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Scientific Update™

Reaching Optimal Blood Pressure: What is the Role of Fixed-Dose Combinations?

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Hypertension is the 3rd leading health risk associated with death worldwide. Despite compelling data linking high blood pressure (BP) to increased risk and the benefit of lowering of BP on clinical outcomes, rates of control of hypertension in Canada, at least based on the Canadian Heart Health Survey, remain poor. Achieving control of BP to target levels using pharmacologic agents is often difficult. Many trials have demonstrated that optimal control of BP requires the use of multiple agents. The most recent published (2001) Canadian recommendations have been updated, from an approach of replacing ineffective monotherapy with another drug, to adding a second drug from a class complementary in its antihypertensive mechanism to the first drug. As a great number of patients would require combination therapy, an attractive alternative approach to the extemporaneous method is to use fixed-dose combinations. In this issue of *Cardiology Scientific Update*, the epidemiology and current management recommendations of hypertension in Canada, the rationale for use of combination therapy, as well as the experience with fixed-dose combination therapy, will be reviewed.

The epidemiology of hypertension in Canada and its role in cardiovascular mortality

Elevated BP remains an important risk factor for stroke, coronary artery disease, heart failure, renal failure, peripheral vascular disease and dementia.[1] Based on the data from the World Health Organization (WHO) Burden of Disease Study,[2] hypertension accounts for 5.8% of mortality globally, immediately following malnutrition and tobacco use. In a recent comparison of the Canadian Heart Health Survey (CHHS) and the Third National Health and Nutrition Examination Survey (NHANES III) in the US,[3] the prevalence of hypertension, defined as systolic blood pressure (SBP) ≥ 140 mm Hg, or diastolic blood pressure (DBP) ≥ 90 mm Hg, was 21% in Canadians aged 18-74 years, similar to the US (20.1%). However, Canadians had a lower proportion of individuals (43% versus 50%) with optimal BP (<120/80 mm Hg) and of hypertensives under control (13% versus 25%). Among the diabetic participants, the level of control in Canada was especially low (9%) compared to US (36%). To determine the proportion of hypertensive patients who are appropriately managed according to the 2001 Canadian Hypertension Recommendations, data from the CHHS were used to determine the proportion of nondiabetic hypertensive patients who are managed according to the 2001 recommendations.[4] Patients who are not recommended for therapy are excluded from the analysis. Based on the recommendations, 25% of hypertensive Canadians in CHHS would not be recommended to receive treatment based on the 2001 Canadian recommendations. Only 16% of hypertensives were treated and had their BP controlled to less than 140/90 mm Hg.

Hypertension has traditionally been defined by level of BP. The risk of cardiovascular (CV) events associated with a given level of BP increases with the number of risk factors.[5] Accordingly, optimal BP thresholds and targets for treatment for individual patients depends on overall CV risk. They may need to be defined even within what is traditionally been considered the "normal" range. Many patients present with a variety of risk factors. Guidelines that define treatment thresholds on the basis of absolute or multifactor risk will best provide *integrated* information for clinicians. Several studies have indicated that physicians are unable to estimate risk accurately without assessment aids.[6] Risk assessment tools based on the Framingham Heart Study have been developed that include devices from paper charts to electronic calculators.[7]

Results of recent clinical trials have led to a lowering of threshold for therapy initiation and targets of optimal BP controls.[8-10] Table 1 lists the inclusion BP criteria in several large clinical trials, a reflection of the perception that a BP level below which treatment is associated with more good than harm.[9,11-14] While some trials

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Table 1: Blood pressure entry criteria of major clinical trials

BP level below which treatment was perceived to be associated with more good than harm	
• INSIGHT	BP ≥ 160/or/95
• LIFE	BP 160-200/or/95-115
• SYST-EUR	SBP ≥ 160-219
• STOP Hypertension-2	BP ≥ 180/or/105
• ALLHAT	BP ≥ 140/or/90
• PROGRESS	No BP criteria

recruited patients with high BP, others recruited those with only modestly elevated BP or with no BP entry criteria at all.[11,14]

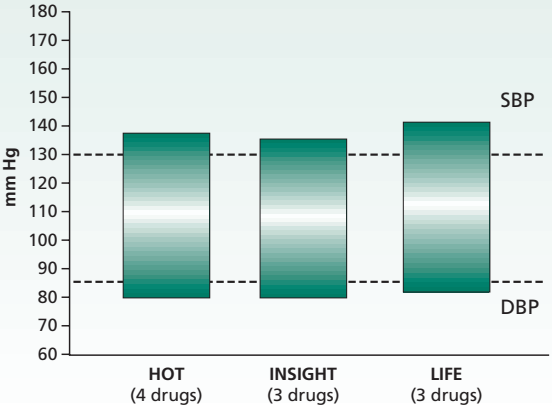
Canada and the world: What do the Guidelines Say?

Guidelines and recommendations for the management of hypertension are widely available. For example, the Canadian recommendations for the management of hypertension have been updated yearly since 1999, with the 2002 recommendations available soon. Recommendations for *initiating drug therapy* for hypertension differ between countries. Based on the 2001 Canadian recommendations, the British Hypertension Society, and the WHO-International Society of Hypertension (WHO/HIS) guidelines,[5,15-17] drug therapy is not recommended for "low risk" patients. On the other hand, the sixth report of the Joint National Committee (JNC-VI) in the US recommended drug treatment if lifestyle modification is unsuccessful.[18]

There is substantial evidence that the existing guidelines and recommendations do not achieve their objectives.[4,19,20] This gap may be due to factors related to both health care deliverer and consumers, as well as the guidelines themselves. Health care deliverers are definitely important as some physicians are either unfamiliar with existing recommendations or are unconvinced of their validity. In an analysis of NHANES III,[21] 27% of the population had hypertension, but only 23% of those with hypertension were taking medications that controlled their BP. The great majority had health insurance. In subjects with untreated or uncontrolled hypertension, the pattern was an elevation in the SBP with a DBP of less than 90 mm Hg. Independent predictors of a lack of awareness of hypertension were age >65 years, male sex, non-Hispanic black race, and not having visited a physician within the preceding 12 months. These findings therefore suggest that most cases of uncontrolled hypertension consist of isolated, mild systolic hypertension in older adults, most of whom actually have access to health care and relatively frequent contact with physicians.

To link process measures of healthcare delivery to BP outcomes, a quality measurement system was developed and tested on hypertensive women in a US west coast health plan.[19] Thirteen indicators were selected by this process. The average woman received 64% of the recommended care, most patients did not receive an adequate initial history, physical examination, or laboratory tests, and only 37% of hypertensive women with persistent elevations to >160/90 mm Hg had changes in therapy or lifestyle modifications. The average adherence proportion to all indicators was lower in patients with uncontrolled BP. These results underscore the role of the process of healthcare delivery in the failure to adequately control BP.

Figure 1: Achieved target blood pressure and number of drugs required



SBP = systolic blood pressure DBP = diastolic blood pressure

Besides the healthcare deliverers, the consumers (ie, the patients) also play an important role in the gap between the guidelines and BP control. Poor compliance, presumably due to side effects of drugs, inconvenient dosing schedules, and the frequent need for multiple drugs, is the major factor.[22,23] Indeed, several large scale clinical trials have demonstrated that a great number of patients require 3 or more drugs in order to achieve optimal BP control (Figure 1).[9,12,13] In the Hypertension Optimal Treatment (HOT) study, to achieve a target DBP of ≤ 90, 85, and 80 mm Hg, 63, 68, and 74% of patients, respectively, needed to use multiple drugs.[9]

Given the fact that a high dose of a single agent may be associated with unacceptable side effects and the risk of poor compliance associated with the use of multiple agents, an attractive approach may be to utilize fixed low-dose combinations. Combining agents acting by different mechanisms is more likely to obtain antihypertensive efficacy. Furthermore, low doses of agents are generally sufficient when used in combination, which explains the excellent tolerability of combination products.[24] Fixed-dose drug combinations also enhance the simplicity of treatment regimens, allowing a reduced number of tablets, thus improving compliance. Finally, the price of fixed-dose drug combinations is lower as compared to extemporaneous combinations.

What is the status of fixed-dose as compared to an extemporaneous form of combination therapy from the perspective of current guidelines/recommendations? Over all, the fixed-dose approach is considered in JNC-VI,[18] the BHS guidelines for hypertension management (1999),[17] as well as the WHO-ISH guidelines.[5,25] JNC-VI clearly recommends fixed-dose combinations in low doses as initial therapy.[18] The BHS also considers fixed-dose combinations as a valid approach when monotherapy is ineffective, individual drug components are appropriate, and there are no major cost implications.[17] A very similar position is taken by the WHO/ISH in their guidelines.[5] In the most recently published (2001) Canadian recommendations, the old approach of replacing ineffective monotherapy with another drug from a different class has been updated to include as an alternative option, the addition of a second drug from a class that is complementary in its antihypertensive mechanism to the first drug.[16] Fixed-dose combinations have not been addressed in the Canadian

Table 2: Combination therapy for hypertension: A historical perspective	
1950s	Potent monotherapy (side effects +++)
1960s	SER – AP – ES
1970s	Aldactazide Dyazide Aldoril
1980s	Inderide Tenorectic Combipres

This table is provided courtesy of Dr. Martin Myers

recommendations (and are unlikely to be addressed in the upcoming 2002 recommendations based on a recent presentation by the Canadian Hypertension Recommendations Working Group), presumably due to the fact that the Canadian recommendations are heavily based on clinical evidence.

Fixed-dose combinations – What are the options?

Combination therapy for hypertension has been present since the 1950s. As shown in Table 2, SER-AP-ES, – consisting of reserpine, hydralazine and hydrochlorothiazide – was one of the most popular antihypertensive agents in the 1960s. In 1970s, physicians prescribed potassium-sparing diuretics in combination with a thiazide. In both circumstances, the combination was selected on basis of complementary effects of the components, to either enhance antihypertensive effects and/or to minimize hypokalemia. By the 1980s, the thiazide diuretics were combined with the then "newer agents" such as the ß-blockers. The most recent combination based on scientific rationale is the combination of angiotensin converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARBs) with thiazides.

As reviewed earlier, aside from patients with mild elevation of BP, most will require multiple agents in order to achieve optimal BP control. The debate on the superiority of one agent such as an ACEI, over another such as a diuretic, is almost a moot point, given that both agents are likely required to obtain optimal BP control.

Currently available ACEI + thiazide combinations include combinations of hydrochlorothiazide with captopril, enalapril, lisinopril, benazepril and quinapril. Formulation of a fixed-dose combination requires meticulous multiple dose-response studies consisting of a matrix of various combinations. One such example of the detailed dose-response studies required for the development of fixed-dose combination therapy as first-line therapy is the combination of the ACEI, perindopril, and the sulfonamide diuretic, indapamide.

Dose response study of perindopril and indapamide

A multinational, randomized, double-blind comparison of perindopril (Per) and indapamide (Ind) versus placebo was performed using a 7-way parallel-group design.[26] A total of 438 patients with supine DBP between 95 and 114 mm Hg (Europe) and between 95 and 109 mm Hg (Canada) were randomized to 8-week treatment: with:

- Placebo
- Per 0/Ind 1.25 mg
- Per 2/Ind 1.25 mg
- Per 8/Ind 1.25 mg
- Per 2/Ind 0.625 mg
- Per 4/Ind 1.25 mg
- Per 8/Ind 2.5 mg

These combinations were designed to explore the impact of doubling the dose of Per 2/Ind 0.625 mg up to Per 8/Ind 2.5 mg, as well as increasing the doses of perindopril from 0 to 8 mg in combination with fixed-dose of indapamide at 1.25 mg daily. A 4-week placebo period preceded the randomization. The primary efficacy outcome was the change from baseline in clinic supine DBP measured 24 hours after the previous dose. Secondary outcomes included the changes in supine SBP, standing BP, ambulatory BP, and response rate.

The 7 groups of patients were comparable in their baseline BP. The effects of doubling the dose of perindopril and indapamide and increasing doses of perindopril in combination with fixed-dose of indapamide are shown in Figures 2A and 2B respectively. As shown in Figure 2A, doubling the dose of perindopril and indapamide resulted in a progressively greater decline in SBP and DBP (all $p < 0.05$ versus placebo). Similarly, as shown in Figure 2B, doubling the dose of perindopril combined with a fixed-dose of indapamide was also associated with a progressively greater decline in SBP and DBP (all $p < 0.05$ versus placebo). Similar patterns of dose-dependent decline in BP were observed in standing

Figure 2a: Effect of increasing doses of perindopril and indapamide[26]

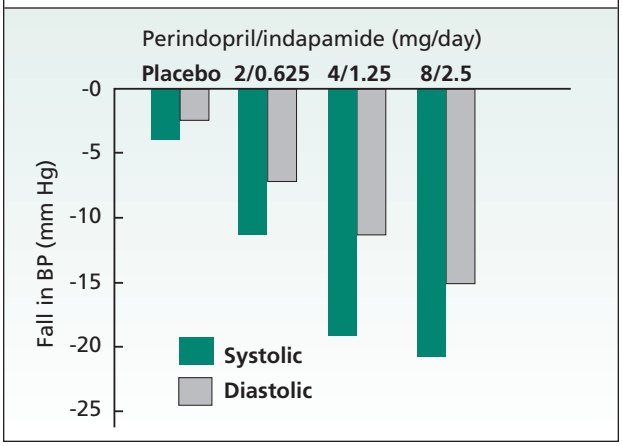


Figure 2b: Effect of increasing doses of perindopril with fixed dose of indapamide[26]

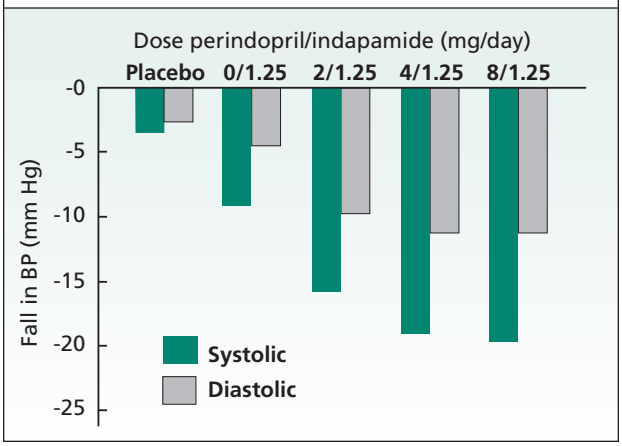
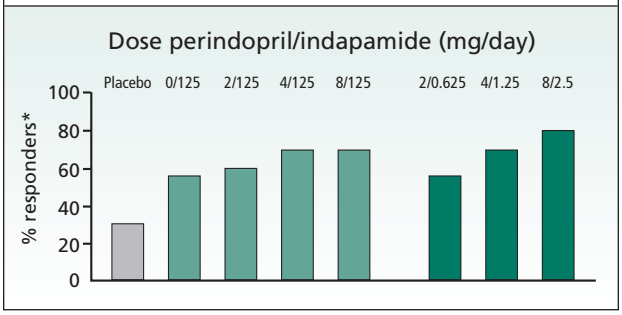


Figure 3: Responder rates in each treatment group[26]



* Decrease of DBP ≥10 mm Hg and/or final supine DBP ≤ 90 mm Hg

BP and 24-hour ambulatory BP. Rates of response based on predefined criteria are shown in Figure 3. For both types of combinations, the percent of patients who responded increased in a dose-dependent manner. Hypokalemia, (defined as serum potassium <3.4 mmol/l) at week 4 was most frequent in the Per 8/Ind 2.5 mg group, occurring in 8 of the 64 patients. The incidence of hypokalemia at any time during the randomization period varied between 0% and 4.6% for all combinations with the exception of Per 8/Ind 2.5 mg, which had an incidence of 9.7%.

In previous studies, low-dose indapamide has been shown to be efficacious in the treatment of patients with mild to moderate hypertension, including those with impaired renal function.[27,28] Furthermore, indapamide reduces left ventricular hypertrophy and microalbuminuria[29,30] and appears to have no adverse effects on the lipid profile, an effect that has been observed with the thiazides.[31] Both 2 and 4 mg of perindopril,[32] as well as 1.25 and 2.5 mg of indapamide,[33-34] have been shown to significantly reduce placebo-corrected supine BP. Compared with these previous studies, the combination of perindopril and indapamide produces a greater decline in BP. Furthermore, both indapamide and the combination of perindopril and indapamide have been demonstrated to reduce the incidence of recurrent stroke,[11,35] a beneficial effect thought to be related to BP control.

Balancing the antihypertensive and hypokalemic effects, together with the observation that the addition of 0.625 mg of indapamide to 4 mg perindopril did not substantially increase the responder rate, suggest that Per 2/ind 0.625 mg and Per 4/Ind 1.25 mg daily are likely the optimal combinations for clinical use.

In summary, fixed low-dose combinations are potentially powerful tools for treating hypertensive patients. Because of their simplicity of use, and the fact that they improve the BP response rate while minimizing the incidence of adverse effects, such combinations are increasingly being considered as suitable for both second-line and first-line therapy in patients with hypertension.

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