Blood pressure independent cardiovascular protection is the reality for stroke prevention!

Rationale for the comparison of ACEI versus AT1-blocker as first add-on therapy in the treatment of hypertension.

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1. The present main therapeutical issue for hypertension is the choice of the first add-on therapy to thiazide.
Indeed ALLHAT trial and Psaty network metaanalysis have pointed out thiazides as the preferred initial treatment of hypertension

2. ACEI are proposed as preferred add-on therapy with thiazides, in spite that in ALLHAT amlodipine was the second best initial treatment, for the following reasons:

- ALLHAT has shown that lisinopril better prevented heart failure than amlodipine
- ANBP2 trial has shown that ACEI compared with thiazides may grant a greater BP-independent global cardiovascular protection in white elderly hypertensives with a higher risk of cardiac complications than of stroke, because of greater prevention of these cardiac complications.
- In contrast to dihydropyridines (DHP), ACEI will have a blood-pressure-lowering (BPL) synergy with thiazides because of their opposite effect on the AT1-receptor.
- Although captopril compared with atenolol has been shown in diabetics (UKPDS 39) to give simular global cardiovascular protection, in non diabetics, ACEI have the advantage of being less diabetogenic than betablockers.
- The other angiotensin II-suppressive drugs have not yet been appropriately evaluated (i.e. centrally-or peripherically-acting sympatholytic drugs or long-acting non-dihydropyridines).

3. AT1- blocker would be the best challenger of ACEI for the following reasons :

- They share with ACEI a BPL-synergy with thiazides because of simular AT1-blunting
- They share with ACEI a lower diabetogenic risk than that of betablockers.
- They probably share the same cardiac protective effect, eventhough in patients with recent myocardial infarction and heart failure, OPTIMAAL trial showed that cardiovascular mortality was higher with losartan (50 mg once a day) than with captopril (50 mg t.i.d). Indeed there is a consensus that titration of losartan was not adequate. Furthermore the risk of myocardial reinfarction was the same. Results of CHARM trial are promising in heart failure patients with LVEF < 40%, since candesartan compared with placebo improved cardiovascular mortality even when given on top of betablocker and/or ACEI, in contrast to VALHEFT trial.

In addition in LIFE diabetic population, cardiovascular mortality (38 versus 61 patients) and more specially sudden cardiac death occurrence (14 versus 30 patients) was significantly lower (p=0.03) with losartan compared with atenolol, probably because of a greater protection against cardiac death from arrythmias.

- They should have a greater BP-independent stroke protective effect (SPE) because they increase and not decrease AII-formation and therefore stimulate non-AT1-mediated SPE, while comparably blunting AT1-mediated deleterious effect.

4. Experimental data evidencing brain-antiischemic mechanisms mediated by AT2-receptor

The greater BP- independent SPE of AT1-blocker over ACEI or betablockers is evidenced and explained by experimental data in the gerbil and the rat. They demonstrate hemodynamic and non hemodynamic brain anti-ischemic effects mediated by AT2-receptor activation, in relation with greater angiotensin II-formation since this latter is suppressed by ACEI and increased with AT1-blocker due to the blunting of AT1-mediated suppression of renin secretion (figure 1):

- In the gerbil model of acute stroke by carotid ligation, the group of Fernandez of Yale and our group, have shown that angiotensin II infusion decreased mortality by accelerating collateral circulation recruitment into the ischemic brain where anoxia stimulates AT2-receptor expression both in the vessels and the neurons. Furthermore pre-administration of AT1-blocker compared with ACEI, decreases mortality.
- In the rat model of brain ischemia-reperfusion, the group of Unger has demonstrated that activation of neuronal AT2-receptor by intracerebroventricular AT1-blocker-pre-treatment, induced a stroke protective effect in association with a decrease of AP-1-transcription factors involved in neuronal apoptosis, since it was abolished by co-administration of an AT2-blocker.

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Figure 1

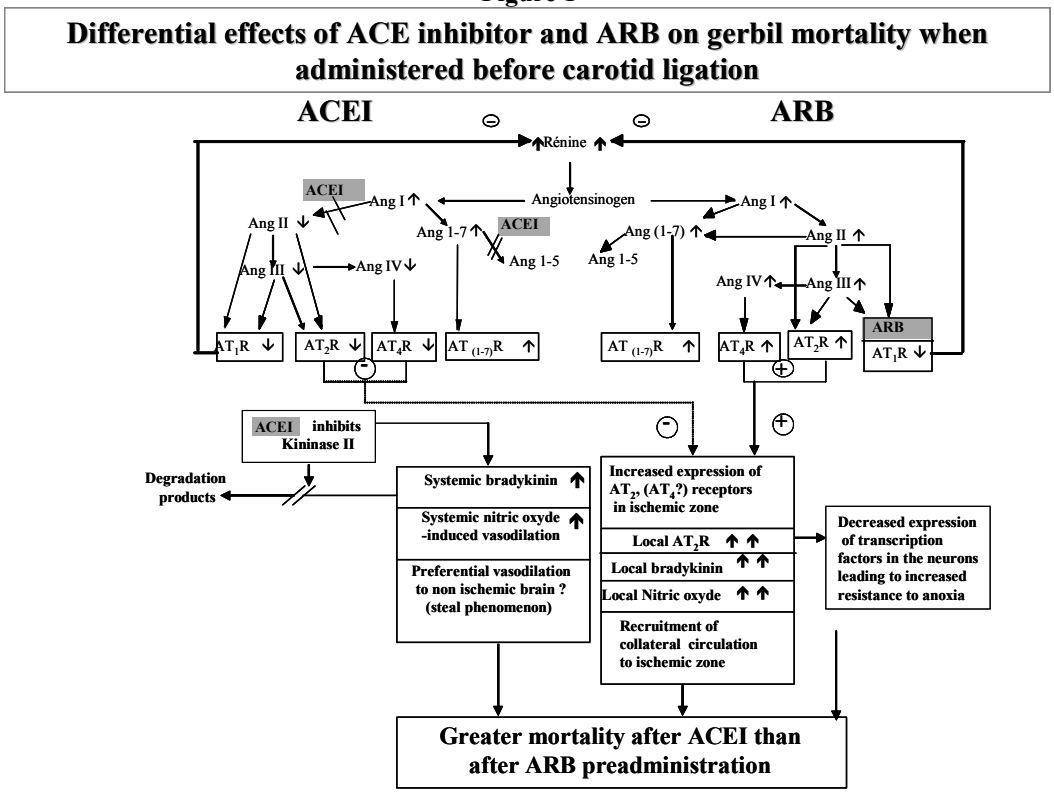
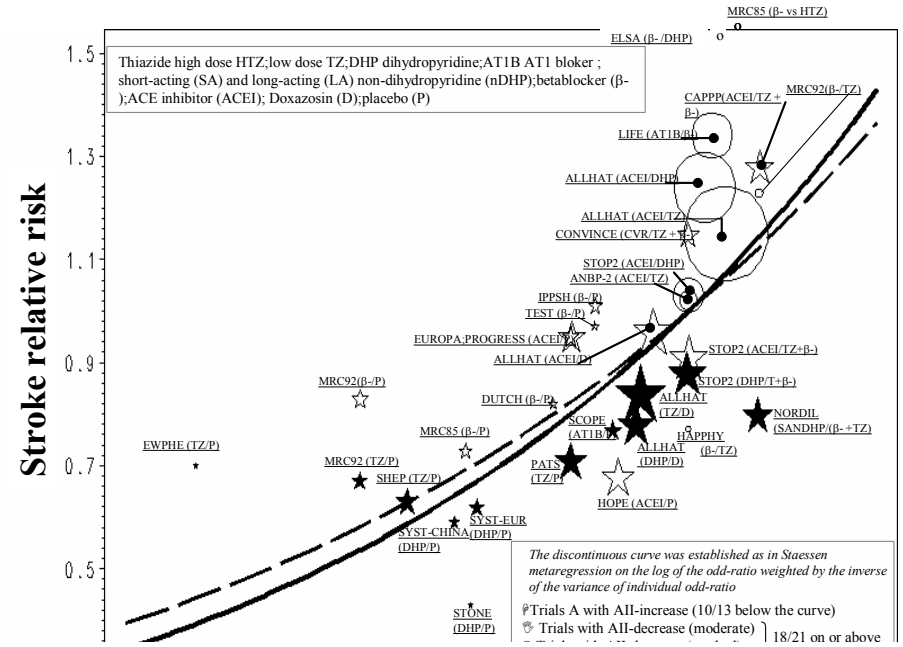


Figure 2



5. The clinical relevance of AT2-mediated brain anti-ischemic effect is supported by LIFE study as well as by a physiopathological metanalysis of all large primary and secondary stroke prevention trials.

5.1. LIFE trial comparing the AII-increasing losartan with AII-decreasing atenolol has shown, for the same BP-control, a 25 to 40% greater selective cerebroprotection, without a better global cardiac protection in spite of greater LVH regression. Since in UKPDS 39 cerebroprotection with atenolol and captopril was comparable, a better stroke prevention is expected with AT1-blocker than with ACEI.

5.2. Our metaanalysis has tested, with all large trials, the hypothesis that AII-increasing drugs are more cerebroprotective than AII-decreasing drug, independently of BP-change.

Drugs that increase AII are: thiazides, DHP, short-acting-non-DHP, and AT1-blockers ; whereas drugs that inhibit AII are : betablockers, ACEI and long-acting-non-DHP. This led us to select trials from Psaty metaanalysis if they could be classified in 1 of the 3 following groups with decreasing AII formation : Group A with AII-increase because AII-increasing drugs are compared with placebo or neutral treatment (doxazosin ; β^-+ LTZ) ; Group B with AII-moderate decrease because of AII-decreasing drugs are compared with placebo or AII-neutral treatment ; Group C with AII- marked decrease because AII-decreasing drugs are compared with AII-increasing ones.

5.2.1. A classical metaanalysis was first performed to compare group A and B and found a lower stroke relative risk (RR) in group A:0.74[0.68;0.79] versus 0.94 [0.87;1.01] (p=0.0001). However the heterogeneity test was significant for both groups. Therefore only the placebo-controlled trials were considered. The mean observed stroke relative risk was significantly lower in group A than in group B being 0.65 [0.56;0.73] vs 0.84 [0.75;0.93] but S/DBP-decrease was greater with the placebo-controlled trials performed with diuretics and DHP compared with betablocker and ACEI (11.7/4.96 versus 6.9/3.53 mmHg ; p=0.01).

An other classical metaanalysis was performed with group C to assess the relative stroke risk with AII-suppressing drugs compared with AII-stimulating drug. It was evaluated at 1.17 [1.10;1.25] while the heterogeneity test was not significant.Furthermore the S/DBP was higher in the AII-suppressed arm but not at a significant level (+1.16 and +0.3 mmHg).

5.2.2. To precisely demonstrate that BP-independent stroke risk is directly linked to AII-suppression, all the trials were first plotted on a graph with the exponential curve relating in cohort study metanalysi,s the stroke RR with the SBP difference. It could be shown that 10 out of the 13 trials of group A with AII increase were below the curve, whereas 18 out of 21 trials of group B and C with AII decrease were on or above the curve (x^2 =12.6 significant at p< 0.0004) (figure 2).

5.2.3. Finally the BP-independent stroke risk change (SRC), was calculated for each trial by substracting on a log-scale, the BP-dependent SRC from the observed SRC. The BP-independent SRC mean was weighted by multiplying each SRC by the ratio of the stroke number of each trial upon that of each group. The weighted-SRC-mean was found to significantly increase from A to C group:

- A= -12.7% ; B=+3.8% ; C=+13.1% for adjustment to SBP (p=0.0007)
- A = -15.5% ; B = +3.8% ; C = +15.6% for adjustment to DBP (p=0.0001)

Thus together with the observation of points 5.1 and 5.2, the significance of the trend tests confirms, on a broad basis of trials with heterogenous populations, that there is a direct link between BP-independent stroke prevention and AII-formation..

6. Population characteristics and potential stroke risk difference between ACEI and AT1-blocker

Although both AT1-blocker and ACEI blunt the deleterious effect of AT1-mediated proatherothrombotic effect, we think that the populations in which a greater difference in SPE between AT1-blocker and ACEI will be found, are those for which a greater SPE has been found in large trials between AII-increasing drugs and AII-decreasing drugs. The likelyhood for a greater SPE with AII-increasing drugs than with AII-suppressing drugs will depend on the likelyhood with which blunting beneficial non-AT1-mediated brain antiischemic mechanisms will not be overrided by the activation of AT1-mediated deleterious proatherothrombotic effects. We suggest that the best clinical indicator of this likelyhood is a low initial prevalence of CHD and peripheral artery disease because it leads to expect a stroke risk higher than that of CHD and related to small artery disease rather than large cerebral artery disease or cardiac emboli. On the contrary the high initial prevalence of these atheromatosis complications like in HOPE and ALLHAT (90 and 50 %) explains that in these trials the strokes are more likely related to large cerebral artery or aortic disease and that the rate of cardiac complications greatly superceded that of strokes (by a factor 5 and 3.5) so that the benefit of blunting AT1-mediated proatherothrombotic effect will easily override or balance the deleterious blunting of non-AT1-mediated brain anti-ischemic mechanisms. Furthermore cardiac complications prevention may significantly participate to stroke prevention since cardiac complications are per se stroke risk factors. It is readily conceivable that the 3 times greater number of prevented cardiac events than of prevented strokes in HOPE, may partially account for the BP-independent stroke risk reduction with ramipril against placebo.

This overriding beneficial effect of AT1-receptor blunting may also account for the fact that in the non-black group of ALLHAT, the stroke-relative-risk of lisinopril compared with chlorthalidone (RR=1) and amlodipine (RR=107) was not increased in spite of 1.5 mmHg higher SBP and lower activation of AT2-mediated brain antiischemic mechanism with lisinopril.

The lack of higher total stroke risk in ANBP2 with ACEI compared with thiazide is puzzling since initial prevalence of CHD was low (8%). However smoking and dyslipidemia prevalence was high (50%) accounting for a higher incidence of cardiac complications than of strokes (by a fac-

tor 2.3). Thus strokes in relation mainly to large cerebral artery disease or cardiac disease were probably predominant, and responsible for an adequate balance between the opposite effects on stroke risk of blunting both AT1 and non-AT1-receptor. Interestingly fatal stroke risk with ACEI was however 1.9 that with thiazide, suggesting the critical rescue role of non-AT1-mediated brain-antiischemic mechanisms.

The contrast between the non-significant 6% SPE of 8mg perindopril in EUROPA and the 32% SPE of 10 mg ramipril in HOPE is puzzling since CHD prevalence was even higher (100 versus 80% explaining that the cardiac event, were also 5 times more frequent than stroke. However the initial prevalence of stroke was 3 times lower in EUROPA than in HOPE (3.5 versus 11%) suggesting that large cerebral artery atheroma was more discrete and therefore less likely to benefit of AT1-blunting.

Therefore we propose to perform the comparison of AT1-blocker with ACEI not in a population like those of HOPE, ALLHAT or ANBP2, but in a population like those of LIFE or PROGRESS.

- The choice of these populations with low initial prevalence of CHD is all the more justified that the ongoing ONTARGET trial is comparing 80 mg telmisartan to 10 mg ramipril in a population like that of HOPE.
- The choice of a population like that of LIFE is justified by the fact that in this population the SPE of an AT1-blocker compared with a betablocker was 25 or 40 % whether only LVH or LVH + isolated systolic hypertension were the inclusion criteria.
- The choice of a population with a history of stroke like in PATS and PROGRESS is justified by a much lower risk of cardiac complications than of strokes (by a factor 0.4), which increases the likelyhood of an overriding beneficial effect of AT2 receptor activation in spite of the deleterious AT1-activation. Indeed brain ischemia increase AT2-receptor expression.This explains that the ratio of the relative risk of stroke with respectively indapamide and perindopril against placebo (0.71 and 0.95) was 0.75, ie 25 % lower with the diuretic than with the ACEI. Therefore this risk difference is also expected when AT1-blocker will be compared to ACEI. Since in contrast to indapamide, AT1-blocker will not only stimulate beneficial non-AT1-mediated SPE but also blunt the deleterious AT1-mediated proatherothrombotic effect, the difference in SPE may even be higher.

Finally we want to point out 2 populations characteristics which may favor a greater SPE with AT1-blocker over that of ACEI :

- the presence of an isolated systolic hypertension as suggested by LIFE trial

A low basal renin secretion like in black hypertensives since it may account for the BP-independent higher stroke with lisinopril compared with chlorthalidone and amlodipine. Indeed the 4 mmHg higher SBP with lisinopril, accounted for a maximum of 16% difference and the stroke-RR of lisinopril was respectively 1.40 and 1.50 when compared with chlorthalidone and amlodipine. It is hypothetized that the lower basal renin secretion makes the black hypertensives more sensitive non only to the BP-lowering effect of thiazide and DHP, but also more sensitive to the stimulation of the AT2-mediated brain anti-ischemic effects of these drugs

7. CONCLUSION

At least for stroke prevention all antihypertensive drugs are not created equal since those with A-II-increase are more protective than those with AII-decrease.