Incident dementia and blood pressure lowering in the Hypertension in the Very Elderly Trial [HYVET]

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The prevalence of dementia rises with increasing age with estimates of around 20% in those aged 80 years rising to 40 percent at age 90.

The prevalence of hypertension also rises with age.

Systolic & diastolic blood pressure in the Framingham cohort related to lower cognitive function at assessment 12-14 years later.

Other studies demonstrate similar findings for systolic/diastolic pressure and cognitive function between 2 and 25 years later.

It has been suggested that high blood pressure in elderly adults may be a risk factor for dementia and that a relatively small reduction in blood pressure (<5/3mmHg) may result in improvements in Mini-Mental State Exam [MMSE] scores.
• Syst-Eur trial: incidence of dementia reduced by 50% with active treatment based upon a calcium channel blocker (CCB). Other trials have not established such a clear answer.

• Meta-analysis of 4 placebo controlled trials: relative risk of 0.80 (95 percent confidence intervals [CI] 0.63-1.02) favouring treatment.

• A review by the Cochrane collaboration included 3 of the above trials and 12,091 hypertensive subjects (mean age of 72.8 years): found ‘no convincing’ evidence that blood pressure lowering prevented the development of dementia or cognitive impairment.

• Syst-Eur trial: success in this area could be due to their unique use of a CCB.

• The Hypertension in the Very Elderly Trial [HYVET]:
  - Designed to assess the relative risks and benefits of treating the very elderly (aged 80 or more)
  - Included assessment of cognitive function.
  - Stopped prematurely due to a beneficial results with regard to preventing both stroke and total death.
Objective

HYVET provided a unique opportunity to assess any effects of blood pressure lowering treatment upon cognitive function and the development of dementia.

Objective of the trial sub-study [HYVET-COG]

To determine whether treatment of hypertension in patients >80s would reduce the incidence of dementia, both Vascular Dementia and Alzheimer’s Disease.
Methods

• Inclusion criteria included age (80 or more) and a sustained sitting systolic blood pressure (BP) of $\geq 160\text{mmHg}$ and $< 200\text{mmHg}$ and a sitting diastolic BP of $< 110\text{mmHg}$.

• Standing BP had to be $\geq 140\text{mmHg}$.

• Participants could not enter HYVET if they required ongoing nursing care, were suffering from a condition that would severely limit their life or had received a clinical diagnosis of dementia.

• Treatment: indapamide (SR) 1.5mg, (or matching placebo) +/- perindopril 2-4mg (or matching placebos). Goal blood pressure was 150/80mmHg.
Cognitive function and incident dementia

- MMSE at baseline and annually (scored by co-ordinating centre)

- A fall to <24 or of >3 points in one year resulted in assessment for possible dementia

- Two data sets.....
  - Patients with baseline MMSE (n=3763)
  - Patients with follow up MMSE (n=3336)

- Possible incident dementia cases were assessed using
  - Diagnostic Statistical Manual edition IV [DSMIV],
  - CT scan (if not possible a full Hachinski Ischemic Score [HIS] was performed)
  - Modified Ischemic Score [MIS].
  - An expert committee, blind to treatment group, assessed each possible case and consensus opinion was achieved.
Analysis

The results were analysed in two ways:

1) to assess the impact of blood pressure lowering on cognitive decline (mean follow up 2 years with 6680 patient years of follow up)

2) to assess the impact of blood pressure lowering on diagnosed dementia (mean follow up 2.2 years with 7400 patient years).
Results

Meta-analysis of double blind placebo controlled trials

Relative risk* meta-analysis plot (random effects)

- **PROGRESS RR**: 0.89 (0.74, 1.07)
- **Syst-Eur RR**: 0.50 (0.25, 1.02)
- **SHEP RR**: 0.84 (0.55, 1.02)
- **HYVET RR**: 0.90 (0.71, 1.13)
- **COMBINED [random]**: 0.87 (0.76, 1.00)

*Relative risks calculated as part of meta-analysis using the numbers above and therefore differ from Hazard Ratios calculated via survival analysis with Cox proportional hazard regression - Relative Risk (95% confidence interval)

Conclusions

• The HYVET trial stopped before the follow-up for cognitive function was complete.

• Despite this, HYVET shows a tendency for a reduction in incident cases with active treatment which could be considered to have clinical although not statistical significance.

• Dementia was the most robust endpoint of the cognitive function assessment in HYVET, and each case was validated and a diagnosis made by the dementia diagnosis committee.

• When the HYVET data is added to that from previous trials using a meta-analytic technique, the result is significantly in favour of treatment.

• The ongoing HYVET extension may provide supplementary data.
• Professor C. Bulpitt (Principal investigator) & Professor A.E. Fletcher (Co-investigator)
• The HYVET co-ordinating office
• The members of the HYVET Committees
  – **Steering Committee** (Dr. T. McCormack, Prof. J. Potter, Prof. B.G. Extremera, Prof. P. Sever, Prof. F. Forette, Assoc. Prof. D. Dumitrascu, Prof. C. Swift, Prof. J. Tuomilehto)
  – **End-points Committee** (Dr. J. Duggan, Prof. G. Leonetti, Dr. N. Gainsborough, Prof. MC. de Vernejoul, Prof. J. Wang, Dr. V. Stoyanovsky)
  – **Data-monitoring Committee** (Dr. J. Staessen, Ms. L. Thijs, Dr R. Clarke, Dr K Narkiewicz)
  – **Ethics Committee** (Prof. R. Fagard, Prof. J. Grimley Evans, Dr. B. Williams)
  – **Dementia Diagnosis Committee** (Prof. J. Tuomilehto, Dr R. Clarke, Dr I. Walton, Dr C. Ritchie, Dr A. Waldman)
• All the HYVET investigators
• All the HYVET national co-ordinators
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• Professor C. Nachev (Steering committee member, National Co-ordinator of Bulgaria and HYVET investigator from 1998 until his death in 2005)
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