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Ipriflavone: Mechanism and Safety

By Nicole Nisly, MD

OSTEOPOROSIS IS ASSOCIATED WITH SIGNIFICANT MORBIDITY, MORtality, and financial burden. The ideal treatment for this condition should be well tolerated and effective as a prophylactic for young menopausal women as well as a treatment for women with established disease. It should have few contraindications or side effects and should not accumulate in the skeleton, where it could become detrimental to normal bone turnover. This article will discuss ipriflavone (IP), a synthetic isoflavone derivative, marketed for treatment of osteoporosis in more than 20 countries worldwide and available as a dietary supplement in the United States.[1]

Background

In the 1930s, an estrogenic effect was first noted in cattle consuming large quantities of clover; this effect was later traced to isoflavones. In 1969, a research project aimed at synthesizing isoflavone derivatives with androgenic, but not estrogenic, activity was created. About 200 new molecules were created and screened. In 1970, 7-isopropoxyisoflavone (IP) was selected because of its calcium-retaining effect in in vitro studies.[2] In the early 1970s, experiments in the treatment of bone diseases related to bone mass loss in humans and other animals were conducted.

Mechanisms of Action

IP has several mechanisms of action that enhance bone density. Its anti-resorptive properties include a dose-dependent inhibition of bone resorption.[3,4] IP also inhibits osteoclastic activity (motility and resorptive activity) by modulating intracellular free calcium.[5,6] IP's bone-forming mechanisms include stimulation of cell proliferation and maturation of osteoblasts by inhibiting calcium influx into osteoblasts and phosphoinositide hydrolysis.[7,8] IP also inhibits the effect of advanced glycation end product on bone resorption.[9] Despite similarities to estrogen, IP possesses no intrinsic estrogenic activity,[10] but does potentiate estrogen.[11] Importantly, IP does not change bone mineral composition or crystalline structure.[12]

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IP has several metabolites: the most important is MI, which has low potency and which increases alkaline phosphatase levels (a marker of new bone formation). Other metabolites are: MII (daidzein), of medium potency and the only metabolite with estrogenic receptor affinity; MIII, the most potent inhibitor of parathyroid hormone-stimulated bone resorption; and MV, a low-potency metabolite, which has been shown to enhance collagen formation.[13-15]

Safety

Data from 60 studies performed in Italy, Japan, and Hungary with a total of 2,769 treated patients showed a similar incidence of adverse reactions for those treated with IP (14.5%) and those treated with placebo (16.1%).[16] Most complaints—77.9% and 81.8% of adverse reactions observed in the treatment and placebo groups respectively—were gastrointestinal, and included heartburn, vomiting, abdominal pain, constipation, and diarrhea. Skin rashes, pruritis, headache, depression, drowsiness, fatigue, and tachycardia also were reported.

Laboratory abnormalities were noted in patients treated with both IP and placebo. An article that summarized IP safety data noted transient changes in liver and kidney function tests, as well as hematological parameters. A slight elevation of liver enzymes occurred in both the treated and control groups; however, the data on the control group were not presented.[16] The percentage of patients with abnormal laboratory values ranged from 0.42% (total proteins) to 3.66% (leukocytes); however, lack of data on the placebo-treated patients rendered these numbers uninterpretable. A dosage reduction was recommended in patients with renal dysfunction (creatinine clearance 40-80 ml/min, 400 mg/d, < 40 ml/min to 200 mg/d).[17]

IP increases the anticoagulant effect of acenocoumarol but does not interact with oral hypoglycemics.[16] It also elevated serum levels of theophylline in one patient (withdrawal of IP resulted in a return of serum theophylline levels to previous levels).[18] In vitro tests of liver microsomes indicate a possible inhibitory effect of IP on cytochrome P450 isoenzymes.[19,20]

Summary

IP has a good safety profile and is well tolerated. Fracture prevention data are still lacking, with results from a large multicenter study expected in 2001. Hormone replacement therapy also lacks adequate, nonvertebral fracture prevention data. In the United States, IP is marketed as a dietary supplement. Because dietary supplements are unregulated in this country, the reliability of various formulations currently available is unknown. IP may turn out to be a viable treatment option for the prevention and treatment of osteoporosis, but better clinical studies with fracture endpoints are needed. ❖

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Ipriflavone: Efficacy Trials

By Adriane Fugh-Berman, MD

IPRIFLAVONE (IP), A RELATIVELY BENIGN SYNTHETIC DRUG marketed as a dietary supplement, is being heavily promoted as an effective therapy for preventing and treating osteoporosis. Although several trials indicate that IP increases vertebral and radial bone density, no trials have examined bone density at the hip, and no trials of adequate size have examined non-vertebral fractures as an endpoint. This article is a review of controlled trials of IP in naturally or surgically menopausal women.

Bone Mineral Density in Menopausal Women

A two-year, double-blind multicenter Italian randomized controlled trial, reported in 1997, enrolled 255 postmenopausal women ages 50-65 with bone mineral density (BMD) of the distal radius of at least one standard deviation (SD) below the mean for normal age-matched women (z-score) measured by dual photon absorptiometry (DPA).[1] Women were randomized to 200 mg IP tid with meals or placebo. Both groups also received 1,000 mg/d elemental calcium. Distal radius BMD and markers of bone metabolism were measured at baseline and every six months.

One hundred ninety-six women completed the trial; of these, 155 (80 in the treatment group) were deemed "valid completers." Analyses were done according to valid completers (VC) and intention-to-treat (ITT) analyses, generally considered a more reliable analysis. VCs were defined as those "who completed the two-year treatment, had all scheduled measures done, and did not violate the protocol in a manner liable to influence the efficacy outcome." In both analyses, after two years, the treated group maintained radial BMD while the control group's BMD declined; the difference between the two groups was significant at both one and two years.

Urinary hydroxyproline/creatinine (HOP/cr), markers of bone loss, were decreased in the IP group and increased in the placebo group, with a significant difference between groups at the end of the first and second year.

There was a high dropout rate in this trial. Thirty-one women (16 in the treatment group) dropped out because of adverse events, 24 for "personal reasons or a change in osteoporosis treatment by their general practitioner," and four because of illness. Reported side effects were primarily gastrointestinal and did not differ between groups.

A paper by Gennari et al, also published in 1997, reported the results of two multicenter studies;[2] however, one of these is clearly a republication of the study above. The other study enrolled 198 women; entry criteria, treatment, duration, and analysis appeared identical to the study just described. However, BMD measurements were taken at the vertebra and dual-energy X-ray absorptiometry (DEXA) was used. These factors make this a better study; DEXA is a better modality for measuring BMD, which is site-specific; radial BMD is not useful for predicting fracture risk at other sites. Actually, even site-specific BMD is not a particularly good predictor for individual risk of fracture, but that's a topic for another article.

In the ITT analysis, the placebo group lost 1.1% vertebral BMD at year 2 while there were no changes from baseline in the IP-treated group. It is not stated whether the between-group difference was significant. In the VC analysis, the IP group showed a 1.4% gain in vertebral bone density at the end of the first year; at two years this gain had dwindled to 0.4%.

At the two-year point, the placebo-treated group lost 1.2% in vertebral bone density. In this analysis, the between-group difference was significant ($P < 0.05$) for both groups. Side effects were minimal (mostly gastrointestinal) and similar between the two groups.

Another two-year study enrolled 56 postmenopausal Caucasian women with vertebral bone density (measured by DEXA) one SD below the age-matched mean and at least two other risk factors (low calcium intake, smoking, alcohol or caffeine "abuse," sedentary life style, or "familiarity with osteoporosis," which presumably means family history). Subjects were randomized to IP (200 mg tid) or placebo; both groups also received 1,000 mg calcium.[3]

Forty of 56 women completed the trial. In the ITT analysis, the placebo group experienced significant decrease in bone (-3.8%) and the IP group had no change (-1.2%); the between-group differences were significant only at year 2. In the VC analysis (including 38 women), vertebral bone density decreased significantly in the placebo group at two years (4.9% ± 1.1%) but did not change significantly in the IP group (-0.4%). A significant between-group difference was noted at the end of both the first and second years. Five patients (one patient in the IP group and four in the calcium group) experienced side effects, primarily gastrointestinal, that caused them to discontinue the study. No significant changes in serum alkaline phosphatase, serum osteocalcin, and urinary Ca/Cr were seen in any groups; urinary hydroxyproline decreased substantially in the IP group.

Fifty-seven postmenopausal women with osteopenia or osteoporosis were randomized to either 600 mg IP or 0.8 g/d calcium lactate for one year.[4] In the IP group, lumbar BMD measured by DEXA decreased from 0.78 ± 0.12 g/cm^2 before treatment to 0.77 after treatment; in the calcium group BMD decreased from 0.81 ± 0.07 to 0.79 ± 0.09. The authors state that the rate of reduction of BMD was significantly greater in the calcium group and that BMD was significantly decreased in the calcium group compared to baseline. Whether the difference between groups was significant is not stated, but it is hard to imagine that this difference was significant.

A double-blind study of 40 postmenopausal women treated with 600 mg/d IP or placebo (all received 1,000 mg/d calcium) found that after a year, BMD (measured by DEXA) in the spine and forearm, compared to baseline, was significantly reduced in the placebo group while BMD was stable in the IP treated group.[5] No changes in bone markers were seen in either group.

Effect on Fractures

Two small, problematic studies published in small journals have looked at vertebral fracture endpoints. Both studies were double-blind, placebo-controlled studies of women over age 65 with vertebral fractures. Treated groups received 200 mg tid IP; all women also received 1,000 mg/d calcium.

The first study was published in the *Italian Journal of Mineral and Electrolyte Research*.[6] Only 27 of 49 women completed the trial, a very high dropout rate. The treated group experienced an increase in radial BMD (measured by DPA), while BMD was unchanged in the placebo group; the between-group difference was significant at year 1 and 2.

HOP/cr ratio was significantly decreased in the treated group and unchanged on the placebo group. The secondary source states that four out of 20 in the treatment group had new vertebral fractures, compared to eight out of 20 in the placebo group; it is not stated in the secondary source whether this is significant, nor at what time point this was taken.[7]

In the second two-year randomized, double-blind study of 100 women (84 completed) over age 65 with osteoporosis and at least one previous vertebral fracture, researchers compared 200 mg IP tid to placebo (all received 1,000 mg/d calcium).[8] A significant increase in radial BMD was seen in the treated group while a significant decrease was seen in the placebo group. Between-group differences were significant at 6, 12, and 24 months. Urinary HOP/cr decreased significantly in the treated and increased in the placebo group. Two new vertebral fractures occurred in the treated group and 11 new vertebral fractures occurred in the placebo group; it

is not stated how many patients this represents nor whether this was statistically significant. Analgesic use decreased significantly in the IP group while it increased in the placebo group.

IP and 1α Vitamin D

Ninety-eight postmenopausal oophorectomized women ages 45-65 were randomized to 600 mg/d IP (n = 28), 1αg/d vitamin D (n = 15), both (n = 20), or neither (n = 35).[9] No explanation is given for the lopsided allotment. Women were assessed at baseline and every six months for 18 months. Seventy-nine women completed the study. Vertebral BMD was measured by DEXA. All groups lost bone, but the IP/vitamin D combination significantly reduced bone loss at all time points compared to all other groups. At 18 months the combination group had lost 0.33%, the IP group lost 2.37%, the vitamin D group lost 1.15%, and the controls lost 3.70%.

IP and Estrogen

There is some evidence that IP may be helpful as an adjunct to estrogen in maintaining bone density, but studies are inconsistent.

A study in 116 recently oophorectomized Japanese women found that IP alone is inadequate to maintain bone density in this group, although it may be helpful in combination with estrogen. Women were randomized to placebo, 0.625 mg/d conjugated equine estrogens (CEE), 600 mg/d IP, or CEE and IP for 48 weeks.[10] At the end of the study, vertebral BMD (measured by DEXA) was reduced significantly by 6.1% in the placebo group, 3.9% in the CEE group, and 5.1% in the IP group; but there was no significant change in the combined-therapy group (vertebral BMD decreased 1.2%).

At 48 weeks urinary pyridinoline decreased 49.5% in the estrogen group, 32% in the IP group, and 41.5% in the combined group; there was no change in the placebo group. Intact human osteocalcin (a marker of bone formation) decreased significantly in both groups that received estrogen; hOC was increased in the group receiving IP alone but not in the group receiving IP with estrogen. The researchers suggest that IP stimulates osteoblasts (while CEE is known to inhibit bone turnover).[10]

Agnusdei et al conducted a study on the combination of IP and low-dose estrogen replacement therapy (ERT).[11] Eighty-three postmenopausal women underwent a double-blind, one-year multicenter study in which they were randomized to a double placebo (n = 24); placebo plus 0.3 mg/d CEE (n = 31), 0.3 mg/d CEE plus 200 mg tid IP (n = 28). Among "valid completers," the placebo group showed a decrease in forearm bone density (measured by DPA) at one year; the CEE group had an average bone loss of 1.4%, and the CEE plus IP group experienced increased BMD (+ 5.6%; $P < 0.01$); the difference was significant ($P < 0.05$). None of the treatments changed biochemical markers of bone turnover.

Another one-year study randomized 105 Caucasian early postmenopausal women to control (500 mg calcium), low-dose hormone-replacement therapy (HRT) (25 μg/d transdermal 17 β-estradiol plus 5 mg/d medrogestone for 12 days/month), high-dose HRT (50 μg/d transdermal 17 β-estradiol plus 5 mg/d medrogestone for 12 days/month), 600 mg/d IP, or IP combined with low-dose HRT.[12] All were given a 1,490 cal/d diet which included 73 g protein, 50 g lipids, 187 g carbohydrates, and 1,550 mg calcium. Ninety-six subjects completed the study, and 81.8% observed the dietary regimen.

Compared to baseline, the only significant change in vertebral BMD (measured by DPA) was in the control group, in which vertebral BMD decreased 3.41%. Mean BMD increased 1.84% in the 50 mg HRT group, increased 0.11% in the IP group, and decreased 0.22% in the combined IP/HRT group. BMD was not significantly different in the 25 mg HRT group (decreased 0.55%). Compared to baseline, 24-hour plasma urinary HOP/cr excretion and bone Gla protein were significantly reduced in the high-dose HRT, IP, and IP/low-dose HRT groups.

Another study randomized 80 postmenopausal women ages 40-49 to 500 mg/d calcium, 200 mg tid IP, 0.3 mg/d CEE, or 400 mg IP plus 0.3 mg/d CEE (all treatment groups also received 500 mg/d calcium). Fifty-two women completed the trial (a high dropout rate). Compared to baseline, vertebral bone density (measured by DEXA) decreased significantly in the control and low-dose CEE groups and increased significantly in both IP groups at one and two years.[13] The difference between both IP groups and the other two groups was significant. IP had no effect on vaginal maturation index, which predictably improved in both groups receiving CEE.

IP vs. Calcitonin

Forty postmenopausal women with BMD > 2 SD below the mean for age-matched controls were studied in a controlled but not blinded study comparing salmon calcitonin to IP over a year.[14] Both treatments significantly increased BMD; 4.3% in the IP group and 1.9% in the calcitonin group (the between-group difference was significant). Four patients in the IP group experienced gastric pain; in the calcitonin group one patient reported pruritis and another epistaxis.

Summary

Seven placebo-controlled trials have looked at the effect of IP on bone density in menopausal women. Five of these (three using DEXA) showed that IP maintained BMD in vertebrae or radius. Two trials published in small journals showed an increase in radial BMD (by DPA); these are also the only trials that showed decreased vertebral fractures.

Two studies in oophorectomized women show that IP alone is not effective treatment; the combination of IP with estrogen or vitamin D reduces but does not eliminate bone loss. Two of three studies found a benefit of the addition of IP to low-dose estrogen. A small unblinded study found a benefit of IP over calcitonin.

Many of these trials have methodological problems. The most glaring problem with this literature is the lack of trials with fracture endpoints. More and better studies of IP are needed. At least one such trial is in progress.

The Ipriflavone Multicenter European Fracture Study (IMEFS) will include 460 Caucasian postmenopausal women, ages 45-75, treated with IP for at least 12 months. The primary endpoint is incidence of vertebral, non-traumatic fractures. BMD of the spine, hip, and distal radius, as well as serum and urinary markers of bone metabolism, will also be evaluated.[15] Results of this trial are expected next year; clinicians should wait for the results of this or other adequately designed trials before recommending IP to patients. ❖

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Do Antioxidants Affect Preeclampsia?

Source: Chappell LC, et al. Effect of antioxidants on the occurrence of pre-eclampsia in women at increased risk: A randomised trial. *Lancet* 1999;354:810-816.

Background: Oxidative stress has been implicated in the pathophysiology of preeclampsia. This randomized controlled trial tested vitamin C and E supplementation in women at increased risk of preeclampsia (based on plasma markers of vascular endothelial activation and placental insufficiency or previous preeclampsia).

Methods: Two hundred eighty-three women at increased risk of preeclampsia by abnormal two-stage uterine artery Doppler analysis (or a prior history of preeclampsis) were randomized to placebo or 1,000 mg/d vitamin C and 400 IU/d vitamin E at 16-22 weeks' gestation. Plasma markers of endothelial activation

(plasminogen-activator inhibitor 1 [PAI-1]) and placental dysfunction (PAI-2) were measured every month until delivery. Preeclampsia was assessed by the development of proteinuric hypertension. Analyses were done by intention to treat (ITT) as well as in the cohort who completed the study.

Results: The group receiving supplemental vitamins C and E experienced a 21% decrease in the PAI-1/PAI-2 ratio during gestation (95% confidence interval 4-35, P = 0.015). In the ITT cohort, preeclampsia occurred in 24 of 142 (17%) women in the placebo group and 11 of 141 (8%) in the vitamin group (adjusted odds ratio [OR] 0.39 [0.17-0.90], P = 0.02). In the cohort who completed the study (81 placebo group, 79 vitamin group), the OR for preeclampsia was 0.24 (0.08-0.70, P = 0.002).

Funding: Tommy's Campaign and the Special Trustees for St. Thomas' Hospital, London, UK.

COMMENTS BY ANTHONY R. SCIALLI, MD

I clearly remember the day the "cause" of preeclampsia was discovered. The year was 1974 and I was a medical student at St. Peter's Hospital in Albany, NY. One morning, my resident came to work very excited. He had just read an article by a fellow named Page in which the pathophysiology of this enigmatic disease was clearly explained. According to Page, preeclampsia occurred as a self-perpetuating cycle in which release of placental thromboplastins led to intravascular coagulopathy, which led to deposition of fibrin in the microcirculation, which led to uteroplacental ischemia, which led to placental damage, which led back to release of placental thromboplastins.

The next quarter-century of my career was to show, of course, that Page's eloquent description was just one of many eloquent descriptions of epiphenomena associated with this protean disorder of pregnancy. A large amount of effort has gone into identifying the cause of preeclampsia and into ways of preventing this potential cause of maternal and neonatal morbidity and mortality. In recent times, there has been considerable attention to prevention of the microangiopathy associated with preeclampsia. The use of calcium and aspirin prophylaxis went through respective phases of popularity, with early studies demonstrating a benefit. Larger trials were disappointing, showing no advantage of either therapy over placebo.

This latest study addressing the disordered vascular system in preeclampsia is a small randomized trial of vitamins C and E. The hypothesis is that free radicals promote endothelial malfunction, and that antioxidant vitamins can interrupt the process of endothelial damage and prevent laboratory and clinical manifestations of the disease. In this study, the laboratory manifestation of the disease is a ratio between PAI-1, which increases in preeclamptic women, and PAI-2, a placental product that decreases in the face of impaired placental function. Elevation of the PAI-1/PAI-2 ratio could, then, be taken as evidence of endothelial activation (increasing PAI-1) and placental dysfunction (decreasing PAI-2).

To test the hypothesis, Chappell et al identified women at high risk of preeclampsia using two methods. The first method used Doppler flow velocity studies of the uterine artery to identify women who failed to develop the expected decrease in resistance indices in the middle trimester. The second method relied on a history of preeclampsia in a previous pregnancy. Women identified by either method were randomized to receive both vitamins C and E or identical placebo vitamins. Women began supplementation at 16-22 weeks, but were excluded from the study at 24 weeks if their Doppler studies became normal. The results of the study were analyzed by ITT (that is, patients removed from the study were counted as though they had continued in their respective groups) and were analyzed separately for women who actually completed the study. Both methods of analysis showed a convincing improvement in the PAI-1/PAI-2 ratios, and a reduction in the incidence of preeclampsia.

This study was performed and reported in an extraordinarily competent manner. Chappell et al deserve applause for many excellent features, especially clear and accurate writing. The use of both vitamins C and E was bold but important; recognizing that these antioxidant vitamins work together, the investigators avoided the costly distraction of testing each vitamin alone, an error that has led investigators of other cardiovascular endpoints to conclude that antioxidant vitamins are ineffective. The use of resistance index by Doppler to identify women at high risk of developing preeclampsia was brilliant, and resulted in the identification of the exact population appropriate for the trial. Eliminating women whose resistance indices normalized further enriched the population with those at highest risk of preeclampsia. The analysis was carefully considered, with ITT and study-completion data displayed side-by-side.

The sole question is why women with a history of preeclampsia were grouped with women who had abnormal Doppler waveforms. Women with a history of preeclampsia are, in fact, at higher risk of developing preeclampsia in a subsequent pregnancy, but their risk is still rather low. Although inclusion of these women increased the sample size from 242 to 283, the cost could have been the introduction of a subgroup of women who would be at lower risk of preeclampsia and

who might have jeopardized the power of the study to demonstrate a treatment effect. Because a treatment effect was clearly shown, it can be argued that inclusion of these women did not sabotage the study; still, one wonders whether these 41 women behaved differently from the others, a point not addressed by the authors.

As an accompanying editorial indicates, the results of this study are almost too promising. Replication in a larger, multicenter trial will be an important step in bringing us to a recommendation that pregnant women at risk, or perhaps all pregnant women, be supplemented with vitamins C and E. In the meantime, we are left with an intriguing question: Is preeclampsia a vascular disease, like some other vascular diseases, caused in whole or in part by a diet deficient in fruits and vegetables? Even before the question of vitamin supplementation is answered by a larger multicenter trial, recommending adequate fruits and vegetables in the diet of pregnant women appears to be a reasonable way to hedge the bet. ❖

CME Questions

8. Ipriflavone is:
a. an isoflavone found in soybeans.
b. a synthetic isoflavone.

9. Ipriflavone:
a. increases vaginal maturation index.
b. has no effect on vaginal maturation index.

10. In oophorectomized women, ipriflavone alone prevents bone loss.
a. True
b. False

11. Most trials of ipriflavone show that it maintains bone density in:
a. vertebrae.
b. hip.
c. both vertebrae and hip.

12. A recent trial of vitamins C and E showed:
a. a reduction in preeclampsia rate.
b. no effect on preeclampsia rate.
c. an increase in preeclampsia rate.

Clinical Abstracts

With Comments by Adriane Fugh-Berman, MD

Can a Cup of Cocoa a Day Keep an MI Away?

Source: Rein D, et al. Cocoa inhibits platelet activation and function. *Am J Clin Nutr* 2000;72:30-35.

Design/Setting/Subjects: Controlled, three-arm study in 30 healthy, nonsmoking subjects 24-50 years old. Ten subjects (four men and six women) were in each group. Subjects ingested a cocoa beverage; a control beverage (containing the same amount of caffeine and sugar as the cocoa beverage), or water. Peripheral blood was taken two and six hours later and platelet activation was measured, utilizing activation-dependent platelet antigens and platelet microparticle formation utilizing labeled monoclonal antibodies and flow cytometry.

Treatment: A 300 ml cocoa beverage was used. The beverage contained 18.75 g procyanidin-enriched cocoa powder (Cocoapro™, Mars, Inc., Hackettstown, NJ) and provided 897 mg total epicatechin and oligomeric procyanadins, 17 mg caffeine, 285 mg theobromine, and 12.5 g sucrose mixed with distilled water. The control beverage contained 17 mg caffeine and 12.5 g sucrose.

Results: Epinephrine or ADP-stimulated expression of fibrinogen-binding confirmation of glycoprotein IIb-IIIa decreased in the cocoa group at both time points tested compared to baseline. These parameters increased after consumption of the caffeine-containing beverage; there was no change in the water group. ADP-stimulated P-selectin expression was also decreased by cocoa. Platelet microparticle formation increased after caffeine and water consumption but decreased after cocoa consumption. In vitro, primary hemostasis in response to epinephrine was inhibited six hours after cocoa consumption; the caffeine-containing beverage inhibited ADP-induced primary hemostasis at two and six hours.

Funding: Not stated. However, Mars Inc. is listed as one of the affiliations.

Comments: Can hot chocolate prevent heart attacks? These results indicate that cocoa inhibits platelet activation and appears to have an aspirin-like effect on platelet function. The authors note that flavonoids may be responsible for all or some of this effect. As the researchers put it, "regular intake of active cocoa components may contribute to a lower thrombotic risk." Good news about chocolate is always welcome. As I write this, I'm eating chocolate-covered soybeans, which didn't sound like a good idea but are not bad at all. Flavonoids, phytoestrogens, methylxanthines, and sugar all in one product; this candy is a multifunctional food. ❖

In Future Issues:

Antioxidants and Breast Cancer

Magnesium and Bone Density