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Cardiovascular safety of denosumab across multiple indications: a systematic review and meta-analysis of randomized trials

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Disclosure Page

Mr Seeto has nothing to disclose.

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Author Contribution

Mr Seeto: Methodology, Writing-original draft and Writing-review & editing

Prof. Abrahamsen: Supervision and Writing-review & editing

Prof. Ebeling: Methodology, Resources, Supervision and Writing-review & editing

Dr. Rodriguez: Conceptualization, Data curation, Formal analysis, Methodology, Project administration, Software, Supervision, Writing-original draft and Writing-review & editing

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Abstract

The cardiovascular safety of denosumab has not yet been evaluated in a systematic review. This systematic review and meta-analysis sought to quantify the number of randomized controlled trials (RCTs) of denosumab (against comparators) reporting cardiovascular adverse events (CAEs) and examine the balance of CAEs between treatment arms. MEDLINE, Embase and clinicaltrials.gov were searched from inception to 26th October 2019 for RCTs of denosumab versus comparators for any indication. Included trials were randomized, enrolled ≥100 participants and reported bone-related outcomes. Primary outcome for analysis was all CAEs; a composite endpoint representing summation of all CAEs as reported by included trials. Secondary outcomes included Major Adverse Cardiovascular Events (MACE). Data were pooled using a fixed effects model to determine relative risk (RR) and 95% confidence interval (95%CI). Risk of bias was assessed using the Cochrane risk-of-bias tool. Of 554 records screened, 49 were included, while 36 reported CAEs. Twenty-seven included trials (twelve eligible for meta-analysis) were conducted in 13,202 post-menopausal women. Compared with bisphosphonates, there was a 46% (95% CI: 1.05 to 2.02) increase in CAEs [85/2136 events in denosumab-treated vs. 58/2131 events in bisphosphonate-treated); seven trials]. There was a similar imbalance in a five-point (stroke, myocardial infarction, cardiovascular death, heart failure, atrial fibrillation) MACE endpoint [28/2053 vs. 12/2050; RR=2.33(1.19, 4.56)]. Compared with placebo-treated women, there was no imbalance in total CAEs [439/4725 events in denosumab vs. 399/4467 in placebo; RR=0.79 (0.41 to 1.52); seven trials]. No imbalance in total AEs [versus bisphosphonates: 0.98 (0.92 to 1.04); versus placebo: 0.99 (0.98 to 1.01)] occurred. Other indications showed no statistically significant results. The excess CAEs in post-menopausal women treated with denosumab compared with

bisphosphonates, but not placebo, indirectly supports claims that bisphosphonates may suppress CAEs. Future trials should use standardized CAE reporting to better describe cardiovascular effects of bone active medications. (PROSPERO: CRD42019135414.)

Key Words: Anti-resorptives; Osteoporosis; menopause; cancer; clinical trials

Introduction

In ageing populations, osteoporosis is a growing public health concern. Osteoporosis does not exist in isolation, but often co-exists with other age-related diseases, particularly cardiovascular diseases [(1)]. Literature suggests that cardiovascular diseases contribute a major proportion to mortality after a fragility fracture[(2)]. Thus, greater appreciation of the need for CV disease management alongside fracture risk is warranted across clinical specialties.

Lessons from previous studies involving bisphosphonates (BPs) have suggested that BPs may suppress CAEs [(3-5)]. Thus, in BP-controlled randomized controlled trials (RCTs) any increase in CAEs could actually represent an artificial elevation. Accordingly, a new agent for osteoporosis, the anti-sclerostin antibody romosozumab, has shown skeletal benefit but an increased risk of cardiovascular adverse events (CAEs) when compared with bisphosphonates (BPs) but not with placebo [(6-8)]. This served as the scientific motivation to re-evaluate the cardiovascular safety profile of denosumab.

Denosumab is a human monoclonal antibody against the receptor activator of nuclear factor-κB ligand (RANKL), which exerts potent anti-resorptive effects [(9)]. Studies have reported that denosumab exhibited a similar safety profile compared with BPs [(10)]. However, given the suspected cardio-protective benefit of BPs, no study has specifically examined the distribution of CAEs in denosumab-treated patients versus BP treatments or indeed for other treatments, including placebo.

Two previous meta-analyses have reported on the cardiovascular safety of denosumab [11,12]. However, these studies exclusively evaluated trials in post-menopausal women and findings were limited. One review only included placebo-controlled trials and the other pooled active and placebo-controlled trials, as well as mixed population groups. Both previous reviews failed to include the trial by McClung *et al.* (2006), the seminal paper in the clinical development of denosumab [13]. Furthermore, denosumab has a number of indications for use and the cardiovascular effects are uncertain in other groups. Our systematic review evaluated cardiovascular safety in all populations and thus provides a more comprehensive overview of the prescribing landscape. Furthermore, these previous meta-analyses did not evaluate the quality of CAE reporting in RCTs. Our review reports the overall quality of CAE reporting in RCTs and aids in the design and CAE reporting of future trials. Thus, the objectives of this systematic review were to: (1) evaluate the overall quality of CAE reporting and (2) assess the balance of CAEs across all indications for which denosumab is prescribed.

Methods

Data Sources and Searches

We searched MEDLINE, EMBASE, and clinicaltrials.gov from inception to 26th October 2019 with no language restrictions for eligible records. Records were identified using the follow title and abstract terms: “denosumab” AND (“fracture” OR “bone density” OR “bone mineral density” OR “skeletal-related events”) AND “random*”. Records were stored using a citation manager and duplicates were removed. We screened all titles and abstracts and following screening; full texts were examined to evaluate eligibility. We also manually screened reference lists of eligible texts and online related article lists to identify potentially relevant manuscripts.

Study Selection

We conducted this systematic review and meta-analysis in accordance with the PRISMA statement [14] and it is registered with PROSPERO (CRD42019135414). We aimed to determine: 1) the number of studies which specifically report CAEs and 2) determine the balance of CAEs across the indications for which denosumab is prescribed. Studies were eligible if the trial was randomized, used denosumab, randomized at least 100 participants, and reported bone-related outcomes including *bone mineral density* (BMD), *incident fractures (at any site) or skeletal-related events* (SREs). Specific exclusion criteria included: non-randomized studies, systematic reviews, reviews, conference abstracts, letters, case reports, animal or cell-based studies.

Data Extraction and Quality Assessment

Data were tabulated by a single reviewer (A.H.S) using a data extraction template and was checked for accuracy by another reviewer (A.J.R). We sought the total enrolled patients; comparator; known fractures at baseline; follow up length; inclusion and exclusion criteria, if study reported CAEs; age, gender, baseline BMD of participants at baseline; dosage, frequency, and route of administration of intervention. A weighted average of age, baseline vertebral and non-vertebral BMD were calculated for meta-regression.

Adverse event (AE) data were collected using a separate data extraction template. We tabulated any and all AEs as well as all specific CAEs listed in each study. Where available, additional data on publications was sought on clinicaltrials.gov. Given the heterogeneity in reported CAEs, we created a composite outcome which was a summation of all reported specific CAEs. Each CAE was assigned equal weight since reporting of CAEs was ultimately event-driven. For studies with available data, we also created a major adverse cardiovascular event (MACE)

endpoint. Our three-point MACE (MACE3) comprised myocardial infarction (MI), stroke and CVD death; four-point MACE (MACE4) comprised MACE3 and heart-failure (HF) and five-point MACE (MACE5) comprised MACE4 and atrial fibrillation.

We used the Cochrane Collaboration risk-of-bias tool for randomized trials to assess risk of bias [15]. This tool evaluates bias across seven domains: Random Sequence Generation, Allocation Concealment, Blinding of Participants and Personnel, Blinding of Outcome Assessment, Incomplete Outcome Data, Selective Reporting, Other Bias (e.g. representativeness). A judgement of low, unclear, or high risk of bias was made for each domain. An overall risk of bias per study was evaluated based on the following criteria: low – all domains low; low/unclear – all domains low except for one which was unclear; unclear – greater or equal to two unclear domains; high – any domain was high. Two independent reviewers (A.H.S and A.J.R) performed the assessment. For studies where there was disagreement between the reviewers regarding the overall risk of bias, discrepancies were resolved by a consensus meeting.

Data Synthesis and Analysis

Studies were eligible for meta-analysis if they initially satisfied the inclusion-exclusion criteria, reported CAE data, were not extensions of clinical trials and there were at least two studies with relevant data per indication or comparator. Analysis was performed separately by indication and by comparator (BP or placebo). For example, within the post-menopausal women population, denosumab was compared to bisphosphonate and placebo in two separate analyses. For all studies that reported CAEs, we additionally analysed the balance of all AEs as a measure of internal validity. We used all AEs as opposed to serious AEs due to the heterogeneous classification of serious AEs between trials. Data were synthesised using a

Mantel-Haenszel fixed effects model reporting relative risk (RR) and 95% confidence interval (95%CI). Where heterogeneity was substantial ($I^2 > 50\%$), a random effects model was used. All data were computed using Stata v14.2 using the *metan* package (College Station, Texas, USA). Sensitivity analysis was performed through a leave one out analysis for any statistically significant result. We identified age, prevalence of smokers, body mass index and vertebral and non-vertebral BMD as potential clinical modifiers for cardiovascular risk. Thus, we investigated these potential sources of heterogeneity by using meta-regression. We also investigated study size as a potential source of methodological heterogeneity. Publication bias was assessed by visual inspection of a funnel plot.

Results

Literature search

The literature search yielded 554 results. Forty-nine duplicates were removed, leaving 505 records for title and abstract screening where 459 records were excluded primarily due to having a population <100 (n=34); no randomization (n=84); conference abstracts (n=92); systematic reviews (n=77) or did not investigate bone related outcomes (n=63). Forty-six full text articles were assessed for eligibility, of which six were removed primarily for having a population size <100, which were not reported in the abstract (n=3). Additional hand searching

found another nine articles. Overall, 49 studies were included in the qualitative synthesis (Figure 1).

Included studies

Of the articles included in the qualitative synthesis, 46 articles had published results and three unpublished trials had relevant data available on clinicaltrials.gov. Studies were conducted across numerous indications: post-menopausal women with osteoporosis or low BMD (n=27), bone metastasis (n=8), multiple myeloma (n=1), prostate cancer (n=4), breast cancer (n=2), elderly men and women (n=3), patients with glucocorticoid-induced osteoporosis (n=1), patients with rheumatoid arthritis (n=2), and men with low BMD (n=1). Twenty-six studies were conducted in the United States; five in Canada and Japan; two each in China, France, Italy and Australia; and one each in Austria, India, Belgium, England, and Korea. All trials supplemented patients with calcium and/or vitamin D. Sixteen of the 46 studies were extensions of primary trials. We focused on primary trials for data analysis since many extensions crossed over patient treatment arms, or were open-label extensions. Once unblinding or crossover takes place, we cannot attribute particular CAEs exclusively to denosumab or other medications. The smallest trial enrolled 111 patients [16], and the largest trial enrolled 7,808 patients [9]. Follow up time varied between a minimum of 6 months [17] and a maximum of 120 months [18]. Nineteen studies enrolled patients who had previous fractures at baseline, four studies excluded patients with fractures at baseline and 23 were unclear. For dose finding studies, we preferentially chose to report on the dose used most widely in clinical practice for the most relevant data (Table 1).

Literature quality

Most studies were rated as high (n=33), unclear (n=11) whilst one was rated low/unclear (Table 2) quality. Most studies reported randomization methods, allocation concealment and blinding poorly. In studies in which post-menopausal women were enrolled, higher nominal risks of bias were often related to trial sponsors participating in study design, data collection and manuscript writing. In trials enrolling patients with bone neoplasms, high risk of bias was predominantly related to high dropout rate attributed to death or withdrawal of consent.

Adverse events

Forty-six trials (93.9%) reported data on any AEs [9,13,16-58]. Of these, only 36 reported CAEs. Twenty-six studies had data available to form a composite cardiovascular disease endpoint [9,13,17,19,21,22,27,33-37,39,41-43,46,47,49-51,53,54,57,58]. Eleven studies already reported an 'any cardiovascular' AEs [9,21,23,24,33-35,38,42,51,53] whilst six reported 'any vascular' AEs [23,33,34,38,42,51]. The most commonly reported specific CAEs were myocardial infarction (n=17), hypertension (n=16), atrial fibrillation (n=16), coronary artery disease (n=13), and cerebrovascular accident (n=13) (Supplementary Table 1). There were 79 specific CAEs which were reported once, for example 'peripheral vascular disease' was reported in only one trial [9]. All studies did not report an imbalance of overall AEs between denosumab and control groups [9,13,16-57].

Meta-analysis

Twenty-six trials, including 30,308 participants were eligible for meta-analysis including 12 placebo-controlled, 11 BP-controlled trials and three trials with placebo and BP-controlled arms.

Post-menopausal women with osteoporosis or low BMD

In post-menopausal women, there were 11 BP-controlled trials (alendronate n=7, risedronate n=1, ibandronate n=1, zoledronic acid n=1, combination n=1) [13,22,23,27,29,31,33,35-37,59]. Nine of these trials were only compared to bisphosphonates whereas two had BP and placebo comparator arms. Seven trials had CAE data for meta-analysis whereby there were 85 CAEs in 2136 women randomised to denosumab compared with 58 CAEs in 2131 women randomised to any bisphosphonate [RR=1.46 (95%CI: 1.05 to 2.02)] (Figure 2). The lower boundary for this effect estimate (1.05) may not represent a clinically important effect. Thus, in a post-hoc exploratory analysis, we calculated up to what level of confidence we can obtain a minimum clinically important effect size of 15%. We determined that this minimum clinically important effect was seen at the 85% level [RR=1.46 (85%CI: 1.15 to 1.85)]. Therefore, whilst we found an excess risk of 46%, we can only refute the 15% risk increase at a p=0.15. Age (beta coefficient = 0.17, 95%CI: -0.11, 0.45), population size (beta coefficient = 0.00, 95%CI: -0.00, 0.00), previous fracture (beta coefficient = 1.01, 95%CI: -2.07, 3.47), baseline BMD (beta coefficient = -0.06, 95%CI: -7.93, 6.66) and baseline non-vertebral BMD (beta coefficient = -1.77, 95%CI: -6.52, 2.98) were adequately reported to enable meta-regression, for which no influence was noted. Funnel plot inspection indicated minimal risk of publication bias (Supplementary Figure 1). A number needed to harm (NNH) analysis found that for every 79 (95%CI: 35-714) patients treated with denosumab compared with BPs, there would be one excess CAE. All the trials that provided data for NNH were 12 months in length. Thus, if 1000 women were treated for one year, there would be an excess of 12.5 events (95%CI: 1.4-27.8) in those receiving denosumab relative to those receiving BPs. Three-point and four-point MACE comparing denosumab to bisphosphonates in post-menopausal women showed non-statistically significant increases (MACE3: 16/2053 vs 10/2050, RR=1.57 (0.73 to 3.39);

MACE4: 21/2053 vs 10/2050, RR 2.04 (0.98 to 4.26). However, there was imbalance using a five-point MACE definition, which included atrial fibrillation [28/2053 vs. 12/2050; RR=2.33(1.19, 4.56)] (Table 4). There was no imbalance in total AEs in post-menopausal women (Supplementary Figure 2).

Fifteen trials were placebo-controlled (n=13 placebo only; n=2 placebo & BPs) [9,13,17-21,24-26,28-31,34,37,38,59]. Of which, seven had CAE data for analysis which found 439 events in 4725 denosumab treated women and 399 events in 4467 placebo treated women [RR [95%CI: RR=0.79 (0.41 to 1.52)] (Table 3). Regarding MACE outcomes, there were non-significant increases in MACE3, MACE4 and MACE5 (Table 4). There was no imbalance in total AEs in post-menopausal women (Table 3)

A leave-one-out sensitivity analysis was performed for the both composite CAE and five-point MACE analysis for the statistically significant results. Within the composite CAE analysis, individual removal of trials by Recknor *et al.* (2013), Roux *et al*. (2014) and Miller *et al.* (2016) led to a loss of statistical significance (Supplementary Table 2) [33,35,36]. In the five-point MACE analysis, when the trial by Recknor *et al*. (2013) was removed, the result lost statistical significance (Supplementary Table 3) [35]. Furthermore, to assess whether the background risk in individual studies was associated with its magnitude of relative risk for the overall effect estimate, we plotted the event rate in the BP-arm (x-axis) against overall effect estimate for the any CAE endpoint analysis (y-axis) (Supplementary Figure 3). Whilst an inverse trend was observed, linear regression for the line of best fit was not significant (β= -10.8 (-27.8 to 6.2)). Owing to the small number of trials, there was quite notable variance between studies and the trials by Brown *et al.* (2009) and Recknor *et al.* (2013) were clear outliers [22,35].

Neoplastic Bone Disease

We grouped together bone metastasis and multiple myeloma into the category of neoplastic bone disease since denosumab is indicated in both disease processes to prevent skeletal-related events due to increases in osteoclast-mediated bone resorption [42,60]. This category encompasses both primary and metastatic neoplasms of bone. Nine trials were BP-controlled (zoledronic acid n=7, combination n=2) [16,39-46]. Five of these trials had CAE data for meta-analysis and found a non-significant increase of CAEs in denosumab treated patients versus bisphosphonates (Table 3). Three-, four- and five-point MACE yielded non-significant increases of CAEs in denosumab-treated patients versus bisphosphonates. There was no imbalance in overall AEs.

Prostate and Breast Cancer

In the prostate cancer indication, three studies were placebo-controlled [47-49] and one study was alendronate-controlled [61]. There were two placebo-controlled trials with CAE data which showed a non-significant increase in CAEs in denosumab treated patients (Table 3). There was no imbalance of overall AEs. The alendronate-controlled trial did not report cardiovascular safety data, nor were any available through clinicaltrials.gov. Two placebo-controlled studies enrolled patients with breast cancer [50,51]. These trials found a non-significant decrease in CAEs in denosumab treated patients versus placebo [51]. There was no imbalance of overall AEs between treatment arms (Table 3). In both the prostate and breast cancer populations, there were insufficient data to construct MACE outcomes.

Men and post-menopausal women with low BMD

Three trials enrolled both men and postmenopausal women [52,53,62]. One trial enrolled post-menopausal women and men over 50 years, comparing denosumab with two control treatments - placebo or open label alendronate [53]. The author was contacted to provide separate data for

men and women to enable these data to be included in the main postmenopausal women analysis above, but no response was received. When compared with open label alendronate, there was a statistically significant increase of CAEs in the denosumab arm (Table 3). However, there was no imbalance in overall AEs. When compared to placebo, there was a non-significant increase in CAEs in the denosumab arm. There was balance of overall AEs between placebo and denosumab. There were insufficient data to construct MACE outcomes.

An additional trial was a one year open-label extension phase of the previous trial in which all subjects received denosumab which was ineligible for meta-analysis [52]. Another trial enrolled men and post-menopausal women comparing denosumab with alendronate or minodoronate [62]. There was no AE data available for analysis.

Other indications

One trial enrolled men with low BMD comparing denosumab with placebo. Non-significant increases in CAEs and overall AEs were observed in the denosumab arm (Table 3) [57]. Two trials enrolled patients with rheumatoid arthritis [54,55] and compared denosumab to placebo. There was a non-significant reduction in CAEs and overall AEs in denosumab-treated patients. Another trial enrolled patients with glucocorticoid-induced osteoporosis and compared denosumab with risedronate [58]. There was a non-significant small increase in CAEs and overall AEs in denosumab treated patients. In each of these indications, there were insufficient data to construct MACE outcomes.

Discussion

In this systematic review of large randomized controlled trials of denosumab versus placebo or active comparators for any indication, we determined that there was an approximate 46% increase in CAEs in denosumab-treated compared with BP-treated post-menopausal women.

Within the same indication, we analysed a five-point MACE endpoint (comprising stroke, MI, HF, cardiovascular death and atrial fibrillation) and determined there was a doubling of risk for these events (Supplementary Figure 2). Given was no such imbalance existed in placebo-controlled trials, we speculate that the imbalance in CAE rate in BP-controlled trials may reflect a relative suppression of events in the BP-treated women. Importantly, these results need to be interpreted with caution since CAEs were adverse event data that were not pre-specified as trial outcomes. Furthermore, we note the potential for a study's background risk to drive the overall effect estimate, however regression analysis for an association found this to be non-significant. There were either insufficient data or non-significant risk differences for other indications. Nevertheless, this highlights the need for careful CV risk management alongside fracture risk management amongst patients treated for osteoporosis. Given a new anabolic osteoporosis agent, romosozumab, has raised concerns over increased CV risk, this is an especially worthwhile consideration [6,7]. Our assessment of whether background risk was associated with relative risk is very pertinent to the trials which evaluated romosozumab, as some have commented that this phenomenon may have been responsible for the apparent chance imbalance in CAEs in BP-controlled romosozumab [63]. Thus, future trial designs may need to pay careful attention to the choice of comparator in order for outcomes to be both interpreted with confidence and relevant to real-world effects.

The increased CAEs in denosumab treated post-menopausal women versus BPs align with previous studies suggesting, controversially that there may be a protective benefit of BPs [3-5]. This hypothesis has gained credence since the reporting of romosozumab having increased serious CAEs compared to alendronate [6] but not against placebo [8]. There is no clear biological explanation for why an anti-sclerostin antibody would increase CV risk. Indeed, the

natural history of patients with sclerosteosis demonstrate no excess CV risk [64]. Similarly, we observed increased risks in denosumab-treated postmenopausal women compared with BPs, but not compared with placebo. Thus, we speculate that the increase in CAEs in denosumab is driven by a suppression of events in BP-treated individuals. This has been similarly observed in a recent RCT where the effects of zoledronate on cancer, cardiac events and mortality in osteopenic women were evaluated [4]. Zoledronate was seen to have a protective effect on cardiovascular endpoints. The authors of this study provided a brief overview of this cardio-protective phenomenon citing bisphosphonate's potential direct action on arteries via nitric oxide mediated vasodilation, immunomodulatory effects in atherosclerosis and influence on the mevalonate and cholesterol synthesis pathway. Indeed, different BPs such as alendronate, which was the most common BP comparator in our paper may have different CVD effects to zoledronate. However, placebo-controlled alendronate and other oral bisphosphonate RCTs that report CAEs (other than atrial fibrillation) are lacking. We note a previous meta-analysis reporting oral alendronate was not associated with atrial fibrillation, but this was limited to Merck-sponsored trials and is thus not reflective of the literature [65]. Similarly, a safety analysis of pivotal oral ibandronate trials suggested no association with atrial fibrillation [66-68]. It is interesting to note that neither oral ibandronate trial reports CAEs in their adverse event analysis from the primary publications, it is provided in the pooled safety analysis [68]. Given this cardio-protective effect in our systematic review was only seen in post-menopausal women (a population known to be at elevated increased CV risk) there may be some underlying explanation for the increased events related to the loss of the protective effect of estrogen and how this interacts with RANKL [69].

Notably, our analysis is presented in the context of a recent meta-analysis which suggested that BP has no mortality benefit and thus prescription of BPs should only be made with skeletal outcomes in mind [70]. Further, Cummings and McCulloch (2020) recently offered an explanation for the CAE findings of the romosozumab trial and determined it was a chance finding [63]. This would appear at odds with the present study's findings, Reid *et al.* (2020) and a meta-analysis by Kranenburg *et al.* (2016), which demonstrated a reduction in cardiovascular mortality and all-cause mortality [4,5]. In clinical practice, extra-skeletal considerations are important in our dialogue with patients when deciding how best to manage bone health and will also impact on the overall cost utility landscape. The specific effect of BPs on CV mortality could be masked by the outcomes contributing to the balance of overall mortality.

Other indications such as bone metastasis had different aetiologies and rationales for prescribing denosumab possibly explaining why non-significant findings were demonstrated in the present study. There were limited data assessing CV risk in the cancer setting (and indeed other indications) thus we are uncertain about the effects of denosumab on CV outcomes in these populations. Equally we are unable to comment if the supposed cardio-protective effect of BPs exists in these populations. Regardless of indication, the present study serves to highlight that these uncertainties are areas where further research is warranted as we cannot rule out potentially clinically important effects. This is especially the case given that of the 49 studies included for review, only 26 had data available to form composite CAEs. This review serves as a timely reminder for future osteoporosis studies to specifically report CV outcomes as part of their study design.

The studies included had some limitations. Risk of bias assessment showed that randomization methods were generally unclear, outcome reporting was poor, and sponsors played a large role

in a number of studies through writing, data collection and study design. Given that these studies were generally monitored by contractors outside the influence of the investigators and that the trials were of sufficient quality and integrity to be accepted by regulators such as the Food and Drug Administration and the European Medicines Agency; it may reflect more the conventions of reporting trials in the musculoskeletal area (where details are often not given of the randomization procedure as this is considered unlikely to be flawed in these circumstances) than any inherent issues with the randomisation procedure or conduct of the study. Indeed, it can be argued that published papers are being held against Cochrane standards that had not yet been developed at the time when these papers were written.

Another limitation, which was more commonly found in the neoplastic bone disease trials there was a large dropout rate. However, this phenomenon is often noted in studies enrolling these patients. Often, this was attributed to deaths during the intervention but also consent withdrawal contributed to the dropout rate. Large multi-centred trials were also limited by heterogeneous AE reporting. By way of example, local hospital guidelines may dictate that a particular event may be classified under a particular ICD code whilst at another centre, it may be classified under a similar but distinct ICD code. In the trial by Raje *et al.* (2018), three separate cardiac failure outcomes reported “cardiac failure”, “cardiac failure congestive” and “cardiac failure chronic” [(42)]. Whilst we can assume the broader classification of cardiac failure would capture these two sub classifications, we are uncertain as to whether all these events are independent. Similarly, most studies stated that overall AEs were either similar between groups or there were no AEs. The validity of such claims is limited since this overall balance of any AEs could be skewed by the selective reporting (or non-reporting) of certain specific AEs or the effect of specific AEs could be nullified by the overall balance between all AEs as described above.

This further highlights the need to specifically assess CAEs and we call for transparent reporting of such outcomes. Without such transparent reporting, any analysis of this literature may be misleading as evidenced by a recent meta-analysis by Lv *et al.* (2020) [(11)]. They observed a balance of CV events between denosumab and control groups. However, in doing this they pooled bisphosphonates and placebo trials, as well as pooling trials of men, pre-menopausal women and post-menopausal women in the same analysis. Our meta-analysis was performed separately by population and comparator, forming more homogenous groups to more comprehensively examine the effects of denosumab on cardiovascular safety. Furthermore, Lv and colleagues only included literature if the trial provided CAEs, however as we have shown, not all trials report these data and often they are provided in online supplements or on their clinical trials registration page. We also note that McClung *et al.* (2006), the seminal trial in the clinical development of denosumab was not included [(13)]. Additionally, Lv and colleagues specifically excluded studies with zero CAEs. Again, this would provide an inaccurate view of the literature because as CAEs are known to occur in these patients, it is also important to consider when CAEs do not occur.

We also note another meta-analysis on this topic, but this too had severe limitations rendering interpretation difficult [(12)]. Ferrieres *et al.* (2020) included extension trials in their overall analysis which means that the AE data presented may not reflect the comparison between denosumab and other treatments. For example, Sugimoto *et al.* (2015) [(52)] was an extension trial where all participants received denosumab for one year (cross-over) after a placebo-controlled initial two-year period. Thus, we are uncertain whether the events reported are attributable to when participants received denosumab or placebo. Furthermore, our analysis has identified some studies not included in their analysis such as the aforementioned seminal

McClung *et al.* (2006) trial [13]. Other limitations were that there was a large degree of heterogeneity between trials due to different inclusion and exclusion criteria.

Our review also has some limitations. Firstly, we used aggregate level data and subsequently statistical analyses were limited to conventional study level meta-analysis. Individual level data was not sought due to the magnitude of outcomes and it did not fit with our primary aim of determining how many trials reported CAEs in the public domain. Secondly, we excluded conference abstracts. Thus, there may have been unpublished data that could have potentially contributed to the review. Thirdly, in dose finding studies, we chose the dose used most commonly in clinical practice to enable relevant comparisons. Fourth, we used a composite cardiovascular outcome, comprising of specific CAEs. We explored the validity of the composite CAE findings by analysing event rates for MACEs which provided consistent findings (when analysing a MACE5 endpoint). We believe the signal of the composite CAE effect estimate is a true and clinically important result because the direction and magnitude of the MACE endpoints increased with further inclusion of outcomes and became statistically significant. This shows the composite CAE was internally validated. It is important to note that a composite outcome assumes the same weight of each individual outcome and a similar aetiology of each. We attempted to explore the balance of specific CAEs between treatment groups but 79 of these CAEs were only reported in one study. Since they were reported they are potentially an AE of interest, therefore, if other studies do not report this AE, it is assumed it did not occur. Indeed, absence of an AE is also of interest. Whilst we appreciate the limitations of reporting all AEs in manuscripts, such data should be readily accessible and consistent. Thus, a composite CAE was created to enable meta-analysis which has been applied in other similar studies [71]. We believe this strategy is robust as it resembles how each study

reports on any AE, regardless of system and regardless of how many events occurred in any individual patient.

In conclusion, this systematic review identified an excess of CAEs in post-menopausal women with osteoporosis or low BMD treated with denosumab compared with bisphosphonates, but not placebo, indirectly supporting the claim that bisphosphates may supress CAEs. Overall, specific cardiovascular safety data were inconsistently reported and were limited for other indications. Future trials of anti-osteoporosis medications should use standardized CAE reporting to more clearly describe the cardiovascular effects of bone active medications.

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Figure Legends

Table 1: Included Study Details

	Study (year), Country	Total Enrolled (n)	Comparator	Follow up	Known fractures at baseline┼	Primary Endpoints	Efficacy	CAE reporting
Neoplastic Bone Disease	Fizazi (2009), France[16]	111	Any bisphosphonate	Variable	Unclear	Progression of Bone Metastasis	↓42% IR*	No
	Fizazi (2011), France[46]	1904	Zolendronate	40.5	Unclear	Time to first on-study skeletal-related event (SRE)	↓18%	Yes
	Henry (2011), United States[39]	1776	Zoledronate	24	Unclear	Time to first on-study SRE	↓16%	Yes
	Henry (2014) United States[44]	1597	Zoledronate	6.7	Unclear	Time to first on-study SRE (Ad Hoc Analysis of [39])	↓19%	No
	Lipton (2007), United States[45]	255	Any bisphosphonate	14	Unclear	Progression of Bone Metastasis	↑8% IR	No
	NCT01920568 (2013), United States[43]	485	Zoledronate	12.25	Unclear	Progression of Bone Metastasis	Mean Difference= 6	Yes
	Raje (2018), United States[42]	1718	Zoledronate	50	Unclear	Time to first on-study SRE	↓2%	Yes
	Smith (2014), United States[40]	1901	Zoledronate	36	Unclear	Symptomatic skeletal events (SSEs) (Study Extension of [46])	↓22%	Yes
	Stopeck (2010), United States[41]	2046	Zoledronate	34	Unclear	Time to first on-study SRE	↓18%	Yes
Post-menopausal women	FREEDOM Trial[9]							
	Cummings (2009), United States[9]	7808	Placebo	36	Yes	New Vertebral Fracture (Primary Trial)	↓68%	Yes
	Adami (2012), Canada[20]	667	Placebo	36	Yes	Delayed Fracture Healing (Extension of [9])	↓	Yes
	Bone (2017), United States[18]	4550	Placebo	120	Yes	Safety monitoring – AE incidence (Extension of [9])	↓	No
	Boonen (2011), Belgium[25]	7762	Placebo	36	Yes	Fracture incidence for those at fracture risk (Post hoc analysis of [9])	↓9.1%IR	No
	Eastell (2011), England[26]	160	Placebo	36	Yes	Bone turnover markers (BTMs) (Extension of [9])	↓	No
	Samelson (2014), United States[38]	1625	Placebo	36	Yes	Progression of aortic calcification, incidence of cardiovascular adverse events (Extension of [9])	=, ↓2%IR	Yes
	McClung et al. (2006) Trial[13]							
	McClung, (2006), United States[13]	93	Placebo	12	Yes	% change in lumbar spine BMD at month 12 (Primary Trial)	↑3.0 - 6.7% vs ↓0.8	Yes
	McClung (2006),United States[13]	94	Alendronate	12	Yes	% change in lumbar spine BMD at month 12 (Primary Trial)	3.0 - 6.7% vs ↑4.6%	Yes
	Lewiecki (2007), United States[29]	365	Placebo	24	Yes	BMD at lumbar spine, total hip and one third radius, BTM (Extension of [13])	↑, ↓	Yes
	Lewiecki, (2007), United States[29]	366	Alendronate	24	Yes	BMD at lumbar spine, total hip and one third radius, BTM (Extension of [13])	↑, ↓	Yes

	Miller, (2008), United States[31]	365	Placebo	48	Yes	BMD at lumbar spine and total hip, BTM (2 year denosumab extension of [13])	↑, ↓	Yes
	Miller, (2008), United States[31]	366	Alendronate	48	Yes	BMD at lumbar spine and total hip, BTM (2 year denosumab extension of [13])	↑, ↓	Yes
	Miller (2011), United States[32]	200	N/a	72	Yes	BMD at lumbar spine, total hip, femoral neck and one third radius, BTM (4 year denosumab extension of [13])	↑, ↓	Yes
	McClung (2013), United States[30]	200	N/a	48	Yes	BMD at lumbar spine and total hip, BTM (8 year denosumab extension of [13])	↑, ↓	Yes
	Other Trials							
	Bone (2008), United States[19]	322	Placebo	24	No	% Change lumbar spine BMD at 24 months (Primary Trial)	↑7.1%	Yes
	Bone (2011), United States[24]	256	Placebo	24	No	% change in BMD, % change BTMs (Off-treatment extension of [19])	↑6.4%, ↓63%	Yes
	Brown (2009), Canada[22]	1189	Alendronate	12	Yes	% change in the total hip BMD at month 12	MD= ↑0.9%	Yes
	Brown (2014), Canada[23]	1703	Any bisphosphonate	12	Yes	% changes from baseline in BMD, % change serum C-telopeptide of type I collagen (sCTX-1) (Combined post-hoc analysis of [35,36])	↑1.4%, ↓23%	Yes
	Kendler (2010), Canada[27]	504	Alendronate	12	Yes	% change in the total hip BMD at month 12	↑0.85%	Yes
	Koh (2016), Korea[28]	135	Placebo	12	Yes	% change in the lumbar spine BMD at month 6	↑3.2%	No
	Miller (2016), United States[33]	643	Zoledronate	12	Yes	% change in lumbar spine BMD at month 12	↑2.1%	Yes
	Nakamura, (2012), Japan[34]	108	Placebo	12	Yes	% change in lumbar spine BMD at month 12 (14mg denosumab)	↑5.71%	Yes
	Nakamura (2012), Japan[34]	109	Placebo	12	Yes	% change in lumbar spine BMD at month 12 (60mg denosumab)	↑6.73%	Yes
	Nakamura (2012), Japan[34]	105	Placebo	12	Yes	% change in lumbar spine BMD at month 12 (100mg denosumab)	↑7.45%	Yes
	NCT01495000 (2012), India[17]	250	Placebo	6	Unclear	% change in lumbar spine BMD at month 6	↑3.06%	Yes
	NCT02014467 (2014), China[21]	484	Placebo	12	Yes	% change in lumbar spine BMD at month 12	↑4.43%	Yes
	Recknor (2013), United States[35]	833	Ibandronate	12	Yes	% change in total hip BMD at month 12	↑1.2%	Yes
	Roux (2014), France[36]	870	Risendronate	12	Yes	% change in total hip BMD at month 12	↑1.5%	Yes
	Seeman (2010), Australia[37]	165	Placebo	12	No	Cortical Thickness of Radius (Primary Trial)	↑4.2%	Yes
	Seeman (2010), Australia[37]	165	Alendronate	12	No	Cortical Thickness of Radius (Primary Trial)	↑1%	Yes
	Zebaze (2014), Australia[59]	92	Alendronate	12	No	% Porosity (Extension of [37])	↓0.78%	No
Pro	Doria (2017), Italy[61]	234	Alendronate	24	Yes	% change in lumbar spine BMD at month 24,	↑6.7%	No

	Egerdie 2012, Canada[48]	1468	Placebo	36	Yes	% change in lumbar spine BMD at month 36 (Responder Analysis of [47])	↑7.9%	No
	Smith (2009), United States[47]	1468	Placebo	36	Yes	% change in lumbar spine BMD at month 24	↑6.6%	Yes
	Smith (2012), United States[49]	1432	Placebo	36	Unclear	Bone-metastasis-free survival (months)	↑4.2 months	Yes
Breast Cancer	Ellis, (2008), United States[50]	252	Placebo	12	No	% change in lumbar spine BMD at month 12	↑5.5%	Yes
	Gnant (2015), Austria[51]	3425	Placebo	72	Unclear	Time from randomisation until the date of the radiograph confirming the first clinical fracture	↓50%	Yes
Men and Women	Nakamura (2014), Japan[53]	952	Placebo	24	Yes	24-month incidence of new or worsening vertebral fracture	↓6.7% IR	Yes
	Nakamura (2014), Japan[53]	714	Alendronate	24	Yes	24-month incidence of new or worsening vertebral fracture	↓5% IR	Yes
	Niimi (2018), Japan[62]	200	Alendronate	24	Yes	% change in lumbar spine BMD at month 12, % change in femoral neck BMD at month 12	↑3%, ↑0.7%	No
	Niimi (2018), Japan[62]	200	Minodoronate	24	Yes	% change in lumbar spine BMD at month 12, % change in femoral neck BMD at month 12	↑3.8%,↑1.2%	No
	Sugimoto (2015), Japan[52]	1262	Placebo	24	Yes	36-month incidence of new or worsening vertebral fracture (1 year open label extension of [53])	↓74%	Yes
GIOP	Saag (2018), United States[58]	795	Risendronate	n/a	Yes	% change in lumbar spine BMD at month 12 in glucocorticoid continuing patients, % change in lumbar spine BMD at month 12 in glucocorticoid initiating patients	↑1.1%,↑3%	Yes
Rheumatoid arthritis	Cohen (2008), United States[54]	146	Placebo	12	Unclear	Mean Change in MRI erosion score from baseline to 6 months	↓1.62	Yes
	Takeuchi (2016), Japan[55]	340	Placebo	12	Unclear	Change in the modified Sharp erosion score from baseline to 12 months	↓0.99	Yes
Men	Orwoll (2012), United States[57]	242	Placebo	24	Yes	% change in lumbar spine BMD at month 12	↑4.8%	Yes

*IR= Incidence Rate

┼Known fractures at baseline indicates that a trial permitted the inclusion of patients with any form of fracture

Table 2: Risk of bias assessment

Indication	Study	Random Sequence Generation	Allocation Concealment	Blinding of Participants and Personnel	Blinding of Outcome Assessment	Incomplete Outcome Data	Selective Reporting	Other Bias	Consensus
Post-Menopausal Women	Adami (2012)[20]	?/?	-/-	?/-	-/?	-/-	-/-	-/?	Unclear
	Bone (2008) [19]	?/?	?/-	-/?	?/?	-/+	-/?	?/-	Unclear
	Bone (2011) [24]	?/?	?/-	-/-	?/?	-/-	-/?	-/+	Unclear
	Bone (2017) [18]	?/?	-/-	?/+	-/?	-/?	-/?	+/-	High
	Boonen (2011) [25]	?/?	-/-	?/-	-/?	?/?	?/-	-/?	Unclear

	Brown (2009) [22]	-/-	?/-	-/?	?/?	-/-	-/-	+/+	High
	Brown (2014) [23]	?/?	?/?	+/+	?/?	?/-	-/-	+/+	High
	Cummings (2009) [9]	?/?	-/-	?/-	-/?	-/-	-/+	-/+	High
	Eastell (2011) [26]	?/?	-/-	?/-	-/?	?/-	?/+	+/+	High
	Kendler (2010) [27]	-/-	?/-	-/-	-/?	-/-	-/-	-/?	Unclear
	Koh (2016) [28]	?/?	?/?	-/?	?/?	-/-	-/-	+/+	High
	Lewiecki (2007) [29]	-/?	?/-	+/+	?/?	-/+	-/-	+/+	High
	McClung (2006) [13]	-/?	?/-	+/+	?/?	-/-	?/-	+/+	High
	McClung (2013) [30]	-/?	?/-	+/+	?/?	?/?	?/+	-/?	High
	Miller (2008) [31]	-/?	?/?	+/+	?/?	-/+	-/?	+/?	High
	Miller (2011) [32]	-/?	?/?	+/+	?/?	?/?	?/?	+/?	High
	Miller (2016) [33]	?/?	?/?	-/-	-/?	-/-	-/-	-/-	Unclear
	Nakamura (2012) [34]	?/?	?/?	-/-	?/-	?/-	-/-	-/-	Unclear
	Recknor (2013) [35]	-/-	?/-	+/-	+/?	+/-	?/-	-/-	High
	Roux (2014) [36]	?/?	?/?	+/+	+/?	?/-	?/-	-/-	High
	Samelson (2014) [38]	?/?	-/-	?/-	-/?	?/?	+/+	-/?	High
	Seeman (2010) [37]	-/-	-/-	-/-	-/?	-/+	-/-	+/+	High
	Zebaze (2014) [59]	-/-	?/-	-/-	?/?	?/-	?/?	-/?	Unclear
Neoplastic Bone Disease	Fizazi (2009) [16]	?/?	?/-	+/+	+/+	-/?	-/?	-/-	High
	Fizazi (2011) [46]	-/-	-/-	-/-	-/-	-/?	-/+	-/+	High
	Henry (2011) [39]	-/-	-/-	-/-	-/-	-/?	-/+	-/-	High
	Henry (2014) [44]	?/?	-/?	-/-	-/?	-/?	-/+	-/?	High
	Lipton (2007) [45]	?/?	?/+	+/+	?/?	?/-	?/+	-/-	High
	Raje (2018) [42]	-/-	-/-	-/-	-/?	-/+	-/?	+/?	High
	Smith (2014) [40]	-/?	-/-	-/-	-/?	?/?	?/?	-/?	Unclear
	Stopeck (2010) [41]	?/-	?/?	-/-	-/?	-/?	-/+	-/?	High
Prostate Cancer	Doria (2016) [61]	?/?	?/?	-/-	?/?	?/?	-/+	?/?	Unclear
	Egerdie (2012) [48]	?/?	-/-	-/-	?/?	?/?	?/+	+/?	High

	Smith (2009) [47]	?/-	?/?	-/?	-/?	?/?	?/-	+/?	High
	Smith (2012) [49]	-/-	-/-	-/?	-/?	-/-	-/-	+/+	High
Breast Cancer	Ellis (2008) [50]	?/?	-/?	-/-	?/?	-/?	-/+	+/?	High
Breast Cancer	Gnant (2015) [51]	-/-	-/-	-/-	-/-	?/?	-/-	+/+	High
Glucocorticoid User	Saag (2018) [58]	-/-	-/-	-/+	?/-	-/+	-/?	-/+	High
Men and Post-Menopausal Women	Nakamura (2014) [53]	?/?	?/?	-/+	-/?	-/?	-/-	-/+	High
Men and Post-Menopausal Women	Niimi (2018) [62]	-/-	?/?	+/?	-/?	-/-	?/?	-/-	High
Men and Post-Menopausal Women	Sugimoto (2014) [52]	?/?	?/?	-/+	?/?	?/?	?/+	-/-	High
Rheumatoid Arthritis	Cohen (2008) [54]	?/-	?/?	-/?	-/-	-/-	-/?	+/?	High
Rheumatoid Arthritis	Takeuchi (2016) [55]	-/-	-/-	-/-	-/-	-/?	-/-	+/?	High
Healthy Older	Orwoll (2012) [57]	-/-	-/?	-/-	-/-	-/-	-/-	+/-	High

Table 3. Relative risk of CAEs in denosumab treated individuals against comparators

Vs.		Indication	Number of studies	RR 95% CI	Events		I^2	Ref.
					Denosumab	Control		
CAE	Bisphosphonates	Post-menopausal women	7	1.46 (1.05, 2.02)	85/2136	58/2131	20.4%	(13,22,27,33,35-37)
		Neoplastic Bone Disease	5	1.01 (0.88, 1.15)	383/4017	380/3847	50.1%	(39,41-43,46)
		Men & Post-menopausal women	1	1.65 (1.04, 2.62)	68/475	21/242	0.0%	(53)
		GIOP	1	1.73 (0.89, 3.36)	23/394	13/385	0.0%	(58)
	Placebo	Post-menopausal women*^	7	0.79 (0.41, 1.52)	439/4725	399/4467	53.6%	(9,13,17,19,21,34,37)
		Prostate Cancer	2	1.07 (0.91, 1.25)	262/1451	242/1430	0.0%	(47,49)
		Breast Cancer	2	0.87 (0.67, 1.12)	103/1838	117/1810	0.0%	(50,51)
		Men + Post-menopausal women	1	1.09 (0.79, 1.50)	68/475	63/481	0.0%	(53)
		Men with low BMD	1	1.67 (0.41, 6.82)	5/120	3/120	0.0%	(57)
		Rheumatoid Arthritis*	2	0.66 (0.18, 2.47)	3/157	5/163	66.5%	(54,55)
Any AE	Bisphosphonates	Post-menopausal women	7	0.98 (0.92, 1.04)	851/2206	870/2206	0.0%	(13,22,27,33,35-37)
		Neoplastic Bone Disease	5	1.00 (0.99, 1.01)	3596/4034	3584/3866	31.6%	(39,41-43,46)
		Men & Post-menopausal women	1	1.00 (0.96, 1.03)	448/475	229/242	0.0%	(53)
		GIOP	1	1.05 (0.96, 1.15)	285/394	265/385	0.0%	(58)
	Placebo	Post-menopausal women	7	0.99 (0.98, 1.01)	3922/4661	3928/4404	0.0%	(9,13,17,19,21,34,37)
		Prostate Cancer	2	1.01 (0.99, 1.03)	1314/1451	1282/1430	0.0%	(47,49)

		Breast Cancer	2	1.01 (0.98, 1.05)	1483/1838	1442/1810	0.0%	(50,51)
		Men & Post-menopausal women	1	1.02 (0.98, 1.05)	448/475	446/481	0.0%	(53)
		Men with low BMD	1	1.02 (0.87, 1.20)	86/120	84/120	0.0%	(57)
		Rheumatoid Arthritis	2	0.94 (0.86, 1.03)	129/156	140/159	0.0%	(54,55)

*Random effects model was used when there was substantial heterogeneity (I^2>50) ^Fixed effects model: RR=1.09 (0.95, 1.23)

Table 4. Relative risk of CAEs in denosumab treated post-menopausal women vs bisphosphonates or placebo

Indication		Number of studies	RR 95% CI	Events		I^2	Ref.
				Denosumab	Control		
Bisphosphonates	CAE Composite	7	1.46 (1.05, 2.02)	85/2136	58/2131	20.4%	(13,22,27,33,35-37)
	3 Point MACE: myocardial infarction (MI), stroke, CVD death	6	1.57 (0.73, 3.39)	16/2053	10/2050	0.0%	(13,22,27,33,35,36)
	4 Point MACE: MI, stroke, CVD death, heart-failure (HF)	6	2.04 (0.98, 4.26)	21/2053	10/2050	0.0%	(13,22,27,33,35,36)
	5 Point MACE: MI, stroke, CVD death, HF, atrial fibrillation	6	2.33 (1.19, 4.56)	28/2053	12/2050	0.0%	(13,22,27,33,35,36)
Placebo	CAE Composite*	7	0.79 (0.41, 1.52)	439/4725	399/4467	53.6%	(9,13,17,19,21,34,37)
	3 Point MACE: myocardial infarction (MI), stroke, CVD death	3	1.19 (0.90, 1.59)	101/4300	83/4039	0.0%	(9,13,21)
	4 Point MACE: MI, stroke, CVD death, heart-failure (HF)	3	1.08 (0.84, 1.38)	128/4300	117/4039	0.0%	(9,13,21)
	5 Point MACE: MI, stroke, CVD death, HF, atrial fibrillation	3	1.08 (0.87, 1.34)	164/4300	150/4039	0.0%	(9,13,21)

MACE outcomes are comprised of MI, stroke, CVD death, HF and atrial fibrillation. MI outcomes consisted of: acute coronary syndrome, acute myocardial infarction, coronary artery disease and myocardial infarction. Stroke consisted of: cerebrovascular accident, cerebral ischemia, haemorrhagic stroke, ischemic stroke. HF consisted of: cardiac failure, cardiac failure acute, cardiac failure chronic, cardiac failure congestive, and heart failure. CVD death and atrial fibrillation outcomes were comprised of CVD death and atrial fibrillation respectively.

* Random effects model was used when there was substantial heterogeneity (I^2>50) Fixed effects model: RR=1.09 (0.95, 1.23)

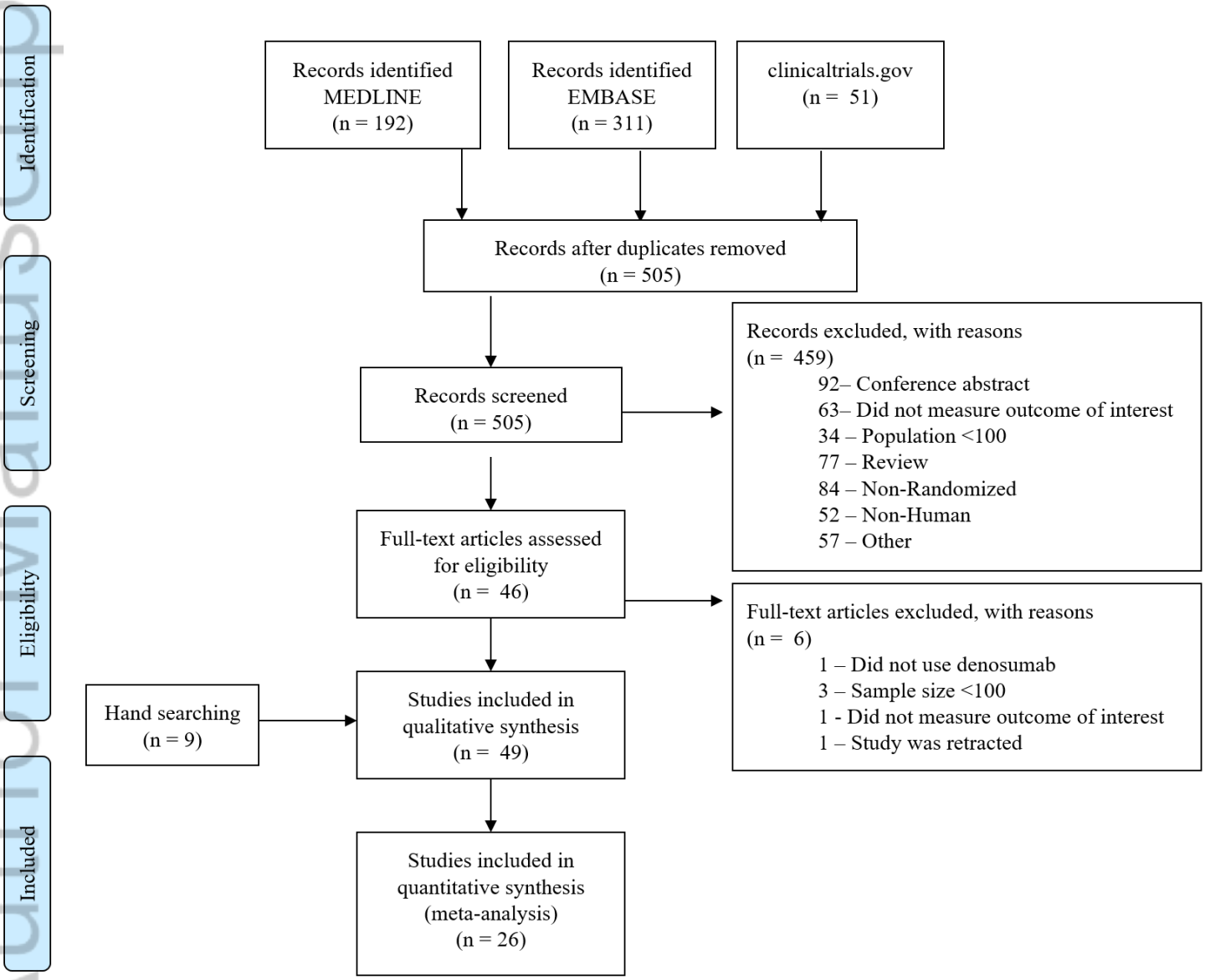
Supplementary Table 1. Selected list and frequency of CAEs reported by included studies		
Outcome	**Frequency**	**References**
Any	29	(9,13,17,21-24,27,28,33-44,47,49-51,53-55)
Serious	24	(9,17,19,21-24,27,28,33-37,39-41,43,44,47,50,53,54,57)
Cardiovascular Disease Composite	26	(9,13,17,19,21,22,27,33-37,39,41-43,46,47,49-51,53,54,57,58)
3-Point MACE	12	(9,13,21,22,27,33,35,36,39,42,46)
4-Point MACE	12	(9,13,21,22,27,33,35,36,39,42,46)
5-Point MACE	12	(9,13,21,22,27,33,35,36,39,42,46)
Any Cardiovascular Disease	11	(9,21,23,24,33-35,38,42,51,53)
Any Cardiac	1	(38)
Any Vascular	6	(23,33,34,38,42,51)
Serious Cardiovascular Disease	3	(23,38,53)
Cardiovascular Disease Death	4	(9,27,36,57)
Acute Coronary Syndrome	8	(9,22,39,42,46,47,49,51)
Acute Myocardial Infarction	11	(9,33,39,42,46,47,49-51,57,58)
Atrial Fibrillation	16	(9,13,22,27,33,35,36,39,42,47,49-51,57,58)
Cardiac Failure	8	(9,39,42,46,47,49,51,58)
Cardiac Failure Acute	5	(9,39,42,46,58)
Cardiac Failure Chronic	3	(9,33,42)
Cardiac Failure Congestive	9	(9,35,39,42,46,47,49,50,58)
Coronary Artery Disease	13	(9,13,21,22,33,35,36,42,46,47,49,51,58)
Cerebral Ischemia	10	(9,22,36,39,42,46,47,49,51,58)
Cerebrovascular Accident	13	(9,22,27,33,35,36,39,42,46,47,49,51,58)
Haemorrhagic Stroke	4	(9,42,46,47)
Heart Failure	3	(42,43,47)
Hypertension	16	(9,13,19,22,27,33,35-37,39,42,46,47,49,51,55)
Ischemic Stroke	5	(9,33,42,46,47)
Myocardial Infarction	17	(9,13,21,22,33,36,39,42,43,46,47,49-51,54,57,58)
Unique Outcome (i.e. reported in one study only)	79	(9,17,22,33,39,41-43,46,47,49,51,57,58)

Supplementary Table 2: Leave one out sensitivity analysis for 'CAE Composite' denosumab vs bisphosphonates relative risk

Study excluded	RR 95% CI Fixed	RR 95% CI Random	Events	
			Denosumab	Control
McClung (2006) [13]	1.56 (1.11, 2.21)	1.54 (1.05, 2.25)	80/2089	51/2085
Brown (2009) [22]	1.63 (1.14, 2.32)	1.58 (1.10, 2.28)	77/1543	47/1535
Seeman (2010) [37]	1.51 (1.07, 2.11)	1.46 (0.95, 2.25)	80/2053	53/2050
Roux (2014) [36]	1.41 (0.95, 2.08)	1.35 (0.81, 2.23)	58/1707	41/1702
Miller (2016) [33]	1.41 (0.98, 2.02)	1.34 (0.84, 2.15)	68/1816	48/1811
Kendler (2010)[27]	1.41 (1.01, 1.98)	1.35 (0.88, 2.06)	78/1883	55/1882
Recknor (2013)[35]	1.30 (0.91, 1.84)	1.28 (0.90, 1.83)	69/1725	53/1721

Supplementary Table 3: Leave one out sensitivity analysis for 'MACE5' denosumab vs bisphosphonates relative risk

Study excluded	RR 95% CI Fixed	RR 95% CI Random	Events	
			Denosumab	Control
McClung (2006) [13]	2.45 (1.22, 4.93)	2.16 (1.04, 4.50)	27/2006	11/2004
Kendler (2010) [27]	2.60 (1.26, 5.37)	2.29 (1.07, 4.90)	26/1800	10/1801
Brown (2009) [22]	2.65 (1.24, 5.69)	2.32 (1.04, 5.18)	24/1460	9/1454
Miller (2016) [33]	2.4 (1.13, 5.27)	2.07 (0.91, 4.72)	22/1733	9/1730
Roux (2014) [36]	2.19 (1.04, 4.61)	1.87 (0.85, 4.12)	22/1624	10/1621
Recknor (2013) [35]	1.72 (0.82, 3.61)	1.69 (0.79, 3.58)	19/1642	11/1640



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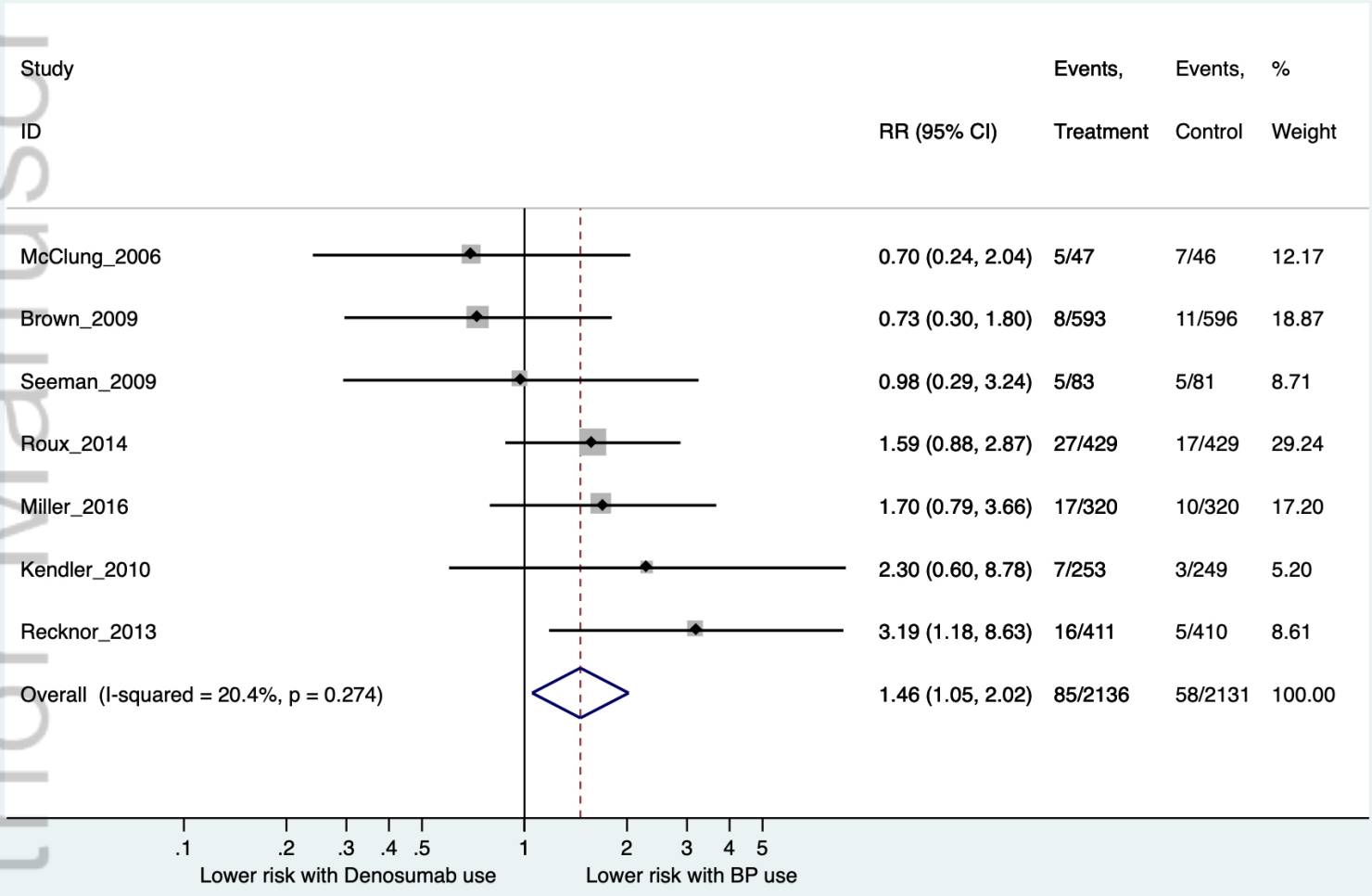

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