



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.



There were also no significant differences from baseline to 3 months in plasma renin activity, which is an indirect measure of angiotensin I production, and the level of the inflammatory markers.

Leptin levels did not significantly change from baseline to 3 months. The levels of nonesterified fatty acid (NEFA), a metabolic biomarker, were significantly reduced (from 1 to 0.4 mEq/L; $p < 0.001$), but there were no significant reductions in body weight, BMI, or waist-to-hip ratio.

In explaining the high baseline NEFA levels in this patient population that has resistant hypertension and high BMI, it should be noted that NEFA has been implicated in elevated BP, particularly in animal studies [Sarafidis PA, Bakris GL. *J Hum Hypertens* 2007]. Furthermore, the levels of NEFA tend to be higher in overweight and obese persons as it is primarily released from adipose tissue [Heptulla R et al. *J Clin Endocrinol Metab* 2001; Koutsari C, Jensen MD. *J Lipid Res* 2006].

NEFA and insulin levels seem to have an inverse relationship, said Prof. Eikelis. Therefore, it is perhaps no surprise that in the present study, NEFA levels significantly decreased while insulin levels significantly increased from baseline (21 uU/mL) to 3 months (28 uU/mL; $p < 0.01$).

Whole body noradrenaline spillover, a measure of whole body sympathetic activity, did not change significantly over the 3 months. However, Prof. Eikelis noted that sympathetic responses are regionalized and global measures lack precision. When looking at regional sympathetic activity, there were significant reductions from baseline to 3 months and to 6 weeks in muscle and kidney sympathetic activity, respectively ($p < 0.05$ for both).

Study findings show that while RDN led to significant reductions in office BP, and muscle and renal sympathetic activity, there were no significant changes in endothelial function and inflammatory markers. There was a significant reduction in NEFA, without changes in body weight, and this may be an indirect measure showing reduction or withdrawal of nervous activity from adipose tissue.

INTERACT2 Results: Intensive BP Lowering Safe and Effective in Acute ICH Patients

Written by John Otrompke

Although physicians have long subscribed to the fear that using intensive methods to lower the blood pressure (BP) of patients who had suffered acute intracerebral hemorrhage (ICH) would result in increased risk of death or neurological deterioration, the technique is safe and effective, and should become the standard of care, according to results of the Second Intensive Blood

Pressure Reduction in Acute Cerebral Haemorrhage Trial [INTERACT2; NCT00716079; Anderson CS et al. *N Engl J Med* 2013].

While there was no reduction in deaths among acute ICH patients treated with an intensive BP-lowering strategy, functional outcomes and health-related quality of life (QoL) were better in these patients, according to John Chalmers, MD, PhD, Georgia Institute for Global Health, University of Sydney, Sydney, Australia, who presented the results of INTERACT2.

In the study, researchers examined the question of whether patients with acute ICH treated with the goal of reducing the BP to < 140 mm Hg within an hour (early intensive group) or those treated with the goal of reducing BP to the current guideline-recommended goal of < 180 mm Hg (standard group) would have improved survival free of major disability.

The study was performed across 144 hospitals in 21 countries. Patients ($n = 2839$) with acute spontaneous ICH and systolic BP of 150 to 220 mm Hg were randomized within 6 hours of ICH to the early intensive ($n = 1403$) or standard group ($n = 1436$) and managed in-hospital for 7 days. The locally available intravenous BP-lowering agent used was based on the physician's choice.

Baseline characteristics of the two groups were similar and ~68% of patients in each group were from China. The patient population had a mean age of 64 years, a mean BP of 179/101 mm Hg, and a median ICH volume of 11 mL.

The occurrence of the primary composite outcome of death or major disability, defined as a 90-day modified Rankin Scale (mRS) score of 3 to 6, was nonsignificantly lower in the intensive group (52%) compared with the standard group (55.6%; OR, 0.87; 95% CI, 0.75 to 1.01; $p = 0.06$; Figure 1). While the rate of death was similar in the two groups (~12%), significantly fewer survivors in the early intensive group (40%) experienced major disability compared with the standard group (43.6%; $p = 0.05$).

A prespecified subgroup analysis showed that the primary outcome findings did not significantly differ by region (ie, China vs other regions; $p = 0.97$). Ordinal analysis of mRS score distribution showed that mRS scores were significantly lower in the intensive group versus the standard group (pooled OR for shift to higher mRS score, 0.87; 95% CI, 0.77 to 1.00; $p = 0.04$).