ABC&D
Ageing, Blood pressure, Calcium Channel Blockers and Dementia.

R. Peters
(Imperial College London)
Ageing

Disease

Lifestyle
HYPERTENSION
Lifetime BP values (population studies)

Epidemiologic population studies suggest better survival with higher levels of blood pressure.
Meta-analysis: increase in mortality

Relative risk meta-analysis plot (random effects)

- **HYVET Pilot**: 1.29 (0.80, 2.07)
- **Syst-Eur**: 1.23 (0.92, 1.67)
- **STOP**: 1.27 (0.55, 2.98)
- **SHEP Pilot**: 4.73 (0.66, infinity)
- **SHEP**: 0.93 (0.67, 1.29)
- **EWPHE**: 1.17 (0.98, 1.41)
- **combined [random]**: 1.16 (1.02, 1.32)

Relative risk (95% confidence interval)
• 3,845 patients – 60% female
• Mean age 83.6yrs
• baseline BP mean: 173/91 mm Hg
• Median follow-up 1.8 years
• indapamide SR 1.5mg ± perindopril v placebo
• Target BP <150/80 mmHg
• primary end point: fatal or nonfatal stroke.
Reduction of:

32% in stroke (fatal or nonfatal)
39% in death from stroke
21% in death from any cause
23% in death from CV causes
29% in death from cardiac causes
64% in heart failure
Subgroups: CV Events

- Men
- Women

80-84.9 years
85 and over

History of CVD
No History of CVD

160-169 mmHg
170-179 mmHg
180 and over

Values:
- 0.69 (0.50, 0.96)
- 0.66 (0.49, 0.89)
- 0.64 (0.49, 0.83)
- 0.75 (0.50, 1.12)
- 0.75 (0.44, 1.25)
- 0.66 (0.52, 0.84)
- 0.65 (0.46, 0.93)
- 0.75 (0.53, 1.06)
- 0.58 (0.36, 0.94)
Mortality
(by age and initial SBP)
CV Events
(by age and initial SBP)
Stroke (by initial SBP)
Impact of frailty on antihypertensive treatment
Higher blood pressure a risk factor in the least frail?

- Faster walkers with high BP had greater risk of mortality
- Slower walkers – no association between BP and mortality


- Has led to suggestions that frailer should not receive antihypertensive treatment…..
  - Issues…
    - Observational data
    - Goal BP
Methods

• FI at baseline, based on 60 deficits (if less than 30 deficits codable for subject – set to missing)

• Cox regression: impact of FI at entry and

• Stroke; total mortality; CV events

• Stratified by region of recruitment; adjusted for age and gender

• Validity of hazards checked
<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Active</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>1324</td>
<td>1332</td>
</tr>
<tr>
<td>Age (yrs), mean (SD)</td>
<td>83.4 (3.0)</td>
<td>83.6 (3.2)</td>
</tr>
<tr>
<td>Male</td>
<td>520 (39.3%)</td>
<td>526 (39.5%)</td>
</tr>
<tr>
<td>Female</td>
<td>804 (60.7%)</td>
<td>806 (60.5%)</td>
</tr>
<tr>
<td>Body mass index*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Underweight</td>
<td>39 (3%)</td>
<td>58 (4%)</td>
</tr>
<tr>
<td>Normal weight</td>
<td>587 (44%)</td>
<td>605 (46%)</td>
</tr>
<tr>
<td>Overweight</td>
<td>566 (43%)</td>
<td>530 (40%)</td>
</tr>
<tr>
<td>Obese</td>
<td>132 (10%)</td>
<td>138 (10%)</td>
</tr>
<tr>
<td>sitting sbp, mean (SD)</td>
<td>173.1 (8.9)</td>
<td>173.3 (8.8)</td>
</tr>
<tr>
<td>sitting dbp, mean (SD)</td>
<td>90.0 (8.9)</td>
<td>89.9 (8.8)</td>
</tr>
<tr>
<td>standing sbp, mean (SD)</td>
<td>168.0 (11.8)</td>
<td>168.2 (11.9)</td>
</tr>
<tr>
<td>standing dbp, mean (SD)</td>
<td>87.9 (9.9)</td>
<td>88.1 (9.8)</td>
</tr>
<tr>
<td>Cardiovascular disease, n(%)</td>
<td>177 (13.4%)</td>
<td>159 (11.9%)</td>
</tr>
<tr>
<td>Antihypertensive treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>prior to entry into the trial, n(%)</td>
<td>830 (62.7%)</td>
<td>828 (62.2%)</td>
</tr>
<tr>
<td>Mini Mental State</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Examination, median (IQR)</td>
<td>26.0 (22-28)</td>
<td>26.0 (22-28)</td>
</tr>
<tr>
<td>Frailty Index, median (IQR)</td>
<td>0.17 (0.11-0.24)</td>
<td>0.16 (0.11-0.24)</td>
</tr>
</tbody>
</table>

N=2656 where FI could be calculated. But treatment groups remained balanced.
HYVET
median 0.17 (IQR 0.11-0.24)
mean 0.19 (SD 0.10)
83.5 (SD 3.1) years
(Warwick et al BMC Medicine 2015)

Newcastle 85+ Study
median 0.20 (IQR 0.13-0.28)
85 years
(Collerton et al Mech Aging Dev 2012)

Honolulu Asia Aging Study
mean 0.15 (SD 0.08)
77.9 years (SD 4.7)
(Armstrong et al Age Aging 2015)
Higher in women

Increased with age

Higher associated with increased risk of

- **Death**: HR 1.24 (95%CI 1.18-1.30)
- **CV events**: HR 1.23 (95%CI 1.16-1.30)
- **Stroke**: HR 1.26 (95%CI 1.15-1.37)
Variables included in the model

<table>
<thead>
<tr>
<th>Frailty Index</th>
<th>Stroke HR</th>
<th>95% CI</th>
<th>Cardiovascular events HR</th>
<th>95% CI</th>
<th>Total mortality HR</th>
<th>95% CI</th>
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</thead>
<tbody>
<tr>
<td>0.1</td>
<td>0.75</td>
<td>0.40-1.38</td>
<td>0.62</td>
<td>0.42-0.92</td>
<td>0.89</td>
<td>0.63-1.25</td>
</tr>
<tr>
<td>0.2</td>
<td>0.66</td>
<td>0.43-1.01</td>
<td>0.60</td>
<td>0.45-0.78</td>
<td>0.84</td>
<td>0.66-1.07</td>
</tr>
<tr>
<td>0.3</td>
<td>0.59</td>
<td>0.36-0.96</td>
<td>0.57</td>
<td>0.42-0.79</td>
<td>0.80</td>
<td>0.61-1.04</td>
</tr>
<tr>
<td>0.4</td>
<td>0.52</td>
<td>0.25-1.09</td>
<td>0.55</td>
<td>0.34-0.89</td>
<td>0.76</td>
<td>0.50-1.14</td>
</tr>
<tr>
<td>0.5</td>
<td>0.47</td>
<td>0.16-1.33</td>
<td>0.53</td>
<td>0.26-1.06</td>
<td>0.72</td>
<td>0.40-1.29</td>
</tr>
<tr>
<td>0.6</td>
<td>0.41</td>
<td>0.10-1.65</td>
<td>0.50</td>
<td>0.20-1.27</td>
<td>0.68</td>
<td>0.32-1.48</td>
</tr>
</tbody>
</table>
Conclusions:

• Burden of frailty in HYVET similar to population studies
• FI strong predictor of stroke, CV events & mortality in HYVET
• No evidence that treatment effects are dependent on frailty at entry to the study
• Further work needed to clarify benefit risk balance in this age group.
No evidence that frailty modifies the positive impact of antihypertensive treatment in very elderly people: an investigation of the impact of frailty upon treatment effect in the HYpertension in the Very Elderly Trial (HYVET) study, a double-blind, placebo-controlled study of antihypertensives in people with hypertension aged 80 and over

Jane Warwick¹*, Emanuela Falaschetti², Kenneth Rockwood³, Arnold Mitnitski⁴, Lutgarde Thijs⁵, Nigel Beckett⁶, Christopher Bul Pitt⁶ and Ruth Peters²
Impact of antihypertensive treatment on frailty
Frailty Index (FI): mean and 95% CI over time

Follow up time (months)

Placebo Active
Joint model for FI over time and survival

- To further assess the impact of deaths on our findings we fitted a joint model for FI over time and survival.
- This model can be used to obtain estimates of survival that are adjusted for repeated measures of FI, or conversely, to adjust repeated measures of FI for survival.
- Linear mixed effects model for FI over time
- Weibull Proportional Hazards model for survival

- Adjusted for covariates age, region of recruitment and sex

- Effect of active trt on FI in longitudinal model -0.004 (95% CI: -0.011 - 0.003)
- Direct effect of active trt on survival (HR=0.88 95% CI 0.70-1.12)
- Effect of FI on survival (HR=2.23 95% CI 1.90-2.62 per 0.1 inc. in FI)
**Sensitivity analysis:**

- FI includes various components relating to CVD
- Active treatment effective at preventing CVD
- Recalculated FI excluding CVD components to assess extent observed impact of active treatment on FI was due to prevention of CVD

- FI in active group differs from placebo group by -0.011 on average (95% CI -0.025-0.003) p=0.11
Conclusion:

• Level of frailty in HYVET similar to population studies
• Suggestion that BP lowering treatment in HYVET
  • did not have an adverse effect on frailty
  • may have had a beneficial impact

Limitations
• Caution about over interpretation
• Potential to impact on frailty progression by treatment of conditions associated with increasing health deficits merits further attention
DEMENTIA & COGNITIVE DECLINE
Vascular Risk factors

Cerebrovascular disease (infarcts, white matter lesions)

Blood-brain barrier dysfunction
- Oxidation
- Hyperinsulinemia
- Adipokines
- Cytokines

Amyloid-β deposition in brain

Vascular cognitive impairment
- Memory impairment (retrieval)
- Dysexecutive syndrome
- Vascular syndrome

Alzheimer disease
- Memory impairment (delayed recall)
- Amnestic mild cognitive impairment
- Dementia
Managing Alzheimer’s Disease – A Lifelong Commitment

Onset of MCI*  
Clinical diagnosis of AD

Asymptomatic phase  
Preclinical phase  
Clinical phase

% of end-stage AD

Degree of cognitive impairment

Estimated start of neuropathological changes

* MCI - mild cognitive impairment

Modified from PJ Visser, 2000
Changing the Trajectory of Alzheimer’s Disease: How a Treatment by 2025 Saves Lives and Dollars

**FIGURE 4**

Impact of a Treatment That Delays Onset by Five Years on the Number of Americans Age 65 and Older Living with Alzheimer’s Disease, 2015-2050

Alzheimer’s Association 2015

<table>
<thead>
<tr>
<th></th>
<th>2035</th>
<th>2040</th>
<th>2045</th>
<th>2050</th>
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<tbody>
<tr>
<td>2035</td>
<td>9.9</td>
<td>11.6</td>
<td>12.8</td>
<td>13.5</td>
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<tr>
<td>2040</td>
<td>5.9</td>
<td>6.6</td>
<td>7.3</td>
<td>7.8</td>
</tr>
<tr>
<td>2045</td>
<td>4.0</td>
<td>5.0</td>
<td>5.5</td>
<td>5.7</td>
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</table>
### Hypertension and cognitive decline (Longitudinal studies)

<table>
<thead>
<tr>
<th>References</th>
<th>n</th>
<th>Baseline</th>
<th>Age</th>
<th>Follow up</th>
<th>Correlation</th>
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</thead>
<tbody>
<tr>
<td>Wilkie 1971</td>
<td>202</td>
<td>68</td>
<td></td>
<td>10 years</td>
<td>Cognitive decline</td>
</tr>
<tr>
<td>Elias 1993</td>
<td>1702</td>
<td>55-88</td>
<td></td>
<td>12-14 years</td>
<td>Cognitive decline</td>
</tr>
<tr>
<td>Launer 1995</td>
<td>3735</td>
<td>50</td>
<td></td>
<td>20-28 years</td>
<td>Cognitive decline /dementia</td>
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<tr>
<td>Starr 1997</td>
<td>603</td>
<td>&gt; 69</td>
<td></td>
<td>4 years</td>
<td>Cognitive decline</td>
</tr>
<tr>
<td>Kilander 1998</td>
<td>999</td>
<td>50</td>
<td></td>
<td>20 years</td>
<td>Cognitive decline</td>
</tr>
<tr>
<td>Swan 1998</td>
<td>717</td>
<td>45</td>
<td></td>
<td>25-30 years</td>
<td>Cognitive decline</td>
</tr>
<tr>
<td>Tzourio 1999</td>
<td>1373</td>
<td>59-71</td>
<td></td>
<td>4 years</td>
<td>Cognitive decline</td>
</tr>
<tr>
<td>Knopman 2001</td>
<td>10 963</td>
<td>47-70</td>
<td></td>
<td>6 years</td>
<td>Cognitive decline</td>
</tr>
<tr>
<td>Kivipelto 2001</td>
<td>1 449</td>
<td>53</td>
<td></td>
<td>21 years</td>
<td>Dementia</td>
</tr>
<tr>
<td>Reinprecht 2003</td>
<td>186</td>
<td>68</td>
<td></td>
<td>13 years</td>
<td>Cognitive decline</td>
</tr>
<tr>
<td>Piguet 2003</td>
<td>377</td>
<td>≥ 75</td>
<td></td>
<td>6 years</td>
<td>Cognitive decline</td>
</tr>
<tr>
<td>Qiu 2003</td>
<td>1 270</td>
<td>81</td>
<td></td>
<td>6 years</td>
<td>Dementia</td>
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<tr>
<td>Whitmer 2005</td>
<td>8 845</td>
<td>44-44</td>
<td></td>
<td>30 years</td>
<td>Dementia</td>
</tr>
<tr>
<td>Luchshinger 2005</td>
<td>1 138</td>
<td>76</td>
<td></td>
<td>6 years</td>
<td>Dementia</td>
</tr>
</tbody>
</table>
Cohort of Japanese American men born between 1900 and 1919
High Systolic blood pressure and incident dementia:

Untreated:
- All dementia Odds Ratio OR 3.88 (95%CI 1.50-10.02)
- Alzheimer’s Disease OR 1.22 (95%CI 0.37-4.04)
- Vascular dementia OR 11.80 (95%CI 3.52-39.50)

Treated:
- All dementia OR 1.07 (0.53-2.17)
- Alzheimer’s Disease OR 0.65 (0.20-2.15)
- Vascular dementia OR 1.46 (0.60-3.53)

Launer et al 2000 Neurobiology of Aging
The Hypertension in the Very Elderly Trial (HYVET) (2008)
N=3336 (with at least 2 assessments of cognitive function)
Mean age 83.5 years
2.2 years
Double blind multinational Randomised Controlled Trial
Thiazide like diuretic +/- ACE inhibitor or placebo

• All aged 80 and over and not diagnosed with dementia at baseline
• Mini-Mental state exam (MMSE) at baseline and annually.
• If MMSE score fell to <24 or by >3 points in any one year additional assessments for possible dementia were required (Including DSMIV criteria and CT scan).
• CT scans reviewed centrally
• Independent blinded committee assessed data collected on potential incident cases.
Incident dementia and blood pressure lowering in the Hypertension in the Very Elderly Trial cognitive function assessment (HYVET-COG): a double-blind, placebo controlled trial

N = 3336
Mean age: 83.5 years
2.2 years

Incident dementia 33/1000 patient years in the actively treated group vs 38/1000 in the placebo group
### Results

<table>
<thead>
<tr>
<th>Dementia type</th>
<th>Hazard Ratio point estimate (active treatment vs placebo)</th>
<th>95% confidence intervals</th>
</tr>
</thead>
<tbody>
<tr>
<td>All dementia</td>
<td>0.86</td>
<td>0.67-1.09</td>
</tr>
<tr>
<td>Alzheimer’s Disease</td>
<td>0.85</td>
<td>0.63-1.15</td>
</tr>
<tr>
<td>Vascular dementia</td>
<td>0.87</td>
<td>0.57-1.34</td>
</tr>
</tbody>
</table>
Meta-analysis of key double blind placebo controlled trials

<table>
<thead>
<tr>
<th></th>
<th>Active (N/n)</th>
<th>Placebo (N/n)</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PROGRESS RR^{12}</td>
<td>3051/193</td>
<td>3054/217</td>
<td>0.89 (0.74-1.07)</td>
</tr>
<tr>
<td>Syst-Eur RR^{10}</td>
<td>1238/11</td>
<td>1180/21</td>
<td>0.50 (0.25-1.02)</td>
</tr>
<tr>
<td>SHEP RR^{14}</td>
<td>2365/37</td>
<td>2371/44</td>
<td>0.84 (0.55-1.30)</td>
</tr>
<tr>
<td>HYVET RR</td>
<td>1687/126</td>
<td>1649/137</td>
<td>0.90 (0.71-1.13)</td>
</tr>
<tr>
<td>Combined (random)</td>
<td></td>
<td></td>
<td>0.87 (0.76-1.00)</td>
</tr>
</tbody>
</table>

Cochran Q=2.409; p=0.491
Test for overall effect; p=0.045
Double blind placebo controlled trials with dementia as an outcome

Relative risk meta-analysis plot (random effects)

<table>
<thead>
<tr>
<th>Trial</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PROGRESS RR</td>
<td>0.89 (0.74, 1.07)</td>
</tr>
<tr>
<td>Syst-Eur RR</td>
<td>0.50 (0.25, 1.02)</td>
</tr>
<tr>
<td>SHEP RR</td>
<td>0.84 (0.55, 1.30)</td>
</tr>
<tr>
<td>HYVET RR</td>
<td>0.90 (0.71, 1.13)</td>
</tr>
<tr>
<td>PROFESS RR</td>
<td>1.00 (0.87, 1.14)</td>
</tr>
<tr>
<td>combined [random]</td>
<td>0.93 (0.83, 1.03)</td>
</tr>
</tbody>
</table>

relative risk (95% confidence interval)
Systolic Hypertension in Europe Trial (Syst-Eur)

- N=2902, Median age 68 years, Follow up 3.9 years
- Double blind multinational Randomised Controlled Trial + open label follow up
- Calcium Channel Blocker (CCB) +/- ACE inhibitor +/- diuretic or placebo
- Incident dementia 3.8/1000 patient years in the actively treated group vs 7.7/1000 in the placebo group  Hazard Ratio (HR) 0.43 (0.25-0.74)
- Numbers of cases were low

CCB Mechanisms

- Decrease risk of stroke
- Protect against calcium dysregulation, neuronal calcium influx and consequent damage
- Increase cell survival, reduce Abeta 1=42 production
- Reversal of structural remodelling in microvasculature

Brain
Does Use of Antihypertensive Drugs Affect the Incidence or Progression of Dementia? A Systematic Review

Kairav Shah, MD, MPH1,2; Salah U. Qureshi, MD2-5; Michael Johnson, PhD6; Nirai Parikh, MS, BPharm7; Paul E. Schulz, MD2,4; and Mark E. Kunik, MD, MPH2-5

The association of antihypertensive medication use with risk of cognitive decline and dementia: a meta-analysis of longitudinal studies

H. Chang-Quan,1,2,∗ W. Hui,2,∗ W. Chao-min,3 W. Zheng-feng,4 H. Yan-You,1 L. Qing-Xiu2

Antihypertensive drugs, prevention of cognitive decline and dementia: a systematic review of observational studies, randomized controlled trials and meta-analyses, with discussion of potential mechanisms

Natacha Levi Marpillat1,a,b,c,d, Laure Rouch, Philippe Cestac, Olivier Hanon, Charline Cool, Catherine Helmer, Beatrice Bouhanick, Bernard Chamontin, Jean-François Dartigues, Bruno Vellas, and Sandrine Andréau
Systematic review looking at CCBs and older adults

Pubmed, Medline, Embase, PsychInfo from 1980 to 22\textsuperscript{nd} August 2013
1968 records retrieved after duplicates removed
17 full text
10 included (9 studies)

1. Cache County Study
2. Baltimore Longitudinal Study of Aging
3. Canadian Study on Health and Aging
4. The Rotterdam study
5. Community based sample of African Americans
6. Syst-Eur (Trial and open follow up)
7. Cohort study of uninstitutionalised elderly in Israel
8. Ginkgo Evaluation Memory trial
9. Honolulu Asia Aging Study

Peters et al J Hypertens 2013
Results

- Standard assessment of cognitive function

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>CCB Events</th>
<th>CCB Total</th>
<th>Other/no treatment Events</th>
<th>Other/no treatment Total</th>
<th>Risk ratio</th>
<th>Risk ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>M-H, random, 95% CI</td>
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</tr>
<tr>
<td>BLSA</td>
<td>18</td>
<td>220</td>
<td>97</td>
<td>872</td>
<td>0.74 [0.45, 1.19]</td>
<td></td>
</tr>
<tr>
<td>Cache country study</td>
<td>14</td>
<td>460</td>
<td>88</td>
<td>2737</td>
<td>0.95 [0.54, 1.65]</td>
<td></td>
</tr>
<tr>
<td>GEM</td>
<td>46</td>
<td>333</td>
<td>244</td>
<td>1915</td>
<td>1.08 [0.81, 1.45]</td>
<td></td>
</tr>
<tr>
<td>Syst-Eur (AD)</td>
<td>12</td>
<td>1480</td>
<td>29</td>
<td>1417</td>
<td>0.40 [0.20, 0.77]</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>2493</td>
<td>6941</td>
<td></td>
<td></td>
<td>0.79 [0.53, 1.17]</td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>90</td>
<td>458</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: $\tau^2 = 0.10; \chi^2 = 8.09, df = 3 (P = 0.04); I^2 = 63%$

Test for overall effect: $Z = 1.18 (P = 0.24)$

Figure 2: Forest plot for the outcome of incident Alzheimer’s disease.
Questions?

- Something different in the oldest old?
- Something different for post stroke populations?
- Something different due to different CCBs?
Newcastle 85+ Study

- Population based cohort
- **All those aged 85 (born in 1921) in Newcastle**
- Accessed via family practice records
- Cognitive testing at baseline and 3 years
- ~20% with prior cerebrovascular disease
- N=238 with hypertension and taking antihypertensives
- CCB use associated with a lower rate of decline by 1.29 MMSE points (0.16-2.42)
- Same pattern when rerun adjusting for all classes and in those with baseline MMSE >24

Limitations,

- Overlap in antihypertensive classes, small numbers

But, population sample and 3 year follow up
The OXford VASCular Study, OXVASC

- Covers a population of ~100,000 people living in Oxfordshire, UK.
- Cohort study
- Includes patients post stroke, TIA or MI and...
- Age-matched controls.
- Recruited over 6000

- Collecting data on pre event measures eg blood pressure and
- Post event measures eg cognitive function and dementia

- Initial analyses suggest no impact of pre event antihypertensive class on post event cognitive function or incident dementia
Assessing the Impact of Calcium Channel Blockers on Cognitive function in the very elderly (AI-COG)

- Ongoing observational study
- Collecting data from 6 general practice sites
- Participants aged 80 and over and receiving drug treatment for hypertension
- Cognitive assessments (3MS) baseline and 12 months
- N=332
- Follow up complete in 249 (75%)
- 249 Attended follow up visit
- 3 Died
- 24 Refused
- 2 enrolled in error
- Results due January
Currently,

- Almost at the limit of what can be gleaned from observational studies
- Logical next step are trials…

- Some ongoing in differing populations…
Ongoing trials

• **The AFFECT trial**
amlodipine in vascular dementia n=588 age 50 years and over. Treatment for 1 year.

• **The NILVAD trial**
nilvadipine in Alzheimer’s Disease n=250 age 50 years and over. Treatment/follow up up to 7 years

• **The NICE trial**
post stroke treatment with nimodipine, population to be recruited within 7 days of stroke and without dementia. Follow up 6 months after stroke.
Future directions

• Trials?
• CCBs or other antihypertensive classes?
• Different age groups?
• Primary or secondary prevention populations? .....cardiovascular and cognitive....
• Key subgroups eg APOE4 positive
• Meaningful outcomes?