**Online supplement**

**Predictors of blood pressure control in patients with Resistant Hypertension after intensive management in two expert centres:**

**the Brussels-Torino experience**

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**Methods (supplement)**

*Clinical data extraction*

In order to get a broad and precise picture of the clinical profile of patients with RHTN in our cohort, we collected information on demographics, clinical characteristics, comorbidities, office and out-of-office BP and pulse pressure (PP) values, drug classes and side effects as well as data about adherence, screening for secondary hypertension and invasive treatments, both at baseline and at the last follow-up visit.

Left ventricular hypertrophy (LVH) was defined as left ventricular mass index > 125 g/m2 in men and > 110 g/m2 in women; diabetes was defined as fasting blood glucose ≥ 126 mg/dl or the use of antidiabetic medication [1]; dyslipidaemia was defined as total cholesterol levels > 240 mg/dl and/or triglyceride plasmatic levels > 200 mg/dl [2]; chronic kidney disease (CKD) was defined as estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73m2 [3].

Biochemical evaluation included serum potassium, creatinine and haemoglobin concentrations, eGFR, HbA1c and transaminase levels, and urinary albumin and protein excretion (assessed using 24-hour urine collection).

Patients were explored for secondary hypertension such as renovascular hypertension (by performing a Duplex ultrasound of renal arteries and/or a computer tomography angiography or magnetic resonance angiography looking for atherosclerotic and/or Fibromuscular Dysplasia-related stenosis), parenchymal renal disease (by performing renal ultrasound, determination of plasma creatinine and electrolytes levels, urine sample test and evaluation of urinary albumin and 24-hour urinary protein), primary aldosteronism (by evaluation of aldosterone and renin plasmatic levels and aldosterone/renin ratio; in case of dubious laboratory findings, a confirmatory test - saline infusion test – and/or a CT scan of adrenal gland were performed), pheochromocytoma (by evaluation of plasmatic and 24-hour urinary fractionated metanephrines), thyroid disease (by dosage of thyroid hormones) and obstructive sleep apnoea syndrome (OSAS) (by performing a polysomnography in case of positive history of snoring and/or nocturnal apneas).

Adherence to drug therapy was assessed in a subsets of patients using a liquid chromatography system coupled with a tandem mass spectrometer as detector [4-6] (LC-MS/MS). According to the results of therapeutic drug monitoring, patients were considered 1)“fully adherent” when 100% of prescribed medications were detected in urine or blood samples, 2)“partly adherent”, when 80% to 99% of prescribed medications were detected in urine or blood samples, and 3)“non-adherent” when <80% of prescribed medications were detected in biological samples, respectively.

Along adherence evaluation, four validated psychological questionnaires (The *Toronto Alexithymia Scale* – TAS-20, The *Emotion Regulation Questionnaire* – ERQ, The *Post Traumatic Diagnostic Scale* – PTDS, and The *Brief Symptom Inventory* - BSI) [7] were administered in a subgroup of patients at baseline. The TAS-20 questionnaire [8] is meant to explore three features associated with the alexithymia construct: the difficulty to identify feelings, to describe feelings, and externally-oriented thinking. The ERQ questionnaire [9] evaluates two emotion regulation’s strategies, and the PTSD questionnaire [10] provides a full assessment of posttraumatic stress disorders (PTDS) according to patients’ past traumatic experiences. Finally, the BSI [11], a 53-items multidimensional test measuring the levels of nine primary psychological symptoms, was used to assess patients’ general psychopathological profile.

Both therapeutic drug monitoring and psychological tests were performed after signature of the written informed consent and agreement of the corresponding Institutional Review Boards.

Finally, data on antihypertensive drugs and related side-effects, as well as on invasive treatment (e.g., RDN) and other medications (such as statins and other lipid lowering agents, oral antidiabetic agents and insulin, hormone replacement therapy, non-steroidal anti-inflammatory drugs – NSAIDs -, aspirin, anticoagulant and antidepressant agents) were also collected.

*Blood pressure measurements*

Office BP (OBP) was measured by a physician on both arms at each patient’s visit following the European Society of Hypertension (ESH) recommendation [12] (3 consecutive BP readings after 5 min rest with at least 1-minute interval between them) by using digital oscillometric BP electronic devices (Omron HEM 907; OMRON Health Care, Kyoto, Japan / Omron M6; OMRON, Kyoto, Japan). Both seated and standing BP readings were registered and the mean of the 3 measurements was used as BP reference value.

ABPM readings were recorded using SpaceLabs 90207 (SpaceLabs Healthcare Ltd., Issaquah, Washington, USA) or Mobil-O-Graph, I.E.M (Mobil-O-Graph, I.E.M GmbH, Stolberg, Germany). Both devices were programmed to measure BP at 15-min intervals during the day (from 06:00 to 23:00) and at 30-min intervals during the night (from 23:00 to 06:00). All patients were instructed to immobilize their arms and refrain from speaking during BP readings and to keep a precise diary of their daily activities. Both 24-hour, daytime, and night-time systolic BP (SBP) and diastolic BP (DBP) were evaluated and daytime BP values were then calculated after taking into account the actual awake and sleep period as reported in each patient’s diary.

*Statistical analysis*

Statistical analysis was performed using IBM SPSS Statistics version 21.0 (IBM Corp., Armonk, New York). Categorical variables are expressed as percentages and continuous data as mean ± standard deviation (SD), if normally distributed, or median (interquartile range [IQR]), if asymmetrically distributed. Categorical variables were compared using the χ2 test and continuous variables using Student’s *t* test or Mann-Whitney test according to their distribution. Finally, we performed a multivariate logistic regression to identify independent predictors of controlled resistant hypertension at the end of the follow-up. A *p* value < 0.05 was considered to be statistically significant.

All analysis was performed both in the overall cohort and in the subgroup of fully adherent patients, according to the results of therapeutic drug monitoring.

**Results (supplement)**

*Follow-up*

Standing SBP and DBP values reduced by -17 ± 29 mmHg and -10 ± 18 mmHg, respectively. When considering ABPM BP readings, reductions in terms of BP values at the end of the follow-up were slighter but sill significant.

*Patients with persistent RHTN vs. controlled RHTN at follow-up*

Even at the end of the follow-up PP values were significantly higher in patients who did not reach BP control (Seated Office PP: 76 vs. 56 mmHg, p-value<0.001– Standing Office PP: 75 vs. 45 mmHg, p-value<0.001– Daytime monitoring PP: 62 vs. 49 mmHg, p-value<0.001 – Night-time monitoring PP: 59 vs. 47 mmHg, p-value<0.001 – 24-h monitoring PP: 61 vs. 49 mmHg, p-value<0.001). (Table S1).

*Subgroup analysis*

1*. Brussels vs. Torino*

Belgian (*n* = 258) and Italian (*n* = 55) samples were comparable in terms of age, sex, comorbidities and major CV risk factors. Despite the fact that both daytime (SBP 160 vs. 149 mmHg, p-value<0.001; DBP 95 vs. 88 mmHg, p-value=0.005), night-time (SBP 146 vs. 136 mmHg, p-value=0.006; DBP 84 vs. 76 mmHg, p-value=0.005) and 24-h ambulatory BP values (SBP 155 vs. 145 mmHg, p-value=0.001; DBP 91 vs. 84 mmHg, p-value=0.015) were almost 10 mmHg higher in Belgian patients at baseline, while the prevalence of LVH was higher in Italian patients (56% vs. 38%; p-value=0.007). In contrast, no difference was found in terms of systolic and diastolic Office BP at baseline (Table S4). Neither PP values at baseline or at follow-up differed significantly between patients from Brussels and Torino. (Table S4-S5). Furthermore, there were no differences in terms of systolic and diastolic BP values at the follow-up between the two subgroups (Table S5).

Italian patients were more likely to report antihypertensive drug intolerance at the time of diagnosis (46% vs. 23%, p-value=0.001) for all antihypertensive drug classes (ACE-I/ARBs 21% vs. 8%, p-value=0.004; CCBs 33% vs. 15%, p-value=0.002; diuretics 15% vs. 5%, p-value=0.010). While loop diuretics and alpha-adrenergic receptor blockers were more frequently prescribed in the Torino centre (31% vs. 24%, p-value=0.019 and 51% vs. 11%, p-value<0.001, respectively), in the Brussels centre patients had a higher prescription of central adrenergic agonists (54% vs. 24%, p-value<0.001) and thiazide or thiazide-like diuretics (78% vs. 66%, p-value=0.043). In spite of the difference in terms of antihypertensive drugs prescribed between the two European centres, the prevalence of patients eventually controlled after therapeutic adjustments in the expert centres did not differ after a similar median follow-up.

*2. Men vs. Women.*

Sex was equally distributed in our population (160 M; 153 F). At the time of diagnosis, males were more likely to have a history of myocardial infarction (21% vs. 11%, p-value=0.015) and OSAS requiring CPAP (24% vs. 9%, p-value<0.001). Interestingly, both seated and standing Office SBP were higher in women than in men (182 vs. 172 mmHg, p-value=0.001 and 181 vs. 171 mmHg, p-value=0.001, respectively). Similarly, women had also higher Office diastolic BP values (seated DBP 101 vs. 94 mmHg, p-value=0.001 – standing DBP 103 vs. 96 mmHg, p-value=0.002), while no differences were found in terms of ambulatory BP values (Table S4).

Neither PP values at baseline or at follow-up differed significantly between male and female (Table S4-S5). When compared to women at the end of the follow-up, men showed significantly lower systolic and diastolic Office BP values (Seated Office BP 154/83 mmHg ± vs. 162/91 mmHg, p-value=0.02/<0.001 – Standing Office BP 153/83 mmHg vs. 162/94 mmHg, p-value<0.001/<0.001), despite no difference in terms of BP response to treatment (Δ Seated Office BP -18/-11 vs. -21/-11 mmHg, p-value=0.9/0.7, and Δ Standing Office BP -16/-11 vs. -19/-9 mmHg, p-value=0.5/0.3, male vs. female respectively) (Table S5 –TableS6).

*3. Patients < 60 years old vs. > 60 years old.*

While prevalence of smoking (28% vs. 15%, p-value=0.007) and LVH (47% vs. 34%, p-value=0.041) was higher among younger patients, older subjects, as expected, had a higher prevalence of all major CV risk factors and comorbidities. In particular, dyslipidaemia (70% vs. 56%, p-value=0.04), diabetes mellitus (42% vs. 24%, p-value=0.001) and chronic kidney diseases (33% vs. 15%, p-value<0.001) were significantly more common among older resistant hypertensives.

No differences were found in terms of SBP both at Office and out-of-office measurements either at baseline or at follow-up (Table S4-S5). On the contrary, DBP values were significantly higher in younger than in older patients across all measurements both at baseline (seated office DBP 105 vs. 87 mmHg, p-value<0.001; standing DBP 108 vs. 88 mmHg, p-value<0.001; daytime ambulatory DBP 100 vs. 85 mmHg, p-value<0.001; night-time ambulatory DBP 88 vs. 74 mmHg, p-value<0.001; 24-h ambulatory DBP 95 mmHg vs. 82 mmHg, p-value<0.001) and at follow-up (seated office DBP 93 vs. 78 mmHg, p-value<0.001; standing DBP 95 vs. 81 mmHg, p-value<0.001; daytime ambulatory DBP 91 vs. 83 mmHg, p-value<0.001; night-time ambulatory DBP 78 vs. 72 mmHg, p-value=0.03; 24-h ambulatory DBP 89 mmHg vs. 79 mmHg, p-value <0.001). (Table S4 – S5)

As expected, PP values were significantly higher in older patients, both at baseline (Seated Office PP 90 vs. 71 mmHg, p-value<0.001 – Standing Office PP 86 vs. 68 mmHg, p-value<0.001 – Daytime ambulatory PP 70 vs. 59 mmHg, p-value<0.001 – Night-time ambulatory PP 66 vs. 57 mmHg, p-value<0.001 – 24-h ambulatory PP 69 vs. 60 mmHg, p-value<0.001) and at follow-up (Seated Office PP 81 vs. 63 mmHg, p value<0.001 – Standing Office PP 78 vs. 60 mmHg, p-value<0.001 – Daytime ambulatory PP 63 vs. 56 mmHg, p-value<0.001 – Night-time ambulatory PP 60 vs. 53 mmHg, p-value=0.003 – 24-h ambulatory PP 63 vs. 55 mmHg, p-value<0.001) across all measurements (Table S4 – S5).

Dihydropyridine CCBs (81 vs. 89%, p-value=0.028) and aldosterone antagonists (22% vs. 42%, p-value<0.001) were less frequently prescribed in older patients, on the contrary of direct vasodilators (14% vs. 7%, p-value=0.032) and central adrenergic agonists (56% vs. 42%, p-value=0.015).

Finally, the prevalence of adherence was higher in older than in younger patients (90% vs. 65%, p-value=0.004).

*4.* *Patients undergoing RDN vs. not undergoing RDN.*

Patients who underwent RDN (*n* = 73) were generally younger (57 vs. 63 years, p-value<0.001), even at the time of diagnosis (51 vs. 58 years, p-value<0.001), had higher office and out-of-office systolic and diastolic BP values (seated Office BP 185/108 vs. 175/95 mmHg, p-value=0.002/<0.001; standing Office BP 184/109 vs. 173/97 mmHg, p-value=0.004/<0.001; daytime ambulatory BP 164/102 vs. 156/91 mmHg, p-value=0.003/<0.001; night-time ambulatory BP 151/91 vs. 141/79 mmHg, p-value=0.003/<0.001; 24-h ambulatory BP 160/97 vs. 151/87 mmHg, p-value=0.002/<0.001) (Table S4), and had lower serum creatinine and higher eGFR levels (0.92 vs. 1.10 mg/dl, p-value<0.001; 85 vs. 73 ml/min/1.73m2, p-value=0.001, respectively).

Both systolic and diastolic BP values of patients who underwent RDN remained significantly higher both at Office and out-of-office measurements at the end of the follow-up (Seated Office BP: 167/97 vs. 156/83 mmHg, p-value=0.001/<0.001 – Standing Office BP: 164/98 vs. 155/86 mmHg, p-value=0.056/<0.001 – Daytime ambulatory BP: 156/96 vs. 143/85 mmHg, p-value<0.001/<0.001 – Night-time ambulatory BP: 142/83 vs. 128/72 mmHg, p-value<0.001/<0.001 – 24-h ambulatory BP: 154/94 vs. 139/81 mmHg, p-value<0.001/<0.001) (Table S5). No differences were found in terms of PP between patients who underwent RDN and those only on medical therapy, either at baseline or at follow-up (Table S4 – S5)

While both subgroups of patients reported similar Office BP changes from baseline to follow-up, reductions in term of systolic and diastolic BP values from baseline to follow-up at the ABPM readings were significantly higher in patients who only received a medical treatment (Δ Daytime ambulatory SBP/DBP: -15/-8 vs. -2/-2 mmHg, p-value=0.002/0.02 – Δ Night-time ambulatory SBP/DBP: -14/-9 vs. -1/-1 mmHg, p-value=0.003/0.002 – Δ 24-h ambulatory SBP/DBP: -13/-8 vs. -2/-2 mmHg, p-value=0.01/0.03) (Table S6). Furthermore, patients who did not undergo any invasive procedure reported higher reductions in terms of PP values from baseline to follow-up only at daytime monitoring measurements (Δ Daytime ambulatory PP: -6 vs. 0 mmHg, p-value=0.01), while changes in night-time monitoring PP did not reach statistic significance (Δ Night-time ambulatory PP: -5 vs. 0 mmHg, p-value=0.05). (Table S6)

Concerning adherence, patients who underwent RDN were more likely to be non-adherent to antihypertensive regimen (37% vs. 21%, p-value=0.001), had a higher median number of antihypertensive medications (6 vs. 5, p-value=0.004) and, interestingly, of antidepressant drugs (33% vs. 19%, p-value=0.011).

Finally, despite a higher prescription of aldosterone antagonists (48% vs. 30%; p-value=0.005) and direct renin inhibitors (25% vs. 12%, p-value=0.024), the proportion of patients controlled at follow-up was lower among patients who underwent RDN than in patients who only received antihypertensive drug therapy (14% vs. 30%; p-value=0.008).

**Online supplement references**

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**Table S1**. Significant differences in general characteristics and BP values between patients eventually controlled and those still refractory at the end of the follow-up.

CABG = Coronary Artery Bypass Graft; PCI = Percutaneous Coronary Intervention; LVH = Left Ventricular Hypertrophy; BP = Blood Pressure; SBP = Systolic Blood Pressure; DBP = Diastolic Blood Pressure; FU = Follow-up; ERQ = the *Emotion Regulation Questionnaire*.

|  |  |  |  |
| --- | --- | --- | --- |
| Variables | Persistent resistant hypertensives  *n* = 232 | Eventual controlled hypertensives  *n* = 81 | p-value |
|  |  |  |  |
| BP values at baseline |  |  |  |
| Seated Office SBP | 180 (± 26) | 168 (± 23) | 0.001 |
| Standing Office SBP | 178 (± 27) | 168 (± 24) | 0.003 |
|  |  |  |  |
| PP at baseline |  |  |  |
| Seated Office PP | 82 (± 25) | 71 (± 18) | 0.001 |
| Standing Office PP | 79 (± 25) | 68 (± 20) | 0.001 |
| Daytime ambulatory PP | 65 (± 15) | 60 (± 16) | 0.04 |
|  |  |  |  |
| BP values at FU |  |  |  |
| Seated Office SBP at FU | 167 (± 25) | 132 (± 18) | <0.001 |
| Seated Office DBP at FU | 91 (± 19) | 76 (± 13) | <0.001 |
| Δ seated Office SBP | -13 (± 27) | -36 (± 27) | <0.001 |
| Δ seated Office DBP | -7 (± 15) | -21 (± 16) | <0.001 |
|  |  |  |  |
| Standing Office SBP at FU | 167 (± 25) | 127 (± 14) | <0.001 |
| Standing Office DBP at FU | 92 (± 20) | 77 (± 10) | <0.001 |
| Δ standing Office SBP | -10 (± 26) | -39 (± 27) | <0.001 |
| Δ standing Office DBP | -6 (± 16) | -22 (± 17) | <0.001 |
|  |  |  |  |
| Daytime ambulatory SBP at FU | 153 (± 19) | 127 (± 11) | <0.001 |
| Daytime ambulatory DBP at FU | 91 (± 15) | 78 (± 8) | <0.001 |
| Δ Daytime ambulatory SBP | -5 (± 21) | -31 (± 20) | <0.001 |
| Δ Daytime ambulatory DBP | -3 (± 12) | -18 (± 14) | <0.001 |
|  |  |  |  |
| Night-time ambulatory SBP at FU | 138 (± 23) | 112 (± 10) | <0.001 |
| Night-time ambulatory DBP at FU | 79 (± 16) | 65 (± 7) | <0.001 |
| Δ Night-time ambulatory SBP | -4 (± 22) | -29 (± 22) | <0.001 |
| Δ Night-time ambulatory DBP | -3 (± 13) | -19 (± 15) | <0.001 |
|  |  |  |  |
| 24-h ambulatory SBP at FU | 149 (± 19) | 124 (± 11) | <0.001 |
| 24-h ambulatory DBP at FU | 88 (± 15) | 75 (± 8) | <0.001 |
| Δ 24-h ambulatory SBP | -4 (± 21) | -31 (± 21) | <0.001 |
| Δ 24-h ambulatory DBP | -3 (± 12) | -18 (± 15) | <0.001 |
|  |  |  |  |
| PP at FU |  |  |  |
| Seated Office PP at FU | 76 (± 23) | 56 (± 15) | <0.001 |
| Δ seated Office PP | -6 (± 22) | -15 (± 19) | 0.003 |
| Standing Office PP at FU | 75 (± 24) | 49 (± 13) | <0.001 |
| Δ standing Office PP | -4 (± 21) | -17 (± 19) | <0.001 |
| Daytime ambulatory PP at FU | 62 (± 15) | 49 (± 8) | <0.001 |
| Δ daytime ambulatory PP | -2 (± 13) | -12 (± 15) | <0.001 |
| Night-time ambulatory PP at FU | 59 (± 17) | 47 (± 8) | <0.001 |
| Δ night-time ambulatory PP | -1 (± 13) | -11 (± 12) | <0.001 |
| 24-h ambulatory PP at FU | 61 (± 15) | 49 (± 9) | <0.001 |
| Δ 24-h ambulatory PP | -0 (± 16) | -12 (± 11) | 0.001 |
| Cardiovascular Complications   * Coronary Artery Disease   + Acute Myocardial Infarction     - CABG     - PCI | 45 (20%)  18 (8%)  36 (16%) | 5 (6%)  1 (1%)  5 (6%) | 0.005  0.03  0.03 |
| LVH | 101 (44%) | 29 (36%) | 0.04 |
| No. of antihypertensive drugs at FU  RDN | 5 (4-6)  62 (27%) | 5 (4-6)  10 (12%) | 0.02  0.008 |
| Psychological tests | | | |
| ERQ test   * Cognitive reappraisal score | 3.9 (± 1) | 4.8 (± 1) | 0.009 |

**Table S2.** Comparison on general characteristics and blood pressure values between overall population and fully adherent subgroup of patients, according to results of therapeutic drug monitoring (n 67).

|  |  |  |  |
| --- | --- | --- | --- |
| Variables | Overall population  *n* = 246 | Fully adherent patients  *n* = 67 | p-value |
| Age | 62 (± 13) | 61 (± 10) | 0.8 |
| Age at diagnosis of RHTN | 56 (± 13) | 57 (± 10) | 0.7 |
| Sex [n (%)] | 123 (49.8) | 30 (44.8) | 0.4 |
| BMI (kg/m2) | 31 (± 7) | 30 (± 6) | 0.08 |
| Current smokers | 59 (24) | 13 (19) | 0.5 |
| Dyslipidaemia | 159 (65) | 37 (55) | 0.3 |
| Type 2 Diabetes Mellitus | 78 (32) | 21 (31.3) | 0.9 |
| CKD | 55 (22.5) | 16 (23.9) | 0.8 |
| Cardiovascular Complications   * Coronary Artery Disease   + Acute Myocardial Infarction     - CABG     - PCI   + Unstable Angina * Heart Failure * Valvular disease * Arrhythmia   + Atrial fibrillation   + Other | 48 (19.7)  18 (7.4)  37 (15.2)  3 (1.2)  13 (5.3)  14 (5.7)  14 (5.7)  5 (2) | 3 (4.5)  1 (1.5)  5 (7.5)  1 (1.5)  1 (1.5)  3 (4.5)  4 (6)  2 (3) | **0.003**  0.08  0.1  0.9  0.2  0.7  0.9  0.6 |
| LVH | 99 (40.6) | 31 (46) | 0.7 |
| OSAS   * Requiring cPAP * Not requiring cPAP | 66 (27)  40 (18)  26 (10.7) | 19 (28.4)  12 (18)  5 (7.5) | 0.9  0.6  0.5 |
| Cerebrovascular complications   * Stroke * Transient Ischaemic Attack | 17 (7)  7 (3) | 4 (6)  0 (0) | 0.8  0.2 |
| Peripheral Vascular Disease | 23 (9.4) | 6 (9) | 0.9 |
| Alcohol or drug abuse | 17 (7) | 8 (13) | 0.2 |
| Hepatic impairment | 9 (3.7) | 5 (7.5) | 0.06 |
| Current life-threatening disease | 2 (0.8) | 0 (0) | 0.6 |
| Retinopathy (III or IV stage) | 5 (2) | 3 (4.5) | 0.3 |
| Malignant HTN | 5 (2) | 3 (4.5) | 0. 3 |
|  |  |  |  |
| BP values at baseline |  |  |  |
| Seated Office SBP  Seated Office DBP | 179 (± 26)  100 (± 20) | 169 (± 25)  92 (± 16) | **0.003**  **0.004** |
| Standing Office SBP  Standing Office DBP | 178 (± 26)  101 (± 20) | 167 (± 24)  93 (± 19) | **0.004**  **0.004** |
| Daytime ambulatory SBP  Daytime ambulatory DBP | 160 (± 20)  95 (± 17) | 149 (± 16)  88 (± 13) | **<0.001**  **0.005** |
| Night-time ambulatory SBP  Night-time ambulatory DBP | 146 (± 23)  84 (± 18) | 134 (± 19)  76 (± 13) | **0.001**  **0.005** |
| 24-hours ambulatory SBP  24-hours ambulatory DBP | 156 (± 20)  91 (± 19) | 144 (± 16)  85 (± 12) | <0.001  0.04 |
|  |  |  |  |
| PP at baseline |  |  |  |
| Seated Office PP | 80 (± 24) | 77 (± 24) | 0.4 |
| Standing Office PP | 77 (± 24) | 74 (± 24) | 0.4 |
| Daytime ambulatory PP | 65 (± 15) | 60 (± 18) | **0.03** |
| Night-time ambulatory PP | 62 (± 15) | 58 (± 17) | 0.06 |
| 24-h ambulatory PP | 65 (± 19) | 60 (± 16) | 0.09 |
|  |  |  |  |
| BP values at FU |  |  |  |
| Seated Office SBP at FU | 160 (± 30) | 151 (± 20) | **0.02** |
| Seated Office DBP at FU | 88 (± 20) | 83 (± 14) | 0.08 |
| Δ seated Office SBP | -20 (± 29) | -17 (± 28) | 0.5 |
| Δ seated Office DBP | -12 (± 17) | -9 (± 14) | 0.3 |
|  |  |  |  |
| Standing Office SBP at FU | 160 (± 29) | 145 (± 22) | **0.002** |
| Standing Office DBP at FU | 90 (± 20) | 81 (± 14) | **0.003** |
| Δ standing Office SBP | -18 (± 29) | -16 (± 28) | 0.8 |
| Δ standing Office DBP | -11 (± 18) | -7 (± 14) | 0.3 |
|  |  |  |  |
| Daytime ambulatory SBP at FU | 148 (± 22) | 140 (± 17) | **0.04** |
| Daytime ambulatory DBP at FU | 89 (± 15) | 84 (± 12) | 0.07 |
| Δ Daytime ambulatory SBP | -10 (± 24) | -12 (± 21) | 0.8 |
| Δ Daytime ambulatory DBP | -6 (± 14) | -5 (± 13) | 0.8 |
|  |  |  |  |
| Night-time ambulatory SBP at FU | 134 (± 24) | 125 (± 21) | 0.052 |
| Night-time ambulatory DBP at FU | 77 (± 16) | 70 (± 13) | **0.03** |
| Δ Night-time ambulatory SBP | -9 (± 23) | -10 (± 28) | 0.9 |
| Δ Night-time ambulatory DBP | -6 (± 15) | -8 (± 16) | 0.7 |
|  |  |  |  |
| 24-h ambulatory SBP at FU | 144 (± 21) | 137 (± 18) | 0.09 |
| 24-h ambulatory DBP at FU | 86 (± 15) | 79 (± 13) | **0.02** |
| Δ 24-h ambulatory SBP | -9 (± 24) | -7 (± 21) | 0.7 |
| Δ 24-h ambulatory DBP | -6 (± 14) | -5 (± 12) | 0.6 |
|  |  |  |  |
| PP at FU |  |  |  |
| Seated Office PP at FU | 72 (± 23) | 68 (± 21) | 0.2 |
| Δ seated Office PP | -8 (± 21) | -8 (± 22) | 0.9 |
| Standing Office PP at FU | 70 (± 25) | 64 (± 22) | 0.2 |
| Δ standing Office PP | -7 (± 20) | -9 (± 24) | 0.6 |
| Daytime ambulatory PP at FU | 59 (± 15) | 56 (± 14) | 0. 3 |
| Δ daytime ambulatory PP | -4 (± 14) | -4 (± 16) | 0.9 |
| Night-time ambulatory PP at FU | 57 (± 16) | 55 (± 17) | 0.4 |
| Δ night-time ambulatory PP | -3 (± 13) | -3 (± 14) | 0.9 |
| 24-h ambulatory PP at FU | 58 (± 15) | 58 (± 17) | 0.9 |
| Δ 24-h ambulatory PP | -2 (± 17) | -2 (± 12) | 0.9 |
|  |  |  |  |
| Controlled (%) | 60 (24.6) | 20 (29.9) | 0.4 |
| Follow-up duration | 1.5 [1-4] | 3 [1-5.8] | **<0.001** |
| Serum creatinine (mg/dL) | 1 (± 0.4) | 1 (± 0.4) | 0.4 |
| Serum potassium (mmol/L) | 4.0 (± 0.5) | 4.0 (± 0.5) | 0.6 |
|  |  |  |  |
| Drug intolerance at the diagnosis | 64 (26.2) | 21 (31.3) | 0.4 |
| No. of antihypertensive drugs | 5 (4-6) | 4 (3-5) | **0.005** |
| ACE inhibitor | 87 (36) | 13 (19.4) | **0.01** |
| AT1R blocker | 166 (68) | 44 (66) | 0.8 |
| Direct renin inhibitor | 44 (18) | 3 (4.5) | 0.02 |
| Beta-blocker | 197 (80.7) | 45 (67.2) | 0.02 |
| Calcium channel blocker   * Dihydropyridine * Non-dihydropyridine | 210 (86.0)  11 (4.5) | 60 (89.5)  1 (1.5) | 0.4  0.3 |
| Diuretics   * Loop diuretic * Thiazide or thiazide-like diuretic * Potassium sparing diuretic | 67 (27.5)  193 (79)  16 (6.7) | 12 (18)  45 (67.2)  8 (12) | 0.4  0.06  0.1 |
| Aldosterone antagonist | 89 (36.5) | 18 (26.9) | 0.2 |
| Alpha-adrenergic receptor blocker | 38 (15.6) | 19 (28.4) | **0.01** |
| Adrenergic depleter | 1 (0.4) | 0 (0) | 0.6 |
| Direct vasodilator | 24 (9.8) | 6 (9) | 0.8 |
| Central adrenergic agonist | 130 (53.3) | 21 (31.3) | **0.002** |
|  |  |  |  |
| NSAID | 19 (7.8) | 2 (3) | 0.2 |
| Statin | 111 (45.5) | 25 (37.3) | 0. 3 |
| Other lipid lower-drugs | 27 (11) | 3 (4.5) | 0.1 |
| Oral anti-diabetic agents | 60 (24.5) | 12 (18) | 0.6 |
| Insulin | 27 (11) | 3 (4.5) | 0.1 |
| Glitazone | 2 (0.8) | 0 (0) | 0.5 |
| Hormone replacement therapy | 15 (6) | 2 (3) | 0.3 |
| Aspirin | 99 (40.6) | 25 (37.3) | 0.8 |
| Anticoagulant | 27 (11) | 3 (4.5) | 0.1 |
| Antidepressant drug | 55 (22.5) | 14 (20.9) | 0.8 |
|  |  |  |  |
| RDN | 64 (26.2) | 9 (13.4) | **0.03** |
| No. of antihypertensive drugs at FU | 5 (4-6) | 4 (4-5) | **<0.001** |
| Total No. of pills | 9 [5-11] | 6 [4-9] | **0.004** |
| ACE inhibitor at FU | 38 (15.6) | 7 (10.4) | 0. 4 |
| AT1R blockers at FU | 175 (71.7) | 45 (67.2) | 0.8 |
| Direct renin inhibitor at FU | 21 (8.6) | 1 (1.5) | 0.06 |
| Beta-blockers at FU | 152 (62.3) | 27 (40.3) | **0.003** |
| Calcium channel blockers at FU   * Dihydropyridine * Non-dihydropiridine | 184 (75.4)  12 (5) | 49 (73)  2 (3) | 0.4  0.6 |
| Diuretics at FU   * Loop diuretics * Thiazide or thiazide-like diuretics * Potassium sparing diuretics | 58 (23.8)  173 (70.9)  17 (7) | 6 (9)  45 (67.2)  4 (6) | **0.01**  0.7  0. 9 |
| Aldosterone antagonists at FU | 128 (52.5) | 22 (32.8) | **0.01** |
| Alpha-adrenergic receptor blocker at FU | 24 (9.8) | 10 (14.9) | 0.2 |
| Adrenergic deplete | 0 (0) | 0 (0) | *null* |
| Direct vasodilators at FU | 20 (8.2) | 6 (9) | 0.7 |
| Central adrenergic agonists at FU | 111 (45.5) | 20 (30) | 0.00 |
| Psychological tests | | | |
| ERQ test   * Cognitive reappraisal score | 4.3 (± 1.2) | 4.9 (± 1) | **0.027** |

BMI = Body Mass Index; CKD = Chronic Kidney Disease; CABG = Coronary Artery Bypass Graft; PCI = Percutaneous Coronary Intervention; LVH = Left Ventricular Hypertrophy; OSAS = Obstructive Sleep Apnea Syndrome; cPAP = continuous Positive Airway Pressure; HTN = Hypertension; eGFR = estimated Glomerular Filtration Rate; SBP = Systolic Blood Pressure; DBP = Diastolic Blood Pressure; ABPM = Ambulatory Blood Pressure Monitoring; PP = Pulse Pressure; FU = Follow-Up; NSAID = non steroidal anti-inflammatory drug; RDN = renal denervation.

**Table S3.** Predictors of eventual blood pressure control at last follow-up: subgroup of fully adherent patients (n=67)

SBP = Systolic Blood Pressure; PP = Pulse Pressure

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | Univariate Analysis | | | Multivariate Analysis | | |
| Variable | **Odds Ratio (95% IC)** | | ***P Value*** | **Odds Ratio (95% IC)** | | ***P Value*** |
| Seated Office SBP\* | 0.99 | [0.97 – 1.01] | 0.3 |  |  |  |
| Seated Office PP\* | 0.98 | [0.96 – 1.00] | 0.15 |  |  |  |
| Daytime ambulatory PP | 0.95 | [0.91 – 0.98] | **0.01** | 0.97 | [0.91 – 1.02] | 0.23 |
| N. of antihypertensive drugs at baseline | 0.83 | [0.66 – 1.05] | 0.14 |  |  |  |
| Cognitive reappraisal score | 1.95 | [1.11 – 3.40] | **0.019** | 1.90 | [0.95 – 3.82] | 0.71 |

\*OR/mmHg

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Table S4. Differences in blood pressure values at baseline between different subgroups. | | | | | | | | | | | | | | | |
|  | **Brussels** | **Torino** | ***p*** |  | **Men** | **Women** | ***p*** |  | **<60 y.** | **>60 y.** | ***p*** |  | **Medical therapy** | **RDN** | ***p*** |
| Seated SBP | 178±26 | 174±26 | 0.3 |  | 172±23 | 182±28 | **0.001** |  | 177±27 | 177±24 | 0.8 |  | 175±25 | 185 ± 27 | **0.002** |
| Seated DBP | 98 ± 19 | 98 ± 19 | 0.9 |  | 94 ± 19 | 101±19 | **0.001** |  | 105±18 | 87 ± 15 | **<0.001** |  | 95 ± 19 | 108 ± 18 | **<0.001** |
| Seated PP | 80 ± 24 | 76 ± 25 | 0.3 |  | 78 ± 23 | 81 ± 25 | 0.3 |  | 71±20 | 90±23 | **<0.001** |  | 80 ± 24 | 77 ± 23 | 0.4 |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Standing SBP | 176±27 | 173±24 | 0.5 |  | 171±23 | 181±29 | **0.001** |  | 176±27 | 175±26 | 0.6 |  | 173±26 | 184 ± 26 | **0.004** |
| Standing DBP | 100 ± 19 | 99 ± 22 | 0.7 |  | 96 ± 19 | 103±20 | **0.002** |  | 108±18 | 88 ± 16 | **<0.001** |  | 97 ± 19 | 109 ± 18 | **<0.001** |
| Standing PP | 76 ± 24 | 74 ± 26 | 0.5 |  | 75 ± 22 | 78 ± 26 | 0.3 |  | 68±20 | 86±24 | **<0.001** |  | 77 ± 25 | 75 ± 20 | 0.6 |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| DT\_ABPM SBP | 160 ± 19 | 149±18 | **<0.001** |  | 159±20 | 157±19 | 0.3 |  | 159±21 | 156±17 | 0.2 |  | 156±20 | 164 ± 17 | **0.003** |
| DT\_ABPM DBP | 95 ± 16 | 88 ± 17 | **0.005** |  | 95 ± 15 | 93 ± 17 | 0.4 |  | 100±15 | 85 ± 13 | **<0.001** |  | 91 ± 15 | 102 ± 15 | **<0.001** |
| DT\_ABPM PP | 65 ± 16 | 61 ± 15 | 0.2 |  | 64 ± 17 | 64 ± 14 | 0.9 |  | 59±13 | 70±16 | **<0.001** |  | 64 ± 16 | 62 ± 14 | 0.3 |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| NT\_ABPM SBP | 146±22 | 136±22 | **0.006** |  | 145±22 | 142±23 | 0.3 |  | 145±24 | 141±20 | 0.2 |  | 141±22 | 151 ± 22 | **0.003** |
| NT\_ABPM DBP | 84 ± 16 | 76 ± 17 | **0.005** |  | 84 ± 16 | 81 ± 18 | 0.2 |  | 88 ± 18 | 74 ± 13 | **<0.001** |  | 79 ± 15 | 91 ± 18 | **<0.001** |
| NT\_ABPM PP | 62 ± 15 | 60 ± 16 | 0.4 |  | 61 ± 16 | 61 ± 15 | 0.8 |  | 57±12 | 66±16 | **<0.001** |  | 62 ± 16 | 60 ± 14 | 0.5 |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| 24 ABPM SBP | 155±19 | 145±19 | **0.001** |  | 156±19 | 151±20 | 0.07 |  | 154±21 | 151±16 | 0.2 |  | 151±20 | 160 ± 18 | **0.002** |
| 24 ABPM DBP | 91 ± 18 | 84 ± 16 | **0.015** |  | 91 ± 16 | 88 ± 19 | 0.2 |  | 95 ± 19 | 82 ± 12 | **<0.001** |  | 87 ± 16 | 97 ± 19 | **<0.001** |
| 24 ABPM PP | 64 ± 19 | 61 ± 15 | 0.3 |  | 64 ± 17 | 63 ± 19 | 0.5 |  | 60±19 | 69±14 | **<0.001** |  | 64 ± 17 | 63 ± 22 | **0.7** |

SBP = Systolic Blood Pressure; DBP = Diastolic Blood Pressure; DT\_ABPM = Daytime Ambulatory Blood Pressure Monitoring; NT\_ABPM = Nighttime Ambulatory Blood Pressure Monitoring; ABPM = Ambulatory Blood Pressure Monitoring.

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Table S5. Differences in blood pressure values at follow-up between different subgroups. | | | | | | | | | | | | | | | |
|  | **Brussels** | **Torino** | ***p*** |  | **Men** | **Women** | ***p*** |  | **<60 y.** | **>60 y.** | ***p*** |  | **Medical therapy** | **RDN** | ***p*** |
| Seated SBP | 157±27 | 163±30 | 0.1 |  | 154±26 | 162±30 | **0.02** |  | 157±29 | 159±25 | 0.5 |  | 155±27 | 167±30 | **0.001** |
| Seated DBP | 86 ± 19 | 92 ± 18 | **0.03** |  | 83 ± 18 | 91 ± 20 | **<0.001** |  | 93±19 | 78±15 | **<0.001** |  | 83±18 | 97±17 | **<0.001** |
| Seated PP | 71 ± 23 | 71 ± 25 | 0.9 |  | 71 ± 23 | 71 ± 23 | 0.8 |  | 63±19 | 81±23 | **<0.001** |  | 71 ± 23 | 70 ± 23 | 0.7 |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Standing SBP | 157±29 | 161±30 | 0.7 |  | 153±26 | 162±31 | **0.009** |  | 155±30 | 159±26 | 0.3 |  | 155±29 | 164±28 | 0.056 |
| Standing DBP | 89 ± 19 | 80 ± 12 | 0.08 |  | 83 ± 16 | 94 ± 21 | **<0.001** |  | 95±19 | 81±16 | **<0.001** |  | 86 ± 19 | 98 ±1 8 | **<0.001** |
| Standing PP | 68 ± 24 | 81 ± 29 | 0.06 |  | 69 ± 25 | 68 ± 24 | 0.6 |  | 60±20 | 78±24 | **<0.001** |  | 70 ± 25 | 66 ± 24 | 0.4 |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| DT\_ABPM SBP | 147±21 | 151±18 | 0.4 |  | 146±21 | 148±22 | 0.5 |  | 147±22 | 147±20 | 0.9 |  | 143±18 | 156±24 | **<0.001** |
| DT\_ABPM DBP | 88 ± 15 | 88 ± 12 | 0.9 |  | 87 ± 14 | 89 ± 16 | 0.6 |  | 91±14 | 83±15 | **0.001** |  | 85 ± 14 | 96 ± 14 | **<0.001** |
| DT\_ABPM PP | 59 ± 15 | 63 ± 16 | 0.3 |  | 59 ± 14 | 59 ± 16 | 0.8 |  | 56±14 | 63±15 | **0.001** |  | 58 ± 14 | 61 ± 17 | 0.3 |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| NT\_ABPM SBP | 132±24 | 139±20 | 0.3 |  | 131±23 | 134±25 | 0.3 |  | 131±24 | 133±23 | 0.6 |  | 128±21 | 142±26 | **<0.001** |
| NT\_ABPM DBP | 76 ± 16 | 75 ± 15 | 0.9 |  | 74 ± 14 | 77 ± 17 | 0.2 |  | 78±16 | 72±15 | **0.03** |  | 72 ± 14 | 83 ± 17 | **<0.001** |
| NT\_ABPM PP | 56 ± 16 | 64 ± 20 | 0.08 |  | 56 ± 16 | 57 ± 17 | 0.8 |  | 53±15 | 60±17 | **0.002** |  | 56 ± 16 | 58 ± 18 | 0.4 |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| 24 ABPM SBP | 143±21 | 147±17 | 0.4 |  | 142±20 | 145±21 | 0.4 |  | 143±22 | 142±18 | 0.8 |  | 139±18 | 154±22 | **<0.001** |
| 24 ABPM DBP | 85 ± 15 | 83 ± 15 | 0.6 |  | 84 ± 13 | 86 ± 17 | 0.2 |  | 89±14 | 79±13 | **<0.001** |  | 81 ± 13 | 94 ± 14 | **<0.001** |
| 24 ABPM PP | 58 ± 14 | 65 ± 20 | 0.09 |  | 58 ± 15 | 58± 15 | 0.9 |  | 55±14 | 63±15 | **0.001** |  | 58 ± 15 | 60 ± 17 | 0.4 |

SBP = Systolic Blood Pressure; DBP = Diastolic Blood Pressure; DT\_ABPM = Daytime Ambulatory Blood Pressure Monitoring; NT\_ABPM = Nighttime Ambulatory Blood Pressure Monitoring; ABPM = Ambulatory Blood Pressure Monitoring.

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Table S6. Differences in blood pressure changes from baseline to follow-up between different subgroups. | | | | | | | | | | | | | | | |
|  | **Brussels** | **Torino** | ***p*** |  | **Men** | **Women** | ***p*** |  | **<60 y.** | **>60 y.** | ***p*** |  | **Medical therapy** | **RDN** | ***p*** |
| ΔSeated SBP | -21 ± 28 | -11 ±32 | **0.04** |  | -18±27 | -21±31 | 0.9 |  | -20±31 | -18±27 | 0.6 |  | -20±28 | -18± 31 | 0.7 |
| ΔSeated DBP | -12 ± 16 | -6±18 | **0.02** |  | -11±17 | -11±17 | 0.7 |  | -12±19 | -9±13 | 0.1 |  | -11±16 | -11±19 | 0.9 |
| ΔSeated PP | -9 ± 21 | -6±22 | 0.3 |  | -7±20 | -10±23 | 0.2 |  | -8±20 | -9±23 | 0.5 |  | -9±21 | -7±23 | 0.6 |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Δ Standing SBP | -18±29 | -7±32 | 0.2 |  | -16±26 | -19±32 | 0.5 |  | -19±30 | -15±28 | 0.3 |  | -17±30 | -19±27 | 0.7 |
| Δ Standing DBP | -10±17 | -2±21 | 0.09 |  | -11±17 | -9±19 | 0.3 |  | -12±19 | -7±15 | **0.03** |  | -10±18 | -11±17 | 0.7 |
| Δ Standing PP | -8 ± 20 | -6±30 | 0.7 |  | -5±19 | -10±23 | 0.1 |  | -7±19 | -8±22 | 0.8 |  | -7±21 | -8±20 | 0.9 |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Δ DT\_ABPM SBP | -11±25 | -6±13 | 0.4 |  | -12±24 | -10±24 | 0.6 |  | -10±26 | -11±20 | 0.7 |  | -15±23 | -2±23 | **0.002** |
| Δ DT\_ABPM DBP | -6 ± 14 | -5 ± 12 | 0.7 |  | -7 ± 14 | -6 ± 14 | 0.4 |  | -7±15 | -5±12 | 0.3 |  | -8±14 | -2±14 | **0.02** |
| Δ DT\_ABPM PP | -4 ± 14 | -1 ± 7 | 0.3 |  | -4±14 | -4±14 | 0.9 |  | -2±13 | -5±14 | 0.2 |  | -6±14 | 0±12 | **0.01** |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Δ NT\_ABPM SBP | -10 ± 25 | -3 ± 12 | 0.2 |  | -11±26 | -8±23 | 0.3 |  | -10±25 | -8±23 | 0.7 |  | -14±25 | -1±20 | **0.003** |
| Δ NT\_ABPM DBP | -7 ± 15 | -4 ± 9 | 0.5 |  | -8±15 | -5±14 | 0.3 |  | -8±17 | -5±12 | 0.3 |  | -9±15 | -1±13 | **0.002** |
| Δ NT\_ABPM PP | -4 ± 14 | 1 ± 7 | 0.2 |  | -4±14 | -3±12 | 0.7 |  | -3±12 | -4±14 | 0.6 |  | -5±14 | 0±10 | 0.05 |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Δ 24 ABPM SBP | -10 ± 24 | -5 ± 12 | 0.5 |  | -11±23 | -7±14 | 0.3 |  | -9±26 | -9±18 | 0.9 |  | -13±24 | -2±20 | **0.01** |
| Δ 24 ABPM DBP | -6 ± 14 | -6 ± 9 | 0.9 |  | -7±14 | -5±13 | 0.5 |  | -7±15 | -5±11 | 0.3 |  | -8±14 | -2±12 | **0.03** |
| Δ 24 ABPM PP | -3 ± 17 | 1 ± 8 | 0.4 |  | -4±13 | -0.2±19 | 0.2 |  | -2±15 | -3±18 | 0. |  | -4±16 | 1±15 | 0.2 |

SBP = Systolic Blood Pressure; DBP = Diastolic Blood Pressure; DT\_ABPM = Daytime Ambulatory Blood Pressure Monitoring; NT\_ABPM = Nighttime Ambulatory Blood Pressure Monitoring; ABPM = Ambulatory Blood Pressure Monitoring.