Hypertension, cognitive decline, and dementia: an epidemiological perspective.

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Hypertension, cognitive decline and dementia : an epidemiological perspective

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Abbrevations and acronyms :

ACE : angiotensin converting enzyme

MMSE : mini mental state examination

MRI : Magnetic resonance imaging

PROGRESS : perindopril protection against recurrent stroke study

SCOPE : Study on Cognition and Prognosis in the Elderly

SHEP : Systolic Hypertension in the Elderly Program

Syst-Eur : Systolic Hypertension in Europe Trial

WML : white matter lesions

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Abstract

Hypertension is a known risk factor for stroke and thus for vascular dementia. However, recent large observational studies have suggested that high blood pressure may also play a role in Alzheimer's disease. The mechanisms linking hypertension to Alzheimer's disease still remain to be fully elucidated but white matter lesions seen on cerebral MRI appear to be a good markers of this association. It is not yet clearly established if lowering blood pressure reduces the risk of white matter lesions and of dementia, so large trials dedicated to this topic are eagerly awaited. These future trials could confirm the hope that, by lowering blood pressure, we may dispose of a preventive treatment for dementia. This issue is of major importance as the number of cases of dementia is expected to rise sharply in the near future in many countries around the world.

Introduction

Dementia is one of the major causes of loss of autonomy and the main reason for the institutionalization of the elderly. Epidemiological studies conducted in the last 10 years have shown that the prevalence of dementia is close to 5% in the population over 65 years of age. These studies have also shown that incidence increases exponentially with age, and as a result of the expected shift in population demographics, the incidence and prevalence of dementia are expected to increase dramatically over the coming decades. The worldwide number of demented patients is projected to grow from 24.3 million in 2001 to 81.1 million in 2040.[1] Significantly, the vast majority of new cases are expected to appear in developed countries. For example, the number of demented persons in China and India will increase by 300% during this period.[1] Prevention and management of dementia is therefore a major public health challenge in the majority of countries around the world.

As a general rule, the occurrence of dementia is not a sudden phenomenon. It is the final stage of cognitive deterioration, the speed of which varies from one individual to the other. But, even in cases where its development is rapid, the process is measured in terms of months. Taking into account the life expectancy of individuals at risk, retarding the development of dementia for a few months may have important consequences on the prevalence of dementia.[2]

Such expectations have been raised in recent years with the discovery of a relationship between hypertension and dementia. Overall, published studies suggest that high blood pressure increases the risk of cognitive decline and dementia, and therefore, that lowering blood pressure might reduce this risk. This paper will review the evidence for this, as well as raise some of the important questions that still remain unanswered.

Hypertension and cognitive decline: evidence from observational studies

What has been known for decades is the direct, causal relationship between high blood pressure and the risk of stroke, and therefore the risk of dementia (Figure 1). It is common knowledge that large strokes or multiple strokes contribute directly to cognitive decline and to the risk of dementia, consequently called vascular dementia. But it is only in the past ten years that studies have reported that hypertension may be related to cognitive decline and dementia without the occurrence of a stroke.

Hypertension and stroke-related dementia, a well-established relationship

Hospital- and population-based studies have firmly established that dementia is more frequent in patients with stroke than in patients without.[3-8] Cognitive assessment performed three months after stroke revealed that 20 to 30% of patients are demented.[7,9,10] In one of the largest clinical series of 453 patients who were examined 3 months after their stroke, 26% were demented.[11]. It is estimated that stroke multiplies the risk of dementia by a factor of two to five, thus constituting one of the strongest risk factors for dementia.[3,5,10,12,13] The strength of this association suggests a causal link between stroke and dementia, although numerous other factors influence this relationship, some pertaining to the patient – such as age, level of education, cognitive level before stroke, white matter lesions on MRI, ApoE4 allele, etc -, and others to the stroke itself, mainly its size, severity, and location.

Interestingly, in the few studies that have implemented a classification of dementia, typical vascular dementia represented only 57%[11] to 64%[7] of all dementias with stroke, thus suggesting that a significant proportion of stroke-associated dementias may be classified as Alzheimer's disease or mixed dementia. This was confirmed in population-based studies in Rochester and New-York, where a 50% to 60% increase in Alzheimer's disease in individuals with stroke compared to those without was observed.[5,14] These data were interpreted as if the occurrence of a stroke may actually simply unmask an ongoing Alzheimer’s disease. This

hypothesis was also suggested by studies showing that pre-stroke cognition is altered in 15% to 20% of patients with a post-stroke dementia.[15,16] This interaction between neurodegenerative factors or lesions and stroke on the risk of dementia has been demonstrated in the Nun study.[17] In this autopsy study, small lacunar strokes were found to multiply the risk of dementia in individuals meeting the neuropathologic criteria for Alzheimer's disease by a factor of 20.

To summarize, even if the relationship between stroke and dementia is not disputed, it appears that the question of the type of dementia is more complex than initially believed. In many cases, post-stroke dementia might be related to pre-existing neurodegenerative lesions. Conversely, some small and not always clinically noticeable small infarcts may precipitate individuals in a clinically conspicuous Alzheimer's disease. What is not yet understood is the extent of these phenomena. If they were not infrequent, the relevance of the existing classification of dementia, based on a clear-cut separation of vascular dementia and Alzheimer's disease, would undoubtedly be questioned.

Hypertension and cognitive decline unrelated to a stroke

Several studies have shown an inverse association between blood pressure and cognitive function without the occurence of a stroke (Figure 1). In the Framingham Heart Study, Elias *et al*. examined cognitive function and memory performance as related to initial blood pressure measurement over a 12 to 14 year period.[18] Among 1,702 subjects, cognitive performance was inversely correlated with initial systolic and diastolic blood pressure readings: the higher the blood pressure, the lower the cognitive performance. In the Honolulu-Asia Aging Study, in which 3,735 Japanese-American male subjects living in Hawaii were enrolled, elevated systolic blood pressure at midlife predicted future reduced cognitive function. A 10-mmHg increase in systolic blood pressure was associated with a significantly increased risk for both intermediate and poor cognitive function. This relationship

remained after adjustment for stroke, coronary heart disease, and subclinical atherosclerosis.[19] Our group conducted a longitudinal study in 1,373 older adults (aged 59-71 years), the EVA study, to examine whether baseline hypertension and use of antihypertensive medication predicted cognitive decline at a 4-year follow-up assessment.[20] We found a relationship between cognitive decline and a history of hypertension (systolic blood pressure ≥ 160 mmHg or diastolic blood pressure ≥ 95 mmHg), and we also discovered that the risk was the highest in patients with untreated hypertension. Hypertensive subjects receiving adequate treatment had no increased risk of cognitive decline compared with normotensive subjects.[20] In another prospective, longitudinal, population-based study, it was also found that among 2,068 elderly individuals, subjects aged 65 years or older were more likely to make errors on a mental status questionnaire when their systolic blood pressure taken 9 years earlier was at least 160 mmHg.[21] Some studies have not found any association between high blood pressure and cognitive function.[22-26] This inconsistency has been attributed to the selection of populations investigated, differences between the methods used to assess cognitive function, and perhaps a misunderstanding of the synchronicity in the development of hypertension and cognitive impairment. However, a majority of cross sectional and longitudinal studies have found a deleterious effect of high blood pressure on cognition.[27,28]

With regard to dementia, several studies have reported a similar association between high blood pressure and the risk of dementia. In a longitudinal study in Sweden, a significant link was found between the presence of high systolic and diastolic blood pressures and the development of dementia 10 to 15 years later.[29] Similar findings were reported in other studies, such as the Honolulu-Asia Aging Study[30], a Finnish study with a 21-year long follow-up[28], and the Kaiser Permanente study[31]. However, in comparison with the study of simple cognitive decline, there is a greater number of studies that show no association between dementia and high blood pressure, and some even suggest that dementia is associated with low blood pressure.[32,33] This could be explained, in full-blown dementia, by the neuronal

depopulation of deep brain structures involved in the control of blood pressure or by the apathy of severely demented individuals who may have lessened their activity and consequently their blood pressure.

Antihypertensive treatment was sometimes found as being protective in observational studies. In a community cohort study of 1,810 persons aged 75 years or older, the prevalence of dementia was significantly lower among patients being treated for hypertension than among those not taking antihypertensive medications ($P < 0.001$).[34] In The Honolulu-Asia Aging Study, early and aggressive blood pressure control lessened the likelihood of cognitive impairment in later life.[19] Similarly, in the EVA study, hypertensive subjects receiving adequate treatment had no increased risk of cognitive decline compared with normotensive subjects.[20]

Randomized trials of blood pressure lowering drugs on the risk of dementia

Prevention of dementia in stroke patients : the PROGRESS study

Blood pressure lowering therapy with the long-acting ACE inhibitor perindopril combined with the diuretic indapamide reduces the risk of post-stroke dementia by one-third and the risk of severe cognitive decline by nearly one-half, according to the results from the PROGRESS study.[35] PROGRESS was a randomized, double-blind, placebo-controlled trial that enrolled 6,105 men and women, mean age 64 years, with prior stroke or TIA, from 172 institutions in 10 countries in Asia, Australia, and Europe. Participants were randomized to active treatment (n = 3051) or placebo (n = 3054).[36,37] Active treatment was comprised of perindopril 4 mg daily for all participants, along with 2.5 mg daily of the diuretic indapamide (2 mg in Japan) whether the drug was neither specifically indicated nor contraindicated. The main results of PROGRESS[38] demonstrated that active treatment with perindopril alone or

with indapamide reduced blood pressure by 9/4 mm Hg over 4 years of follow-up and was associated with an overall reduction of 28% in the risk of recurrent strokes (the primary outcome of the study) compared with placebo (P < .0001 among hypertensive and nonhypertensive patients with a history of stroke or transient ischemic attack [TIA]). Active treatment also reduced the risk of total major vascular events by 26%. Combination therapy with perindopril plus indapamide reduced blood pressure by 12/5 mm Hg and stroke risk by 43%. One of the secondary outcomes of PROGRESS was dementia and severe cognitive decline. During the follow-up period of 4 years, dementia (diagnosed according to *DSM-IV* criteria) and severe cognitive decline (a drop of ≥ 3 points in the Mini Mental State Examination [MMSE]) were assessed. Median MMSE score at baseline was 29 (range, 27-30); a large proportion of patients (41%) had good cognitive function (MMSE = 30), but 16% had cognitive impairment (MMSE < 26). Over 25% of patients screened positive for dementia (768 and 812 in the active treatment and placebo groups, respectively). After independent assessment by an expert in dementia, 410 patients were identified as having dementia (equivalent to an incidence of 17 per 1,000 patient years), of whom 108 had a dementia preceded by a stroke. Cognitive decline was identified in 610 patients (incidence of 25 per 1000 patient years), of whom 134 had a previous stroke. Overall, there was a nonsignificant 12% (range, -8% to -28%) reduction in the risk of dementia in the active treatment group. Evaluation within the two dementia subgroups (with or without prior stroke), however, showed a significant reduction of 34% (P = .03) in the risk of dementia with active treatment in patients with prior stroke and a 1% reduction in patients without prior stroke. A similar pattern was observed for cognitive decline, with an overall risk reduction of 19% with active treatment overall, but a significant risk reduction of 45% (P < .001) with active treatment in patients with prior stroke and a 9% reduction in patients without stroke. Combination therapy was more effective in reducing the risk of dementia (23%) than monotherapy (-8%). In patients with no cognitive impairment at baseline (84%), active treatment reduced the risk of dementia by 31%, but there was no effect in patients with cognitive impairment at baseline (-3%). Among the patients without cognitive impairment at baseline, a 50% reduction in the

risk of dementia was observed in those with prior stroke, compared with a 16% reduction in those without stroke.

Trials in hypertensive patients without stroke

Four large-scale randomized controlled trials using blood pressure lowering agents have reported the effects of treatment on the risk of dementia or measures of cognitive function.[39-42] While three trials identified no clear effect of the treatment under study on the risk of dementia[39,42] or on cognitive function,[40,42] one reported a significant benefit from treatment on the risk of dementia.[41]

In the Systolic Hypertension in the Elderly Program (SHEP),[39] active treatment had no discernible effect on the incidence of dementia. Similarly, in the UK Medical Research Council's trial in older hypertensive patients, there was no apparent effect of treatment on any other measure of cognitive impairment.[40] However, in the Systolic Hypertension in Europe Trial (Syst-Eur), the incidence of dementia among those assigned active treatment was about half that of patients assigned placebo, although there was no effect on MMSE scores in either group.[41] These inconsistencies may be due to random error, since the numbers of cases of dementia reported in the previous studies were small (in total, there were 113 cases of confirmed dementia in the earlier studies compared with 410 in the present study), or to differences in the populations studied. A recent analysis of data from the SHEP study suggests that differential drop-out rates in active treatment and placebo groups in that study may have introduced a bias towards the null in the assessment of treatment effects on dementia.[43]

The most exciting data with regard to the prevention of dementia by lowering blood pressure have come from the Syst-Eur trial.[41,44] The Syst-Eur trial was a double-blind, placebo-controlled trial of nitrendipine, a calcium antagonist, with the addition of enalapril, hydrochlorothiazide, or both, titrated or combined as needed to reduce systolic blood pressure by at least 20 mmHg so as to reach a target of <150 mmHg in over 4,000 patients

aged over 60 years. Syst-Eur included a dementia sub-study on a subset of 2,418 patients (1,180 in the placebo group and 1,238 in the active-treatment group). At the end of the trial, which was stopped prematurely after a median follow-up of 2 years because the preplanned interim analyses demonstrated a significant benefit for stroke, 1,861 patients remained on double-blind treatment; 60% received nitrendipine alone, 32% received nitrendipine plus enalapril, and 15% received these two drugs plus hydrochlorothiazide. Dementia was diagnosed in 21 cases in the placebo group and in 11 cases in the active treatment group, resulting in a 50% reduction in the incidence of dementia in the active arm. Interestingly, the majority of cases prevented were of Alzheimer's disease. This remarkable finding should, however, be interpreted with caution because of the small number of outcome events. As result, the possible impact of blood pressure lowering can extend from having no effect to a massive 76% reduction in the risk of dementia. Moreover, the large number of participants who were lost to follow-up further undermines the validity of the study.

In another randomized trial, the Study on Cognition and Prognosis in the Elderly (SCOPE), no treatment effect on cognition was observed.[42,45] SCOPE was a prospective, double-blind, randomized, parallel-group study conducted from 1997 to 2002, in which 4,964 patients aged 70 to 89 years, with SBP 160-179 mm Hg and/or DBP 90-99 mm Hg (untreated or thiazide-treated) and MMSE test score ≥ 24, were assigned to receive candesartan or placebo with open-label active antihypertensive therapy added if necessary. No significant difference was observed in mean final MMSE score between the candesartan group (final score 28.0) and the control group (final score 27.9) (P = .20), and the proportion of patients who had a significant cognitive decline or who developed dementia was not different in the 2 treatment groups.[42] However, due to ethical concerns, this study was finally redesigned to compare effects between the candesartan-based treatment and the usual antihypertensive therapy regimens and, as result, the reduction of blood pressure was limited (Table).

In summary, there are still very few large trials that have assessed the prevention of dementia by blood pressure lowering drugs (Table). PROGRESS is the only study that has assessed the risk of dementia in patients with stroke. It reports a reduction of the risk of post-stroke dementia and no clear effect on the risk of dementia without stroke.[35] The most convincing to date in non-stroke patients, the Syst-Eur trial, is hampered by the relatively small number of cases. In an open extension of the follow-up the results of the main study were confirmed with a doubling of the number of cases.[46] However, special caution is needed to interpret these results because of the limitations and the potential biases of an open follow-up. A large and specifically-designed trial is therefore needed to confirm and to quantify the reduction of the risk of dementia by blood pressure lowering drugs in hypertensive subjects.

Mechanisms of the relationship between hypertension and cognition when there is no stroke : the white matter lesions hypothesis

The mechanisms by which high blood pressure can operate at the cerebral level are widely unknown. Recently, the development of cerebral imaging and more particularly of MRI (Magnetic resonance imaging) has shown that silent strokes, and more broadly, white matter lesions (WML) are common, in particular in patients with hypertension and in the elderly (Figure 2).

WML: definition and risk factors

WML are areas of high signal on T2-weighted images located in the cerebral white matter, and among them, silent strokes may be singled out by their low signal on T1-weighted images. These lesions share the same risk factors as stroke, mainly age[47-53] and hypertension[54-58]. Some studies have shown that a sustained high blood pressure level

increases the risk of WML, suggesting that there was a dose-response relationship.[56,57] The level of blood pressure also seems to play a role, the highest blood pressure values being associated with the higher grades of WML.[59] This aspect of dose-response in terms of duration and level of exposure are important arguments to suggest that the relationship between high blood pressure and WML may be causal, as it is for stroke.

The mechanisms leading to WML are not yet fully understood but degeneration of small caliber arteries (arteriosclerosis) has been consistently found,[60-62] as well as a reduced cerebral blood flow,[63-66] which are both known consequences of high blood pressure on the brain.[67-69] Therefore, it is generally assumed that WML are a marker of a chronic state of cerebral ischemia in hypertensive patients.

Consequences of WML

One general hypothesis is that the accumulation of lesions in the white matter can lead to a subsequent cognitive deterioration by disconnection of cortico-subcortical pathways. Several studies have indeed shown that WML are associated with cognitive impairment[47,52,53,59,70-72] and with dementia[73-75] (Figure 1). Several aspects are however still poorly understood: What is the relative importance of the location, the type, and the extent of WML on the risk of cognitive impairment? Are there major effect modifiers on this relationship, such as the apolipoprotein E polymorphism and education level? Are WML associated with cortical atrophy? If yes, as suggested by some studies,[76-78] what is the relative importance of both on the risk of cognitive impairment? Some of these questions have already been addressed, though very often with small series of selected patients. Further, the evaluation of WML is highly variable across studies and no clear consensus has yet emerged to date.

WML have been also found to be associated with gait disturbances and a higher risk of falls,[79-83] symptoms resembling Parkinson's disease,[84-86] as well as a higher risk of stroke[87,88] and depression[89-93]. It is therefore not an overstatement to say that WML – at least when

their load is elevated – are guilty of accelerating aging of the brain. Trying to control their aggravation is therefore an important goal.

Preventing the evolution of WML: the PROGRESS-MRI study

This was a substudy of the PROGRESS trial just described above. In this substudy, we analyzed data gathered on 192 people (average age 60) recruited in ten centers in France. Each participant had a brain MRI at baseline which was repeated after an average follow up of 36 months. At baseline, a neuroradiologist examined each scan and determined that 42 percent of participants had no WML; 26 percent had mild WML, 13 percent had moderate WML and 19 percent had severe WML. Eighty-nine patients were in the active treatment arm, and 103 were under placebo. About half of the subjects were already being treated for high blood pressure. At the time of the second MRI, blood pressure had decreased at an average of 11.2 mm Hg systolic and 4.3 mm Hg diastolic. In order to limit the variability between the two exams attributable to the MRI technique (position of the head of the patient, different slicing, etc.), we performed an automatic registration and segmentation of both MRI exams after their storage in an Object Oriented Relational Database. By doing so, we made both exams as comparable as possible, and an independent observer, blinded to the data and the order of the MRI exams, would be able to compare them precisely and detect and measure any new lesion. Overall, the risk of new WML was reduced by 43 percent in the treatment group compared to the placebo group, although the difference did not reach significance (P=0.10). The volume of new areas of WML in the treatment group was one-fifth of that in the untreated group (0.4 cubic millimeters versus 2 cubic millimeters) (P = 0.047). The most striking difference was noted in the 27 patients who already had severe WML at the first MRI. In this group, no new areas of abnormality developed in those in the treatment group, compared with an average of 7.6 cubic millimeters of new WML in patients on placebo (P = 0.001).

This study showed, for the first time, that it is possible to limit the development of WML by lowering blood pressure even though the number of subject was rather small. As result of this low power, there was no sufficient power to study simultaneously the impact of treatment on cognition in this sample. Further studies are needed to confirm these results in larger and independent samples. Also, studies should be performed in patients who do not have a past history of cerebrovascular disease.

Tentative conclusions and future prospects

There is no doubt that high blood pressure is associated with cognitive deterioration and dementia independently of the occurrence of a stroke. Conflicting results came in part from the various ways of testing cognition and defining cognitive decline, and the lack of precisely diagnosing dementia in its early stage. Another, and yet unsolved, issue is the modification of this relationship with age. It is likely that the risk of cognitive deterioration related to high blood pressure decreases with increasing age. A similar modification of the risk with age is observed in the relationship between hypertension and stroke. Further, there appears to be spontaneous lowering of blood pressure in the stage of advanced dementia, probably through neuronal depopulation in the centers regulating blood pressure, which renders the relationship even more complex. Finally, the true relative risk of dementia associated with hypertension is probably relatively modest compared to other stronger risk factors for dementia like age, education, and the apoE polymorphism. Therefore, some degree of fluctuation is not unexpected when estimating this risk and some of the controversial results could be thus explained.

Despite these difficulties, clarifying this relationship remains of major importance. With the ageing of our societies, we are facing an epidemic of dementia for which we have no curative or preventive treatment. In this context, even a modest reduction of the risk would have important consequences. Moreover, even if high blood pressure is associated with a

moderate relative risk of dementia, its very high prevalence means that the risk of dementia attributable to high blood pressure may be high and that an improved control of hypertension may translate into a dramatic reduction of the number of cases of dementia.[94]

Several questions remain however unanswered:

What is the true magnitude of the relationship? The data are still insufficient and we definitively need more population-based studies in the elderly in order to accurately estimate the risk of dementia attributable to high blood pressure and other vascular factors. Some of the existing large population-based studies in this domain should also combine their efforts in a view of producing an exact measure of this risk.

Is it possible to identify individuals or groups at high risk? It is likely that the effect of high blood pressure on the brain varies dramatically between individuals, even among hypertensive patients. Those at high risk of hypertension-related cognitive decline or dementia would benefit the most from an accurate control of their hypertension. Again, these high risk groups can be properly identified only in large observational studies with a long follow-up.

Are WML an appropriate marker of the bad tolerance of high blood pressure by the brain? The answer is most likely positive but several issues on the true mechanisms linking WML to cognition remain unresolved, in particular regarding their characteristics : location, size, signal intensity, etc. In addition, what is not well understood, too, is the natural history of WML. Results from a few studies suggest that some patients have a rapid increase of their WML load and that they would be those who have a higher risk of severe cognitive decline, but this remain to be confirmed.

These questions are important and must be answered to improve our understanding of the relationship between hypertension and dementia. However, it is also sustainable to state that we have enough data at hand to set up a clinical trial on the reduction of the risk of dementia by lowering blood pressure. This trial, specifically designed to study dementia,

should be very large so as to produce a significant number of cases with the longest follow-up as possible. Among some other important variables, the investigators of this trial will have to choose the type of patients that should be included : old-old patients are more exposed to a short-term risk of dementia but blood pressure lowering drugs might be less effective in these patients than in young-old patients who are, in turn, less prone to dementia. Demonstrating a treatment effect in youngest hypertensives would require a much larger number of patients or a longer follow-up. The choice of the type of drug could also be important as it is not yet known if the protective effect observed is uniquely due to the lowering of blood pressure or if there is a class effect. A meta-analysis[95] suggests that calcium antagonists are more effective than other drugs in reducing the risk of stroke in hypertensive patients. Could this apparent class effect also apply on the risk of dementia is an open question. Finally, an important decision is whether to perform or not MRI's on part of or on the entire sample. The data from MRI exams would be of great value in confirming the impact of the blood pressure lowering drug on the brain and in understanding the variability of this impact across categories of patients.

Epidemiology of dementia and cognitive deterioration has now completed its first phase which begun in the early nineties and provided extensive descriptive data. Given the growing epidemiological and clinical evidence for the implication of vascular factors on the risk of dementia, the identification and control of these factors in middle-aged and elderly individuals may represent an important approach for decreasing the incidence of dementia. This could be demonstrated properly only through large randomized trials. One can expect that, as for coronary heart diseases, the second phase of the epidemiology of dementia will be devoted to such trials.

Table. Main randomized trials on antihypertensive drugs and the risk of dementia

Study	Sample size	SBP/DBP difference (active vs. placebo)	Drug tested	Duration of follow up	Reduction of the risk of dementia	P value
SHEP[39]	4736	-12 / 4 mmHg	BB ± diuretic	4.5 years	16%	NS
SYST-EUR[41]	2418	- 8.3 / 3.8 mmHg	CCB ± ACE ± diuretic	2 years	50% (0-76%)	0.05
PROGRESS[35]	6105	- 9 / 4 mmHG	ACE ± diuretic	4 years	All dementia : 12% (-8-28%)	NS
					Dementia with recurrent stroke : 34% (3-55%)	0.03
SCOPE[42]	4964	- 3.2 / 1.6 mmHg	ARB	4 years	7%	NS

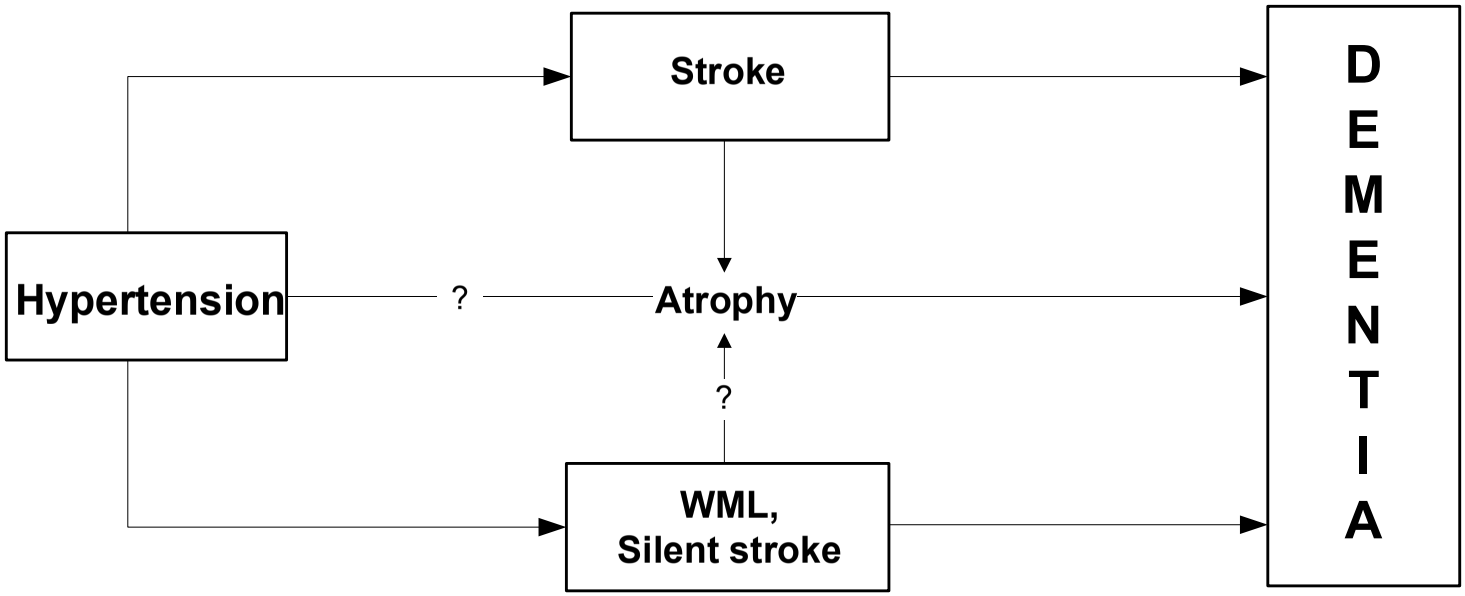
BB : Beta Blocker ; CCB : Calcium Channel Blocker ; ACE : Angiotensin Converting Enzyme Inhibitor ; ARB : Angiotensin II type1 Receptor Blocker ; NS : non significant

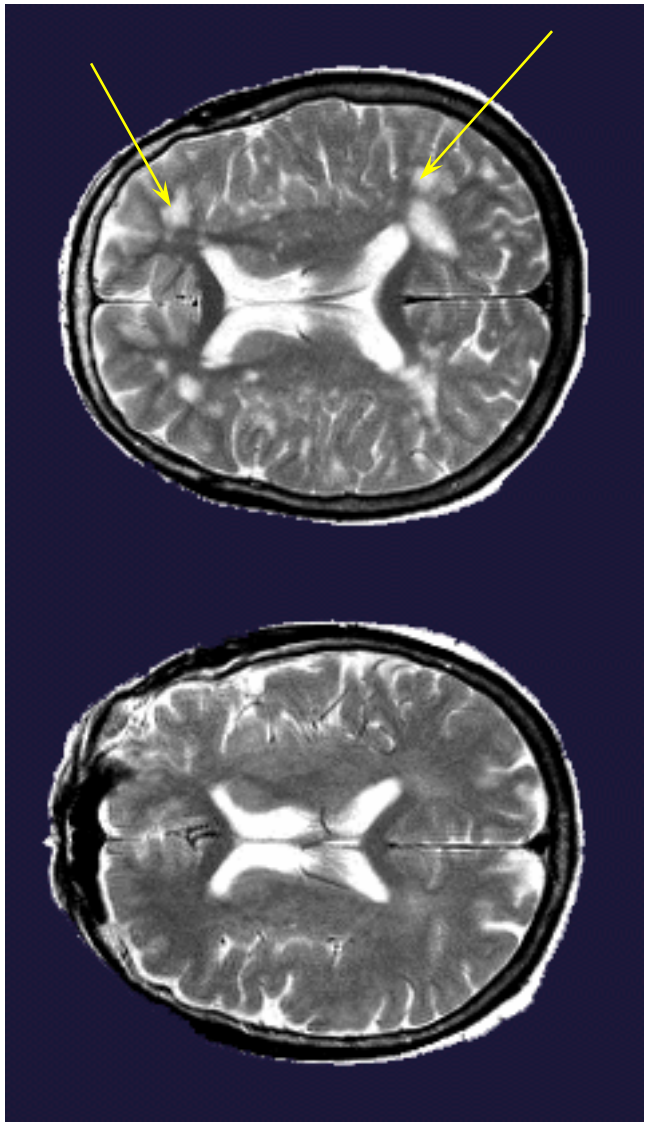
Figure 1. Diagram of the consequences of hypertension on the brain

Legend : WML : white matter lesions

Figure 2. White matter lesions on cerebral MRI

Legend : Cerebral MRI of two women 67 years of age without (on the left) and with (on the right) hypertension. Participant with hypertension had several deep and periventricular white matter lesions (arrows).





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