Does intra-articular hyaluronate decrease symptoms of osteoarthritis of the knee?


- **BACKGROUND** Current therapies for osteoarthritis (OA) include long-term NSAIDs and joint replacement surgeries, but these are not without significant morbidity and mortality. HA is a joint component that acts as a shock absorber and lubricant, and its concentration declines with advancing age. “Viscosupplementation” is an intriguing idea as an alternative to exclusive treatment with NSAIDs. This study evaluated the effectiveness of hyaluronate injections to decrease symptoms associated with OA and improve functioning.

- **POPULATION STUDIED** The investigators of this study recruited 120 subjects from an outpatient referral center. Included patients displayed radiographic evidence of medial compartment unilateral knee OA grades 1 – 3. Allocation concealment was not mentioned, meaning that the investigators could have chosen patients on the basis of what therapy they were about to receive in the study.

- **STUDY DESIGN AND VALIDITY** This study was a randomized, controlled, double-blind comparison of (1) HA, (2) an NSAID, (3) both, or (4) neither. Physicians, patients, and analysis staff were all blinded. Each patient received both 3 weekly intra-articular knee injections of either placebo or hyaluronate sodium and 12 weeks of twice daily placebo or diclofenac 75 mg plus misoprostol 200 µg. The follow-up period lasted 12 weeks, with a 99.2% follow-up rate and 9.2% dropout rate. Pain, stiffness, and disability were evaluated at baseline and weeks 4 and 12 using the Western Ontario McMaster Universities (WOMAC) Index, a visual analog scale for pain and performance. Analysis was by intention-to-treat.

- **RESULTS** The authors declared HA effective on the basis of changes within each group from baseline to the end of therapy. However, the accompanying editorial performed a more appropriate statistical analysis that evaluated the effect across all 4 groups and found no evidence to suggest that hyaluronate sodium in this trial is more effective than placebo.

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REFERENCE

- **RECOMMENDATIONS FOR CLINICAL PRACTICE** Contrary to the assertions of the authors, careful evaluation of the results of this study reveal that hyaluronic acid (HA) injection is no better than placebo in the treatment of osteoarthritis (OA) of the knee. Do not let yourself be fooled when shown this study – the analysis was not carried out across all 4 groups. When this was carried out, no benefit could be found. Previous studies have also failed to find a benefit of HA versus placebo. This is another good idea that does not work. For now, stick with acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs).
Does fecal occult blood screening reduce colorectal cancer morbidity?


- **BACKGROUND** This is 1 of 3 randomized trials undertaken to demonstrate a reduction in mortality from CRC by annual or biennial screening with an FOBT. In this study, the authors report on their 13-year experience of biennial screening with FOBT and its effect on mortality from CRC. They also evaluated the possible influence of compliance with screening on mortality from CRC.

- **POPULATION STUDIED** In August 1985, 140,000 people aged 45 to 75 years were living in Funen, Denmark. On the basis of information obtained from public registers, inhabitants with a known history of CRC, colorectal adenomas, or any type of malignancy with distant spread were not included by the authors for randomization. A balanced randomization was carried out in groups of 14 (3 to the screening group, 3 to the control group, and 8 not enrolled). Married couples were allocated to the same group. Subjects in the screening group were mailed invitations requesting participation. Only those attending previous screening rounds were invited back for repeat screening. Subjects in the control group were not informed of their participation in the study. In total, 61,933 men and women were studied; 30,967 subjects were assigned to biennial screening with Hemoccult II and 30,966 in the control group received usual care. Subjects were followed up until death or August 1, 1998.

- **STUDY DESIGN AND VALIDITY** This was a population-based, randomized controlled trial. Randomization of subjects in this trial was performed in a single-blinded fashion. Hemoccult II was used without rehydration but with dietary restrictions (no red meat, fresh fruit, iron preparations, vitamin C, aspirin, or other nonsteroidal anti-inflammatory drugs). Subjects were asked to provide 2 fecal samples from each of 3 consecutive stools. Subjects with a positive FOBT result (1 or more blue slides) were offered colonoscopy. It is not known how many in this group may have received screening for CRC as part of their usual care. Events (CRC, adenoma, death) in both groups were tracked using public databases and registers. The authors were unaware of the subjects’ screening status during assessment of death certificates.

- **OUTCOMES MEASURED** The primary outcome measured was death from CRC.

- **RESULTS** The risk of death from CRC was significantly reduced in the screening group compared with the control group (relative risk [RR] = 0.82; 95% confidence interval [CI], 0.69-0.97), even after adjusting for age, sex, and complications from treatment (RR = 0.86; 95% CI, 0.73–1.0). There was no difference in the rate of all-cause mortality between groups. In the screening group, the cumulative risk of having a positive test result was 5% over 13 years and 7 rounds of screening. Of those who tested positively, 94% went on to have at least 1 colonoscopy. There were 55 fewer deaths due to CRC in the screening group over 13 years in a population of 30,762 patients invited for screening. That is, screening saved 1 life for every 559 patients screened every other year for 13 years.

- **CONCLUSIONS** Subjects who refused any screening had a significantly increased risk of death from CRC compared with those who participated in all screening rounds (RR = 1.65; 95% CI, 1.30-2.08).

**RECOMMENDATIONS FOR CLINICAL PRACTICE**

Use of the fecal occult blood test (FOBT) every other year for 13 years to screen patients aged 45 years to 75 years will save 1 life for every 559 patients screened. Screening with FOBT does not alter the risk of death from all causes, which is felt by some physicians to be a more unbiased end point than cancer-specific mortality. This study, and others, suggests that individuals who refuse screening with FOBT may be at increased risk of dying from colorectal cancer (CRC). Special efforts should be made to ensure their participation in screening programs.

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REFERENCES


CONTINUED ON PAGE 415
Can aspirin prevent cardiovascular events in patients without known cardiovascular disease?


- **BACKGROUND** In patients with known cardiovascular disease aspirin has well-established benefits, including improved outcomes of ischemic CHD, stroke, and all-cause mortality. Because of their lower risk, it is less clear whether using aspirin for preventing cardiovascular disease is beneficial in patients without preexisting disease.

- **POPULATION STUDIED** This meta-analysis reviewed studies that evaluated the role of aspirin in patients with no previous history of cardiovascular disease, including myocardial infarction (MI), stroke, angina, transient ischemic attack, and peripheral vascular disease. The authors excluded trials in which more than 10% of participants had diagnosed vascular disease. Of the approximately 50,000 patients included, most were middle-aged men.

- **STUDY DESIGN AND VALIDITY** This study was a meta-analysis of RCTs used as evidence for the US Preventive Services Task Force (USPSTF) in developing recommendations for the use of aspirin in the primary prevention of cardiovascular disease. The authors conducted a MEDLINE search for RCTs comparing aspirin with placebo (or simply no aspirin) in patients with no previous history of cardiovascular disease; these studies measured the outcomes of MI, stroke, and mortality. The authors included case-control and systematic reviews or meta-analyses in addition to RCTs to assess any harm of aspirin use (eg, rates of hemorrhagic stroke or gastrointestinal bleeding).

  The authors clearly stated their search strategy to locate relevant studies, and supplemented the MEDLINE search with review of bibliographies of pertinent articles and discussion with content experts. They did not specifically note a search for unpublished data or the use of other databases. Five RCTs met the inclusion criteria, and they all concealed allocation of randomization. Aspirin dosage was 500 mg per day in 1 study, and 162 mg or less per day in the other 4 studies. Researchers and participants were blinded in 3 studies, and in 2 trials patients were not blinded and were not given placebo pills. Analysis was by intention to treat in all the studies, and in 4 of the 5 studies follow-up was greater than 97%. Although study assessment was performed by 2 investigators, the article did not clearly state if the assessments were performed independently of each other.

  It is reasonable to combine the 5 studies to perform a meta-analysis. They were statistically homogenous, with the exception of possible heterogeneity in the data on the effect of aspirin on CHD, which the authors explained as a reflection of an anomalous result in 1 study.

- **OUTCOMES MEASURED** The authors combined data from the RCTs for the following outcomes: total CHD events, (defined as nonfatal MI or death due to CHD), stroke, and all-cause mortality. For assessing adverse effects of aspirin, the investigators extracted rates of hemorrhagic stroke and major gastrointestinal bleeding events.

- **RESULTS** Patients taking aspirin had a lower risk of a CHD event (odds ratio [OR] = 0.72; 95% CI, 0.60 - 0.87), which equates to a number needed to treat (NNT) of 195 patients to prevent 1 nonfatal MI or death due to CHD. For comparison, treatment of severe hypertension benefits 1 in 15 patients, but treatment of mild hypertension benefits 1 in 700 treated patients. In their subgroup analysis the authors found that the effect of aspirin in preventing CHD events in women was smaller than in men and not statistically significant. They concluded that it remains unclear as to whether gender influences the effects of aspirin. Regarding prevention of stroke and all-cause mortality, there was no significant benefit in taking aspirin.

  As for the potential harm of primary prevention with aspirin, there appears to be a trend toward increased risk of hemorrhagic stroke that did not reach statistical significance (OR = 1.4; 95% CI, 0.9 - 2.0). Patients taking aspirin seem to have 1 1/2 to 2 times the risk for a major gastrointestinal bleeding event (OR = 1.7; 95% CI, 1.4 - 2.1).

**RECOMMENDATIONS FOR CLINICAL PRACTICE**

Discuss the potential risks and benefits of aspirin with your patients, especially those at increased risk for cardiovascular disease. This meta-analysis of randomized controlled trials (RCTs), which included mostly middle-aged men, showed aspirin can prevent a first heart attack in patients without known cardiovascular disease. The Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure gives a grade A recommendation for discussing aspirin with men older than 40 years, postmenopausal women, and patients with risk factors for coronary heart disease (CHD), such as hypertension, diabetes, or smoking.

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Does uterine contraction frequency adequately predict preterm labor and delivery?


**BACKGROUND** Ambulatory uterine activity monitoring in high-risk women continues despite the results from randomized trials indicating no relationship between monitoring and actual reduction of preterm delivery. The value of uterine contraction frequency as a predictor of preterm delivery, however, remains unclear.

**POPULATION STUDIED** A total of 2205 women with a singleton gestation of longer than 22 weeks were screened; 454 met eligibility criteria. Data from 306 women were analyzed, including 254 high-risk women with either a history of preterm delivery (between 20 and 36 weeks) or bleeding in the 2nd trimester of the current pregnancy, and 52 low-risk women. Exclusion criteria included previous or scheduled use of an ambulatory contraction monitor, use of tocolytic therapy, scheduled cerclage, placenta previa, major fetal anomalies, or no home phone. The mean age of participants was 26.2 years, with a mean parity of 1.8. The majority of participants were black (60%), with at least 12 years of education (74%). Many participants smoked (26%).

**STUDY DESIGN AND VALIDITY** The authors used an observational study to determine whether the frequency of contractions could predict spontaneous preterm delivery at less than 35 weeks. Contractions were monitored for at least 30 minutes, twice a day (daytime and nighttime) on 2 or more days per week until 28 weeks, then 4 times per week. Two trained nurses, masked to risk status, analyzed monitor recordings. Contractions were defined as deflections from a clear baseline, with a rounded peak lasting 40 seconds to 120 seconds. Cervical examinations were performed every 2 to 3 weeks, beginning at 22 weeks, up to 6 times, depending on length of gestation. Data collected included cervicovaginal fluid for fetal fibronectin analysis, cervical length by transvaginal ultrasound, and assessment of Bishop score. Assessment of contraction recordings was validated by repeat audits during which samples were re-analyzed. Interpretation discordance occurred in 14% to 28% of recordings, but discrepancies were not greater than 1 contraction per hour.

**OUTCOMES MEASURED** The primary outcome was the ability of uterine contraction frequency (daytime and nighttime) to predict spontaneous preterm delivery. In addition, fetal fibronectin, cervical length, and a Bishop score higher than 4 were studied as possible predictors at these same gestational ages.

**RESULTS** There was no difference in frequency of contractions between the high-risk and low-risk group and therefore all data were pooled for analysis. The maximal frequency of contractions was inconsistently related to preterm delivery, with the largest association found for nighttime contractions at 27 to 28 weeks (odds ratio [OR] = 1.2; 95% CI, 1.1-1.4). Logistic regression revealed a consistent relationship between ultrasound cervical length and preterm delivery across all gestational age groupings, with statistically significant ORs ranging from 4.0 at 27 to 28 weeks to 7.5 at 31 to 33 weeks. The sensitivity for maximal daytime and nighttime contraction frequency was low, ranging from less than 10% at 22 to 24 weeks to 28% at 27 to 28 weeks and 51 to 33 weeks. Positive PPVs were correspondingly low, with none higher than 25%. Although the sensitivities for fetal fibronectin, ultrasound cervical length assessment, and Bishop scoring were generally somewhat higher (ranging from a low of 19% for fetal fibronectin at 22 to 24 weeks to a high of 82% for cervical length at 31 to 33 weeks) the corresponding PPVs were also low (range = 15% to 37%).

**RECOMMENDATIONS FOR CLINICAL PRACTICE** Uterine activity monitoring in asymptomatic high- and low-risk women is inadequate for predicting preterm birth. A recent systematic review of preterm labor management found home uterine activity monitoring by itself ineffective in preventing preterm birth. In the current study, contraction frequency monitoring has very poor sensitivity and a low positive predictive value (PPV) for spontaneous preterm delivery before 35 weeks’ gestation. Other commonly used screening tests, such as fetal fibronectin, cervical length assessment, and Bishop scoring, also generally have poor sensitivities and PPVs. The usefulness of any of these tests lies in the reassurance provided by a negative test result, as nearly all of them have negative predictive values of greater than 90%. Understanding, preventing, and treating known causes appears to offer the best current approach to reducing prematurity and its sequellae.

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**REFERENCE**
Does use of oxytocin and dinoprostone inserts shorten labor more than use of oxytocin after removal of dinoprostone?


**BACKGROUND** Simultaneous use of oxytocin and prostaglandin E2 preparations may offer a more efficient approach to labor induction by shortening the induction to delivery time. However, the manufacturer of sustained-release dinoprostone inserts warns against concurrent use with oxytocin since the risks of uterine hyperactivity and complications are unknown. This study compared the use of oxytocin immediately after placement of a sustained-release dinoprostone insert with delayed use of oxytocin after removal of dinoprostone.

**POPULATION STUDIED** The study included 71 women who presented to the University of New Mexico Health Sciences Center with indications for labor induction, singleton gestations with cephalic presentation, intact membranes, reactive nonstress tests, no previous uterine surgery, and unfavorable cervixes (Bishop score ≥ 6). These patients are similar to those encountered in a primary care setting. Women with vaginal bleeding, more than 2 contractions in 10 minutes, asthma, known hypersensitivity to prostaglandins, or conditions that would contraindicate the induction of labor were excluded.

**STUDY DESIGN AND VALIDITY** Women were randomly assigned (concealed allocation assignment) to either low-dose oxytocin infusion (2 mIU/min with 2-mIU/min increases every 20 minutes, up to a maximum dose of 36 mIU/min) started either 10 minutes after placement of a 10-mg sustained-release dinoprostone insert (immediate group) or 30 minutes after the removal of the insert (delayed group). Inserts were left in place for 12 hours if possible. The exact time of dioprostone insert placement into the posterior fornix was recorded. Evaluation of the cervix and Bishop scoring were performed prior to placement and immediately following removal of the insert. Two investigators blinded to group assignment monitored tracings of contractions.

The study included patients who in clinical practice are candidates for induction therapy, and was powered to detect a 6-hour difference in induction to delivery times. However, the sample size was too small to detect differences in morbidities such as difference in cesarean delivery and uterine hyperstimulation. Analysis by intention to treat was not performed. Three women were excluded from the final statistical analysis for protocol violation, no delivery data, and withdrawal of consent.

**OUTCOMES MEASURED** The primary outcome measured was the time from induction to delivery. Secondary outcomes included changes in cervical score at 12 hours, frequency of deliveries within 24 hours, incidence of uterine hyperstimulation, rate of cesarean deliveries, and maternal and neonatal complications.

**RESULTS** The mean induction to delivery time was 972 minutes in the immediate group versus 1516 minutes in the delayed group (P = .001). The change in Bishop score at the time of the insert removal was significantly greater in the immediate oxytocin group as compared with the delayed oxytocin group (P = .01). Immediate versus delayed administration of oxytocin increased the likelihood of delivery within 24 hours of induction (90% vs 53%, respectively; P = .002). No cases of hyperstimulation syndrome occurred with the immediate group versus 3 cases in the delayed group (P = .24). Cesarean delivery rates were similar (16% vs 13% for the immediate and delayed groups, respectively; P = .73), and cesarean deliveries were needed only in nulliparous women. No women developed intra-partum chorioamnionitis, and 1 woman in each group developed postpartum endometritis. Neonatal Apgar scores measuring less than 7 at 5 minutes were similar between groups (0% vs 6% for the immediate and delayed groups, respectively; P = .49).

**RECOMMENDATIONS FOR CLINICAL PRACTICE** Concurrent administration of oxytocin and sustained-release dinoprostone (prostaglandin) reduced the time from induction to delivery compared to oxytocin after removal of dinoprostone. This study found no increased risk of adverse events with concurrent administration. However, caution should be applied when using this concurrent therapy regimen until maternal and neonatal safety has been properly evaluated with larger studies.

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**Do disease-specific mortality effects correlate with all-cause mortality effects in cancer screening trials?**

- **BACKGROUND.** Cancer screening trials have traditionally focused on disease-specific mortality, the number of subjects whose death is attributed to the screened disease. This end point is generally easier to study than all-cause mortality (the overall death rate), because fewer subjects are needed to achieve a statistically significant result. However, this approach has many potential biases, and it neglects the possibility that screening may lead to potentially fatal complications. The authors of this study compared disease-specific mortality changes to all-cause mortality changes in a collection of cancer screening trials.

- **POPULATION STUDIED.** This study examined 12 published randomized trials of cancer screening. Of 16 initial trials identified, the 12 chosen for study were those in which disease-specific and all-cause mortality could be determined. The 12 chosen studies included 7 of mammography, 3 of fecal occult blood testing, and 2 of chest x-rays for lung cancer.

- **STUDY DESIGN AND VALIDITY.** The researchers used a list published in a text on cancer screening to identify randomized trials for inclusion in this study. Updated information from each of the trials was obtained by performing a PubMed search of authors’ names and other relevant terms. This was not an exhaustive, systematic review of the literature. A more extensive literature search would have used multiple databases, evidence-based search methods, and possibly unpublished data. Very little information is given on the search terms used in PubMed. However, since this was a comparison of different outcome measures rather than a meta-analysis, a systematic review is not necessarily required.

- **OUTCOMES MEASURED.** For each study, the difference in mortality between screened and unscreened (control) groups was reported as the screening benefit. The screening benefits from both disease-specific mortality and all-cause mortality data were then compared in terms of number of deaths per 10,000 person-years of observation.

- **RESULTS.** One would expect that if a screening program decreased mortality related to the disease, overall mortality would be less as well. The authors found that this correlation did not occur in most of these studies. Five of the studies found that disease-related mortality and overall mortality went in different directions. Three of these 5 studies reported a statistically significant benefit in disease-specific mortality, but the all-cause mortality was either not affected or was worse. Two trials showed no benefit in disease-specific mortality but a trend in a positive or negative direction in all-cause mortality.

  The second finding was a different magnitude of benefit when comparing disease-specific mortality with overall mortality. A mammography trial reported an all-cause mortality benefit with screening that was more than 20 times better than the disease-specific mortality benefit with screening. A chest x-ray trial reported a trend of higher death rates in the screened group for both disease-specific and all-cause mortality, but the difference in all-cause mortality was nearly 3 times higher than that reported for lung cancer.

  The authors outlined several theories to explain these 2 types of discrepancies. They postulated that inconsistencies in magnitude were not likely the result of screening but rather the result of problems with randomization or misclassification of outcomes. Discrepancies in direction were accounted for by 2 phenomena: the “sticky-diagnosis” bias and the “slippery-linkage” bias. A sticky-diagnosis bias occurs if a death from another cause in the screened group is falsely attributed to the screened disease simply because the disease has been previously diagnosed. Alternately, a death from this disease in the control group may be falsely attributed to another cause because screening had not occurred. The slippery-linkage bias occurs when deaths resulting from a screening-related intervention are not directly linked to the disease itself. For example, the authors present a hypothetical example of a fatal hemothorax after a needle biopsy for a benign pulmonary nodule. This type of death may not be considered a lung cancer death included in the disease-specific mortality figure.

**RECOMMENDATIONS FOR CLINICAL PRACTICE**

Although disease-specific mortality has been the standard for reporting mortality benefit in cancer screening, it does not necessarily correlate with significant benefits in all-cause mortality. In other words, some cancer screening may decrease deaths due to the screened disease, but patients still die at the same (or even higher) rate despite the screening. Inconsistent results are evident in trials studying mammography screening for breast cancer, fecal occult blood testing for colon cancer, and chest x-ray screening for lung cancer. When deciding whether a screening intervention is potentially beneficial, we may be misled by reports of disease-specific mortality.

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Does raloxifene affect risk of cardiovascular events in osteoporotic postmenopausal women?

- **BACKGROUND** Physicians seek new therapies to reduce the risk of fractures in osteoporotic postmenopausal women without increasing the risk of cardiovascular events or cancers. Raloxifene (Evista), a selective estrogen receptor modulator, may be a new choice for therapy. Using original data from the Multiple Outcomes of Raloxifene Evaluation, the authors present a secondary analysis of this randomized trial to evaluate its effect on cardiovascular events.

- **POPULATION STUDIED** The researchers enrolled 7705 women who were at least 2 years postmenopausal, from outpatient and community settings at 180 sites in 25 countries. Average age was similar by treatment group (overall mean = 67 years). All patients had osteoporosis documented by either prior vertebral fracture or a bone mineral density T score of less than -2.5. Study women were predominantly white (95%). Baseline characteristics of women were similar for most cardiovascular risk factors and concomitant cardiovascular medications, although women receiving raloxifene were significantly more likely to have diabetes.

- **STUDY DESIGN AND VALIDITY** The study was a double-blind randomized, controlled trial with concealed allocation assignment. It originally was designed to determine the effect of raloxifene on bone mineral density and vertebral fractures. Women were randomized to receive placebo, or 60 mg or 120 mg of raloxifene per day. This study was a secondary analysis of the data for cardiovascular outcomes. Risk scores, based on evidence of established coronary heart disease or the presence of cardiovascular risk factors, were assigned to a subgroup of women with increased cardiovascular risk.

This study was well designed and defined but suffered a large validity flaw, which limits the usefulness of the data to that obtained only in the first year. Only 75% of the women enrolled completed follow-up through the 4 years of study. Overall, the dropout rate (because of adverse events, personal decision, general loss to follow-up, or other reasons) was similar in both treatment and placebo groups. Loss of information on cardiovascular outcomes in such a large number of study participants translates to a potentially large measurement error. The direction of this error—that is, whether lost, treated patients suffered more or fewer cardiovascular events than did placebo patients—is impossible to ascertain. In their original report, however, the authors present data suggesting that the women who took raloxifene were significantly more likely to withdraw from the study due to an adverse event than were the women who took placebo (10.3% vs. 8.8%; *P* = .04).

- **OUTCOMES MEASURED** The authors collected cardiovascular event outcome data by asking women at each visit whether they had experienced a myocardial infarction, coronary artery bypass graft, percutaneous coronary intervention, or stroke since the previous visit. Unsolicited reports of cardiovascular events were also recorded.

- **RESULTS** The follow-up data were 90.8% complete for women who took placebo and 89.6% for those who took raloxifene at 1 year. There was no significant difference between combined treatment and placebo groups in the number of women with cardiovascular events during the first year of the trial. Nor was there a difference in the high-risk subset. The serious loss to follow-up for the 4 years of the study (25% of placebo and 22% of raloxifene women) makes the analysis unreliable for longer than the first year of study. We can use intention-to-treat analysis to assess the potential effect of missing cardiovascular events in those lost to follow-up. The resulting relative risk ranges from 0.11, for the extreme assumption that all missing women taking raloxifene suffered a cardiovascular event while those on placebo did not, to 6.89, for the opposite extreme that all missing women taking raloxifene suffered a cardiovascular event while those on placebo did not. The true relative risk lies somewhere between these boundaries. With so much data missing, we are unable to assess raloxifene’s effect on cardiovascular events in postmenopausal osteoporotic women in the longer term.

**RECOMMENDATIONS FOR CLINICAL PRACTICE**

After 1 year of therapy, raloxifene did not increase the risk of cardiovascular events in older postmenopausal women with osteoporosis. Its effect on cardiovascular risk has not been assessed in women taking it for more than 1 year. Absence of a detrimental cardiovascular effect is a benefit, compared with estrogen replacement therapy, although both approaches prevent osteoporotic fractures. However, both of these hormonal approaches carry the same risk for thromboembolism. Raloxifene may cause or worsen hot flushes, whereas estrogen prevents them. Long-term compliance with either therapy is not good. Given the cost and risks of the biphosphonates, the optimal approach to osteoporosis prevention and treatment is a difficult clinical decision.

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**REFERENCE**

How do calcium channel blockers compare with beta-blockers, diuretics, and angiotensin-converting enzyme inhibitors for hypertension?


**BACKGROUND** Calcium channel blockers are used extensively in the treatment of hypertension. The authors systematically reviewed recent large, long-term trials that compared calcium channel blockers with beta-blockers or diuretics. A secondary analysis compared calcium channel blockers with ACE inhibitors in hypertensive patients with diabetes.

**POPULATION STUDIED** The patients in this meta-analysis were pooled from 3 large European, multicenter studies (n = 21,611), that compared calcium channel blockers with diuretics or beta-blockers in elderly men and women with hypertension. A separate analysis included 3 smaller studies, bringing the total patients to 24,322. Most of these patients did not have active cardiovascular disease, including coronary artery disease and left ventricular hypertrophy; approximately 25% smoked; and approximately 50% had hypercholesterolemia. Only 1318 were included in a separate analysis of calcium channel blockers and ACE inhibitors in patients with hypertension and diabetes.

**STUDY DESIGN AND VALIDITY** This was a meta-analysis of several randomized, controlled studies, which were double-blinded or assessed by a committee blinded to treatment assignment. Patients were followed for at least 2 years. The studies evaluated patients for major cardiovascular events, including myocardial infarction (MI), stroke, heart failure, and death. In the 3 major trials, target blood pressures were < 140/90 mm Hg, < 160/95 mm Hg, and < 90 mm Hg diastolic, respectively.

This meta-analysis was well done. Although the authors did not provide their specific search strategy, they included pertinent mega-trials of calcium channel blockers compared with the gold standard therapies for hypertension. Additionally, the authors rigorously evaluated the quality of the trials, tested the data for homogeneity, and corrected for multiple comparisons. The blood pressure goals in the studies were homogeneous, possibly influencing event rates in the trials and limiting generalization of the data to typical clinical practice. The inability to generalize data was particularly true in the diabetes group analysis, in which patients achieved a mean systolic blood pressure of 159 mm Hg, which is considerably higher than the 130 mm Hg that the national hypertension guidelines and the American Diabetes Association currently recommend.

**OUTCOMES MEASURED** The outcomes measured were fatal and nonfatal MI and stroke, development of congestive heart failure, and cardiovascular and total mortality.

**RESULTS** Calcium channel blockers were associated with fewer nonfatal strokes than diuretics or beta-blockers (relative risk [RR]=0.751; 95% confidence interval [CI], 0.653-0.864; absolute risk reduction [ARR]=0.9%; number needed to treat [NNT]=111). Fatal stroke rates were not different between the 2 groups (RR=0.918; 95% CI, 0.779-1.083). Also, there were fewer total strokes with calcium channel blockers (RR=0.809; 95% CI, 0.769-0.982; ARR=0.6%; NNT=167). Calcium channel blockers were associated with more nonfatal myocardial infarctions (RR=1.177; 95% CI, 1.011-1.370; absolute risk increase [ARI]=0.5%; number needed to harm [NNH]=200) and total myocardial infarctions (RR=1.182; 95% CI, 1.036-1.349; ARI=0.6%; NNH=167) compared with beta-blockers or diuretics. Rates of congestive heart failure, cardiovascular mortality, and total mortality were not different between the 2 groups.

In patients with diabetes and hypertension, ACE inhibitors were associated with fewer nonfatal, fatal, and total myocardial infarctions (RR=2.204; 95% CI, 1.501-3.238; ARR=6.0%; NNT=17 for total MIs) than were calcium channel blockers. The rates of development of congestive heart failure or stroke were similar with ACE inhibitors and calcium channel blockers. Cardiovascular and total mortality also were not different between the 2 groups.

**RECOMMENDATIONS FOR CLINICAL PRACTICE**

Calcium channel blockers are associated with slightly fewer strokes and slightly more myocardial infarctions compared with beta-blockers or diuretics. No significant differences in total or cardiovascular mortality between the classes of medications were noted in this meta-analysis. These data support the notion that calcium channel blockers are as safe as, but no more effective than, conventional treatments for hypertension. In diabetic patients, an angiotensin-converting enzyme (ACE) inhibitor should be used before a calcium channel blocker. The Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) compared the calcium channel blocker amlodipine and the ACE inhibitor lisinopril with the diuretic chlorthalidone in 30,000 elderly patients with hypertension and 10,000 with comorbid diabetes. Results of ALLHAT should be available by fall 2002. Meanwhile, primarily because of high costs, calcium channel blockers should remain fourth-line agents in the treatment of hypertension, after diuretics, beta-blockers, and in diabetic patients particularly, ACE inhibitors.

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