Recent Developments in the Assessment and Management of Hypertension: CHEP, ALLHAT and LIFE

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Poor blood pressure control, particularly among the older Canadian population, remains an important cause of preventable cardiovascular morbidity and mortality. It behooves Canadian health care workers to identify, treat and control hypertension. Recent trials, including ALLHAT and LIFE, add to the information clinicians need to achieve these targets. ALLHAT establishes the central role of thiazide-like diuretics for many hypertensive patients. ALLHAT demonstrates that good blood pressure control can be achieved in the majority of hypertensive patients if a systematic effort is maintained. LIFE adds important information regarding angiotensin receptor blockers as an effective alternative to the other commonly used classes of antihypertensive drugs, particularly among patients with diabetes or isolated systolic hypertension. Finally, the Canadian Hypertension Education Program will continue to produce and disseminate annually updated systematic reviews and recommendations related to the assessment and management of hypertension.

Key words: hypertension, recent clinical trials, clinical practice guidelines.

Hypertension continues to be an important, yet modifiable, risk factor for vascular morbidity and mortality. However, much of the prevention of atherosclerotic morbidity and mortality remains to be achieved—not only in Canada, but worldwide. This has greater relevance for the elderly, not only because of the higher prevalence of hypertension in this group, but also because of the higher prevalence of concomitant vascular risk factors and, as a consequence, higher rates of vascular events.

Due to its high prevalence in clinical practice, hypertension becomes a mundane problem. Perhaps because of this, clinicians become desensitized to its importance as a public health issue. It is necessary to remember that elevated blood pressure is the single most important cause of stroke, accounting for up to 40% of such events. Hypertension also is an important risk factor for both the development and progression of coronary heart disease, heart failure, atrial fibrillation and renal disease. It dramatically increases the risk of diabetes-related micro- and macrovascular complications. Hypertension is estimated to be the third leading risk associated with death worldwide.[1] Thus, it behooves all health care professionals to prioritize hypertension as a public health issue and to aggressively identify, treat and control hypertension according to the best available evidence and recommendations.

In Canada, a group of individuals with interest and expertise in hypertension have committed themselves to producing and disseminating annually updated systematic reviews and recommendations related to the assessment and management of hypertension.[2] The group is called the Canadian Hypertension Education Program (CHEP) and is currently working on the fourth annual iteration of this process. Previous iterations have been published recently,[3,4] and summary documents and slide sets can easily be accessed at the Canadian Hypertension Society website (www.chs.md).

The following article will highlight issues that have led to changes in the recommendations over the past year, as well as references to other recently published data that may be of considerable clinical importance.

Assessment of Blood Pressure

Accurate assessment of blood pressure (BP) remains important for proper diagnostic labeling, cardiovascular risk assessment and gauging the necessity for and adequacy of therapy. Deviations from optimal BP measurement techniques, such as incorrect arm position and support, leg crossing, talking, exposure to cold, ingestion of alcohol and inappropriate cuff size, will result in significant variation in BP values from those observed using standardized methods.

Any diagnostic algorithm based on only a few mild to moderately elevated measurements will result in a substantial risk of assigning false-positive labels of hypertension and false-negative reassurances of "normal" blood pressure. With our aging population, isolated systolic hypertension remains an important diagnostic and prognostic factor. The physical examination should include an assessment for possible target organ damage, including a search for retinopathy, focal neurological signs, abnormal cardiac findings, vascular bruits, abdominal aortic aneurysm and peripheral pulse deficits. The presence of such target organ damage shortens the period of observation before assigning a diagnosis of hypertension and highlights the importance of achieving optimal BP control.

Regarding the criteria for diagnosis of office-based hypertension and recommendations for follow-up, it is important to check for factors that are easily reversible. These include exogenous substances that may increase or aggravate

high BP. A diagnostic algorithm for office-based hypertension differentiates individuals whose blood pressure remains 160–180/100–105mmHg, and those who have blood pressure ranges of 140–159/90–99mmHg. For the former group, three visits may be sufficient to reasonably assign a diagnosis of hypertension. However, because even this number of visits at these thresholds is associated with a 10% false-positive and false-negative diagnostic labeling, two to three more visits may be added if uncertainty persists and the estimated cardiovascular risk is acceptably low. Those with BP in the lower range should be assessed over a total of at least five further visits (Table 1).

Regarding persons who, at their last diagnostic visits, had BP < 140/90mmHg and who are otherwise at low overall cardiovascular risk, a distinction is made at a threshold of 130/85mmHg. This is due to a relatively high risk of progression to sustained hypertension among those whose BP is higher than 130/85mmHg. The four-year rates of progression to sustained hypertension may be as high as 37% for those younger than 65 years and 50% for those 65 years and older.

The assessment of overall cardiovascular risk remains a topic of immense importance and interest. By including information regarding multiple cardiovascular risk factors and possibly their severity, patient-specific recommendations for treatment may enhance efficiency of treatment.

It is important to emphasize that out-of-clinic BP measurements should be interpreted against lower thresholds than those taken in a clinical setting to achieve similar estimates of cardiovascular risk. Whether using home or self-blood pressure measurement or ambulatory BP measurement devices, it is important that the device is independently tested and meets the criteria for precision, accuracy and reliability of the Association for Advancement in Medical Instrumentation, the current British Hypertension Society Protocol or the new International Validation Protocol.

Echocardiography need not be conducted in all hypertensive patients. However, it is important to recognize that existing data clearly establish a pronounced increased risk for hypertensive patients with left ventricular hypertrophy (LVH) compared to those without.

ALLHAT: Implications for Treatment

One of the most noteworthy publications for hypertension treatment has been the long-awaited Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT).[5] What follows is a brief summary of the study and comments based on the results.

ALLHAT compared cardiovascular and mortality effects of antihypertensive treatment when started with amlodipine, lisinopril or doxazosin versus chlorthalidone in 42,418 participants older than 55 years with hypertension and at least one other coronary heart disease (CHD) risk factor or established vascular disease. The target blood pressure was < 140/90mmHg. Protocol-accepted second- and third-line therapies included the unblinded addition of reserpine, atenolol or clonidine and hydralazine, respectively. The primary endpoint was fatal CHD or non-fatal myocardial infarction (MI).

The primary hypothesis assessed whether each of the "newer" representatives of their respective drug class was superior to the thiazide-like diuretic. Because chlorthalidone served as the control for each drug comparison, a higher proportion of subjects was randomized to the diuretic arm (1.7:1:1:1).

At baseline, the mean age of the study population was 67 years and 35% were black, 47% were women and 36% had diabetes mellitus. Baseline BP was 146/84mmHg. No meaningful baseline differences among treatment groups were reported (only a trivially higher baseline rate of CHD in the chlorthalidone group reached statistical significance).

As previously reported,[6] the doxazosin arm was stopped after a median follow-up of 3.3 years due to higher rates of the following secondary outcomes: stroke, congestive heart failure, angina, coronary revascularization and combined CVD (which included all of the former).

The median length of follow-up of the three remaining arms was 4.9 years (up to 8.1 years). At five years follow-up, 80.5% of the chlorthalidone group remained on a diuretic (57% at maximal dose [MD]) and the respective rates for the amlodipine and lisinopril arms were 80.4% (65.7% MD) and 72.6% (60.3% MD). At 3.3 years follow-up, the doxazosin group rate was 75%. At least one second- or third-line drug was added in 41–47% of subjects, with atenolol being the most commonly used. Unblinded complete or partial cross-overs occurred in 22–24% of subjects in each group. Withdrawal of drug use (withdrawals were related to both adverse effects and ineffectiveness) was lowest in the chlorthalidone group and highest in the lisinopril group.

Table 1
Suggested Number of Clinic Follow-up Visits Prior to Assigning a Diagnosis of Hypertension According to Blood Pressure at Intial Visit

Clinic BP at initial office visit	Number of further visits and BP assessments to assign a diagnosis of hypertension	Risk of false-positive or false-negative diagnostic assignment
140–159/90–99mmHg	At least 5 visits	±20–25%
160–180/100–105mmHg	At least 3 visits for those at higher overall cardiovascular risk Up to 5 visits for those at lower overall cardiovascular risk	±10% (for 3 visits)

Table 2
Summary of ALLHAT Results Including the Prematurely Terminated Doxazosin Arm

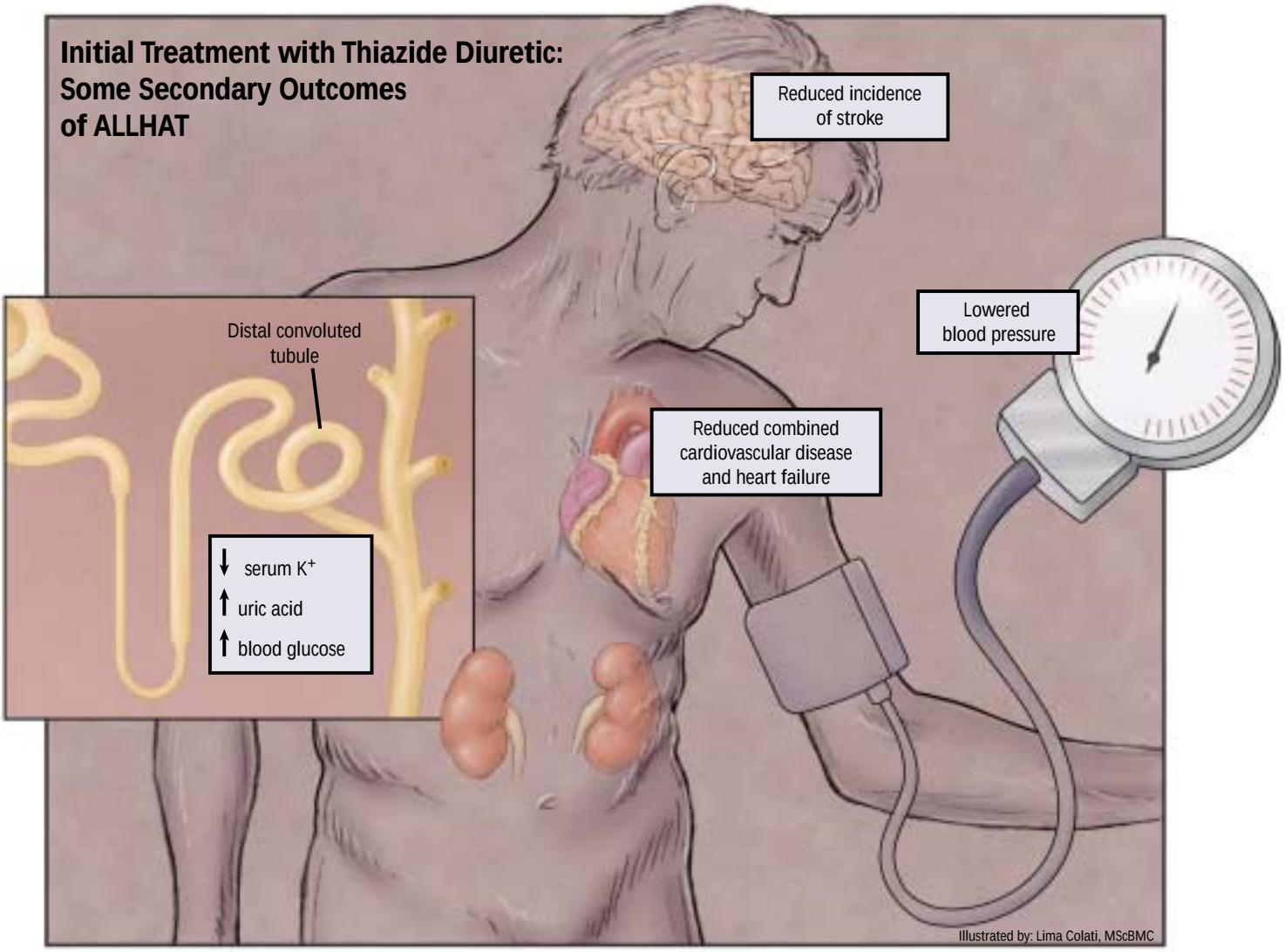
	Chlorthalidone n=15,268	Amlodipine n=9,048		Lisinopril n=9,054			Doxazosin** n=9,067	
Outcome measure	**Chlorthalidone 6-year event rates (%)**	**RR (95% CI)**	**AR increase c/w chlorthalidone (p value)**	**RR (95% CI)**	**AR increase c/w chlorthalidone (p value)**	**Chlorthalidone 4-year event rates (%)**	**RR (95% CI)**	**AR increase c/w chlorthalidone (p value)**
Coronary heart disease (CHD)*	11.5	0.98 (0.90-1.07)	NA (0.65)	0.99 (0.91-1.08)	NA (0.81)	6.3	1.03 (0.90-1.17)	NA (0.71)
All-cause mortality	17.3	0.96 (0.89-1.02)	NA (0.20)	1.00 (0.94-1.08)	NA (0.90)	9.1	1.03 (0.90-1.15)	NA (0.56)
Combined CHD	19.9	1.00 (0.94-1.07)	NA (0.97)	1.05 (0.98-1.11)	NA (0.18)	12.0	**1.10 (1.00-1.12)**	**1.1% (0.05)**
Combined CVD	30.9	1.04 (0.99-1.09)	NA (0.12)	**1.10 (1.00-1.12)**	**2.4% (<0.001)**	21.8	**1.25 (1.17-1.33)**	**3.7% (<0.001)**
Stroke	5.6	0.93 (0.82-1.06)	NA (0.28)	**1.15 (1.02-1.30)**	**0.7% (0.02)**	3.6	**1.19 (1.01-1.40)**	**0.6% (0.04)**
Congestive heart failure (CHF)	7.7	**1.38 (1.25-1.52)**	**2.5% (<0.001)**	**1.19 (1.07-1.31)**	**1.0% (<0.001)**	4.5	**2.04 (1.79-2.32)**	**3.7% (<0.001)**
Hospitalized CHF	6.5	**1.35 (1.21-1.50)**	**1.9% (<0.001)**	1.10 (0.98-1.23)	NA (0.11)			
Angina	12.5	1.02 (0.94-1.10)	NA (0.67)	**1.11 (1.03-1.20)**	**1.5% (0.01)**	10.2	**1.16 (1.05-1.27)**	**1.3% (<0.001)**
Coronary revascularization	9.2	1.09 (1.00-1.20)	NA (0.06)	**1.10 (1.00-1.20)**	**1.0% (0.05)**	5.2	**1.15 (1.00-1.32)**	**1.0% (0.05)**

*Primary outcome measure: CHD=fatal CHD (34–36%) + nonfatal MI (64–66%).
**Comparison is over four, not six, years for doxazosin-chlorthalidone comparisons due to early termination of doxazosin arm.
RR: relative risk; AR: absolute risk.

Among the intermediate outcomes, overall systolic blood pressure (SBP) was lower in the chlorthalidone group than in the amlodipine (-1mmHg), lisinopril (–2mmHg) and doxazosin (–3mmHg) groups. Diastolic blood pressure control was 1mmHg lower in the amlodipine arm than the chlorthalidone arm while the other two treatment groups did not differ over the follow-up period. Total cholesterol (+0.2mmol/L) and serum glucose (+0.2mmol/L) were higher and potassium (–0.3mmol/L) was lower in the chlorthalidone group compared with the other treatment strategies. The rate of new-onset diabetes mellitus was highest among those treated initially with chlorthalidone (11.6%) compared with those in the amlodipine (9.8%) or lisinopril (8.1%) groups. The decline in glomerular filtration rate (GFR) was greater in the chlorthalidone group compared to amlodipine (–4.7 mL/min/1.73m^2) and lisinopril (–0.6 mL/min/1.73m^2) groups.

Primary and *A Priori* Secondary Outcome Measures

Overall, neither the primary outcome measures nor all-cause mortality differed among the paired treatment groups. Among the secondary outcomes, compared with chlorthalidone the incidence of heart failure was significantly higher in the amlodipine (38%; relative risk [RR] 1.38), lisinopril (19%; RR 1.19) and doxazosin (104%; RR 2.04) groups. Compared with chlorthalidone use, the incidence of combined CVD was significantly higher with the use of lisinopril (10%; RR 1.10) and doxazosin (25%; RR 1.25). Compared with chlorthalidone, the incidence of stroke was significantly higher in the lisinopril (15%; RR 1.15) and doxazosin (19%; RR 1.19) groups. Among all comparisons between chlorthalidone and the comparators, no individual primary, secondary or composite outcome measure was found to be significantly favorable for an individual comparator (exception: non-cardiovascular causes of death, and



in particular, the combination of injury, suicide and homicide, were higher in chlorthalidone than amlodipine groups) (Table 2).

A priori subgroup analyses assessing the impact of age, race, sex and diabetes mellitus at baseline suggest the overall observed treatment effects described above were consistent across all subgroups with the exception of the presence of an interaction between race (black versus non-black subjects) and treatment for the lisinopril-chlorthalidone comparison for stroke. Notably, the SBP difference between lisinopril- and chlorthalidone-treated black subgroups was reported as being ~ 4mmHg. Including BP control over the follow-up period as a time-dependent covariate reduced the magnitude of the treatment differences by 3% overall and by 5–6% in the black subgroup. However, this adjustment did not change the direction or statistical significance of these subgroup analyses.

Interpretation

ALLHAT is an internally valid, double-blind clinical trial that has adequate precision for many clinically relevant cardiovascular outcomes and represents in large numbers many subgroups of higher risk hypertensive patients.

The primary conclusion that chlorthalidone is at least as effective as either amlodipine, lisinopril or doxazosin in reducing CHD and hypertension-related cardiovascular risks when used as initial therapy in the 55 years and older high-risk hypertensive population is unambiguous. The conclusion is robust across many clinically important subgroups. As initial therapy, chlorthalidone was significantly superior to each of the three comparators in at least one clinically relevant *a priori* secondary outcome. The magnitude of these differences is clinically relevant.

These results in clinical outcomes were observed in the context of less consistent observations among the intermediate outcome measures. Better blood pressure control was observed with the thiazide diuretic than the calcium blocker (+Δ2mmHg pulse pressure), lisinopril (+Δ2mmHg SBP) or doxazosin (+Δ2mmHg SBP). Glucose and total cholesterol levels favoured each of the three comparators over the chlorthalidone treatment. The rate of new onset diabetes was 3.5% higher with chlorthalidone than lisinopril. The rate of decline of GFR was lower with amlodipine or lisinopril than with chlorthalidone.

Questions arise as to how we should interpret these results when the primary outcome does not differ among treatment groups (i.e., overall, a "negative trial"), but some clinically important secondary outcomes do. On one hand, the differences in secondary outcomes that were observed did not translate into a mortality difference. There were many secondary analyses and it could be argued that some of these are simply the play of chance. Furthermore, diabetes might not be considered an intermediate laboratory-based outcome, but rather one of direct clinical relevance. On the other hand, the secondary outcomes for which differences were observed are highly clinically relevant (CHF, stroke), and the analyses found differences of a clinically important magnitude (e.g., 2.5% excess CHF with amlodipine compared to chlorthalidone) with a degree of certainty that reasonably excludes the play of chance ($p < 0.001$). Although multiple in number, these secondary analyses were preplanned.

As a precedent, one could compare how clinicians reacted to the doxazosin-chlorthalidone results with how the lisinopril-chlorthalidone results should be interpreted. Many clinicians now avoid the use of alpha-blockers as first-line agents. It would appear the respective benefits of chlorthalidone over both doxazosin and lisinopril are quite similar in direction, with modest differences in magnitude and precision, but over a sizable difference in time horizon (3.3 years vs. 4.9 years of follow-up).

An issue that will be debated is whether the differences in BP explain some, if not all, of the differences in clinical outcomes. The article did not present details of the analyses that include differences in BP as potential explanatory covariates. Undoubtedly, these will be the subject of more extensive future analyses, as was done in the recent detailed report of the doxazosin-chlorthalidone comparison.[7] In this recent analysis, adjustment for follow-up BP had a small impact on the estimated RR (2.04 to 2.00) for CHF. Are the differences in results between agents compared in the current analysis explainable by the BP differences? The authors suggest that the differences in BP control are only partially responsible for their findings. Regarding CHF in the recent paper,[5] it would appear that the mean arterial pressure of both chlorthalidone and amlodipine would have been very similar over the course of the trial. Any amlodipine-chlorthalidone BP differences would have been smaller than the lisinopril-chlorthalidone BP differences. However, the magnitude of the difference in rates of CHF would appear to be opposite, thus differences in BP alone are unlikely to explain the differences in rates of heart failure. On the other hand, the BP differences, particularly in the black / non-black lisinopril-chlorthalidone subgroup comparison, would appear to be most closely associated with the treatment-race-BP differences and, as such, the BP differences may well explain some or much of the differences in stroke rates.

One way or another, the diuretic strategy was associated with a higher rate of reaching the target BP than the other approaches. Differences in BP control among the treatment groups might be explained by the regimens available for second-line treatment (i.e., addition of beta-blockers and centrally-acting drugs, of which the former would be expected to have less of a synergistic effect with lisinopril vs. chlorthalidone). This would have been especially important in the large black population, where an ACE inhibitor / beta-blocker combination would be expected to be much less effective in lowering BP than a diuretic / beta-blocker or dihydropyridine calcium channel blocker / beta-blocker combination. Thus, a pharmacological rationale may be proposed to explain these differences, which requires detailed post-hoc analyses that undoubtedly will be presented. That being said, the overall rate of achievement of target BP was quite good (61–68%) when compared with both routine clinical practice and with many other hypertension trials. Furthermore, this was achieved with the frequent use of drugs often thought of as residing in the "bottom of the barrel".

In summary, ALLHAT clearly will be widely cited as a landmark study confirming the importance of diuretics as a critical and, many would argue, initial component of antihypertensive drug regimens for many subgroups of hypertensive patients. These subgroups include persons with diabetes mellitus and established atherosclerotic diseases. Furthermore, if pharmacoeconomic considerations are given their due weight, the case for the early or initial use of thiazide-like diuretics becomes all the more compelling.

LIFE: Impact on Treatment

Another trial that has received much attention in the last year has been the LIFE (Losartan Intervention For Endpoint) trial and its substudies.[8-10] In brief, LIFE compared the angiotensin II type 1 receptor antagonist losartan with atenolol in older (age 55–80) hypertensive patients with ECG-defined LVH. In 9,193 participants followed for 4.8 years, those randomized to losartan compared with atenolol experienced a 13% lower rate of the primary composite outcome (cardiovascular death, nonfatal stroke and MI). Total mortality did not differ in the overall trial (OR 0.90; $p=0.128$).[8] However, in two important subgroups—persons with diabetes (n=1,195)[9] and with isolated systolic hypertension (n=1,326)[10]—the composite outcome as well as cardiovascular and overall mortality was reduced.

The major issue regarding the interpretability of the LIFE trial is the choice of the comparator drug, atenolol. For many years, beta-blockers have not been recommended as first-line therapy in the elderly, largely based on the results of the Medical Research Council–Older Adults trial, which suggested that beta-blockers are not much more effective than placebo for preventing hypertension-related complications in elderly hypertensive patients.[11,12] If this argument is maintained, LIFE, in the narrowest interpretation, convincingly demonstrates that the ARB losartan provides benefit in hypertensive patients with LVH, but does not demonstrate superiority over other commonly used and recommended therapies in the elderly—particularly diuretics,

ACE inhibitors and dihydropyridine calcium antagonists. However, many clinical readers may feel comfortable generalizing the results of LIFE, particularly among patients with diabetes or isolated systolic hypertension, and would consider ARBs an alternative among first-line therapies, which include diuretics, ACE inhibitors, calcium channel antagonists and, for younger hypertensive patients, beta-blockers. However, this "upward ranking" of ARBs must be put into perspective with the results of the much larger ALLHAT that confirmed the benefits of the much less costly thiazide-like diuretics, discussed above.

Summary of Consequences

Both ALLHAT and the LIFE trial should impact on current recommendations for hypertensive patients with diabetes, given that the former reported at least equivalent primary and some better secondary outcomes associated with chlorthalidone compared to lisinopril and the latter reported that losartan reduces cardiovascular events compared to atenolol in diabetics with LVH.

The prevention of diabetes with drugs that interrupt the renin-angiotensin system (ACE inhibitors and ARBs) is a pattern previously seen in CAPPP, HOPE and now both ALLHAT and LIFE. It is interesting that many in the hypertension field would consider this an intermediate outcome (i.e., reduction in the rate of asymptomatic hyperglycemia) whereas those in the diabetes field may interpret the prevention of diabetes as a directly relevant clinical outcome.

As a consequence of trials such as ALLHAT and LIFE that compared two active therapies, those in the hypertension field as well as those with strong ties to the marketing of particular products will spend much time debating the relative positions of and definitions for first-line therapies for the many subgroups of hypertensive patients. However, in many if not most clinical situations, this debate may be of only marginal relevance. First, many hypertensive patients will require more than one drug to achieve optimal BP control. Most clinical trials exhibit this necessity and thus many become comparisons not of an individual drug with another, but rather comparisons of different treatment strategies that involve multiple drug therapies. Second, many higher risk hypertensive patients, particularly among the elderly, have concomitant risk factors or diseases that affect the choice of antihypertensive therapies. For example, a patient who remains hypertensive after a MI may benefit optimally from the combination of a thiazide-like diuretic, a beta-blocker and an ACE inhibitor.

In summary, poor BP control, particularly among the older Canadian population, remains an important cause of preventable cardiovascular morbidity and mortality and thus a significant treatment gap. It behooves Canadian health care workers to identify, treat and control hypertension. The recent trials, ALLHAT and LIFE, add to the information clinicians need to achieve these targets. ALLHAT establishes the central role of thiazide-like diuretics for the majority of hypertensive patients and demonstrates that good BP control can be achieved in the majority of hypertensive patients if a systematic effort is maintained. The LIFE trial adds important information regarding ARBs as an effective alternative to the other commonly used classes of antihypertensive drugs, particularly among patients with LVH, diabetes or isolated systolic hypertension. Finally, the CHEP will continue to produce and disseminate annually updated systematic reviews and recommendations related to the assessment and management of hypertension to serve as tools to improve hypertension control in Canada. ◆

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