

The impact of currently recommended antihypertensive therapy on depression and other psychometric parameters: preliminary communication

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Összefoglalás

Célkitűzés: Az antihipertenzív gyógyszerek pszichológiai hatásával kapcsolatban rendelkezésre álló adatok ellentmondásosak. Vizsgálatunk célja a korszerű antihipertenzív kezelés pszichometriai paramétereire és szérumban brain-derived neurotrophic factor (BDNF) szintre kifejtett hatásának vizsgálata volt

Módszerek: Gyógyszeres kezelést nem kapó hipertóniás betegekben (HT, n=31) a gyógyszeres kezelés előtt, majd azt követően három hónappal, valamint egészséges kontrollokban (CONT, n=22) egyszeri alkalommal vizsgáltunk pszichometriai, hemodinamikai, artériás érfal merevség és vérvételi paramétereiket. Az alanyok az alábbi pszichometriai tesztekkel töltötték ki: Beck Depresszió Kérdőív (BDI), Hamilton Szorongás Skála (HAM-A), SCL-90-R Kérdőív (SCL-90), Temperamentum Kérdőív, Big 5 Kérdőív, Fájdalom-vigilancia és Tudatosság Kérdőív, Berkeley Kifejezőképesség Kérdőív. Amlodipin és/vagy perindopril alapú volt az antihipertenzív kezelés. A szérumban BDNF szint mérése ELISA-val történt.

Eredmények: Három hónapos antihipertenzív kezelés hatására a brachiális szisztolés vérnyomás (153.3 ± 15.9 Hgmm versus 129.5 ± 10.0 Hgmm) és a pulzushullám terjedési sebesség (8.2 ± 1.4 m/s versus 7.5 ± 1.6 m/s) is szignifikánsan csökkent. Ezzel párhuzamosan szignifikáns javulást találtunk a BDI pontszámában (0,73 pont) és számos SCL-90 alskálában. A szérumban BDNF szint nem különbözött a CONT és a HT csoportok között és nem változott a gyógyszeres kezelés hatására.

Következtetések: Eredményeink arra utalnak, hogy még gyógyszeres kezelést nem kapó hipertóniás betegekben a jelenleg javasolt antihipertenzív hatóanyagok bevezetése egyaránt jótékony hatással lehet a pszichés státusra és az életminőségre.

Abstract

Aims: Current evidence on the psychological effects of antihypertensive medications is controversial. The aim of this study was to evaluate the effect of current antihypertensive medication on different psychometric parameters and on serum brain-derived neurotrophic factor (BDNF) level.

Methods: Psychometric, haemodynamic, arterial stiffness and laboratory parameters were evaluated before and 3 months after the initiation of antihypertensive medication in untreated hypertensive patients (HT, n=31), and once in healthy controls (CONT, n=22). Subjects completed the following psychometric tests: Beck Depression Inventory (BDI), Hamilton Anxiety Scale (HAM-A), Symptom Checklist 90 Revised (SCL-90), Temperament Evaluation of Memphis, Pisa, Paris, and San Diego Autoquestionnaire, Big Five Inventory, Pain Vigilance and Awareness questionnaire and Berkeley Expressivity Questionnaire. Amlodipine and/or perindopril compounds were preferred medications. Serum BDNF was measured with ELISA.

Results: Brachial systolic blood pressure, as well as pulse wave velocity were significantly improved in the HT group over the 3 months follow-up (153.3 ± 15.9 mmHg vs. 129.5 ± 10.0 mmHg and 8.2 ± 1.4 m/s vs 7.5 ± 1.6 m/s, respectively). Similarly, we found improvements in BDI (0.73 points) and in several Scl-90 subscales. Serum BDNF was not different between CONT and HT and did not change for therapy.

Conclusions: Our results indicate that initiation of currently recommended antihypertensive medications in newly diagnosed patients may have a significant impact on psychological well-being of patients and could influence quality of life as well.

Keywords: antihypertensive medication, depression, arterial stiffness, psychiatric symptoms, affective temperaments, brain-derived neurotrophic factor

List of abbreviations

AIx: augmentation index

ARB: angiotensin II receptor blocker

BDI: Beck Depression Inventory

BFI-44: Big Five Questionnaire

BMI: body mass index

Cyclothymic temp. score: cyclothymic affective temperament score

DBPbrach: brachial diastolic blood pressure

GFR-EPI: glomerular filtration rate assessed by the chronic kidney disease

epidemiology collaboration glomerular filtration rate equation

HAM-A: Hamilton Anxiety Scale

HR: heart rate

Hyperthymic temp. score: hyperthymic affective temperament score

PPAmp: pulse pressure amplification

PPbrach: brachial pulse pressure

PPcentr: central pulse pressure

PPB: brachial pulse pressure

PWV: pulse wave velocity

SCL-90: Symptom Checklist-90 Questionnaire

SBPbrach: brachial systolic blood pressure

SBPcentr: central systolic blood pressure

TEMPS-A: The Temperament Evaluation of Memphis Pisa, Paris and San Diego
questionnaire

Introduction

A causal relationship between elevated blood pressure and cardiovascular morbidity/mortality has been clearly demonstrated (Lewington et al., 2002). If lifestyle modifications by themselves are insufficient to treat hypertension, pharmacological interventions are required to control blood pressure and avoid late cardiovascular complications. This decision is a complex procedure, where severity of hypertension, age of the patient, presence of comorbidities, total cardiovascular risk, and additional features of different drug classes must also be taken into consideration (Mancia et al., 2013).

Antihypertensive medications from different pharmacological classes may cause different side effects. In contrast, different agents can also have unexpected beneficial effects. For example losartan may be beneficial in gout patients (Wurzner et al., 2001) or nebivolol may improve erectile dysfunction (Fongemie and Felix-Getzik, 2015). While impact of antihypertensive agents on psychological symptoms had also been studied, results are controversial. Case reports demonstrated depressive effects of the beta-blocker propranolol and timolol (McNeil et al., 1982; Nolan, 1982). Furthermore, more frequent use of antidepressants was observed in patients taking beta-blockers (Avorn et al., 1986). A case control study of incident depression cases and population-based controls however found a null-effect after adjusting for potential confounders including co-morbidities (Bright and Everitt, 1992). Similarly, the ACE-inhibitor enalapril was found to have a depressive effect in a case report (Patterson, 1989), however another small-scale study suggested an antidepressive impact of enalapril (Braszko et al., 2003). Calcium channel blockers have been suggested to be associated with increased incidence of mood disorders (Hallas, 1996), but others could not confirm these findings (Dunn et al., 1999; Patten et al., 1995). Most of the above-mentioned studies were case reports or were based on prescription databases allowing for potential bias and confounding.

Furthermore, they investigated older agents that are not state-of-the-art any more. Surprisingly, no data are available about the psychosomatic impact of currently preferred medications, such as perindopril or amlodipine in incident hypertensive patients who are free from mood disorders.

Different personality traits or dimensions can also influence cardiovascular diseases or risk factors. Trait anger was found to be associated with arterial stiffness in men (Williams et al., 2006), dominant cyclothymic affective temperament showed correlation with chronic hypertension and with acute coronary events in hypertensive patients (Eory et al., 2014a; Eory et al., 2014b) and cyclothymic temperament score is an independent determinant of brachial systolic blood pressure in chronic hypertension (Laszlo et al., 2016). However, no data are available about the stability of different dimensions of personality around the initiation of antihypertensive medications.

Brain-derived neurotrophic factor (BDNF), a member of the neurotrophic factor family, plays an important role in the regulation of neuronal growth, maintenance and survival (Mattson et al., 2004). Its involvement in psychiatric disorders is fundamental and was confirmed by a meta-analysis, as in major depressive disorder the decreased serum BDNF (seBDNF) level was elevated following a course of antidepressant treatment (Sen et al., 2008). It is hypothesized to play a protective role in cardiovascular pathophysiology as its higher serum level was found to be associated with decreased risk of cardiovascular disease and mortality (Kaess et al., 2015). Recently, we found elevated seBDNF in chronic hypertension (Nemcsik et al., 2016), but its level in drug-free hypertensive patients and its changes for antihypertensive therapy has never been studied yet.

The aim of our study was to evaluate the effect of modern antihypertensive medications, based mostly on perindopril and/or amlodipine on depression, anxiety, psychiatric symptoms, affective temperaments and different other dimensions of personality and seBDNF level. We

hypothesized a positive impact of these modern medications on depression, anxiety, the intensity of psychiatric symptoms in different psychopathological dimensions and seBDNF, and the stability of affective temperaments and other dimensions of personality.

Methods

Patients

This was a cross-sectional and prospective study in two urban primary care practices, between August 2013 and February 2016. In the cross-sectional part Caucasian patients with medically untreated essential hypertension, grade 1 or 2 (HT) and healthy controls (CONT) were included. Among HT, grade I hypertensive patients who were already in care and trained for lifestyle modifications previously and newly recognized hypertensive patients were also involved. In the HT group patients with atrial fibrillation, treated depression, anxiety or with dementia potentially interfering with the completion of questionnaires were excluded. In case of CONT denial of consent was the only exclusion criterion. During the screening visit, when the patient was evaluated for hypertension signed informed consent was obtained. Then questionnaires were given to the patients, home blood pressure monitoring (HBPM) or ambulatory blood pressure monitoring (ABPM) were initiated and an appointment within a week for arterial stiffness measurement and blood sampling was scheduled. Based on HBPM, or ABPM results subjects with white coat hypertension were excluded. If the effect of lifestyle modification was unable to control blood pressure values or the patient reported hypertension-related symptoms or either risk factors or absolute cardiovascular risk required treatment, antihypertensive drug therapy was initiated based on the current guideline (Mancia et al., 2013).

The choice of the antihypertensive agent was personalized taking into account the age, sex, comorbidities and grade of hypertension, and was based on the recent European guideline as

well (Mancia et al., 2013). Amlodipine from the calcium channel blocker group, perindopril from the ACE-inhibitor group and indapamide from the diuretic group were used as first line agents. When indicated, bisoprolol, carvedilol, nebivolol or long-lasting metoprolol were the preferred beta-blockers. In subjects with gout the uricosuric angiotensin receptor blocker (ARB) losartan was initiated, if an ARB was considered. When more than one agent was necessary we preferentially initiated the single-pill combination of perindopril and amlodipine. Within 10 days after the initiation of antihypertensive therapy, patients had a follow-up visit and therapy was modified if necessary.

All 31 hypertensive patients took part in the prospective part of the study, when all baseline measurements were repeated 3 months after the initiation of antihypertensive medication. No untreated hypertensive control group was formed, as we thought that it would be unethical to withhold antihypertensive treatment in a population with symptomatic or more severe hypertension. Routine laboratory, psychometric and arterial stiffness parameters were evaluated at baseline for hypertensive and control patients. The hypertensive group also had repeat measurements after 3 months of therapy.

The study was approved by the Scientific and Research Ethics Committee of the Medical Research Council, the Hungarian Ministry of Health (ETT TUKEB 842/PI/2011) and was carried out in accordance with the tenets of the Declaration of Helsinki.

Evaluation of different psychometric parameters

The *Beck Depression Inventory* (BDI) is a 21-question multiple-choice self-report questionnaire and is one of the most widely used instruments for assessing depression severity. Participants are asked to make ratings on a four-point scale, where a higher score correlates with more severe depression (Beck et al., 1961).

The *Hamilton Anxiety Scale* (HAM-A), evaluated by the examiner was used to study the severity of anxiety. The scale consists of 14 items, each item is scored on a scale of 0 (not present) to 4 (severe anxiety) (Hamilton, 1959).

The *Symptom Checklist 90 Revised* (SCL-90), a self-rated test consisting of 90 multiple-choice items ranging 0–4 (Delogatis, 1994) was used to identify the presence and quantify the intensity of psychiatric symptoms distributed among 9 psychopathological dimensions: 1) somatization; 2) obsessiveness–compulsiveness; 3) interpersonal sensitivity; 4) depression; 5) anxiety; 6) hostility; 7) phobic anxiety; 8) paranoid ideation; 9) psychoticism. The instrument has three global indices of distresses as well: the global severity index (GSI), the positive symptom distress index (PSDI) and the positive symptom total (PST).

The *Temperament Evaluation of Memphis, Pisa, Paris and San Diego Autoquestionnaire* (TEMPS-A) was used to assess affective temperaments on depressive, cyclothymic, hyperthymic, irritable and anxious subscales, requiring ‘yes’ (score 1) or ‘no’ (score 0) answers (Akiskal et al., 2005). TEMPS-A, which contains 110 items (109 in the version for males), has been extensively studied, translated into more than 25 languages and validated in several of the latter.

The *Big Five Inventory* (BFI-44) was used to measure the five big dimensions of personality; extraversion, agreeableness, conscientiousness, neuroticism and openness (John and Srivastava, 1999). On the 44-item questionnaire, each item is answered on a 5-point scale ranging from 1 (strongly disagree) to 5 (strongly agree).

The *Berkeley Expressivity Questionnaire* (BEQ) was used to evaluate the subjects' emotional expressivity. The 16-item scale is separated into 3 facets: negative expressivity, positive expressivity and impulse strength (Gross and John, 1997). Each item is answered on a 7-point scale ranging from 1 (strongly disagree) to 7 (strongly agree).

The *Pain Vigilance and Awareness Questionnaire* (PVAQ), a 16-item instrument was used to measure the subjects' pain vigilance and awareness (Roelofs et al., 2003). All items are rated on a scale: 0 (never) to 5 (always).

Measures of blood pressure and arterial stiffness

Measurements were performed in a temperature-controlled room, between 7.00 and 8.00 a.m. prior to blood collection. Patients were required to fast overnight and refrain from smoking and drinking caffeine-containing beverages before the procedure, but to take their usual blood pressure medication (only at the follow-up visit). Upon arrival and after a 5-minute rest, two brachial blood pressure measurements were taken on each arm in the sitting position with a validated oscillometric blood pressure device (Omron M3). The mean value from the arm with the higher systolic value was further used as brachial systolic (SBPbrach) and diastolic (DBPbrach) blood pressure and heart rate. Brachial pulse pressure (PPbrach) was also calculated from these data. The subjects were next fitted with an arterial stiffness measurement device and were asked to rest in the supine position for approximately 15 minutes before being measured. Arterial stiffness and central haemodynamic parameters were evaluated with the gold-standard tonometric method (PulsePen, DiaTecne, Milan, Italy) (Salvi et al., 2004). This method provides estimates of pulse wave velocity (PWV), augmentation index (Aix), central systolic blood pressure (SBPcentr), and central pulse pressure (PPcentr). In each subject, two sequences of arterial stiffness measurements were performed and their mean was used for statistical analysis. In PWV calculations, 80% of the carotid-femoral distance was used, according to the most recent recommendation (Van Bortel et al., 2012). The intra- and interobserver variability of PWV measurements obtained by the PulsePen device in hypertensive patients was 4.6 and 6.3%, respectively. Since PulsePen calculates pressures based on brachial diastolic blood pressure calibration, the calculated central

diastolic blood pressure is identical to the brachial diastolic blood pressure assessed in the supine position (Salvi et al., 2004).

Measurement of seBDNF concentration

Peripheral blood samples of patients were collected in anticoagulant-free tubes, right after the measurement of arterial stiffness. After centrifugation (3600 rpm for 6 min) the serum was stored at -20°C . SeBDNF was measured using commercially available sandwich enzyme-linked immunosorbent assay (R&D Systems, Minneapolis MN, USA) according to the manufacturer's protocol and serum BDNF level was determined in ng/mL.

Statistical analysis

Normality of the parameters was tested with the Kolmogorov-Smirnov test. Descriptive characteristics, laboratory, arterial stiffness, haemodynamic parameters and psychometric scores were compared between CONT and HT groups using 2-sample Student's *t*-tests or independent samples Mann–Whitney rank-sum test for data failing tests of normality at baseline. Laboratory, arterial stiffness, haemodynamic and psychometric variables were compared between baseline and follow-up within the HT group using paired Student's *t*-tests or dependent samples Mann–Whitney rank-sum test for data failing tests of normality. We also run a sensitivity analysis on participants with already known hypertension under our care who received lifestyle education before study initiation to minimize study effect related to care initiation and education.

Data are expressed as mean \pm standard deviation or median with interquartile ranges. For psychometric parameters with non-normal distribution mean with interquartile ranges are presented. $P < 0.05$ was considered to be significant. SPSS 22.0 for Windows was used for all calculations.

Results

Altogether 31 patients with hypertension and 22 controls were included in the cross-sectional analysis. 15 of the 31 hypertensive patients were already in hypertension care and were previously educated for lifestyle modifications. The rest 16 of them were educated around study involvement. All 31 hypertensive patients completed the 3-month follow-up and were included in the longitudinal analysis.

The final antihypertensive and vasculoprotective medications of the hypertensive group at follow-up are shown in table 1. More than 80% of the patients received the ACE-inhibitor perindopril and three-quarter the calcium-channel blocker amlodipine. Only 4 patients were on indapamide therapy, 2 of them took the ARB losartan. Altogether 12 patients required beta-blockers and bisoprolol was the most frequently used. Only one patient received additional blood pressure lowering drug (doxazosin). Equally 3 patients were on statin and acetylsalicylic acid therapy, but none of them were initiated parallel with the antihypertensive medication. Most of the patients were on a dual combination of antihypertensive agents. In the hypertensive group 4 patients (12.9%) were treated for gastroesophageal reflux disease, 3 patients (9.7%) for hypercholesterinaemia, equally 2 patients (6.4%) had gout, bronchial asthma, inflammatory bowel disease or non-pharmacologically treated type 2 diabetes and 1 patient (3.2%) had peripheral artery disease.

Baseline demographic, laboratory, haemodynamic and arterial stiffness parameters are shown in Table 2. CONT subjects were younger than HT subjects. Their waist circumference, BMI, blood glucose, uric acid, total cholesterol and triglyceride levels were lower than of hypertensive patients' at baseline. No significant changes in these parameters were found after 3 months of antihypertensive treatment. All brachial and central haemodynamic and arterial

stiffness parameters were impaired in hypertensive compared with control subjects and all improved significantly with blood pressure medication.

Table 3. demonstrates psychometric measures of the groups at baseline and follow-up. Anxiety measured by HAM-A, somatization, obsessiveness-compulsiveness and positive symptom distress index measured by SCL-90 and overall emotional expressivity and negative emotional facet scores of the Berkeley Expressivity Questionnaire were significantly different between the hypertensive and control groups. After 3 months of antihypertensive treatment depression score measured by BDI improved significantly with 0.73 points. Many SCL-90 dimensions also improved during follow-up, such as somatization, obsessiveness-compulsiveness, interpersonal sensitivity, anxiety, psychoticism, the global severity index and the positive symptom total.

Our sensitivity analysis on 15 patients already under care for hypertension before study initiation showed similar point estimates to the main analysis although some of the changes did not reach statistical significance (results are available on request.)

Discussion

The results of the present study demonstrated, that in newly diagnosed hypertensive patients free from psychiatric disorders the initiation of currently recommended antihypertensive medications markedly improves blood pressure and arterial stiffness and also beneficially effects depression and psychiatric symptoms in different directions of psychopathological dimensions, besides unchanged seBDNF.

Angiotensin-converting enzyme (ACE) mediates the production of angiotensin II, which, throughout its brain receptors besides its important role in blood pressure control (Unger et

al., 1988) also participates in the regulation of mood (Gard et al., 1999). In our study, more than 80% of the hypertensive patients received the ACE-inhibitor perindopril. In contrast to enalapril, perindopril due to its high lipophilicity and central nervous system (CNS) permeability, is regarded as centrally active agent. It has been found to ameliorate cognitive impairment in an animal model of vascular dementia (Yamada et al., 2011). However, its antidepressant effect has not been studied so far.

More than 70% of our patients were taking the calcium channel blocker amlodipine therapy. According to a previous study in hypertensive patients with coronary artery disease, verapamil-based treatment improved depressive symptoms during one-year follow-up (Ried et al., 2005). Similarly to verapamil and perindopril, amlodipine also penetrates into the CNS, where it may have beneficial pleiotrophic effects, such as potentiating the antiepileptic effect of lamotrigine, suggested by an animal study (Luszczki et al., 2007). Moreover, in spontaneously hypertensive rats the concomitant administration of amlodipine and atorvastatin improves cognitive dysfunction and exerts antioxidant effects in the hippocampus and in the rostral ventricular medulla (Kishi and Sunagawa, 2012). Although animal data are accumulating on the neuroprotective role of amlodipine in the CNS, no data are currently available regarding its effect on psychometric parameters in humans. Therefore our data are the first to show the possible beneficial psychiatric effect of perindopril and amlodipine, two very popular antihypertensive medications.

Another possible pathophysiological mechanism that may explain our findings may be the influence of the used medications on the hypothalamic-pituitary-adrenal (HPA) axis, which plays an important role in depression and other psychopathological conditions as well as in cardiovascular pathology (Penninx, 2016). In animal models both the administration of the ACE-inhibitor ramipril or different calcium channel blockers were found to reduce HPA axis activity (Kumar et al., 2012; Raasch et al., 2006).

The possible effect of neurotrophins has never been studied in this context yet. Although we recently reported, that in treated chronic hypertension seBDNF is elevated compared with controls and chronic hypertension is an independent determinant of seBDNF (Nemcsik et al., 2016), but in our study seBDNF was not elevated in untreated hypertensive patients. Previously perindopril and the combination of amlodipine and irbesartan were both found to modify BDNF beneficially on cellular level (Ali et al., 2016; Hasegawa et al., 2016), but contrary to expectations, in our study seBDNF was unchanged after three months of mostly perindopril and/or amlodipine based therapy, although a tendency of increase appeared. As in our previous study the average duration of hypertension was 11 years (Nemcsik et al., 2016), it is plausible, that seBDNF elevation is not an acute event, but might be a part of a long-term compensatory process. Longer follow-up and higher number of untreated hypertensive patients involved would be required to clarify this question as well as the possible impact of particular antihypertensive agent groups on seBDNF.

Personality is thought to be relatively stable throughout the lifespan, but their quantitative changes considered important research question (Ibanez et al., 2016). Temperament is regarded as an inherited part of personality and represents the biologically stable core of emotional reactivity (Bouchard, 1994); although, there is an ongoing discussion regarding the influence of age on depressive temperament with differences between men and women (Vazquez et al., 2012). Furthermore, psychoactive medications were found to have an effect on personality measures. For example, paroxetine was shown to have a specific pharmacologic effect on measures of neuroticism and extraversion in major depressive disorder independent from its effect on depression (Tang et al., 2009). Based on these findings, it seemed to be reasonable to study the potential effect of centrally active currently recommended antihypertensive medications on personality. In the present study no significant changes in affective temperaments and in the big five dimensions of personality were found

after the initiation of antihypertensive medications, thus our results may indicate that these agents do not influence measures of these personality constructs.

It is important to note that low levels of blood pressure can also be associated with depression, especially in the elderly (Kim et al., 2010). Moreover, according to a study performed in elderly subjects between 1991 and 1995, low diastolic blood pressure and a decrease of either systolic or diastolic blood pressure during a two-year follow-up was associated with an increase of depressive symptoms. While only 25% of patients took any antihypertensive medications (very likely old-type agents), the results were unchanged when patients on antihypertensive medications were excluded from analysis (Paterniti et al., 2000). No cut-off blood pressure values were reported below which severity of depressive symptoms would worsen so far, as in both studies arbitrary blood pressure categories were used based on the study sample (the lowest 10 percentile (Kim et al., 2010) or the first quartile (Paterniti et al., 2000) of systolic/diastolic blood pressure). It is also important to note, that in both of these studies the mean age of subjects was 65, which is much higher compared with our study. We suppose that in younger patients the correction of elevated blood pressure with currently recommended medications may have beneficial psychological impact while with aging very low blood pressure may be associated with psychopathological and somatic symptoms.

Arterial stiffness and central blood pressure were also measured in our patients. Carotid-femoral pulse wave velocity, the most accepted arterial stiffness parameter is recommended for cardiovascular risk prediction both in the recent European Hypertension Guideline and in an American Heart Association scientific statement (Mancia et al., 2013; Townsend et al., 2015). As pulse wave velocity changes slowly, the remarkable decrease observed in the present study reflects the good medication compliance of our participants.

There are data available about the possible association between arterial stiffness and mood disorders. In a population-based cross-sectional study Tiermeier et al. found, that patients with increased arterial stiffness were more likely to have depressive symptoms. The authors concluded that arterial stiffening may partly explain the proposed relationship between vascular factors and depression (Tiemeier et al., 2003). Moreover, in middle-aged patients arterial stiffness measured by the augmentation index was found to be associated with anxiety sensitivity (Seldenrijk et al., 2013). Less data is available about the association between arterial stiffness and personality traits: low hyperthymic affective temperament score was found to be associated with an increased level of arterial stiffening (Laszlo et al., 2016), while high trait anger was found to be associated with arterial stiffness in men (Williams et al., 2006). Whether initial arterial stiffness or its changes are related to the observed improvement of depression and psychiatric symptoms and whether they are related to the antihypertensive medications used in our study are questions that require further studies with large samples.

There are several limitations of our study. First, the number of patients involved limits the potential for multivariable analysis by adjusting for potential confounders. As the medication of the patients was heterogeneous, the individual contribution of different agents cannot be identified. Additionally, as the follow-up period was only 3 months, the stability of the observed changes in a longer time period still has to be investigated. Moreover, although our methodology used standardized questionnaires and excluded patients with dementia, a complete exclusion of misinterpretations or mistakes by patients is nevertheless impossible. Finally, as our study had a non-controlled design, we investigated the effect of at least 2 types of interventions: medication effect and study effects related to initiation of care (like education or discussion with the physician and nurses). Although it is impossible to entangle the individual effect of these interventions, our sensitivity analysis suggest that medication initiation provides a substantial portion of the observed changes in psychometric and

biological parameters. The major limitation is that, due to ethical considerations it is an uncontrolled study without a proper control group for the follow-up period.

Conclusions

In conclusions, currently recommended antihypertensive medications, based on perindopril and/or amlodipine might have beneficial impact on depression and on the intensity of numerous psychiatric symptoms. If these effects are confirmed in other studies, they may broaden the range of factors considered when antihypertensive medications are selected. However, the contribution of identical agents or the regular patient care itself and the persistence of these effects on longer period of time still needs to be clarified.

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References

Akiskal, H.S., Akiskal, K.K., Haykal, R.F., Manning, J.S., Connor, P.D., 2005. TEMPS-A: progress towards validation of a self-rated clinical version of the Temperament Evaluation of the Memphis, Pisa, Paris, and San Diego Autoquestionnaire. *Journal of affective disorders* 85, 3-16.

Ali, M.R., Abo-Youssef, A.M., Messiha, B.A., Khattab, M.M., 2016. Tempol and perindopril protect against lipopolysaccharide-induced cognition impairment and amyloidogenesis by modulating brain-derived neurotrophic factor, neuroinflammation and oxido-nitrosative stress. *Naunyn-Schmiedeberg's archives of pharmacology* 389, 637-656.

Avorn, J., Everitt, D.E., Weiss, S., 1986. Increased antidepressant use in patients prescribed beta-blockers. *Jama* 255, 357-360.

Beck, A.T., Ward, C.H., Mendelson, M., Mock, J., Erbaugh, J., 1961. An inventory for measuring depression. *Arch Gen Psychiatry* 4, 561-571.

Bouchard, T.J., Jr., 1994. Genes, environment, and personality. *Science (New York, N.Y.)* 264, 1700-1701.

Braszko, J.J., Karwowska-Polecka, W., Halicka, D., Gard, P.R., 2003. Captopril and enalapril improve cognition and depressed mood in hypertensive patients. *Journal of basic and clinical physiology and pharmacology* 14, 323-343.

Bright, R.A., Everitt, D.E., 1992. Beta-blockers and depression. Evidence against an association. *Jama* 267, 1783-1787.

Delogatis, L.R., 1994. SCL-90-R: Administration, Scoring and Procedures Manual. Third Edition. Minneapolis: National Computer Systems Inc.

Dunn, N.R., Freemantle, S.N., Mann, R.D., 1999. Cohort study on calcium channel blockers, other cardiovascular agents, and the prevalence of depression. *British journal of clinical pharmacology* 48, 230-233.

Eory, A., Gonda, X., Lang, Z., Torzsa, P., Kalman, J., Jr., Kalabay, L., Rihmer, Z., 2014a. Personality and cardiovascular risk: association between hypertension and affective temperaments-a cross-sectional observational study in primary care settings. *The European journal of general practice* 20, 247-252.

Eory, A., Rozsa, S., Torzsa, P., Kalabay, L., Gonda, X., Rihmer, Z., 2014b. Affective temperaments contribute to cardiac complications in hypertension independently of depression. *Psychotherapy and psychosomatics* 83, 187-189.

Fongemie, J., Felix-Getzik, E., 2015. A Review of Nebivolol Pharmacology and Clinical Evidence. *Drugs* 75, 1349-1371.

Gard, P.R., Mandy, A., Sutcliffe, M.A., 1999. Evidence of a possible role of altered angiotensin function in the treatment, but not etiology, of depression. *Biological psychiatry* 45, 1030-1034.

Gross, J.J., John, O.P., 1997. Revealing feelings: facets of emotional expressivity in self-reports, peer ratings, and behavior. *Journal of personality and social psychology* 72, 435-448.

Hallas, J., 1996. Evidence of depression provoked by cardiovascular medication: a prescription sequence symmetry analysis. *Epidemiology (Cambridge, Mass.)* 7, 478-484.

Hamilton, M., 1959. The assessment of anxiety states by rating. *Br J Med Psychol* 32, 50-55.

Hasegawa, Y., Nakagawa, T., Uekawa, K., Ma, M., Lin, B., Kusaka, H., Katayama, T., Sueta, D., Toyama, K., Koibuchi, N., Kim-Mitsuyama, S., 2016. Therapy with the Combination of Amlodipine and Irbesartan Has Persistent Preventative Effects on Stroke Onset Associated with BDNF Preservation on Cerebral Vessels in Hypertensive Rats. *Translational stroke research* 7, 79-87.

Ibanez, M.I., Viruela, A.M., Mezquita, L., Moya, J., Villa, H., Camacho, L., Ortet, G., 2016. An Investigation of Five Types of Personality Trait Continuity: A Two-Wave Longitudinal Study of Spanish Adolescents from Age 12 to Age 15. *Frontiers in psychology* 7, 512.

John, O.P., Srivastava, S., 1999. The Big-Five trait taxonomy: History, measurement and theoretical perspectives. , In: Pervin, L.A., John, O.P. (Eds.), *Handbook of personality: Theory and research*. New York: Guilford Press, pp. 102-138.

Kaess, B.M., Preis, S.R., Lieb, W., Beiser, A.S., Yang, Q., Chen, T.C., Hengstenberg, C., Erdmann, J., Schunkert, H., Seshadri, S., Vasan, R.S., Assimes, T.L., Deloukas, P., Holm, H.,

Kathiresan, S., Konig, I.R., McPherson, R., Reilly, M.P., Roberts, R., Samani, N.J., Stewart, A.F., 2015. Circulating brain-derived neurotrophic factor concentrations and the risk of cardiovascular disease in the community. *Journal of the American Heart Association* 4, e001544.

Kim, B.S., Bae, J.N., Cho, M.J., 2010. Depressive symptoms in elderly adults with hypotension: different associations with positive and negative affect. *Journal of affective disorders* 127, 359-364.

Kishi, T., Sunagawa, K., 2012. Combination therapy of atorvastatin and amlodipine inhibits sympathetic nervous system activation and improves cognitive function in hypertensive rats. *Circulation journal : official journal of the Japanese Circulation Society* 76, 1934-1941.

Kumar, N., Singh, N., Jaggi, A.S., 2012. Anti-stress effects of cilnidipine and nimodipine in immobilization subjected mice. *Physiology & behavior* 105, 1148-1155.

Laszlo, A., Tabak, A., Korosi, B., Eorsi, D., Torzsa, P., Cseprekal, O., Tisler, A., Reusz, G., Nemcsik-Bencze, Z., Gonda, X., Rihmer, Z., Nemcsik, J., 2016. Association of affective temperaments with blood pressure and arterial stiffness in hypertensive patients: a cross-sectional study. *BMC cardiovascular disorders* 16, 158.

Lewington, S., Clarke, R., Qizilbash, N., Peto, R., Collins, R., 2002. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet* 360, 1903-1913.

Luszczki, J.J., Trojnar, M.K., Trojnar, M.P., Kimber-Trojnar, Z., Szostakiewicz, B., Zadrozniak, A., Borowicz, K.K., Czuczwar, S.J., 2007. Effects of three calcium channel antagonists (amlodipine, diltiazem and verapamil) on the protective action of lamotrigine in the mouse maximal electroshock-induced seizure model. *Pharmacological reports : PR* 59, 672-682.

Mancia, G., Fagard, R., Narkiewicz, K., Redon, J., Zanchetti, A., Bohm, M., Christiaens, T., Cifkova, R., De Backer, G., Dominiczak, A., Galderisi, M., Grobbee, D.E., Jaarsma, T., Kirchhof, P., Kjeldsen, S.E., Laurent, S., Manolis, A.J., Nilsson, P.M., Ruilope, L.M., Schmieder, R.E., Sirnes, P.A., Sleight, P., Viigimaa, M., Waeber, B., Zannad, F., Redon, J., Dominiczak, A., Narkiewicz, K., Nilsson, P.M., Burnier, M., Viigimaa, M., Ambrosioni, E., Caulfield, M., Coca, A., Olsen, M.H., Schmieder, R.E., Tsioufis, C., van de Borne, P., Zamorano, J.L., Achenbach, S., Baumgartner, H., Bax, J.J., Bueno, H., Dean, V., Deaton, C., Erol, C., Fagard, R., Ferrari, R., Hasdai, D., Hoes, A.W., Kirchhof, P., Knuuti, J., Kolh, P., Lancellotti, P., Linhart, A., Nihoyannopoulos, P., Piepoli, M.F., Ponikowski, P., Sirnes, P.A., Tamargo, J.L., Tendera, M., Torbicki, A., Wijns, W., Windecker, S., Clement, D.L., Coca, A., Gillebert, T.C., Tendera, M., Rosei, E.A., Ambrosioni, E., Anker, S.D., Bauersachs, J., Hitij, J.B., Caulfield, M., De Buyzere, M., De Geest, S., Derumeaux, G.A., Erdine, S., Farsang, C., Funck-Brentano, C., Gerc, V., Germano, G., Gielen, S., Haller, H., Hoes, A.W., Jordan, J., Kahan, T., Komajda, M., Lovic, D., Mahrholdt, H., Olsen, M.H., Ostergren, J., Parati, G., Perk, J., Polonia, J., Popescu, B.A., Reiner, Z., Ryden, L., Sirenko, Y., Stanton, A., Struijker-Boudier, H., Tsioufis, C., van de Borne, P., Vlachopoulos, C., Volpe, M., Wood, D.A., 2013. 2013 ESH/ESC guidelines for the management of arterial hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *European heart journal* 34, 2159-2219.

Mattson, M.P., Maudsley, S., Martin, B., 2004. BDNF and 5-HT: a dynamic duo in age-related neuronal plasticity and neurodegenerative disorders. *Trends in neurosciences* 27, 589-594.

McNeil, G.N., Shaw, P.K., Dock, D.S., 1982. Substitution of atenolol for propranolol in a case of propranolol-related depression. *The American journal of psychiatry* 139, 1187-1188.

Nemcsik, J., Laszlo, A., Lenart, L., Eorsi, D., Torzsa, P., Korosi, B., Cseprekal, O., Tisler, A., Tabak, A., Gonda, X., Rihmer, Z., Hodrea, J., Nemcsik-Bencze, Z., Fekete, A., 2016.

Hyperthymic affective temperament and hypertension are independent determinants of serum brain-derived neurotrophic factor level. *Annals of general psychiatry* 15, 17.

Nolan, B.T., 1982. Acute suicidal depression associated with use of timolol. *Jama* 247, 1567.

Paterniti, S., Verdier-Taillefer, M.H., Geneste, C., Bisserbe, J.C., Alperovitch, A., 2000. Low blood pressure and risk of depression in the elderly. A prospective community-based study. *The British journal of psychiatry : the journal of mental science* 176, 464-467.

Patten, S.B., Williams, J.V., Love, E.J., 1995. Self-reported depressive symptoms in association with medication exposures among medical inpatients: a cross-sectional study. *Canadian journal of psychiatry. Revue canadienne de psychiatrie* 40, 264-269.

Patterson, J.F., 1989. Depression associated with enalapril. *Southern medical journal* 82, 402-403.

Penninx, B.W., 2016. Depression and cardiovascular disease: Epidemiological evidence on their linking mechanisms. *Neuroscience and biobehavioral reviews*.

Raasch, W., Wittmershaus, C., Dendorfer, A., Voges, I., Pahlke, F., Dodt, C., Dominiak, P., Jöhren, O., 2006. Angiotensin II inhibition reduces stress sensitivity of hypothalamo-pituitary-adrenal axis in spontaneously hypertensive rats. *Endocrinology* 147, 3539-3546.

Ried, L.D., Tueth, M.J., Handberg, E., Kupfer, S., Pepine, C.J., 2005. A Study of Antihypertensive Drugs and Depressive Symptoms (SADD-Sx) in patients treated with a calcium antagonist versus an atenolol hypertension Treatment Strategy in the International Verapamil SR-Trandolapril Study (INVEST). *Psychosomatic medicine* 67, 398-406.

Roelofs, J., Peters, M.L., McCracken, L., Vlaeyen, J.W., 2003. The pain vigilance and awareness questionnaire (PVAQ): further psychometric evaluation in fibromyalgia and other chronic pain syndromes. *Pain* 101, 299-306.

Salvi, P., Lio, G., Labat, C., Ricci, E., Pannier, B., Benetos, A., 2004. Validation of a new non-invasive portable tonometer for determining arterial pressure wave and pulse wave velocity: the PulsePen device. *Journal of hypertension* 22, 2285-2293.

Seldenrijk, A., van Hout, H.P., van Marwijk, H.W., de Groot, E., Gort, J., Rustemeijer, C., Diamant, M., Penninx, B.W., 2013. Sensitivity to depression or anxiety and subclinical cardiovascular disease. *Journal of affective disorders* 146, 126-131.

Sen, S., Duman, R., Sanacora, G., 2008. Serum brain-derived neurotrophic factor, depression, and antidepressant medications: meta-analyses and implications. *Biological psychiatry* 64, 527-532.

Tang, T.Z., DeRubeis, R.J., Hollon, S.D., Amsterdam, J., Shelton, R., Schalet, B., 2009. Personality change during depression treatment: a placebo-controlled trial. *Archives of general psychiatry* 66, 1322-1330.

Tiemeier, H., Breteler, M.M., van Popele, N.M., Hofman, A., Witteman, J.C., 2003. Late-life depression is associated with arterial stiffness: a population-based study. *Journal of the American Geriatrics Society* 51, 1105-1110.

Townsend, R.R., Wilkinson, I.B., Schiffrin, E.L., Avolio, A.P., Chirinos, J.A., Cockcroft, J.R., Heffernan, K.S., Lakatta, E.G., McEniery, C.M., Mitchell, G.F., Najjar, S.S., Nichols, W.W., Urbina, E.M., Weber, T., 2015. Recommendations for Improving and Standardizing Vascular Research on Arterial Stiffness: A Scientific Statement From the American Heart Association. *Hypertension (Dallas, Tex. : 1979)* 66, 698-722.

Unger, T., Badoer, E., Ganten, D., Lang, R.E., Rettig, R., 1988. Brain angiotensin: pathways and pharmacology. *Circulation* 77, 140-54.

Van Bortel, L.M., Laurent, S., Boutouyrie, P., Chowienczyk, P., Cruickshank, J.K., De Backer, T., Filipovsky, J., Huybrechts, S., Mattace-Raso, F.U., Protogerou, A.D., Schillaci, G., Segers, P., Vermeersch, S., Weber, T., Artery, S., European Society of Hypertension Working Group on Vascular, S., Function, European Network for Noninvasive Investigation

of Large, A., 2012. Expert consensus document on the measurement of aortic stiffness in daily practice using carotid-femoral pulse wave velocity. *J Hypertens* 30, 445-448.

Vazquez, G.H., Tondo, L., Mazzarini, L., Gonda, X., 2012. Affective temperaments in general population: a review and combined analysis from national studies. *Journal of affective disorders* 139, 18-22.

Williams, J.E., Din-Dzietham, R., Szklo, M., 2006. Trait anger and arterial stiffness: results from the Atherosclerosis Risk in Communities (ARIC) study. *Preventive cardiology* 9, 14-20.

Wurzner, G., Gerster, J.C., Chioloro, A., Maillard, M., Fallab-Stubi, C.L., Brunner, H.R., Burnier, M., 2001. Comparative effects of losartan and irbesartan on serum uric acid in hypertensive patients with hyperuricaemia and gout. *Journal of hypertension* 19, 1855-1860.

Yamada, K., Horita, T., Takayama, M., Takahashi, S., Takaba, K., Nagata, Y., Suzuki, N., Kanda, T., 2011. Effect of a centrally active angiotensin converting enzyme inhibitor, perindopril, on cognitive performance in chronic cerebral hypo-perfusion rats. *Brain research* 1421, 110-120.

Table 1. Antihypertensive and vasculoprotective medications of HT2 group.

Regular medications	N (total=31)
ACE inhibitor (perindopril)	26 (83.9 %)
Angiotensin-receptor blocker (losartan)	2 (6.5 %)
Calcium channel blocker (amlodipine)	22 (71.0 %)
Beta-blockers	12 (38.7 %)
bisoprolol	7 (22.6 %)
carvedilol	2 (6.5 %)
metoprolol	1 (3.2 %)
nebivolol	2 (6.5 %)
Alfa-adrenergic receptor blocker (doxazosin)	1 (3.2 %)
Diuretic (indapamid)	4 (12.9 %)
Antiplatelet medications	3 (9.7 %)
Statins	3 (9.7 %)
1 type of antihypertensive agent	4 (12.9 %)
2 types of antihypertensive agents	19 (61.3 %)
3 types of antihypertensive agents	6 (19.4 %)
4 types of antihypertensive agents	2 (6.4 %)

Table 2. Demographic, laboratory, haemodynamic and arterial stiffness parameters of controls (CONT) and hypertensive patients at baseline (HT1) and during therapy (HT2).

	CONT	HT1	HT2
Subjects [man/woman]	22 (8/14)	31 (22/9)	31 (22/9)
Age [year]	31 (26-41.2)	47 (38-63)*	48 (39-63)
Smoking [n (%)]	4 (18.2%)	10 (32.3%)	10 (32.3%)
Waist circumference [cm]	83 (77-93)	98.5 (91-105)*	97 (94-104.5)
BMI [kg/m ²]	22.9 (2.9)	28.6 (5.4)*	28.3 (5.4)
Blood glucose [mmol/l]	4.9 (4.7-5.3)	5.1 (4.8-5.9)*	5.4 (4.9-5.5)
eGFR-EPI [mmol/l]	87.1 (19.9)	88.4 (17.1)	88.0 (17.6)
Uric acid [μmol/l]	299.9 (76,6)	357.9 (79.2)*	381.2 (97.6)
Total cholesterol [mmol/l]	4.8 (0.79)	5.9 (1.04)*	5.6 (1.04)
Triglyceride [mmol/l]	0.8 (0.28)	1.9 (0.83)*	1.9 (1.06)
SBPbrach [Hgmm]	117.1 (10.1)	153.3 (15.9)*	129.5 (10.0)#
DBPbrach [Hgmm]	70 (64-71.2)	91.5 (85.6-99.2)*	80.5 (73.5-85)#
PPbrach [Hgmm]	49.7 (8.2)	57.9 (11.3)*	50.6 (10.2)#
Heart rate [1/min]	68.1 (9.3)	79.7 (12.5)*	74.5 (9.3)#
SBPcentr [Hgmm]	112.4 (8.4)	138.1 (14.2)*	121 (11.5)#
DBPcentr [Hgmm]	65.9 (6.8)	84.4 (8.5)*	74.7 (7.6)#
PPcentr [Hgmm]	46.5 (7.6)	53.8 (12.1)*	46.3 (10.4)#
Augmentation index [%]	1.7 (13.2)	18.3 (16.8)*	10.1 (17.3)#
PWV [m/sec]	6.2 (0.9)	8.2 (1.4)*	7.5 (1.6)#
seBDNF (ng/ml)	22.7 (20.4-26.2)	22.1 (18.2-28.7)	23.9 (17.9-28.4)

Continuous data are presented as mean (\pm SD) or medians (25-75 percentiles). CONT: control subjects; HT1: hypertensive patients before blood pressure medication; HT2: treated hypertensive patients 3 months after initiation of medication. BMI: body mass index; eGFR-EPI: glomerular filtration rate assessed by the chronic kidney disease epidemiology collaboration glomerular filtration rate equation; SBPbrach: brachial systolic blood pressure;

DBPbrach: brachial diastolic blood pressure; PPbrach: brachial pulse pressure; SBPcentr: central systolic blood pressure; DBPcentr: central diastolic blood pressure; PPcentr: central pulse pressure; PWV: pulse wave velocity; seBDNF: serum brain-derived neurotrophic factor.

* $p < 0.05$ between CONT-HT1; # $p < 0.05$ between HT1-HT2.

Table 3. Comparison of psychometric scores of hypertensive at baseline and during therapy and control patients.

	CONT	HT1	HT2
BDI	3.8 (0-6)	5.1 (2-8)	4.4 (0-7)#
HAM-A	4.1 (4.1)	6.4 (6.0)*	7.8 (8.0)
SCL-90-R			
Somatization	2.7 (1-4)	8.7 (3.7-13.5) *	5 (2-6) #
Obs-comp	10.5 (3.9)	14.9 (10-17.2) *	12.1 (8.7-14) #
Interpersonal sensitivity	3.4 (0.2-5)	5.1 (0-7.2)	3.5 (0-6.5) #
Depression	4.8 (2-5.7)	5.8 (0-5.7)	4.2 (0-4.5) #
Anxiety	2.9 (1-4.7)	5.2 (0.7-8.2)	3.5 (0-6.5) #
Hostility	1.6 (0-2.7)	2.2 (0-2)	1.5 (0-2)
Phobic anxiety	0.5 (0-1)	1.6 (0-2)	1.4 (0-2)
Paranoid ideation	1.5 (0-2)	2.9 (0-4.2)	2.6 (0-3.2)
Psychoticism	1.5 (0-2)	3.6 (0-4.2)	1.7 (0-2) #
GSI	0.3 (0.1-0.4)	0.5 (0.1-0.6)	0.4 (0.1-0.5)#
PSDI	1.3 (1.1-1.4)	1.6 (1.1-1.8) *	1.5 (1.1-2)
PST	17.9 (10-26)	23.5 (10-27.2)	19.8 (5.7-32)#
TEMPS-A			
Depressive	6.6 (5-8)	6 (4-8)	6.2 (3-8)
Irritable	4.1 (2-5)	4.4 (2-6)	4.6 (2-5)
Anxious	4.6 (2-6)	4.3 (1-7)	4.8 (1-6)
Hyperthymic	11.8 (8-15)	13.8 (11-15)	12.9 (11-14)
Cyclothymic	3.5 (1-7)	4.2 (1-7)	3.9 (1-5)
BFI-44 (Big Five Questionnaire)			
Extraversion	3.6 (3.1-4)	3.9 (3.5-4.2)	3.7 (3.4-4.2)
Agreeableness	3.8 (3.2-4.2)	3.9 (3.4-4.2)	3.8 (3.6-4.4)
Conscientiousness	3.8 (0.7)	4.1 (0.5)	4.1 (0.5)
Neuroticism	2.5 (2.2-2.7)	2.3 (1.7-2.9)	2.3 (1.9-2.6)
Openness	4.0 (0.8)	4.1 (0.4)	4.0 (0.6)
Berkeley Expressivity Questionnaire			
Overall emotional expressivity	75 (71-84)	66.8 (57-75) *	65.7 (60-73)
Negative emotionality facet	26 (5.2)	22 (7.7) *	22.1 (6.9)
Positive emotionality facet	23.4 (4.1)	22.96 (4.2)	21.4 (4.8)
Impulse strength facet	24.7 (7.7)	21.8 (7.2)	22.2 (8.4)
The Pain Vigilance and Awareness Questionnaire			

Sum	38.8 (13.3)	45.5 (13.6)	42.8 (14)
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Continuous data are presented as mean (\pm SD) or means (25-75 percentiles). BDI: Beck Depression Inventory; HAM-A: Hamilton Anxiety Scale; SCL-90-R: SCL-90 autoquestionnaire; GSI: global severity index; PSDI: positive symptom distress index; PST: positive symptom total. TEMPS-A: Temperament Evaluation of Memphis, Pisa, Paris and San Diego Autoquestionnaire; BFI-44: The Big Five Inventory; Obs-comp: obsessiveness-compulsiveness; * $p < 0.05$ between CONT-HT1; # $p < 0.05$ between HT1-HT2.