**Appendix Table N1. Characteristics of eligible studies: lipid lowering** **interventions in adults with normal cognition**

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| --- | --- | --- | --- | --- | --- | --- | --- |
| **Intervention Type** | **Study**  **Design Country**  **RoB** | **N=** | **Population**  **Inclusion**  **Age (mean)**  **Sex (% female)**  **Race (% White)**  **Education (mean years)**  **Baseline Cog** | **Intervention (INT)**  **Mode**  **Components**  **Frequency**  **Duration** | **Comparison**  **Mode**  **Components**  **Frequency**  **Duration** | **Outcome measurement**  **Timing** | **Outcome (Instrument)** |
| *Statins Versus Placebo* | Trompet 2010[1](#_ENREF_1), [2](#_ENREF_2)  RCT  Multinational High | 5804 | Adults aged 70 to 82 years with preexisting vascular disease or at increased risk of vascular disease and normal cognition.  Mean age (SD): 75 (3)  52% Female  Race: NR  Mean years of education (SD): 15.1 (2)  Mean MMSE (SD): 28 (1.5) | Pravastatin | Placebo | 42 months mean follow up | Brief Cognitive Test Performance [MMSE]  Executive/Attention/Processing Speed [SCWT] [Letter-Digit Coding Test]  Memory [15-Picture Learning Test Immediate And Delayed] |
| Parale 2006[3](#_ENREF_3)  Observational  India  High | 97 | Adults age ≥40 years with cardiovascular indications for statin use and normal cognition.  Mean age (SD): 56.5 (8)  67% Female  Race: NR  Mean years education (SD): 11 (2.9)  Mean MMSE (SD): 28.4 (1.8) | Atorvastatin 10 mg daily | Placebo | 6 months | Brief Cognitive Test Performance [MMSE]  Executive/Attention/Processing Speed [DSST] [DVT] [TMT B]  Memory [Picture-Word Learning] [COWAT] [Auditory Vigilance]  Adverse Events |
| Muldoon  2004[4](#_ENREF_4)  RCT  United States  Medium | 308 | Adults aged 35 to 70 years with low-density lipoprotein cholesterol level between 160 and 220 mg/dL and normal cognition.  Mean age (SD): 53.7 (9.1)  52% Female  86% White  Mean years education (SD): 14.8 (3.4)  Mean Digit Vigilance (errors), and Recurring Words (errors): 6.6, 81.84. | Simvastatin 10 mg daily or Simvastatin 40 mg daily | Placebo | 6 months | Executive/Attention/Processing Speeda [Composite]  Memory [Memory Composite 1] [Memory Composite 2]  Adverse Events |
| Heart Protection Study 2002[5](#_ENREF_5)  RCT  United Kingdom  Medium | 20,536 | Adults aged 40-80 years with total cholesterol concentrations ≥ 135 mg/dL and with substantial 5-risk of death from coronary heart disease and normal cognition.  28% > 70 years  28% Female  Race: NR  Education: NR  Mean TICS-M (SD): 24.07 (NR) | Simvastatin 40 mg daily | Matching-placebo | 5 years mean follow up | Diagnosis  Brief Cognitive Test Performance [TICS]  Adverse Events [Hospitalizations] |
| Muldoon  2000[6](#_ENREF_6)  RCT  United States  Medium | 209 | Adults aged 24 to 60 with hypercholesterolemia (serum low-density-lipoprotein cholesterol level ≥160 md/dL) and normal cognition.  Mean age (SD): 46.4 (8.9)  46% Female  88% White  Mean years education (SD): 15 (3)  Mean Digit Span (SD), Digit Symbol (SD), Trailing Making B (SD): 7 (1.3), 11.8 (2.5), 65 (21). | Lovastatin 20 mg daily | Matching placebo | 6 months | Executive/Attention/Processing Speedb [Composite Measure of Attention] [Composite of Mental Flexibility] [Composite Measure of Psychomotor Speed]  Executive/Attention/Processing Speedb  Memory [Working Memory Composite] [Memory Retrieval Composite] |
| Santanello 1997[7](#_ENREF_7)  RCT  United States  Medium | 431 | Adults aged ≥65 years with low-density lipoprotein-cholesterol >159 md/dL and < 221 mg/dL and normal cognition and MMSE ≥ 24.  Mean age (SD): 71.2 (NR)  71% Female  24% White  Education: NR  Mean Digit Symbol Substation Score (SD): 41.86 (13.88) | (I1) lovastatin 20 mg daily  (I2) lovastatin 40 mg daily | Placebo | 6 months | Executive/Attention/Processing Speed [DSST]  Adverse Events [Number of Events] |
| *Statin Plus Ezetimibe Versus Placebo* | Tendolkar 2010[8](#_ENREF_8)  RCT  Netherlands  Low | 34 | Elderly stroke-free patients with chronic or paroxysmal atrial fibrillation and normal cognition.  Mean age (SD): 74 (4)  24% Female  Race: NR  Education: NR  Mean MMSE (SD): 27.4 (2) | Atorvastatin 20mg for 2 weeks then increased to 40mg, after 4 weeks ezetimibe 10mg was added. Standard anticoagulant therapy | Matching-placebo and standard anticoagulant therapy | 1 year | Biomarker [Brain Volume Change]  Brief Cognitive Test Performance [MMSE]  Executive/Attention/Processing Speed [DSST]  Memory [Dutch Modified Version RAVLT]  Immediate and Delayed Word Recall] |
| *Statin Plus Fenofibrate Versus Statin Plus Placebo* |  |  |  |  |  |  |
| Willamson 2014[9](#_ENREF_9)  (ACCORD Lipid trial)  RCT  United States  Medium | 1538 | Middle-aged and older adults with diabetes at high risk of cardiovascular events with low-density lipoprotein cholesterol levels of less than 100 mg/dL and normal cognition.  Mean age (SD): 62.5 (5.7)  38.9% Female  73% White  13% <High school  25% High school graduate  33% Some college  28% college graduate or more  Median MMSE (25th and 75th percentile): 28 (26-29) | Fenofibrate plus statin | Placebo plus statin | 40 months | Brief Cognitive Test Performance [MMSE]  Executive/Attention/Processing Speed [SCWT] [DSST]  Memory [RAVLT] |
| *Comparative Effectiveness* | Muldoon  2004[4](#_ENREF_4)  RCT  United States  Medium | 189 | Adults aged 35 to 70 years with low-density lipoprotein cholesterol level between 160 and 220 mg/dL and normal cognition.  Mean age (SD): 53.7 (9.1)  52% Female  86% White  Mean years education (SD): 14.8 (3.4)  Mean Digit Vigilance (errors), and Recurring Words (errors): 6.6, 81.84. | Simvastatin 10 mg daily | Simvastatin 40 mg daily | 6 months | Executive/Attention/Processing Speeda [Composite 1] [Composite 2]  Memory [Memory Composite]  Adverse Events |
| Carlsson 2002[10](#_ENREF_10)  RCT-Crossover  United States  Medium | 41 | Adults ≥70 years with low-density lipoprotein-cholesterol ≥140 mg/dl and tri-glyceride levels ≤140 mg/dl and normal cognition.  Mean age (SD): 76.3 (4.3)  68% Female  Race: NR  Education: NR  Mean Digit Symbol Substitution (SD): 42.45 (9.69) | Pravastatin 20 mg daily | Tocopherol 440 IU daily | 6 months | Executive/Attention/Processing Speed [DSST]  Adverse Events [Physical Adverse Events] [Hospitalizations] |

aMuldoon 20043 grouped tests into composite measures and if there was a significant difference in the composite measure individual items were evaluated. The composite measures were: 1) composite Executive/Attention/Processing Speed 1: Elithorn mazes, digit vigilance, recurring words, grooved pegboard; 2) memory composite 1: mirror tracing, 4-word short term memory, 3) memory composite 1: digit symbol, stroop interference, trail making B, digit span, complex figure, letter rotation;  
bMuldoon 20005 grouped tests into composite measures and if there was a significant difference in the composite measure individual items were evaluated. The composite measures were: 1) composite measure of attention: digit vigilance, letter rotation, digit span, recurring words; 2) composite measure of psychomotor speed: grooved pegboard, Elithorn Maze, Digit Symbol; 3) composite of mental flexibility: Stroop Interference, Trail Making Digit Vigilance, Letter Rotation; 4) working memory composite: Associative Learning, Digit Span, 5) memory retrieval composite: Controlled Oral Word Association, Digit Symbol Recall, Verbal Recall, Complex Figure.

DVT=Digit Vigilance Test; COWAT=Controlled Oral Word Association Test; DSST=Digit Symbol Substitution Test; IU=international units; mg=milligrams; MMSE=Mini-Mental State Examination; NR=not reported; RCT=randomized controlled trial; RAVLT=Rey’s Auditory Verbal Learning Test; SCWT = Stroop Color Word Test; SD=standard deviation; TICS=Telephone Interview for Cognitive Status