The value of lowering blood pressure

Jacques LeLorier MD PhD FRCPC

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According to the Canadian Heart Health Survey, only 14% of Canadian hypertensive patients are aware of their disease and are treated appropriately. One of the reasons for this could be that physicians are confused by an excess of confusing and contradictory information regarding the choice of drugs. Two recent publications may contribute to a much-needed simplification of the problem. The Blood Pressure Lowering Treatment Trialists' Collaboration published a meta-analysis based on 29 randomized trials that comprised a total of more than 162,000 participants. The treatment regimens were based on angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, diuretics, beta-blockers and calcium channel blockers. The main finding of the meta-analysis was that treatment with any of the blood pressure-lowering regimens reduced the risk of major cardiovascular events, and the extent of these risk reductions was directly related to the degree of blood pressure lowering.

The Valsartan Antihypertensive Long-term Use Evaluation (VALUE) compared valsartan with amlodipine. At the end of the study, the reductions in blood pressure from baseline were 17.3/9.9 mmHg in the amlodipine group and 15.2/8.2 mmHg in the valsartan group ($P < 0.0001$). There was a significantly lower incidence of myocardial infarction in the amlodipine group (4.1%) than in the valsartan group (4.8%). From these two studies, it would be reasonable to conclude that the treatment of elevated blood pressure has two main goals: to achieve a normal blood pressure and to produce a happy patient. The agent or agents used to obtain these goals are relatively unimportant.

Key Words: *Coronary artery disease; Hypertension; Stroke*

Two recent papers, a clinical trial (1) and a meta-analysis (2), shed light on the overriding importance of manometric success in the treatment of hypertension. In the present paper, I will attempt to highlight the importance of these two papers for medical practitioners and guideline writers.

The Canadian Heart Health Survey (3) paints a dismal picture of the state of the detection and treatment of hypertension in Canada. Twenty-one per cent of Canadians between the ages of 18 and 70 years have hypertension. This percentage rises to 50% among those older than 65 years of age. Furthermore, 43% of patients with hypertension are unaware that they have it. Almost one-quarter (22%) are aware of their status but remain untreated, while an additional 21% are receiving medical care for their hypertension but the disease is inadequately controlled by their current treatment regimen. The end result is that only 14% of Canadian hypertensive patients are aware of their disease and treated appropriately. Given the well-known and very serious sequelae of untreated hypertension, and the plethora of medications available for its

La valeur d'abaisser la tension artérielle

D'après l'Enquête canadienne sur la santé cardiovasculaire, seulement 14 % des Canadiens hypertendus sont conscients de leur maladie et traités convenablement. Il se pourrait que ce phénomène s'explique, entre autres, par le fait que les médecins sont déconcertés par l'excès de renseignements contradictoires et confus sur le choix de médicaments. Deux publications récentes pourraient contribuer à une simplification bien nécessaire de ce problème. La collaboration d'essais des traitements pour abaisser la tension artérielle a publié une méta-analyse de 29 essais aléatoires faisant appel à plus de 162 000 participants. Les schémas thérapeutiques s'appuyaient sur les inhibiteurs de l'enzyme de conversion de l'angiotensine, les antagonistes des récepteurs de l'angiotensine, les diurétiques, les bêta-bloquants et les inhibiteurs calciques. La principale conclusion de la méta-analyse, c'est que l'un ou l'autre des schémas d'abaissement de la tension artérielle réduisait le risque de grave événement cardiovasculaire, et la mesure de ces diminutions du risque était directement proportionnelle au degré d'abaissement de la tension artérielle.

L'essai VALUE sur l'évaluation de l'utilisation prolongée de l'antihypertenseur valsartan a permis de comparer le valsartan à l'amlodipine. À la fin de l'étude, les réductions de tension artérielle par rapport aux valeurs de départ étaient de 17,3/9,9 mmHg au sein du groupe prenant de l'amlodipine et de 15,2/8,2 mmHg au sein de celui prenant du valsartan ($P < 0,0001$). L'incidence d'infarctus du myocarde était considérablement plus faible au sein du groupe prenant de l'amlodipine (4,1 %) que de celui prenant du valsartan (4,8 %). À partir de ces deux études, il serait raisonnable de conclure que le traitement de l'hypertension artérielle comporte deux objectifs principaux : revenir à une tension normale et rendre le patient heureux. L'agent ou les agents utilisés pour réaliser ces objectifs sont relativement sans importance.

treatment, the results of the Canadian Heart Health Survey are difficult to understand.

It is therefore worthwhile to consider the possibility that, from the perspective of the family physician, the problem is one not of a lack of information but rather of an excess of confusing and often contradictory information, resulting in 'input overload'. A significant part of this input overload might be due to the attribution to some antihypertensive drugs of quasi-magical properties that extend the benefits beyond their blood pressure (BP)-lowering effects. If such is the case, two recent publications may help significantly to demystify the treatment of hypertension: the Blood Pressure Lowering Treatment Trialists' Collaboration (2) and the Valsartan Antihypertensive Long-term Use Evaluation (VALUE) trial (1).

The participating authors of the Blood Pressure Lowering Treatment Trialists' Collaboration (2) included 29 trials prospectively designed to investigate the effects of antihypertensive agents on mortality and major cardiovascular (CV) events. Patients were randomly assigned to either a BP-lowering agent

Centre de recherche, Hôtel-Dieu, CHUM, Montreal, Quebec

Correspondence and reprints: Dr J LeLorier, Centre de recherche, Hôtel-Dieu, CHUM, Pavillon Masson, 3850 Saint-Urbain, Montreal, Quebec

H2W 1T8. Telephone 514-890-8000 ext 12918, fax 514-412-7174, e-mail jacques.le.lorier@umontreal.ca

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or placebo, to different classes of BP-lowering agents or to different BP goals. Various treatment regimens were based on angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), diuretics, beta-blockers or calcium channel blockers (CCBs). More than 162,000 participants were included, for a total of more than 700,000 patient-years.

For each treatment group, the authors calculated changes in weighted average BP during follow-up, as well as the effects on relative risk for total mortality and for each of the major cause-specific outcomes of hypertension, including stroke, coronary artery disease, heart failure, major CV events and CV death.

BP reductions occurred in all of the active treatment groups. Reductions were largest in the CCB (8/4 mmHg) and ACE inhibitor (5/2 mmHg) treatment groups compared with the control group; the reduction in the ARB-treated group was 2/1 mmHg compared with the control group. BP was also lower by 4/3 mmHg in the treatment arms with lower, stricter BP goals than in the treatment arms with less stringent BP targets. Treatment with any of the BP-lowering regimens reduced the risk of total major CV events, and the extent of these risk reductions was directly related to the degree of BP reduction.

CCBs and ACE inhibitors reduced the risk of stroke by 38% and 28%, respectively, versus placebo, while ARBs reduced the risk by 21%. The reduction in the risk of stroke may be primarily due to the extent of BP reduction because larger reductions in risk were seen with regimens with lower BP targets. The key to reducing stroke, then, appears to be effective control of BP.

These results tell us to focus on lowering BP first to reduce the risk of hypertension-associated outcomes, especially stroke – a particularly dreaded outcome of poorly managed or untreated hypertension. Furthermore, the extent of reductions in the risk of coronary artery disease, major CV events and CV deaths also appeared to be directly related to the degree of BP reduction.

The primary message from these current analyses is straightforward: focus on BP reductions first and select the appropriate antihypertensive agent accordingly.

The VALUE trial was designed and implemented to test the following hypothesis: for the same degree of BP control, valsartan would, in hypertensive patients at high CV risk, reduce cardiac morbidity and mortality more than amlodipine. Using a parallel-group, double-blind study design, Julius et al (1) randomly assigned 15,245 hypertensive patients aged 50 years or older and at high risk of cardiac events to valsartan or amlodipine treatment. The primary end point was the time to a composite of cardiac events. Stroke was categorized as the secondary end point. The initial doses of valsartan and amlodipine were 80 mg and 5 mg, respectively. The investigators were told to double these doses and add hydrochlorothiazide (and other

drugs, if necessary) to reach the prespecified goals: systolic BP less than 140 mmHg and diastolic BP less than 90 mmHg.

The target BPs were obtained in 62% of the amlodipine group and in 56% of the valsartan group. After only one month of treatment, the BP was already substantially lower in the amlodipine group (4.0/2.1 mmHg). At the end of the study, the reductions in BP from baseline were 17.3/9.9 mmHg in the amlodipine group and 15.2/8.2 mmHg in the valsartan group ($P < 0.0001$).

The total composite cardiac mortality and morbidity end point was not different between the two VALUE treatment arms. However, there was a significantly lower incidence of myocardial infarction in the amlodipine group (4.1%) than in the valsartan group (4.8%). The authors also reported a lower incidence of stroke in the amlodipine group (3.7%) than in the valsartan group (4.2%), although this difference was not statistically significant ($P = 0.08$).

The time sequence of the events across the duration of the trial was quite striking. Higher odds ratios for all primary and secondary events, in favour of amlodipine, were already evident after three and six months, respectively, when the BP difference between the treatment groups was the largest.

The findings of the VALUE trial provide useful pragmatic information on the treatment of high BP: first, successful prevention of CV events is directly proportional to manometric success and, second, BP goals should be reached in weeks rather than months.

On the basis of these two studies, it would be reasonable to conclude that, from a practical point of view, the treatment of elevated BP has two main goals: to achieve a BP as close to target as feasible, and to do so without producing unwanted side effects. In other words, the physician wants a normal BP and a happy patient. The agent or agents used to obtain these goals are relatively unimportant. Putting more emphasis on this fact may hopefully have a beneficial effect on a public health catastrophe: the undertreatment of Canadian hypertensive patients.

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