Cardiovascular Therapeutics Watch Page

As noted at the end of last issue's column, drug-resistant hypertension (RHTN) is a very 'hot topic' in the hypertension literature. While professional societies in various regions of the world publish "Position Papers" that present their definitions, a commonly cited definition of RHTN in the United States (US) comes from an American Heart Association (AHA) Scientific Statement that discussed two components of RHTN: uncontrolled RHTN and controlled RHTN.[1] Uncontrolled RHTN is defined as blood pressure (BP) above goal on an appropriate pharmacologic regimen consisting of three or more drugs with complementary mechanisms of action at optimal doses and preferably including a diuretic. The goals have been clinic (or doctor's office) BP values of < 140/90 mm Hg in general, and < 130/80 mm Hg for patients with diabetes or chronic kidney disease. Controlled RHTN is defined by the AHA as BP that is controlled to goal by four or more drugs at optimal doses, preferably including a diuretic. The European Society of Hypertension has used a similar definition as the AHA for uncontrolled RHTN.[2] Other authors have suggested the inclusion of a time dimension in the definition, for example that the treatment regimen must have been in place for at least three months before a determination of RHTN is made.[3] Out of the overall hypertensive population, it has been estimated that perhaps as many as 10% of patients have RHTN.[2]

What options exist for the treatment of these patients? Ideally, they may be referred to hypertension specialists who are experts in sophisticated pharmacologic regimens that may benefit these hard-to-treat patients; suboptimal medication regimens are common in referred patients.[4,5] Improvements to prescribed regimens can include switching standard thiazide diuretics to chlorthalidone or to a loop diuretic. In some patients, the aldosterone antagonists eplerenone and spironolactone may be beneficial (spironolactone therapy was discussed in a recent Cardiovascular Watch Column published in *International Pharmaceutical Industry*[6]). Additionally, consolidation of antihypertensive therapies using 3-drug single pill combination therapy (diuretic, angiotensin receptor blocker, and dihydropyridine calcium antagonist) is likely to both improve control and adherence (itself a major consideration) in subsets of patients with RHTN.[7]

Increasing attention in the literature is focusing on interventional procedures to treat RHTN, of which renal sympathetic denervation (RDN) has received most attention. In RDN, a catheter is passed via the femoral artery into both renal arteries and radiofrequency energy is then used to ablate the sympathetic nerve fibres. While

RDN has not yet received regulatory approval in the US, as of October 2013 six European Commission marked (CE-marked) RDN devices were available for use in clinical practice outside the US. In an early study of RDN in severe hypertension (in which the mean baseline BP of participants on three or more antihypertensive drugs was 177/101 mmHg), 45 patients received RDN.[8] Decreases from baseline in clinic BP at 1, 3, 6, 9, and 12 months post-procedure ranged between -14/-10 and -27/-17 mm Hg. A report from the same group of investigators was published addressing BP reductions after 24 months,[9] and a recent publication in the Lancet presented the final three-year report of this trial, known as the Symplicity HTN-1 trial. In this paper, complete data at 36 months were available for 88 patients, for whom the mean clinic baseline BP was 175±16/98±14 mm Hg. Mean reductions in BP were -32.0/-14.4 mmHg.[10]

In the Symplicity HTN-2 trial, participants were allocated in a 1:1 ratio to undergo RDN (maintaining previous antihypertensive treatment) or to maintain previous antihypertensive treatment without RDN.[11] The primary efficacy endpoint of change in seated clinic systolic BP six months post-procedure was assessed in 49 patients receiving RDN and 51 patients in the control group. For the RDN treatment group, mean clinic BP was

reduced significantly by -32/-12 mmHg, while for the control group the respective values were -1/0 mmHg. The numbers of adverse events did not differ between groups, and no serious procedure- or device-related complications were noted. The results from the Symplicity HTN-3 trial[12] are due to be reported early in 2014. Those results will attract a lot of attention since it is a pivotal trial that is prospective, randomised, and uses a masked procedure with observers blinded to treatment.

It should be emphasised that the BP reductions just discussed are based on clinic BP values. As discussed at an American Society of Hypertension (ASH) Interactive Forum on the Detection, Evaluation, and Management of Severe Hypertension and RHTN held on October 10th, 2013, when BP changes are assessed via 24-hour ambulatory BP monitoring (ABPM), the reductions are typically considerably smaller.[3, 13, 14] Experts in pharmacological and device-based treatment of RHTN from the US, Europe, and Australia attended this meeting, which included presentations and multiple interactive discussion sessions. The proceedings from the meeting will be published in due course in the official journal of ASH, the *Journal of Clinical Hypertension*. We will notify readers of this column in due course when it has been published.

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J. Rick Turner, PhD, is Senior Scientific Director, Clinical Communications, Quintiles. He is also a Senior Fellow at the Center for Medicine in the Public Interest, and a Fellow of the Society of Behavioral Medicine. Email: rick.turner@quintiles.com.

Philip Galtry is Vice President and Cardiovascular Therapeutic Strategy Head, Cardiovascular and Metabolic Therapeutic Delivery Unit, Quintiles. Philip holds an Honours degree in Biochemistry from the University of Bristol, UK, and has worked in the management of cardiovascular studies for almost 25 years.