



ENCOREd: Meta-Analysis of Renal Denervation in 10 European Expert Centers

Written by Mary Mosely

Renal denervation (RDN) is a novel treatment of resistant hypertension, based on the Renal Denervation in Patients With Uncontrolled Hypertension study [Symplicity HTN-2; Symplicity HTN-2 Investigators. *Lancet* 2010]. Yet, the magnitude and determinants of office and ambulatory blood pressure (BP) response to RDN have not been established due to the lack of randomized studies, few reports of postprocedural changes in ambulatory BP (or their lack of significance), and publication bias [Persu A et al. *Expert Rev Cardiovasc Ther* 2013].

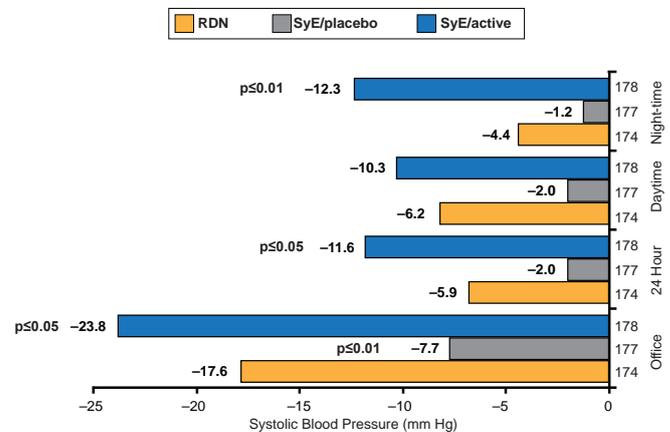
Alexandre Persu, MD, Université Catholique de Louvain, Brussels, Belgium, presented the results of the first patient-level meta-analysis of the BP changes 6 months post RDN at 10 expert centers participating in the European Network Coordinating Research on Renal Denervation study [ENCOREd].

The study objective was to compare the BP changes in the ENCOREd RDN patients and those observed in the treatment and placebo arms of the Systolic Hypertension in Europe study [Syst-Eur; Staessen JA et al. *J Hypertens* 1994; Staessen JA et al. *Lancet* 1997], and the Symplicity HTN-2 study.

For the comparison with Syst-Eur, the three patient groups were ENCOREd RDN (n=109), Syst-Eur placebo (n=73), and Syst-Eur active treatment (n=79). The RDN patients were younger than the other groups (mean age, 58.2 vs 71.4 vs 70.3 years, respectively), more overweight (body mass index, 29.5 vs 26.3 vs 26.0 kg/m²), and had more target organ damage. The estimated glomerular filtration rate was greater in the RDN group (RDN, 82.2 mL/min/1.73 m²; Syst-Eur placebo, 67.9 mL/min/1.73 m²; Syst-Eur active, 67.2 mL/min/1.73 m²). The baseline systolic BP (SBP) levels were similar for office (175 to 178 mm Hg) and ambulatory (153 to 157 mm Hg) measures. Nearly half of each group was women and nearly all were white.

In the RDN group, the office SBP was reduced by 17.6 mm Hg and the 24-hour ambulatory SBP (ASBP) by 5.9 mm Hg from baseline to 6 months (p<0.03 for both) at 6 months. Reduction from baseline to 6 months in office, ambulatory, daytime, and night-time SBP values in the RDN group were between the respective values for the Syst-Eur placebo and Syst-Eur active groups (Figure 1). The reduction in ASBP was only one-third that on office BP measure. The less impressive decrease in ASBP may reflect a specific effect of RDN on white coat hypertension (WCH), noted Prof. Persu. WCH was decreased in each group.

Figure 1. Change From Baseline to 6 Months in SBP

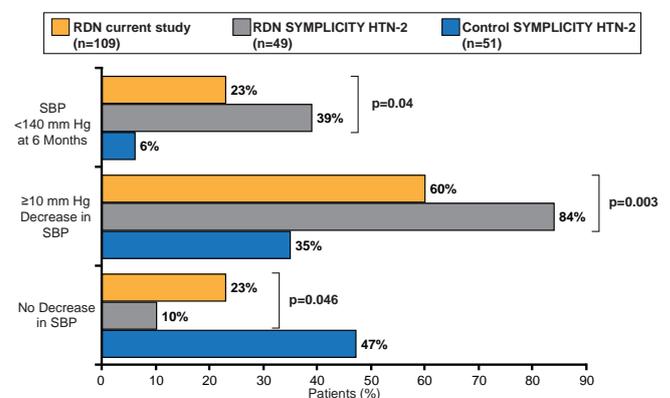


RDN=renal denervation; SyE=Syst-Eur. p values for comparison with RDN group.

The nonresponder rate for a reduction in office SBP at 6 months was 23% for RDN, 33% for Syst-Eur placebo, and 8% for Syst-Eur active. The nonresponder rate for ASBP at 6 months was 35% in the RDN, 45% in the Syst-Eur placebo, and 17% in the Syst-Eur active group.

Compared with the RDN group in Symplicity HTN-2, there was a significantly lower proportion of responders and controlled patients in the ENCOREd RDN group at 6 months (p=0.003 and p=0.04, respectively; Figure 2). For the patients with a baseline SBP ≥160 mm Hg, the responder rate at 6 months was similar in the ENCOREd and Symplicity HTN-2 RDN groups (72% vs 84%; p=0.12), but significantly fewer ENCOREd RDN patients had BP control (16% vs 39%; p=0.005).

Figure 2. BP Response Over 6 Months in RDN and Symplicity HTN-2 Patients



RDN=renal denervation; SBP=systolic blood pressure.



CLINICAL TRIAL HIGHLIGHTS

In ENCOReD RDN patients, a higher baseline SBP predicted better 24-hour ASBP control, whereas a higher serum creatinine predicted a lower probability of control.

The meta-analysis suggests an important impact of the placebo or Hawthorne effects, and/or regression to the mean. RDN should be the last resort for truly resistant hypertension until there is sufficient evidence to identify reliable predictors of BP response.

COLM Results: Hypertensive Patients Aged ≥ 75 Years Have Better Clinical Outcomes and Fewer AEs on CCBs Than Diuretics

Written by John Otrompke

Hypertensive patients aged ≥ 75 years have a lower risk of stroke when they take calcium channel blockers (CCBs) along with olmesartan than when they take diuretics with olmesartan, according to the results of the Combination of Olmesartan and CCB or Low Dose Diuretics in High Risk Elderly Hypertensive Patients Study [COLM; NCT00454662]. Furthermore, the incidence of serious adverse events and discontinuation from the trial due to drug-related serious adverse events were also lower in elderly hypertensive patients receiving CCBs. The findings of this study were presented by Toshio Ogihara, MD, PhD, Morinomiya University of Medical Sciences, Osaka, Japan.

COLM is the first study to compare the effects of CCBs with those of diuretics in preventing cardiovascular disease when used in conjunction with olmesartan [Ogihara T et al. *Hypertens Res* 2009]. It was a multicenter, randomized, open-label, blinded-endpoint trial, conducted at 707 centers in Japan. High-risk elderly hypertensive Japanese patients ($n=5141$) aged 65 to 84 years were randomized to either CCBs plus olmesartan ($n=2568$) or low-dose diuretics plus olmesartan ($n=2573$). Of those in the CCB group, 38.1% were on CCBs at the start of enrollment versus with 35.8% in the diuretic group. The target blood pressure (BP) was $<140/90$ mm Hg.

Patients were followed-up for a median of 3.3 years. In both groups, BP decreased similarly, from 158/87 mm Hg at baseline to 132/73 mm Hg at the study end. The primary composite endpoint of fatal and nonfatal cardiovascular events was similar between the CCB and diuretic groups during the study (4.5% vs 5.3%; HR, 0.83; 95% CI, 0.65 to 1.07; $p=0.16$). None of the components of this endpoint were significantly different between the two groups.

In the subgroup of patients aged ≥ 75 years, the risk of the primary composite endpoint was significantly lower in the CCB group (5.2%) versus the diuretic group (7.2%; HR, 0.70; $p=0.04$). The risk of stroke was also significantly lower

in the CCB group (2.4% vs 3.8%; HR, 0.63; $p=0.05$). However, there was no significant difference in the risk of cardiac events between the CCB and diuretic groups (1.9% vs 2.2%; HR, 0.83; $p=0.68$).

Overall, and regardless of the age subgroup (<75 or ≥ 75 years), 25.3% of CCB versus 29.1% of diuretic group patients experienced an adverse event ($p=0.002$). 8.2% of patients in the CCB group experienced serious adverse events compared with 9.8% in the diuretic group ($p=0.046$). The rate of discontinuation due to drug-related serious adverse events was also significantly lower in the CCB group (0.2% vs 0.6%; $p<0.026$).

COLM findings show that while CCBs and diuretics were equally effective at controlling BP in elderly patients with hypertension when given in combination with olmesartan, CCBs were more effective in preventing stroke in patients aged ≥ 75 years and were associated with a decreased risk of adverse events in all patients.

Effects of Renal Denervation on Endothelial Function, and Inflammatory and Metabolic Markers

Written by Mary Mosely

It has been shown that renal denervation (RDN; also called renal nerve ablation) can lower blood pressure (BP) in patients with resistant hypertension and that this effect can be maintained to more than 24 months [Symplicity HTN-1 Investigators. *Hypertens* 2011]. However, there are few data about the effect of RDN on organs and the sympathetic nervous system. There is an independent association between hypertension and inflammatory markers, but it is unknown whether treatment of one of these conditions impacts the other and whether lowering BP can also reduce vascular inflammation.

Nina Eikelis, MD, Baker IDI Heart & Diabetes Institute, Melbourne, Australia, presented data from a study to determine whether RDN has an effect on inflammation and endothelial function in patients with resistant hypertension.

Assessments were conducted at baseline and at 3 months after RDN in 63 patients with resistant hypertension (male, 64%; mean age, 61 years). At baseline, patients had a high body mass index (BMI; 32.3 kg/m²), and were taking an average of 4.6 antihypertensive medications.

BP was significantly reduced from baseline (169/90 mm Hg) to 3 months (156/84 mm Hg; $p<0.001$), but there was no significant change in HR.

There were no significant changes from baseline to 3 months in the reactive hyperemia index, which is a measure of endothelial function, and the augmentation index, which is an indirect measure of arterial stiffness.