APPENDIX 1

HIPARCO Randomized control trial

Throughout 2012-2013, 194 patients with a diagnosis RH were recruited from 24 hospital specialized hypertension units in Spain. Patients were included if they had primary RH. All the major causes of resistant hypertension were ruled out in each Hypertension Clinical Unit including primary aldosteronism, renal artery stenosis, and renal insufficiency. Initial exclusion criteria also included pregnancy, disabling hypersomnia requiring urgent treatment (defined as an Epworth Sleepiness Scale [ESS] ≥18), current use of CPAP treatment, poor adherence with antihypertensive treatment, long-term treatment with oral corticosteroids or nonsteroidal anti-inflammatory drugs, renal insufficiency (creatinine concentration higher than 1.5 mg/dL [to convert to micromoles per liter, multiply by 88.4] in peripheral blood sample), a cardiovascular event in the month prior to the inclusion in the study, and the regular use of sedative drugs such as benzodiazepines, major opiates, and antipsychotics, which could significantly modify the results of sleep studies and alcohol intake (more than 100 grams of alcohol per day).Good adherence to antihypertensive treatment was verified during the study using the Haynes-Sackett test (1). All patients underwent a 24-hour ambulatory BP monitoring to confirm the diagnosis of RH (SpaceLabs 90217 ®, Washington, USA). Those patients who had their RH confirmed underwent a sleep study. Those who presented an AHI≥15 events/hour. The HIPARCO study concluded that CPAP treatment resulted in a clinically significant decrease in 24-hour mean (3.1 mmHg), systolic (3.1 mmHg) and diastolic (3.2 mmHg) BP readings.

APPENDIX 2

Sleep Studies and CPAP pressure

All the included patients with proven RH underwent attended respiratory polygraphy in the sleep laboratory of each center. Respiratory polygraphy included continuous recording of oronasal flow and pressure, heart rate, thoracic and abdominal respiratory movements, and oxygen saturation (SaO2).

Polygraphy data were scored manually by trained personnel. Apnea was defined as an interruption of oronasal airflow for more than 10 seconds. Hypopnea was defined as a 30-90% reduction in oronasal airflow for more than 10 seconds, associated with an oxygen desaturation of 4% or more. AHI was defined as the number of apneas plus hypopneas per hour of recording, and TSat90 was defined as the percentage of recording time with SaO2 of less than 90%. Those tests in which the patients claimed to sleep less than 4 hours, or in which there were less than 5 hours of nocturnal recording, were repeated. Central sleep apnea was defined as at least 50% of respiratory events having a pattern of apnea or hypopnea without respiratory effort.

CPAP pressure titration was calculated by means an Autoset S8 (Resmed, Sydney). The optimal pressure was determined by two blinded expert researchers, based on the visual evaluation of the raw data recording from the night study, with no significant leaks (less than 0.40 L/s). This fixed pressure was then maintained throughout the study in those patients assigned to the CPAP group. CPAP was considered to be badly tolerated when it was used for less than 4 hours per night on average at the end of the study. All the patients in all the centers continued their training programs and underwent new pressure titrations when considered necessary, and every effort was made to resolve any side effects of CPAP to optimize compliance.

1. Haynes RB, Sackett DL, Gibson ES, et al. Improvement of medication compliance in uncontrolled hypertension. Lancet.1976;1(7972):1265-126