Accurate Diagnosis and Treatment Options for RH

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Accurate blood pressure (BP) measurement is essential to reduce cardiovascular (CV) risk and accurately identify treatment resistant hypertension (RH), said Gianfranco Parati, MD, University of Milano-Bicocca, Milan, Italy. Home BP monitoring (HBPM) and 24-hour ambulatory BP monitoring (ABPM) are complementary to office BP measurement (OBPM). Dr. Parati reviewed the recommendations for their use by the European Society of Hypertension (ESH) and European Society of Cardiology (ESC) Hypertension Guidelines [Mancia G et al. *J Hypertens* 2013].

OBPM is recommended for screening and diagnosing hypertension (≥2 measurements at ≥2 visits) and is currently used for risk stratification. HBPM and ABPM are recommended to confirm the diagnosis of hypertension, distinguish the phenotype (eg, white coat hypertension [WCH], masked hypertension [MH], sustained hypertension, and true normotension); detect hypotensive episodes, and maximize CV risk prediction. The BP levels to diagnose hypertension with each approach are shown in Table 1.

Table 1. Definitions of Hypertension Using Office, Ambulatory, and Home Measurements

Category	Systolic		Diastolic
Office BP	≥140	or	≥90
Ambulatory BP			
Daytime (or awake)	≥135	or	≥85
Nighttime (or asleep)	≥120	or	≥70
24-hour	≥130	or	≥80
Home BP	≥135	or	≥85

BP=blood pressure.

The ESH Practice Guidelines for HBPM, developed with general practitioners, provides a concise course of action for its use and data to support its better risk prediction compared with OBPM in a general hypertensive population, in the elderly, and in patients with chronic kidney disease [Parati G et al. *J Human Hypertens* 2010].

Important prognostic information is also obtained with HBPM by assessing changes in BP, such as day-to-day BP variability. Data from Japan showed that patients with the highest level of day-to-day BP variability on HBPM had the highest rate of CV mortality [Kikuya M et al. *Hypertension* 2008].

HBPM is useful as a tool to improve patient adherence by involving patients in the monitoring and management of their condition, especially when coupled with web-based systems that are interactive. The TeleBPCare study showed a significant improvement in daytime BP control in patients with the BP telemonitoring system (HBPM group) compared with OBPM (62% vs 50%; $p<0.05$) and less frequent changes in treatment (9% vs 14%; $p<0.05$), as well as a higher quality of life and lower costs [Parati G et al. *J Hypertens* 2009].

According to the ESH/ESC Guidelines, ABPM has an even greater prognostic significance than HBPM, with a better correlation with organ damage, a stronger relation with clinical outcomes, and better predictive values [Mancia G et al. *J Hypertens* 2013]. ABPM is also used to distinguish among hypertension phenotypes, identify other conditions such as obstructive sleep apnea

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(OSA), assess responses to treatment, and assess the impact of hypertension on CV targets.

The ESH Position Paper on ABPM, which complements the ESH/ESC Hypertension Guidelines, also provides detailed instructions for its use [O'Brien E et al. *J Hypertens* 2013]. The updated document provides even greater detail in terms of its clinical use, including a thorough review of ABPM to identify WCH, MH, and nocturnal hypertension, and its use in research [Parati G et al. *J Hypertens* 2014].

In patients with OSA, the first sign of hypertension may be the identification of a "nondipper" pattern at night with ABPM [O'Brien E et al. *J Hypertens* 2013]. A consensus statement from the European Respiratory Society and the ESH for the management of patients with OSA and hypertension recommends the use of ABPM to diagnose hypertension and manage patients to ensure adequate 24-hour protection.

TREATMENT OF RESISTANT HYPERTENSION

True RH is rather uncommon, according to Sverre E. Kjeldsen, MD, Oslo University Hospital, Oslo, Norway. Poor adherence to prescribed drug treatment is the number one cause of apparent RH and must be ruled out for accurate diagnosis, along with evaluating the adequacy of the treatment regimen and other factors.

Four randomized controlled trials, including one large sham-controlled trial of renal denervation (RDN), have shown minimal benefit. Ongoing research of RDN may eventually demonstrate utility in selected patients. In theory, RDN is an attractive approach to treating true RH, although the balance of the evidence does not currently support its use, stated Prof. Kjeldsen.

The open-label SYMPLICITY HTN-2 study showed a significant reduction in systolic and diastolic BP (SBP; DBP) at Months 1, 3, and 6 ($p \leq 0.005$ for each time point vs sham control) [SYMPLICITY HTN-2 Investigators. *Lancet* 2010]. However, Prof. Kjeldsen stated that the lack of blinding and 24-hour ABPM are issues with this trial, along with regression to the mean, the Hawthorne effect, in which participant performance is enhanced because of increased attention, and the placebo effect.

The first prospective, randomized study of RDN versus clinical drug adjustment, the OsloRDN study, found a small non-significant reduction in SBP using OPBM at Months 3 and 6, and the BP was found to be normalized in the drug treatment arm [Fadl Elmula EE et al. *Hypertension* 2014]. Using daytime ABPM, there were small changes only in SBP or DBP at Months 3 and 6. This finding fits well with the placebo effect of RDN, stated Prof. Kjeldsen, and showed that the strategy of adjusting drug treatment was superior to RDN.

The Oslo RDN study used the same inclusion criteria as the SYMPLICITY HTN-2, plus the witnessed intake of antihypertensive medications by patients prior to ABPM. Notably, after the

witnessed intake of medication, 14 of 65 screened patients had controlled BP [Fadl Elmula EE et al. *Hypertension* 2014], whereas only 6 of 18 patients qualified as having true RH in an earlier open study [Fadl Elmula EE et al. *Hypertension* 2013]. At baseline, patients who qualified were taking an average of 5 antihypertensive drugs.

The SYMPLICITY HTN-3 was the first randomized, sham-controlled study of RDN and failed to show a significant benefit in the primary endpoint of office SBP (–14.1 mmHg vs –11.7 mmHg, respectively; $p<0.001$ for both) and no significant difference at Month 6 from baseline (–2.39 mm Hg; 95% CI, –6.89 to 2.12; $p=0.26$) [Bhatt DL et al. *N Engl J Med* 2014]. There was also no difference between groups in the secondary efficacy endpoint of change in 24-hour systolic ABPM (–1.96 mmHg; 95% CI, –4.97 to 1.06; $p=0.98$).

The BEAUTY study investigated the use of an integrated, noninvasive monitoring system that applies a predefined algorithm of drug selection in reducing ambulatory-based SBP. The system showed that BP control was achieved early and correlated with improvement in hemodynamics at Month 6 and that the system was associated with improved tolerability of antihypertensive agents [Parati G et al. *ESH* 2014]. Selected patients with volume overload required a high-dose thiazide diuretic.

Baroreceptor activating therapy with an implanted device has been shown to be effective, with a mean BP reduction of 35/16 mmHg and 55% of long-term responders achieving goal BP levels [Bakris GL et al. *J Am Soc Hypertens* 2012]. Prof. Kjeldsen anticipates that it will be increasingly used in the United States and Europe.