

ABSTRACTS**Stroke****LONG TERM RISKS OF STROKE, MYOCARDIAL INFARCTION, AND VASCULAR DEATH IN “LOW RISK” PATIENTS WITH A NON-RECENT TRANSIENT ISCHAEMIC ATTACK.**

BACKGROUND: Previous studies of prognosis after a transient ischaemic attack (TIA) have recruited patients soon after the event, when the risk of stroke is very high. However, the majority of patients survive for many years after a TIA, and the need for continued preventive treatment to lower vascular risk will need to be reassessed at a later date. **OBJECTIVE:** To determine the long term risks of stroke and other vascular events in patients with TIA who survive the initial high risk period. **METHODS:** 290 patients were studied who had initially been followed up after a TIA in the Oxford community stroke project and in a contemporaneous hospital based cohort study, and who were alive and stroke-free at the end of planned follow up in 1988. All patients were followed for a further 10 years, and the risks of major vascular events (stroke, myocardial infarction, vascular death) were determined. Standardised mortality ratios (SMR) were calculated from the observed numbers of fatal events and the number expected on the basis of age and sex in the general population. **RESULTS:** Median time since last TIA was 3.8 years (interquartile range, 2.2 to 5.8 years). The risk of major vascular events was constant through time. The 10 year risk of first stroke was 18.8% (95% confidence interval (CI), 13.6 to 23.7; 45 events). The 10 year risk of myocardial infarction or death from coronary heart disease was 27.8% (95% CI, 21.8 to 33.3; 67 events) and there was a significant excess of fatal coronary events compared with that expected in the general population (SMR = 1.47; 95% CI, 1.10 to 1.93; $p = 0.009$). A total of 114 patients had at least one major vascular event, with a 10 year risk of any first stroke, myocardial infarction, or vascular death of 42.8% (95% CI, 36.4 to 48.5). **CONCLUSIONS:** The overall risk of major vascular events remains high for 10 to 15 years after a TIA. It is important therefore that preventive treatments are continued in the long term, even in apparently “low risk” patients who have already survived free of stroke for several years.

J Neurol Neurosurg Psychiatry. 2003 May;74(5):577-80

COMPARISON BETWEEN MEASURES OF ATHEROSCLEROSIS AND RISK OF STROKE: THE ROTTERDAM STUDY.

BACKGROUND AND PURPOSE: Several measures of atherosclerosis predict the risk of stroke. However, a comparison between various measures of atherosclerosis is lacking, and limited information exists on the added value of individual measures of atherosclerosis to cardiovascular risk factors. We compared different measures of atherosclerosis in relation to stroke. **METHODS:** The study was based on the prospective cohort of the Rotterdam Study and included 6,913 participants who did not suffer from previous stroke. At baseline, carotid intima-media thickness and plaques, ankle-arm index, and aortic calcifications were assessed; 3,996 participants (53%) had measures of all studied markers of atherosclerosis. After a mean follow-up of 6.1 years, 378 strokes occurred. Data were analyzed with Cox proportional-hazards regression and Akaike information criteria scores. **RESULTS:** Carotid intima-media thickness and aortic calcifications were related most strongly to the risk of stroke (relative risk, 2.23 and 1.89; 95% confidence interval, 1.48 to 3.36 and 1.28 to 2.80 for highest versus lowest tertile, respectively). The relations between intima-media thickness, aortic calcifications, and carotid plaques and stroke remained after adjustment for cardiovascular risk factors. Intima-media thickness and aortic calcifications were related to the risk of stroke independently of each other. The relation between ankle-arm index and stroke disappeared after adjustment for cardiovascular risk factors. **CONCLUSIONS:** Carotid intima-media thickness and aortic calcifications are stronger predictors of incident stroke than carotid plaque or ankle-arm indexes. They have additional value to each other and to classic risk factors and may reflect different processes.

Stroke. 2003 Oct;34(10):2367-72. Epub 2003 Sep 04

THE SEVENTH REPORT OF THE JOINT NATIONAL COMMITTEE ON PREVENTION, DETECTION, EVALUATION, AND TREATMENT OF HIGH BLOOD PRESSURE: THE JNC 7 REPORT.

“The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure” provides a new guideline for hypertension prevention and management. The following are the key messages(1) In persons older than 50 years, systolic blood pressure (BP) of more than 140 mm Hg is a much more important cardiovascular

disease (CVD) risk factor than diastolic BP; (2) The risk of CVD, beginning at 115/75 mm Hg, doubles with each increment of 20/10 mm Hg; individuals who are normotensive at 55 years of age have a 90% lifetime risk for developing hypertension; (3) Individuals with a systolic BP of 120 to 139 mm Hg or a diastolic BP of 80 to 89 mm Hg should be considered as prehypertensive and require health-promoting lifestyle modifications to prevent CVD; (4) Thiazide-type diuretics should be used in drug treatment for most patients with uncomplicated hypertension, either alone or combined with drugs from other classes. Certain high-risk conditions are compelling indications for the initial use of other antihypertensive drug classes (angiotensin-converting enzyme inhibitors, angio-tensin-receptor blockers, beta-blockers, calcium channel blockers); (5) Most patients with hypertension will require 2 or more antihypertensive medications to achieve goal BP (<140/90 mm Hg, or <130/80 mm Hg for patients with diabetes or chronic kidney disease); (6) If BP is more than 20/10 mm Hg above goal BP, consideration should be given to initiating therapy with 2 agents, 1 of which usually should be a thiazide-type diuretic; and (7) The most effective therapy prescribed by the most careful clinician will control hypertension only if patients are motivated. Motivation improves when patients have positive experiences with and trust in the clinician. Empathy builds trust and is a potent motivator. Finally, in presenting these guidelines, the committee recognizes that the responsible physician's judgment remains paramount.

JAMA. 2003 May 21;289(19):2560-72

EFFECT OF ANTIHYPERTENSIVE AGENTS ON CARDIOVASCULAR EVENTS IN PATIENTS WITH CORONARY DISEASE AND NORMAL BLOOD PRESSURE: THE CAMELOT STUDY: A RANDOMIZED CONTROLLED TRIAL.

CONTEXT: The effect of antihypertensive drugs on cardiovascular events in patients with coronary artery disease (CAD) and normal blood pressure remains uncertain. **OBJECTIVE:** To compare the effects of amlodipine or enalapril vs placebo on cardiovascular events in patients with CAD. **DESIGN, SETTING, AND PARTICIPANTS:** Double-blind, randomized, multicenter, 24-month trial (enrollment April 1999-April 2002) comparing amlodipine or enalapril with placebo in 1991 patients with angiographically documented CAD (>20% stenosis by coronary angiography) and diastolic blood pressure <100 mm Hg. A substudy of 274 patients measured atherosclerosis progression by intravascular ultrasound (IVUS). **INTERVENTIONS:** Patients were randomized to receive amlodipine, 10 mg; enalapril, 20 mg; or placebo. IVUS was performed at baseline and study completion. **MAIN OUTCOME MEASURES:** The primary efficacy parameter was incidence of cardiovascular events for amlodipine vs placebo. Other outcomes included comparisons of amlodipine vs enalapril and enalapril vs placebo. Events included cardiovascular death, nonfatal myocardial infarction, resuscitated cardiac arrest, coronary revascularization, hospitalization for angina pectoris, hospitalization for congestive heart failure, fatal or nonfatal stroke or transient ischemic attack, and new diagnosis of peripheral vascular disease. The IVUS end point was change in percent atheroma volume. **RESULTS:** Baseline blood pressure averaged 129/78 mm Hg for all patients; it increased by 0.7/0.6 mm Hg in the placebo group and decreased by 4.8/2.5 mm Hg and 4.9/2.4 mm Hg in the amlodipine and enalapril groups, respectively ($P < .001$ for both vs placebo). Cardiovascular events occurred in 151 (23.1%) placebo-treated patients, in 110 (16.6%) amlodipine-treated patients (hazard ratio [HR], 0.69; 95% CI, 0.54-0.88 [$P = .003$]), and in 136 (20.2%) enalapril-treated patients (HR, 0.85; 95% CI, 0.67-1.07 [$P = .16$]). Primary end point comparison for enalapril vs amlodipine was not significant (HR, 0.81; 95% CI, 0.63-1.04 [$P = .10$]). The IVUS substudy showed a trend toward less progression of atherosclerosis in the amlodipine group vs placebo ($P = .12$), with significantly less progression in the subgroup with systolic blood pressures greater than the mean ($P = .02$). Compared with baseline, IVUS showed progression in the placebo group ($P < .001$), a trend toward progression in the enalapril group ($P = .08$), and no progression in the amlodipine group ($P = .31$). For the amlodipine group, correlation between blood pressure reduction and progression was $r = 0.19$, $P = .07$. **CONCLUSIONS:** Administration of amlodipine to patients with CAD and normal blood pressure resulted in reduced adverse cardiovascular events. Directionally similar, but smaller and nonsignificant, treatment effects were observed with enalapril. For amlodipine, IVUS showed evidence of slowing of atherosclerosis progression.

JAMA. 2004 Nov 10;292(18):2217-25

BODY MASS INDEX IN MID-LIFE IS ASSOCIATED WITH A FIRST STROKE IN MEN: A PROSPECTIVE POPULATION STUDY OVER 28 YEARS.

BACKGROUND AND PURPOSE: Data on the association between obesity and stroke are still limited. We examined the possible association between mid-life body mass index (BMI) and risk of stroke in the prospective Multifactor Primary Prevention Study in Goteborg, Sweden. **METHODS:** 7,402 apparently healthy men aged 47 to 55 at baseline were followed-up over a 28-year period. Incidence of fatal and nonfatal stroke was recorded in a local stroke registry through the Swedish National Register on Cause of Death and the Swedish Hospital Discharge Registry. **RESULTS:** A total of 873 first strokes were recorded, including 495 ischemic, 144 hemorrhagic, and 234 unspecified strokes. Compared with men with low normal weight (BMI, 20.0 to 22.49 kg/m²), men with BMI >30.0 kg/m² had a multiple adjusted hazard ratio of 1.93 (95% CI, 1.44 to 2.58) for total stroke, 1.78 (95% CI, 1.22 to 2.60) for ischemic stroke, and 3.91 (95% CI, 2.10 to 7.27) for unspecified stroke. There was no significant association between BMI and hemorrhagic stroke. Adjustment for potential mediators, eg, hypertension, diabetes and serum cholesterol levels, attenuated but did not eliminate the risk. **CONCLUSIONS:** In this prospective population-based study of men, increased BMI in mid-life was associated with an increased risk for total, ischemic, and unspecified stroke, but not with hemorrhagic stroke. The result supports the role of mid-life BMI as a risk factor for stroke later in life and suggests a differentiated effect on stroke subtypes.

APOLIPOPROTEIN B/APOLIPOPROTEIN A-I IN RELATION TO THE METABOLIC SYNDROME AND CHANGE IN CAROTID ARTERY INTIMA-MEDIA THICKNESS DURING 3 YEARS IN MIDDLE-AGED MEN.

BACKGROUND AND PURPOSE: The apolipoprotein B (apoB)/apolipoprotein A-I (apoA-I) ratio is a measure of the relationship between different lipoprotein particles and a powerful predictor of coronary death. The aim was to examine whether apoB/apoA-I was associated with the metabolic syndrome (MetS) at baseline and also with the future change in carotid artery intima-media thickness (IMT). **METHODS:** In 313 58-year-old men, carotid artery IMT was measured bilaterally by high-resolution B-mode ultrasound at baseline and after 3 years of follow-up. Serum apolipoprotein concentrations and the components of MetS were measured at study entry. **RESULTS:** ApoB/apoA-I showed statistically significant associations with body mass index, waist-to-hip ratio, high-density lipoprotein (HDL) cholesterol, triglycerides, low-density lipoprotein (LDL) particle size, insulin, and diastolic blood pressure. Two thirds of the patients with MetS had high apoB/apoA-I ratios (>0.90) compared with one third of those without the syndrome ($P<0.001$). The IMT change was associated with apoB, total cholesterol, LDL cholesterol, triglycerides, and inversely with HDL cholesterol and LDL particle size at entry, and there was a strong colinearity between these variables. The subjects with apoB/apoA-I above the first tertile (0.74) had a 20-microm-higher (95% CI, 7 to 33) annual increase in IMT compared with those below this level after adjustment for blood pressure and smoking. **CONCLUSIONS:** The apoB/apoA-I ratio was strongly associated with MetS and its components at baseline. ApoB/apoA-I at baseline was related to the change in carotid artery IMT during 3 years of follow-up. There was a strong colinearity between apoB/apoA and the atherogenic lipids.

ABSTRACTS

Hormone Replacement Therapy

A PHYSIOLOGIC ROLE FOR TESTOSTERONE IN LIMITING ESTROGENIC STIMULATION OF THE BREAST.

OBJECTIVE: The normal ovary produces abundant testosterone in addition to estradiol (E(2)) and progesterone, but usually only the latter two hormones are "replaced" in the treatment of ovarian failure and menopause. Some clinical and genetic evidence suggests, however, that endogenous androgens normally inhibit estrogen-induced mammary epithelial proliferation (MEP) and thereby may protect against breast cancer. **DESIGN:** To investigate the role of endogenous androgen in regulating mammary epithelial proliferation, normal-cycling rhesus monkeys were treated with flutamide, an androgen receptor antagonist. To evaluate the effect of physiological testosterone (T) supplementation of estrogen replacement therapy, ovariectomized monkeys were treated with E(2), E(2) plus progesterone, E(2) plus T, or vehicle. **RESULTS:** We show that androgen receptor blockade in normal female monkeys results in a more than twofold increase in MEP, indicating that endogenous androgens normally inhibit MEP. Moreover, we show that addition of a small, physiological dose of T to standard estrogen therapy almost completely attenuates estrogen-induced increases in MEP in the ovariectomized monkey, suggesting that the increased breast cancer risk associated with estrogen treatment could be reduced by T supplementation. Testosterone reduces mammary epithelial estrogen receptor (ER) alpha and increases ERbeta expression, resulting in a marked reversal of the ERalpha/beta ratio found in the estrogen-treated monkey. Moreover, T treatment is associated with a significant reduction in mammary epithelial MYC expression, suggesting that T's antiestrogenic effects at the mammary gland involve alterations in ER signaling to MYC. **CONCLUSIONS:** These findings suggest that treatment with a balanced formulation including all ovarian hormones may prevent or reduce estrogenic cancer risk in the treatment of girls and women with ovarian failure.

Menopause. 2003 Jul-Aug;10(4):292-8

TESTOSTERONE INFLUENCES LIBIDO AND WELL BEING IN WOMEN.

There is increasing awareness of the significant and varied actions of endogenous androgens in women, and acknowledgement that women might experience symptoms secondary to androgen deficiency. There is also substantial evidence that prudent testosterone replacement is effective in relieving both the physical and psychological symptoms of androgen insufficiency in clinically affected women. However, our understanding of the actions of testosterone in women is incomplete, with no consensus as to what constitutes either biochemical or clinical testosterone deficiency. The focus of the limited research into testosterone replacement has been on sexuality, primarily sexual desire. However, the influence of testosterone on mood and well being also requires further exploration.

Trends Endocrinol Metab. 2001 Jan-Feb;12(1):33-7

ANDROGENS AND FEMALE SEXUALITY.

An accumulating body of data indicates that many women experience a cluster of symptoms that are responsive to testosterone treatment and may be due to androgen deficiency. Characteristically, affected women complain of low libido, persistent fatigue, and diminished well-being and are found to have low circulating bioavailable testosterone. Whether the apparent therapeutic effects of testosterone are mediated via the androgen receptor or as a consequence of metabolism to estrogen is not known. Despite the lack of understanding of the mechanism(s) by which testosterone may enhance libido, the prescription of testosterone to women in a variety of formulations is becoming increasingly popular. This article provides an overview of the rationale for testosterone therapy in women, offers a broad definition of androgen deficiency in women based on the clinical experience of the author, and outlines the currently available options and potential risks of testosterone replacement in women.

J Gend Specif Med. 2000 Jan-Feb;3(1):36-40

TRANSDERMAL TESTOSTERONE TREATMENT IN WOMEN WITH IMPAIRED SEXUAL FUNCTION AFTER OOPHORECTOMY.

BACKGROUND: The ovaries provide approximately half the circulating testosterone in premenopausal women. After bilateral oophorectomy, many women report impaired sexual functioning despite estrogen replacement. We evaluated the effects of transdermal testosterone in women who had impaired sexual function after surgically induced menopause. **METHODS:** Seventy-five women, 31 to 56 years old, who had undergone oophorectomy and hysterectomy received conjugated equine estrogens (at least 0.625 mg per day orally) and, in random order, placebo, 150 microg of testosterone, and 300 microg of testosterone per day

transdermally for 12 weeks each. Outcome measures included scores on the Brief Index of Sexual Functioning for Women, the Psychological General Well-Being Index, and a sexual-function diary completed over the telephone. RESULTS: The mean (+/-SD) serum free testosterone concentration increased from 1.2+/-0.8 pg per milliliter (4.2+/-2.8 pmol per liter) during placebo treatment to 3.9+/-2.4 pg per milliliter (13.5+/-8.3 pmol per liter) and 5.9+/-4.8 pg per milliliter (20.5+/-16.6 pmol per liter) during treatment with 150 and 300 microg of testosterone per day, respectively (normal range, 1.3 to 6.8 pg per milliliter [4.5 to 23.6 pmol per liter]). Despite an appreciable placebo response, the higher testosterone dose resulted in further increases in scores for frequency of sexual activity and pleasure-orgasm in the Brief index of Sexual Functioning for Women (P=0.03 for both comparisons with placebo). At the higher dose the percentages of women who had sexual fantasies, masturbated, or engaged in sexual intercourse at least once a week increased two to three times from base line. The positive-well-being, depressed-mood, and composite scores of the Psychological General Well-Being Index also improved at the higher dose (P=0.04, P=0.03, and P=0.04, respectively, for the comparison with placebo), but the scores on the telephone-based diary did not increase significantly. CONCLUSIONS: In women who have undergone oophorectomy and hysterectomy, transdermal testosterone improves sexual function and psychological well-being.

N Engl J Med. 2000 Sep 7;343(10):682-8

SEX HORMONE ADJUVANT THERAPY IN RHEUMATOID ARTHRITIS.

RA is an autoimmune rheumatic disorder resulting from the combination of several predisposing factors, including the relation between epitopes of possible triggering agents and histocompatibility epitopes, the status of the stress response system, and the sex hormone status. Estrogens are implicated as enhancers of humoral immunity, and androgens and progesterone are natural immune suppressors. Sex hormone concentrations have been evaluated in RA patients before glucocorticoid therapy and have frequently been found to be altered, especially in premenopausal women and male patients. In particular, low levels of gonadal and adrenal androgens (testosterone and DHT, DHEA and DHEAS) and a reduced androgen:estrogen ratio have been detected in body fluids (i.e., blood, synovial fluid, smears, saliva) of male and female RA patients. These observations support a possible pathogenic role for the decreased levels of the immune-suppressive androgens. Exposure to environmental estrogens (estrogenic xenobiotics), genetic polymorphisms of genes coding for hormone metabolic enzymes or receptors, and gonadal disturbances related to stress system activation (hypothalamic-pituitary-adrenocortical axis) and physiologic hormonal perturbations such as during aging, the menstrual cycle, pregnancy, the postpartum period, and menopause may interfere with the androgen:estrogen ratio. Sex hormones might exert their immune-modulating effects, at least in RA synovitis, because synovial macrophages, monocytes, and lymphocytes possess functional androgen and estrogen receptors and may metabolize gonadal hormones. The molecular basis for sex hormone adjuvant therapy in RA is thus experimentally substantiated. By considering the well-demonstrated immune-suppressive activities exerted by androgens, male hormones and their derivatives seem to be the most promising therapeutic approach. Recent studies have shown positive effects of androgen replacement therapy at least in male RA patients, particularly as adjuvant treatment. Interestingly, the increase in serum androgen metabolism induced by RA treatment with CSA should be regarded as a possible marker of androgen-mediated immune-suppressive activities exerted by CSA, at least in RA and at the level of sensitive target cells and tissues (i.e., synovial macrophages). The absence of altered serum levels of estrogens in RA patients and the reported immune-enhancing properties exerted by female hormones have represented a poor stimulus to test estrogen replacement therapy in RA. The different results obtained with OC use seem to depend on dose-related effects and the different type of response to estrogens in relation to the cytokine balance between Th1 cells (cellular immunity, i.e., RA) and Th2 cells (humoral immunity, i.e., SLE). The androgen replacement obtained directly (i.e., testosterone, DHT, DHEAS) or indirectly (i.e., antiestrogens) may represent a valuable concomitant or adjuvant treatment to be associated with other disease-modifying antirheumatic drugs (i.e., MTX, CSA) in the management of RA.

Rheum Dis Clin North Am. 2000 Nov;26(4):881-95

RISKS AND BENEFITS OF ESTROGEN PLUS PROGESTIN IN HEALTHY POSTMENOPAUSAL WOMEN: PRINCIPAL RESULTS FROM THE WOMEN'S HEALTH INITIATIVE RANDOMIZED CONTROLLED TRIAL.

CONTEXT: Despite decades of accumulated observational evidence, the balance of risks and benefits for hormone use in healthy postmenopausal women remains uncertain. OBJECTIVE: To assess the major health benefits and risks of the most commonly used combined hormone preparation in the United States. DESIGN: Estrogen plus progestin component of the Women's Health Initiative, a randomized controlled primary prevention trial (planned duration, 8.5 years) in which 16,608 postmenopausal women aged 50-79 years with an intact uterus at baseline were recruited by 40 US clinical centers in 1993-1998. INTERVENTIONS: Participants received conjugated equine estrogens, 0.625 mg/d, plus medroxyprogesterone acetate, 2.5 mg/d, in 1 tablet (n = 8506) or placebo (n = 8102). MAIN OUTCOMES MEASURES: The primary outcome was coronary heart disease (CHD) (nonfatal myocardial infarction and CHD death), with invasive breast cancer as the primary adverse outcome. A global index summarizing the balance of risks and benefits included the 2 primary outcomes plus stroke, pulmonary embolism (PE), endometrial cancer, colorectal cancer, hip fracture, and death due to other causes. RESULTS: On May 31, 2002, after a mean of 5.2 years of follow-up, the data and safety monitoring board recommended stopping the trial of estrogen plus progestin vs placebo because the test statistic for invasive breast cancer exceeded the stopping boundary for this adverse effect and the global index statistic supported risks exceeding benefits. This report includes data on the major clinical outcomes through April 30, 2002. Estimated hazard

ratios (HRs) (nominal 95% confidence intervals [CIs]) were as follows: CHD, 1.29 (1.02-1.63) with 286 cases; breast cancer, 1.26 (1.00-1.59) with 290 cases; stroke, 1.41 (1.07-1.85) with 212 cases; PE, 2.13 (1.39-3.25) with 101 cases; colorectal cancer, 0.63 (0.43-0.92) with 112 cases; endometrial cancer, 0.83 (0.47-1.47) with 47 cases; hip fracture, 0.66 (0.45-0.98) with 106 cases; and death due to other causes, 0.92 (0.74-1.14) with 331 cases. Corresponding HRs (nominal 95% CIs) for composite outcomes were 1.22 (1.09-1.36) for total cardiovascular disease (arterial and venous disease), 1.03 (0.90-1.17) for total cancer, 0.76 (0.69-0.85) for combined fractures, 0.98 (0.82-1.18) for total mortality, and 1.15 (1.03-1.28) for the global index. Absolute excess risks per 10 000 person-years attributable to estrogen plus progestin were 7 more CHD events, 8 more strokes, 8 more PEs, and 8 more invasive breast cancers, while absolute risk reductions per 10 000 person-years were 6 fewer colorectal cancers and 5 fewer hip fractures. The absolute excess risk of events included in the global index was 19 per 10 000 person-years.

CONCLUSIONS: Overall health risks exceeded benefits from use of combined estrogen plus progestin for an average 5.2-year follow-up among healthy postmenopausal US women. All-cause mortality was not affected during the trial. The risk-benefit profile found in this trial is not consistent with the requirements for a viable intervention for primary prevention of chronic diseases, and the results indicate that this regimen should not be initiated or continued for primary prevention of CHD.

JAMA. 2002 Jul 17;288(3):321-3

ABSTRACTS

Ginkgo

EFFECTS OF GINKGO BILOBA ON MENTAL FUNCTIONING IN HEALTHY VOLUNTEERS.

BACKGROUND: There has been a lack of investigations examining the effects of Ginkgo biloba extract EGb 761 on mental functions and quality of life in healthy subjects with no cognitive impairment. Thus, the objective of the present study was to evaluate the relatively short-term (i.e., 4 weeks) effects of EGb 761 on mental functioning and quality of life in healthy volunteers. **METHODS:** The trial was conducted as a 4-week, randomized, double-blind, placebo-controlled, parallel-group, monocentric study. Sixty six healthy volunteers aged between 50 and 65 years without age-associated cognitive impairment were randomized, 32 into the placebo and 34 into the EGb 761-treatment group (240 mg, t.i.d.). Safety and compliance were monitored after 1, 2, 3 and 4 weeks. Primary outcome measures in this study are the subjects' judgment of their own mental health (MH), their general health (GH) and their quality of life (QoL) operationalized on the basis of three different visual analog scales (VAS). Secondary outcome measures are 15 tests and experimental procedures based on a neurobiologically based classification or taxonomy of functions. **RESULTS:** Intergroup differences in self-estimated mental health as well as self-estimated quality of life were significant in favor of EGb 761. No intergroup differences were found in self-estimated general health. Secondary outcomes supporting the notion of superiority of the active drug were found for both motor performance and emotional evaluation. This study did not reveal evidence of unknown drug-induced side effects or intolerance. No serious adverse events were observed during the study. **CONCLUSIONS:** Both questions treated in this study, efficacy and safety, are important from a medical perspective because many persons take the agent studied in an effort to enhance their mental functioning and general well-being. The findings of this study support the adequacy of intake of EGb 761 to improve the functions indicated previously.

Arch Med Res. 2003 Sep-Oct;34(5):373-81

THE EFFECTS OF GINKGO BILOBA EXTRACT (LI 1370) SUPPLEMENTATION AND DISCONTINUATION ON ACTIVITIES OF DAILY LIVING AND MOOD IN FREE LIVING OLDER VOLUNTEERS.

The aim of the study was to investigate the effects of continuing treatment with Ginkgo biloba extract (GBE) 120 mg/day on the activities of daily living (ADLs) and mood in healthy older volunteers who had immediately previously participated in a survey of the effects of a 4 month treatment with the drug. Following a prior postal survey investigating the effects of 4 months supplementation with GBE on ADLs and various aspects of mood and sleep, 1,570 volunteers continued onto a 6 month follow-up postal survey. Subjects selected their own treatment option for the follow-up survey, which effectively created four groups: a continuation group who received GBE in the initial 4 month study and during the 6 month follow-up (GBE-GBE), a discontinuation group who received GBE in the initial study but not during the follow-up (GBE-NT), a new treatment group who did not receive GBE in the initial 4 month study but who did receive GBE during the 6 month follow-up (NT-GBE), and a no treatment group who received no treatment in either survey (NT-NT). At the end of the 6 month follow-up period each subject completed a line analogue rating scale (LARS) and a self-rating activities of daily living scale (SR-ADL). There were significant differences in the mean overall LARS and SR-ADL scores between the four treatment combination groups at the end of the follow-up period. A factor analysis of the LARS revealed two factors, 'mood' and 'alertness'. When scores from each of the treatment groups were examined over the whole 10 month period it was evident that the ratings of overall competence in the SR-ADL and both factors of the LARS were diminished on cessation of treatment with GBE, and improved when GBE treatment was initiated. The magnitude of the improvements on all scales was related to the overall duration of GBE supplementation. Significant differences between the groups of subjects treated with GBE for different periods of time (4-10 months) suggests that the extract has a demonstrable effect in improving mood and the self-assessed performance of the tasks of everyday living.

Phytother Res. 2004 Jul;18(7):531-7

STUDIES ON MOLECULAR MECHANISMS OF GINKGO BILOBA EXTRACT.

In the past decade, interest by the general public in the use of herbal dietary supplements has risen exponentially. As throughout history, individuals are now turning to the use of "natural" therapies for the prevention, treatment and cure of almost every ailment and aging malady imaginable, often without substantial proof of safety or efficacy. One of the most popular herbal supplements is Ginkgo biloba extract, taken for its perceived "memory enhancing" properties. Given the inordinate popularity, growing use, and substantial number of pharmaceutical products containing G. biloba, coupled with demands for product safety and "hard evidence," science has followed this trend closely with an ever-expanding body of pharmacological and clinical data on such preparations. Claims that standardized G. biloba extract (EGb 761) can modulate the cellular environment of an organism under both physiological and stress conditions may be attributed to its multivalent or totipotent properties, and can now be substantiated by the availability of modern molecular techniques. As opposed to pharmacologically manufactured or synthetic

drugs, which provide a single target for a single receptor as the mechanism of action, EGb 761 is able to up- or down-regulate signaling pathways, gene transcription, cellular metabolism, etc., and thus assist in the regulation of the general physiological status of the cell and/or organism in response to stressors posed by both intracellular and extracellular conditions. Presumably, this is one of the biggest advantages of using natural products for the prevention and treatment of infirmity, as well as the maintenance of health in an organism.

Appl Microbiol Biotechnol. 2004 May;64(4):465-72

EFFECTS OF BILOBALIDE ON CEREBRAL AMINO ACID NEUROTRANSMISSION.

Bilobalide is one of many active constituents found in EGb 761 (definition see editorial), which is extracted from Ginkgo biloba leaves. Whilst there is good, sound evidence that bilobalide exhibits neuroprotective actions in a variety of model systems, there is currently no consensus on its mechanism of action. This present communication summarises the results we have obtained with this compound on excitatory amino acid neurotransmission in the central nervous system using both neurochemical and electrophysiological techniques. Bilobalide was shown to reduce glutamate and aspartate release elicited by both high potassium-containing artificial cerebrospinal fluid (aCSF) or veratridine from mouse cortical slices. In addition, bilobalide had a very potent effect (IC (50) 2.7 microM) on glutamate release elicited by hypoxia/hypoglycaemia-induced release from rat cortical slices. Electrophysiologically, bilobalide also decreased the frequency of gamma-amino-butyric acid (GABA) uptake inhibitor-induced depolarisations in mouse cortical slices, an effect probably mediated by a decrease in glutamate release. No definitive conclusions can be reached concerning the mechanism of action of bilobalide, but an ability to decrease excitotoxic amino acid release, particularly glutamate, would suggest that this is a probable mechanism to account for its neuroprotective properties.

Pharmacopsychiatry. 2003 Jun;36 Suppl 1:S84-8

IMPROVED HAEMORRHOLOGICAL PROPERTIES BY GINKGO BILOBA EXTRACT (EGB 761) IN TYPE 2 DIABETES MELLITUS COMPLICATED WITH RETINOPATHY.

BACKGROUND & AIMS: Abnormal haemorrhological property changes in erythrocyte deformability, plasma and blood viscosity, and blood viscoelasticity may play very important roles in the development of microangiopathies in diabetes mellitus (DM). In this study, we demonstrate the improvement in abnormal haemorrhological parameters in DM with ingestion of Ginkgo biloba extract 761 (Egb 761). **METHODS:** Haemorrhological parameters before and 3 months after Egb 761 oral ingestion were determined in 25 type 2 DM patients with retinopathy. These parameters included lipid peroxidation stress of erythrocytes, erythrocyte deformability, plasma and blood viscosity, blood viscoelasticity, and retinal capillary blood flow velocity. **RESULTS:** After taking Egb 761 orally for 3 months, the blood viscosity was significantly reduced at different shear rates, by 0.44 +/- 0.10 (gamma = 400), 0.52 +/- 0.09 (gamma = 150) and 2.88 +/- 0.57 (gamma = 5). Viscoelasticity was significantly reduced in diabetic patients by 3.08 +/- 0.78 (0.1 Hz). The level of erythrocyte malondialdehyde (MDA) was reduced by 30%; however, the deformability of erythrocyte was increased by 20%. And lastly, retinal capillary blood flow rate was increased from 3.23 +/- 0.12 to 3.67 +/- 0.24 cm min(-1). **CONCLUSION:** In this preliminary clinical study, 3 months of oral administration of Egb 761 significantly reduced MDA levels of erythrocytes membranes, decreased fibrinogen levels, promoted erythrocytes deformability, and improved blood viscosity and viscoelasticity, which may facilitate blood perfusion. Furthermore, it effectively improved retinal capillary blood flow rate in type 2 diabetic patients with retinopathy.

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