

LE Magazine December 2002

## ABSTRACTS

### Hormones

Postmenopausal estrogen and progestin use and the risk of cardiovascular disease.

**BACKGROUND:** Estrogen therapy in postmenopausal women has been associated with a decreased risk of heart disease. There is little information, however, about the effect of combined estrogen and progestin therapy on the risk of cardiovascular disease.

**METHODS:** We examined the relation between cardiovascular disease and postmenopausal hormone therapy during up to 16 years of follow-up in 59,337 women from the Nurses' Health Study, who were 30 to 55 years of age at base line. Information on hormone use was ascertained with biennial questionnaires. From 1976 to 1992, we documented 770 cases of myocardial infarction or death from coronary disease in this group and 572 strokes. Proportional-hazards models were used to calculate relative risks and 95% confidence intervals, adjusted for confounding variables. **RESULTS:** We observed a marked decrease in the risk of major coronary heart disease among women who took estrogen with progestin (multivariate adjusted relative risk, 0.39; 95% confidence interval, 0.19 to 0.78) or estrogen alone (relative risk, 0.60; 95% confidence interval, 0.43 to 0.83), as compared with women who did not use hormones [corrected]. However, there was no significant association between stroke and use of combined hormones (multivariate adjusted relative risk, 1.09; 95% confidence interval, 0.66 to 1.80) or estrogen alone (relative risk, 1.27; 95% confidence interval, 0.95 to 1.69). **CONCLUSIONS:** The addition of progestin does not appear to attenuate the cardioprotective effects of postmenopausal estrogen therapy.

N Engl J Med 1996 Aug 15;335(7):453-61

Postmenopausal estrogen therapy and cardiovascular disease. Ten-year follow-up from the nurses' health study.

**BACKGROUND.** The effect of postmenopausal estrogen therapy on the risk of cardiovascular disease remains controversial. Our 1985 report in the Journal, based on four years of follow-up, suggested that estrogen therapy reduced the risk of coronary heart disease, but a report published simultaneously from the Framingham Study suggested that the risk was increased. In addition, studies of the effect of estrogens on stroke have yielded conflicting results. **METHODS.** We followed 48,470 postmenopausal women, 30 to 63 years old, who were participants in the Nurses' Health Study, and who did not have a history of cancer or cardiovascular disease at base line. During up to 10 years of follow-up (337,854 person-years), we documented 224 strokes, 405 cases of major coronary disease (nonfatal myocardial infarctions or deaths from coronary causes), and 1,263 deaths from all causes. **RESULTS.** After adjustment for age and other risk factors, the overall relative risk of major coronary disease in women currently taking estrogen was 0.56 (95% confidence interval, 0.40 to 0.80); the risk was significantly reduced among women with either natural or surgical menopause. We observed no effect of the duration of estrogen use independent of age. The findings were similar in analyses limited to women who had recently visited their physicians (relative risk, 0.45; 95% confidence interval, 0.31 to 0.66) and in a low-risk group that excluded women reporting current cigarette smoking, diabetes, hypertension, hypercholesterolemia, or a Quetelet index above the 90th percentile (relative risk, 0.53; 95% confidence interval, 0.31 to 0.91). The relative risk for current and former users of estrogen as compared with those who had never used it was 0.89 (95% confidence interval, 0.78 to 1.00) for total mortality and 0.72 (95% confidence interval, 0.55 to 0.95) for mortality from cardiovascular disease. The relative risk of stroke when current users were compared with those who had never used estrogen was 0.97 (95% confidence interval, 0.65 to 1.45), with no marked differences according to type of stroke. **CONCLUSIONS.** Current estrogen use is associated with a reduction in the incidence of coronary heart disease as well as in mortality from cardiovascular disease, but it is not associated with any change in the risk of stroke.

N Engl J Med 1991 Sep 12;325(11):756-62

Impact of postmenopausal hormone therapy on cardiovascular events and cancer: pooled data from clinical trials.

**OBJECTIVE:** To examine the incidence of cardiovascular diseases and cancer from published clinical trials that studied other outcomes of postmenopausal hormone therapy as some surveys have suggested that it may decrease the incidence of cardiovascular diseases and increase the incidence of hormone dependent cancers. **DESIGN:** Trials that compared hormone therapy with placebo, no therapy, or vitamins and minerals in comparable groups of postmenopausal women and reported cardiovascular or cancer outcomes were searched from the literature. **SUBJECTS:** 22 trials with 4,124 women were identified. In each group, the numbers of women with cardiovascular and cancer events were summed and divided by the numbers of women

originally allocated to the groups. RESULTS: Data on cardiovascular events and cancer were usually given incidentally, either as a reason for dropping out of a study or in a list of adverse effects. The calculated odds ratios for women taking hormones versus those not taking hormones was 1.39 (95% confidence interval 0.48 to 3.95) for cardiovascular events without pulmonary embolus and deep vein thrombosis and 1.64 (0.55 to 4.18) with them. It is unlikely that such results would have occurred if the true odds ratio were 0.7 or less. For cancers, the numbers of reported events were too low for a useful conclusion. CONCLUSIONS: The results of these pooled data do not support the notion that postmenopausal hormone therapy prevents cardiovascular events.

BMJ 1997 Jul 19;315(7101):149-53

Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. Heart and Estrogen/progestin Replacement Study (HERS) Research Group.

CONTEXT: Observational studies have found lower rates of coronary heart disease (CHD) in postmenopausal women who take estrogen than in women who do not, but this potential benefit has not been confirmed in clinical trials. OBJECTIVE: To determine if estrogen plus progestin therapy alters the risk for CHD events in postmenopausal women with established coronary disease. DESIGN: Randomized, blinded, placebo-controlled secondary prevention trial. SETTING: Outpatient and community settings at 20 U.S. clinical centers. PARTICIPANTS: A total of 2,763 women with coronary disease, younger than 80 years, and postmenopausal with an intact uterus. Mean age was 66.7 years. INTERVENTION: Either 0.625 mg of conjugated equine estrogens plus 2.5 mg of medroxyprogesterone acetate in 1 tablet daily (n = 1380) or a placebo of identical appearance (n = 1383). Follow-up averaged 4.1 years; 82% of those assigned to hormone treatment were taking it at the end of one year, and 75% at the end of three years. MAIN OUTCOME MEASURES: The primary outcome was the occurrence of nonfatal myocardial infarction (MI) or CHD death. Secondary cardiovascular outcomes included coronary revascularization, unstable angina, congestive heart failure, resuscitated cardiac arrest, stroke or transient ischemic attack, and peripheral arterial disease. All-cause mortality was also considered. RESULTS: Overall, there were no significant differences between groups in the primary outcome or in any of the secondary cardiovascular outcomes: 172 women in the hormone group and 176 women in the placebo group had MI or CHD death (relative hazard [RH], 0.99; 95% confidence interval [CI], 0.80-1.22). The lack of an overall effect occurred despite a net 11% lower low-density lipoprotein cholesterol level and 10% higher high-density lipoprotein cholesterol level in the hormone group compared with the placebo group (each P<.001). Within the overall null effect, there was a statistically significant time trend, with more CHD events in the hormone group than in the placebo group in year one and fewer in years four and five. More women in the hormone group than in the placebo group experienced venous thromboembolic events (34 vs 12; RH, 2.89; 95% CI, 1.50-5.58) and gallbladder disease (84 vs 62; RH, 1.38; 95% CI, 1.00-1.92). There were no significant differences in several other end points for which power was limited, including fracture, cancer, and total mortality (131 vs 123 deaths; RH, 1.08; 95% CI, 0.84-1.38). CONCLUSIONS: During an average follow-up of 4.1 years, treatment with oral conjugated equine estrogen plus medroxyprogesterone acetate did not reduce the overall rate of CHD events in postmenopausal women with established coronary disease. The treatment did increase the rate of thromboembolic events and gallbladder disease. Based on the finding of no overall cardiovascular benefit and a pattern of early increase in risk of CHD events, we do not recommend starting this treatment for the purpose of secondary prevention of CHD. However, given the favorable pattern of CHD events after several years of therapy, it could be appropriate for women already receiving this treatment to continue.

JAMA 1998 Aug 19;280(7):605-13

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 to 79 years with an intact uterus at baseline were recruited by 40 U.S. clinical centers in 1993 to 1998. INTERVENTIONS: Participants received conjugated equine estrogens, 0.625 mg/d, plus medroxyprogesterone acetate, 2.5 mg/d, in one 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 two 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 seven more CHD events, eight more strokes, eight more PEs, and eight

more invasive breast cancers, while absolute risk reductions per 10,000 person-years were six 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 U.S. 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):321-33

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## ABSTRACTS

### Natural HRT

Flaxseed and its lignan and oil components reduce mammary tumor growth at a late stage of carcinogenesis.

Flaxseed, a rich source of mammalian lignan precursor secoisolariciresinol-diglycoside (S.D.) and alpha-linolenic acid (ALA), has been shown to be protective at the early promotion stage of carcinogenesis. The objective of this study was to determine whether supplementation with flaxseed, its lignan or oil fractions, beginning 13 weeks after carcinogen administration, would reduce the size of established mammary tumors (present at the start of treatment) and appearance of new tumors in rats. Dietary groups consisted of the basal diet (BD, 20% corn oil) alone or supplemented with a gavage of 2200 nmol/day S.D. [S.D., equal to level in 5% flaxseed (F)], 1.82% flaxseed oil (OIL, equal to level in 5% F) or 2.5% or 5% flaxseed (2.5% F and 5% F, respectively). After seven weeks of treatment, established tumor volume was over 50% smaller in all treatment groups (OIL, 2.5% F, 5% F,  $P < 0.04$ ; S.D.,  $P < 0.08$ ) while there was no change in the BD group. New tumor number and volume were lowest in the S.D. ( $P < 0.02$ ) and 2.5% F ( $P < 0.07$ ) groups. The combined established and new tumor volumes were smaller for the S.D., 2.5% F and 5% F groups ( $P < 0.02$ ) compared to the OIL and BD groups. The high negative correlation ( $r = -0.997$ ,  $P < 0.001$ ) between established tumor volume and urinary mammalian lignan excretion in the BD, S.D., 2.5% F and 5% F groups indicates that the reduction in tumor size is due in part to the lignans derived from the S.D. in flaxseed. However, there was no relationship between new or total tumor development and urinary lignan levels. The effect of flaxseed oil may be related to its high ALA content. In conclusion, the S.D. in flaxseed appears to be beneficial throughout the promotional phase of carcinogenesis whereas the oil component is more effective at the stage when tumors have already been established.

Carcinogenesis 1996 Jun;17(6):1373-6

Flaxseed consumption influences endogenous hormone concentrations in postmenopausal women.

Lignans, similar in structure to endogenous sex steroid hormones, may act in vivo to alter hormone metabolism and subsequent cancer risk. The objective of this study was to examine effects of dietary intake of a lignan-rich plant food (flaxseed) on serum concentrations of endogenous hormones and binding proteins (estrone, estrone sulfate, 17 beta-estradiol, sex hormone-binding globulin, progesterone, prolactin, dehydroepiandrosterone sulfate, dehydroepiandrosterone, androstenedione, testosterone and free testosterone) in postmenopausal women. This randomized, crossover trial consisted of three seven-week feeding periods, during which 28 postmenopausal women, aged 52 to 82 yr, consumed their habitual diets plus 0, 5, or 10 g of ground flaxseed. Serum samples collected during the last week of each feeding period were analyzed for serum hormones using standard diagnostic kits. The flaxseed diets significantly reduced serum concentrations of 17 beta-estradiol by 3.26 pg/ml (12.06 pmol/l) and estrone sulfate by 0.09 ng/ml (0.42 nmol/l) and increased prolactin by 1.92 micrograms/l (0.05 IU/ml). Serum concentrations of androstenedione, estrone, sex hormone-binding globulin, progesterone, testosterone, free testosterone, dehydroepiandrosterone, and dehydroepiandrosterone sulfate were not altered with flaxseed feeding. In this group of postmenopausal women, consuming flaxseed in addition to their habitual diets influenced their endogenous hormone metabolism by decreasing serum 17 beta-estradiol and estrone sulfate and increasing serum prolactin concentrations.

Nutr Cancer 2001;39(1):58-65

Case-control study of phyto-oestrogens and breast cancer.

**BACKGROUND:** Phyto-oestrogens are a group of naturally occurring chemicals derived from plants; they have a structure similar to oestrogen, and form part of our diet. They also have potentially anticarcinogenic biological activity. We did a case-control study to assess the association between phyto-oestrogen intake (as measured by urinary excretion) and the risk of breast cancer. **METHODS:** Women with newly diagnosed early breast cancer were interviewed by means of questionnaires, and a 72 h urine collection and blood sample were taken before any treatment started. Controls were randomly selected from the electoral roll after matching for age and area of residence. 144 pairs were included for analysis. The urine samples were assayed for the isoflavonic phyto-oestrogens daidzein, genistein and equol, and the lignans enterodiol, enterolactone and matairesinol. **FINDINGS:** After adjustment for age at menarche, parity, alcohol intake, and total fat intake, high excretion of both equol and enterolactone was associated with a substantial reduction in breast-cancer risk, with significant trends through the quartiles: equol odds ratios were 1.00, 0.45 (95% CI 0.20, 1.02), 0.52 (0.23, 1.17), and 0.27 (0.10, 0.69)—trend  $p = 0.009$ —and enterolactone odds ratios were 1.00, 0.91 (0.41, 1.98), 0.65 (0.29, 1.44), 0.36 (0.15, 0.86)—trend  $p = 0.013$ . For most other phytoestrogens there was a reduction in risk, but it did not reach significance. Difficulties with the genistein assay precluded analysis of that substance.

**INTERPRETATION:** There is a substantial reduction in breast-cancer risk among women with a high intake (as measured by

excretion) of phyto-oestrogen equol and the lignan enterolactone. These findings could be important in the prevention of breast cancer.

Lancet 1997 Oct 4;350(9083):990-4

O-Glycosylation of human sex hormone-binding globulin is essential for inhibition of estradiol-induced MCF-7 breast cancer cell proliferation.

Human sex hormone-binding globulin (SHBG) is a homodimeric plasma glycoprotein, and each SHBG monomer may have an O-linked oligosaccharide at Thr(7) and up to two N-linked oligosaccharides at Asn(351) and Asn(367). In addition, a common genetic variant of SHBG exists with an extra site for N-glycosylation at residue 327. In the present study, we isolated MCF-7 derived cell lines expressing human SHBG cDNAs encoding the wild type protein or various glycosylation mutants. Estradiol (1 nM) treatment of parental (untransfected) MCF-7 cells or MCF-7 cells transfected with control expression vectors resulted in an increase in proliferation which was fully abrogated by co-incubation with an equimolar amount of human SHBG. In contrast, the same amount of purified SHBG added to MCF-7 cells expressing wild type SHBG partially inhibited the estradiol-induced cell proliferation. A high affinity binding site for SHBG was detectable on untransfected and control cells, but not on MCF-7 cells expressing wild type SHBG. Moreover, the treatment of MCF-7 cells with the conditioned medium containing wild type SHBG caused the disappearance of the SHBG plasma membrane-binding site. Media containing SHBG N-glycosylation mutants exerted the same effect, but mutants lacking the O-linked oligosaccharide at Thr(7) failed to do so. Estradiol-induced proliferation of parental MCF-7 cells was also inhibited by treatment with conditioned medium containing wild type SHBG or SHBG mutants lacking N-linked oligosaccharides, or containing an additional N-linked oligosaccharide at residue 327. However, MCF-7 conditioned medium containing SHBG mutants lacking an O-linked oligosaccharide at Thr(7) failed to exert this effect. These data suggest that O-glycosylation of SHBG is essential for SHBG binding to a membrane receptor that is responsible for inhibiting the estradiol-induced proliferation of MCF-7 breast cancer cells.

Mol Cell Endocrinol 2002 Mar 28;189(1-2):135-43

Effect of soy protein foods on low-density lipoprotein oxidation and ex vivo sex hormone receptor activity—a controlled crossover trial.

Plant-derived estrogen analogs (phytoestrogens) may confer significant health advantages including cholesterol reduction, antioxidant activity, and possibly a reduced cancer risk. However, the concern has also been raised that phytoestrogens may be endocrine disrupters and major health hazards. We therefore assessed the effects of soy foods as a rich source of isoflavonoid phytoestrogens on LDL oxidation and sex hormone receptor activity. Thirty-one hyperlipidemic subjects underwent two one-month low-fat metabolic diets in a randomized crossover study. The major differences between the test and control diets were an increase in soy protein foods (33 g/d soy protein) providing 86 mg isoflavones/2,000 kcal/d and a doubling of the soluble fiber intake. Fasting blood samples were obtained at the start and at weeks two and four, with 24-hour urine collections at the end of each phase. Soy foods increased urinary isoflavone excretion on the test diet versus the control ( $3.8 \pm 0.7$  v  $0.0 \pm 0.0$  mg/d,  $P < .001$ ). The test diet decreased both oxidized LDL measured as conjugated dienes in the LDL fraction ( $56 \pm 3$  v  $63 \pm 3$  micromol/L,  $P < .001$ ) and the ratio of conjugated dienes to LDL cholesterol ( $15.0 \pm 1.0$  v  $15.7 \pm 0.9$ ,  $P = .032$ ), even in subjects already using vitamin E supplements (400 to 800 mg/d). No significant difference was detected in ex vivo sex hormone activity between urine samples from the test and control periods. In conclusion, consumption of high-isoflavone foods was associated with reduced levels of circulating oxidized LDL even in subjects taking vitamin E, with no evidence of increased urinary estrogenic activity. Soy consumption may reduce cardiovascular disease risk without increasing the risk for hormone-dependent cancers.

Metabolism 2000 Apr;49(4):537-43

Cardioprotection by the phytoestrogen genistein in experimental myocardial ischaemia-reperfusion injury.

1. Soybean phytoestrogens have no oestrogen agonist effects on the reproductive system and therefore it is reasonable to explore the potential of these naturally occurring plant oestrogens in the cardiovascular pathology. We therefore investigated the effects of genistein in a rat model of myocardial ischaemia-reperfusion injury. 2. Anaesthetized rats were subjected to total occlusion (45 min) of the left main coronary artery followed by five h reperfusion (MI/R). Sham operated rats were used as controls. Myocardial necrosis, myocardial myeloperoxidase activity (MPO), serum creatinine phosphokinase activity (CPK), serum and macrophage Tumour Necrosis Factor-alpha (TNF-alpha), cardiac intercellular adhesion molecule-1 (ICAM-1) immunostaining, cardiac mRNA for ICAM-1 evaluated by the means of reverse transcriptase polymerase chain reaction (RT - PCR), ventricular arrhythmias and myocardial contractility (left ventricle  $dP/dt(max)$ ) were evaluated. 3. Myocardial ischaemia and reperfusion in untreated rats produced marked myocardial necrosis, increased serum CPK activity and MPO activity both in the area-at-risk and in the necrotic area, reduced myocardial contractility, caused ventricular arrhythmias and induced a marked increase in serum and macrophage TNF-alpha. Furthermore myocardial ischaemia-reperfusion injury increased ICAM-1 expression in the myocardium. 4. Administration of genistein (1 mg kg<sup>-1</sup>), i.v., five min after coronary artery occlusion) lowered myocardial necrosis and MPO activity in the area-at-risk and in the necrotic area, decreased serum CPK activity, increased myocardial contractility, decreased the occurrence of

ventricular arrhythmias, reduced serum and macrophages levels of TNF-alpha and blunted ICAM-1 expression in the injured myocardium. Finally genistein added in vitro to peritoneal macrophages collected from untreated rats subjected to myocardial ischaemia-reperfusion injury significantly reduced TNF-alpha production. 5. Our data suggest that genistein limits the inflammatory response and protects against myocardial ischaemia-reperfusion injury.

Br J Pharmacol 1999 Dec;128(8):1683-90

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## ABSTRACTS

Soy protein versus soy phytoestrogens in the prevention of diet-induced coronary artery atherosclerosis of male cynomolgus monkeys.

Soy protein, long recognized as having cardiovascular benefits, is a rich source of phytoestrogens (isoflavones). To distinguish the relative contributions of the protein moiety versus the alcohol-extractable phytoestrogens for cardiovascular protection, we studied young male cynomolgus macaques fed a moderately atherogenic diet and randomly assigned to three groups. The groups differed only in the source of dietary protein, which was either casein/lactalbumin (casein, n = 27), soy protein with the phytoestrogens intact (soy+, n = 27), or soy protein with the phytoestrogens mostly extracted (soy-, n = 28). The diets were fed for 14 months. Animals fed soy+ had significantly lower total and LDL plus VLDL cholesterol concentrations compared with the other two groups. They soy+ animals had the highest HDL cholesterol concentrations, the casein group had the lowest, and the soy- group was intermediate. A subset was necropsied for atherosclerosis evaluations (n = 11 per group). Morphometric and angiochemical measures were done to quantify atherosclerosis. Coronary artery atherosclerotic lesions were smallest in the soy+ group (90% less coronary atherosclerosis than the casein group and 50% less than the soy- group), largest in the casein group, and intermediate in the soy- group. The effects of the diets on lesion size and arterial lipid measures of the peripheral arteries were similar to those in the coronary arteries, with greatest prevention of atherogenesis with soy+ and intermediate benefit with soy- relative to casein. We could not determine whether the beneficial effects seen in the soy- group relate to the protein itself or to the remaining traces of phytoestrogens. The beneficial effects of soy protein on atherosclerosis appear to be mediated primarily by the phytoestrogen component. Testicular weights were unaffected by the phytoestrogens.

Arterioscler Thromb Vasc Biol 1997 Nov;17(11):2524-31

Phytoestrogens reduce bone loss and bone resorption in oophorectomized rats.

To examine a potential role for phytoestrogens in postmenopausal bone loss, the oophorectomized (OOX) rat model has been used in three studies to investigate the effects of the phytoestrogens coumestrol, zearalanol and a mixture of isoflavones on estrogen-dependent bone loss. In the studies of coumestrol and zearalanol, the rats were allocated to a control group, a phytoestrogen-treated group (1.5 micromol coumestrol or 3.1 mmol zearalanol twice per week, intramuscular) or, in the coumestrol study, an estrogen-treated group (28.1 nmol, intramuscular). In the isoflavone study, the rats were allocated to a control group, an estrogen treated group or a treatment group that received 131.25 mg of phytoestrogens per week incorporated into the nonpurified rat diet. Bone mineral density was measured globally and at the spine and femur at base line and six wk post-oophorectomy. In the coumestrol study, blood and urine samples were collected. Compared with the control group, rats receiving coumestrol and zearalanol had significantly reduced bone loss at all sites measured. The estrogen-treated group had significantly greater bone density than the control and the coumestrol-treated groups in the spine and global measurements. Coumestrol reduced urine calcium excretion and the bone resorption markers pyridinoline and deoxypyridinoline after one wk of treatment. Oral isoflavone phytoestrogens had no effect on oophorectomized rats including bone loss at the dose used. Thus, for the first time, the bioactivity of coumestrol and zearalanol in preventing bone loss has been demonstrated in a well-recognized model of postmenopausal bone loss.

J Nutr 1997 Sep;127(9):1795-9

Potassium iodide

Thyroid uptake and radiation dose after (131)I-lipiodol treatment: is thyroid blocking by potassium iodide necessary?

In radionuclide therapy with iodine-131 labelled pharmaceuticals, free (131)I may be released and trapped by the thyroid, causing an undesirable radiation burden. To prevent this, stable iodide such as potassium iodide (KI) can be given to saturate the thyroid before (131)I is administered. The guidelines of the European Association of Nuclear Medicine do not, however, recommend special precautions when administering (131)I-lipiodol therapy for hepatocellular carcinoma. Nevertheless, some authors have reported (131)I uptake in the thyroid as a consequence of such therapy. In this study, the influence of prophylactic KI on the thyroid uptake and dose (MIRD dosimetry) was prospectively investigated. (131)I-lipiodol was given as a slow bolus selectively in the proper hepatic artery or hyperselectively in the right and/or left hepatic artery. Patients were prospectively randomised into two groups. One group received KI in a dose of 100 mg per day starting two days before (131)I-lipiodol administration and continuing until two weeks after therapy (KI group; n=31), while the other group received no KI (non-KI group; n=37). Thyroid uptake was measured scintigraphically as a percentage of administered activity seven days after (131)I-lipiodol (n=68 treatments). The absorbed radiation dose to the thyroid was assessed by scintigraphy after seven and 14 days using a mono-exponential fitting model and MIRD dosimetry (n=40 treatments). The mean activity of (131)I-lipiodol administered was 1,835 MBq in a volume of 2 (n=17) or 4 (n=51) ml. Thyroid uptake

was lower in the KI group, being 0.23%±0.06% of injected activity (n=31) compared with 0.42%±0.20% in the non-KI group (n=37); the mean thyroid dose was 5.5±1.6 Gy in the KI group (n=19) versus 11.9±5.9 Gy in the non-KI group (n=21). These differences were statistically significant (P<0.001). No effect of the amount of added cold lipiodol (4 vs 2 ml total volume) or selectivity of (131)I-lipiodol administration was evident (P>0.1). (131)I-lipiodol is associated with a generally low thyroid uptake and dose that may be significantly decreased by KI premedication. Given the low cost and the very good tolerance of the KI treatment, we believe the use of KI should be recommended in the majority of the patients.

Eur J Nucl Med Mol Imaging 2002 Oct;29(10):1311-6

Inactivation of the antibacterial activity of iodine potassium iodide and chlorhexidine digluconate against *Enterococcus faecalis* by dentin, dentin matrix, type-I collagen, and heat-killed microbial whole cells.

The antibacterial activity of chlorhexidine digluconate and potassium iodide on *Enterococcus faecalis* A197A was tested in the presence of dentin, dentin matrix, dentin pretreated by EDTA and citric acid, collagen, and heat-killed cells of *Enterococcus faecalis* and *Candida albicans*. Medications were preincubated for 1 h with each of the potential inhibitors and tested for their antibacterial activity against *E. faecalis*, strain A197A. Surviving bacteria were sampled after one and 24 h of incubation. Dentin matrix and heat-killed microbial cells were the most effective inhibitors of chlorhexidine, whereas dentin pretreated by citric acid or EDTA showed only slight inhibition. Dentin and skin collagen showed some inhibition at one h but not after 24 h. Iodine potassium iodide was effectively inhibited by dentin, dentin matrix, and heat-killed microbial cells. Skin collagen and dentin pretreated by EDTA or by citric acid showed little or no inhibitory effect on iodine potassium iodide. Different components of dentin are responsible for the divergent patterns of inhibition of the antibacterial activity of chlorhexidine digluconate and iodine potassium iodide. Chemical treatment of dentin before applying the medication into the root canal may alter the antibacterial effect of the medication.

J Endod 2002 Sep;28(9):634-7

Effect of iodine or iopanoic acid on thyroid Ca<sup>2+</sup>/NADPH-dependent H<sub>2</sub>O<sub>2</sub>-generating activity and thyroperoxidase in toxic diffuse goiters.

**OBJECTIVE:** The aim of the present study was to compare the effects of iopanoic acid (IOP) or a saturated solution of potassium iodide (SSKI) administration to patients with toxic diffuse goiters (TDG). **DESIGN:** Patients with TDG are treated with thionamides and high doses of iodine preoperatively. In this study, two types of preoperative drug regimens were used: propylthiouracil or methimazole plus SSKI for 10-15 days (n=8) or IOP for seven days (n=6). **METHODS:** Serum thyroid hormones (total and free thyroxine (T<sub>4</sub>), total tri-iodothyronine (T<sub>3</sub>) and reverse T<sub>3</sub> (rT<sub>3</sub>)), were evaluated after seven days of either SSKI or IOP treatment, and after 10-15 days of SSKI administration. During thyroidectomy, samples of thyroid gland were obtained to evaluate thyroperoxidase and thyroid H<sub>2</sub>O<sub>2</sub>-generating activities. **RESULTS:** Serum total T<sub>3</sub> was significantly decreased after seven days of either treatment, and serum rT<sub>3</sub> was significantly increased in IOP-treated patients. Serum total and free T<sub>4</sub> were unaffected by seven days of IOP treatment, but decreased after seven days of SSKI treatment, although significantly diminished levels were only reached after a further three to eight days of SSKI administration. During both drug regimens, serum TSH remained low (SSKI: 0.159±0.122; IOP: 0.400±0.109 microU/ml). Thyroperoxidase activity was significantly lower in thyroid samples from patients treated with SSKI for 10 to 15 days than in the thyroid glands from IOP-treated patients. However, thyroid H<sub>2</sub>O<sub>2</sub> generation was inhibited in samples from patients treated with either IOP or SSKI. **CONCLUSIONS:** We show herein that IOP treatment can be effective in the management of hyperthyroidism and that this drug inhibits thyroid NADPH oxidase activity, just as previously described for SSKI, probably due to its iodine content.

Eur J Endocrinol 2002 Sep;147(3):293-8

High incidence of thyroid dysfunction despite prophylaxis with potassium iodide during (131)I-meta-iodobenzylguanidine treatment in children with neuroblastoma.

**BACKGROUND:** Treatment modalities like targeted radiotherapy with (131)I-meta-iodobenzylguanidine ((131)I-MIBG) improve survival rates after neuroblastoma (NB). Radiation to the thyroid gland can lead to hypothyroidism and even malignancy. Because hypothyroidism after (131)I-MIBG treatment was reported, the current KI prophylaxis against thyroidal radiation damage was evaluated. **METHODS:** The incidence, pathogenesis and consequences of thyroid dysfunction among 42 NB patients treated with (131)I-MIBG were evaluated retrospectively. Efficacy of KI prophylaxis was established by measuring thyroidal radioiodide uptake. Thyroid damage was expressed as thyrotropin elevation (TE, plasma concentration of thyroid stimulating hormone > or = 4.5 mU/L). **RESULTS:** The mean followup was 2.3 years (range, 0.1-8.5). The mean number of treatments with (131)I-MIBG was 3.3. Of 428 scintigrams, uptake of (131)I in the thyroid was visible in 92 (21.0%). Twenty two patients (52.4 %) presented TE after a mean period of 1.4 years (range, 0.1-5.8). Clinical signs of hypothyroidism were not observed. Eight patients received suppletion therapy with thyroxine. Thyrotropin elevation was transient in four patients. Of 25 survivors, with a mean followup of 3.5 years, 16 (64%) developed TE. No correlation was found between TE and thyroid visualization after (131)I-MIBG administration or the number of treatments. No abnormalities were seen by ultrasound imaging of the thyroid. **CONCLUSIONS:** Occurrence of thyroid dysfunction after treatment with (131)I-MIBG for NB is high, in spite of KI prophylaxis. Close followup of thyroid function and structure is required

in patients treated with (131)I-MIBG. New ways of protecting the thyroid during exposure to radioiodine should be developed.

Cancer 2002 Apr 1;94(7):2081-9

Thyroidal uptake and radiation dose after repetitive I-131-MIBG treatments: influence of potassium iodide for thyroid blocking.

**BACKGROUND:** In I-131-MIBG therapy, I-131-iodide can be released from the I-131-MIBG molecule. Hypothyroidism might result from the undesirable irradiation of the thyroid gland. To prevent this, stable iodide such as potassium iodide (KI) is given to oversaturate the thyroid before I-131-MIBG is administered. **PROCEDURE:** In the present study, the incidence of hypothyroidism (elevated TSH) was correlated with the thyroidal uptake of I-131 and dose (MIRD dosimetry) after 35 individual treatments in ten patients. Iodine-131-MIBG therapy was performed using a modified dosage of 1.9-11.1 GBq (50-300 mCi) IV. Premedication with KI was done as recommended with a dose of 100 mg KI orally from two days before until four weeks after I-131-MIBG. **RESULTS:** The absorbed thyroidal dose amounted to a very variable range of 0.2 (patient # 1) up to 30.0 (patient 3) Gy with 7.1 +/- 7.9 Gy per treatment and 24.1 +/- 19.2 Gy per patient (mean +/- SD), despite the same and compliantly taken KI premedication protocol. Up to now, 4/10 or 40% of patients have developed hypothyroidism after a mean follow-up period of 11 months and a mean total administered dose of 18.7 GBq (505 mCi). A trend towards higher thyroidal doses was seen in the hypothyroid patients. **CONCLUSIONS:** This study observes a general high inter- and intra-individual variability in radio-iodide uptake in the thyroid after I-131-MIBG therapy despite KI premedication, as well as possible occurrence of hypothyroidism. A dose-response relationship needs confirmation on a larger cohort of patients to reach statistical value. An alternative thyroid cytoprotection strategy for possible long-term survivors may be considered.

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## ABSTRACTS

### C-reactive protein

Lack of association between cholesterol and coronary heart disease mortality and morbidity and all-cause mortality in persons older than 70 years.

**OBJECTIVES:** To determine whether elevated serum cholesterol level is associated with all-cause mortality, mortality from coronary heart disease, or hospitalization for acute myocardial infarction and unstable angina in persons older than 70 years. Also, to evaluate the association between low levels of high-density lipoprotein cholesterol (HDL-C) and elevated ratio of serum cholesterol to HDL-C with these outcomes. **DESIGN:** Prospective, community-based cohort study with yearly interviews. **PARTICIPANTS--**A total of 997 subjects who were interviewed in 1988 as part of the New Haven, Conn. cohort of the Established Population for the Epidemiologic Study of the Elderly (EPESE) and consented to have blood drawn. **MAIN OUTCOME MEASURES:** The risk factor-adjusted odds ratios of the four-year incidence of all-cause mortality, mortality from coronary heart disease, and hospitalization for myocardial infarction or unstable angina were calculated for the following: subjects with total serum cholesterol levels greater than or equal to 6.20 mmol/L ( $\geq$  240 mg/dL) compared with subjects with cholesterol levels less than 5.20 mmol/L ( $<$  200 mg/dL); subjects in the lowest tertile of HDL-C level compared with those in the highest tertile; and subjects in the highest tertile of the ratio of total serum cholesterol to HDL-C level compared with those in the lowest tertile. **RESULTS:** Elevated total serum cholesterol level, low HDL-C, and high total serum cholesterol to HDL-C ratio were not associated with a significantly higher rate of all-cause mortality, coronary heart disease mortality or hospitalization for myocardial infarction or unstable angina after adjustment for cardiovascular risk factors. The risk factor-adjusted odds ratio for all-cause mortality was 0.99 (95% confidence interval [CI], 0.56 to 2.69) for the group who had cholesterol levels greater than or equal to 6.20 mmol/L ( $\geq$  240 mg/dL) compared with the group that had levels less than 5.20 mmol/L ( $<$  200 mg/dL); 1.00 (95% CI, 0.59 to 1.70) for the group in the lowest tertile of HDL-C compared with those in the highest tertile; and 1.03 (95% CK, 0.62 to 1.71) for subjects in the highest tertile of the ratio of total serum cholesterol to HDL-C compared with those in the lowest tertile. **CONCLUSIONS:** Our findings do not support the hypothesis that hypercholesterolemia or low HDL-C are important risk factors for all-cause mortality, coronary heart disease mortality or hospitalization for myocardial infarction or unstable angina in this cohort of persons older than 70 years.

JAMA 1994 Nov 2;272(17):1335-40

Report of the conference on low blood cholesterol: mortality associations.

**BACKGROUND:** A National Heart, Lung and Blood Institute (NHLBI) Conference was held October 9-10, 1990, to review and discuss existing data on U-shaped relations found between mortality rates and blood total cholesterol levels (TC) in some but not other studies. Presentations were given from 19 cohort studies from the United States, Europe, Israel and Japan. A representative of each study presented its findings and also submitted tables of proportional hazards regression coefficients for entry TC levels in regard to death, and these were incorporated into a formal statistical overview adjusted for age, diastolic blood pressure, cigarette smoking, body mass index and alcohol intake, as available. **METHODS AND RESULTS:** The U-shape for total mortality in men and the flat relation in women resulted largely from a positive relation of TC with coronary heart disease death and an inverse relation with deaths caused by some cancers (e.g., lung but not colon), respiratory disease, digestive disease, trauma and residual deaths. Risk for combined noncardiovascular, noncancer causes of death decreased steadily across the range of TC. The conference considered possible explanations for the statistical associations found between low TC levels or active TC lowering and certain causes of death. One is that TC is lowered by some disease conditions themselves, such as wasting in chronic pulmonary disease or reduced production and secretion of cholesterol-bearing lipoproteins with liver disease. In this sort of situation, the TC:mortality association found in observational studies may be due to preexisting disease. This was addressed by excluding early deaths from the analysis, which did not change the results. The conference considered as well the biological function of cholesterol, which, if seriously deranged, might hypothetically cause a wide variety of diseases and dysfunction. The conference also considered the biological functions that might provide plausible mechanisms for the associations found. **CONCLUSIONS:** Definitive interpretation of the associations observed was not possible, although most participants considered it likely that many of the statistical associations of low or lowered TC level are explainable by confounding in one form or another. The conference focused on the apparent existence and nature of these associations and on the need to understand their source rather than on any pertinence of the findings for public health policy. Further research is recommended to explain the observed associations of low TC levels (and TC lowering) with certain noncardiovascular diseases. This includes studies of the time course of TC change in disease, the relation of TC to morbidity, further studies of possible epidemiological confounding, monitoring of population trends in TC and mortality, further studies of the relations in women, auditing of noncardiovascular events in trials, studies of cell membrane, genetic and molecular links to cholesterol metabolism, TC level and disease, studies of disease manifestations in specific lipid disorders, and further study of the proposed causal mechanisms linking low TC and hemorrhagic stroke.

Circulation 1992 Sep;86(3):1046-60

Inflammatory markers and coronary heart disease.

**PURPOSE OF REVIEW:** Despite changes in lifestyle and the use of effective pharmacologic interventions to lower cholesterol levels, coronary heart disease remains the major cause of morbidity and mortality in the developed world. Cholesterol screening fails to identify almost 50% of those individuals who will present with acute coronary syndromes. Recent evidence from laboratory and prospective clinical studies demonstrates that atherosclerosis is not simply a disease of lipid deposition, but rather is an inflammatory process with highly specific cellular and molecular responses. The clinical utility of inflammatory markers has been examined in a variety of atherothrombotic diseases. Because C-reactive protein is highly stable in stored frozen samples, and automated and robust analytical systems for its measurement are available, it has become the most widely examined inflammatory marker. **RECENT FINDINGS:** C-reactive protein has consistently been shown to be a useful prognostic indicator in acute coronary syndromes and is a strong predictor of future coronary events in apparently healthy individuals. In addition, C-reactive protein can identify individuals with normal lipid levels who are at increased risk for future coronary events. Because drugs such as aspirin and statins reduce inflammatory risk, C-reactive protein has the potential to guide the use of these therapies in high-risk individuals for primary prevention. **SUMMARY:** C-reactive protein may have a role in global risk assessment for primary prevention and in targeting those patients who will benefit from anti-inflammatory therapies. In addition, it may also be a good prognostic indicator in patients with acute coronary syndromes.

Curr Opin Lipidol 2002 Aug;13(4):383-9

Prospective study of C-reactive protein, homocysteine and plasma lipid levels as predictors of sudden cardiac death.

**BACKGROUND:** Sudden cardiac death (SCD) is an important cause of mortality even among apparently healthy populations. However, our ability to identify those at risk for SCD in the general population is poor, and more specific markers are needed. **METHODS AND RESULTS:** To compare and contrast the relative importance of C-reactive protein (CRP), homocysteine and lipids as long-term predictors of SCD, we performed a prospective, nested, case-control analysis involving 97 cases of SCD among apparently healthy men enrolled in the Physician's Health Study. Of these plasma markers measured, only baseline CRP levels were significantly associated with the risk of SCD over the ensuing 17 years of follow-up (P for trend=0.001). The increase in risk associated with CRP levels was primarily seen among men in the highest quartile, who were at a 2.78-fold increased risk of SCD (95% CI 1.35 to 5.72) compared with men in the lowest quartile. These results were not significantly altered in analyses that (in addition to the matching variables of age and smoking status) controlled for lipid parameters, homocysteine, and multiple cardiac risk factors (relative risk for highest versus lowest quartile 2.65, 95% CI 0.79 to 8.83; P for trend=0.03). In contrast to the positive relationship observed for CRP, neither homocysteine nor lipid levels were significantly associated with risk of SCD. **CONCLUSIONS:** These prospective data suggest that CRP levels may be useful in identifying apparently healthy men who are at an increased long-term risk of SCD.

Circulation 2002 Jun 4;105(22):2595-9

C-reactive protein, statins and the primary prevention of atherosclerotic cardiovascular disease.

Emerging data implicate inflammation as integral to atherosclerosis and its complications. From a clinical perspective, the inflammatory biomarker C-reactive protein has demonstrated consistent predictive value in the detection of individuals at high risk for cardiovascular disease. Therapy with 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) reduces C-reactive protein as well as low-density lipoprotein cholesterol, thus providing a potential additional mechanism for the reduction in cardiovascular events associated with the use of these agents. Evidence from the Air Force/Texas Coronary Atherosclerosis Prevention Study suggests that statin therapy may be effective in reducing incident coronary events among those with elevated levels of C-reactive protein but normal levels of low-density lipoprotein cholesterol. These data, along with accumulating laboratory data, support a potential anti-inflammatory benefit of statins. Large-scale, randomized trials in the primary prevention of acute coronary events among individuals without overt hyperlipidemia but with evidence of elevated C-reactive protein are now needed to directly test this hypothesis.

Prev Cardiol 2002 Winter;5(1):42-6

Inflammatory mechanisms in atherosclerosis: from laboratory evidence to clinical application.

From the initial stages of leukocyte recruitment to diseased endothelium, to eventual rupture of unstable atheromatous plaque, pro-inflammatory mechanisms mediate key steps in atherogenesis and its complications. Lipid lowering, both with diet and statin therapy, has been shown to have favorable effects on inflammatory processes in atheromatous plaque. Several plasma markers of inflammation have been found to predict future cardiovascular risk, both among patients with acute coronary syndromes and myocardial infarction, and among healthy men and women. C-reactive protein (CRP), a pattern recognition molecule linked to the innate immune system, is a sensitive marker of low-grade vascular inflammation, which may also have direct pro-inflammatory actions. Recent studies have shown that statin therapy may lower CRP levels independent of lipid-lowering effects. Statin therapy

may also be highly effective for the prevention of cardiovascular events among individuals with elevated CRP levels. The role of statin therapy for plaque stabilization in acute coronary syndromes, and for prevention of future plaque rupture among healthy individuals with evidence of vascular inflammation, is an area of active research.

Ital Heart J 2001 Nov;2(11):796-800

Inflammatory biomarkers, hormone replacement therapy and incident coronary heart disease: prospective analysis from the Women's Health Initiative observational study.

**CONTEXT:** Postmenopausal hormone replacement therapy (HRT) has been shown to elevate C-reactive protein (CRP) levels. Several inflammatory biomarkers, including CRP, are associated with increased cardiovascular risk. However, whether the effect of HRT on CRP represents a clinical hazard is unknown. **OBJECTIVES:** To assess the association between baseline levels of CRP and interleukin 6 (IL-6) and incident coronary heart disease (CHD) and to examine the relationship between baseline use of HRT, CRP, and IL-6 levels as they relate to subsequent vascular risk. **DESIGN, SETTING, AND PARTICIPANTS:** Prospective, nested case-control study of postmenopausal women, forming part of the Women's Health Initiative, a large, nationwide, observational study. Among 75,343 women with no history of cardiovascular disease or cancer, 304 women who developed incident CHD were defined as cases and matched by age, smoking status, ethnicity, and follow-up time with 304 study participants who remained event free during a median observation period of 2.9 years. **MAIN OUTCOME MEASURE:** Incidence of first myocardial infarction or death from CHD. **RESULTS:** Median baseline levels of CRP (0.33 vs 0.25 mg/dL; interquartile range [IQR], 0.14-0.71 vs 0.10-0.47;  $P < .001$ ) and IL-6 (1.81 vs 1.47 pg/mL; IQR, 1.30-2.75 vs 1.05-2.15;  $P < .001$ ) were significantly higher among cases compared with controls. In matched analyses, the odds ratio (OR) for incident CHD in the highest vs lowest quartile was 2.3 for CRP (95% confidence interval [CI], 1.4-3.7;  $P$  for trend = .002) and 3.3 for IL-6 (95% CI, 2.0-5.5;  $P$  for trend  $< .001$ ). After additional adjustment for lipid and nonlipid risk factors, both inflammatory markers were significantly associated with a two-fold increase in odds for CHD events. As anticipated, current use of HRT was associated with significantly elevated median CRP levels. However, there was no association between HRT and IL-6. In analyses comparing individuals with comparable baseline levels of either CRP or IL-6, those taking or not taking HRT had similar CHD ORs. In analyses stratified by HRT, we observed a positively graded relationship between plasma CRP levels and the OR for CHD among both users and nonusers of HRT across the full spectrum of baseline CRP. **CONCLUSIONS:** These prospective findings indicate that CRP and IL-6 independently predict vascular events among apparently healthy postmenopausal women and that HRT increases CRP. However, use or nonuse of HRT had less importance as a predictor of cardiovascular risk than did baseline levels of either CRP or IL-6.

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