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The scene for clinical trials of hypertension management is in transition. The era of mega trials may not be over but is certainly in decline, and in the past 2 years there have been no studies reporting primary outcome data the scale of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), The ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial (ONTARGET), Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT), and other major studies that marked clinical trial activity and informed guideline committees during the past 2 to 3 decades. This reflects in part the view that the present benchmark pharmacological agents for treating hypertension are difficult to improve, some systemic issues affecting the pharmaceutical industry influencing the ability to make the large investment required to perform mega trials and the quality of the antihypertensive drug pipeline. Together these considerations have tended to drive interest toward equivalence rather than efficacy studies (ie, trials designed to show an investigational agent is as good as, not better than, existing treatment), surrogate end points, including new blood pressure (BP) variables, and studies of combinations and algorithms rather than single interventions. Population studies around the world, however, continue to show that large numbers of people have hypertension that is not treated satisfactorily and are not achieving the goals set by the major national guidelines. These guidelines themselves are under continual scrutiny on the basis of recent data casting doubt on the validity of present BP goals. Guideline committees also face the issue that evidence based on expensive large-scale clinical trials is more often funded by the pharmaceutical or device industries than by government, leaving large evidence gaps in areas of public importance but no direct interest to industry funders. The purpose of the present article is to briefly review clinical trials of interventions in hypertension during the past 2 years.

Incremental improvement in the therapies available in the face of a large global disease burden has meant that hypertension researchers have also focused on getting better efficacy and value from the available treatments through system improvement, combinations, and algorithms. There has been continued interest in the role of nonpharmacological measure in prevention and management of hypertension.

Resistant Hypertension

The highlight in terms of treatment advances, however, has been in the management of resistant hypertension. Defined as failure to achieve a BP goal of <140/90 mm Hg, despite treatment with ≥3 different antihypertensive medication classes at a maximally tolerated dose and, including a diuretic, recent trials of resistant hypertension have shown some success with the inclusion of darusentan, an endothelin A antagonist or the aldosterone antagonists spironolactone or eplerenone, although the latter are underused in practice.[1,2]

However, most interest in the management of resistant hypertension has been on interventions that target the sympathetic nervous system, especially devices. Catheter-based renal denervation procedures and carotid baroreceptor stimulation have been the subject of intense investigation with early reports of dramatic improvement of BP control. Development of evidence on the former is more advanced than with carotid stimulation, but both techniques await blinded randomized controlled trials comparing the device-based intervention with structured best available medical therapy.

Resistant Hypertension and the Sympathetic Nervous System

There has never been doubt that the sympathetic nervous system is a key regulatory system involved in the pathogenesis of hypertension. Surgical sympathectomy was the first effective way of lowering BP in hypertension,[3] and the earliest antihypertensive drugs targeted the sympathetic nervous system. Despite widespread use of both α- and β-adrenergic antagonists and centrally acting sympatholytic agents, these have been supplanted by antagonists of the renin-angiotensin system and by calcium channel blockers and diuretics all of which are generally better tolerated. A large body of historical work in our laboratories and elsewhere showed that a proportion of people with hypertension have elevated sympathetic efferent activity. This is largely targeted to the kidney, causing sodium retention, increased vascular resistance, and renin secretion.[4] Reflexes originating in the kidney involving renal afferents also have pressor effects. This was the basis for the development of techniques that reduce renal innervation. Renal denervation occurs with renal transplantation, providing an argument for safety of a deliberate procedure. The development took advantage first of the fact that renal afferent and efferent fibers

reach the kidney through the adventitia of renal arteries and are, therefore, accessible by an endovascular technique, and second the knowledge gained from experience with catheter-based radiofrequency ablation of arrhythmias in the heart.

To date there are >20 medical equipment manufacturers developing denervation devices. The most advanced in clinical trials is the Symplicity device, which has been the subject of several trials, including Symplicity-HTN-2, a randomized controlled trial.[5] The approach to date has a good safety profile. Work is ongoing to define the mechanisms, as these seem to be more complex than disruption of sympathetic efferents to the kidney. Afferent pathways for renal autonomic reflexes may be important. As well as BP reduction there is preliminary evidence after treatment of effects on central noradrenergic activity,[6] preserved renal function,[7] metabolic benefits, and improved quality of life measures.[8] Before handing management of resistant hypertension over to the interventionists, however, there is evidence that pharmacological management could be improved with evidence-based regimens.[9–12] There is a need for rigorous trial design, comparisons with benchmark pharmacotherapy, and better classification of patient groups that will benefit from renal denervation therapy. Extension of indications beyond that supported by trial data should be monitored and generally avoided.[13]

Electric stimulation of the carotid sinus is an alternative approach to resistant hypertension under investigation in clinical trials. Early promising results await larger multicenter trials that are presently underway. The results to date are the subject of recent reviews.[14,15]

Trials of Pharmacotherapy

The single large outcome trial reported in the past 2 years was the Aliskiren Trial in Type 2 Diabetes Mellitus Using Cardio renal Endpoints of 8561 patients with type 2 diabetes mellitus and chronic kidney disease, cardiovascular disease, or both. The trial was stopped prematurely after the second interim analysis after a median follow-up of 32.9 months. Despite lower BP patients assigned to aliskiren in addition to angiotensin-converting enzyme (ACE) inhibitor had a trend toward excess primary end point, a composite of time to cardiovascular death or a range of major cardiovascular or renal events (18.3% versus 17.1% for aliskiren+ACE inhibitor and placebo+ACE inhibitor, respectively; hazard ratio, 1.08; 95% confidence interval limit, 0.98–1.2).[16] Although not conclusive the result supports the earlier ONTARGET result, where a different combination of 2 agents that suppress the renin-angiotensin system were less beneficial than either agent alone.[17] The ONTARGET ambulatory BP substudy has since been reported, confirming that the trend in adverse events on the combination was at odds with the BP changes which were greater than on the single agents.[18]

Are Chlorthalidone and Nonthiazides the Best Diuretics for Treatment of Hypertension?

Hydrochlorothiazide is the most widely used diuretic for the treatment of hypertension and is both used alone and in combination. For some time there has been concern that older antihypertensive efficacy studies showed much stronger evidence for chlorthalidone in preventing major cardiovascular events than hydrochlorothiazide. This question was the subject of a recent systematic review and meta-analysis, which concluded that chlorthalidone was indeed superior. The number needed to treat to prevent 1 cardiovascular event >5 years with chlorthalidone rather than hydrochlorothiazide was only 27.[19] This curious disequilibrium between the evidence in favor of chlorthalidone and common clinical practice favoring hydrochlorothiazide was further examined in another meta-analysis comparing the effects of these drugs, along with bendroflumethiazide on BP, serum potassium, and urate. The potency order was bendroflumethiazide>chlorthalidone>hydrochlorothiazide and was similar for BP (not dose related), potassium, and urate. In another study, chlorthalidone proved more effective than hydrochlorothiazide as part of a combination in systolic hypertension.[20] These findings may account for some of the outcome data supporting chlorthalidone over hydrochlorothiazide, particularly in the light of a post hoc analysis of the ALLHAT study that showed a slight increase in mortality in people with hypokalemia, which was unrelated to specific effects of chlorthalidone in the diuretic arm.[21]

Old Ground, New Findings

In the absence of new mega trials, there has been continuing analysis of those done in the past. One interesting finding also seen in diabetes mellitus trials was that mortality reduction seen in trials of BP-lowering medications persisted well after the trial phase when most people in both intervention and control groups are on active therapy. This is interesting albeit circumstantial evidence in favor of early intervention in hypertension, perhaps before present guidelines suggest.[22] These results also support the notion that participation in clinical trials is a good thing in itself. In a retrospective cohort study, the benefits of participation in clinical trials irrespective of the treatment allocation were illustrated by better persistence and adherence to prescribed medication in the long term.[23]

The trend toward continuing reanalysis of data gathered some time ago is not without potential flaws. It is proving more and more difficult to show incremental benefit of new therapies over standard therapy in control groups that are on background therapy marked by high statin, antiplatelet, and other antihypertensive therapy rates, as well as more overweight and obesity and less tobacco use than in the past.[12,16] Patient cohort data collected in the past will inevitably become less representative of everyday contemporary practice with time. Nevertheless, a recent update of the findings of ASCOT[24] emphasizes the added benefit of follow-up of large cohorts provided planning takes place well ahead and funding is available. Collection of samples and careful curation for future biomarker studies, substudies collecting data on intermediate end points and their validity as predictors of outcome, and the ability to re-examine the data as new controversies arise have proven extremely valuable. Contemporary interest in pulse pressure and other more direct measures of arterial properties and new BP variables, such as BP variability, have been explored in this way. In the Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) study, pulse pressure was the strongest BP variable predicting future atrial fibrillation.[25] Visit-to-visit BP was very high in patients on hemodialysis in a reanalysis of the Fosinopril in

Dialysis (FOSIDIAL) study and was a strong predictor of cardiovascular events.[26] Day-to-day variability of home BP measurements was reduced significantly by a combination of angiotensin II receptor blocker and calcium channel blocker, and by more than an angiotensin II receptor blocker/diuretic combination in a Japanese study, perhaps because of effects on arterial stiffness.[27]

ASCOT showed better outcomes with a regimen of amlodipine with or without perindopril than with atenolol with or without bendroflumethiazide. This finding plays a key part in the transatlantic debate on guidelines for the management of hypertension, favoring the ABCD approach,[28] recently updated to ACD (A—angiotensin inhibition, B—beta antagonist, C—calcium channel blocker, and D—diuretic) to initial therapy adopted by previous UK National Institute of Clinical Excellence (NICE) guidelines over the US Joint National Committee (JNC7) recommendation to commence therapy with a thiazide diuretic. This will soon be updated to JNC8, and at the time of writing it is unclear whether this recommendation will change. As stated above what is clear is that thiazide-like diuretics are preferred, especially chlorthalidone over the more widely used hydrochlorothiazide. Arguably, however, there are far more important implications of future guidelines than initial drug choice. Most patients need >1 drug. Initial single-pill combinations were shown using electronic health records of 180 practice sites to provide better hypertension control and perhaps better cardiovascular outcomes in the first year of treatment than free combinations or monotherapy.[29]

BP Targets and Treatment

A number of post hoc analyses of major trials have led to controversy on whether BP targets set in present guidelines are optimal, achievable, and appropriate, particularly the more aggressive targets set for patients with diabetes mellitus, renal disease, and history of a cardiovascular event. This debate will continue in the absence of a major contemporary trial specifically designed to address systolic BP targets and supported by further data on the relationship of BP to various target organ manifestations of hypertensive vascular disease.[30–32]

The choice of thresholds for initiation of therapy and targets for BP lowering have far greater implications than the relatively small differences in efficacy and tolerability between drug classes. These recommendations vary considerably as authoritative international bodies examine the same evolving body of evidence. For example, a 2007 American Heart Association (AHA) Scientific statement recommended a target BP <130/80 among those at high risk for coronary artery disease, people with diabetes mellitus, chronic kidney disease, coronary artery disease, or its equivalent, or a 10-year Framingham risk score above 10%. By 2011 a joint American College of Cardiology (ACC)/AHA hypertension guideline for the elderly recommended a less aggressive approach with a target <140/90. The difference in the number of Americans requiring antihypertensive drug therapy between the 2007 and 2011 recommendations was estimated as 7 million adults.[33] Clearly, future guidelines will need to take into account not only the clinical trial data on efficacy and safety of drugs but also the consequences of the recommendations for the community as a whole.

Prescriber inertia, patient acceptance, perseverance, and adherence also play a large part in the present treatment gap for hypertension globally. A controlled study of guideline-based treatment algorithms compared with usual care showed that some gains can be made with electronic physician support but that more aggressive targets (eg, <130/80) in groups, such as people with diabetes mellitus, may be impractical in the real world with conventional drug regimens.[34]

Lifestyle and Nonpharmacological Approaches to Hypertension

Sodium

Although there are enough data to convince public health bodies and guideline committees that reduction of salt intake is an important element in the community control and prevention of hypertension controversy continues unabated. The American Medical Association (AMA) has published a scientific report supporting their recommendation of sodium reduction in processed and restaurant foods because these are the source of 80% of national intake.[35] In the meantime, an analysis of the ONTARGET clinical trial program suggested that both high (>7 g/day) and low sodium intake (<3 g/day) was associated with increased cardiovascular events compared with those consuming moderate intake (4–6 g/day), although hazard ratios were numerically greater with the former.[36]

The low sodium, Dietary Approaches to Stop Hypertension (DASH) diet was examined in a small, uncontrolled study of patients with hypertensive heart failure with preserved ejection fraction. Drug therapies have been disappointing in large trials of this important long-term consequence of hypertension. The DASH diet was associated with reduced BP, arterial stiffness, and markers of oxidative stress after 14 days, all of which would be expected to be beneficial if sustained.[37]

Other Trials of Nutrition and BP

Although there have been many trials examining the effects of dairy foods on BP and the successful DASH diet included significant amount of low fat dairy foods, the large variation in types of dairy intake and serving sizes among populations has made it difficult to draw firm conclusions. The data have now accumulated to allow a meta-analysis of >57 000 subjects and 15 000 incident cases of hypertension with follow-up times of 2 to 15 years.[38] The pooled relative risks for 200 g/d of total dairy, low-fat dairy, or milk were in the range 0.96–0.97, suggesting a small benefit of these forms of dairy foods in preventing hypertension. Data on high-fat dairy, total fermented dairy, yogurt, and cheese were more limited and no statistically significant effects were seen.

Nut consumption has been another area of interest in the prevention of cardiovascular disease. In a randomized crossover controlled feeding study, a typical Western diet was compared with diets in which 10% and 20% of energy was derived from pistachios.[39] Although resting BP was not changed with the pistachio diets some hemodynamic changes were observed, particularly the BP responses to a mathematical mental stress test.

Weight loss in the obese and overweight is recommended in every guide to hypertension management. However, as every

clinician will have observed, there is substantial interindividual variation in the BP responses to weight loss and indeed other nonpharmacological interventions, such as exercise. An interesting recent observation from the 2-year randomized Preventing Overweight Using Novel Dietary Strategies Trial was that a neuropeptide Y promoter polymorphism (NPY rs16147) modulated the interaction between dietary fat intake and BP.[40] We will see more studies of this kind in the future, paving the way for more personalized and predictable lifestyle interventions.

Resistance Exercise and BP

Aerobic (isotonic) exercise is firmly established as an effective measure for lowering BP and reducing cardiovascular risk. Interestingly, it preferentially reduces renal sympathetic activity and so may be a nonpharmacological approach to partial renal denervation.[41] The case for resistance exercise is more flimsy. BP during resistance exercise increases more rapidly than with aerobic forms and stroke is a rare but well-known event associated with heavy lifting and in power athletes. The studies to date have been largely unconvincing and in this light a recent meta-analysis of resistance training on BP and other cardiovascular risk factors is very welcome.[42] The studies included in the analysis were generally quite small (28 studies, 33 study groups, 1012 participants) and the exercise intervention varied and further division of the studies by patient characteristics or type of exercise is fraught. However, on average, the intervention groups had BP that was ≈4/4 mm Hg lower than controls in normotensive and prehypertensive study groups. No significant difference in BP was seen in 5 study groups with established hypertension but the limited amount of data available does not afford firm conclusions.

Summary: What Can Be Learned From Clinical Trials Reported in the Present Decade?

- Systems for blood pressure management in the community can be improved because a large treatment gap remains.
- Drug combinations from different classes with different modes of action are useful.
- Drug combinations that include drugs with similar mode of action do not generally enhance efficacy and come at a cost in adverse events.
- Small but important nutritional effects on blood pressure demand further examination.
- The sympathetic nervous system has returned as an important target for therapy of hypertension.
- Blood pressure targets and goals need refining, preferably on the basis of specifically designed clinical trials.

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Disclosures

None.

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