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Editorial

Hypertension, New Data and Implications

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Hypertension is a major global public health burden. According to the WHO, it is the leading risk factor for mortality, being responsible for 13% of deaths annually [1]. Globally, 51% of stroke and 45% of ischemic heart disease deaths are attributable to high systolic blood pressure (BP). At any given age, the risk of dying from high BP in low- and middle-income countries is more than double that in high-income countries. In the high-income countries, only 7% of deaths caused by high BP occur under age 60; in the African Region, this number increases to 25% [1]. The prevalence of hypertension, along with other cardiovascular (CV) risk factors, is believed to be high in the Middle Eastern region. A systematic review analyzed 51 studies performed between 1980 and 2005 in the Middle East to examine CV risk factors. This review reported an overall prevalence of hypertension of 21.7% (95% CI: 18.7-24.9) afflicting more women than men [2]. Exciting developments have taken place in the field of hypertension over the past decade, some of which have already been reflected in the latest international guidelines.

Blood Pressure Measurement

Increased attention is being paid to the technique and precision of BP measurement. Powers and colleagues performed a clinical trial to assess the effects of repeated BP measurements by 3 methods: standard clinic measurements obtained during routine outpatient visits, research measurements taken during study visits, and measurements recorded at home. Participants included 444 subjects with uncontrolled hypertension who had BP measured frequently over 18 months. The researchers documented substantial within-patient variability with each technique, leading to a high probability that subjects would be misclassified if a BP measurement from just one visit was used to classify them. The study also documented a striking difference between clinic and research BP measurements that confirms findings from previous studies. At baseline, mean clinic systolic BP (144.9 mm Hg) was 15.5 mm Hg higher than mean research systolic BP (129.4 mm Hg). In 51.6% of participants, the difference exceeded 10 mm Hg.

A number of studies have suggested that the risk of hypertensive CV and renal complications correlates more closely with 24-hour, daytime, or nighttime ambulatory BP measurements (ABPM) than with the office measurements. ABPM is determined using a device worn by the patient that takes BP measurements over a 24 to 48 hour period. The device usually records pressures every 15 to 20 minutes during the daytime and every 30 to 60 minutes during sleep; an average is determined from the data. ABPM has also allowed more awareness and better characterization of the so called white coat and masked hypertension as well as "non-dipping". Non-dipping refers to failure of the BP to fall by at least 10% during sleep since the average nocturnal BP is approximately 15% lower than daytime values in both normal individuals and hypertensive patients. Recent data have demonstrated prognostic CV value for non-dipping in patients who are normotensive on office or on ambulatory daytime BP measurement [3]. A cohort study recorded ABPMs and clinic BPs of 217 subjects with CKD. The composite renal end point was end-stage renal disease (ESRD) or death over a median follow-up of 3.5 years. The study found that elevated BP by ABPM correlated more strongly with progression to ESRD than clinic systolic BP. Furthermore, non-dipping was associated with increased risk of total mortality and composite end point. Multiple studies have

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suggested increased CV risk associated with white coat hypertension and masked hypertension compared with persistent normotension. Recent British National Institute for Clinical Excellence (NICE) Guideline released in August 2011 has incorporated ABPMs as a new tool in the management of hypertension. It recommended that the diagnosis of primary hypertension should be confirmed using 24-hour ABPM, or home blood pressure monitoring (HBPM), rather than solely be based on measurements of BP taken in the clinic [4]. ABMP is often not feasible or too costly; studies have looked into HBPM as a cost effective and readily accessible tool to manage BP. A metanalysis that reviewed 37 randomized controlled trials with 9,446 participants found that compared with clinic-based measurements (control group), BPs improved with home-based BP monitoring. Reductions in home BP monitoring-based therapy were greater when telemonitoring was used [5].

Treatment Targets

New data have emerged regarding BP treatment targets and pharmacologic approaches to lower BP. Most major guidelines advocate BP targets of below 140/90 mm Hg for uncomplicated hypertension whereas lower targets are recommended for patients with diabetes mellitus and chronic kidney disease. Those recommendations were mainly derived from earlier studies such as the HOT and ABCD clinical trials that showed some benefit of lower targets only in diabetics. A recent Cochrane systematic review examined seven trials involving 22,089 patients which compared different diastolic BP targets. It showed no evidence of benefit with lower targets below140/90 in terms of reducing total mortality, myocardial infarction, stroke, congestive heart failure or stroke. It is therefore unlikely that the treatment goals for uncomplicated hypertension will change. The SPRINT trial is currently underway in the USA. This is a large multicenter randomized clinical trial to determine whether maintaining BP levels lower than currently recommended further reduces the risk of CV and kidney disease. It will hopefully settle the question of lower BP targets in the elderly, nondiabetic and CKD patients.

Regarding diabetic hypertensive patients, new evidence has emerged from the ACCORD clinical trial. This was a randomized controlled trial for diabetic patients at high risk for CV events who were followed up for 4.7 years. The study had three arms among which the BP arm involved 4,733 patients who were randomized to standard systolic BP of less than 140 mm Hg versus more intensive lowering of less than 120 mm Hg. The study found no significant difference in the annual all-cause mortality or the primary CV composite outcome. The intensive therapy group had a significantly lower incidence of stroke, but nevertheless at the cost of significantly more frequently encountered serious adverse events attributable to antihypertensive drugs (hypotension, syncope, bradycardia or arrhythmia, hyperkalemia, angioedema, and renal failure). The ACCORD findings are expected to reflect on new BP treatment targets for diabetics. Goal BP target of less than 140/90 mm Hg is likely to be recommended while perhaps a lower target can be considered for patients at greater risk for stroke who can be closely monitored for adverse hemodynamic effects.

Pharmacologic Approaches

The ALLHAT trial had a major impact on earlier hypertension guidelines in adults. It was a large prospective clinical trial of different antihypertensive medications for mild hypertension. The study enrolled 42,000 patients who were 55 or more years of age with mild hypertension and one additional risk factor for coronary artery disease. Patients were randomly assigned to receive chlorthalidone, amlodipine, lisinopril, or doxazosin and followed up for a mean of 4.9 years. The doxazosin arm was terminated early because of an increased incidence of heart failure. Each of the three other drug classes was associated with equivalent rates of the primary CV outcome whereas chlorthalidone was superior in preventing new onset heart failure. The study demonstrated the superiority of thiazides in preventing one or more major forms of CVD, and given their lower cost, made a strong case for the US Joint National Committee (JNC) on its seventh report to recommend them as the drugs of choice for first-step antihypertensive drug therapy. Following the publication of ALLHAT the prescriptions for thiazide diuretics increased significantly; however, those were mostly for hydrochlorothiazide rather than chlorthalidone tested in the study. New evidence has then emerged highlighting the pharmacologic and clinical differences between chlorthalidone (which is more portent and longer acting) and hydrocholrothizide. A systematic review of nine trials including over 50,000 patients testing the relative efficacy of the two drugs compared with other antihypertensives found that chlorthalidone significantly reduced the 5-year risk of all CV events, including congestive heart failure [6]. Based upon those observations, some experts (including the 2011 NICE hypertension guidelines) suggest that chlorthalidone (12.5-25 mg/day) may be

more effective than hydrochlorothiazide and is the low dose thiazide of choice.

Another major study that could have implications on the way we manage hypertension is the ACCOMPLISH trial [7]. This was a randomized clinical trial set out to test whether the combination of benazepril/amlodipine will reduce CV morbidity and mortality in hypertensive patients when compared to the combination of benazepril/hydrochlorothiazide. The study enrolled 11,506 patients with high-risk hyperteison (defined as prior CV disease, diabetes, and/or impaired renal function) and, despite prior antihypertensive therapy in 97 percent, had a mean baseline BP of 145/80 mm Hg. The trial was terminated early at a mean follow-up of 36 months when the prespecified stopping rule was exceeded. The primary end point was the time to the first event, which was a composite of death from CV causes, nonfatal myocardial infarction, nonfatal stroke, and hospitalization for angina, resuscitation after sudden cardiac death or coronary revascularization. The primary end point was achieved significantly less often in the benazepril/amlodipine group. Further analysis revealed that treatment with the ACE inhibitor/calcium channel blocker reduced the secondary renal endpoint (doubling of serum creatinine or ESRD) [8]. To address the question of the duration of antihypertenive medications used in the ACCOMPLISH trial a 24-hour BP monitoring in a subset of 573 patient revealed a nonsignificant difference between the two groups. Consequently, the benefits demonstrated with the ACE inhibitor/calcium channel blocker combination cannot be explained by mere better BP control. The ACCOMPLISH trial made a stong case for angiotensin converting enzyme inhibitor (or angiotensin receptor blocker)/calcium channel blocker compared to a diuretic/calcium channel blocker initial combination therapy of choice for high-risk hypertensive patients and is likely to notably impact future guidelines regarding antihyeprtensive therapy.

Beta blockers have fallen out of favor as a primary antihypertenvie option when a specific indication for their useage is absent. Several metanalyses have cast doubt about the safety of beta blcokers in the context of essential hypertension. A meta-analysis of five clinical trials compared atenolol with other antihypertensive drugs and found it to be associated with a significantly increased risk of all cause mortality and stroke [9]. Another meta-analysis incorporating data from 21 hypertension trials found an increased risk of stroke with beta blockers in patients 60 years of age or older [10]. Beta blockers were therefore withdrawn from the initial choice of antihypertensive medications in the uncomplicated cases in the 2011 NICE guidelines.

In summary, hypertension is an important and a common cardiovascular risk factor. Exciting developments have taken place over the past decade, and have the potential to modify the way BP is managed. Those changes are being reflected on new guidelines including the highly anticipated JNC-8.

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