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Review Article

Recent Clinical Trials in Hypertension – An Encapsulated Summary

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Abstract

Hypertension (HTN) is a risk factor for cardiovascular (CV) morbidity and mortality. Evidence from studies result in changing strategies for treating HTN. The impact of these trials is evidenced by change in guidelines as well as recommendations for managing HTN with respect to choice of drugs or interventions, as well as goals of treatment.

Key words: Blood pressure, randomized, goal, treatment, cardiovascular risk, intensive

High blood pressure is still a major cause of cardiovascular morbidity and mortality. Management approach of treating hypertension keeps evolving. Hypertension guidelines keep changing based on evidence from trials which influence the changes in recommendation for management of hypertension and the goals of therapy.

HOPE 3 Trial[1-3]

HOPE 3 trial was a landmark primary prevention trial which compared safety and efficacy of cholesterol lowering, blood pressure (BP) lowering, or both.

The trial included males >55 years and females >65 years with at least one CV risk factor. The trial also included women >60 years of age who had ≥2 such risk factors. The patients were randomized to either rosuvastatin 10 mg or placebo in the cholesterol lowering arm, BP lowering arm group received candesartan + hydrochlorothiazide (HCTZ), or placebo. The third group was randomized to receive rosuvastatin + candesartan + HCTZ or placebo.

The highlight of this trial was, enrollment was done based on baseline CV risk irrespective of baseline values of low-density lipoprotein cholesterol (LDL-C) or BP.

The results indicate the benefits of using statins as a primary prevention strategy in moderate risk group irrespective of baseline LDL-C. A fixed-dose combination of all three drugs also showed CV benefits which was mostly driven by rosuvastatin.

The BP arm did not show overall benefit for antihypertensive therapy. However, in normotensives, it caused more harm whereas benefit was noted in patients with high BP. The benefits of statins were seen irrespective of LDL levels.

This shows that all patients at moderate CV risk should be offered statins, but antihypertensive therapy should only be given to those who are hypertensives. In hypertensive patients, benefit is doubled by lowering BP with antihypertensives and also lowering cholesterol simultaneously.

Systolic BP (SBP) Intervention Trial (SPRINT)[4-6]

The SPRINT was a randomized open-label trial. It compared two strategies, one with intensive BP control (SBP <120 mmHg) and other with standard control (SBP <140 mmHg) in non-diabetic individuals with high CV risk. The trial was designed to evaluate the effects of intensive BP control on heart, kidneys, and brain.

The trial was designed to find out whether intensive BP control was better than earlier standard of <140 mmHg.

It included adults age 50 or older who had SBP ≥130 mmHg and at least one other CV disease risk factor (n = 9361). Significant number (28%) of patients were elderly with age >75 years of age and also good number of patients who had chronic kidney disease (CKD). Dose adjustment was based on average of three BP readings with unattended automated measurement system.

The results indicate that in high-risk diabetic population with HTN, intensive BP lowering to <120 mmHg is better than

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standard target of <140 mmHg. The above strategy was found to be safe in elderly patients as well. Intensive BP control reduced CV events by 25% and overall mortality by 27%. The same was observed in patients with CKD subgroup. Intensive BP control resulted in greater LVH regression among those who already had LVH and also reduced the risk of developing LVH. Intensive BP control resulted in greater LVH regression among those who already had LVH and also reduced the risk of developing LVH in subjects with no baseline LVH. The trial also suggested that HTN treatment should be tailored according to the CV risk rather than BP measurements alone.

PATHWAY 2 Trial[7]

The goal of the trial was to evaluate treatment with spironolactone compared with doxazosin or bisoprolol or placebo among subjects with resistant HTN.

PATHWAY 2 was designed for the evaluation of better treatment of resistant HTN. This trial is particularly useful as there is high number of patients with resistant HTN leading to high CV risk.

A total of 335 subjects with resistant HTN defined as uncontrolled BP despite three BP medications that also included a diuretic, with mean age of 61 years, who were randomized to receive spironolactone, bisoprolol, doxazosin, or placebo, in addition to their baseline treatment.

Spironolactone was substantially more effective than placebo and also almost 60% of patients had controlled home SBP, and spironolactone was significantly better than doxazosin or bisoprolol. The aldosterone antagonist was well tolerated with no increase in adverse events.

The trial suggested that in patients with resistant HTN, spironolactone was superior add-on drug for improved BP control. Spironolactone should be considered in the management of patients with resistant HTN. Amiloride is also a suitable alternative for resistant HTN, as few patients at study conclusion received it which showed similar reduction in BP. Furthermore, the risk of thiazide-induced glucose intolerance is mitigated when combined with amiloride.[8]

SYMPLICITY HTN 3 Trial[9-11]

The SYMPLICITY HTN-3 study was a randomized, multicenter, prospective, double-blinded study which investigated the safety and efficacy of renal artery denervation (RDN) in refractory HTN. The trial included patients with uncontrolled BP on maximum tolerated doses of three or more drugs, which also included a diuretic. All patients underwent renal angiography and only patients in the treatment group were subjected to RDN with Symplicity renal denervation catheter which used radiofrequency energy.

The trial results did not show any difference in office and ambulatory BP at 6 months between RDN group and medically managed group while at the same time, RDN did not increase the development of new significant renal artery stenosis. The results of this trial are in contrary to the results of smaller trials that did not include a sham control, thus highlighting the usefulness of sham controls in catheter intervention-based trials. The trial also showed that true treatment-resistant HTN is very uncommon than previously thought as only small number of patients from the overall group with apparent treatment-resistant HTN could be recruited. There were few reasons for the failure of this trial. Most operators in the trial had less experience and also some had no previous experience with the procedure. The success of the procedure could not be objectively assessed, as only indirect electrical impedance was utilized to establish contact with the arterial wall. Because of this, incomplete ablation might have happened, irrespective of operator experience.[12,13]

SPYRAL HTN-OFF MED[14]

The trial was designed to find out whether renal sympathetic denervation compared with sham procedure will make a difference in uncontrolled hypertensive patients who are not on any BP drugs. Patients with uncontrolled HTN defined as office SBP ≥150 and <180 mmHg, or ambulatory SBP ≥140 and <170 mmHg, or office diastolic BP ≥90 mmHg and not on treatment were randomized to renal denervation (n = 38) versus sham (n = 42). Mean patient age was 56 years. The primary outcome, improvement in ambulatory SBP control at 3 months, was −5.5 mmHg in the denervation group versus −0.5 mmHg in the sham group (P = 0.04).

This trial among patients with uncontrolled HTN not on treatment showed the efficacy of RDN. There were no excess adverse events from this intervention. A significant difference of this trial was that more ablation attempts were made in the main as well as branch renal arteries as compared to SYMPLICITY HTN-3.

The SPYRAL HTN-ON MED Trial[15]

This trial looked at renal denervation versus sham control in patients with uncontrolled BP on treatment with BP drugs.

Patients with uncontrolled BP (SBP 150–180 mmHg and DBP ≥90 mmHg, and 24 h ambulatory SBP 140–170 mmHg) on treatment were included. Thirty-eight subjects underwent renal denervation and 42 subjects underwent sham procedure. Mean patient age was 54 years.

Renal denervation was performed with the Symplicity Spyral or the Symplicity G3 denervation catheter. Patients in control group underwent a renal angiogram alone.

Renal denervation resulted in 7 mmHg drop in 24 h SBP at 6 months, with no adverse effects. In this trial again, more ablation attempts were made in the main as well as branch renal vessels as compared to SYMPLICITY HTN-3 trial.

This trial showed that renal denervation was superior at improving BP. The study findings are similar to SPYRAL HTN-OFF MED trial.

RADIANCE-HTN SOLO

The normal depth of radiofrequency energy penetration is 3–4 mm.[16] This penetration may not be adequate in the main renal arteries to ablate a large number of sympathetic fibers.[17] This was overcome using a new device that used ultrasound energy which allowed deeper penetration up to 6–7 mm. The Paradise system used in the trial facilitated full circumference cauterization with adequate penetration into the tissue, simultaneously cooling the tissues with a water-filled balloon.[18,19] Deep cauterization will achieve significant denervation of efferent and afferent renal sympathetic nerves in renal artery adventitia.[20] If radiofrequency energy is used to get similar reduction in BP, then many more sites have to be ablated which will prolong procedure time, as energy is delivered from individual electrodes as compared to circumferential energy delivery with ultrasound catheters.

The RADIANCE-HTN SOLO trial[21,22] is a randomized trial comparing renal denervation versus a sham procedure to lower BP.

This trial was done for safety and efficacy assessment of renal denervation for mild-to-moderate HTN.

Patients were randomized to either renal denervation (n = 74) or a sham procedure (n = 72). BP medications were stopped 4 weeks before randomization. Patients in ablation group underwent endovascular ultrasound nerve ablation with Paradise endovascular ultrasound renal denervation system, whereas sham group had only renal angiogram done.

The results show that renal denervation with ultrasound energy resulted in a greater reduction in BP at 2 months. This effect was maintained at 6 months, and also number of medications for controlling BP was also less. The effect of renal denervation appeared reasonably stable.

A Three-arm Randomized Trial of Different Renal Denervation Devices and Techniques in Patients with Resistant HTN (Radiosound-HTN)[23]

This was a randomized head-head comparison trial conducted at a single center which compared three different renal denervation techniques and devices (radiofrequency denervation of main renal arteries [RFM-RDN] vs. denervation of main renal arteries, side branches, and accessory branches [RFM-RDN] vs. endovascular ultrasound [USM-RDN] technique of denervation of main renal artery) in patients with resistant HTN.

Patients with resistant HTN were included. White coat HTN was excluded with ambulatory BP monitoring (ABPM). All patients underwent magnetic resonance imaging (if possible) or duplex scan to rule out renal artery stenosis. Other secondary HTNs were excluded including hyperaldosteronism or obstructive sleep apnea.

Radiofrequency ablation was done with Spyral catheter whereas Paradise catheter was used for ultrasound denervation.

Systolic daytime ABPM significantly decreased with ultrasound denervation group compared with radiofrequency ablation of main renal artery group (13.2 mmHg vs. 6.5 mmHg, P = 0.043), Additional side branch denervation did not show significant difference (8.3 mmHg) either with ultrasound denervation (p-NS) or main branch denervation (p-NS).

This single-center study demonstrated that all three approaches reduce daytime SBP at 3 months of follow-up. Ultrasound denervation was superior in SBP reduction to radiofrequency denervation of main renal arteries alone. However, ultrasound denervation was not found superior, if radiofrequency denervation is done to side branches and accessories along with main branch.

Sympathetic nervous system activation is an important cause of HTN. Percutaneous renal denervation is an option to reduce elevated BP as evidenced from many randomized, sham-controlled trials which demonstrated a convincing and clinically significant reduction of ambulatory BP when compared with sham control groups.[14,15,21]

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