Antihypertensive drugs demonstrate varying levels of hip fracture risk: A systematic review and meta-analysis

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**Abstract**

Objective: By aggregating the literature, we evaluated the association between use of specific antihypertensive drugs and the risk of hip fractures compared with nonuse.

Study design and setting: We systematically searched the Pubmed, Embase, and Cochrane databases from inception of each database until July 30, 2020 to identify articles including patients 18 years of age or older reporting on the association between antihypertensive drugs and the risk of hip fracture. Antihypertensive drugs were restricted to thiazides; beta-blockers; calcium-channel blockers; angiotensin-converting enzyme (ACE) inhibitors; and angiotensin receptor blockers. Nonusers encompass all patients that are not using the specific antihypertensive drug that has been reported. Unadjusted odds ratios with 95% confidence intervals (CIs) of the association between antihypertensive drug use and hip fractures were reported. Meta-analysis was performed when a minimum of five studies were identified for each antihypertensive drug class. Quality assessment was done using ROBINS-I tool. The GRADE approach was used to evaluate the certainty of the evidence.

Results: Of 962 citations, 22 observational studies were included; 9 studies had a cohort design and 13 studies were case-control studies. No randomized controlled trials were identified. We found very low certainty of evidence that both thiazides (pooled odds ratio: 0.85, 95% CI 0.73 to 0.99, \(p = 0.04\)) as well as beta-blockers (pooled odds ratio: 0.88, 95% CI 0.79 to 0.98, \(p = 0.02\)) were associated with a reduced hip fracture risk as compared to specific nonuse. One study, reporting on angiotensin receptor blockers, also suggested a protective effect for hip fractures, whereas we found conflicting findings in four studies for calcium-channel blockers and in two studies for ACE inhibitors.

Conclusion: Among 22 observational studies, we found very low certainty of evidence that, compared to specific nonuse of antihypertensive drugs, use of thiazides, beta-blockers, and angiotensin receptor blockers were associated with a reduced protective hip fracture risk, while conflicting findings for calcium-channel blockers and ACE inhibitors were found. Given the low quality of included studies, further research –randomized controlled trials– are needed to definitively assess the causal relationship between specific antihypertensive drug classes and (relatively infrequent) hip fractures.

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Introduction

Hip fracture risk increases with age and can lead to loss of function and independence, and mortality [1]. Meanwhile, fractures related to osteoporosis are a major threat due to the aging of the population, eventually resulting in a substantial health and economic burden [2].

Antihypertensive drugs are primarily prescribed to control high blood pressure, which is one of the most important modifiable risk factors to prevent cardiovascular disease. However, evidence suggests that these drugs may result in orthostatic hypotension, gait impairment and dizziness, potentially increasing the risk of falls [3,4]. As such, treatment with antihypertensive
drugs are hypothesized to result in increased osteoporotic fracture risk [5].

Prior studies have assessed the association between antihypertensive drugs and hip fractures but focused largely on diuretics and beta-blockers [6–8]. However, the evidence regarding the association between antihypertensive drug use and osteoporotic fracture risk is conflicting [9]. We therefore feel that a more comprehensive synthesis of the literature is justified in which the following five most commonly prescribed antihypertensive drugs are evaluated and grouped: thiazide; beta-blocker; calcium-channel blocker; angiotensin-converting enzyme (ACE) inhibitor; and angiotensin receptor blocker [10].

By aggregating the literature, we evaluated the association between use of specific antihypertensive drugs and the risk of hip fractures compared with no use.

Methods

We performed a systematic review with meta-analyses in concordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and Meta-analysis of Observational Studies in Epidemiology (MOOSE) checklist [11,12]. Prior to study selection, our review protocol was registered in PROSPERO (CRD42020201768; July 30, 2020), an international database of protocols for systematic reviews, and amended on August 27, 2020.

Literature search and study selection

We searched eligible studies using the PubMed, Embase, and Cochrane libraries from inception of each database until July 30, 2020. A medical librarian helped us construct the search using the following keywords “hypertension”, “hip fractures”, and “antihypertensive agents” including synonyms and MeSH terms (Appendix 1). Two reviewers (DWGL, LPEV) independently screened titles and abstracts according to the predefined protocol. Studies were included if they reported on patients, 18 years of age or older, in which the association between use of specific antihypertensive drugs after initiation and hip fractures was investigated compared with no use. Nonusers encompass all patients that are not using the specific antihypertensive drug that has been reported. Initiation was defined as the date when antihypertensive drugs were first dispensed (i.e. index date). There were no restrictions on the minimum time of follow-up. Antihypertensive drugs were restricted to the following five most commonly prescribed classes and grouped: (1) thiazide; (2) beta-blocker; (3) calcium-channel blocker; (4) ACE inhibitor; and (5) angiotensin receptor blocker [10]. We excluded narrative review articles, letters to editors, meeting abstracts, technique papers, studies with less than ten hip fractures per group, studies not published in English, studies not reporting on hip fracture and antihypertensive drugs use, and studies reporting on a combination therapy of antihypertensive drugs. Bibliographies of included studies were checked to assess whether articles were missed by the systematic search.

Data extraction

Two reviewers (DWGL, LPEV) independently extracted data of included studies on full-text level. A data extraction sheet was created based on outcome measures and explanatory variables and piloted by two reviewers (DWGL, LPEV) using the first five articles. The following data was extracted from each included article: first author’s name, year of publication, inclusion years, country, institution, study design, matching criteria (for case-control studies), follow-up duration (mean, median, minimum, and range), total sample size as well as the number of patients that did and did not use antihypertensive drugs separately, number of reported hip fractures per group (users versus nonusers), number of reported patients without a hip fracture per group (users versus nonusers), sex distribution, mean/median age (including standard deviation and range), the variables adjusted for, antihypertensive drug class, unadjusted and adjusted odds ratio (OR), and number needed to harm.

Two reviewers (DWGL, LPEV) independently extracted the same data from all included studies. Consistency was calculated by dividing the number in which both reviewers extracted the same data divided by the total data points of the studies. For inconsistencies, agreement was reached after discussion without need of a third reviewer.

Quality assessment

Two reviewers (DWGL, LPEV) independently appraised methodological quality of the studies according to predefined criteria. Observational- and case-control studies were evaluated by using the ROBINS-I tool [13]. This tool encompasses seven domains that facilitates judging risk of bias within each domain, eventually leading to an overall risk of bias score (that is, low, moderate, serious, or critical risk of bias) [14]. A well-performed randomized trial is for example a study with an overall low risk of bias; a non-randomized study could be judged as moderate risk of bias when it provides sound evidence; a study with some important limitations is appraised as serious risk of bias; and studies that are too problematic to provide any useful evidence are judged as critical risk of bias. A panel meeting with a third reviewer was not needed as high consistency during quality assessment was attained.

To evaluate the certainty of the evidence for our pooled estimates of the association between antihypertensive drugs and hip fracture, the GRADE (Grading of Recommendations, Assessment, Development, and Evaluations) approach was used [15]. The following eight domains for pooled estimates of meta-analyses were assessed by two reviewers (DWGL, LPEV): risk of bias, inconsistency, indirectness, imprecision, publication bias, effect magnitude, presence of residual confounding, and dose-response relationship. Risk of bias assesses whether included studies had limitations in design or execution; inconsistency determines if the results were inconsistent among studies; indirectness evaluates whether the evidence answers the study question directly; imprecision assesses if results are precise enough or if any imprecision warrants downgrading the quality of evidence; publication bias determines the probability of publication bias; effect magnitude evaluates whether the effect was large or very large for a certain outcome; presence of residual confounding assesses whether the influence of all plausible confounding reduces an effect estimate or investigates spurious effects when results show no effect; and dose-response relationship rates the presence of a dose-response gradient. Appraisal of the body of evidence was reached during a consensus meeting (DWGL, LPEV).

Outcomes

Unadjusted odds ratios with 95% confidence intervals (CIs) of the association between antihypertensive drug use and hip fractures of each individual study were used as primary estimates for the association in our meta-analysis. The outcome of interest (i.e. hip fractures) was expected to be uncommon (< 10%) and therefore, odds ratios were appropriate [16]. We also calculated the number needed to harm (NNH) to indicate the number of people exposed to a specific antihypertensive drug to result in increased hip fracture.
Statistical analysis

We performed a meta-analysis by pooling odds ratios and 95% CIs from individual studies using a random-effects model with an inverse variance weighted method. The results were summarized both qualitatively and quantitatively. Heterogeneity among studies was evaluated by calculating I² and a chi-square Q test [17]. A p value of < 0.05 indicates significant heterogeneity. Unadjusted odds ratios with 95% CIs were presented as forest plots. Irrespective of study quality, we pooled data for each antihypertensive drug class independently. To achieve appropriate power, inclusion of data from a minimum of five studies was deemed necessary [18]. To evaluate whether publication bias existed among the included studies, we created funnel plots when at least ten studies were included in a meta-analysis [19]. Analyses were conducted using Review Manager (RevMan version 5.4, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014).

Results

Study selection

The systematic search yielded 962 citations (Fig. 1). After removing 92 duplicates, we screened 870 titles and abstracts. We excluded 820 articles, leaving 50 studies for full-text screening. Nineteen studies met the inclusion criteria. By screening bibliographies of included studies, we found three additional relevant articles [25,30,31]. Finally, 22 studies were included [4-6,20-38]. One study reported data for male and female patients separately; however, we decided to merge individual data in order to calculate one risk estimate for further analysis [27]. In addition, another study reported on findings from two distinct patient cohorts [6]. We decided to extract these findings separately. Except for five studies, which only included female patients [20,30,32,35,38], the majority of included studies reported on mixed gender groups. Five studies were omitted from quantitative analysis as they did not report absolute numbers to calculate unadjusted odds ratios [4,21,22,34,37].

Quality assessment

Of 22 observational studies, 9 studies had a cohort design and 13 studies were case-controlled (Table 1). No randomized controlled trials were identified. Overall, nine studies were appraised as moderately biased [21,24,27-30,32,34,37], eight studies were appraised as seriously biased [4,6,20,22,23,26,35,36], and five studies were appraised as critically biased [5,26,31,33,38]. The domains “deviation from the intended interventions” and “measurement of outcomes” was low risk of bias for all 22 included studies. Participant selection was at serious risk of bias for all 13 case-control studies, potentially introducing selection bias [4-6,20,22,23,25,26,31,33,35,36,38]. Sixteen studies properly adjusted for confounders (i.e. moderate risk of bias)—leaving the remaining six studies at risk of residual confounding (serious risk of bias [n = 1 study] and critical risk of bias [n = 5 studies]) [5,25,31,33,35,38]. Missing data was reported in fourteen studies and handled appropriately, whereas the remaining eight studies did not report how missing data was handled and therefore information bias cannot be excluded [4,22,25-27,31,36,38]. One study was at risk of selectively reporting study results [5], whereas in all other studies selection of results was adequately described (low risk of bias [n = 15 studies] and moderate risk of bias [n = 6 studies]). A funnel plot appeared symmetrical and showed no publication bias for thiazide use (Fig. 2).

Study characteristics

In total, 587,776 patients were included between 1981 and 2012, reporting on 59,686 hip fractures (Table 2). The average age
Table 1
Quality Assessment according to ROBINS-I tool.

|                           | Overall bias | Confounding | Participant selection | Classification of intervention | Deviations from intervention | Missing data of outcomes | Selection of results |
|---------------------------|--------------|-------------|-----------------------|---------------------------------|------------------------------|-------------------------|----------------------|
| **Cohort**                |              |             |                       |                                 |                              |                         |                      |
| Bokrantz et al. [28]      | moderate     | moderate    | moderate              | moderate                         | low                          | low                     | low                  |
| Cauley et al. [30]        | moderate     | moderate    | low                   | low                             | low                          | low                     | low                  |
| Feskanich et al. [32]     | moderate     | moderate    | moderate              | moderate                         | low                          | low                     | low                  |
| Guo et al. [21]           | moderate     | moderate    | low                   | low                             | low                          | low                     | low                  |
| Kunutsor et al. [29]      | moderate     | moderate    | moderate              | moderate                         | low                          | low                     | low                  |
| LaCroix et al. [34]       | moderate     | moderate    | low                   | low                             | low                          | low                     | low                  |
| Schoofs et al. [37]       | moderate     | moderate    | low                   | low                             | low                          | low                     | low                  |
| Thorell et al. [24]       | moderate     | moderate    | moderate              | low                             | low                          | low                     | low                  |
| Yang et al. [27]          | moderate     | moderate    | low                   | low                             | low                          | low                     | low                  |
| **Case-control**          |              |             |                       |                                 |                              |                         |                      |
| Corrao et al. [5]         | critical     | serious     | serious               | low                             | low                          | low                     | critical             |
| De Vries et al. [6]       | serious      | moderate    | serious               | moderate                         | low                          | low                     | low                  |
| Grisso et al. [20]        | serious      | moderate    | serious               | low                             | low                          | low                     | low                  |
| Jensen et al. [33]        | critical     | critical    | serious               | moderate                         | low                          | low                     | low                  |
| Paganini-Hill et al. [35] | critical     | critical    | serious               | low                             | low                          | low                     | low                  |
| Rashiq et al. [31]        | critical     | serious     | moderate              | low                             | low                          | low                     | moderate             |
| Ray et al. [36]           | serious      | moderate    | serious               | moderate                         | low                          | low                     | low                  |
| Reijnen et al. [22]       | serious      | moderate    | serious               | moderate                         | low                          | low                     | low                  |
| Reijnen et al. [4]        | serious      | moderate    | serious               | moderate                         | low                          | low                     | low                  |
| Stevens et al. [23]       | serious      | moderate    | serious               | low                             | low                          | low                     | moderate             |
| Taggart et al. [38]       | critical     | critical    | serious               | low                             | low                          | low                     | low                  |
| Wang et al. [25]          | critical     | critical    | serious               | low                             | low                          | low                     | moderate             |
| Weiland et al. [26]       | serious      | moderate    | serious               | low                             | low                          | low                     | low                  |

Fig. 2. Funnel plot of comparison thiazide use versus nonuse for detection of publication bias.

ranged between 63 and 82 years and 75% (range 52–100%) were female. Among the included studies, thiazide was the most commonly reported antihypertensive drug class (n = 17 studies) [5,20-23,25,26,28,30-38], followed by beta-blocker (n = 7 studies) [4-6,24,27-29], calcium-channel blocker (n = 4 studies) [4,5,24,28], ACE inhibitor (n = 2 studies) [4,28], and angiotensin receptor blocker (n = 1 study) [28]. For data extraction, a high level of consistency (93%) was reached between two observers (DWGL, LPEV).

Two studies, reporting on thiazide use, were excluded in a meta-analysis because they reported less than ten hip fractures per group [29,39].

**Antihypertensive drug use and hip fracture risk**

Thirteen studies compared the risk of hip fracture for thiazide use and nonuse. Among them, six studies demonstrated a reduction of hip fracture risk among users [20,25,28,31,36,38], six studies found no statistically significant difference [5,23,26,32,33,35], and one study demonstrated higher fracture risk for patients using thiazides [30]. Meta-analysis of 13 studies, including 173,264 patients with 8,219 hip fractures, showed a reduction of hip fracture risk in favor of thiazide use (pooled odds ratio: 0.83, 95% CI 0.73 to 0.95, p = 0.04; Fig. 3) [5,20,23,25,26,28,30-33,35,36,38]. Using a
| Author, year       | Study design | Country         | Inclusion years | Mean follow-up in years | Participants (drugs users versus nonusers) | Number of hip fractures | Mean age in years | Age restrictions in years | Or (95% CI) | NNH |
|-------------------|--------------|-----------------|-----------------|-------------------------|------------------------------------------|------------------------|------------------|--------------------------|-------------|-----|
| **Angiotensin converting enzyme inhibitor** |              |                 |                 |                         |                                          |                        |                  |                          |             |     |
| Bokrantz et al. [28] | Cohort       | Sweden          | 2006–2012       | NR                      | 59,246 (28,779 vs 30,467)                | 2593                   | 56%              | ≥ 50                     | 0.56 (0.52 to 0.61) | -43 |
| Rejnmark et al. [4]    | Case-control | Denmark         | 1995–2000       | NA                      | 42,120 (10,530 vs 31,590)               | 10,530                 | 72%              | NR                       | 1.02 (0.96 to 1.08) | .   |
| **Angiotensin receptor blocker** |              |                 |                 |                         |                                          |                        |                  |                          |             |     |
| Bokrantz et al. [28] | Cohort       | Sweden          | 2006–2012       | NR                      | 59,246 (15,218 vs 44,028)               | 2593                   | 56%              | ≥ 50                     | 0.57 (0.51 to 0.63) | -48 |
| **Beta-blocker**      |              |                 |                 |                         |                                          |                        |                  |                          |             |     |
| Bokrantz et al. [28] | Cohort       | Sweden          | 2006–2012       | NR                      | 59,246 (36,629 vs 22,617)               | 2593                   | 56%              | ≥ 50                     | 0.82 (0.76 to 0.89) | -125|
| Corrao et al. [5]     | Case-control | Italy           | 2005–2009       | NA                      | 8603 (471 vs 8132)                      | 2153                   | 76%              | 70–90                    | 1.00 (0.81 to 1.24) | .   |
| De Vries et al. Cohort 1, [6]    | Case-control | the Netherlands | 1987–1999       | NA                      | 44,494 (2314 vs 42,180)                | 22,247                 | 76%              | ≥ 18                     | 0.75 (0.67 to 0.83) | -14 |
| De Vries et al. cohort 2, [6]    | Case-control | the Netherlands | 1991–2002       | NA                      | 33,104 (4448 vs 28,656)                | 6763                   | 76%              | ≥ 18                     | 0.89 (0.81 to 0.97) | -50 |
| Kunutsor et al. [29] | Cohort       | Finland         | 1998–2001       | 14.8                    | 1453 (375 vs 1078)                     | 63                     | 52%              | 62.9 (SD 6.5)             | 1.82 (1.08 to 3.07) | 36  |
| Rejnmark et al. [4]    | Case-control | Denmark         | 1995–2000       | NA                      | NR                                     | 10,530                 | 72%              | NR                       | 1.00 (0.94 to 1.07) | .   |
| Thorell et al. [24]  | Cohort       | Sweden          | 2006–2007       | NR                      | 38,407 (16,738 vs 21,669)              | 795                    | NR               | ≥ 75                     | 0.96 (0.83 to 1.11) | -1000|
| Yang et al. [27]     | Cohort       | Australia       | 1989–1993       | NR                      | 3488 (673 vs 2815)                     | 177                    | 64%              | ≥ 50                     | 0.60 (0.38 to 0.93) | -48 |
| **Calcium-channel blocker** |              |                 |                 |                         |                                          |                        |                  |                          |             |     |
| Bokrantz et al. [28] | Cohort       | Sweden          | 2006–2012       | NR                      | 59,246 (28,762 vs 30,484)              | 2593                   | 56%              | ≥ 50                     | 0.74 (0.68 to 0.80) | -77 |
| Corrao et al. [5]     | Case-control | Italy           | 2005–2009       | NA                      | 8603 (511 vs 8092)                     | 2153                   | 76%              | 70–90                    | 0.94 (0.76 to 1.16) | -100|
| Rejnmark et al. [4]    | Case-control | Denmark         | 1995–2000       | NA                      | NR                                     | 10,530                 | 72%              | NR                       | 1.06 (1.01 to 1.12) | .   |
| Thorell et al. [24]  | Cohort       | Sweden          | 2006–2007       | NR                      | 38,407 (8199 vs 30,208)                | 795                    | NR               | ≥ 75                     | 0.82 (0.68 to 0.98) | -250|
| **Thiazide**          |              |                 |                 |                         |                                          |                        |                  |                          |             |     |
| Bokrantz et al. [28] | Cohort       | Sweden          | 2006–2012       | NR                      | 59,246 (24,890 vs 34,336)              | 2593                   | 56%              | ≥ 50                     | 0.79 (0.73 to 0.86) | -100|
| Cauley et al. [30]   | Cohort       | USA             | 1986–1988       | 3.3                     | 9689 (2637 vs 7052)                    | 136                    | 100%             | ≥ 65                     | 1.00 (0.68 to 1.46) | .   |
| Corrao et al. [5]     | Case-control | Italy           | 2005–2009       | NA                      | 8603 (756 vs 7847)                     | 2153                   | 76%              | 70–90                    | 0.85 (0.71 to 1.02) | -33 |

(continued on next page)
| Author, year           | Study design | Country    | Inclusion years | Mean follow-up in years | Participants (drugs users versus nonusers) | Number of hip fractures | Female | Mean age (years) | Age restrictions (years) | Or (95% CI) | NNH |
|------------------------|--------------|------------|-----------------|--------------------------|--------------------------------------------|-------------------------|--------|----------------|--------------------------|-------------|-----|
| Feskanich et al. [32]  | Cohort       | USA        | 1982–1992       | 9.2                      | 83,738 (11,411 vs 72,327)                  | 229                     | 100%   | NR             | NR                       | 1.35 (0.97 to 1.88) | 100 |
| Griso et al. [20]      | Case-control | USA        | 1987–1992       | NA                       | 36 (83 vs 279)                            | 144                     | 100%   | NR             | ≥ 45                      | 0.58 (0.34 to 0.98) | -8  |
| Guo et al. [21]        | Cohort       | Sweden     | 1987–1989       | 4.4                      | 1608                                       | 400                     | 43 vs 157 | NR             | ≥ 59                      | 1.05 (0.54 to 2.08) | 100 |
| Jensen et al. [33]     | Case-control | Denmark    | 1988           | NA                       | 82 (75 to 101)                            | 200                     | 83%    | NR             | ≥ 65                      | 0.65 (0.47 to 0.89) | -5  |
| LaCroix et al. [34]    | Cohort       | USA        | 1981–1983       | 3.6                      | 9518 (2566 vs 6952)                       | 242                     | 61%    | 74             | ≥ 65                      | 0.79 (0.37 to 1.73) | -5  |
| Paganini-Hill et al. [35] | Case-control | USA        | 1974–1978       | NA                       | 285 (95 vs 190)                           | 38                      | 100%   | 72             | NR                       | 1.67 (1.02 to 2.71) | -5  |
| Rashiq et al. [31]     | Case-control | UK         | 1984           | NA                       | 306 (70 vs 236)                           | 102                     | 88%    | 78.6           | NR                       | 0.38 (0.20 to 0.73) | -33 |
| Ray et al. [36]        | Case-control | USA        | 1970–1983       | NA                       | 6042 (1827 vs 4215)                       | 905                     | NR     | NR             | NR                       | 0.70 (0.56 to 0.92) | -33 |
| Rejnmark et al. [22]   | Case-control | Denmark    | 1995–2000       | NA                       | 235,937 (35,090 vs 200,847)               | 10,139                  | 64%    | 66.5 (SD 15.4) | ≥ 40                      | 1.06 (1.02 to 1.14) | -5  |
| Schoofs et al. [37]    | Cohort       | the Netherlands | 1990–1993 | 7.4                      | 7891 (NR)                                 | 281                     | 61%    | 69 (SD 9.9)   | ≥ 55                      | 0.71 (0.47 to 1.06) | -5  |
| Stevens et al. [23]    | Case-control | UK         | 1985           | NA                       | 307 (60 vs 247)                           | 173                     | 79%    | 78.4           | NR                       | 1.11 (0.63 to 2.00) | 50  |
| Taggart et al. [38]    | Case-control | Northern Ireland | 1981–1985 | NA                       | 427 (172 vs 255)                          | 282                     | 100%   | 83             | ≥ 74                      | 0.56 (0.37 to 0.84) | -8  |
| Wang et al. [25]       | Case-control | USA        | 1993–1995       | NA                       | 6110 (1099 vs 5011)                       | 1222                    | 84%    | 82.4           | ≥ 65                      | 0.74 (0.63 to 0.90) | -20 |
| Weiland et al. [26]    | Case-control | Germany    | 1986–1990       | NA                       | 224 (32 vs 192)                           | 98                      | 100%   | 73.4           | 70–79                     | 0.74 (0.34 to 1.60) | 14  |

OR = odds ratio, NNH = number needed to harm, NR = not reported, NA = not applicable, . = no absolute numbers reported to calculate number needed to harm.
* = median, . = not reported in study and no absolute numbers reported to calculate unadjusted number needed to harm, ρ = no absolute numbers reported to calculate unadjusted OR.
random effects model, heterogeneity among included studies was detected (I² = 73%, p < 0.01). Among seven studies, four studies found an association between beta-blocker use and reduction of hip fracture risk [6,27,28], whereas two other studies found no such association [5,24]. Only one study found a reduced risk of hip fracture among nonusers [29]. A meta-analysis of seven studies, comprising 188,795 patients with 34,791 hip fractures, showed that beta-blocker use was associated with reduced hip fracture risk (pooled odds ratio: 0.88, 95% CI 0.79 to 0.98, p = 0.02; Fig 4) [5,6,24,27–29]. Again, heterogeneity was observed (I² = 77%, p < 0.01).

Of four studies addressing the use of calcium-channel blockers [4,5,24,28], two studies found a reduced hip fracture risk among users compared to nonusers (odds ratio: 0.74, 95% CI 0.68 to 0.80, NNH, -77; and odds ratio: 0.82, 95% CI 0.68 to 0.98, NNH, -250) [24,28]; one study demonstrated no association (odds ratio: 0.94, 95% CI 0.76 to 1.16, NNH, -100) [5], whereas another study found an increased hip fracture risk (odds ratio: 1.06, 95% CI 1.01 to 1.12) [4].

Two studies evaluated the risk of hip fracture among ACE inhibitor users and nonusers [4,28]. Bokrantz et al. [28] showed a reduced hip fracture risk in favor of ACE inhibitors (odds ratio: 0.56, 95% CI 0.52 to 0.61, NNH, -43), whereas fracture risk among ACE inhibitor use and nonuse did not differ for Rejmark et al. (odds ratio: 1.02, 95% CI, 0.96 to 1.08) [4].

The study by Bokrantz et al. [28], evaluating 59,246 patients with 2,593 hip fractures, observed a reduced in hip fracture risk towards angiotensin receptor blocker use as compared to nonuse (odds ratio: 0.57, 95% CI 0.51 to 0.63, NNH, -48).

Grade evidence

Using the GRADE approach, certainty of the evidence was considered to be “very low” for the pooled estimate derived from a meta-analysis of 13 observational studies that assessed the association between hip fracture risk and thiazide use (Table 3). Also, the certainty of the evidence was “very low” for the association that was evaluated in seven observational studies between beta-blocker use and the risk of hip fracture. A downgrade from high to very low evidence was warranted for both analyses due to the combination of serious risk of selection bias, heterogeneity among reported results, and wide 95% confidence interval.

Discussion

Osteoporotic hip fractures are a major threat to the aging population and can lead to loss of function, independence, and mortality [1,2]. Antihypertensive drugs are hypothesized to increase the risk of falls due to hypotension, gait impairment, and dizziness, potentially increasing osteoporotic fracture risk among elderly [3–5]. We aggregated data from 22 observational studies to evaluate the association between the five most commonly prescribed antihypertensive drugs and the risk of hip fracture. We found very low certainty of evidence that both thiazides as well as beta-blockers were associated with a reduced hip fracture risk.

This study has several limitations. First, a subset of nonusers in the control group of several included studies used other antihypertensive drugs. Our findings should therefore be interpreted as antihypertensive drug use versus nonuse of the specific antihypertensive drug that has been evaluated. Inherently, due to study designs of these included studies, our comparison is therefore less informative than we initially planned. Second, it would have been interesting to stratify by the administered dose of antihypertensive drugs and the risk of hip fracture; however, most included studies did not specifically report on this. While prior evidence demonstrated no clear dose-response relationship between antihypertensive drug use and hip fracture risk [37,40,41], we regard such an effect unlikely and it therefore should not influence our conclusions.
Table 3
GRADE evidence for observational studies comparing thiazide use/beta-blocker use and nonuse with hip fracture as outcome.

| Effect | No. of patients | Antihypertensive drug | No. of cases | Relative Risk (95% CI) | Certainty of evidence | Risk of bias | Study design | Risk of confounding | Other considerations |
|--------|-----------------|-----------------------|--------------|------------------------|-----------------------|----------------------|--------------|-------------------|---------------------|
| Thiazide use | 13 | Observational | Serious α | β-blocker | 8 fewer per 1,000 (from 0.73 to 0.98) | Low | Serious β | Serious β | Serious β |
| Beta-blocker use | 7 | Observational | Serious α | None | 3 fewer per 1,000 (from 0.79 to 0.98) | Low | None | None | None |

- **Certainty of evidence**: Low, very low.
- **Risk of bias**: Serious α.
- **Study design**: Observational.
- **Risk of confounding**: Serious β.
- **Other considerations**: None.

Third, it is likely that nonuser patients had both elevated as well as non-elevated blood pressure. A prior study demonstrated that high blood pressure may negatively impact bone mineral density, and therefore a retrospective cohort or case-control study design is not optimal [42]. However, it may go without saying that restricting administration of antihypertensive drugs to reduce elevated blood pressure is unethical when these drugs are actually proven effective. Fourth, among patients using antihypertensive drugs, we cannot be certain that hip fractures due to major trauma were excluded. The included studies did not specifically report on major traumatic accidents relating to hip fracture. However, evidence suggests that only 10% of hip fractures is due to high energy traumatic accidents, leaving the majority of hip fractures subjected to low energy trauma [43]. Fifth, most studies regarded an antihypertensive drug prescription as a proxy for actual patient compliance. Although many included studies were register-based and evaluated large populations, information bias cannot be excluded. Finally, we checked five large randomized placebo controlled trials on antihypertensive drug use to determine the occurrence of hip fractures reported as a complication [44–48]. Among antihypertensive drug users as well as nonusers, there were no hip fractures reported during follow-up of these trials. It is therefore unlikely that we missed potentially relevant trials that were not identified by our systematic search.

Our observation that thiazides reduce the odds of a hip fracture with 15% is in line with prior systematic reviews of observational studies [8,49]. Even though the majority of included studies overlapped among these reviews, we decided to exclude some studies in our analysis to primarily avoid amalgamation of risk estimates (i.e. hazard- and odds ratios). One should consider that our findings should be interpreted cautiously as GRADE certainty of evidence was very low. Currently, several biological theories suggest potential protective effects of thiazides. Amongst others, a reduced urinary calcium excretion, an increased bone retention of calcium, and a more susceptible gastrointestinal calcium resorption are plausible explanations that act preventive [50–52]. In contrast, thiazides are known to induce hyponatremia that is associated with osteoporosis, and as such potentially contradicts the aforementioned protective effect [53]. This may potentially also explain the heterogeneity among our included studies. It therefore merits further study to determine the relationship between thiazides and the relative infrequent hip fracture risk in the elderly, for example in a randomized placebo controlled trial design. If efficacy would be proven, then thiazides could potentially play a role in the primary prevention of osteoporotic hip fractures among the elderly.

Our meta-analysis of seven observational studies found a very low certainty of evidence that beta-blocker use was associated with a 12% reduced odds of developing a hip fracture. Kunutsor et al. [29] was the only study reporting on a hip fracture risk that favored nonusers. Overall, they included a relatively young patient cohort that is less susceptible to hip fractures, while it is known that the majority of fractures have a tendency towards the elderly. The exact mechanism of the protective association has not been elucidated yet, but translational evidence from animal studies suggests that beta-blocker use stimulates skeletal remodeling and bone formation [54].

We found conflicting results as to whether an association exist between calcium-channel blocker use and the risk of hip fracture. It is not yet clear whether calcium-channel blocker use affect bone remodeling in humans, but some experimental studies do suggest a stimulating calcium uptake into osteoblast-like cells and an inhibition of bone resorption [55,56].

Furthermore, the protective effect of ACE inhibitors and angiotensin receptor blockers on hip fracture risk have been described by Bokrantz et al. [28]; however, Reijnmark et al.
demonstrated no association between ACE inhibitor use and the risk of hip fracture. A prior meta-analysis [29], comprising only two studies but analyzing different risk estimates (i.e., standardized incidence rate and hazard ratio), separately evaluated the use of ACE inhibitors and angiotensin receptor blockers [9,42]. Both analyses reported a relative risk reduction of hip fractures. The potential role of the renin-angiotensin-system on bone formation have been described by experimental studies, but more research in a human population is needed to either confirm or refute these findings [57,58].

Conclusions

Across different antihypertensive drug classes, we found very low certainty of evidence that use of thiazides, beta-blockers, and angiotensin receptor blockers were protective for hip fractures, while conflicting findings for calcium-channel blockers and ACE inhibitors were found. To further determine the causal relationship between specific antihypertensive drug classes and (relatively infrequent) hip fractures, large high quality randomized placebo controlled trials are needed.

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Ethical review committee statement

N.A.

Declaration of Competing Interest

N.A.

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Supplementary material

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.injury.2021.09.036.

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