HYPERTENSION CANADA

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Treatment of Hypertension

A Primer in Pharmacoeconomics

by K.B. Zarnke

Chronic hypertension is an important risk factor for cardiovascular disease that increases in prevalence with age. As the proportion of elderly persons in society increases, the allocation of health-care resources for the management of this condition is likely to rise. In the present environment of fiscal restraint, it is necessary to evaluate the benefit derived from treating hypertension in relation to resource expenditures committed to this activity.

Methods which may aid in health-care and policy decision-making include analysis of cost effectiveness, cost utility, cost benefit and cost minimization. All approaches are similar in that they compare costs of one programme to those of another (or to those associated with offering no treatment). They differ in the method in which health outcomes are measured and valued.

The most widely used economic evaluation method is cost-effectiveness analysis (CEA). This approach yields estimates of the incremental costs necessary to achieve additional units of health, such as cost per stroke prevented or cost per year of life saved. CEA appeals to clinicians because units of health are expressed in familiar terms.

CEA has been used to assess the value of antihypertensive drug therapy. While units of measurement may be familiar in CEA, the method suffers from limitations when more than a single health outcome is relevant; for example, when both myocardial infarctions and strokes are prevented to differing degrees.

Cost-utility analysis attempts to overcome limitations

Comparisons between programmes assessing different outcomes is also limited with this method. For example, the cost per stroke prevented cannot be easily compared to the cost per cancer prevented. Furthermore, interpretation becomes difficult when costs are expressed as years of life preserved. Nonfatal health states will not be counted, yet may be clinically important. This issue is rele-

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vant to the assessment of hypertension because its treatment may frequently result in short-term reduction of quality of life due to adverse drug effects in exchange for an expected long-term risk reduction in the occurrence of less frequently but clinically important cardiovascular events.

Cost-utility analysis (CUA) attempts to overcome these limitations. CUA measures health outcomes in time periods adjusted for quality of life. Time periods are adjusted not only for survival but also for changes in health status attributable to nonfatal health events and side effects of interventions.

Commonly used constructs include quality-adjusted life years (QALYs) and healthy-year equivalents (HTEs). CUA has a conceptual appeal and allows for comparisons between differing health programmes. This method has been used in hypertension. However, important limitations are inherent in a cost utility-based approach to hypertension.

Final cost per QALY ratios are very sensitive to small differences in quality of life while patients are otherwise well, whether on or off treatment. To date, such estimates of quality of life have been chosen empirically. To measure the most likely utilities between being on or off drug therapy is a large undertaking. Vigorous debate continues as to the most appropriate and valid method for assigning utilities

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Vascular Dementia and Hypertension

by Richard K. T. Chan and Vladimir Hachinski

Vascular dementia is a clinical syndrome of acquired intellectual impairment resulting from brain injury due to a cerebrovascular disorder. Clinically it is characterized by a stepwise deterioration of cognitive function and presence of focal neurological signs. Cerebral infarcts, leukomalacia or leukoaraiosis detected by neuroimaging of the brain differentiate vascular dementia from degenerative dementia. As with most western societies, vascular dementia is the second most common type of dementia in Canada. The Canadian Health and Aging Study revealed the prevalence of vascular dementia to be 0.6 to 4.8% among those aged 65 or more. It is estimated that by 2021, Canadians with vascular dementia will number 100 000.

Hypertension does not lead invariably to the development of vascular dementia. However, the substrates of vascular dementia—cerebral infarcts and intracerebral hemorrhages—are intimately linked to hypertension. Hypertension, with or without other vascular risk factors, predisposes individuals to atherosclerosis. Atheromatous plaques in the carotid arteries in turn lead to local thrombosis or embolism in the cerebral circulation, resulting in cerebral cortical or subcortical infarcts. If the atheromatous plaque causes critical stenosis or occlusion of the carotid artery, it also increases the risk of watershed infarction of the brain.

Atheroma in the coronary artery, with or without concomitant

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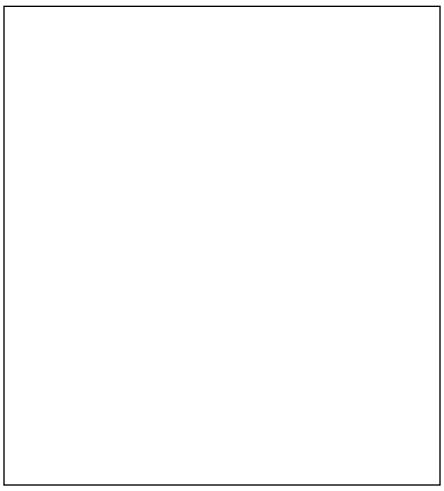
Jacques Genest, Jacques de Champlain Receive Top Honours

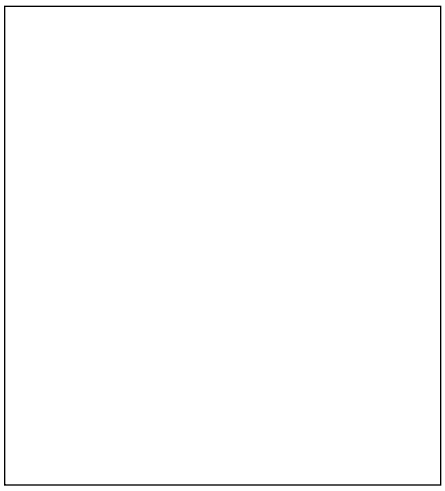
Two of Quebec's most distinguished medical researchers, Jacques de Champlain and Jacques Genest, have been awarded the Quebec Government's highest distinctions in the field of health sciences, the Wilder Penfield Prize and the Armand Frappier Prize. Both are recognized for their work in the field of hypertension.

Jacques de Champlain, a founding member of the Canadian Hypertension Society and a past president (1981-1982) has been awarded the Wilder Penfield Prize, the highest distinction given by Government of Quebec for significant achievement in the field of biomedical research. In addition, Dr de Champlain was awarded the title of officer of the Order of Canada.

Dr de Champlain is a member of the Sacre-Coeur Hospital Research Centre, where he directs the research group on the autonomous nervous system. His work on hypertension has been discussed regularly in these pages, and he continues to be a very active contributor to the advance of scientific knowledge in the field.



Dr Jacques de Champlain



Dr Jacques Genest

Jacques Genest has been honoured with the Armand Frappier Award, which recognizes an exceptional contribution to the development of research institution or the promotion of science and technology. Dr Genest founded the Clinical Reserach Institute of Montreal in 1967. He was also cofounder of the Canadian Society of Clinical Research, in 1955, the Quebec Club for Clinical Research, in 1959, and the Quebec Health Research Council, in 1963. The Clinical Research Centre of Montreal is one of the most prestigious research centres in North America, grouping more than 400 researchers, students and technicians from throughout the world. This recent honour is only the latest of many to be bestowed on Jacques Genest.

Data Entered in Provincial FAMUS Database

Family Physicians Prefer Terminal Digits in Measurement of Blood Pressure

by A. Vanasse, P. Laplante, M. Xhignesse, E. Delisle, A. Grant and R. Bernier

In the 1980s, expert recommendations on techniques for recording blood pressure readings were widely disseminated in publications intended for family physicians and were the focus of numerous training programs. Several publications highlighted errors and biases that can skew blood pressure measurements. These are usually classified as either patient-related, observer-related (*i.e.,* measurement technique) or instrument-related (*i.e.,* the instrument used by the observer). This article concentrates on observer-related biases, particularly the preference of family physicians with respect to the terminal digit in blood pressure readings.

Recent articles on this subject clearly describe the phenomenon of systematic recording of terminal blood pressure digits read to 0, and to a lesser degree, those read to 5. This phenomenon is consistent for both systolic and diastolic readings, in both first and second measurements. Some studies have even identified this type of problem with the use of a random-zero sphygmomanometer, although to a lesser degree. This practice is found among both physicians and others trained in blood pressure-measurement techniques.

The impact of a preference for a terminal digit of 0 on the prevalence of a diagnosis of hypertension may be considerable when the long-term medical, economic and social consequences of erroneous diagnosis of hypertension, or conversely, those associated with fail-

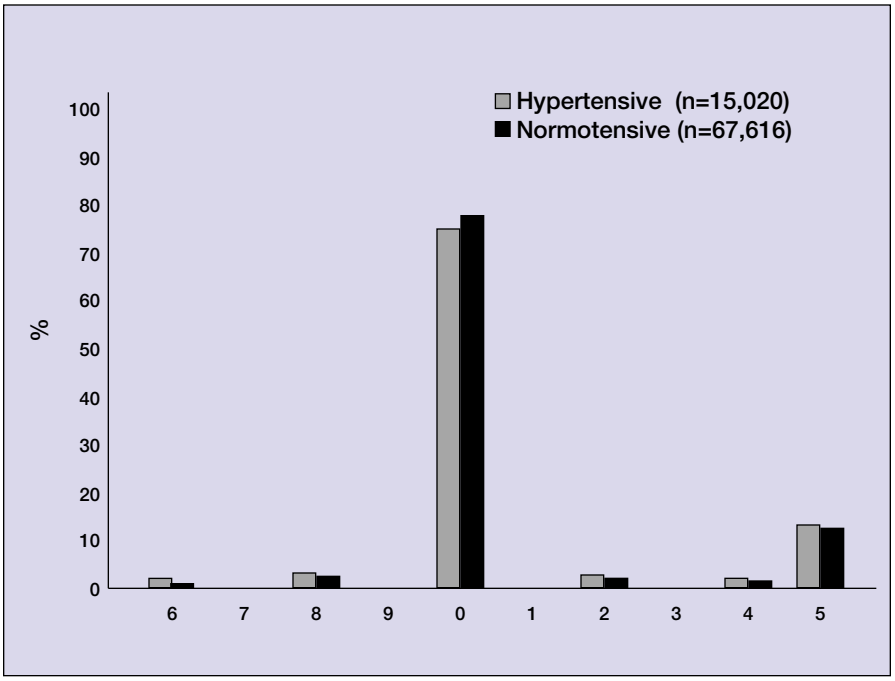


Figure 1. Frequency distribution of terminal digits in BP readings

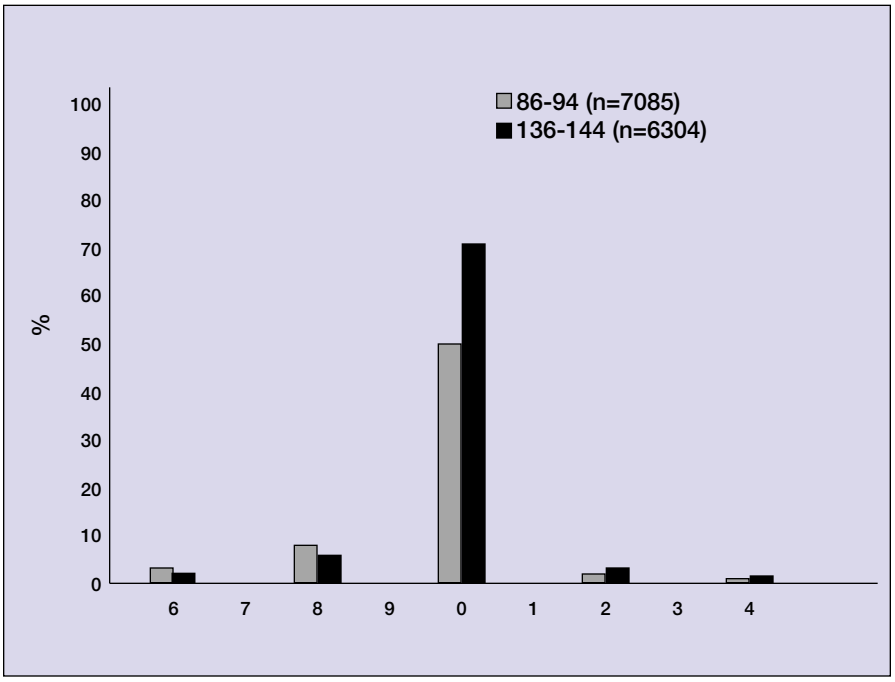


Figure 2. Frequency distribution of terminal digits in BP readings near cutoff values of 90 and 140.

TABLE

PERCENT OF BLOOD PRESSURE READINGS WITH A 0 TERMINAL DIGIT

	Observers (n)	Readings (n)	SBP	DBP	BP (n/s)
McKay (1992)	MD (48)	134	44%	51%	
Stoneking (1992)	Nurse (146)	292	n/s	n/s	62%
Bottini (1992)	n/s	n/s	36%	43%	
Wen (1993)	MD/Nurse (n/s)	28,841	78%	n/s	
Scherwitz (1982)	Nurse (7)	127	42%	65%	
	MD (n/s)	n/s	49%	65%	
FAMUS (1996)	*MD (233)*	*41,318*	*78%*	*75%*	

*n/s: not specified

ure to diagnose and adequately treat hypertension, are considered. The Canadian Coalition for High Blood Pressure Prevention and Control and the Canadian Hypertension Society, in order to minimize this type of error, recommend that blood pressure readings be recorded to the nearest even number.

FAMUS database reflects daily reality

The computerized front-line-care research network associated with the FAMUS project (Family Medicine, University of Sherbrooke) compiles data on patients presenting with cardiovascular disease risk factors. Consultations with the first 100 patients registered in the FAMUS database were analyzed for each of the 233 physicians participating in the study. The current study deals with 14,269 patients, for a total of 41,318 BP readings. The use of a database such as FAMUS reflects the daily reality of family physicians and allows for a realistic estimate of the bias associated with 0 terminal digit preference.

Ours is a descriptive retrospective study based on computerized files completed during consultations, for which the data were transmitted by modem to a central database. Family physicians who volunteered to participate were unaware at the time they completed their patients' records that preference for the terminal digit 0 in blood pressure measurement would be assessed. A simple analysis of frequency distribution showed whether or not they exhibited 0 terminal digit preference, based on the premise that blood pressure is equally distributed over the curve and that the percentage of blood pressure readings which truly have 0 as their terminal digit is 20%.

An analysis of results demonstrates a clear preference for the terminal digit 0, regardless of whether or not the patient is hypertensive. This preference persists even when blood pressure readings are near the cutoff values of 90 and 140. The percentage of blood pressure figures read to 0 is higher than that generally reported in the literature, with the exception of a Quebec study (Wen 1993), which reports findings similar to our own. The Quebec study is a retrospective one as well, based on the assessment of medical records and involving observers who were unaware that preference for terminal 0 would be assessed.

The results obtained suggest that the majority of family physicians read the terminal digit to 0 when measuring blood pressure. The recommendations made in order to minimize this type of error do not appear to have had the desired impact. In light of this observation, it is appropriate to pose questions regarding the specificity and sensitivity of indirect blood pressure readings such as those actually taken by family physicians and reported in patient files. New recommendations may help to reduce the cognitive type of errors such as preference for terminal 0 in BP measurement (*e.g.,* through the use of automated instruments). These recommendations must be realistic and take into account the context of current medical practice.

A. Vanasse, Department of Public Health, Lower St. Lawrence; P. Laplante, M. Xhignesse, E. Delisle, A. Grant and R. Bernier, University of Sherbrooke, Department of Family Medicine. The study was subsidized by the FRSQ and Merck-Frosst Canada Inc.

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to these health states. It is unlikely to be resolved in the near future.

Cost-benefit analysis (CBA) measures resources used and health effects in monetary units. Expressing both costs and health benefits in monetary units facilitates the calculation of a programme's net benefit. This gives policy makers a single measure of a programme's desirability from a perspective of efficiency. CBA, like CUA, can measure, evaluate and amalgamate a composite of possible health outcomes. This, at least theoretically, allows comparisons of different health programmes.

Controversy related to health outcomes

The main controversy surrounding CBA concerns the measurement of values attached to health outcomes. Willingness to pay surveys have been lauded as the most theoretically sound method of determining such values. These surveys ask the public, as a means of valuing health, how much it would be willing to pay, for example, to prevent a stroke. It suffers from practical instrumentation problems, such as the positive association between income and willingness to pay.

The most commonly used method of assigning monetary values to health status in published CBAs is a human capital approach. This method equates the worth of health to contribution to gross domestic product or, in other words, income. Obvious limitations to the human capital method include the failure to place a value for health on those not involved in the labour market. Thus, both methods may assign differing values to health states according to income. This inequity is clearly not desirable. Not surprisingly, recent pharmacoeconomic guidelines have expressed reservations about basing policy decisions on the results of CBA assessments. Applications of CBA to hypertension management have been limited.

Cost minimization analysis avoids the dilemmas of measuring and evaluating health outcomes when evidence exists for two programmes producing identical health effects at differing costs. Under such circumstances, the goal is to determine the least costly programme. With the strength of existing evidence of the benefits of treatment for hypertension, a cost minimization approach comparing antihypertensive treatment with no treatment is irrelevant. In contrast, there may be situations in which this method is useful in comparing antihypertensive drug classes. There are no high-quality data to support claims of equal efficacy or differences between drug classes in reducing risks of cardiovascular event. Furthermore, from a statistical perspective, the determination of therapeutic equivalence is problematic.

Improvements in cost effectiveness shown

As with most modern health-care interventions, the economic evaluation of hypertension treatment has found that such programmes produce important health benefits, but do not result in cost savings to society. The estimates of cost-effectiveness and cost-utility ratios for pharmacological interventions in hypertension from an economic analyses found a median cost per year of life or cost per QALY of $25,000-30,000 with a range from $1,000 to $600,000. This reflects the variation of cost effectiveness with respect to factors such as the severity of hypertension, age and gender, and the heterogeneity of methodology.

Such subgroup analysis consistently reveals improvement in cost effectiveness with higher pretreatment blood pressure (BP). For example, Weinstein and Stason estimated the cost per QALY of treatment of diastolic BP readings <105 mmHg to be in the range of $14,000-43,000 for younger age groups in both sexes. This dropped to half for those with diastolic BPs >105 mmHg. In contrast to the consistent findings of improvements in cost-effectiveness ratios with increased BP, estimates are inconsistent when assessing gender- and age-dependent differences in cost effectiveness.

Heterogeneity of methodology is an important factor in any review of economic analyses of antihypertensive therapy. Decision analysis, logistic modelling, randomized trials, observational data sets and meta-analysis are employed to varying extents in the different studies. Furthermore, there are differences among studies in the choice of discount rates and time periods over which effects are measured. This lack of standardization makes results difficult to compare. In this respect, it may be useful to adopt a "reference case" analysis, using a standard set of assumptions and methods.

Are median costs for treatment of hypertension of $25,000-30,000 per life year or per QALY high or low? Because these ratios compare favourably to other common medical activities such as hemodialysis, it may be argued that this is acceptable value for the quantity of resources uses. However, this comparative approach implies that previous allocation of resources to the comparison programmes is optimal. Attempts to formalize such comparisons have been made through the construction of "league tables".

League tables list the results of multiple studies in descending order of cost effectiveness. Median ratios for the treatment of hypertension are slightly higher than the median cost-effectiveness ratio of health-care interventions studies ($24,000 per life-year) and much lower than the overall median ratio of public-sector interventions ($53,000 per life-year). However, such comparisons are not without limitations, including the lack of standardization of methods between studies and the large number of possible incremental comparisons from which these cost-effectiveness ratios are calculated.

Equity issues arise with such decisions

Another approach to interpretation of cost effectiveness ratios is to compare estimates with what might

arguably be considered arbitrary thresholds. According to such an approach, a recent Canadian proposal would rate hypertension treatment as a "Grade Ca" technology ($22,000-112,000/QALY), indicating that there is only moderate evidence for adoption and appropriate utilization.

Regardless of the approach used, none indicate where resources will come from under conditions of a fixed budget or how much society is prepared to pay to obtain gains in health. A closer look at the discrepancies in relative cost effectiveness of hypertension between gender and age groups reveals a larger ethical issue, that of equity. Suppose the cost-effectiveness estimate of treating one subgroup is quite low, and therefore falls into what might be considered a strongly desirable range from the perspective of utilization, while the estimate for a different age or gender subgroup is very high and therefore undesirable. Should therapy be available to only some members of the population?

Estimates of the cost effectiveness of pharmacological intervention for hypertension suggest that it falls into the range of estimates of other common medical interventions. However, cost effectiveness varies widely over different populations depending on pre-existing cardiovascular risk, severity of hypertension and drug-acquisition cost. Furthermore, interpretation of these results is limited by methodological issues, most of which are not unique to the evaluation of hypertension management.

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Vascular Dementia

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left-ventricular hypertrophy, causes myocardial ischemia or infarction, which in turns increases the risk of cardioembolic stroke. Hypertension also induces changes in the arterioles of the brain, leading to changes of lipo-hyalinosis and formation of Charcot-Bouchard aneurysms. Lipo-hyalinosis leads to lacunar infarcts, while Charcot-Bouchard aneurysms increase the risk of intracerebral hemorrhage. Overzealous antihypertensive treatment or use of inappropriate antihypertensives may cause orthostatic hypotension, leading to watershed territory infarction.

Key is stopping first cerebral infarct

Many community-based epidemiological studies have shown that hypertension is more common in individuals with dementia. Incidence of vascular dementia ranges from 7 per 1,000 person-years in normal volunteers to 16 per 1,000 person-years in hypertensive individuals. In one study, elevation of systolic and diastolic blood pressure appeared to be equally important in the development of vascular dementia.

The key to preventing vascular dementia is stopping the first cerebral infarct or hemorrhage from occurring. The risk of cerebrovascular disorder can be reduced significantly by timely intervention. The prudent use of appropriate antithrombotics (*e.g.*, acetylsalicylic acid or ticlopidine in carotid artery stenosis, warfarin sodium in atrial fibrillation), lowering of cholesterol level through dietary or pharmacological agents, cigarette smoking cessation and carotid endarterectomy for severe symptomatic atheromatous carotid artery stenosis have been shown to reduce the risk of cerebral infarction. It is clear that careful treatment of hypertension can reduce the risk of intracerebral hemorrhage and cerebral infarction.

It is unclear if treatment of hypertension reduces the risk of vascular dementia. For example, it has not been established whether treatment of hypertension prevents the small vessel alterations that cause white-matter changes. Anti-hypertensive treatment may also cause orthostatic hypotension or systemic hypotension that lead to more cerebral ischemia. Based on the current understanding of the pathogenesis of vascular dementia, as well as the benefits to the other organ systems, treatment of hypertension should be included as part of the vascular dementia prevention strategy. However, physicians should exercise caution so as to avoid systemic or postural hypotension.

All patients should receive antihypertensives

Once vascular dementia is established, there is no proven therapy that can reverse the neurological insult nor the cognitive decline. Further cognitive decline occurs with subsequent recurrent cerebrovascular events. In a study involving a relatively small number of patients with vascular dementia, the cognitive deficit remained stable with control of vascular risk factors (including hypertension). Aggressive preventive measures mentioned above should be introduced to prevent further brain injury and cognitive deterioration.

Based on the assumption that treatment of hypertension reduces the risk of subsequent cerebrovascular events, all patients with vascular dementia and hypertension should receive antihypertensives. There is no consensus as to what constitutes significant hypertension in the elderly. Systolic hypertension is probably pathological even in the very old. We suggest that patients with vascular dementia and persistently elevated systolic blood pressure above 180 mmHg be treated.

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Regardless of the age of patients, diastolic hypertension (diastolic blood pressure >95 mmHg) should also be treated with antihypertensives.

Lowering of blood pressure reduces the risk of cerebrovascular event, but excessive lowering may cause impaired cerebral perfusion leading to increase risk of cerebral infarction. In elderly patients (who are more likely to have disturbed autoregulatory mechanisms), we tend to keep the systolic blood pressure around 140-170 mmHg and the diastolic blood pressure below 95 mmHg. In younger individuals, blood pressure management can be more aggressive.

All classes of antihypertensives probably have the same efficacy in terms of stroke prevention. In patients with vascular dementia, it is probably wise to avoid antihypertensives that can potentially worsen the cognitive deficit, or antihypertensives that causes excessive orthostatic hypotension. "Central-acting" antihypertensives such as methyldopa or reserpine interfere with neurotransmitter function in the brain, and are known to cause cognitive disturbance in elderly patients. Adrenergic beta-blockers can cause depression in susceptible individuals.

Significant indirect risk factor

Depression can also worsen the cognitive deficit. To avoid further deterioration of cognitive functions, centrally acting antihypertensives should not be prescribed, and adrenergic beta-blockers should be avoided if possible. Postural hypotension is almost unavoidable with antihypertensive therapy. When the postural drop is severe (>20 mmHg), the autoregulatory mechanisms in the brain vasculature may be unable to prevent a drop in cerebral perfusion. Antihypertensives in which postural hypotension is especially problematic include the centrally acting antihypertensives, vasodilators and diuretics.

There is little doubt that hypertension increases the risk of cerebral infarcts and intracerebral hemorrhage. Indirectly, hypertension can also be seen as a significant risk factor for the development of vascular dementia. Vascular dementia cannot be "treated", but it can be prevented. While there is no direct evidence to suggest that treatment of hypertension reduces the risk of vascular dementia, there is compelling evidence to treat all hypertensive patients to reduce the deleterious effect of hypertension on the brain and other body systems. In patients with established vascular dementia, treatment of hypertension is even more crucial. Careful control of blood pressure will reduce the risk of further cerebrovascular events and may lead to stabilization of the cognitive deficit. No specific class of antihypertensive is particularly indicated for vascular dementia, although agents that might worsen cognitive impairment and agents that produce severe postural hypotension should be avoided.

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The Canadian Hypertension Society has established an Internet home page.

The address is: http://www.umanitoba.ca/outreach/chs. Readers of *Hypertension Canada* are invited to visit the homepage, and to submit suggestions on how its effectiveness may be improved.

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