Hypertension
Guidelines Revisited

Close to 25% of Canadians today are affected by hypertension, despite advancements in therapy and better education. Which agents are the most effective, and who will benefit?

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Danny's case

Danny, a 51-year-old smoker with left ventricular hypertrophy on ECG, is repeatedly diagnosed with stage I hypertension with a blood pressure averaging 155/95.

The usual screening investigations are unremarkable. His lipid profile shows a low density lipoprotein (LDL) of 3.4 mm/L, total cholesterol to high density lipoprotein (HDL) ratio of 5.5, and a routine urinalysis is negative for proteinuria.

What would you do for Danny?

For more on Danny, go to page 22.

Despite improved education and newer therapies, hypertension remains highly prevalent, affecting nearly 25% of the Canadian population. It predisposes patients to cardiac, cerebral, and peripheral vascular disease, remains a leading cause of renal dysfunction, and contributes to an exacerbation of declining cognitive function in the elderly.

The 2004 Canadian Hypertension Education Program (CHEP) recommendations represent the fifth annual update offering guidance in hypertension management. While some of the evidence appears to support previously held beliefs or strategies, recent findings have placed an emphasis on therapies not previously highlighted in hypertensive patients.

Co-morbidity of hypertension

Hypertension rarely occurs in isolation; of the 40% of treated hypertensive patients, 83% have concommittent illnesses. Many suffer from diabetes, hyperlipidemia, or both. According to data from the National Health and Nutrition Examination Survey (NHANES), 60% of those with diabetes have either hypertension (defined as a blood pressure > 130/85) or are on antihypertensive therapy.[1] That percentage increases with associated proteinuria. Therefore, the majority of patients with hypertension would be classified as having a compelling indication for specific therapy due to the identified co-morbidity.

The recommendations made by CHEP for the diabetic and hyperlipidemic patients are consistent with the Canadian Diabetic Association and the Working Group on Hyperlipidemia in regards to treatment thresholds and choice of therapy. The benefits of anti-atherosclerotic medication in the hypertensive population, in particular acetylsalicylic acid (ASA) and lipid-lowering agents, are also highlighted.

What agents should I use?

The choice of first-line agents for patients with

Followup on Danny

Since Danny doesn't have a significant, compelling indication of hypertension or a co-morbid condition, he could be placed on any of the usual classes of first-line therapy. Once his hypertension is controlled, he should also be placed on a daily dose of acetylsalicyclic acid.

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diastolic hypertension, without a compelling indication for specific therapy, remains similar to previous guidelines (Table 1). The majority of patients require combination therapy in order to reach targets.

The results of the Valsartan Antihypertensive Long-term Use Evaluation (VALUE) trial were recently released, comparing angiotensin receptor blocker/diuretic versus calcium blocker/diuretic combinations. There was no significant difference in the primary composite endpoint.

This study provides further evidence for the use of ARBs as first-line agents.

Diuretics or ACE inhibitors?

The Antihypertensive and Lipid Lowering treatment to prevent Heart Attack Trial (ALLHAT) was a randomized, double-blind, multi-centered trial involving 42,418 high risk hypertensive patients over 55, with one additional risk factor for coronary artery disease. The trial confirmed diuretics as important first-line agents. Some researchers even suggest diuretics are superior to angiotensin-converting enzyme (ACE) inhibitors.[2]

While significantly more patients reached target values in the diuretic group, a major criticism of the study was the inclusion of a high percentage (35%) of blacks, known to be less responsive to ACE inhibitor therapy. Despite their differences, the various regimes all showed similar primary outcomes.

The second Australian National Blood Pressure (ANBP-2) trial, was recently published involving 95% Caucasian patients. It demonstrated a significant reduction of the primary end point of cardiovascular death with ACE inhibitors as compared with diuretic therapy; an apparent contradiction to the ALLHAT trial.[4] As a result, a new recommendation from the CHEP report advises against the use of ACE inhibitors in first-line therapy for black patients.

Table 1

Available first-line agents

1. Diuretics
2. Beta-blockers
3. Calcium blockers
4. Angiotensin-converting enzyme inhibitor
5. Angiotensin receptor blockers in patients under age 60 (beta-blockers contra-indicated in those over 60)

Hypertension rarely occurs in isolation; of the 40% of treated hypertensive patients, 83% have con-committent illness.

Where does ASA fit in?

Another recommendation suggests physicians strongly consider the addition of low dose ASA to patients over 50 with controlled hypertension.

The Hypertension Optimal Treatment (HOT) study enrolled 18,790 hypertensive patients to assess optimal target diastolic blood pressure for prevention of cardiovascular events and to determine the impact of the addition of ASA to an anti-

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Revisiting Danny

Although Danny has left ventricular hypertrophy, current guidelines do not recommend any class of agent. There are comparative trials and metanalyses to suggest that ACE inhibitors and angiotensin receptor blockers offer significant regression in left ventricular hypertrophy as compared to other classes of agents. Although left ventricular hypertrophy is recognized as a risk factor for cardiovascular events, only observational data is available to suggest regression may result in a reduction of such events.

hypertensive treatment.[3] Those randomized to ASA had a significant reduction in major cardiovascular events without a significant increase in fatal bleeds. Exercise caution using ASA in patients with poorly controlled hypertension because of bleeding.

Is combination therapy the answer?

The Losartan Intervention For Endpoint reduction in hypertension (LIFE) trial compared the effects of losartin versus atenolol on cardiovascular morbidity and mortality in 9,193 patients aged 55 to 80 with hypertension (160-200/95-115) and ECG evidence of left ventricular hypertrophy. Extrapolation of data from the trial has led to the inclusion of angiotensin receptor blockers as first-line therapy in the CHEP guidelines.[7] The trial noted a 13% risk reduction for losartin as compared with atenolol in cardiovascular mortality, fatal/non-fatal myocardial infarction, and fatal/non-fatal cerebral vascular accidents.

Angiotensin receptor blockers are first-line therapy in CHEP guidelines.

One might ask, why extrapolate? The decision was based on the assumption that a significant proportion of patients with hypertension included in previous trials would also have left ventricular hypertrophy. While one criticism noted the study used beta-blockers, which are not considered effective first-line agents in patients over 60, the great majority in both the angiotensin receptor blocker and beta-blocker arms were on multiple drugs, with approximately 10% in each group achieving target with mono-therapy.

Combination therapy, with a complimentary mechanism of action for anti-hypertensives, remains a major recommendation as it enhances the antihypertensive effect and improves tolerability and compliance.

Table 2

Cardiovascular risk factors

1. Male
2. Age > 55
3. Left ventricular hypertrophy or other ECG abnormalities (i.e., left bundle branch block, abnormal Q waves or ST-T changes compatible with ischemic heart disease)
4. Previous cerebral vascular event
5. Peripheral vascular disease
6. Micro-albumin uria
7. Diabetes
8. Smoking
9. Family history of premature coronary artery disease

The scoop on lipid-lowering agents

There are three large, randomized, significant trials examining the role of lipid-lowering agents in the hypertensive patient:

- the Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm (ASCOT-LLA),
- the Prospective Study of Pravastatin in the Elderly at Risk (PROSPER), and

The ASCOT-LLA enrolled approximately 10,000 hypertensive patients, aged 40 to 79,

Take-home message

- Key CHEP recommendations:
  - Advise against the use of ACE inhibitors in first-line therapy for black patients;
  - Physicians are strongly recommended to consider the addition of low dose ASA to patients over age 50 with controlled hypertension;
  - Combination therapy remains recommended as it enhances antihypertensive effect, improves tolerability and compliance; and
  - Statin therapy is recommended in hypertensive hyperlipidemic pateitns with ≥ 3 cardiovascular risk factors.

with a total cholesterol > 6.5 mm/L (mean low density lipoprotein [LDL] 3.4 mm/L), and three other risk factors (Table 2).[4] Once a mean LDL reduction of 1.1 mm/L was achieved, a significant reduction in fatal and non-fatal myocardial infarction was noted after roughly three years. Stroke and total cardiovascular events were also significantly reduced. Benefits were irrespective of baseline total cholesterol values.

The PROSPER trial randomized nearly 6,000 patients, aged 75, with a history of vascular disease, or risk factors including hypertension.[5] After a median follow-up of 3.2 years, and a reduction of LDL by 1 mm/L, the primary end point (non-fatal myocardial infarction, fatal and non-fatal stroke and coronary death) were significantly reduced in both hypertensive and non-hypertensive patients.

Approximately 10% of patients in both ARB and beta-blocker arms achieved targets with mono-therapy.

The Heart Protection Study randomly assigned 20,000 patients, aged 40 to 80, with a mean LDL cholesterol of 3.4 mm/L, to placebo or statin.[6] Lowering LDL by a similar level as the two previous trials once again reduced all cause mortality and the composite end point of major vascular events.

Response to the trials

Based on the results of these three trials, involving 36,000 patients on three different statins, CHEP recommends statin therapy be considered in hypertensive hyperlipidemic patients with three or more cardiovascular risk factors in those with established cardiovascular disease.

What does the future hold?

Future research will evaluate various antihypertensive classes and their effect on regression of left ventricular hypertrophy, and how this might alter prognosis.

There will also be studies comparing which type of calcium blocker therapy (rate reducing vs. dihydropyridine calcium channel blocker) will be better tolerated in hypertensive patients with renal disease.

Currently, patients with diabetes and/or established coronary artery disease should be placed on ACE inhibitors. Ongoing studies will determine if ARBs also have a vascular-protective effect.

The guidelines for the management of hypertension require an annual review. Reiteration of important concepts, expert review, and critical appraisal of information from new trials allows for new recommendations and expansion of strategies to enhance management of the hypertensive patient.

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