

Dutch Study Update at five

In July 2006 I attended the 10th International Conference on Alzheimer's Disease and Related Disorders in Madrid, Spain. A more complete report of this conference has been delayed due to a political campaign for public office in Bernards Township prevented the kind of effort that would be required. Still, the Alzheimer's Disease prevention program (ADPP) has been diligently followed and only modified slightly. The blood chemistry has been followed through-out the period with satisfying results most especially regards C-reactive Protein determination under sustained use of lovastatin and intensified use of Niacin to shape the lipid profile and maximize HDL.

Table I shows the extension in the blood data and Table II shows the updated Medicinal and Nutritional Agents employed in the ADPP. See the Blood Table Spreadsheet in [Blood Table Spreadsheet](#), available on the WEB Page

Highlights from Madrid

There were many interesting findings presented in Madrid for the entire field of the diseases especially in Magnetic Resonance Imaging and Positron Electron Tomography (MRI and PET) neuro imaging and biomarkers to aid in diagnosis many years ahead of the clinical determinations. Reliable clinical diagnoses are possible through interactive tests administered by AD professionals in an office setting where a patient is asked to perform simple memory and cognition tests establishing a Mini Mental State Examination (MMSE) score. However it has been firmly established that classic AD pathology (brain amyloid deposits and neurofibrillary tangles) have been extensive long before a clinical examination will detect the disease. Research into drugs that can change or delay the course of the disease have to be seen as altering this prodromal state by objective methods well before the disease progresses to the clinical categories of Mild Cognitive Impairment (MCI) or AD.

The Erasmus Medical Center (EMC), managers of the Rotterdam Study on which my ADPP is based in its central anti-inflammatory premise, reported on a six year update of their NSAID findings. The paper was only presented slides from the draft of their paper, which was shown but was not presented to any journal at that time and has still not surfaced in the medical literature. Dr. Monique Breteler who led her group in the presentation of several papers indicated to me, ahead of their NSAID presentation that I would be pleased with their findings. Abstract O2-06-04 (below) disclosed and the slide presentation developed in greater detail that select A β -42 reducing, NSAID's, when taken for ≥ 24 months exclusively resulted in AD risk reductions of 58%.

EMC's inclusion of Diclofenac as an A β -42 lowering agent, shown by the Koo-Golde group in August 2003, to be the least lowering of the select group, may have limited or restrained this conclusion. The non-select NSAIDs were shown to have a non significant (statistically) lowering of 22% after a ≥ 2 -year period of use. The EMC cohort had expanded in the 1998-2004 period and the number of AD cases had grown from 293 with an average of 6.8 years of examination to 582

AD cases in 9 years of examination. The cohort size remained at approximately 7000, through growth with additional 55 year olds and deaths of the oldest entering the cohort in 1990.

Dr. Koo suggested to me that EMC re-compute the analysis, leaving Diclofenac out to see if risk reduction with the stronger NSAID inhibitors became greater. This suggestion was passed to Dr. Breteler who felt they had already done the equivalent of this. Diclofenac is a very popular prescription anti-inflammatory in Europe (43% prescriptions, and 36% durations in the original 2001 Rotterdam Study analysis). All NSAIDs were only available by prescription at the time in 1990 that the Rotterdam Study was started (www.epib.nl/ergo.htm), and very likely Diclofenac is still only available in that form. I believe the heavy weighting of Diclofenac in terms of patient use and duration contributes a slight bias to the EMC work and their bow to the physicians prescribing this for arthritis and joint pain.

The slide presentation graphically presented a strengthening statistical case for the confidence one could place in these findings as the spread in the range of confidence narrowed as time progressed in each category.

When their findings are finally published I will present a more thorough evaluation of the conclusions I have drawn from the EMC work as it applies to the ADPP.

Maxi Mental State Exam No.2

As a footnote to this update, my recent campaign for Bernards Township Committee represented a second Maxi Mental State Exam of sorts. Over a 12 week period from August 15th to November 7th 2006, I visited 6000 of 9000 homes in our 24 square mile township. This required 240 hours of bike riding, door knocking, stoop talking and question answering in this Republican Party stronghold. I was the lone Democrat running against two incumbents for two seats on the committee. It was a great experience. I came close to unseating the incumbent mayor. The bike riding and meal deferring resulted in a loss of 35 pounds. You had to be alert at all times to guard dogs and sharp questioning by voters of all ages. On the whole I believe I held up pretty well in this exam and credit the ADPP as a real help. I did not loose a day of campaigning due to illness and the weather went from blistering hot in August to downright wet and chilly in October. I gained a lot of respect for anybody who makes these kinds of efforts and the greatest satisfaction comes when I meet someone who thanks me for making the run.

02-06-04 AMYLOID β 42-LEVEL LOWERING NON-STEROIDAL ANTI-INFLAMMATORY DRUGS AND THE RISK OF ALZHEIMER'S DISEASE

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Background: Initial interest in non-steroidal anti-inflammatory drugs (NSAIDs) for prevention of Alzheimer's disease (AD) was driven by evidence of inflammation in AD pathology. We previously demonstrated that long-term use of NSAIDs was associated with a decreased risk of AD. Results from *in vitro* and *in vivo* studies now suggest that a protective effect of NSAIDs may be mediated by their effect on amyloid- β 42 (A β 42) levels, rather than by anti-inflammatory activity. Not all NSAIDs lower A β 42 levels.

Objective: To determine whether use of A β 42-lowering NSAIDs is associated with a lower risk of AD.

Methods: The study population consisted of 6992 participants of the prospective, population-based Rotterdam Study, who were 55 years or older and free of dementia at baseline. Complete information on filled prescriptions was obtained from automated pharmacy records. NSAIDs were classified as A β 42-lowering or non-A β 42-lowering agents. We defined four mutually exclusive time-dependent categories of cumulative NSAID use: no use, short-term (≤ 1 month), intermediate-term (1 to 24 months) and long-term use (≥ 24 months). The reference group for all analyses was no use of any NSAID. Data were analysed with Cox proportional-hazard models, adjusting for age, sex, concomitant cumulative use of other NSAIDs, education, diabetes mellitus and cumulative use of oral anticoagulants and antihypertensives. In addition, we stratified on APOE genotype.

Results: During follow-up (mean 9.0 years) 739 persons developed dementia, of whom 582 developed AD, 81 vascular dementia and 76 other types of dementia. Long-term use of any NSAID was associated with a non-significant risk reduction of AD (RR 0.65; 95% confidence interval (CI); 0.40-1.06) compared to no use of any NSAID. Long-term use of A β 42-lowering NSAIDs was associated with a significantly decreased risk of AD (RR 0.42; 95%CI 0.20-0.90) compared to no use of any NSAID, whereas use of non-A β 42-lowering NSAIDs was not associated with a decreased risk of AD (RR 0.78; 95%CI 0.32-1.90). Relative risks were lower in presence of the APOE4 allele, but interactions were not significant.

Conclusions: Long-term use of A β 42-lowering NSAIDs seems to protect against AD. These findings are in agreement with the effects of NSAIDs on A β 42 levels observed *in vitro* and *in vivo*.

Table II Alzheimer's Disease Prevention Program Medicinal & Nutritional Agents

Class of ADPP Agent	Agent	Daily Dosage (total)	Taken in Aliquots	Notes and Purposes
Anti-inflammatory	Ibuprofen	600 mg/day	3	NSAID, Mainstay of Program Multifunctional
	Curcumin	1000 mg/day	2	
Anti-oxidant	Curcumin	1000 mg/day	2	Paired with Folic Acid Paired with E when taken d isomer and γ isomer, natural
	Vitamin C	1000 mg/day	2	
	Vitamin E	1200 IU/day	3	
Cardiovascular:				
-Anti-hypertensive	Atenolol	50 mg/day	1	β blocker, taken in am. Diuretic, taken in am. BBB transiting ACE inhibitor, taken in pm.
	Chlorothio.	25 mg/day	1	
	ramapril	5 mg/day	1	
-Lipid adjusting	Lovastatin	20 mg/day	1	BBB transiting statin; LDL & TG lowering Timed release, HDL elevating
	Niacin	1000 mg/day	1	
-Vascular Perfusion	Vitamin B12	530 mcg/day	1	Nerve protection, Homocysteine lowering tHst lower, prevent hippocampal atrophy Temper vascular inflammation, B50 3x wk.
	Folic acid	2175 mcg/day	3	
	Vitamin B6	27 mg/day	1(a)	
Cell Repair & General Nutritional Supplementation	Fish Oil	2000 mg/day	2	DHA 400 mg, EPA 600 mg, capsules DHA 550 mg, EPA 400 mg, liquid
	Cod Liver Oil	4800 mg/day	1	
	Multivitamin	Standard MDR	1	Senior formulation, copy of Centrum As Carbonate, Tums, aggregate D, 800 IU
	Calcium	600 mg/day	2	

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Updated May 20, 2006 with Niacin raised to 1000 mg/day from 500, recommended by BJM