD)</b>	1146	73.70 (8.90)	73.33 (8.74)	0.800
<b>SBP-PWV (SD)</b>	1151	146.5 (18.99)	140.40 (16.53)	<0.0001
<b>DBP-PWV (SD)</b>	1151	73.19 (9.25)	72.32 (8.66)	0.200
<b>HR-PWV (SD)</b>	1151	61.46 (9.73)	62.64 (9.59)	0.110
<b>Diff-SBP1 (SD)</b>	1146	21.75 (13.18)	3.55 (10.64)	<0.0001
<b>Diff-SBP2 (SD)</b>	1142	13.91(12.06)	-1.56 (9.80)	<0.0001
<b>Diff-SBP3 (SD)</b>	1137	13.91(13.51)	-2.48 (10.20)	<0.0001
<b>Diff-DBP1 (SD)</b>	1146	3.79 (7.21)	-2.89 (6.44)	<0.0001
<b>Diff-DBP2 (SD)</b>	1142	1.19 (8.15)	-4.75 (6.39)	<0.0001
<b>Diff-DBP3 (SD)</b>	1137	-0.06 (6.67)	-4.93 (6.11)	<0.0001
<b>Diff-HR1 (SD)</b>	1035	-5.08 (5.47)	-4.53 (4.69)	0.147
<b>Diff-HR2 (SD)</b>	1031	-4.20 (5.23)	-3.87(4.33)	0.370
<b>Diff-HR3 (SD)</b>	1026	-4.98 (4.94)	-3.83 (4.39)	0.001
<b>PWV (SD)</b>	1151	15.49 (3.51)	14.53 (3.17)	0.0001

<b>SSD-D-to-D (SD)</b>	1144	11.84 (4.35)	10.85 (3.96)	0.001
<b>SCV-D-to-D (SD)</b>	1144	8.17 (2.83)	7.68 (2.62)	0.018
<b>%Hypotens-Med</b>	1151	71.90	62.27	0.008
<b>%Beta blocker (n)</b>	1151	31.90 (67)	15.19 (143)	0.039
<b>%Calcium blocker (n)</b>	1151	20.48 (43)	16.58 (156)	0.177
<b>%RAS blocker (n)</b>	1151	44.29 (93)	36.13 (340)	0.013
<b>%Diuretic (n)</b>	1151	17.62 (37)	19.55 (184)	0.519

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**SD**: standard deviation; **SBP**: systolic blood pressure; **DBP**: diastolic blood pressure; **V5**: visit-5 HR: heart rate; **Diff-SBP(1,2,3)**: difference between mean SBP in sitting position and SBP in standing position(1,2 and 3minutes); ; **Diff-SDBP(1,2,3)**: difference between mean DBP in sitting position and DBP in standing position(1,2 and 3minutes); **Diff-HR(1,2,3)**: difference between mean HR in sitting position and HR in standing position(1,2 and 3minutes; **SSD-D-to-D**:standard deviation of day-to-day SBP; **SCV-D-to-D**:coefficient of variation of day-to-day SBP; **beta blocker**: proportion of subject with beta blocker; **Hypotens-Med**: Use of hypotensive treatment for indicated arterial hypertension and other cardiovascular indications at visit 5; **Stroke**: proportion of subject with history of stroke; **MI**: proportion of subject with an history of myocardial infarction

**Table 5:** Logistic Regression of occurrence of Orthostatic Hypotension (N=210) according to day-to-day systolic BP variability and PWV in the 3-City cohort (N=1151)

	<b>SSD-D-to-D</b> per quartiles		<b>PWVSD</b> per quartiles		<b>SCV-D-to-D</b> per quartiles		<b>PWVCV</b> per quartiles	
	OR CI 95%	p- value	OR CI 95%	p- value	OR CI 95%	p- value	OR CI 95%	p- value
<b>Univariate</b>	1.203 1.048- 1.381	0.009	1.221 1.038- 1.435	0.015	1.169 1.016- 1.345	0.029	1.211 1.055- 1.389	0.006
<b>Model 1</b>	1.170 1.011- 1.354	0.034	1.208 1.021- 1.429	0.027	1.159 1.005- 1.335	0.042	1.183 1.027- 1.363	0.020
<b>Model 2</b>	1.143 0.988- 1.321	0.072	1.223 1.033- 1.447	0.019	1.220 1.050- 1.416	0.009	1.161 1.001- 1.346	0.048

Model 1: N=1133; adjusted for sex, age, home SBP measurements

Model 2: N=1112; adjusted for sex, age, hypertension status during follow-up 5

**SSD:** Systolic Standard Deviation; **SCV:** Systolic Coefficient of Variation; **PWVsd:** quartiles of PWV for the analysis with **SSD** day-to-day BP; **PWVcv:** quartiles of PWV for the analysis with **SCV** day-to-day BP

**Table 6:** Stratified logistic regression of occurrence of orthostatic hypotension (N=210) according to the intake of beta-blocker in the 3-City cohort (N=1151)

	<b>SSD-D-to-D</b> per quartiles		<b>PWVSD</b> per quartiles		<b>SCV-D-to-D</b> per quartiles		<b>PWVCV</b> per quartiles	
	OR	p-value	OR	p-value	OR	p-value	OR	p-value
	CI 95%		CI 95%		CI 95%		CI95%	
<b><i>Population <u>with</u> intake of beta-blocker (N=302, OH=67)</i></b>								
<b>Univariate</b>	1.360	0.013	1.007	0.958	1.354	0.021	1.028	0.824
	1.065- 1.736		0.768- 1.321		1.046- 1.753		0.808- 1.307	
<b>Model 1</b>	1.354	0.019	1.007	0.960	1.334	0.030	0.995	0.968
	1.052- 1.743		0.763- 1.329		1.029- 1.731		0.778- 1.272	
<b>Model 2</b>	1.313	0.05	0.921	0.604	1.318	0.051	0.941	0.663
	0.990- 1.729		0.676- 1.255		0.999- 1.754		0.716- 1.237	
<b><i>Population <u>without</u> intake of beta-blocker (N=849, OH=143)</i></b>								
<b>Univariate</b>	1.093	0.316	1.371	0.002	1.075	0.404	1.310	0.002
	0.919- 1.300		1.118- 1.681		0.907- 1.273		1.107- 1.551	
<b>Model 1</b>	1.050	0.602	1.351	0.006	1.078	0.395	1.302	0.003
	0.873- 1.265		1.090- 1.674		0.907- 1.280		1.093- 1.551	
<b>Model 2</b>	1.147	0.145	1.330	0.013	1.055	0.542	1.308	0.002
	0.954- 1.380		1.061- 1.666		0.888- 1.254		1.099- 1.558	

Model 1: adjusted for sex, age, home SBP measurements

Model 2: adjusted for sex, age, hypertension status during follow-up 5



## Annex 1: Description of the population according the beta-blocker status

	<b>N</b>	<b>With beta-blocker (N=302)</b>	<b>Without beta-blocker (N=848)</b>	<b>P-value</b>
<b>Age</b>	1151	80.68 (3.65)	79.83 (3.70)	0.001
<b>Sex (% Male)</b>	1151	42.59	39.12	0.323
<b>BMI</b>	1151	26.19 (3.60)	25.84 (3.58)	0.808
<b>Diabetes M</b>	1130	13.91	7.92	0.002
<b>Dyslipidaemia</b>	1148	48.65	37.08	0.005
<b>Active Smoker</b>	1150	2.33	3.77	0.237
<b>Hypertensive</b>	1146	80.68	48.74	<0.0001
<b>Stroke</b>	1151	0.99 (3)	1.18 (10)	0.791
<b>MI</b>	1151	1.42 (3)	0.00 (0)	0.508
<b>Heart Failure</b>	1151	6.09 (17)	1.32 (11)	<0.0001
<b>Cancer</b>	1151	12.58 (38)	9.55 (81)	0.0.137
<b>SBP V5</b>	1151	142.36	141.34	0.323
<b>DBP V5</b>	1151	72.13	74.46	0.0003
<b>HR V5</b>	1037	71.35	63.66	<0.0001
<b>PWV</b>	1151	14.81	14.67	0.533
<b>SSD-D-to-D</b>	1144	11.80	10.76	0.001

SD: standard deviation; SBP: systolic blood pressure; DBP: diastolic blood pressure; V5: visit-5 HR: heart rate; Diff-SBP(1,2,3): difference between mean SBP in sitting position and SBP in standing position(1,2 and 3minutes); ; Diff-SDBP(1,2,3): difference between mean DBP in sitting position and DBP in standing position(1,2 and 3minutes); Diff-HR(1,2,3): difference between mean HR in sitting position and HR in standing position(1,2 and 3minutes); SSD-D-to-D:standard deviation of day-to-day SBP; SCV-D-to-D:coefficient of variation of day-to-day SBP; Stroke: proportion of subject with history of stroke; MI: proportion of subject with an history of myocardial infarction

**Annex 2:** Logistic regression analysis of the PWV in quartiles, in the 3-City cohort (N=1151)

	SSD-D-to-D			SCV-D-to-D		
	per quartiles			per quartiles		
	OR	95% CI	p-value	OR	95% CI	p-value
<b>Model 1</b>	0.992	0.963-1.022	0.593	0.992	0.952-1.034	0.709
<b>Model 2</b>	1.016	0.988-1.046	0.261	0.988	0.948-1.030	0.578

Model 1: N=1133; adjusted for sex, age, home SBP measurement

Model 2: N=1112; adjusted for sex, age, hypertension status during follow-up 5

SSD: Systolic Standard Deviation; SCV: Systolic Coefficient of Variation

## 5.2 DISCUSSION :

L'HO est un marqueur de variabilité tensionnel immédiat provoqué par le passage à l'orthostatisme. La qualité du réseau vasculaire, en particulier artériel, est un des déterminants du maintien de la PA en position debout au même titre que la fonction du baroréflexe qui est son autre déterminant principal. C'est ce déterminant vasculaire qui en fait la richesse et l'intérêt de son étude par rapport aux autres marqueurs de variabilités tensionnelles. Il apparaît ainsi de plus en plus clairement que la variabilité tensionnelle est un marqueur de la fonction du baroréflexe qui n'apporte pas d'information sur la qualité du réseau artériel. Nous avons des données en population hypertendus qui confirment en effet que variabilité tensionnelle de court terme et rigidité artérielle ne sont pas associées. Nous avons montré chez 968 sujets hypertendus, que la variabilité tensionnelle nocturne mesurée à partir de la déviation standard en holter tensionnel était associée à la survenue d'évènements cardiovasculaires après ajustement sur la PA, les facteurs de risque cardiovasculaire traditionnel et sur la rigidité artérielle (article en cours de soumission, manuscrit en annexe). Ces résultats, obtenus dans une population différente et avec des outils de mesure différents (variabilité court terme sur 24H et rigidité artérielle par QKD) confirment que la rigidité artérielle et la variabilité tensionnelle sont bel et bien deux paramètres indépendants et qui sont chacun associé à un sur-risque cardiovasculaire. Ces résultats sont en cohérence avec les résultats des études ancillaires d'ASCOT décrites en introduction selon lesquels la PA centrale d'une part<sup>13</sup> et la variabilité tensionnelle inter-visite d'autre part<sup>15</sup> sont deux paramètres qui expliquent la supériorité de la stratégie thérapeutique basée sur la prise de l'amlodipine au-delà de la simple baisse de PA.

L'identification de ces deux déterminants permet d'identifier des situations cliniques à risque d'HO. Les sujets avec une rigidité artérielle marquée (calcifications vasculaires, patient artéritique) et ceux avec une variabilité de court ou moyen terme augmentée (SD nocturne sur les rapports de holter tensionnel >12 mmHg) devraient bénéficier d'un dépistage d'HO.

D'autre part ces déterminants permettent de proposer des stratégies thérapeutiques complémentaires. Ainsi, les choix de traitement anti-HTA devront prendre en compte le risque associé de majorer la variabilité tensionnelle et la capacité à réduire la rigidité artérielle. Il s'agit en pratique des mêmes classes de traitement anti-hypertenseur qui sont déjà recommandées par les sociétés savantes à savoir les inhibiteurs calciques type/comme les dihydropyridines et les bloqueurs du SRAA.

L'HO prend donc une dimension clinique que n'ont pas les autres marqueurs de variabilité. Cependant, cette utilité clinique se heurte à un dépistage en pratique clinique qui limite sa diffusion. Une autre méthodologie diagnostic pourrait sans doute améliorer ce taux de dépistage.

## 6 DEPISTAGE DE L'HYPOTENSION ORTHOSTATIQUE EN AUTOMESURE TENSIONNELLE

### 6.1 PRESENTATION DE L'ARTICLE

Comme nous l'avons vu, la mise en évidence d'une HO répond à un protocole de mesure de PA complexe et de consultation. Ce sont les deux limites principales au dépistage.

Ce travail propose une méthode de dépistage original de l'HO au cours de l'automesure tensionnelle. En effet, l'automesure tensionnelle est un moyen recommandé pour suivre l'équilibre tensionnel des sujets hypertendus, population à risque d'HO. En déléguant le dépistage de l'HO au patient, on espère améliorer le diagnostic et réduire la prévalence de l'HO en adaptant le traitement anti-hypertenseur.

Ce travail a été publié dans le Journal of Hypertension en 2019.

Il s'agit d'une revue de rang B, l'impact factor des 5 dernières années est mesuré à 4.43.

## Screening for orthostatic hypotension

### Using home blood pressure measurements

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**Abstract:** Orthostatic hypotension (OH) is a common condition associated with adverse cardiovascular and cognitive prognosis. Screening for OH consists of blood pressure measurements in supine (or sitting) and standing position during clinical consultations. Since OH is a poorly reproducible clinical condition, it is likely that the simple measurement carried out during consultations underestimates the true prevalence of the condition. The objective of this study is therefore to determine whether screening for OH with home blood pressure measurements (HBPM) may improve OH diagnosis without compromising the quality of the blood pressure readings. **Materials and Methods:** We asked all patients with indications for HBPM in the Hypertension unit and in a general medical practice to perform a series of home blood pressure measurements, ending each series with a measurement in standing position. **Results:** We recruited 505 patients of mean age 68 y.o and with 93% of hypertensive. The success rate of HBPM complying with the ESH criteria (12 out of 18 measurements) was 94.5% which is comparable to previously published series of measurements. 91% of subjects measured their blood pressure at least once in standing position and 88% of subjects recorded all six standing measurements. OH prevalence defined as the presence of one episode of OH was 37.47%, much higher than OH prevalence measured in the same cohort in a clinic setting (15%). **Conclusion:** the measurement of blood pressure in standing position during HBPM is feasible without altering the quality of the blood pressure readings in seated position. Our findings show that OH is significantly more often detected at home by the patient than at the doctor's office which may allow quicker initiation of preventive and therapeutic strategies.

The drop in blood pressure (BP) in response to orthostatism is a common condition. Consequently, about 6 to 10% of the general population<sup>166, 180</sup> experience a decrease in systolic BP of more than 20mm Hg or a diastolic BP drop of more than 10mm Hg on standing up, the consensus definition of orthostatic hypotension (OH)<sup>67</sup>. OH is associated with increased mortality and risk of cardiovascular events (coronary events, heart failure and stroke)<sup>113</sup>, as well as increased risk of dementia<sup>166</sup>. This clinical sign is therefore associated with unfavorable prognosis thus justifying effective systematic screening for OH.

The fall in blood pressure on standing up is a poorly reproducible condition<sup>191, 192</sup>. Given the multiple reasons behind the lack of reproducibility, the simple screening for OH during consultation could miss the diagnosis. Moreover, changes in blood pressure observed during consultation can be biased by the medical or para-medical presence with a significant occurrence of white coat hypertension or its obverse - masked hypertension. Today, these blood pressure phenotypes justify the use of BP measurements outside the clinic setting in the management of arterial hypertension<sup>193</sup>. Home blood pressure measurements (HBPM) are recommended to confirm the diagnosis of hypertension and monitor blood pressure<sup>194</sup>. This technique consists of performing repeated BP measurements in standard condition outside the clinic setting. It has been well established that HBPM are more strongly associated with cardiovascular events and mortality than office BP measurements<sup>195, 196</sup>. Consequently, OH screening based on HBPM may also be more relevant than office screening.

Before responding to these important questions, it is necessary to check the feasibility of measuring BP in standing position out of a clinic setting. Therefore, we decided to test the feasibility of screening for OH using an original protocol for HBPM.

## **Materials and Method**

### **Study population**

The study comprised all adult patients who consecutively consulted the Fleurance and Montestruc-sur-Gers general medical practice, in Gers, France, as well as the Hypertension Excellence Center (HEC) of the Bordeaux Hospital University Center (CHU), in Bordeaux, France. HBPM was proposed in the 2 following cases: 1) to confirm high BP before starting antihypertensive treatment 2) to check blood pressure control in treated hypertensive patients. Subjects were informed of the study and gave their oral consent to participate. The exclusion criteria included a subject's inability to

stand in an upright position, a subject's failure to obtain a home BP measuring device and/or a subject's refusal to participate in the study.

### **Clinic blood pressure measurement**

Blood pressure measurements in the clinic setting were carried out following the practice guidelines recommended by the European Society for Hypertension (ESH), three measurements in sitting or supine position with a cuff adapted to the size of the arm circumference<sup>197</sup> after a period of rest of 5 minutes. The size of the cuff was standard for the large majority of patients (12 cm wide and 26 cm long) but were longer for obese adults (12 cm wide and 40 cm long) or shorter for lean adults (12 cm wide and 18 cm long).

In the general practice, blood pressure measurements were performed with validated automated oscillometric devices, whereas the auscultatory method with mercury sphygmomanometer was used in the HEC.

After the last measurement in supine or sitting position, the subject was asked to stand up and a new single measurement was performed immediately upon standing.

Clinical hypertension is defined as systolic BP > 140mmHg or diastolic BP > 90mmHg based on an average of the two measurements or as current use of antihypertensive treatment.

OH is defined by expert consensus using the agreed threshold<sup>67</sup> of a fall in systolic BP of more than 20mmHg or diastolic BP of more than 10mmHg at orthostatism compared to the previous BP measurement in supine or sitting position.

### **Procedure for home measurement of blood pressure**

The devices used to carry out HBPM were automated oscillometric measuring devices belonging to the subject or borrowed from the doctor. In the former case, the subject was requested to bring in the device for comparison with the reference measuring device used in the clinic setting. Three simultaneous measurements with each device positioned on separate arms were performed and averaged. Agreement between the two devices was determined by a mean difference below 10mmHg for systolic and below 5mmHg for diastolic.

The HBPM protocol consisted of performing four consecutive BP measurements, three in sitting position, followed by one in standing position twice a day - in the morning just after waking up and before taking any medication, and in the evening after dinner.



These series of measurements were repeated over three consecutive days to stay close from the French Society of Hypertension guidelines, resulting in a total of 24 BP measurements, 18 in sitting position and 6 in standing position<sup>198</sup>.

#### Other variables

Diabetic status was defined by a level of fasting blood glucose greater than 7mmol/l or the use of anti-diabetic treatment (oral treatment or insulin). Smoking status accounted for non-smokers, and former and active smokers. Former smokers were defined as having had quit smoking for at least six months.

Subjects were considered dyslipidemic if their total cholesterol level was greater than 5.2 mmol/l or if they were taking hypolipidemic treatment. Cardiovascular history was defined as the record of at least one coronary event, heart failure or stroke in the subject's medical file.

### **Statistical Analysis**

We performed a descriptive analysis of the total sample by center using the Student's t-test and the chi-square test.

To evaluate the quality of the HBPM, we measured the proportion of HBPM that met the ESH qualitative criteria, that is, the completion of at least 12 out of the 18 BP measurements at home in sitting position<sup>193, 199</sup>.

Then, regarding the BP measurements in standing position, we considered records containing at least one BP standing measurement and those with the full set of BP measurements in standing position (six measurements in total).

We then ran a logistic regression analysis with the diagnosis of OH using HBPM as the dependent variable and the presence of clinic OH as the main explanatory variable. Additional adjustment variables were selected a priori from the variables known to be associated with OH or cardiovascular event. We explored for interactions between the main explanatory variables. We verified the log-linearity of the quantitative variables. A backward stepwise regression analysis was carried out on a fixed sample size by conserving only the adjustment variables associated with a p-value < 0.005.

The statistical analysis was performed using SAS version 9.4 (California, USA).

## Results

We included in this study 505 patients allowing us to collect 505 records of HBPM including measurements of standing blood pressure over a period of one year from 1 January to the 31 December 2016. The characteristics of the study population are presented in Table 7.

It is important to note that 75% of HBPM records were collected from subjects in the general practice (center 1). There were marked differences among subjects from the two centers due to the different activity focus of each center. In the HT unit (center 2) the population is younger (mean age = 58.67 vs 70.58,  $p < 0.001$ ), with a higher BP level (140 vs 134,  $p < 0.001$ ) (Table 8).

In the total sample, 386 patients have been their blood pressure measured in sitting (or lying) position and in standing position. Thus, we identified 56 cases of clinic OH (prevalence of 15%). These figures are consistent with the prevalence rates observed in this type of population<sup>66</sup>.

Out of the 505 HBPM records, 477 meet the ESH criteria, which represent a success rate of 94.5%. The success rate of recording HBPM with at least one measurement of standing BP is 94%. It is 85% for subjects who carried out the full series of standing BP measurements (i.e. the six measurements). Subjects who did not meet the ESH quality criteria (at least 12 measurements out of 18) ( $n = 28$ ), also failed to perform the standing BP measurements. In contrast, only three subjects who met the ESH criteria did not perform at least one BP measurement while standing (Table 9).

The prevalence of OH based on HBPM is 40%. Subjects diagnosed with OH using HBPM are older (mean age = 71.13 vs 65.78,  $p < 0.001$ ) (Table 10). In the multivariate logistic regression analysis, we observe that OH diagnosed with HBPM is not associated with clinic OH. However, we find an association between home OH and female subjects (OR = 1.17, 0.80-1.72,  $p < 0.001$ ), age (OR = 1.04, 1.02-1.05,  $p = 0.003$ ) and the level of SBP (OR = 1.00;  $p = 0.03$ ) (Table 11).

## Discussion

### Feasibility of home blood pressure measurements

Several studies have investigated the feasibility of conventional HBPM without measuring standing BP. The PAMELA cohort from the general population in Italy comprises a sample of 1438 subjects without antihypertensive treatment. In this study, the HBPM procedure consisted of only 2 measurements: one in the evening and

another one the next morning<sup>200</sup>. The Ohasama study, involving a cohort of 3744 subjects from the general population, used several different protocols, the most recent of which consists of one BP measurement in the morning and in the evening consecutively over four weeks<sup>201</sup>. There is no data on the quality criteria used for either of these two historic cohorts.

In the general population cohort of the Three-City study, a sub-sample of 1814 subjects, with a mean age of 79.1 years, were asked to perform a series of HBPM on two occasions using the same procedure as in our study, that is, three measurements in the morning and three in the evening for three days. 95.9% (n=1,737) and 94.2% (n=1,708) of the subjects performed at least 12 of the 18 measurements<sup>202</sup> during the two series of HBPM.

The measurement protocol used in the Finn-Home study, involving a cohort (n=2035) from the general population, consisted of performing two BP measurements in the morning and in the evening over seven days, with a total of 28 measurements. The mean number of measurements was  $26.7 \pm 3.7$  with a success rate of about 95%<sup>203</sup>. The Didima study measured the home BP of 694 subjects with a mean age of 52 years in a Greek population-based cohort. The measurement protocol consisted of performing two BP measurements in the morning and the evening over three consecutive work days. 29 out of 694 subjects did not correctly complete their home BP measurement, resulting in a success rate of 96%<sup>204</sup>.

The SHEAF study examined the feasibility of HBPM in hypertensive subjects aged over 60 years in the French population. The measurement procedure involved three BP measurements in the morning and evening for four days. The quality criterion for a subject to be included in the study was at least 15 valid measurements out of a possible total of 24 (representing a minimum of 62.5% of valid measurements as opposed to 66.6% according to the ESH recommendations). Out of the 5463 subjects included in the study, 252 were excluded for not meeting the HBPM quality criteria, resulting in an overall success rate of approximately 95.5%<sup>205</sup>.

Even if the study populations and HBPM protocols differ in each of these cohort studies, the success rate of HBPM is very stable from one study another and is in the 95% range. In our study, the success rate according to the ESH criteria is very similar: 94.50%. In addition, the clear majority of subjects (94%) performed at least one standing BP measurement and 85% carried out all six standing BP measurements. Lastly, 91% of subjects who did not make a single BP measurement in standing

position (n = 31), also did not meet the quality criteria of conventional HBPM. Asking subjects to measure their BP in standing position after each BP measurement series in sitting position did not decrease the success rate conventional HBPM without standing BP measurement in our study cohort.

### **Choice of OH definition and OH prevalence in HBPM**

Considering OH low reproducibility, it seemed logical to define OH as the occurrence of OH in at least one of the measurements in the context of repeated HBPM measurements. This explains why we adopt this measurement method as our reference in our study. By increasing the number of measurements on consecutive days and at different times of the day, this increases the possibility of detecting OH. In our study, OH prevalence accordingly increases from 15% during screening in a clinic setting to 37.43% using a series of HBPM. This increased sensitivity is certainly at the expense of lower specificity and the clinical value of this definition will have to be confirmed by long term outcome studies.

Under the assumption that recurrent OH is probably more detrimental than the isolated cases of OH, we are therefore interested in subjects diagnosed with OH based on two out of the six standing BP measurements. Thus, the OH prevalence reduces to 7.72%.

An alternative hypothesis would have been to look at differences in mean sitting and standing BP. The mean difference in mean sitting and standing BP values is  $0.52 \text{ mmHg} \pm 9.6 \text{ mmHg}$  for systolic BP and  $3.00 \text{ mmHg} \pm 5 \text{ mmHg}$  for diastolic BP. We observe that subjects who have a distribution of their differences beyond 2 standard deviations have differences in sitting and standing BP of approximately 20mmHg for systolic BP and 10mmHg for diastolic BP, in line with agreed threshold values of clinic OH. However, this calculation method based on calculating the mean of a set of values, yields a low OH prevalence rate of approximately 3%. This prevalence is much lower than that of the clinic OH measurements, and is therefore probably not very useful.

Finally, the prevalence depends also of the threshold chosen for the diagnosis. In this work we decided to use the consensual threshold. If we define OH by a BP drop of more than 30mmHg for the systolic or more than 15mmHg for the diastolic, the prevalence is reduced and represent 19.21% of the population.

In the logistic regression analysis, we observe that OH diagnosed using HBPM is not associated with clinic OH regardless of the definition of OH in HBPM, once again

illustrating the poor reproducibility of this condition but clinic OH and HBPM OH share some characteristics such as association with age and BP level. However, only clinic OH is associated with antecedents of cardiovascular events which is consistent with the literature data.

### **Interest of OH screening using HBPM versus in clinic setting**

Out of the 505 subjects in this cohort, only 386 were screened for OH in consultation, making up 76% of the sample. We have not clearly evaluated why this figure is so low, however our main assumption concerns the lack of time during consultations. Another explanation is perhaps the fact that this measure is not yet common practice even if it is now recommended at least in cases where the subject is at risk of OH. This figure is significantly lower than the 91% of subjects in the study who performed at least one standing measurement in the series of HBPM. Although this study was dedicated to observing BP in response to postural changes, we note that OH screening is more effective by authorizing the patients to carry out HBPM than when left to the doctors.

### **Limitations:**

This work is preliminary feasibility study. We therefore did not establish a control group to perform a series of HBPM excluding standing BP measurements, which is necessary to objectively observe a difference between the two HBPM methods. Nevertheless, the success rate of HBPM with a standing BP measurement in our series is 94% and is therefore equivalent to those found in the literature without standing measurement.

We only analyzed HBPM records that were reported to us and that were therefore more likely to be correctly completed. The proportion of HBPM records collected but not reported by the patients is unknown as this was not measured. Consequently, the absolute number of medical forms collected was 505 over one year, corresponding to a collection rate of 80 forms per practitioner per year. This ensured the implication of every stakeholder in the study and therefore limited the risk of collection bias.

Not all the devices used to carry out the HBPM were validated. Indeed, most subjects did not bring in their measuring device. However, we were able to check the accuracy of the BP measuring devices in 48 subjects (10%), with an acceptable accuracy. The accuracy of the home BP devices could not affect the feasibility of measuring standing BP at home, this may nevertheless question the frequency of OH observed during HBPM in this work.

The nature of antihypertensive treatment was not systematically noticed despite the large majority of patients were under treatment. Moreover, the influence of the time of the medication intake on the occurrence of an HO may have influenced its prevalence. Indeed, we noticed 116 HO in the morning and 140 in the evening which also raises questions about some potential clinical significance differences between morning and evening HO.

At this stage we do not have a longitudinal follow-up to validate the value of standing BP measurements during HBPM or to define the most relevant measurement protocol. This would require a future study to evaluate the association with clinical events.

### **Conclusion and future perspectives**

Conclusion: Screening for OH using HBPM is easily feasible. Moreover, OH screening based on HBPM seems to be more efficient than when carried out by the doctor in consultation. Increasing the sensitivity of OH determination is certainly an important goal to limit its consequences with preventive and therapeutic strategies. Our data have to be confirmed with longitudinal studies in population at high OH risk.

**TABLE 7: DESCRIPTION OF THE STUDIED POPULATION ACCORDING THE PRESENCE OF AT LEAST ONE EPISOD OF OH DURING THE HBPM, N=505**

	<b>Subject with OH (n=189)</b>	<b>Subject without OH (n=316)</b>	<b>P-value</b>
<b>Women (%)</b>	51.6	47.8	0.40
<b>Age (mean)</b>	71.1	65.8	<0.001
<b>BMI&gt;25 (%)</b>	66.9	75.8	0.08
<b>HTN (%)</b>	94.1	94.0	0.95
<b>Smoker (%)</b>	12.5	13.7	0.70
<b>Diabetes M (%)</b>	17.4	18.2	0.82
<b>Dyslipidemia (%)</b>	51.1	48.2	0.54
<b>CV history (%)</b>	9.2	6.1	0.20
<b>Home SBP (mean)</b>	137	135	0.08
<b>Home DBP(mean)</b>	79	79	0.80

**N:** size of the sample; **SD:** standard deviation; %: proportion; n: number; **BMI:** body mass index; **SBP:** systolic blood pressure; **DBP:** diastolic blood pressure; **OH:** orthostatic hypotension; **HTN:** proportion of patient with Hypertension; **Smoker:** proportion of active smoker; **Diabetes M:** proportion of patients with diabetes mellitus; **CV history:** proportion of patients with a previous cardiovascular event history

**TABLE 8: DESCRIPTION OF THE POPULATION ACCORDING THE CENTER**

	Center1 (n=383)		Center 2 (n=122)		p
	N	Mean/%	N	Mean/%	
<b>Women</b>	384	50	118	46.6	0.52
<b>Age (years)</b>	384	70.6	116	58.7	<0.001
<b>BMI&gt;25</b>	241	69.3	70	82.8	0.02
<b>Hypertensive</b>	382	92.7	118	98.3	0.02
<b>Active</b>	382	10.0	115	24.4	<0.001
<b>Smoker</b>					
<b>Diabetes Mellitus</b>	382	15.2	115	27.0	<0.001
<b>Dyslipidemia</b>	382	49.5	115	48.7	0.88
<b>CV history</b>					
<b>Clinic SBP</b>	360	153	69	151	0.39
<b>Clinic DBP</b>	360	86	68	85	0.80

#: proportion; **BMI**: body mass index; **CV**: cardiovascular (coronaropathy, heart failure or stroke); **SBP**: systolic blood pressure; **DBP**: diastolic blood pressure



**TABLE 9: SUCCESS OF THE HOME BP MEASUREMENT ACCORDING ITS DEFINITION**

	<b>N</b>	<b>Success</b>	<b>Failure</b>	<b>Success rate (%)</b>
<b>ESH Home BP</b>	505	477	28	94.5
<b>Home BP with 6 standing BP</b>	505	430	75	85.1
<b>Home BP with at least one standing BP</b>	505	474	31	93.8

N: sample size; ESH Homme BP: at least 12/18 BP measurements;

**TABLE 10: MULTIVARIATE LOGISTIC ANALYSIS OF THE OCCURRENCE OF AN OH DURING HOME BP MEASUREMENT**

<b>Variables</b>	<b>OR</b>	<b>CI</b>	<b>p</b>
<b>sex</b>	1.24	0.80-1.72	0.274
<b>Age</b>	1.04	1.02-1.05	<0.001
<b>Home sitting</b>	1.01	1.00-1.03	0.003
<b>SBP</b>			

**OR:** odds ratio; **CI:** confidence interval at 95%; **SBP:** systolic blood pressure

## 6.2 DISCUSSION

### 6.2.1 FAISABILITE DU DEPISTAGE DE L'HO PAR L'AUTO-MESURE TENSIONNELLE

Notre travail a été depuis conforté par un autre travail français qui a évalué également la faisabilité du dépistage chez une population âgée de plus de 65 ans<sup>206</sup>. 241 sujets ont été inclus dans ce dernier travail. Le protocole de dépistage est un peu différent avec la réalisation de 2 mesures de pression artérielle en position debout à 1 et 3 minutes. Le taux de succès de cette méthode reste acceptable avec 83% mais est bien inférieur à celui de notre étude (92%). Les raisons de cette différence sont sans doute la population plus âgée et un protocole un peu plus complexe puisqu'il est demandé de réaliser une deuxième mesure à 3 minutes en position debout.

Ceci étant, cela démontre une fois de plus la possibilité d'améliorer le diagnostic de l'HO par la multiplication des mesures au cours des auto-mesures tensionnelles tout en soulageant le médecin qui n'a plus qu'à lire la fiche d'auto-mesure pour faire le dépistage (Figure 7).

## RELEVÉ D'AUTOMESURE

<b>NOM :</b>		<b>PRENOM :</b>				<b>DATE DE NAISSANCE :</b>				
Appareil présent	OUI	NON	Type d'appareil		Bras	Poignet	Refus du patient			
<b>A DOMICILE</b>		<b>JOUR 1</b>		<b>JOUR 2</b>		<b>JOUR 3</b>				
		SYSTOLIQUE	DIASTOLIQUE	SYSTOLIQUE	DIASTOLIQUE	SYSTOLIQUE	DIASTOLIQUE			
Le MATIN avant le petit déjeuner (après 5 minutes de position assise)										
Mesure 1										
Mesure 2										
Mesure 3										
Debout										
Le SOIR entre le dîner et le coucher (après 5 minutes de position assise)										
Mesure 1										
Mesure 2										
Mesure 3										
Debout										
<b>MOYENNE SYSTOLIQUE :</b>				<b>MOYENNE DIASTOLIQUE :</b>						
<b>EN CONSULTATION</b>		<b>TA Assise :</b>				<b>TA Debout :</b>				
<u>BMI (kg/m<sup>2</sup>):</u>										
<u>Traitements en cours :</u>										
<u>Antécédents :</u>										
<u>Clairance de la créatinine (µmol/L) :</u>										

Figure 7 : Exemple de relevé d'automesure avec dépistage de l'Hypotension Orthostatique

## 6.2.2 DEMONTRER L'INTERET DE CETTE METHODE : COHORTE DE TRANSPLANTES RENAUX

Pour généraliser cette méthode de dépistage, il reste à démontrer son utilité pronostic. La population insuffisante rénale est une population peu étudiée en termes d'association entre HO et évènements cardiovasculaires, ainsi qu'entre HO et fonction rénale. Le sujet insuffisant rénal a pourtant toutes les caractéristiques du sujet à très haut risque d'HO de par la très forte prévalence du diabète, une rigidité artérielle majeure par dépôt calcique et de l'importance de l'état d'hydratation dans la régulation de la PA. Ainsi, chez 304 sujets dialysés de 63 ans en moyenne, la prévalence de l'HO est de 42%. Sur un suivi moyen de 4 ans, 136 décès sont enregistrés dans cette cohorte permettant de montrer que l'HO est associée à un sur-risque de mortalité et d'évènements cardiovasculaire multiplié par 2<sup>207</sup>. Cet échantillon reste limité et le taux de mortalité est largement supérieur aux cohortes européennes. Plus récemment, l'étude SPRINT, sur une population non diabétique à haut niveau de risque cardiovasculaire, montre de manière transversale que la prévalence de l'HO augmente avec la diminution du débit de filtration glomérulaire (DFG). Ainsi, on passe d'une prévalence de 6% pour les DFG>60ml/mn à 12% pour les DFG<45ml/mn ( $p<0.0001$ )<sup>208</sup>. Ces résultats sont confirmés par un autre travail chez 4204 sujets de population générale qui montre une association entre le DFG classé par strate de 15ml/mn et la fréquence de l'HO par le finomanometer sur 2 minutes d'orthostatisme. Le risque d'HO apparaît deux fois plus important chez les sujets avec un DFG<60ml/mn par rapport à ceux qui ont un DFG normal<sup>209</sup>.

Nous sommes donc en train de monter une cohorte de suivi de patients transplantés rénaux avec un double objectif :

- **Objectif principal:** Comparer l'incidence de survenue d'un évènement cardiovasculaire chez des sujets transplantés rénaux selon le statut HO dépisté par l'auto-mesure tensionnelle.
- **Objectif secondaire :** Montrer l'intérêt du dépistage de l'HO par l'auto-mesure par rapport au dépistage de consultation.

D'après les premières estimations, un recrutement de 200 sujets transplantés suivi sur 5 ans devrait permettre de répondre à ces objectifs.

## 7 CONCLUSION

Si l'HO est une situation clinique courante bien identifiée, les données sur population générale indiquant un sur-risque cardiovasculaire globale important sont récentes. Ces résultats sont cohérents avec les informations apportées par d'autres marqueurs de variabilité tensionnelle qui sont les marqueurs dit conventionnels à savoir la variabilité inter-visite, la variabilité de moyen terme en auto-mesure et la variabilité de court terme en holter tensionnel.

L'HO se distingue de ces marqueurs de variabilité par le caractère dynamique de cette mesure. En effet, l'HO se définit par une chute de PA lors du passage à la position debout. Cette caractéristique unique en fait un bon reflet de l'état de notre réseau artériel ainsi qu'un bon moyen de tester nos capacités à réguler la PA finement.

Ce travail de thèse avait donc comme objectifs principaux de compléter l'exploration de la variable HO d'un point de vue pronostic au regard des autres marqueurs conventionnels de la variabilité tensionnelle mais également d'explorer ces relations avec ces mêmes marqueurs de variabilité.

En l'état des connaissances au commencement de cette thèse, l'association avec la démence n'avait pas encore été démontrée. D'autre part, les relations entre HO et les marqueurs de variabilité tensionnelle conventionnels n'avaient jamais été directement étudiées. Un déterminant commun proposé était la rigidité artérielle qui par perte de la compliance aortique et artérielle est une explication encore courante à l'excès de variabilité tensionnelle.

Nous avons pu réaliser ces analyses au sein d'une cohorte de population générale française âgée de plus de 65ans: la cohorte des 3 Cités.

L'HO a été mesurée à l'inclusion dans l'étude chez 7425 sujets permettant de diagnostiquer 978 HO. Au suivi à 12ans, la présence d'une HO à l'inclusion est associée à un sur-risque de démence de l'ordre de 25% après ajustement sur les principaux facteurs confondants. Ce résultat a depuis été conforté par d'autres études de cohortes avec des résultats comparables.

De plus, au cours d'une étude transversale, nous avons pu étudier en même temps dans un échantillon d'environ 1100 sujets du centre de Dijon les relations entre l'HO, la vitesse d'onde de pouls carotido-fémorale et la variabilité tensionnelle mesurée en auto-mesure. Il apparaît que contrairement aux idées reçues, l'HO est associée à la

fois à la rigidité artérielle et à la variabilité tensionnelle en auto-mesure. La rigidité artérielle et la variabilité en auto-mesure sont deux variables indépendantes qui ne mesurent donc pas la même chose. La variabilité tensionnelle est plutôt le marqueur d'une dysfonction du baroréflexe quand la rigidité artérielle est plutôt le marqueur du vieillissement vasculaire. Ces deux déterminants expliquent le sur-risque lié à l'HO.

**Nos résultats montrent donc que l'hypotension orthostatique est un paramètre pronostic cardiovasculaire et cognitif majeur.**

C'est pourquoi un dépistage le plus systématique possible est nécessaire mais les limites de la mesure de l'HO en consultation sont nombreuses. Le temps de mesure est sans doute la principale.

La mesure tensionnelle de référence aujourd'hui est la mesure en dehors du cabinet médical. Un protocole de dépistage de l'HO s'adaptant à ces recommandations apparaît donc nécessaire. Nous avons validé dans ce travail de thèse, un protocole de dépistage sur 505 patients utilisant l'auto-mesure tensionnelle qui répond aux critères qualité de l'auto-mesure tensionnelle classique (94.5% de succès selon les critères de l'ESH) tout en multipliant les mesures en position debout (18 mesures). La diffusion de cette pratique pourrait permettre une meilleure identification de ces sujets.

L'HO est donc un marqueur hémodynamique qui apporte des informations à la fois sur le niveau de rigidité artérielle et sur la fonction du baroréflexe. La mise en œuvre via les automesures tensionnelles de son dépistage devrait permettre de faciliter la détection des sujets à haut risque cardiovasculaire et à mauvais pronostic cognitif..

La prise en charge thérapeutique de l'HO reste cependant encore une page vierge pour laquelle il n'y a ce jour pas d'essais thérapeutiques en cours. Ainsi, la démonstration de la réduction du risque cardiovasculaire et cognitif par la correction de l'HO reste à faire.

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## Original Article

## Orthostatic Hypotension and Risk of Incident Dementia Results From a 12-Year Follow-Up of the Three-City Study Cohort

Antoine Cremer, Aicha Soumaré, Claudine Berr, Jean-François Dartigues, Audrey Gabelle, Philippe Gosse, Christophe Tzourio

**Abstract**—Several studies indicate a potential link between orthostatic hypotension (OH) and incident dementia but without substantial evidence to date. Our objective is to study the association between OH and dementia in a cohort of elderly individuals. To do so, baseline lying and standing blood pressure measurements were taken from 7425 subjects in the Three-City study. These subjects were then followed-up for 12 years. Cox proportional hazard models, adjusted for potential confounders, were used to estimate the risk of incident dementia according to OH status. Sensitivity analysis was performed using the so-called illness-death model, a specific statistical method which takes into account competitive risk with death. OH frequency was found to be around 13%, and 760 cases of dementia were diagnosed during follow-up. We observed significant associations between the presence of OH at baseline and the occurrence of dementia during the follow-up, with an increased risk of at least 25% observed regardless of the OH threshold and the statistical method used. In conclusion, there is an association between OH and dementia. Considering that OH is a common condition and is easy to measure, OH measurements could help to identify subjects with higher risk of dementia. Moreover, reducing OH could be a step to prevent conversion to dementia. (*Hypertension*. 2017;70:00-00. DOI: 10.1161/HYPERTENSIONAHA.117.09048.) • [Online Data Supplement](#)

**Key Words:** blood pressure ■ dementia ■ orthostatic hypotension ■ risk ■ vascular ageing community-based cohort

In clinical practice, orthostatic hypotension (OH), a blood pressure drop in standing position, is a common condition affecting at least 6% of the population.<sup>1</sup> OH has been consistently associated with increased mortality and risk of cardiovascular events.<sup>2</sup> This leads us to question whether cerebral perfusion variations induced by OH could contribute to an increased risk of dementia. An increase in the prevalence of OH in patients with dementia,<sup>3</sup> as well as increased risk of conversion to dementia, has been shown among patients with mild cognitive impairment and OH.<sup>4</sup> In general population, relationships between OH and cognitive impairments are highlighted<sup>5-8</sup> but without drawing substantive conclusions given the too short duration of the follow-up and insufficient number of subjects or as a result of an unequal distribution of the Mini-Mental State Examination score according to OH status. Given these results, there is currently no significant evidence to support the prospective relationship between OH and the risk of dementia.

The Three-City study, a community-based cohort of 9294 individuals above the age of 65 years with a follow-up of 12 years,<sup>9</sup> thus, seems to be an adequate resource to attempt to make progress on this research topic.

### Methods

#### Study Population

The principal objective of the Three-City study was to examine the vascular determining factors of incident dementia.<sup>9</sup> The study participants, aged ≥65 years, noninstitutionalized, were recruited from 1999 to 2001 (inclusive) on a voluntary basis using the electoral rolls in 3 French cities: Bordeaux, Dijon, and Montpellier. There was a 37% acceptance rate among the contacted subjects. After excluding those who refused to participate in the medical interview (n=392), the sample comprised 9294 participants (Bordeaux, n=2104; Montpellier, n=2259; and Dijon, n=4931). The initial interview took place either in a health center or at the subject's home and consisted of a face-to-face interview with a trained investigator to collect data related to background information, lifestyle, and medical history. In addition, a fasting blood sample was taken, and physical and cognitive assessments were performed. During the 12-year follow-up period, 5 follow-up visits took place every 2 or 3 years.

The working sample of this study consisted of subjects without prevalent dementia and who had their blood pressure measured while sitting and standing at baseline.

#### Diagnosis of Dementia

Diagnosis of dementia was based on a 3-step procedure at each follow-up screening, as described elsewhere.<sup>10</sup>

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First, at baseline and at each follow-up visit, trained psychologists assessed cognitive function, and dementia was actively screened. Depending on the score obtained in the Mini-Mental State Examination and Isaac test, subjects could be identified as at risk for dementia.<sup>11</sup> On the Bordeaux and Montpellier sites, a neurologist evaluated all subjects. However, and because of a large number of subjects, only at-risk subjects were evaluated by the neurologist on the Dijon site. Finally, after this examination based on clinical evaluation, the final diagnosis of dementia was made by an independent panel of neurologists and geriatricians with a strong expertise in dementia. They used the information available from the Three-City study examination and all exams performed by the patients' physicians who could include, but not systematically, neuroimaging exams. The diagnosis of dementia was established on the basis of the Diagnosis and Statistical Manual of Mental Disorders-IV from the American Psychiatric Association. Alzheimer's disease was classified as possible or probable, using the criteria of the National Institute of Neurological and Communication Disorders and Stroke and of the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA criteria).<sup>12</sup>

### Blood Pressure Measurement and Diagnosis of OH

The protocol for blood pressure measurement has been described previously.<sup>9</sup>

For OH diagnosis, participants had to first lie down and relax for at least 5 minutes. Then, an appropriate size cuff was placed on the right arm, close to the level of the heart. The measuring devices used consisted of automatic oscillometric devices developed by OMRON CP750 (Japan) rated A/A by the British Hypertension Society.<sup>13</sup> Blood pressure was measured once in lying position. After this measurement in lying position and without removing the cuff, the participant had to stand up, and then another one blood pressure measurement was immediately performed in standing position without delay. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) values and heart rate were also recorded in the database. No data on symptoms that could potentially indicate a drop in BP were recorded. Standing blood pressures were not measured during the follow-up.

The diagnosis of OH is based on a consensus, and there are several diagnostic thresholds defined in the literature. We conducted analysis not only with the most consensual threshold (a reduction in SBP of at least 20 mmHg or DBP of at least 10 mmHg<sup>14</sup>) but also with 2 other thresholds commonly referred to as mild OH (reduction in SBP of at least 10 mmHg or DBP of at least 5 mmHg)<sup>15</sup> and severe OH (reduction in SBP of at least 30 mmHg or DBP of at least 15 mmHg).<sup>16</sup>

For hypertension diagnosis, 2 series of blood pressure measurements were conducted, the first at the beginning of the interview and the second after the ECG to diagnose OH for the Bordeaux and Dijon centers. In Montpellier, only 1 series of blood pressure measurements was performed after the ECG, which was, therefore, the same measurement used to diagnose OH and hypertension.

Hypertension was defined as an SBP $\geq$ 140 mmHg, a DBP $\geq$ 90 mmHg, or taking antihypertensive drugs.

### Clinical Events and Death During Follow-Up

During follow-up, participants were asked to declare their cardiovascular history (interview or questionnaire). This included information on previous coronary events (acute coronary syndrome, myocardial revascularization) and stroke, regardless of the cause. If the subject answered affirmatively, the potential cases were further documented by medical data obtained from general practitioners, specialists, and hospital records where possible and were reviewed by 2 panels of experts, 1 for coronary events and 1 for stroke.

Mortality was ascertained from the civil registry by systematic request for all subjects not included in follow-up visits. The date of death was defined as the date of event and the date of the last follow-up or phone contact for the 10-year follow-up as the date of censoring.

### Other Variables

The level of education was divided into 4 categories from no school or only primary schooling to participants with studies in higher education.

The Mini-Mental State Examination score was used to determine cognitive state. If the score was  $\geq$ 24/30, we considered the subject's cognitive state as normal.<sup>17</sup> Scores below this threshold were used to define a cognitive impairment.

Diabetic status was defined by a level of fasting blood glucose  $>$ 7 mmol/L or the intake of antidiabetic treatment (oral treatment or insulin).

Smoking status accounted for nonsmokers and former and active smokers. Former smokers were defined as having had quit smoking for at least 6 months.

Subjects were considered dyslipidemic if their total cholesterol level was  $>$ 5.2 mmol/L or if they were under hypolipidemic treatment.

Hypotensive medication was defined by the taking of medication which decreases the blood pressure whatever the indication: hypertension or other cardiovascular condition.

Psychotropic medication was defined by the taking of a chronic treatment for psychiatric disorder.

The diagnosis of depression was established on the basis of the score obtained on the depression scale established by the Center for Epidemiology Studies-Depression. Depression in a subject was defined by a score of  $>$ 16 for men and  $>$ 23 for women.<sup>18</sup>

### Statistical Analysis

Participants who did not have their blood pressure measured in standing position were removed from the analysis but were compared with the cohort whose blood pressure was measured while standing to determine whether these values were missing at random. Comparative statistical tests adapted to independent data series were conducted to analyze subjects with OH and subjects without OH (variance analysis and Chi-squared test).

We used a Cox proportional hazard model with delayed entry to study the risk of incident dementia in relation to OH. Because it is difficult to define the date of onset of the dementing process, which is generally insidious, the age of diagnosis of dementia was defined as the age at the midpoint of the interval between the date of diagnosis and the date of the previous visit without dementia. The selected time axis is the age of subject, with delayed entry and left truncation. Participants without dementia were right censored at the end of their last visit or in the event of death. The principal explanatory variable was OH status. Model 1 was a univariate model, uniquely adjusted for the variable center. Model 2 was adjusted for the variables known to be associated with dementia or with OH—ApoE4 status,<sup>19</sup> cognitive state, depression,<sup>20</sup> education level,<sup>21</sup> diabetes mellitus, high blood pressure, cardiovascular history, and center, which were selected during a step-by-step manual procedure, in descending order, using a cohort without missing data to ensure a constant sample size.

A sensitivity analysis was performed using an illness-death model taking into account the competing risk by death and interval censoring.<sup>22</sup> The illness-death model is a semiparametric multistate model, which has been designed to take into account properly the competitive risk with death induced by the interval censoring and, thus, avoids bias.<sup>23</sup> Therefore, it incorporates the different transition states applicable to this study.<sup>24</sup> The first transition (baseline to dementia) is adjusted for the center, using only univariate analysis, and for the adjustment variables from model 2 of the principal multivariate analysis. The second transition (baseline to death) is adjusted in univariate analysis for sex and center. In the multivariate analysis, the cardiovascular risk factors are introduced into the model. The third transition (dementia to death) is adjusted by default for the variables used in the first transition.

In a second analysis, we explored the potential association of the OH to the 2 main different causes of dementia, which are Alzheimer disease and vascular dementia. Cox proportional hazard models with delayed entry were performed with Alzheimer disease and then vascular dementia as primary outcome. The adjustment variables were taken from model 2 of our primary analysis.

All analyses were performed using SAS v9.4 (SAS Institute, Inc, Cary, NC) except those concerning the illness-death model that used R's smooth-hazard package. A 2-tailed *P* value  $\leq$ 0.05 was considered to be statistically significant.

**Results**

The initial sample of the Three-City study was composed of 9294 subjects. However, 1745 of the subjects did not have their blood pressure measured in standing position, rendering the diagnosis of OH impossible, and 214 subjects had already been diagnosed with dementia at the start of the study. Our final study sample, therefore, consisted of 7425 participants (Figure). Subjects who had not undergone a standing blood pressure measurement represented ~20% of the total cohort. These subjects were equally represented between the 3 centers. In comparing the general characteristics of these participants with those in the study sample, we observe that the former are a significantly older population group ( $P<0.0001$ ) with an accumulation of cardiovascular risk factors (Table S1 in the online-only Data Supplement).

Using the conventional significance threshold to diagnose OH, we observe an overall OH in 978 participants (13% of the working sample). With the second definition proposed, numbers are different: mild OH was present in 2411 participants (32%) and severe OH in 330 participants (4.5%).

Participants with OH had an increased cardiovascular risk compared with participants without OH, were older ( $P=0.0016$ ), had a higher proportion of cardiovascular history ( $P<0.0001$ ), and had higher SBP ( $P<0.0001$ ). Distribution of ApoE4<sup>+</sup> state, cognitive state, and level of education was comparable in the 2 groups (Table 1).

During a mean follow-up of 7.5 years representing 55 539 person-years, 760 cases of dementia were diagnosed. Among these, 304 died during the course of follow-up. The average period between diagnosis of dementia and death was 4.96 years ( $\pm 2.26$ ). We recorded 1962 deaths during the study. An association between the OH status and death was observed ( $P<0.0001$ ; Table S2 in the online-only Data Supplement). OH was associated with an increased risk of ~20% of incident dementia for conventional and mild OH thresholds (Table 2). This association seemed stronger using the severe OH threshold with an increased risk of incident dementia of 54% and 57% in the univariate and multivariate analyses, respectively. Most of these associations were found to be statistically significant.

In the sensitive analysis using the illness-death model, the relative risks of developing dementia were of the same

**Table 1. Comparison of the 3C Subjects According to Their OH Status at Baseline, n=7425**

Variables	N	Subjects Without OH (n=6447)	Subjects With OH (n=978)	P Value
Age, y, mean ( $\pm$ SD)	7425	73.39 ( $\pm 4.9$ )	74.27 ( $\pm 5$ )	<0.0001
Sex (% M)	7425	39.46	42.84	0.0440
BMI, mean ( $\pm$ SD)	7414	25.74 ( $\pm 4$ )	25.32 ( $\pm 4$ )	0.0023
SBP, mean ( $\pm$ SD)	7425	140.00 ( $\pm 20$ )	150.00 ( $\pm 22$ )	<0.0001
DBP, mean ( $\pm$ SD)	7425	80.00 ( $\pm 10$ )	85.00 ( $\pm 13$ )	<0.0001
HR, mean ( $\pm$ SD)	7410	67.00 ( $\pm 10$ )	67.50 ( $\pm 11$ )	0.3850
Cardiovascular history, %	7424	8.56	10.73	0.0250
Diabetes mellitus, %	7391	7.40	8.80	0.1060
Hypertension, %	7378	39.70	47.44	<0.0001
Active smoker, %	7379	35.53	32.82	0.1050
Dyslipidemia, %	7315	33.45	39.33	0.0650
Psychotropic medication, %	7425	25.56	26.07	0.7300
Hypotensive medication, %	7425	48.14	59.30	<0.0001
ApoE4, %	7234	20.32	21.72	0.3166
Cognitive status, %	7341	4.69	4.11	0.4210
Depression, %	7396	13.02	14.92	0.1040
Education, %	7412	24/36/20/20	24/35/22/19	0.9015

Cardiovascular history was defined as acute coronary syndrome, myocardial revascularization, and stroke; Diabetic status was defined by a level of fasting blood glucose  $\geq 7$  mmol/L or the intake of antidiabetic treatment (oral treatment or insulin); Dyslipidemia was defined by a cholesterol level  $> 5.2$  mmol/L or a hypolipidemic treatment; and Depression was defined by a CESD score of  $> 16$  for men and  $> 23$  for women. % indicates proportion; 3C, Three-City study; BMI, body mass index; CESD, Center for Epidemiology Studies-Depression; DBP, diastolic blood pressure in mm Hg; HR, heart rate per minute; M, male; SBP, systolic blood pressure in mm Hg; and SD, standard deviation.

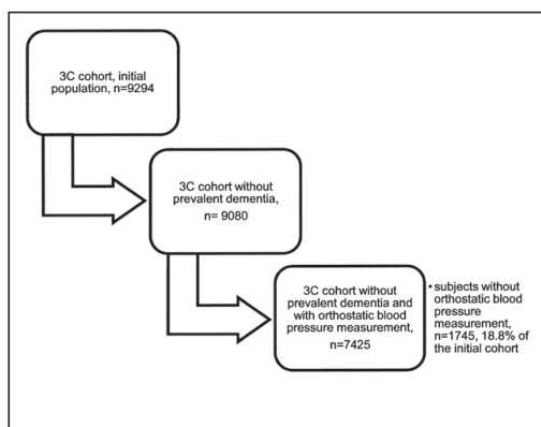
order of magnitude as in the Cox proportional hazard model (Table 2), regardless of the definition of OH.

In our second analysis, according to dementia pathogenesis (Alzheimer or vascular), we noted 512 incident Alzheimer cases, and 151 incident vascular dementia represented 87% of the overall incident dementia. The Cox regression analysis after adjustment did not show a significant association between OH and Alzheimer disease (hazard ratio, 1.19; 95% confidence interval, 0.91–1.57;  $P=0.212$ ) and between OH and vascular dementia (hazard ratio =1.42; 95% confidence interval, 0.92–2.15;  $P=0.111$ ), respectively.

**Discussion**

In the Three-City study, OH at baseline was associated with an increased risk of incident dementia during the 12 years of follow-up. This association is not explained by the initial differences in the distribution of risk factors of dementia because no significant differences were observed between the populations with and without OH, in terms of cognitive state ( $P=0.42$ ), depression score ( $P=0.10$ ), education level ( $P=0.90$ ), and ApoE4<sup>+</sup> status ( $P=0.31$ ).

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**Figure.** Flow chart of selection of participants from the Three-City (3C) study cohort.

**Table 2. Results From the Univariate and Multivariate Analyses of the Risk of Incident Dementia at 12 Years of Follow-Up**

Variable of Interest	Model 1 (n=7129)			Model 2 (n=6773)		
	HR	95% CI	PValue	HR	95% CI	PValue
<b>OH* (n=117)</b>						
Cox	1.19	0.98–1.46	0.0783	1.23	1.01–1.51	0.0457
ID model	1.26	1.03–1.53	0.0244	1.24	1.02–1.52	0.0412
<b>Mild OH* (n=278)</b>						
Cox	1.20	1.04–1.40	0.0149	1.23	1.05–1.43	0.0086
ID model	1.23	1.06–1.43	0.0074	1.23	1.05–1.43	0.0086
<b>Severe OH* (n=46)</b>						
Cox	1.54	1.15–2.08	0.0043	1.57	1.15–2.14	0.0043
ID model	1.51	1.11–2.04	0.0077	1.51	1.12–2.04	0.0077

Cox analysis compared with illness-death model of the Three-City study cohort, n=7425. For Cox analysis: Model 1, adjusted for center; Model 2, adjusted for center, diabetes mellitus, cardiovascular history, hypertension, APOE4\* status, education, depression, and cognitive status. For illness-death model (ID-model): Model 1, transition 0–1 (baseline to dementia) adjusted for center; transition 0–2 (baseline to death) adjusted for sex and center; Model 2, transition 0–1 adjusted for center, diabetes mellitus, cardiovascular history, hypertension, APOE4\* status, education, depression, and cognitive status.

OH: drop of >20 mm Hg for SBP or >10 mm Hg for DBP; mild OH: drop of >10 mm Hg for SBP or >5 mm Hg for DBP; and severe OH: drop of >30 mm Hg for SBP or >15 mm Hg for DBP. CI indicates confidence interval; HR, hazard ratio; ID, illness-death; and OH, orthostatic hypotension.

\*Incident dementia with OH.

Atrial fibrillation is another factor which has been described as associated to dementia.<sup>25</sup> However, in our study sample, if we noticed a slightly significant higher frequency of atrial fibrillation in subject with OH (3.46% versus 2.30%;  $P=0.0372$ ), atrial fibrillation was not associated to incident dementia (hazard ratio, 1.18; 95% confidence interval, 0.71–1.895;  $P=0.503$ ). Furthermore, the higher the prominence of OH, the stronger the association, with an increased risk of dementia of 50% observed for severe OH. Similar results were found in the sensitivity analysis with a dedicated method,<sup>23</sup> which reinforces the strength of the association.

Blood pressure drop in standing position is a marker of autonomic dysfunction and may lead to increased BP variability. Blood pressure variability has been studied through several markers: visit-to-visit variability, variability for 24H, and home blood pressure variability. The association of all of these markers with the increased incidence of cardiovascular events has been proven.<sup>26</sup> To date, visit-to-visit variability is the only marker able to predict incident dementia as a long-term marker of variability.<sup>27</sup> OH, which is a short-term marker of variability, offers additional evidence of the link between blood pressure variability and dementia.

This work, thus, provides new insight on the relationship between blood pressure and dementia. In mid-life adults, high blood pressure is associated with an increased risk of dementia.<sup>28–30</sup> High blood pressure and different cardiovascular risk factors result in accelerated vascular aging, structurally modifying both large and small arteries. About

the large arteries (the aorta in particular), the wall loses its elastic properties and grows stiffer. This arterial stiffness is accompanied by poorer blood pressure regulation, with an increase in blood pressure variability, and prevalence of OH.<sup>31</sup> In elderly individuals, we have now evidences<sup>27</sup> that it is the blood pressure variability not the blood pressure level which is associated with increased risk of dementia, leading to blood pressure surges accompanied by impaired cerebral microcirculation, most likely responsible for repeated episodes of ischemia.

However, contrary to other markers of blood pressure variability, OH has many causes. OH can be related to an insufficiency of the central regulation system of blood pressure as is the case for neurodegenerative diseases<sup>32</sup> (in particular, Parkinson's disease and diabetes mellitus) or to an inadequacy of the peripheral baroreceptors as is the case for vascular aging. Given this complexity, it is difficult to identify whether OH is a pure marker of vascular aging or whether it is an early marker of an ongoing neurodegenerative dementia process. Despite that OH is not more strongly associated to vascular dementia than Alzheimer disease in our second analysis, OH as a vascular aging marker lead seems to be the most likely for several reasons. First, in our cohort, subjects with OH are significantly older ( $P<0.0001$ ), hypertensive ( $P<0.0001$ ), and have a greater proportion of cardiovascular events ( $P=0.0250$ ) than those without OH (Table 1). So, this population with OH has a higher cardiovascular risk than those without. Furthermore, as aforementioned, many studies have shown that OH is a risk factor of cardiovascular events (coronary artery disease, heart failure, and stroke).<sup>2,33</sup> Otherwise, subjects in the Three-City study centers are screened during each visit to allow early diagnosis of dementia. Therefore, the possibility that OH remains for the years as the only sign of an ongoing dementia process is quite unlikely. Moreover, OH of central origin is generally associated with other dysautonomic signs, such as abnormal heart rate regulation. However, in our study, we did not observe any association between heart rate variability (defined as the difference between lying and standing heart rate) and incident dementia (hazard ratio=1.00; 95% confidence interval, 0.990–1.008;  $P=0.783$ ). Finally, diabetes mellitus is a frequent cause of dysautonomia and OH. However, in our study, there is no significant difference of diabetes mellitus distribution according to OH status ( $P=0.1060$ ; Table 1).

### Limitations

About 20% of the population did not have their blood pressure measured in standing position. This group does not have the same characteristics as the study sample (Table 1); in particular, the former is significantly older with a higher cardiovascular risk, thus, with increased risk of dementia and OH. The reasons why some subjects in the study did not have their blood pressure measured in standing position have not been specified in the database, but the proportion of missing data are somewhat similar in each of the 3 cities. This suggests that the reasons behind the lack of blood pressure measurements in standing position by investigators were similar and associated with the condition of patients (subject tiredness and clinical weakness seem evident here).

Our study incorporated a unique way of measuring orthostatism, which did not follow the general consensus on repeating the orthostatism measurements for 3 minutes, which, in turn, undeniably reduced the initial prevalence recorded in our study. Moreover, symptoms induced by OH were not collected at the start of the study. Indeed, symptomatic OH reflects the reality of cerebral hypoperfusion and could be better correlated to the clinical outcome. However, recent data suggest that symptomatic hypotension makes up <10% of OH and does not have a stronger association with occurrence of cardiovascular event than asymptomatic OH.<sup>34</sup>

These limitations could partially explain the relatively weak prevalence of OH of  $\approx 13\%$  compared with other studies. However, this does not question the strength of the association between OH and dementia, which is probably underestimated as a result of these limitations.

An important limitation of the current results is the lack of representativeness of the Three-City study sample. Because the participation rate was  $\approx 37\%$ ,<sup>9</sup> our sample was, therefore, not representative of the general population, and the association observed might not be true in the general population.

### Conclusion and Perspectives

OH, a simple marker of blood pressure variability, is associated with an increased risk of developing dementia of about at least 25%. Thus, it could help to identify subjects with high risk of dementia.

Moreover, it raises the question of the need to take into account blood pressure variability and in particular OH among subjects with high risk of dementia and to test whether reducing OH could reduce the incidence of dementia.

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### Disclosures

None.

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### Novelty and Significance

#### What Is New?

- Orthostatic hypotension (OH) is strongly associated with incident dementia.
- This work highlights the particular relationship between blood pressure and brain aging according to the age of the subject.

#### What Is Relevant?

- Two different statistical methods and different OH thresholds were used in a large cohort of subject with an important follow-up and, therefore, confirmed the strength of the association.

- OH is a common situation, in particular, in old subject, and, thus, could help to identify subjects with a high risk of dementia.

#### Summary

Because OH is common and easy to measure, OH measurements could help to identify subjects with higher risk of dementia.



# Hypertension

## Original Article

# Orthostatic hypotension: a marker of blood pressure variability and arterial stiffness: a cross-sectional study on an elderly population: the 3-City study

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**Background:** Orthostatic hypotension, blood pressure (BP) variability, and arterial stiffness are three markers of cardiovascular risk beyond the average BP. However, the relationships between these three parameters are not well known.

**Aim:** To examine the relationships between orthostatic hypotension, BP variability, and arterial stiffness.

**Methods and results:** In the Three-City study, a sample of 1151 elderly participants (mean age = 80 ± 3 years) was screened for orthostatic hypotension, undertook home BP and pulse wave velocity (PWV) measurements. We performed logistic regression analyses to look at the associations between orthostatic hypotension and both day-to-day (D-to-D) BP variability quartiles and PWV quartiles. Orthostatic hypotension was detected in 210 participants who were more likely to be hypertensive, exhibit higher BP variability and have increased arterial stiffness. In the multivariate logistic regression analysis, the frequency of orthostatic hypotension increased by 20% with every quartile of D-to-D SBP variability and by 20% with every quartile of PWV. PWV and D-to-D BP variability were not associated. In stratified analysis, the use of beta-blocker changes these relationships: orthostatic hypotension was not associated to PWV anymore but its association with D-to-D SBP variability was apparently stronger.

**Conclusion:** In this large sample of elderly individuals, orthostatic hypotension was independently associated with both BP variability and PWV. BP variability being more indicative of a baroreflex dysfunction and PWV being a marker of vascular ageing, these two components would participate to the orthostatic hypotension mechanisms.

**Keywords:** arterial stiffness, baroreflex impairment, beta-blocker, blood pressure variability, orthostatic hypotension

**Abbreviations:** BP, blood pressure; HR, heart rate; PWV, pulse wave velocity

## INTRODUCTION

Orthostatic hypotension defined as a drop in blood pressure (BP) on standing up, is associated with increased risk of mortality [1,2], occurrence of cardiovascular events [3] and dementia [4–6] in the general

population. Day-to-day (D-to-D) BP variability shares the same kind of risk for cardiovascular diseases [7,8] and dementia [9]. Moreover, orthostatic hypotension and D-to-D BP variability seem to have a common physiopathology via the baroreflex function [10,11]. Thus, an association has been found between orthostatic hypotension and D-to-D BP variability which reinforces its physiopathology hypothesis [12].

Arterial stiffness has also proven its association with cardiovascular disease [13,14] and cognitive decline [15]. Vascular ageing decreases arterial elasticity and could possibly decrease the carotid baroreceptor sensitivity to BP changes [16]. Indeed arterial stiffness and baroreflex sensitivity have demonstrated their association in different populations [17,18] as well as arterial stiffness with short-term BP variability [19]. However, this explanation is not fully convincing. The baroreceptors are reset every minute to allow a quick adaptation of BP [20] which contrasts with a very stable parameter which is arterial stiffness. Moreover, it has been suggested recently, that the link from arterial stiffness to orthostatic hypotension may be due to a loss of the cushioning effect of the ascending aorta and to an early return of pressure waves [21].

In the Three-City study, a study from the French general population, a sample from the Dijon study was screened for orthostatic hypotension and also undertook home BP and pulse wave velocity (PWV) measurements.

This population sample gives us a unique opportunity to determine the relationships between orthostatic hypotension, BP variability and arterial stiffness in a cross-sectional study to clarify the relationship between three major markers of cardiovascular risk.

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## MATERIALS AND METHODS

### Study population

The Three-City study is a study from the French general population, comprising 9294 individuals, over the age of 65 years, randomly selected from the electoral lists of Bordeaux, Dijon, and Montpellier, recruited between 1999 and 2001 [22].

Around visit 5 (10 years after inclusion in the study) individuals from the Dijon centre were invited to benefit from several additional measurements, including PWV assessment and home BP measurements. These two sets of analyses were carried out at different times than visit 5 but within the same year.

### Measurement of blood pressure and heart rate in sitting and standing position

At visit 5, BP measurements were performed on the participants from the Dijon centre according to the following protocol: first, participants were in sitting position, and left to rest in this position for 5 min, with a cuff placed on the right arm, adjusted to the arm circumference. The cuff was connected to an Omron M4 (Kyoto, Japan), an oscillometric validated automatic BP device and three consecutive BP measurements were taken. The mean value of the last two BP measurements was retained for the analysis. For each BP measurement, heart rate (HR) was measured by the automatic pressure device in sitting position and averaged.

Orthostatic hypotension was then detected according to guidelines [23]. BP was measured at 1, 2, and 3 min after standing up. Orthostatic hypotension was defined as a drop of SBP greater than 20 mmHg or a drop in DBP greater than 10 mmHg between sitting and standing BP after 1, 2, or 3 min of standing [23]. HR was measured for each series of BP measurements at 1, 2, and 3 min after standing up.

### Home blood pressure measurement protocol and day-to-day blood pressure variability

The participants of Dijon were invited in a nested interventional study investigating the role of home BP measurement on dementia [24]. The home BP measurement was performed with the same device following the recommendations of the French Hypertension Society with three measurements in the morning before taking any treatment and three measurements in the evening after dinner over three consecutive days thus producing 18 measurements used for calculation of mean home BP. D-to-D BP variability was estimated by the SD and coefficient of variation for SBP and DBP based on the 18 BP measurements. SD and coefficient of variation are the two established approaches and are the most suitable for studying D-to-D BP variability [25]. Quartiles of D-to-D BP variability were used in the main analysis.

### Pulse wave velocity measurements

Carotid–femoral PWV measurements were performed on participants from the Dijon centre. After measuring the brachial BP following the same method as at follow-up 5, the distance  $dl$  between the two tonometric sites (carotid and femoral) relative to the sternal notch was measured

using a tape measure. The carotid and femoral pressure waves were then detected using tonometry. It is thus possible to measure the time delay  $dt$  between these two recordings. The speed at which the pressure wave travels from the carotid to the femoral artery is therefore equal to  $0.8 \times dl/dt$  and is estimated in m/s [26,27]. The measurements were performed with the SphygmoCor tonometer (AtCor Medical, Sydney, New South Wales, Australia). Quartiles of PWV were used for the analysis.

### Factors associated with the occurrence of orthostatic hypotension

**Age:** Despite participants were seen at three different times during the various BP measurements protocols but within the same year, the age at visit 5 was used for the statistical analysis.

**Hypotensive treatment:** Use of hypotensive treatment for indicated arterial hypertension and other cardiovascular indications (coronary artery disease, arrhythmias, and heart failure).

**Beta-blockers:** including the use of acebutolol, bisoprolol, atenolol, celiprolol, nebivolol, propranolol, sotalol, or metoprolol.

Hypertensive status is defined by SBP more than 140 mmHg or DBP more than 90 mmHg or the use of anti-hypertensive treatment at the time of consultation during visit 5.

Diabetic status was defined by a level of fasting blood glucose greater than 7 mmol/l or the use of anti-diabetic treatment at visit 5.

History of stroke (ischaemic or haemorrhagic), myocardial infarction, and heart failure were reported during the visit-5 interview.

### Other factors

Dyslipidaemia was defined by the use of hypolipidemic treatment or by total cholesterol level more than 5.2 mmol/l at visit 5.

The status of an active smoker was defined by active smoking or having quit smoking for less than 6 months at the time of visit 5.

### Statistical analyses

The analysis was carried out on the population sample who had BP measurements in standing position, home BP and PWV measurements. The sample was described by orthostatic hypotension status according to the consensus definition, using the chi-square test for the qualitative variables and the Student  $t$  test for the quantitative variables. Continuous variables were presented by mean value with its SD. They were tested for normality. Qualitative variables were presented by a proportion.

Logistic regressions analyses were used to explain the occurrence of orthostatic hypotension as it seems more illustrative to apprehend these variables in quartiles. Log-linearity was tested for both D-to-D BP variability and PWV.

We first looked at the univariate analysis with both D-to-D BP variability quartiles and PWV quartiles. We then performed multivariate regression analyses using the backward stepwise technique. We thus included all the variables associated with orthostatic hypotension in the initial model.

## Orthostatic hypotension A marker of blood pressure variability

The variables not statistically associated with orthostatic hypotension were then removed one at a time, starting with the variable with the largest *P* value. We repeated this procedure until all the remaining variables retained in the model were associated with orthostatic hypotension with a significance threshold *P* less than 0.05.

Two multivariate models were therefore constructed to capture the maximum of information linked to the BP and hypertensive status and to avoid over correlation with D-to-D BP variability and PWV.

Model 1 is based on mean home SBP (which is assumed to be the most associated with cardiovascular prognosis compare with office BP) and the use of hypotensive treatment.

Model 2 is based on hypertensive status at visit 5 which also takes into account BP during the consultation and the use of hypotensive treatment.

We investigated interactions among the principal variables, particularly between D-to-D BP variability, PWV, and sex.

We then plotted a three-dimensional bar graph of the relations between the systolic SD quartile, the PWV quartile, and the orthostatic hypotension proportion.

In a secondary analysis, we stratified the main analysis according to the presence of a beta-blocker to explore further the role of the baroreflex loop and its association with the D-to-D BP variability and PWV.

Finally, we explored the association between D-to-D BP variability and PWV quartiles via a logistic regression analysis according to the same methodology of the main analysis. Logistic regression was chosen for being close to the main analysis but linear regression with continuous variables showed the same results.

We performed analyses with SAS 9.4 (Cary, North Carolina, USA) and Excel 2010 (Microsoft, Redmond, Washington, USA). The threshold of significance *P* less than 0.05 was used.

## RESULTS

Out of the 4920 participants included in the baseline Dijon study, 2283 showed up for visit 5, 1733 followed the home BP measurement protocol and 1561 had measurements of PWV. The entire series of BP and hemodynamic measurements were performed on 1151 participants in total.

The sample comprises elderly people (mean age =  $80 \pm 3$  years) and is predominantly female (60%). Included participants were comparable with nonincluded participants except for age, (80.06 vs. 81.40 years,  $P < 0.0001$ ).

Using the consensus definition [23], orthostatic hypotension was detected in 210 participants, representing 18% of the sample. During the BP measurements in standing position, from the first set of measurements, 81% of the total participants were diagnosed with orthostatic hypotension ( $n = 146/210$ ). It is during this first measurement that we observed the greatest drop in SBP ( $-21.75$  vs.  $13.91$  mmHg in the following measurement). The SBP values, regardless of the method and time of measurement (office during visit 5, during PWV measurement or home BP measurement) are all significantly associated with orthostatic hypotension. This is not the case for DBP (Table 1) apart from the initial

measurement taken just prior to standing up at visit 5. Participants with orthostatic hypotension were more likely to be hypertensive ( $P = 0.013$ ), have increased arterial stiffness (PWV:  $15.5$  vs.  $14.5$  m/s  $P < 0.0001$ ) and exhibit higher D-to-D BP variability [systolic SD:  $11.84$  vs.  $10.85$  mmHg ( $P = 0.001$ )] (Table 1). Only 119 participants of the whole study showed an HR decrease in response to orthostatism with no statistical difference according to orthostatic hypotension status.

Among the other factors usually associated with orthostatic hypotension, only the use of hypotensive drugs was associated with orthostatic hypotension and in particular the use of a beta-blocker ( $P = 0.039$ ). Participants under beta-blocker are more likely diabetic ( $P = 0.002$ ) and associated with heart failure ( $P < 0.0001$ ) (Annex 1, <http://links.lww.com/HJH/B266>).

In the multivariate logistic regression analysis, the prevalence of orthostatic hypotension increased by 20% with every quartile of D-to-D BP variability and by 20% with every quartile of PWV, regardless of the measurement considered (Table 2) and independently of BP level. This main result is illustrated by Fig. 1 which shows that the prevalence of orthostatic hypotension increases for each quartile of systolic SD D-to-D BP and PWV separately and the increase is steeper when both systolic SD D-to-D BP and PWV are increasing.

In the secondary analysis, the intake of beta-blocker influences the association between our variables of interest. In the subgroup with beta-blocker intake, the association of PWV with orthostatic hypotension disappears but the association with systolic SD D-to-D BP is stronger. In the absence of a beta-blocker, we observed the opposite (Table 3). These results are not explained by the different prevalence of diabetes mellitus or heart failure between these two subgroups. Indeed these two variables are not associated with orthostatic hypotension in each of the subgroups (with or without beta-blocker) and do not change the results of the multivariate analysis when they are forced into the models.

Finally, we did not find any association between PWV and systolic SD D-to-D BP (Annex 2, <http://links.lww.com/HJH/B267>).

## DISCUSSION

The main finding of this study is that orthostatic hypotension is associated with both systolic D-to-D BP variability and PWV in a large elderly population-based sample.

The sample is rather homogenous with a mean age above 80 years and presenting marked arterial stiffness (mean PWV =  $14.71 \pm 3.25$ ) as expected. The responses of HR to the standing position show a large majority of acceleration of the HR (90% of the sample). In essence, this population is in good health without major cardiovascular comorbidities or neurodegenerative disorders. Thus, orthostatic hypotension characteristics are consistent with idiopathic orthostatic hypotension [28]. The causes of these types of orthostatic hypotension are unknown and vascular ageing is the likely hypothesis. It may, therefore, be surprising to find no association between age and orthostatic hypotension. However, this is explained by the very



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**TABLE 1. Description of the population according to the occurrence of an orthostatic hypotension**

	N	OH+, N=210	OH-, N=942	P value
Age (SD)	1151	80.28 (3.79)	80.01 (3.81)	0.354
% Male	1151	49.48	37.82	0.003
BMI (SD)	1151	25.87 (3.68)	25.94 (3.80)	0.808
% Diabetes mellitus	1130	10.58	9.26	0.556
% Dyslipidaemia	1148	41.29	39.85	0.705
% Active smoker	1150	5.71	2.87	0.178
% Hypertensive	1146	65.85	55.14	0.005
% Stroke, n	1151	0.48 (1)	1.28 (12)	0.585
% MI, n	1151	1.42 (3)	0.00 (0)	0.508
% Heart failure, n	1151	1.42 (3)	2.66 (25)	0.323
% Cancer, n	1151	11.90 (25)	10.00 (94)	0.412
SBP V5 (SD)	1151	153.09 (18.52)	138.86 (17.64)	<0.0001
DBP V5 (SD)	1151	77.27 (9.82)	73.09 (9.60)	<0.0001
HR V5 (SD)	1037	68.04 (11.55)	69.80 (10.95)	0.043
SBP-home BP (SD)	1146	144.80 (16.86)	141.00 (16.52)	0.003
DBP-home BP (SD)	1146	73.70 (8.90)	73.33 (8.74)	0.800
SBP-PWV (SD)	1151	146.5 (18.99)	140.40 (16.53)	<0.0001
DBP-PWV (SD)	1151	73.19 (9.25)	72.32 (8.66)	0.200
HR-PWV (SD)	1151	61.46 (9.73)	62.64 (9.59)	0.110
Diff-SBP1 (SD)	1146	21.75 (13.18)	3.55 (10.64)	<0.0001
Diff-SBP2 (SD)	1142	13.91 (12.06)	-1.56 (9.80)	<0.0001
Diff-SBP3 (SD)	1137	13.91 (13.51)	-2.48 (10.20)	<0.0001
Diff-DBP1 (SD)	1146	3.79 (7.21)	-2.89 (6.44)	<0.0001
Diff-DBP2 (SD)	1142	1.19 (8.15)	-4.75 (6.39)	<0.0001
Diff-DBP3 (SD)	1137	-0.06 (6.67)	-4.93 (6.11)	<0.0001
Diff-HR1 (SD)	1035	-5.08 (5.47)	-4.53 (4.69)	0.147
Diff-HR2 (SD)	1031	-4.20 (5.23)	-3.87 (4.33)	0.370
Diff-HR3 (SD)	1026	-4.98 (4.94)	-3.83 (4.39)	0.001
PWV (SD)	1151	15.49 (3.51)	14.53 (3.17)	0.0001
SSD-D-to-D (SD)	1144	11.84 (4.35)	10.85 (3.96)	0.001
SCV-D-to-D (SD)	1144	8.17 (2.83)	7.68 (2.62)	0.018
% Hypotens-Med	1151	71.90	62.27	0.008
% Beta blocker, n	1151	31.90 (67)	15.19 (143)	0.039
% Calcium blocker, n	1151	20.48 (43)	16.58 (156)	0.177
% RAS blocker, n	1151	44.29 (93)	36.13 (340)	0.013
% Diuretic, n	1151	17.62 (37)	19.55 (184)	0.519

Beta blocker, proportion of participants with beta blocker; Diff-DBP (1,2,3), difference between mean DBP in sitting position and DBP in standing position (1, 2, and 3 min); Diff-HR (1,2,3), difference between mean HR in sitting position and HR in standing position (1, 2, and 3 min); Diff-SBP (1,2,3), difference between mean SBP in sitting position and SBP in standing position (1, 2, and 3 min); HR, heart rate; Hypotens-Med, use of hypotensive treatment for indicated arterial hypertension and other cardiovascular indications at visit 5; MI, proportion of participants with a history of myocardial infarction; OH, orthostatic hypotension; PWV, pulse wave velocity; RAS, renin-angiotensin system; SCV-D-to-D, coefficient of variation of day-to-day SBP; SSD-D-to-D, standard deviation of day-to-day SBP; Stroke, proportion of participants with history of stroke; V5, visit-5.

homogenous age distribution as participants are  $80 \pm 3$  years old, which masks the effect of age.

In our main analysis, orthostatic hypotension was independently associated to both PWV and D-to-D BP variability. These two parameters have already been described as being associated with orthostatic hypotension but have never been

studied simultaneously. The results from this analysis help to better understand the relationships between these different hemodynamic markers. Indeed in our models, orthostatic hypotension is associated with both D-to-D BP variability and PWV but PWV is not associated with D-to-D BP variability (Annex 2, <http://links.lww.com/HJH/B267>). D-to-D BP

**TABLE 2. Logistic regression of occurrence of orthostatic hypotension (N=210) according to day-to-day systolic BP variability and pulse wave velocity in the Three-City cohort (N=1151)**

	SSD-D-to-D per quartiles		PWVSD per quartiles		SCV-D-to-D per quartiles		PWVCV per quartiles	
	OR	P value	OR	P value	OR	P value	OR	P value
Univariate	1.203 1.048–1.381	0.009	1.221 1.038–1.435	0.015	1.169 1.016–1.345	0.029	1.211 1.055–1.389	0.006
Model 1	1.170 1.011–1.354	0.034	1.208 1.021–1.429	0.027	1.159 1.005–1.335	0.042	1.183 1.027–1.363	0.020
Model 2	1.143 0.988–1.321	0.072	1.223 1.033–1.447	0.019	1.220 1.050–1.416	0.009	1.161 1.001–1.346	0.048

Model 1: N=1133; adjusted for sex, age, home SBP measurements. Model 2: N=1112; adjusted for sex, age, hypertension status during follow-up 5. CI, confidence interval; OR, odds ratio; PWV, pulse wave velocity; PWVCV, quartiles of PWV for the analysis with SCV day-to-day BP; PWVSD, quartiles of PWV for the analysis with SSD day-to-day BP; SCV, systolic coefficient of variation; SCV-D-to-D, coefficient of variation of day-to-day SBP; SSD, systolic standard deviation; SSD-D-to-D, standard deviation of day-to-day SBP.

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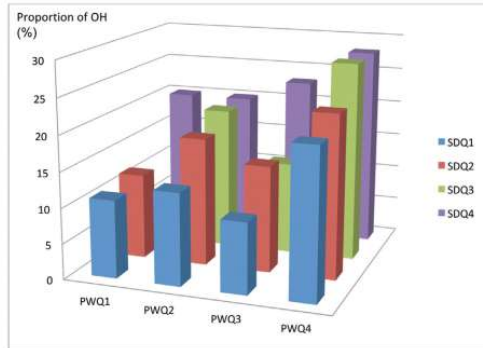


FIGURE 1 Proportion of orthostatic hypotension according quartiles of pulse wave velocity and quartiles of systolic SD day-to-day blood pressure.

variability and PWV, therefore, do not measure the same phenomenon and orthostatic hypotension is associated with both.

In the case of stiff arteries, the early return of the pressure waves to the heart and the loss of compliance of the aorta during diastole may contribute to the drop in BP. This explanation has been proposed by Sung *et al.* [21] based on the association they found between PWV and orthostatic hypotension in a general population. But the hypothesis that arterial stiffness alters the quality of baroreceptors, particularly the carotid baroreceptor, resulting in an increase in BP variability is therefore called into question [29].

On standing up, the sympathetic nervous system is immediately activated, mainly by mechanoreceptors in the heart and the aorta. The latter contribute to an acceleration of the HR, an increase of myocardial inotropism and peripheral resistance to restore the initial level of BP [30]. Therefore, in the case of autonomic system dysfunction, we can observe large short term BP variability and orthostatic hypotension [31]. Indeed, in our stratified analysis, the

intake of beta-blockers by reducing the adrenergic response to the standing position induces an increase of BP variability (Table 3). This is consistent with the analysis of Coats *et al.* which showed that a more stable HR that results from an ineffective baroreflex is associated with a more variable SBP [32]. At the opposite, in the absence of beta-blockers and with a more effective baroreflex loop, arterial stiffness is the most predominant component of orthostatic hypotension in our study (Table 3).

This interpretation of the data is supported by several studies. First, in the Paris Prospective study III, Sharman *et al.* [33] showed that impaired baroreflex sensitivity but not carotid stiffness is independently associated with exaggerated exercise BP which is basically another way to measure BP variability. The results from DENER-HTN trial showed that short-term night-time BP variability is associated with the BP response to renal denervation and therefore of the adrenergic tone [34]. In addition it has been shown that beta-blockers increased the risk of both orthostatic hypotension [35,36] and BP variability [37,38], thus strengthening our hypothesis. BP variability seems to be therefore a better marker of sympathetic activity than arterial stiffness.

However, the links between short-term BP variability and arterial stiffness have been demonstrated in hypertensive patients (with or without treatment) previously [19]. But we can note some critical differences with our study. First, with a mean age of 49 years old and a larger distribution ( $\pm 11$ ), this population is much younger than our study sample (mean age 80 years old). Second, the compliance of the aorta is considered normal with a mean PWV value around 9.3 m/s, while in our study, mean PWV is around 15 m/s which indicates very stiff arteries (even if these values are expected in such range of age [39]). Moreover, authors admitted that contribution of BP variability to aortic stiffness was of limited size and that mechanisms which linked one to the other were unsolved. We could assume that this association has been found because they both provide evidence for global individual ageing with parallel

TABLE 3. Stratified logistic regression of occurrence of orthostatic hypotension (N = 210) according to the intake of beta-blocker in the Three-City cohort (N = 1151)

	SSD-D-to-D per quartiles		PWVSD per quartiles		SCV-D-to-D per quartiles		PWVVCV per quartiles	
	OR 95% CI	P value	OR 95% CI	P value	OR 95% CI	P value	OR 95% CI	P value
Population with intake of beta-blocker (N = 302, OH = 67)								
Univariate	1.360 1.065–1.736	0.013	1.007 0.768–1.321	0.958	1.354 1.046–1.753	0.021	1.028 0.808–1.307	0.824
Model 1	1.354 1.052–1.743	0.019	1.007 0.763–1.329	0.960	1.334 1.029–1.731	0.030	0.995 0.778–1.272	0.968
Model 2	1.313 0.990–1.729	0.05	0.921 0.676–1.255	0.604	1.318 0.999–1.754	0.051	0.941 0.716–1.237	0.663
Population without intake of beta-blocker (N = 849, OH = 143)								
Univariate	1.093 0.919–1.300	0.316	1.371 1.118–1.681	0.002	1.075 0.907–1.273	0.404	1.310 1.107–1.551	0.002
Model 1	1.050 0.873–1.265	0.602	1.351 1.090–1.674	0.006	1.078 0.907–1.280	0.395	1.302 1.093–1.551	0.003
Model 2	1.147 0.954–1.380	0.145	1.330 1.061–1.666	0.013	1.055 0.888–1.254	0.542	1.308 1.099–1.558	0.002

Model 1: adjusted for sex, age, home SBP measurements. Model 2: adjusted for sex, age, hypertension status during follow-up 5. CI, confidence interval; OH, orthostatic hypotension; OR, odds ratio; PWV, pulse wave velocity; PWVVCV, quartiles of PWV for the analysis with SCV day-to-day BP; PWVSD, quartiles of PWV for the analysis with SSD day-to-day BP; SCV, systolic coefficient of variation; SCV-D-to-D, coefficient of variation of day-to-day SBP; SSD, systolic standard deviation; SSD-D-to-D, standard deviation of day-to-day SBP.

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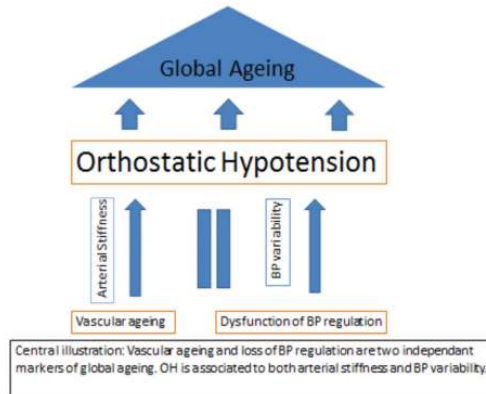


FIGURE 2 Illustration and key message.

trajectories [40]. This relation probably disappears in our elderly population because of the small age range which gave us a unique opportunity to show this double component of the orthostatic hypotension fully and truly adjusted over calendar age.

A potential interpretation of our results is therefore that orthostatic hypotension would have a mechanical part (approached by arterial stiffness) and an adrenergic part (BP variability) (Fig. 2).

### Limitations

The current study is cross-sectional with intrinsic limitations. It could help in understanding the relationships between three major markers of cardiovascular risk there is no possible cause-consequence conclusion between them.

Because, the participants of this study are volunteers from the general population, there is a potential self-participation bias. Thus, the sample is not representative of the population and the results of these analyses cannot be generalized.

The protocol for diagnosing orthostatic hypotension is rigorous and difficult to implement in clinical practice. Indeed, after 5 min of rest in lying position, the participant must stand up and undertake three measurements at 1, 2, and 3 min intervals in standing position. In this study, the initial measurement is made in a sitting position. However, in clinical practice, orthostatic hypotension is more often detected from measurements in sitting position and this is how we show the association of orthostatic hypotension with the occurrence of dementia in this sample [41]. Furthermore, the medical community agrees that a single measurement in a sitting position and a single measurement in standing position are acceptable [42] even though the diagnostic thresholds may need to be revisited [43]. Based on these points, we can consider the screening of orthostatic hypotension in this study acceptable.

The different hemodynamic parameters are measured at different times. This is particularly true for PWV which is measured, on average, 6 months after visit 5. However, although the age difference is statistically significant

between visit 5 and when the PWV measurement took place, this difference is not clinically relevant (6 months) in view of the age of the participants and the relative stability of PWV at these advanced ages [44]. The same applies to the series of home measurements, even if it is not possible to be 100% sure that there was no medical intervention between visit 5 and the home BP measurement.

In conclusion, orthostatic hypotension is a major cardiovascular risk marker that takes into accounts two well-known cardiovascular risk factors: D-to-D BP variability and arterial stiffness.

BP variability is more likely informative of a baroreflex impairment while PWV is a marker of vascular ageing which are two independent components of the orthostatic hypotension mechanisms.

Beta-blockers are more likely to induce an orthostatic hypotension via a less effective baroreflex which can be approached by a wider D-to-D BP variability. Therefore, this class should be avoid in patients with high risk of orthostatic hypotension.

Finally, screening for orthostatic hypotension should be done more systematically to improve cardiovascular risk assessment.

### ACKNOWLEDGEMENTS

#### Conflicts of interest

There are no conflicts of interest.

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# Screening for orthostatic hypotension using home blood pressure measurements

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**Objective:** Orthostatic hypotension is a common condition associated with adverse cardiovascular and cognitive prognosis. Screening for orthostatic hypotension consists of blood pressure measurements in supine (or sitting) and standing position during clinical consultations. As orthostatic hypotension is a poorly reproducible clinical condition, it is likely that the simple measurement carried out during consultations underestimates the true prevalence of the condition. The objective of this study is, therefore, to determine whether screening for orthostatic hypotension with home blood pressure measurements (HBPM) may improve orthostatic hypotension diagnosis without compromising the quality of the blood pressure readings.

**Materials and methods:** We asked all patients with indications for HBPM in the hypertension unit and in a general medical practice to perform a series of home blood pressure measurements, ending each series with a measurement in standing position.

**Results:** We recruited 505 patients of mean age 68 years of which 93% were hypertensive patients. The success rate of HBPM complying with the ESH criteria (12 out of 18 measurements) was 94.5%, which is comparable with previously published series of measurements. Ninety-one percent of patients measured their blood pressure at least once in standing position, and 88% of patients recorded all six standing measurements. Orthostatic hypotension prevalence defined as the presence of one episode of orthostatic hypotension was 37.47%, much higher than orthostatic hypotension prevalence measured in the same cohort in a clinic setting (15%).

**Conclusion:** The measurement of blood pressure in standing position during HBPM is feasible without altering the quality of the blood pressure readings in seated position. Our findings show that orthostatic hypotension is significantly more often detected at home by the patient than at the doctor's office, which may allow quicker initiation of preventive and therapeutic strategies.

**Keywords:** home blood pressure measurement, hypertension, orthostatic hypotension, screening

**Abbreviations:** BP, blood pressure; ESH, European Society of Hypertension; HBPM, home blood pressure measurement

## INTRODUCTION

The drop in blood pressure (BP) in response to orthostatism is a common condition. Consequently, about 6–10% of the general population [1,2] experience a decrease in SBP of more than 20 mmHg or a DBP drop of more than 10 mmHg on standing up, the consensus definition of orthostatic hypotension (OH) [3]. Orthostatic hypotension is associated with increased mortality and risk of cardiovascular events (coronary events, heart failure and stroke) [1], as well as increased risk of dementia [2]. This clinical sign is, therefore, associated with unfavorable prognosis, thus justifying effective systematic screening for orthostatic hypotension.

The fall in blood pressure on standing up is a poorly reproducible condition [4,5]. Given the multiple reasons behind the lack of reproducibility, the simple screening for orthostatic hypotension during consultation could miss the diagnosis. Moreover, changes in blood pressure observed during consultation can be biased by the medical or para-medical presence with a significant occurrence of white-coat hypertension or its obverse – masked hypertension. Today, these blood pressure phenotypes justify the use of BP measurements outside the clinic setting in the management of arterial hypertension [6]. Home blood pressure measurements (HBPM) are recommended to confirm the diagnosis of hypertension and monitor blood pressure [7]. This technique consists of performing repeated BP measurements in standard condition outside the clinic setting. It has been well established that HBPM are more strongly associated with cardiovascular events and mortality than office BP measurements [8,9]. Consequently, orthostatic hypotension screening based on HBPM may also be more relevant than office screening.

Before responding to these important questions, it is necessary to check the feasibility of measuring BP in

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standing position out of a clinic setting. Therefore, we decided to test the feasibility of screening for orthostatic hypotension using an original protocol for HBPM.

## MATERIALS AND METHOD

### Study population

The study constituted all adult patients who consecutively consulted the Fleurance and Montestruc-sur-Gers general medical practice, in Gers, France, as well as the Hypertension Excellence Center (HEC) of the Bordeaux Hospital University Center (CHU), in Bordeaux, France. HBPM was proposed in the two following cases: to confirm high BP before starting antihypertensive treatment, to check blood pressure control in treated hypertensive patients. Patients were informed of the study and gave their oral consent to participate. The exclusion criteria included a patient's inability to stand in an upright position, a patient's failure to obtain a home BP measuring device and/or a patient's refusal to participate in the study.

### Clinic blood pressure measurement

Blood pressure measurements in the clinic setting were carried out following the practice guidelines recommended by the European Society for Hypertension (ESH), three measurements in sitting or supine position with a cuff adapted to the size of the arm circumference [10] after a period of rest of 5 min. The size of the cuff was standard for the large majority of patients (12 wide and 26 cm long) but were longer for obese adults (12 cm wide and 40 cm long) or shorter for lean adults (12 wide and 18 cm long).

In the general practice, blood pressure measurements were performed with validated automated oscillometric devices, whereas the auscultatory method with mercury sphygmomanometer was used in the HEC.

After the last measurement in supine or sitting position, the patient was asked to stand up and a new single measurement was performed immediately upon standing.

Clinical hypertension is defined as SBP greater than 140 mmHg or DBP greater than 90 mmHg based on an average of the two measurements or as current use of antihypertensive treatment.

Orthostatic hypotension is defined by expert consensus using the agreed threshold [3] of a fall in SBP of more than 20 mmHg or DBP of more than 10 mmHg at orthostatism compared with the previous BP measurement in supine or sitting position.

### Procedure for home measurement of blood pressure

The devices used to carry out HBPM were automated oscillometric measuring devices belonging to the patient or borrowed from the doctor. In the former case, the patient was requested to bring in the device for comparison with the reference measuring device used in the clinic setting. Three simultaneous measurements with each device positioned on separate arms were performed and averaged. Agreement between the two devices was determined by a mean difference below 10 mmHg for systolic and below 5 mmHg for diastolic.

The HBPM protocol consisted of performing four consecutive BP measurements, three in sitting position,

followed by one in standing position twice a day – in the morning just after waking up and before taking any medication, and in the evening after dinner. These series of measurements were repeated over three consecutive days to stay close from the French Society of Hypertension guidelines, resulting in a total of 24 BP measurements, 18 in sitting position and six in standing position [11].

### Other variables

Diabetic status was defined by a level of fasting blood glucose greater than 7 mmol/l or the use of antidiabetic treatment (oral treatment or insulin). Smoking status accounted for nonsmokers, and former and active smokers. Former smokers were defined as having had quit smoking for at least 6 months.

Patients were considered dyslipidemic if their total cholesterol level was greater than 5.2 mmol/l or if they were taking hypolipidemic treatment. Cardiovascular history was defined as the record of at least one coronary event, heart failure or stroke in the patient's medical file.

### Statistical analysis

We performed a descriptive analysis of the total sample by center using the Student's *t*-test and the chi-square test.

To evaluate the quality of the HBPM, we measured the proportion of HBPM that met the ESH qualitative criteria, that is, the completion of at least 12 out of the 18 BP measurements at home in sitting position [6,12].

Then, regarding the BP measurements in standing position, we considered records containing at least one BP standing measurement and those with the full set of BP measurements in standing position (six measurements in total).

We then ran a logistic regression analysis with the diagnosis of orthostatic hypotension using HBPM as the dependent variable and the presence of clinic orthostatic hypotension as the main explanatory variable. Additional adjustment variables were selected a priori from the variables known to be associated with orthostatic hypotension or cardiovascular event. We explored for interactions between the main explanatory variables. We verified the log-linearity of the quantitative variables. A backward stepwise regression analysis was carried out on a fixed sample size by conserving only the adjustment variables associated with a *P* value less than 0.005.

The statistical analysis was performed using SAS version 9.4 (SAS Institute Inc., Cary, North Carolina, USA).

## RESULTS

We included in this study, 505 patients allowing us to collect 505 records of HBPM including measurements of standing blood pressure over a period of 1 year from 1 January to 31 December 2016. The characteristics of the study population are presented in Table 1.

It is important to note that 75% of HBPM records were collected from patients in the general practice (center 1). There were marked differences among patients from the two centers because of the different activity focus of each center. In the hypertension (HT) unit (center 2), the population is younger (mean age = 58.67 versus 70.58,

**TABLE 1. Description of the studied population according to the presence of at least one episode of orthostatic hypotension during the home blood pressure measurements**

	Patient with orthostatic hypotension (n = 189)	Patient without orthostatic hypotension (n = 316)	P value
Women (%)	51.6	47.8	0.40
Age (mean)	71.1	65.8	<0.001
BMI greater than 25 (%)	66.9	75.8	0.08
HTN (%)	94.1	94.0	0.95
Smoker (%)	12.5	13.7	0.70
Diabetes mellitus (%)	17.4	18.2	0.82
Dyslipidemia (%)	51.1	48.2	0.54
CV history (%)	9.2	6.1	0.20
Home SBP (mean)	137	135	0.08
Home DBP (mean)	79	79	0.80

N=505. %, proportion; CV history, proportion of patients with a previous cardiovascular event history; diabetes mellitus, proportion of patients with diabetes mellitus; HTN, proportion of patient with hypertension; n, number; N, size of the sample; orthostatic hypotension, orthostatic hypotension; SD, standard deviation; smoker, proportion of active smokers.

$P < 0.001$ ), with a higher BP level (140 versus 134,  $P < 0.001$ ) (Table 2).

In the total sample, 386 patients had their blood pressure measured in sitting (or lying) position and in standing position. Thus, we identified 56 cases of clinic orthostatic Hypotension (prevalence of 15%). These figures are consistent with the prevalence rates observed in this type of population [13].

Out of the 505 HBPM records, 477 meet the ESH criteria, which represent a success rate of 94.5%. The success rate of recording HBPM with at least one measurement of standing BP is 94%. It is 85% for patients who carried out the full series of standing BP measurements (i.e. the six measurements). Patients who did not meet the ESH quality criteria (at least 12 measurements out of 18) ( $n = 28$ ), also failed to perform the standing BP measurements. In contrast, only three patients who met the ESH criteria did not perform at least one BP measurement while standing (Table 3).

The prevalence of orthostatic hypotension based on HBPM is 40%. Patients diagnosed with orthostatic hypotension using HBPM are older (mean age = 71.13 versus 65.78,  $P < 0.001$ ) (Table 4). In the multivariate logistic regression analysis, we observe that orthostatic hypotension diagnosed with HBPM is not associated with clinic orthostatic hypotension. However, we find an association between home orthostatic hypotension and female patients [odds ratio (OR) = 1.17, 0.80–1.72,  $P < 0.001$ ], age (OR = 1.04,

1.02–1.05,  $P = 0.003$ ) and the level of SBP (OR = 1.00;  $P = 0.03$ ).

## DISCUSSION

### Feasibility of home blood pressure measurements

Several studies have investigated the feasibility of conventional HBPM without measuring standing BP. The PAMELA cohort from the general population in Italy constitutes a sample of 1438 individuals without antihypertensive treatment. In this study, the HBPM procedure consisted of only two measurements: one in the evening and another one the next morning [14]. The Ohasama study, involving a cohort of 3744 individuals from the general population, used several different protocols, the most recent of which consists of one BP measurement in the morning and in the evening consecutively over 4 weeks [15]. There is no data on the quality criteria used for either of these two historic cohorts.

In the general population cohort of the Three-City study, a sub-sample of 1814 individuals, with a mean age of 79.1 years, were asked to perform a series of HBPM on two

**TABLE 2. Description of the population according the center**

	Center 1 (n = 383)		Center 2 (n = 122)		P
	N	Mean/%	N	Mean/%	
Women	384	50	118	46.6	0.52
Age (years)	384	70.6	116	58.7	<0.001
BMI greater than 25	241	69.3	70	82.8	0.02
Hypertensive	382	92.7	118	98.3	0.02
Active smoker	382	10.0	115	24.4	<0.001
Diabetes mellitus	382	15.2	115	27.0	<0.001
Dyslipidemia	382	49.5	115	48.7	0.88
CV history					
Clinic SBP	360	153	69	151	0.39
Clinic DBP	360	86	68	85	0.80

%, proportion; CV, cardiovascular (coronaryopathy, heart failure or stroke).

**TABLE 3. Success of the home blood pressure measurement according its definition**

	N	Success	Failure	Success rate (%)
ESH home BP	505	477	28	94.5
Home BP with six standing BP	505	430	75	85.1
Home BP with at least one standing BP	505	474	31	93.8

ESH home BP, at least 12/18 blood pressure measurements; N, sample size.

**TABLE 4. Multivariate logistic analysis of the occurrence of an orthostatic hypotension during home blood pressure measurement**

Variables	OR	CI	P
Sex	1.24	0.80–1.72	0.274
Age	1.04	1.02–1.05	<0.001
Home sitting SBP	1.01	1.00–1.03	0.003

CI, confidence interval at 95%; OR, odds ratio.

occasions using the same procedure as in our study, that is, three measurements in the morning and three in the evening for 3 days. 95.9% ( $n = 1737$ ) and 94.2% ( $n = 1708$ ) of the participants performed at least 12 of the 18 measurements [16] during the two series of HBPM.

The measurement protocol used in the Finn-Home study, involving a cohort ( $n = 2035$ ) from the general population, consisted of performing two BP measurements in the morning and in the evening over 7 days, with a total of 28 measurements. The mean number of measurements was  $26.7 \pm 3.7$  with a success rate of about 95% [17].

The Didima study measured the home BP of 694 individuals with a mean age of 52 years in a Greek population-based cohort. The measurement protocol consisted of performing two BP measurements in the morning and the evening over three consecutive work days. Twenty-nine out of 694 individuals did not correctly complete their home BP measurement, resulting in a success rate of 96% [18].

The SHEAF study examined the feasibility of HBPM in hypertensive individuals aged over 60 years in the French population. The measurement procedure involved three BP measurements in the morning and evening for 4 days. The quality criterion for an individual to be included in the study was at least 15 valid measurements out of a possible total of 24 (representing a minimum of 62.5% of valid measurements as opposed to 66.6% according to the ESH recommendations). Out of the 5463 individuals included in the study, 252 were excluded for not meeting the HBPM quality criteria, resulting in an overall success rate of approximately 95.5% [19].

Even if the study populations and HBPM protocols differ in each of these cohort studies, the success rate of HBPM is very stable from one study another and is in the 95% range. In our study, the success rate according to the ESH criteria is very similar: 94.50%. In addition, the clear majority of individuals (94%) performed at least one standing BP measurement and 85% carried out all six standing BP measurements. Lastly, 91% of participants who did not make a single BP measurement in standing position ( $n = 31$ ), also did not meet the quality criteria of conventional HBPM. Asking participants to measure their BP in standing position after each BP measurement series in sitting position did not decrease the success rate conventional HBPM without standing BP measurement in our study cohort.

### Choice of orthostatic hypotension definition and orthostatic hypotension prevalence in home blood pressure measurements

Considering orthostatic hypotension's low reproducibility, it seemed logical to define orthostatic hypotension as the occurrence of orthostatic hypotension in at least one of the measurements in the context of repeated HBPM measurements. This explains why we adopt this measurement method as our reference in our study. By increasing the number of measurements on consecutive days and at different times of the day, this increases the possibility of detecting orthostatic hypotension. In our study, orthostatic hypotension prevalence accordingly increases from 15% during screening in a clinic setting to 37.43% using a series of HBPM. This increased sensitivity is certainly at the expense of lower specificity and the clinical value of this definition will have to be confirmed by long-term outcome studies.

Under the assumption that recurrent orthostatic hypotension is probably more detrimental than the isolated cases of orthostatic hypotension, we are, therefore, interested in individuals diagnosed with orthostatic hypotension based on two out of the six standing BP measurements. Thus, the orthostatic hypotension prevalence reduces to 7.72%.

An alternative hypothesis would have been to look at differences in mean sitting and standing BP. The mean difference in mean sitting and standing BP values is  $0.52 \pm 9.6$  mmHg for SBP and  $3.00 \pm 5$  mmHg for DBP. We observe that individuals who have a distribution of their differences beyond two standard deviations have differences in sitting and standing BP of approximately 20 mmHg for SBP and 10 mmHg for DBP, in line with agreed threshold values of clinic orthostatic hypotension. However, this calculation method based on calculating the mean of a set of values, yields a low orthostatic hypotension prevalence rate of approximately 3%. This prevalence is much lower than that of the clinic orthostatic hypotension measurements, and is therefore probably not very useful.

Finally, the prevalence depends also of the threshold chosen for the diagnosis. In this work, we decided to use the consensual threshold. If we define orthostatic hypotension by a BP drop of more than 30 mmHg for the systolic or more than 15 mmHg for the diastolic, the prevalence is reduced and represent 19.21% of the population.

In the logistic regression analysis, we observe that orthostatic hypotension diagnosed using HBPM is not associated with clinic orthostatic hypotension regardless of the definition of orthostatic hypotension in HBPM, once again illustrating the poor reproducibility of this condition but clinic orthostatic hypotension and HBPM orthostatic hypotension share some characteristics, such as association with age and BP level. However, only clinic orthostatic hypotension is associated with antecedents of cardiovascular events, which is consistent with the literature data.

### Interest of orthostatic hypotension screening using home blood pressure measurements versus in clinic setting

Out of the 505 patients in this cohort, only 386 were screened for orthostatic hypotension in consultation, making up 76% of the sample. We have not clearly evaluated why this figure is so low; however, our main assumption concerns the lack of time during consultations. Another explanation is perhaps the fact that this measure is not yet common practice even if it is now recommended at least in cases where the patient is at risk of orthostatic hypotension. This figure is significantly lower than the 91% of patients in the study who performed at least one standing measurement in the series of HBPM. Although this study was dedicated to observing BP in response to postural changes, we note that orthostatic hypotension screening is more effective by authorizing the patient to carry out HBPM than when left to the doctors.

### Limitations

This work is a preliminary feasibility study. We, therefore, did not establish a control group to perform a series of



HBPM excluding standing BP measurements, which is necessary to objectively observe a difference between the two HBPM methods. Nevertheless, the success rate of HBPM with a standing BP measurement in our series is 94%, and is therefore, equivalent to those found in the literature without standing measurement.

We only analyzed HBPM records that were reported to us and that were, therefore, more likely to be correctly completed. The proportion of HBPM records collected but not reported by the patient is unknown as this was not measured. Consequently, the absolute number of medical forms collected was 505 over 1 year, corresponding to a collection rate of 80 forms per practitioner per year. This ensured the implication of every stakeholder in the study, and therefore, limited the risk of collection bias.

Not all the devices used to carry out the HBPM were validated. Indeed, most patients did not bring in their measuring device. However, we were able to check the accuracy of the BP measuring devices in 48 patients (10%), with an acceptable accuracy. The accuracy of the home BP devices could not affect the feasibility of measuring standing BP at home, this may nevertheless question the frequency of orthostatic hypotension observed during HBPM in this work.

The nature of antihypertensive treatment was not systematically noticed despite the large majority of patients were under treatment. Moreover, the influence of the time of the medication intake on the occurrence of an OH may have influenced its prevalence. Indeed, we noticed 116 OH in the morning and 140 in the evening, which also raises questions about some potential clinical significance differences between morning and evening OH.

At this stage, we do not have a longitudinal follow-up to validate the value of standing BP measurements during HBPM or to define the most relevant measurement protocol. This would require a future study to evaluate the association with clinical events.

### Conclusion and future perspectives

Screening for orthostatic hypotension using HBPM is easily feasible. Moreover, orthostatic hypotension screening based on HBPM seems to be more efficient than when carried out by the doctor in consultation.

Increasing the sensitivity of orthostatic hypotension determination is certainly an important goal to limit its consequences with preventive and therapeutic strategies. Our data has to be confirmed with longitudinal studies in populations at high orthostatic hypotension risk.

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#### Conflicts of interest

There are no conflicts of interest.

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**Short-term blood pressure variability, arterial stiffness and cardiovascular events:  
Results from the Bordeaux cohort**

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**Abstract:**

Short-term blood pressure variability derived from 24 h ambulatory monitoring is associated with poor cardiovascular prognosis. However, previous analyses of this have clearly been influenced by clinical cofounders, particularly blood pressure (BP) level. Arterial stiffness is a powerful marker of cardiovascular risk which may influence BP variability. In this study, we assessed the prognostic value of BP variability based on 24 h ambulatory measurements and adjusted for arterial stiffness in the Bordeaux cohort of hypertensive patients. Inclusion criteria were 24 h ambulatory BP monitoring at baseline with measurements every 15' day and night, determination of wake-up time and bedtime, and assessment of arterial stiffness with monitoring of Korotkoff sound arrival time. A total of 969 patients (age  $54 \pm 14$  years) with an average follow up of  $120 \pm 78$  months and 178 cardiovascular recorded events were included. In univariate survival analyses, the standard deviations of day, night, and 24 h systolic BP were associated with the occurrence of cardiovascular events. The standard deviation of nighttime SBP showed the strongest association with the outcome variable and was entered into multivariate analyses. In multivariate analyses, nighttime SBP variability remained significantly associated with the occurrence of cardiovascular events after adjusting for major cardiovascular risk factors, 24 h SBP, and arterial stiffness. BP variability and arterial stiffness showed no significant association. In conclusion, our results suggest that variability of nighttime SBP is an important marker of the risk of cardiovascular events in hypertensive patients, independently of average 24 h BP and arterial stiffness.

There are accumulating data on prognostic value of short-term BP variability derived from 24h ambulatory blood pressure monitoring (ABPM).<sup>1</sup> In particular, the recent Spanish ABPM registry confirmed the poor cardiovascular prognosis of hypertensive subjects with nighttime systolic SD > 12 mmHg. Nighttime variability of BP appears to be of special interest<sup>2,3</sup> as it is less likely to be influenced by emotional state and physical effort than diurnal variability, and therefore may better reflect the mechanisms involved in BP regulation. However, the variability, regardless of how it is measured, is closely related to BP level, which remains a clinical cofounder. Arterial stiffness, a surrogate for vascular ageing and a powerful marker of cardiovascular risk, independent of BP<sup>4</sup> and left ventricular mass,<sup>5</sup> has also been found to be associated with BPV. The main explanation being that increased arterial stiffness could reduce the sensitivity of baroreceptors. Therefore, arterial stiffness could partially explain the cardiovascular risk associated with BP variability<sup>6,7</sup>.

In this study we assessed the prognostic value of BP variability derived from 24 h ABPM in hypertensive individuals, taking into account mean BP and arterial stiffness.

## METHODS

### STUDY POPULATION

The study population consisted of the Bordeaux cohort of hypertensive subjects, which characteristics have previously been described<sup>5,8</sup>. Briefly, this is a prospective single-center registry that includes all hypertensive patients referred to our center prior to receiving antihypertensive treatment. We included patients whose 24 h BP measurements had been paired with recordings of Korotkoff sound appearance time (QKD interval) and with collected data on BP variability. Baseline ambulatory BP measurements were performed in subjects before treatment, or if not possible, we used the first available 24 h BP recording on treatment fulfilling the inclusion criteria.

## ETHICAL CONSIDERATIONS

Patients who provided their consent to participate in the study were listed in the registry. The registry was thereafter approved by a committee of ethics and protection of the individual (Committee for Protection of Persons in the South-West of France and Overseas III).

## FOLLOW-UP AND CARDIOVASCULAR EVENTS

Information related to cardiovascular events was collected through regular contact with the patients. The patients were contacted either during follow-up visits or by telephone. Contact by telephone was systematically carried out on average every 2 years by a dedicated staff member (e.g., the research coordinator). In the case of an event of interest, the medical team subsequently verified the reported event using medical files from the patient's general practitioner (GP), and from hospitalization or any other report. Recorded cardiovascular events included coronary events defined as acute coronary syndrome with or without ST elevation, stroke events defined as ischemic or hemorrhagic cerebral stroke confirmed by cerebral CT or MRI, and other vascular events defined as aortic dissection, aneurism of the abdominal aorta (operated or ruptured), arteriopathy of the lower limbs, or carotid artery requiring revascularization. Deaths were identified from contact with the GP or the family of the patient. Cardiovascular death was determined by the medical team using data collected from hospital records or by contacting the patient's GP.

## AMBULATORY BP MEASUREMENTS

All BP measurements were obtained with validated ambulatory monitor devices: initially DIASYS 200 monitor (Novacor, Rueil-Malmaison, France) and more recently DIASYS integra (Novacor). These monitors use the auscultatory method and detect ECG signals with three electrodes allowing measurement of Korotkoff sound arrival time (QKD interval).<sup>5</sup> They were programmed to perform four measurements per hour, day and night. Bedtime and wake-up times were not defined over arbitrary periods<sup>8</sup> but were determined: prior to 1994 by a recording initiated by the patient when going to bed (lying down) and when getting up<sup>9</sup>, and after 1994 by a sensor placed on the patient's chest to distinguish between lying versus sitting or standing position.

## ARTERIAL STIFFNESS FROM MONITORING OF TIMING OF KOROTKOFF SOUNDS

Arterial stiffness was determined based on the timing of Korotkoff sounds as described previously (QKD interval)<sup>5,10-12</sup>. Monitoring of QKD interval and BP and heart rate (HR) measurement during 24 h ABPM allows calculation of an index of arterial stiffness, i.e., QKD<sub>100-60</sub>. This index yields an isobaric index of arterial stiffness, and is dependent on the length of

the arterial segment considered. We defined its correlation with height in a population of young adults (<30 years) without risk factors<sup>10</sup> and the measured value of QKD<sub>100–60</sub> is presented with reference to the value predicted by height in the normal population, where 100% is the normal value for each subject and decreases with increasing arterial stiffness.

## BP VARIABILITY

We used the standard deviation (SD) of BP and the coefficient of variation as a measure of BP variability. Variability was estimated during the day, night, and over 24 h.

## OTHER VARIABLES

Smokers were defined as active smokers or as former smokers if they had quit smoking less than 3 years prior to the study. Dyslipidemia was defined as total cholesterol > 5.2 mmol/L or treatment with statins. Type 2 diabetes mellitus was defined as fasting blood glucose > 7 mmol/L or treatment with antidiabetic agents.

## STATISTICAL ANALYSES

We first analyzed the main characteristics of our study population, and then explored the associations between the different phenotypes of BP variability and age, sex, average BP, HR, and QKD<sub>100–60</sub> using univariate linear regression. Next, we performed univariate Cox proportional hazard analyses to study the risk for cardiovascular events in relation to each BP variability marker. We selected the BP variability marker most closely associated with the cardiovascular outcome for multivariate analyses. The time axis was the date of inclusion in the registry. The model was adjusted for variables known to be significantly associated with the incidence of cardiovascular events: age, sex, body mass index (BMI), diabetes, smoking, hypercholesterolemia, 24 h SBP, and QKD<sub>100–60</sub>. We examined interactions particularly between arterial stiffness and BP variability. Log-linearity of the quantitative variables was checked. Then we performed multivariate regression analyses using the backward stepwise technique. Variables that were not significantly associated with the outcome were removed one at a time, starting with the variable with the largest *P*-value. We repeated this procedure until all of the remaining variables retained in the model were associated with the primary outcome with a significance threshold of  $P < 0.05$ .

Next, we identified the most appropriate threshold of BP variability to identify high risk cardiovascular patients. We plotted a Kaplan–Meier curve for two subgroups according to the BP variability threshold. The log-rank test was performed between these two groups.

A significance threshold of  $\alpha = 5\%$  was adopted for all statistical analyses, which were performed using SPSS 25 software (IBM, Chicago, IL).

## RESULTS

The Bordeaux Cohort consisted of 1069 patients; 980 patients had ABPM with QKD<sub>100-60</sub> at inclusion and 11 patients were lost to follow-up immediately after inclusion. Therefore, the study population consisted of 969 patients (male, 55%) with a mean age of  $54 \pm 14$  years. At the time of ABPM recording with QKD monitoring, 388 patients were already receiving treatment for hypertension. The number of BP measurements over 24 h by ABPM was  $85 \pm 11.50$  (Table 1).

In linear regression analyses, the SBP SD was associated with age, mean BP, mean HR, and QKD<sub>100-60</sub> with some differences according to the BP phenotype (Table 2). However, overall, the influences of these different factors on BP variability were limited; in particular, QKD<sub>100-60</sub> was not associated with nighttime SBP SD.

Over a mean follow-up for the study population of  $123.25 \pm 80.63$  months, 178 cardiovascular events (86 acute coronary events, 53 strokes, 39 other vascular events) were recorded. In univariate survival analyses, the SD of SBP (daytime, nighttime, and 24 h) was associated with the occurrence of cardiovascular complications (Table 3). Among these parameters of variability, nighttime SBP SD showed the strongest association with the occurrence of cardiovascular events and was therefore considered the main explanatory variable of variability in multivariate survival analyses. Nighttime SBP SD increased the risk for cardiovascular events by about 17% for each SD in multivariate analyses, including sex, age, BMI, diabetes, dyslipidemia, smoking, 24 h SBP, and QKD<sub>100-60</sub> (Table 4). Nighttime SPB SD and QKD<sub>100-60</sub> were not associated with risk for cardiovascular events ( $r = 0.016$ ,  $P = 0.627$ ). A cutoff of 14 mmHg for nighttime SBP SD provided the best compromise between sensitivity (40%) and specificity (75%) to predict future cardiovascular events (Appendixes 1 and 2). Kaplan–Meyer curves indicated a significantly poorer prognosis for patients with SBP SD  $> 14$  mmHg (log rank: 17.516,  $P \leq 0.0001$ ) (Figure 1).

## DISCUSSION

In this population of hypertensive patients with low cardiovascular risk, BP, BP variability, and arterial stiffness were measured at the same time and over 24 h. Short-term BP variability was associated with increased cardiovascular risk even after adjusting for BP and arterial stiffness. Short-term BP variability and arterial stiffness were two independent markers of cardiovascular risk.

ABPM is the current reference method for assessment of cardiovascular risk associated with elevated BP.<sup>13</sup> The added value of short-term BP variability to cardiovascular prognosis was first described by Palatini *et al.*<sup>14</sup> and was recently confirmed in a large registry of more than 60,000 patients examined by ABPM<sup>15</sup>. Both studies indicated that nighttime systolic BP variability is the marker most closely associated with cardiovascular outcome. In addition, both

studies yielded the same cutoff for cardiovascular risk discrimination (>12 mmHg).

In our cohort using a strict protocol of BP measurement, the nighttime SPB SD appeared to be the parameter demonstrating the strongest association with the incidence of cardiovascular complications which is consistent with previous studies. Importantly, the cutoff (>14 mmHg) was very close to the value proposed previously.

Moreover, this result persisted after adjusting for arterial stiffness. Indeed, BP variability showed no significant correlation with arterial stiffness measured using the QKD method ( $r = 0.016$ ;  $P = 0.31$ ) (Table 2). Use of the QKD method has the advantage of providing isobaric indices of arterial stiffness that may explain a weaker correlation with SBP SD than observed with carotid-femoral pulse wave velocity (PWV), which is influenced by both HR and SBP at the time of measurement<sup>16</sup>. Indeed, arterial stiffness when measured using the carotid-femoral PWV has been proposed to be a determinant of short-term BP variability via loss of compliance of baroreceptors<sup>7</sup>. Schillaci *et al.* described this association in a large cohort of untreated and treated hypertensive patients<sup>7</sup>. However, this interpretation has been called into question. Indeed, the coefficient of correlation between 24 h, day or nighttime SBP SD with carotid-femoral PWV was rather low (between 0.13 and 0.25) in that study. A recent study in a large elderly population<sup>17</sup> showed that the degrees of arterial stiffness measured using carotid-femoral PWV and day-to-day BP variability were not associated, suggesting that BP variability is a marker of baroreflex dysfunction when arterial stiffness is a marker of vascular aging and that both are associated with poorer cardiovascular prognosis.

#### LIMITATIONS

The analyses in the present study were limited to the SD of BP. Several other indices of BP variability have been proposed with the key objective of avoiding the relationship between variability and average BP<sup>18</sup>. Many methods and indices have been proposed to describe this variability, thus complicating the analyses and interpretation of data from the literature<sup>1</sup>. Moreover, the SD remains the most used index in studies and is the easiest to obtain<sup>18</sup>. Finally, the influence of BP level remains significant and adjusting for arterial stiffness is a good option to limit this influence. These results were obtained in a single-center cohort of hypertensive patients and cannot be generalized to the general population.

#### STRENGTHS

As the variability of nighttime SBP has good predictive value<sup>2,3</sup>, it seems logical to increase the frequency of measurement during this period. Therefore, we set up our device to take four measurements per hour at night. This could explain the negative results for variability of nighttime BP in noninvasive studies where BP was measured only twice every hour<sup>19,20</sup> and the positive results in invasive studies despite the much smaller sample sizes<sup>21,22</sup>. Moreover, the period of rest at night was precisely defined for each patient.

## CONCLUSIONS

In conclusion, the variability of nighttime SBP derived from 4 h ambulatory measurements was significantly related to the occurrence of cardiovascular events, independently of the average 24 h SBP and arterial stiffness assessed using the QKD method. Arterial stiffness and short-term BP variability are two independent markers of cardiovascular risk that should be assessed.

### WHAT IS NEW?

- Nighttime systolic BP variability is associated with the occurrence of cardiovascular events after adjusting for BP level and arterial stiffness in hypertensive patients.
- Systolic BP variability and arterial stiffness are two independent markers of cardiovascular risk.

### WHAT IS RELEVANT?

- Adjustment with arterial stiffness highlights the utility of BP variability for cardiovascular risk assessment.
- Nighttime systolic BP variability is a strong predictor of cardiovascular events. SD > 14 mmHg could be a useful threshold for identifying patients at risk for cardiovascular events.



Table 1. Main characteristics of the study population ( $n = 969$ )

<b>Variables</b>	<b>Mean or Value</b>	<b>SD or <math>n</math></b>
<b>Age</b>	54.40	13.8
<b>% Male</b>	55.31	536
<b>BMI</b>	25.94	4.10
<b>% Active smoker</b>	17.75	172
<b>% Diabetes mellitus</b>	9.29	90
<b>% Dyslipidemia</b>	21.15	205
<b>Office systolic BP</b>	152.61	17.39
<b>Office diastolic BP</b>	91.75	11.23
<b>QKD<sub>100-60</sub></b>	97.30	8.59
<b>Number of BP measurements over 24 h</b>	85.11	11.50
<b>24 h systolic BP</b>	129.98	15.27
<b>24 h diastolic BP</b>	84.04	11.12
<b>24 h HR</b>	73.71	10.48
<b>24 h systolic BP SD</b>	17.09	4.37
<b>24 h systolic BP CV</b>	13.24	3.39
<b>24 h diastolic BP SD</b>	11.27	2.78
<b>Number of BP measurements during daytime</b>	49.51	12.58
<b>Daytime systolic BP</b>	137.31	15.96
<b>Daytime diastolic BP</b>	89.05	11.79
<b>Daytime HR</b>	79.10	11.65
<b>Daytime systolic BP SD</b>	14.69	4.10
<b>Daytime systolic BP CV</b>	10.78	3.02
<b>Daytime diastolic BP SD</b>	9.33	2.48
<b>Number of nighttime BP measurements</b>	35.59	11.41
<b>Nighttime systolic BP</b>	118.93	15.78
<b>Nighttime diastolic BP</b>	76.72	11.03
<b>Nighttime HR</b>	66.34	9.64
<b>Nighttime systolic BP SD</b>	12.91	5.76
<b>Nighttime systolic BP CV</b>	10.93	4.52
<b>Nighttime diastolic BP SD</b>	8.84	3.96

BMI, body mass index; BP, blood pressure; CV, coefficient of variation; HR, heart rate; SD, standard deviation  
 QKD<sub>100-60</sub> is presented as a percentage of the normal value according to the patient's height.

Table 2. Univariate and multivariate linear regression analyses of variables linked to SBP SD

Variables	24-h SBP SD	<i>P</i>	Daytime SBP SD	<i>P</i>	Nighttime SBP SD	<i>P</i>
age	0.169	< 0.001	0.290	< 0.001	0.098	0.001
Sex (M = 1, F = 0)	-0.088	0.003	-0.173	< 0.001	-0.035	0.141
Treatment (Yes = 1, No = 0)	-0.024	0.223	0.114	< 0.001	0.066	0.019
SBP (according to phenotype)	0.211	< 0.001	0.189*	< 0.001	0.156	< 0.001
HR (according to phenotype)	0.067	0.018	-0.032	0.162	0.030	0.177
Number of measurements	0.017	0.295	-0.057	0.04	0.102	0.001
QKD <sub>100-60</sub>	-0.077	0.008	-0.112	< 0.0001	-0.016	0.31

SBP, systolic blood pressure; SD, standard deviation.

Table 3. Univariate Cox regression analyses of risk for cardiovascular events (*n* = 968, 178 cardiovascular events) according to different variables of BP variability

	Hazard ratio	95% CI	<i>P</i>
Nighttime SBP SD	1.029	1.016–1.042	< 0.001
Nighttime SBP CV	1.030	1.006–1.054	0.013
Daytime SBP SD	1.051	1.018–1.085	0.002
Daytime SBP CV	1.019	0.972–1.069	0.423
24 h SBP SD	1.035	1.003–1.068	0.031
24 h SBP CV	0.991	0.949–1.035	0.677

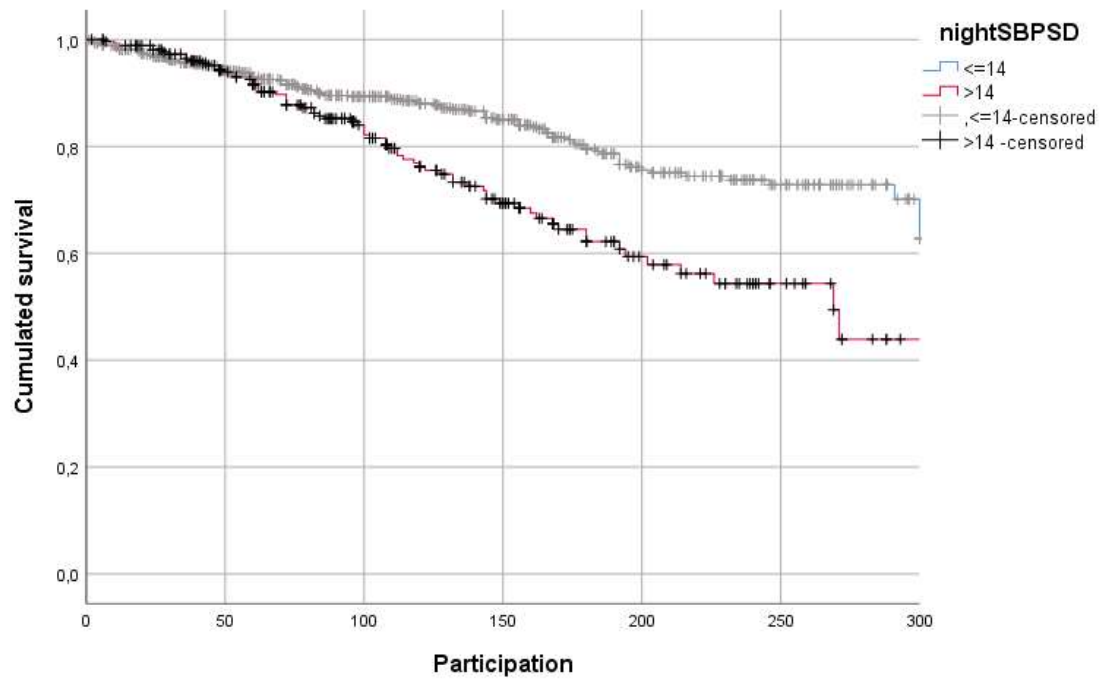
CI, confidence interval; SBP, systolic blood pressure; SD, standard deviation (in mmHg); CV, coefficient of variation (percentage).

Table 4. Multivariate Cox regression analyses of the risk for cardiovascular events (*n* = 968 and 178 cardiovascular events)

	Hazard ratio	95% CI	<i>P</i>
Age	1.053	1.038–1.068	< 0.0001
Male	1.526	1.089–2.139	0.014
Active Smoker	1.764	1.250–2.489	0.01
24 h SBP	1.017	1.007–1.027	0.001
Nighttime SBP SD	1.028	1.004–1.053	0.022
QKD <sub>100-60</sub>	1.026	1.007–1.046	0.009

95% CI, 95% confidence interval; SBP SD, systolic blood pressure standard deviation; HR, Hazard ratio.

Figure 1. Kaplan–Meir curve of the risk for cardiovascular events according to nighttime SBP SD threshold (log-rank test = 17.516;  $P < 0.0001$ )

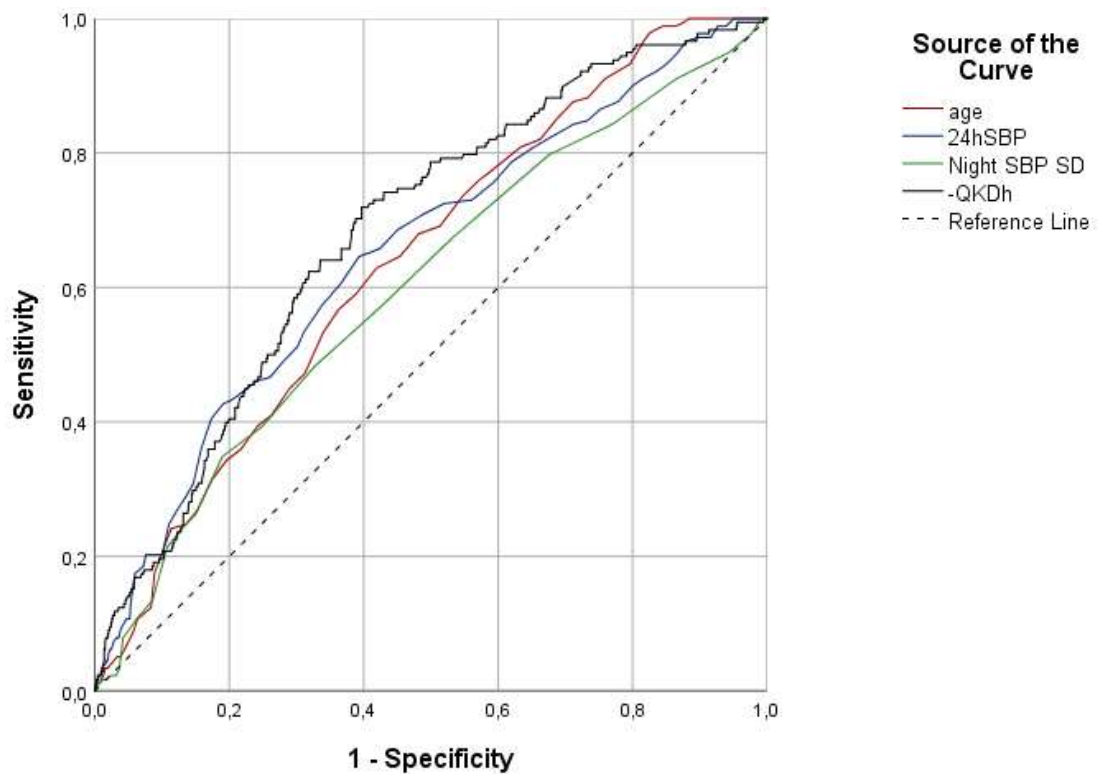


## Appendix 1: Areas under the ROC curve of significant continuous variables of the Cox analyses

Variables	Area	Std. Error <sup>a</sup>	Asymptotic <i>P</i> <sup>b</sup>	Asymptotic 95% CI	
				Lower Bound	Upper Bound
<b>QKD<sub>100-60</sub></b>	0.684	0.021	< 0.0001	0.642	0.725
24 h SBP	0,652	0,023	< 0.0001	0,607	0,697
Age	0,639	0,022	< 0.0001	0,596	0,681
Nighttime SBP SD	0.601	0.024	< 0.001	0.554	0.647

<sup>a</sup>Under the nonparametric assumption. <sup>b</sup>Null hypothesis: true area = 0.5.

## Appendix 2: ROC curve of significant continuous variables in Cox analyses



Résumé : L'hypotension orthostatique correspond à une baisse de la pression artérielle lors du passage à la position debout. Ce paramètre est associé à un sur-risque d'accident vasculaire cérébral, d'infarctus du myocarde, d'insuffisance cardiaque et de mortalité totale. Il est de ce point de vue proche des marqueurs de variabilité tensionnelle conventionnels que sont la variabilité tensionnelle inter-visite, la variabilité de moyen terme mesurée en auto-mesure tensionnelle et la variabilité de court terme mesurée en holter tensionnel. Cependant, contrairement à ces marqueurs conventionnels, l'association avec la démence n'a pas été démontrée. D'autre part, les relations entre l'hypotension orthostatique et ces autres marqueurs de variabilités ne sont pas connus. Enfin, si le diagnostic de l'hypotension orthostatique est relativement simple, la généralisation du dépistage en consultation n'est pas réalisée faute de temps. Objectifs : Nous proposons dans ce travail de mesurer l'association entre la présence d'une hypotension orthostatique et la survenue d'une démence. Nous réaliserons une étude mécanistique des déterminants de l'hypotension orthostatique à travers ses relations avec deux paramètres particuliers qui sont la variabilité tensionnelle en auto-mesure et la rigidité artérielle. Enfin, nous proposerons une méthode diagnostique par l'usage de l'auto-mesure tensionnelle. Matériel et méthode : Ces travaux sont réalisés à partir de la cohorte des 3 Cités qui est une cohorte de population générale de sujets de plus de 65ans recrutés sur trois centres : Bordeaux, Dijon et Montpellier. Une première étude longitudinale étudiera l'association entre la présence d'une hypotension orthostatique à l'inclusion dans la cohorte et la survenue d'une démence dans le suivi à 12 ans à travers des analyses de survie. Une deuxième étude transversale, utilisera un échantillon des sujets de Dijon autour du suivi à 10 ans qui ont bénéficié à la fois d'un dépistage de l'hypotension orthostatique, de la mesure de la rigidité artérielle et de la réalisation d'une série d'auto-mesure tensionnelle. Enfin, le dernier travail proposera une étude de faisabilité en soins courants de dépistage de l'hypotension orthostatique à travers un protocole d'auto-mesure tensionnelle adapté. Résultats : 7425 sujets ont été suivis sur une période de 12ans. La prévalence de l'hypotension orthostatique était de 13%. Le nombre de cas incidents de démence était de 512 cas. Les analyses de survie ont montré que l'hypotension orthostatique était associée à un sur-risque de démence de l'ordre de 25% dans des modèles ajustés en particulier sur le niveau de pression artérielle. Dans le deuxième travail une analyse transversale chez 1150 sujets a montré que l'hypotension orthostatique était associée de manière indépendante à la fois à la variabilité tensionnelle en autom-esure et à la rigidité artérielle. La variabilité tensionnelle et la rigidité artérielle ne sont pas associés. Dans le troisième travail, plus de 500 séries d'auto-mesure tensionnelle furent réalisées avec mesure de la pression artérielle en position debout sans altérer la qualité de l'auto-mesure tensionnelle classique. Conclusion : L'hypotension orthostatique est un paramètre hémodynamique riche qui reflète à la fois un vieillissement vasculaire marquée et un défaut de régulation de la pression artérielle immédiate. Elle est associée de manière indépendante au risque de démence. Une amélioration du diagnostic est possible par l'auto-mesure tensionnelle qui permet de multiplier les mesures en position debout et qui améliore le taux de dépistage.

Abstract ; Orthostatic hypotension is a blood pressure drop when moving to standing position. It is associated with an over-risk of stroke, myocardial infarction, heart failure and total mortality. From this point of view, it is close to the conventional markers of blood pressure variability which are the inter-visit blood pressure variability, the mid-term variability measured by home blood pressure and the short-term variability measured by an ambulatory blood pressure monitoring. However, unlike these conventional markers, the association with dementia has not been demonstrated. In addition, the relationships between orthostatic hypotension and these other markers of variability are not known. Finally, although the diagnosis of orthostatic hypotension is relatively simple, the generalization of screening in consultation is not achieved. Objectives: In this work, we propose to measure the association of the orthostatic hypotension and the occurrence of dementia. In addition, we will carry out a mechanistic study of the determinants of orthostatic hypotension through its relations with two particular parameters : mid term variability and arterial stiffness. Finally, we will propose a diagnostic method using home blood pressure measurement. Material and methods: This work is based on the "3 Cities" cohort which is a general population cohort of subjects over 65 years old recruited from three centres: Bordeaux, Dijon and Montpellier. We will first study the association between orthostatic hypotension at baseline cohort and the occurrence of dementia in the 12-year follow-up through survival analyses. A second cross-sectional study will use a sample of Dijon subjects around the 10-year follow-up who were screened for orthostatic hypotension, pulse wave velocity measurement and performed a series of home blood pressure measurement. Finally, the last work will propose a feasibility study on the routine care of screening for orthostatic hypotension using an adapted blood pressure self-measurement protocol. Results: 7425 subjects were followed over a 12-year period. The prevalence of orthostatic hypotension was 13%. The number of incident cases of dementia was 512. Survival analyses showed that orthostatic hypotension was associated with an over-risk of dementia in the order of 25% adjusted with blood pressure level. In the second work, a cross-sectional analysis in 1000 subjects showed that orthostatic hypotension was independently associated with both mid-term blood pressure variability and arterial stiffness. Pressure variability and arterial stiffness were not associated. In the third work, we performed 500 series of home blood pressure with a BP measurement in the standing position without altering the quality of the classical report. Conclusion: Orthostatic hypotension is a rich hemodynamic parameter that reflects both a marked vascular ageing and a defect of immediate blood pressure regulation. It is independently associated with the risk of dementia. An improvement in diagnosis is possible through self-measurement of blood pressure, which allows more measurements to be taken in the standing position and improves the screening rate.