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Lipid Club Letter

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Contents

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Editorial

On 27 January 2007 the Belgian Lipid Club and the Belgian Stroke Council organised a symposium on the subject of Stroke and Lipids in Brussels. The epidemiological, physiopathological, diagnostic and therapeutic aspects of strokes and cognitive disorders were examined from the lipidology point of view. Attached you will find summaries of the contributions of the various English, French, Luxembourg and Belgian speakers. To be emphasized is the recent data regarding the beneficial effect of atorvastatin on lipid reduction in primary prevention (SPARCL Study) and that of the aspirin-dipyridamole association on strokes, the lack of coherent data concerning cholesterol and cognitive disorders etc.

Furthermore the Belgian Lipid Club participated actively in the Orbita Symposium organised on 17 March 2007 by Pfizer which honoured the work of the young Belgian researcher, Dorien SCHRIJVERS from UZ Antwerp, who has so nicely opened up a new line of research into the physiopathology of atherosclerosis.

I am particularly happy at the end of my term of office as President to pass the torch to my friend, Professor Guy De Backer.

Prof. F.R. Heller
President

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Responsible editor: Prof. F. HELLER (C.H. Jolimont) Editorial staff: Prof. J. DUCOBU (CHU Tivoli)

ABSTRACT OF THE SYMPOSIUM : "STROKE AND LIPIDS"

27 Jan. 2007 organized by
the Belgian Lipid Club and the Belgian Stroke Concil

EPIDEMIOLOGY AND RISK FACTORS OF CEREBROVASCULAR DISEASES

Peter U. HEUSCHMANN – King's College London, Great Britain

Stroke is one of the major causes of death and disability worldwide. It is estimated that about 10% of all deaths in developed and developing countries are directly caused by strokes (5.5 million in 2002). In Western societies between 2-4% of all health care expenditure is on acute treatment and long-term management of stroke patients.

Stroke is a heterogeneous disease condition, consisting of different pathological and aetiological subtypes. In European populations the incidence of stroke increases with age; the mean age for the onset of stroke is about 70 in men and about 75 in women. In central Europe it is estimated that about 200 new stroke events occur per 100,000 inhabitants per year, but data on the epidemiology of stroke are scarce and substantial variations in stroke incidence are observed between different populations.

Factors influencing stroke risk vary among the different stroke subtypes. For ischemic stroke the main risk factors are similar to those for other vascular diseases. However, the weighting of the main vascular risk factors differs from that in other vascular diseases and a number of stroke-specific risk factors exist.

In most developed countries stroke-related mortality is decreasing. However, due to the ageing population it is anticipated that the impact of strokes on society in terms of absolute numbers and health-care expenditure will increase in the next decades. The current incomplete understanding of the epidemiology of stroke makes it difficult to design an adequate plan of action to deal with the advent of a "stroke epidemic".

CAROTID ATHEROSCLEROSIS: CAUSES AND TREATMENT

Dirk W. DROSTE - Department of Neurology,
Centre Hospitalier de Luxembourg and University of Münster, Germany

The main risk factors for carotid atherosclerosis are age, arterial hypertension and smoking. Hypercholesterolemia and the other common vascular risk factors are less relevant. Tunica intima and media thickness also constitutes part of these risk factors, but its risk role seems to be increased [(1)] as a precursor of plaque formation and [(2)] as a form of vessel-wall remodelling. These 2 elements cannot be distinguished by ultrasound. Carotid atherosclerosis can easily be detected and monitored using carotid colour-coded duplex sonography.
Patients with carotid artery stenosis benefit from aspirin therapy which lowers the rate of myocardial infarction in these patients.

Before considering carotid artery surgery, the following data need to be known: complications record of the surgeon, life expectancy of patient, sex, whether the patient is symptomatic or asymptomatic, how long symptoms have been present, degree of stenosis (50/ 70%).
General rules are : complications record of the surgeon should be good (ideally <3%). Life expectancy of the patient should be at least 4-5 y. Male patients with a 50% to 69% stenosis will benefit if operated on within 14 days following an ischemic event.
Symptomatic: 70%-99% of all men benefit; women only within 2 weeks.

Asymptomatic: all men <75 years, (60%-99%) benefit. Asymptomatic women do not benefit. The following items are important for the patient's information on risk : string sign (lower stroke risk if medically treated), contralateral occlusion (higher operative risk), ulceration occlusion (higher stroke risk if medically treated).
However all these 3 conditions benefit from surgery when the other criteria (see above) are fulfilled [1-3]. Echogenecity (only in symptomatic patients), progression, and presence of MES are less helpful as they all indicate higher stroke risk, but there are no data available on the associated operative risk [4-6].
The indication for endarterectomy is an individual one that has to be carefully discussed with the patient. Carotid stenting is not more effective than endarterectomy [7-8]. When compared to endarterectomy, the results of carotid stenting only seem favorable in the context of several anatomical conditions that render surgery technically difficult, such as: restenosis after previous endarterectomy, previous radical neck surgery, and previous radiation therapy involving the neck. The results of stenting are also good in patients with severe concomitant cardiac disease [9].

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LIPID AND CEREBROVASCULAR DISEASE INSIGHTS FROM SPARCL

Pierre AMARENCO

Department of Neurology and Stroke Center, Bichat Hospital, Paris, France

The incidence of stroke increases with age, particularly affecting the most advanced in years; a population also at higher risk of coronary heart disease (CHD). Epidemiological and observational studies have not shown a clear association between cholesterol levels and all causes of stroke. Nonetheless, large-scale, long-term statin trials in patients at high risk of or with established coronary heart disease have shown that statins decrease the incidence of stroke.

We performed a systematic review and meta-analysis of all statin trials, which up to the present have included over 90,000 patients, to determine the effect of statins and LDL-C reduction on stroke prevention.[1] The relative risk reduction for stroke was 21% (OR 0.79 [0.73–0.85]) with no heterogeneity between trials.

Fatal strokes were reduced, but not significantly, by 9% (OR 0.91 [0.76–1.10]). There was no increase in haemorrhagic strokes (OR 0.90 [0.65–1.22]). Statins were closely associated with LDL-C reduction. LDL reduction explained 34 % to 80% of the observed benefit, also leaving room for other, pleiotropic, effects. Each 10% reduction in LDL-C was estimated to reduce the risk of all strokes by 13.2% (95% CI, 4.8–20.6) and carotid intima-media thickness (IMT) by 0.73% per year (95%CI=0.27–1.19). By comparison, the number of strokes prevented per 1000 patients with coronary heart disease and treated for 5 years is 6.4 for statins versus 17.3 for antiplatelet agents. Our meta-analysis shows that statins may reduce the incidence of all strokes without any increase in hemorrhagic strokes, and this effect is mainly associated with the extent of between-group LDL-C reduction.

Recent studies have confirmed that statins reduced the incidence of primary stroke in patients with coronary artery disease in the Heart Protection Study (HPS) and the Treat to New Target (TNT) trial and in other high-risk populations – mainly diabetics in HPS and Collaborative AtoRvastatin Diabetes Study (CARDS) and hypertensive patients in the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT)– even with a normal baseline blood cholesterol level, which is an argument in favour of a global cardiovascular risk-based treatment strategy.[2,3,4] Statins have a good overall safety profile with no increased incidence of hemorrhagic stroke or cancer. Possible reasons for the effects of statins in stroke-prevention and the non–cholesterol-lowering mechanisms that may be involved will be discussed.

Statins have not been shown to prevent the recurrence of strokes and additional studies in patients representative of the typical stroke population are needed.

The Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL)

That study is a unique, large-scale, randomized, placebo-controlled trial which provides a definite answer to the secondary pervention of stroke, involving the lowering of cholesterol with atorvastatin 80 mg/day in patients who have suffered a stroke and have no past history of cerebrovascular disease.[5]

In this study, patients having suffered a stroke or TIA within 1-6 months of study entry and with low-density lipoprotein [LDL] cholesterol of 100–190 mg per deciliter, without known coronary heart disease (CHD) (n=4731) were randomly assigned to double-blind treatment with atorvastatin 80 mg per day or a placebo. The primary end point was the occurrence of the first stroke, fatal or non-fatal. (fig.1)

Mean LDL-cholesterol was 73 mg per deciliter on atorvastatin, and 129 mg per deciliter on the placebo over the course of the trial. After 4.9 years median follow-up, a fatal or non-fatal stroke occurred in 265 patients (11.2 percent) receiving atorvastatin and 311 patients (13.1 percent) receiving the placebo (5-year absolute risk reduction 2.2 percent; adjusted hazard ratio=0.84; 95 percent confidence interval (CI) 0.71 to 0.99, P=0.03;). Two hundred and eighteen ischemic and 55 hemorrhagic strokes occurred with atorvastatin and 274 ischemic and 33 hemorrhagic strokes with the placebo.

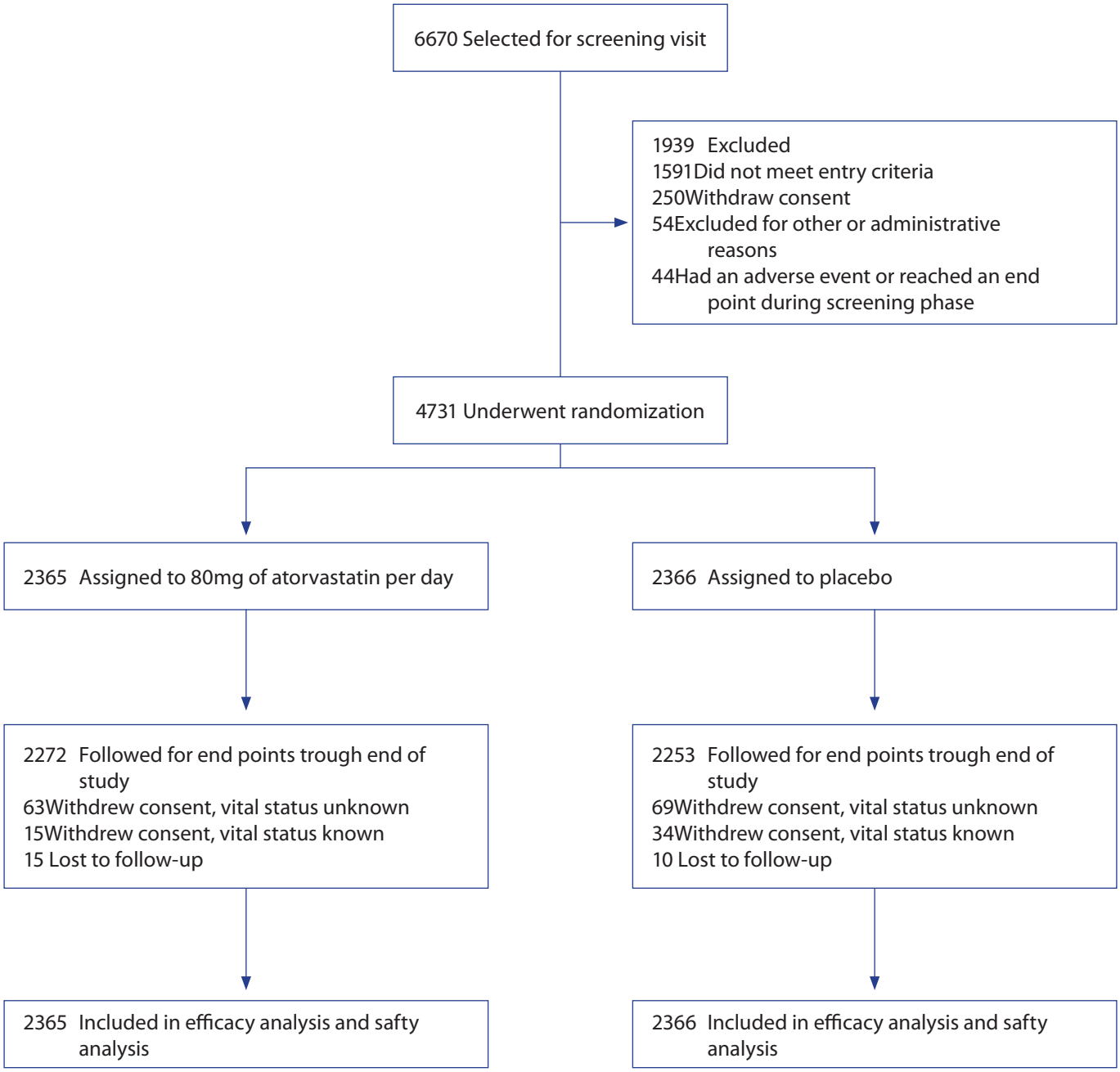

Fig1 : Design of SPARLL

Table 1 : Estimates of the Hazard Ratio for the Primary and Secondary Efficacy Outcome Measures

Outcome *	Atorvastatin (N=2365)	Placebo (N=2366)	Unadjusted P Value †	Prespecified HR (95% CI)	Adjusted Model ‡ P Value
	no. %				
Primary outcome					
Nonfatal or fatal stroke §	265 (11.2)	311 (13.1)	0.05	0.84 (0.71-0.99)	0.03
Nonfatal stroke	247 (10.4)	280 (11.8)	0.14	0.87 (0.73-1.03)	0.11
Fatal stroke	24 (1.0)	41 (1.7)	0.04	0.57 (0.35-0.95)	0.03
Secondary outcomes					
Stroke or TIA	375 (15.9)	476 (20.1)	<0.001	0.77 (0.67-0.88)	<0.001
TIA	153 (6.5)	208 (8.8)	0.004	0.74 (0.60-0.91)	0.004
Major coronary event §	81 (3.4)	120 (5.1)	0.006	0.65(0.49-0.87)	0.003
Death from cardiac causes	40 (1.7)	39 (1.6)	0.90	1.00(0.64-1.56)	1.00
Nonfatal myocardial infarction	43 (1.8)	82 (3.5)	0.001	0.51(0.35-0.74)	<0.001
Resuscitation after cardiac arrest	1 (<0.1)	1 (<0.1)	-	-	-
Major cardiovascular event	334 (14.1)	407 (17.2)	0.005	0.80(0.69-0.92)	0.002
Acute coronary event	101 (4.3)	151 (6.4)	0.001	0.65(0.50-0.84)	0.001
Any coronary event	123 (5.2)	204 (8.6)	<0.001	0.58(0.46-0.73)	<0.001
Revasacularization ¶	94 (4.0)	163 (6.9)	<0.001	0.55(0.43-0.72)	<0.001
Any cardiovascular event	530 (22.4)	687 (29.0)	<0.001	0.74(0.66-0.83)	<0.001
Death	216 (9.1)	211 (8.9)	0.77	1.00(0.82-1.21)	0.98
Death from cardiovascular disease	78 (3.3)	98 (4.1)	0.14	0.78(0.58-1.06)	0.11
Death from cancer	57 (2.4)	53 (2.2)	0.67	1.05(0.72-1.53)	0.80
Death from infection	26 (1.1)	20 (0.8)	-	-	-
Accidental or violent death	11 (0.5)	6 (0.3)	-	-	-
Death from other causes	23 (1.0)	15 (0.6)	-	-	-
Unclassified deaths	21 (0.9)	19 (0.8)	-	-	-

* Only the first event for each patient is counted.
† Unadjusted P values were calculated by the log-rank test.
‡ Treatment hazard ratio (HRs) and P values are from the Cox regression model with adjustment for geographic region, entry event, time since entry event, sex, and age at baseline. Ci denotes confidence interval.
§ Numbers of patients in the outcome subgroup do not total the number for the overall outcome because some patients had multiple events or the outcome could not be subclassified.
¶ revascularization includes coronary, carotid, and perpheral revascularization.

The absolute 5-year risk reduction in major cardiovascular events was 3.5% (hazard ratio=0.80; 95 percent CI 0.69 to 0.92, P=0.002). Overall mortality was unchanged (216 deaths, atorvastatin versus 211 deaths, placebo, P=0.98). Additional per-protocol analysis found an 18% risk reduction in stroke and 42% risk reduction in any CHD event. The rates of serious adverse events were similar. (Table1, fig.2, 3, 4, 5)

In patients having recently suffered a stroke or TIA without known CHD, atorvastatin 80 mg per day reduced the incidence of stroke and cardiovascular events.

Based on 55,045 LDL-C measurements (with an average 11.6 measurements per patient performed during the follow-up), percent change in LDL-C from baseline was classified as no change from baseline, <50% reduction or ≥50% reduction. 88% of atorvastatin patients had at least one measurement corresponding to a ≥50% reduction.

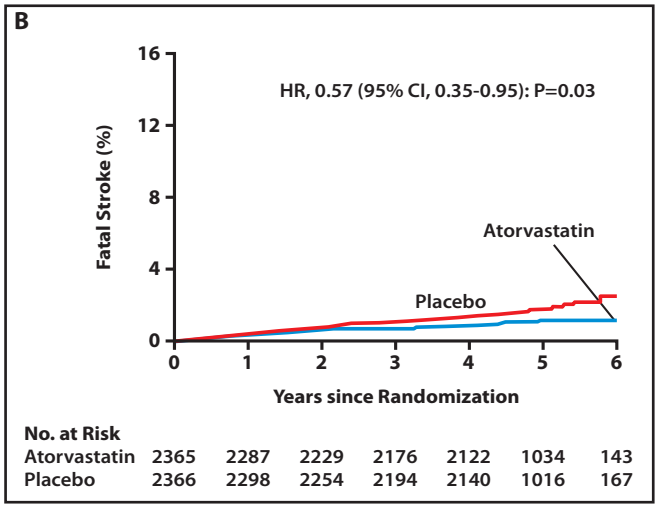

Fig3

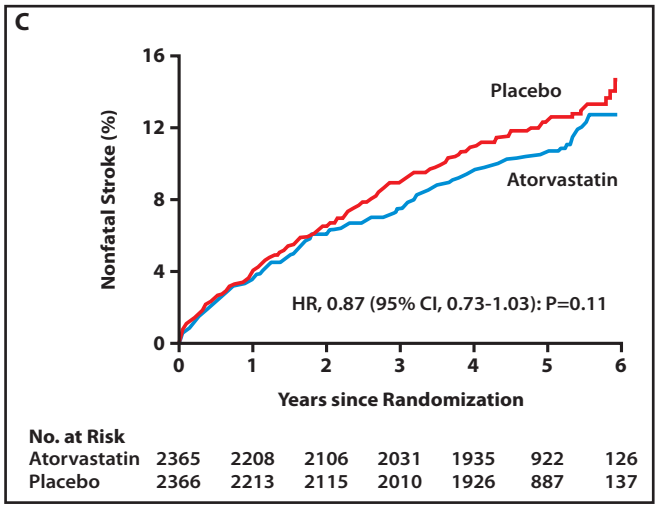

Fig4

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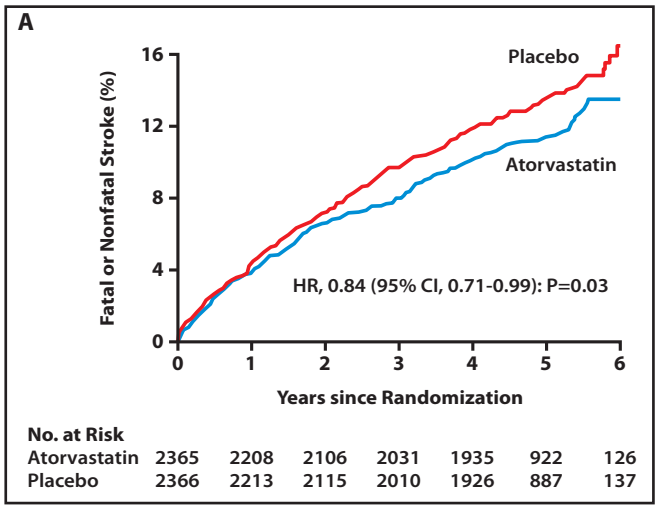

Fig2

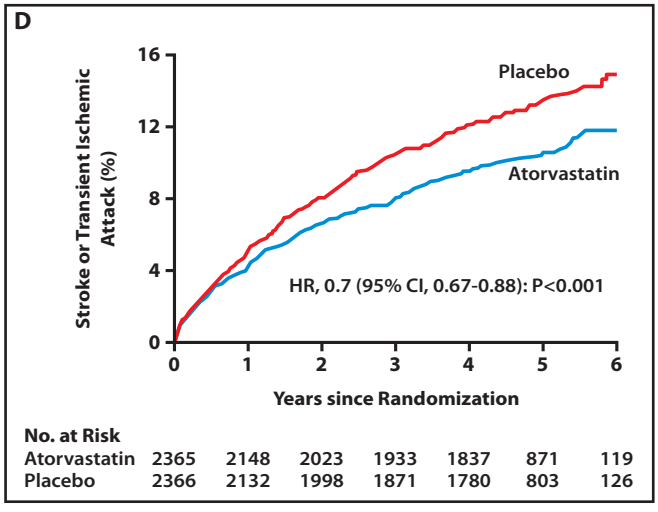

Fig5

LIPIDS, COGNITION AND STROKE

H. HENON, Lille University Hospital, France

Because of population aging, dementia is becoming an increasingly serious health problem. As curative treatments do not yet exist, measures aimed at delaying the onset of the disease could have a major public health impact. Many studies have suggested a link between cholesterol and dementia, leading to the hypothesis that statins might be useful in preventing or even treating dementia.
Many data suggest a relationship between cholesterol and Alzheimer's disease (AD):

(i) Genetic studies have shown a link between apoE, considered as the main cholesterol transporter and AD, the apoε4 allele being a major risk factor for late-onset AD.
(ii) Biological studies have demonstrated that the processing of the amyloid precursor protein (APP) and the production of amyloidβ (Aβ) are modulated by cholesterol.
(iii) Observational studies have suggested an association between elevated serum cholesterol in middle age and increased risk of mild cognitive impairment or AD. Moreover, some studies have shown that the use of statins is associated with a decreased risk of cognitive impairment and dementia.
(iv) In line with epidemiological data, biological data suggest that statins reduce the secretion of Aβ in cell culture and reduce the levels of 24-hydroxycholesterol, an indicator of cerebral cholesterol metabolism.
(v) Lastly, some small-scale clinical trials suggest that statins could slow cognitive decline in AD patients.

However, the nature of the biochemical pathway linking apoε4 with AD remains controversial and does not seem to be mediated by cholesterol level, with no influence of genes usually associated with cholesterol metabolism. Many studies failed to show any difference in the risk of dementia based on current cholesterol concentrations. Moreover, a recent observational study did not confirm the relationship between statins and a decreased risk of cognitive decline, and 2 large-scale prospective clinical trials failed to prove a protective effect of statins on the occurrence of cognitive decline or AD.
Although hypercholesterolemia is better known as a vascular risk factor than as a risk factor for degenerative disease, much less data is available concerning the relationship between cholesterol and vascular dementia (VaD) and the potential benefit of statins in preventing or slowing VaD. If hypercholesterolemia increases the risk of stroke and statins reduce this risk, we can hypothesize that hypercholesterolemia may increase the risk of VaD and statins may prevent and/or slow the evolution of VaD. However, in the few studies that there are on post-stroke dementia, hyperlipemia has not been identified as a risk factor for dementia in stroke patients.
From all the published data, no definite conclusion can be drawn about the relationship existing between cholesterol and dementia, or about the usefulness of statins in preventing or treating dementia. However, given the growing evidence for the coexistence of AD and VaD, identification and aggressive treatment of vascular risk factors may be a crucial strategy for decreasing the incidence of dementia and slowing the progression of cognitive decline. The strong evidence for statin-related stroke prevention at least suggests that statin therapy may reduce the incidence and progression of VaD and mixed dementia. Moreover, further studies are needed to give a better evaluation of the pleiotrophic effect of statins and their usefulness in dementia, especially in AD.

ANTIPLATELET AGENTS IN THE PREVENTION OF STROKE

V. THIJS – UZ Leuven, Louvain, Belgium

Antithrombotic therapy takes a central place in secondary prevention following stroke of arterial and cardiac origin. Combination therapy using clopidogrel and aspirin has been proven to have a supplementary preventive effect in the management of patients with severe symptomatic coronary disease. As recurrences after cerebral ischemic events are frequent and the efficacy of aspirin is low, there are grounds for testing combination therapy in the context of stroke. The MATCH trial showed that addition of aspirin to clopidogrel did not reduce recurrent vascular events in comparison to clopidogrel alone and showed that this combination increased serious bleeding. The CHARISMA trial failed to show an additional effect of clopidogrel and aspirin when compared to aspirin alone in patients with high vascular risk, among whom 5701 patients with stroke or TIA. Similarly, combination therapy in the context of atrial fibrillation

3rd SYMPOSIUM
LIPIDS AND ATHEROSCLEROSIS

Centre Hospitalier Universitaire de Tivoli - (General University Hospital of Tivoli)
av. Max Buset, 34-7100 La Louvière

Saturday 29 September 2007

08:30 Reception and coffee

08h50 **« Introduction »**
J. DUCOBU *(CHU Tivoli – La Louvière)*

09h00 **« Atherosclerosis and inflammation»**
A. HERMAN *(University of Antwerp)*
Questions/answers

09h30 **« DNA and atherosclerosis (microarrays) »**
M. RAES *(FUNDP- Namur)*
09h55 Questions/answers

10h00 **« Fibrinolysis and endothelial dysfunction »**
B. JUDE *(University of Lille)*
10h25 Questions/answers

10h30 Coffee break

11h00 **« Strategy for developing myeloperoxidase inhibitors »**
P. VAN ANTWERPEN *(ULB)* – ***K. ZOUAOUI*** *(CHU Charleroi)*
11h25 Questions/answers

11h30 **« Situation regarding cardiovascular diseases in Hainaut »**
L. BERGHMANS *(Observatoire de Santé [Health Monitoring Body] of Hainaut)*
11h55 Questions/answers

12h00 **« Optimised hyperlipidaemia treatment ».**
A. SCHEEN *(ULg))*

12h30 Closure

13h00 Walking lunch

Information : J.Ducobu 064/277 431 - C.Colson 064/276 097 - email: jean.ducobu@chu-tivoli.be

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