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Management of hypertension in the late 1990s

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The status of hypertension management in this decade allows us some grounds for optimism. We have entered an accelerated phase of large randomized clinical trials that have provided, or are in the process of investigating, the answers to important clinical questions in hypertension. Not only are there short-term clinical studies of new agents or combinations that assess surrogate endpoints, several large clinical trials have also recently evaluated the effects of hypertension treatment on major clinical events. These recent large trials have assessed, among other important issues, the treatment of isolated systolic hypertension, the effects of angiotensin-converting enzyme (ACE) inhibitors compared to traditional agents such as beta-blockers, the use of combination therapy to aggressively lower blood pressure to specific diastolic targets, and the role of different antihypertensive therapies in diabetic patients. Ongoing trials with thousands of patients enrolled will provide important answers about the new antihypertensive agents in addition to other drugs that, while not considered new anymore, are still considered by national guidelines to be important second-line medications.

Hypertension management: current knowledge

Much has been accomplished in the 1990s based on the solid foundation of research from previous decades. This can be illustrated by a recent report from the Framingham Heart Study which followed a total of 10,333 patients between 45 and 74 years of age. During the course of the study (between 1950 and 1989), subjects underwent more than 50,000 examinations.[1] In those four decades, the rate of use of antihypertensive medications increased from 2.3% to 24.6% among men, and from 5.7% to 27.7% among women. At the same time, the age-adjusted prevalence of systolic blood pressure (SBP) of >160 mm Hg or diastolic blood pressure (DBP) of >100 mm Hg decreased from 18.5% to 9.2% among men and from 28.0% to 7.7% among women. This decrease was accompanied by reduced rates of electrocardiographic (ECG) evidence of left ventricular hypertrophy (LVH), from 4.5% to 2.5% among men and from 3.6% to 1.1% among women. Since LVH was shown to be an independent risk factor in the Framingham population, these improvements would be expected to result in significantly better clinical outcomes. In fact, the authors of the study concluded that the increasing use of antihypertensive medications appears to have led to a reduced prevalence of hypertension and a concomitant decline in LVH in the general population that could help explain the considerable decline in mortality from cardiovascular disease observed since the late 1960s.

Well-deserved enthusiasm for the accomplishments of the past must be tempered, however, by more sobering results from other studies. Recent national and international guidelines now call for more stringent criteria for the definition of hypertension and for the targets that must be achieved so that hypertensive patients, particularly those with multiple risks, receive the highest level of protection. Practically all experts would agree, for instance, that the 160 mm Hg SBP and the 100 mm Hg DBP levels evaluated in the aforementioned study would now be unacceptable. Most current guidelines call for a diagnosis of hypertension at considerably lower levels. When stricter definitions are used, a more dismal picture emerges – even in countries with advanced medical systems like Canada and the United States.

Warnings from the Canadian Heart Health Surveys

The Canadian Heart Health Surveys were conducted in all Canadian provinces between 1986 and 1992. These population-based assessments of cardiovascular disease risk factors examined hyperten-

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sion awareness, treatment, and control in more than 23,000 randomly selected individuals between the ages of 18 and 74.[2] With hypertension defined as a SBP/DBP ≥ 140/90 mm Hg, 22% of Canadians (26% of men and 18% of women) were found to be hypertensive. Only 16% of hypertensive individuals were being treated and were controlled (BP < 140/90 mm Hg), while 23% were treated and not controlled, 19% were not treated and not controlled, and 42% were not even aware of their hypertension. Thus, even in a system such as ours in which citizens frequently interact with healthcare professionals, far too many Canadians are not well controlled or remain unaware of their hypertension.

American situation mirrors that of Canada

The trends in prevalence, awareness, treatment, and control of hypertension in the United States population are similar. These were reported by the National Health and Nutrition Examination Surveys III (NHANES III) which were carried out between 1988 and 1991. Using the definition of hypertension as a BP > 140/90 mm Hg, 24% of the population of the US was found to have high BP and, while 69% were aware of their condition, only 53% were being treated with antihypertensive medications and only 29% were adequately controlled.[3] Although these figures represented some improvement since the previous surveys, it could hardly be argued that hypertension management has been optimal.

The decline in the incidence of stroke associated with hypertension has leveled off in the 1990s and there is disturbing recent evidence that some ground has been lost and that the incidence of stroke may actually be increasing. As well, it is clear that hypertension precedes heart failure in a large percentage of cases and that the incidence of heart failure, as well as end-stage renal disease associated with hypertension, is increasing rapidly and will consume growing segments of our health care budgets.

In a recent report that details the magnitude of the present problem without ignoring the significant progress of the last few decades, the National Heart, Lung, and Blood Institute of the United States has issued a "call to action for more aggressive treatment of hypertension" with an emphasis on the elderly and other hard-to-treat populations.[4] In this report, the authors also emphasize that the United States is destined to fall far short of its announced target of controlling 50% of hypertensive individuals by the year 2000.

Patient compliance with antihypertensive therapy

There is a well justified consensus that the decisions that we make daily in our practices should be based on the best possible evidence. Clinical guidelines for the management of hypertension follow evidence derived from clinical trials that allows us to recommend agents that should be first line and those that should be used subsequently. It is therefore disappointing that, while we try to make the most rational decisions about our choice of therapy, the state of hypertension control remains unsatisfactory. This forces us to search for clues to explain why it has been difficult to translate the results of clinical trials into better results in clinical practice. To some extent this may be due to the fact that many trials do not necessarily reflect the day-to-day conditions encountered in clinical practice in which issues of compliance and persistence with the prescribed medication become magnified.

A recent study conducted in Canada evaluated a cohort of patients, identified through the Saskatchewan Health Databases, who were diagnosed with hypertension and were treated between 1989 and 1994. After excluding patients with concurrent diagnoses likely to affect the choice of the initial drug, the investigators identified 79,591 patients, 66% of whom had established hypertension and 34% who were newly diagnosed. The study found that persistence with antihypertensive therapy decreased in the first six months after initiation of treatment and continued to decline over the following four years. Only 78% of patients with newly diagnosed hypertension persisted with therapy at the end of one year compared with 97% of patients with established hypertension ($p<0.001$). Among the patients with newly diagnosed hypertension, older patients and women were more likely to continue with their therapy. The investigators concluded that the barriers to long-term compliance appeared early and that achieving successful therapeutic goals early in treatment is crucial to maintaining long-term persistence with therapy.[5]

In a related study, the same investigators evaluated the effect of initial drug choice on compliance using data from actual clinical practice. All outpatient prescriptions for antihypertensive medications filled in Saskatchewan between 1989 and 1994 by more than 22,000 patients were examined. After six months, persistence with therapy was rather poor and, interestingly, differed significantly according to the class of therapeutic agent initially prescribed. Compliance was lowest with diuretics (80% at one year) and beta-blockers (85% at one year). Calcium channel blockers were slightly better at 86% while ACE inhibitors were the best at 89%. These differences remained significant after correction for age, sex, and health status during the previous year.[6] After analyzing a number of potential confounders the investigators concluded that compliance was not related to cost, as diuretics are the least expensive and were associated with the lowest persistence. The differences could be due to class-related side effects; the higher rates of persistence seen with ACE inhibitors could be explained by their better tolerability. Interestingly, the first-line drugs, diuretics and beta-blockers, had the lowest compliance rates. This should cause us to reflect on our guidelines and whether our initial choices of medications, justified as they are by the evidence of clinical trials, may need some re-evaluation. It seems clear that these first-line agents have served us well, as evidenced by the progress that we have made. But if these drugs have reached a ceiling in tolerability or effectiveness, we owe it to our patients to examine carefully – and with an open mind – the growing evidence from the newer classes of drugs. It is possi-

ble that they can help us overcome the compliance barriers that we continue to face and that prevent us from advancing further in the management of hypertension.

We must also remember that beta-blockers are not the appropriate first-line therapy for hypertension in the elderly, which is the fastest growing hypertensive population in North America. Indeed, a recent analysis that evaluated all randomized trials lasting at least one year found that beta-blockers did not reduce all-cause mortality, myocardial infarctions, or cardiovascular mortality in patients over 60 years of age.[7] This indicates, perhaps surprisingly in view of our experience with secondary prevention of myocardial infarction, that beta-blockers have no primary cardioprotective effect in the elderly hypertensive. In contrast, all of these major clinical endpoints were reduced by diuretics.

It is also worth keeping in mind recent reports that chronic diuretic therapy increases the risk of renal carcinoma. The association between diuretic therapy and renal cell carcinoma was reported in nine case-controlled studies that showed there was an increased risk of about 55%. As well, in three large cohort studies with a total of more than one million patients, the risk of renal cell carcinoma was approximately doubled by diuretic therapy. Despite possible methodological limitations, these data are of concern as they could represent a dark cloud in what has otherwise been the clear horizon of the efficiency of diuretics in reducing cardiovascular mortality and morbidity in hypertension. They should also be viewed in the context of reports that antagonism of the renin-angiotensin system (RAS) with ACE inhibitors may actually decrease all-cause mortality from malignancies.[8]

New 1999 hypertension guidelines

The recently published World Health Organization - International Society of Hypertension guidelines recognized the confusion about the relationship between blood pressure and the risk of cardiovascular events, as well as the arbitrary nature of defining high blood pressure, that contributes to the variability in the definitions established by different national and international guidelines. Consequently, the WHO-ISH adopted the definition and classification of JNC VI, the latest guidelines originating in the United States. This new definition defines the lower limits of hypertension as SBP 140 mm Hg and DBP 90 mm Hg. High-normal is defined as SBP 130-139 and DBP 85-89 mm Hg, whereas normal BP is defined as SBP <130 mm Hg and DBP <85 mm Hg (Table 1). When a patient's SBP and DBP fall into different categories, the higher category should apply; this underscores the importance of systolic hypertension as a significant risk factor.[9]

The WHO-ISH guidelines also advocate, as did the JNC VI guidelines, that the overall burden of the patient's risk factors should determine the aggressiveness of the therapeutic targets. While being stricter with the definitions and targets, the new WHO-ISH guidelines are much more liberal in their approach to the choice of antihypertensive agents and shy away from an explicit stepped-care approach. On the contrary, the statement is made that all classes of antihypertensive drugs have specific advantages and disadvantages for particular patient groups, and that so far there is no incontrovertible evidence that the main benefits of treating hypertension are due to the specific properties of any particular drug class rather than the lowering of blood pressure *per se*. However, it is also recognized that most individual studies have been too small to detect relatively modest differences in major clinical outcomes, such as stroke or myocardial infarction.

Table 1: Definitions and classification of blood pressure levels

Category	Systolic (mm Hg)	Diastolic (mm Hg)
Optimal	<120	<80
Normal	<130	<85
High - normal	130-139	85-89
Grade 1 hypertension ("mild")	140-159	90-99
Subgroup: Borderline	140-149	90-94
Grade 2 hypertension ("moderate")	160-179	100-109
Grade 3 hypertension ("severe")	≥180	≥110
Isolated systolic hypertension	≥140	<90
Subgroup: Borderline	140-149	<90

The WHO-ISH guidelines are, therefore, more flexible and forward-looking in providing guidance to physicians in terms of their choice of medications (Table 2). Diuretics are recommended, for instance, in patients with heart failure, the elderly, and in patients with systolic hypertension. Beta-blockers can be used in patients with angina and after myocardial infarction. ACE inhibitors are the recommended drugs for patients with heart failure, left ventricular dysfunction, or after myocardial infarction, to cite only a few examples.

A new class of antihypertensive agents: the angiotensin II receptor antagonists

Much remains to be done to achieve an adequate control of arterial hypertension and its often devastating consequences. The addition of a safe and effective new family of antihypertensive medications is, therefore, most welcome, especially if this new drug class is likely to represent a significant improvement to our present options. With the growing recognition of the importance of the RAS (particularly the tissue RAS) in target organ damage in hypertension, the development of alternatives for blocking angiotensin II is likely to

Table 2: Guidelines for selecting drug treatment of hypertension

Class of drug	Compelling indications	Possible indications	Compelling contraindications	Possible contraindications
Diuretics	Heart failure Elderly patients Systolic hypertension	Diabetes	Gout	Dyslipidemia Sexually active males
Beta-blockers	Angina After myocardial infarction Tachyarrhythmias	Heart failure Pregnancy Diabetes	Asthma and chronic obstructive pulmonary disease Heart block[a]	Dyslipidaemia Athletes and physically active patients Peripheral vascular disease
ACE inhibitors	Heart failure Left ventricular dysfunction After myocardial infarction Diabetic nephropathy		Pregnancy Hyperkalaemia	Bilateral renal artery stenosis
Calcium antagonists	Angina Elderly patients Systolic hypertension	Peripheral vascular disease	Heart block[b]	Congestive heart failure[c]
Alpha-blockers	Prostatic hypertrophy	Glucose intolerance Dyslipidemia		Orthostatic hypotension
Angiotensin II antagonists	ACE inhibitor cough	Heart failure	Pregnancy Bilateral renal artery stenosis Hyperkalemia	

[a] Grade 2 or 3 atrioventricular block
[b] Grade 2 or 3 atrioventricular block with verapamil or diltiazem
[c] Verapamil or diltiazem

have a significant impact. The angiotensin II peptide is not only a potent vasoconstrictor, but at the tissue level is known to be crucially involved in the processes that lead to cardiac hypertrophy, vascular remodeling, and glomerulosclerosis, some of the most important manifestations of target organ damage in hypertension.

There are various enzymatic pathways that can generate angiotensin II from its precursors independent of ACE. Therefore, the arrival of the angiotensin II AT_1 receptor blockers (ARBs) is particularly noteworthy because they can more effectively prevent angiotensin II activity regardless of the pathway by which it is generated. ARB management could result in greater suppression of the effects of RAS activation and greater target organ protection, although this has yet to be established definitively in clinical trials. One aspect in which the ARBs clearly outperform ACE inhibitors is in their tolerability. With ACE inhibitors, a substantial percentage of patients suffer side-effects, particularly persistent dry cough, that often deny these patients the proven benefits of this class of drugs. Affected patients are reported to be in the range of 5-15%; the incidence has been reported to be higher in African-Americans[10] and more women than men report persistant cough.[11] while in ethnic Chinese populations the incidence of ACE-inhibitor-related cough has been reported to be as high as 30%.[12] In contrast, all studies with ARBs have found that this class of drugs has placebo-like tolerability with no particular or common side-effects. In this respect, the ARBs are not only superior to ACE inhibitors but to diuretics, calcium channel blockers and beta-blockers as well.

Because of their potential to effect a more complete blockade of the RAS, and because of their excellent tolerability profile, the ARBs appear to be ideally positioned to become important new agents in the management not only of hypertension but of heart failure as well. Several large, multicenter, randomized clinical trials are presently underway to assess the role of ARBs in the management of hypertension, heart failure, and renal disease, and to measure their impact on major clinical endpoints such as morbidity and mortality. The results of these trials are several years away. In the meantime, clinicians may want to consider the reported evidence of differences in pharmacokinetic and clinical profiles when selecting one of these new drugs.

Clinical and pharmacokinetic differences between the ARBs

Presently, there are four ARBs available in Canada: losartan, valsartan, candesartan, and irbesartan. More are due for approval in the near future. Several comparative trials of the AT_1 receptor antagonists have been published or reported to date. In one study, the antihypertensive efficacy of valsartan and losartan were compared in 1348 patients with mild to moderate hypertension.[13] The patients were randomized to three treatment groups: valsartan 80 mg (n=545), losartan 50 mg once daily (n=534), or placebo (n=269). No significant differences were seen in the mean reduction of blood pressure at four weeks between the two agents. Subsequently, the drugs were titrated to valsartan 160 mg and losartan 100 mg, the highest recommended doses for both

agents. At eight weeks, there was again no significant difference in mean blood pressure lowering between the drugs, although the response rate was significantly better with valsartan (62% versus 55% with losartan, p=0.021).

Another study compared the antihypertensive efficacy of losartan versus irbesartan. This multicentre, international, double-blind, placebo-controlled study randomized 567 patients to one of four groups: losartan 100 mg once daily (the maximum recommended dose of this agent), irbesartan 150 mg or 300 mg daily, or placebo. The baseline seated SBP and DBP were comparable in the four groups, with a mean of 154/101 mm Hg. After eight weeks, there was no statistically significant difference in blood pressure lowering between the recommended starting dose of irbesartan (150 mg) and the maximum recommended dose of losartan (100 mg). However, irbesartan 300 mg achieved significantly greater SBP and DBP reductions than losartan. Indeed, at eight weeks the differences were -11.7 mm Hg for irbesartan versus -8.7 mm Hg for losartan in DBP reduction ($p<0.01$), and -16.4 mm Hg versus -11.3 mm Hg, respectively, for SBP reduction ($p<0.01$). The differences amount to a remarkable advantage of irbesartan over losartan of 35% and 45%, respectively, for DBP and SBP reduction.[14]

Monotherapy vs combination therapy

In clinical practice, some patients will be controlled with monotherapy whereas others, perhaps most, will require further titration of their initial agent and the addition of other medications. A recently published comparative trial comparing irbesartan and losartan was designed to correspond to the pattern of elective titration more likely to be employed in clinical practice.[15] After a three-week, single-blind, placebo lead-in period, 432 patients with seated DBP of 95-115 mm Hg were randomized to receive irbesartan 150 mg daily or losartan 50 mg daily. The dosages were increased as necessary at week four to irbesartan 300 mg or losartan 100 mg if trough seated DBP was still >90 mm Hg. The same parameter was used at week eight to decide on the addition of hydrochlorothiazide. At this time, the mean reduction in seated DBP was greater in the irbesartan monotherapy group by 2.3 mm Hg ($p<0.02$). This significant difference between the two treatment groups continued into week 12 of the study when the difference was 3.0 mm Hg in favor of the irbesartan regimen ($p<0.002$). The reduction of SBP was also greater with irbesartan than with losartan whereas the percentage of patients requiring the addition of hydrochlorothiazide was lower.

A recently published eight-week study compared the antihypertensive efficacy of the usual starting dose of losartan, 50 mg, with two different doses of candesartan, 8 and 16 mg.[16] This randomized, placebo-controlled, double-blind study included 337 patients with mild to moderate hypertension. There was no difference in SBP between the usual starting dose of losartan and either dose of candesartan. Only the highest dose of candesartan achieved a greater reduction of DBP (-3.7 mm Hg compared to losartan, p=0.013). No other direct comparisons between these agents have been published to date.

Pharmacokinetic differences among the ARBs

All of the available ARBs exhibit excellent selectivity for the AT_1 receptor over other angiotensin receptors. There are, however, pharmacokinetic differences that may be clinically important. Irbesartan and valsartan do not require biotransformation for their pharmacologic activity as they are already active drugs. In contrast, much of the inhibitory properties of losartan and candesartan are mediated by their active metabolites, EXP 3174 and CV-11974, respectively. The major routes of metabolism of irbesartan are glucuronidation and oxidation; the cytochrome P450 isoform 2C9 is the primary pathway for oxidation. Metabolism by the cytochrome P450 isoform 3A4 is negligible, which minimizes the potential for significant drug interactions. As well, irbesartan has the longest half-life, 11-15 hours, of the four agents available in Canada. This is substantially longer than losartan, valsartan and candesartan, all of which are in the range of 5-9 hours. The oral absorption of irbesartan is rapid and complete resulting in an average absolute bioavailability of 60%-80% which compares very favorably to losartan (33%), valsartan (23%), and candesartan (15%). Food does not compromise the bioavailability of irbesartan whereas it decreases the area under the concentration-time curve (AUC) of valsartan by 40% and reduces the maximum concentration by 50%. The absorption of losartan is also slightly delayed by food.

Irbesartan exhibits potent, dose-related, insurmountable antagonism of the AT_1 receptor. This means that even the highest concentrations of angiotensin II tested *in vitro*, at levels that are unlikely to be present in clinically relevant situations, cannot restore fully the maximal contractile response of the blood vessel when the AT_1 receptor is blocked by irbesartan. Two additional distinctive characteristics of irbesartan are that it exhibits the highest plasma free-fraction and volume of distribution in its class. The former property, at 10%, minimizes the potential for interactions with highly protein-bound drugs. Losartan and its metabolite EXP 3174, as well as valsartan and candesartan, are more highly bound to plasma proteins. Irbesartan's volume of distribution, at 53-93 L, is several-fold higher than the other agents and their active metabolites, theoretically allowing irbesartan to access a higher number of AT_1 receptor sites than all the other drugs in its class (Table 3).

Conclusions

As the last year of the millennium draws to a close, much has been accomplished in the management of

TABLE 3: Comparative pharmacokinetics

Angiotensin II AT_1 receptor blockers						
Compound (active metabolite)	**Active metabolite**	**Half-life (h)**	**Bio-availability**	**Volume of distribution (L)**	**Food effect**	**Dosing (mg)**
Irbesartan[1]	No	11-15	60-80%	53-93	No	150-300 od
Losartan[2] **EXP 3174**[3]	Yes	2 6-9	33%	34 12	Minimal	50-100 od
Valsartan[4]	No	5-9	23%	17	Yes ↓ 46%	80-160 od
Candesartan[5]	Prodrug	9	15%	9	No	8-16 od

1 Avapro* (irbesartan) Product Monograph
2 Cozaar® (losartan) Product Monograph
3 Active metabolite of losartan
4 Diovan® (valsartan) Product Monograph
5 Atacand® (candesartan) Product Monograph

hypertension, but much more remains to be done. After so many decades of unrelenting progress, the stabilization, at best, or even worsening of our results sounds a loud alarm that should prompt us to join the call to action for more aggressive treatment of hypertension. New information that is becoming available from surveys and clinical trials allows us to examine our shortcomings closely. Given the seriousness of the situation, we must scrutinize every aspect of hypertension therapy, including current therapeutic guidelines and their possible consequences. The evidence emerging from randomized clinical trials should facilitate a rational re-evaluation of our strategies. Indeed, the WHO-ISH guidelines are a welcome and refreshing step forward with their call for more aggressive definitions and targets and their flexibility in the choice of therapeutic agents. The development of the ARB has provided us with the potential to effect a more complete blockade of the RAS with better tolerability than that now offered by ACE inhibitors, although the indications for this new therapeutic class will only be defined after the ongoing clinical trials are completed.

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