CRD summary
The authors concluded that thiazide diuretics and β-blockers appear to reduce the risk of fracture in older adults, but further research is required. The authors' cautious conclusions appear to reflect limited data from diverse observational studies. However, poor reporting of the review makes it difficult to assess the reliability of the conclusions.

Authors' objectives
To examine the relationship between specified classes of antihypertensive drugs and the risk of fracture, using evidence from observational studies.

Searching
MEDLINE (1966 to December 2005), EMBASE (1980 to December 2005), LILACS and meeting abstracts in the ISI Proceedings database (1990 to 2005) were searched without any language restrictions; the search terms were reported. In addition, the references of retrieved studies were screened.

Study selection
Case-control and cohort studies that reported data on the relationship between explicitly defined exposure to specified classes of antihypertensive drugs (angiotensin-converting enzyme inhibitors), diuretics, β-blockers, calcium-channel blockers and α-blockers) and clearly defined fracture were eligible for inclusion. Studies had report relative risks (RRs) or odds ratios (ORs) with 95% confidence intervals (CIs), or provide sufficient data to enable their calculation.

Most of the included studies selected controls from the population rather than the hospital, and included predominantly women. Where reported, the mean age ranged from approximately 50 to 83 years. The studies assessed any fracture, as well as fracture at specific sites such as hip, femoral neck, vertebrae, tibia/fibula, pelvis, forearm and nonvertebral.

The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
Validity was assessed using a 10-point scale with each item scoring between 0 and 2. All studies were assessed for response rate, adjustments, and matching and assessment of the duration of exposure. In addition, case-control studies were assessed for selection of control and the prevalence or incidence of cases, while cohort studies were assessed for handling of losses to follow-up and evaluation of consistency of exposure during follow-up. Studies scoring 7 or more points were classified as high quality.

The authors did not state how the validity assessment was performed.

Data extraction
Data were extracted onto a standardised form. For each study, RRs with 95% CIs were extracted. The authors did not state how many reviewers performed the data extraction.

Methods of synthesis
Separate analyses were conducted for each class of antihypertensive drug. Pooled RRs with 95% CIs were calculated using a random-effects model; ORs were assumed to approximate to RRs. Details were reported of the methods used to handle studies reporting multiple fracture sites without providing an overall RR.

Statistical heterogeneity was assessed using the Ri statistic, which tests the proportion of the total variance of between-study variance. Potential sources of heterogeneity, including study quality, fracture site and duration of drug use, were
examined.

Publication bias was assessed for studies evaluating thiazide diuretics using a funnel plot and tested using the regression test of Egger.

Results of the review
Thirty-three publications were included. Some publications evaluated more than one drug. These publications provided 54 antihypertensive drug/control 'studies' (the review defined a study as exposure to an antihypertensive medication): 40 case-control studies and 14 cohort studies.

Diuretics (38 studies included in analyses, n=384,533): there was no significant difference between diuretics overall and control (RR 0.90, 95% CI: 0.79, 1.03), based on 38 studies. Thiazide diuretics were associated with a statistically significant reduction in the risk of any fracture compared with control (RR 0.86, 95% CI: 0.81, 0.92), based on 25 studies (including 16 high-quality studies); significant heterogeneity was found (p=0.01). There was no statistically significant difference between nonthiazide diuretics and control (RR 1.19, 95% CI: 0.91, 1.57), based on 11 studies; significant heterogeneity was found (p<0.001). Moderate to large heterogeneity was found for almost all analyses and subgroup analyses of diuretics (p<0.19 to p<0.001); heterogeneity remained after stratification by age, gender and study quality.

Beta-blockers (8 studies, n=224,407) were associated with a statistically significant reduction in the risk of any fracture compared with control (RR 0.86, 95% CI: 0.76, 0.98). Significant heterogeneity was found (p<0.01); this subsided when the analysis was restricted to hip fractures.

Angiotensin-converting enzyme inhibitors were associated with a statistically significant reduction in the risk of any fracture compared with control (RR 0.81, 95% CI: 0.73, 0.89), based on one study (n=151,420).

Calcium-channel blockers were associated with a statistically significant increase in the risk of femoral neck fracture compared with control (RR 1.96, 95% CI: 1.16, 3.30), based on one study (n=484).

There was no statistically significant difference in the risk of any fracture between α-blockers and control (RR 1.12, 95% CI: 0.42, 3.02), based on 2 studies (n=9,142).

The funnel plot for thiazide diuretics was asymmetrical, suggesting the possibility of publication bias, but no evidence of publication bias was found using Egger's test.

Authors' conclusions
Thiazide diuretics and β-blockers appear to reduce the risk of fracture in older adults, but further research is required into their potentially protective effects.

CRD commentary
The review question was stated clearly. Several relevant sources were searched and no language restrictions were applied. No specific attempts were made to minimise publication bias; the potential for this was assessed but the results were inconclusive. Validity was assessed, although only the composite score was presented; this makes it difficult to independently comment on the reliability of the evidence presented. The methods used to select studies, assess validity and extract the data were not described, so it is not known whether any efforts were made to reduce reviewer error and bias. Meta-analyses were conducted, heterogeneity was assessed, and various predefined subgroup analyses were conducted. The significant heterogeneity remaining after subgroup analyses suggests that the results may differ between studies. There were discrepancies between the results presented in the abstract and the main text and tables, which undermines the reliability of the data. The authors' cautious conclusions appear to reflect limited data from diverse observational studies. However, poor reporting of the review, including a lack of reporting of review methods, makes it difficult to assess the reliability of the conclusions.

Implications of the review for practice and research
Practice: The authors stated that the use of diuretics cannot be recommended as prophylaxis for fracture.
Research: The authors did not state any implications for further research.

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