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ORIGINAL ARTICLE

β-adrenergic receptor antagonists and fracture risk: a meta-analysis of selectivity, gender, and site-specific effects

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Abstract
Summary By meta-analysis, the risk of fracture was 15 % lower in patients treated with β-adrenergic blockers compared to controls independent of gender, fracture site, and dose. This might be attributable to β1-selective blockers.
Introduction The aim of this study is to determine by meta-analysis whether β-adrenergic blockers (BBs) reduce fracture risk and whether the effect, if demonstrable, is dependent upon selectivity, dose, gender, or fracture site.
Methods A literature search was performed in electronic databases MEDLINE, EMBASE, and reference sections of relevant articles to identify eligible studies. Adjusted estimates of fracture risk effect size (ES) were pooled across studies using fixed or random-effects (RE) meta-analysis as appropriate. Dose-related effects were evaluated using meta-regression. To explore the relative efficacy of β1-selective blockers in comparison to nonselective BBs, adjusted indirect comparison was performed.
Results A total of 16 studies (7 cohort and 9 case–control studies), involving 1,644,570 subjects, were identified. The risk of any fracture was found to be significantly reduced in subjects receiving BBs as compared to control subjects (16 studies, RE pooled ES=0.86, 95 % CI 0.78–0.93; I^2=87 %). In a sensitivity analysis limited to those studies deemed to be most robust, the BB effect to reduce fracture risk was sustained (four studies, pooled ES=0.79, 95 % CI 0.67–0.94; I^2=96 %). The risk of a hip fracture was lower in both women and men receiving BBs (women: pooled ES=0.86, 95 % CI 0.80–0.91; I^2=1 % and men: pooled ES=0.80, 95 % CI 0.71–0.90; I^2=0 %). Similar risk reductions were found for clinical vertebral and forearm fractures, although statistical significance was not reached. The reduction in risk did not appear to be dose-related (test for a linear trend *p* value 0.150). Using adjusted indirect comparisons, it was estimated that β1-selective agents were significantly more effective than nonselective BBs in reducing the risk of any fracture (six studies, β1-selective blockers vs. nonselective BBs: RE pooled ES=0.82, 95 % CI=0.69–0.97).
Conclusions The findings suggest that the risk of fracture is approximately 15 % lower in patients treated with BBs compared to controls independent of gender, fracture site, and dose. This risk reduction might be associated with the effects of β1-selective blockers.

Keyword β-adrenergic antagonists · Fracture · Osteoporosis

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Introduction

The skeleton is innervated by the autonomous nervous system (1), and osteoblasts express β2-adrenergic receptors (β2AR) (2, 3). A central regulation of bone mass by the sympathetic nervous system (SNS) via β2AR has been demonstrated in mouse models, an effect thought to be leptin-dependent (4, 5).

The interaction between SNS and the skeleton in human subjects is not fully elucidated but may also involve additional factors both at central and peripheral sites (6–8)). In general, SNS activation is considered to contribute to bone loss (9), and, therefore, pharmacological βAR blockade would be expected to have a favorable effect on the skeleton.

Beta-adrenergic receptor antagonists (β-blockers, BBs) are established pharmacological agents, which are being used for a wide variety of indications (e.g., hypertension, arrhythmias, myocardial infarction, congestive heart failure, and angina pectoris). The beneficial effects of BBs are mostly mediated by blockade of presynaptic adrenoceptors that increase the release of norepinephrine from sympathetic nerve terminals and decrease of central vasomotor activity, as well as the inhibition of peripheral catecholamine actions on βARs, leading to a reduction in cardiac output, heart rate, myocardial oxygen demands, renin release, angiotensin II production, and inhibition of vascular smooth muscle cell proliferation (10).

The clinically meaningful effect of BBs on the human skeleton has been estimated by a meta-analysis of observational studies, in which fracture was used as the main outcome. BBs were found to be associated with a significant reduction in risk of any fracture (relative risk 0.86, 95 % confidence interval (CI) 0.70–0.98) (11). However, many relevant studies have been published since (12–21), which collectively are being regarded as inconclusive (22, 23). Moreover, no pooled estimate regarding gender-specific effects of BBs on fracture risk has been reported, even though such an effect has been suggested (24). Gender-specific effects gain biological plausibility in terms of differences among the sex steroids and their respective rates of decline (estrogens vs. androgens), femur geometry (25), volumetric bone mineral density (26), trabecular changes (27), and quantitative trait loci patterns (28). Moreover, a site-specific effect of β-blockers has been suggested (13) as well as a dose–response pattern (24). Also importantly, it has been proposed that any benefit BB may confer to fracture risk reduction is mediated by β1-selective blockers rather than non-selective BBs (19). To address these considerations, a meta-analysis of observational studies, to date, was conducted.

Methods

Search strategy

To identify eligible studies, a computerized literature search was performed in electronic databases MEDLINE and EMBASE over a 7-year period, from January 2006 to January 2013 (English language only). MeSH and free text terms used for the search were combined with methodological filters to limit retrieval of studies to those involving only human subjects (Supplementary appendix). This protocol was complemented by a secondary search involving the scanning of the reference sections of all relevant studies, reviews, and the previous meta-analysis (11). Titles and abstracts were first screened for relevance by two independent reviewers (KAT and SS), and articles deemed potentially relevant were obtained in full. Any disagreements were resolved by discussion and the opinion of a third reviewer, as needed.

Eligibility

To be eligible for inclusion, a study (cohort or case–control, prospective, or retrospective) needed to report an extractable estimate of the fracture risk in patients under treatment with BBs. Predefined exclusion criteria were the following: (1) no control group and (2) treatment with BBs of less than a year. Case–reports, case-series, unpublished studies, and conference abstracts were not considered.

Data extraction and definition of outcomes

Standardized data extraction forms were used independently by two reviewers (SS, KAT). Specific emphasis was placed on the methodology applied in each study for the ascertainment of BB use and fractures, as well as adjustments for confounders. From the within-study reported estimates, the one derived from the model adjusted for the higher number of covariates was considered as the best estimate. Any data on cumulative exposure, BB selectivity, interaction with other agents, and fracture type were also extracted. A subset of studies was characterized as "best available evidence" (higher quality), provided that (1) BB use and fractures were ascertained by an objective (considered to be less vulnerable to bias) method (computerized medical records and/or x-rays as opposed to ascertainment on the basis of interviews/questionnaires), (2) study population was derived from the general population, and (3) reported fractures were rigorously assessed as incident (as opposed to prevalent). The Newcastle–Ottawa scale (NOS) was also used independently by two reviewers to verify the assessment of study quality. If not available, standard errors (SE) were calculated from CIs using the following formula: ln(SE)=[ln(upper 95 % CI) limit – ln (lower 95 % CI limit)] / 3.92. Primary outcome was the risk of any fracture in patients receiving BBs compared to controls. Secondary outcomes were the risk of hip, clinical vertebral, and wrist fractures in female and male patients (gender- and site-specific risk) receiving BBs compared to controls. Risk of any fracture in patients receiving high BB dose compared to that in those receiving low BB dose and in those receiving selective β1-blockers compared to nonselective BB also served as secondary analyses.

Data synthesis

For any of the prespecified outcomes, a relative measure of risk in each study was expressed as an adjusted hazard ratio (aHR) with the corresponding 95 % CI or adjusted odds ratio (aOR) with the corresponding 95 % CI for cohort studies and case–control studies, respectively. Adjusted estimates were used to minimize the potential confounding effect of patient-level characteristics on the risk of fracture. For data synthesis, logarithmic transformation of adjusted estimates was used, back-transformed for reporting. Pooled adjusted estimates were calculated using the generic inverse variance method. Fixed or random-effects (RE) models were used depending on the degree of heterogeneity (random effects used when $I^2 >$ 50 %). To obtain an overall pooled effect size (ES) estimate, the most informative of the effect size estimate (that is the estimate derived from the model with the highest number of covariates) was used, and aOR were considered an approximation of aHR, given the expected low incidence and small effect. Pooled ES estimate was then translated to the number-needed-treat (NNT) (using the formula NNT=1-[PEER*(1-OR)]/(1-PEER)*(PEER)*(1-OR), where PEER=patients expected event rate) to promote interpretation. In addition to the overall pooled estimate, gender- and site-specific estimates were also computed. Sensitivity analysis followed including only those studies characterized as best available evidence. Small study effects (publication bias) were explored by the Egger test (using 0.1 as the p value cutoff, acknowledging the low power of this test). To detect a potential dose-related effect, a meta-regression with linear trend estimation was undertaken (29). To this end, exposure was classified into three categories (low, medium, and high on the basis of the sum of defined daily doses), the sum of prescriptions, the average dose group, or sum of treatment days, and category-specific estimates were used. To explore the relative efficacy of β1-selective blockers in comparison to nonselective BBs, an adjusted indirect comparison was undertaken as explained in (30). Analyses were conducted in Stata/MP 10.0 for Windows (StataCorp LP, 4905 College Station, TX 77845, USA).

Results

From a total of 949 references identified through the computerized search and the secondary search, 15 studies met the inclusion criteria (12–19, 21, 24, 31–35). In one study (16), results from two distinct populations were reported, and this study is therefore treated as two individual studies. Search results (flow chart) and a list of excluded studies on a full-text basis (n=16) may be found in Supplementary file 1. The general characteristics of the studies included in the meta-analysis are summarized in Table 1. In all, fracture data regarding 1,644,570 individuals from 16 studies (7 cohort and 9 case–control studies), with a mean age ranging from 43 to 81 years old, were analyzed.

In general, only clinical vertebral (as opposed to morphometric vertebral fractures) were considered with the exception of one study in which this was not clear (18). On the other hand, prevalent fractures (as opposed to incident fractures) and non-vertebral fractures (as opposed to all fracture sites) were used as the main outcome in a subset of the studies (15, 16, 34), and, thus, their effect on the pooled estimate was investigated in the sensitivity analysis.

Meta-analysis

Primary outcome

Overall risk of any fracture

The risk of any fracture was significantly reduced in subjects receiving BBs compared to controls (16 studies, RE pooled ES=0.86, 95 % CI 0.78–0.93, I^2=87 %; Fig. 1). This finding was consistent in both cohort (7 studies, pooled aHR=0.84, 95 % CI 0.71–0.98; I^2=91 %) and case–control studies (9 studies, pooled aOR=0.87, 95 % CI 0.79–0.95; I^2=70 %). No evidence of publication bias was detected (Egger test p=0.65). Assuming the overall lifetime risk of any osteoporotic fracture at the age of 50 to be 30 % (36), one osteoporotic fracture is prevented for every 30 patients under treatment with BBs.

Sensitivity analyses

In a prespecified sensitivity analysis limited to the best available evidence (12, 13, 19, 24), the risk of any fracture was again found to be significantly reduced in subjects receiving BBs compared to controls (4 studies, pooled ES=0.79, 95 % CI 0.67–0.94; I^2=96 %). This finding was also confirmed in the subgroup analysis of those studies designated as of higher quality (above the median) on the basis of NOS (8 studies, pooled ES=0.84, 95 % CI 0.76–0.92; I^2=92 %). This was also the case in a sensitivity analysis excluding the two studies with the largest sample size (12, 19) (14 studies RE pooled ES=0.87, 95 % CI 0.78–0.95; I^2=66 %). To inspect the effect of duplicate publication bias (37), one of the two studies (16, 24) using General Practice Research Database (GPRD) data was alternately excluded. This finding continued to be robust, excluding either the GPRD study by Schlienger et al. (24) (RE pooled ES=0.86, 95 % CI 0.78–0.95; I^2=88 %) or de Vries et al. (16) (RE pooled ES=0.86, 95 % CI 0.78–0.95; I^2=88 %). No evidence of publication bias was detected by Egger test in any of the above analyses.

Table 1 General characteristics of the studies included in the meta-analysis

Study details	N (% males)	Mean age	βB users (%)	Fractures analyzed	Ascertainment of βB use	Ascertainment of fractures	Covariates	βB dose or duration	βB selectivity
Case–control									
Jensen, 1991, Denmark	400 (17.5)	81	200 (50)	Hip	Interview	Hospital records	(Matched on) age, gender, residency, number of hospital admissions	No	No
Pasco,2004, Australia	1,344 (0.0)	70	569 (42.3)	Hip, vertebral, wrist, ankle, humerus	Questionnaire	X-rays reports	Age, weight, height, diet, alcohol, smoking, physical activity, and selected medications	No	No
Rejnmark, 2004, Denmark	978 (0.0)	50	163 (16.7)	NR	NR	Interview/hospital records and x-rays	Age, prior fracture, BMD, diet, alcohol, smoking, and selected medications (matched on HRT use)	Yes	No
Schlienger 2004, Switzerland	151,420 (39.8)	#	30,601 (20.2)	Hip, vertebral, wrist, ankle, humerus	GPRD	GPRD	BMI, smoking, visits, medications (matched on age, sex)	Yes	Yes
Rejnmark, 2006, Denmark	498,617 (48.2)	43	124,655	Hip, vertebral, wrist, other	Prescription database	National Hospital discharge register	Prior fracture, socioeconomic factors, and medications (matched on age, sex)	Yes	No
Bonnet, 2007, France	499 (0.0)	65	158 (31.7)	Hip, vertebral, wrist, other	Interview	Questionnaire / medical files	Age, weight, smoking, BMD, bone quality parameters and selected medications	No	No
De Vries, 2007, UK GPRD	44,494 (24.2)	§	22,247 (50)	Hip/femur	GPRD	GPRD	BMI, comorbidities and medications (matched on age, sex)	Yes	Yes
De Vries, 2007, PHARMO, NL	33,104 (28.3)	§	6,763 (20.4)	Hip/femur	PHARMO RLS	PHARMO RLS	Comorbidities and medications(matched on age, sex)	Yes	Yes
Sosa, 2011, Spain	188 (0.0)	65	77 (41.0)	Vertebral, non-vertebral	NR	Interviews/x-rays	Matched on age	No	No
Cohort									
Levasseur 2005, France	7,598 (0.0)	81	283 (3.7)	Non-vertebral	Interview	NR	Age, weight, BMD, alcohol, physical activity and selected medications	Yes	No *only non
Reid 2005, USA	8,098 (0.0)	77	1,097 (13.5)	Hip, vertebral, wrist, other	Interview	Interview/x-ray reports	Age, sex, weight, energy expenditure, alcohol, frailty and selected medications	Yes	Yes
Gage, 2006, USA	14,564 (46.6)	80	NR	Hip, vertebral, wrist, rib	Medicare	Medicare	Age, sex, BMI, alcohol, physical activity, smoking, selected co-morbidities and medications	No	No
Meisinger, 2007, Germany	1,793 (46.7)	62	219 (12.2)	Hip, wrist, ankle, humerus , other	Interview	Questionnaire	Age, sex, race, alcoholism, co-morbidities and medications	No	>71 %
Yang, 2010, Australia	3,488 (36.8)	69	673 (19.3)	Hip, vertebral, other	Interview/ records	X-rays	Age, BMI, BMD, smoking, alcohol, dietary calcium intake and physical activity	No	>70 %
Solomon, 2011, USA	376,061 (20)	80ǂ	107,457 (28.6)	Hip, wrist, humerus, pelvis	Medicare	Health care utilization data	Age, sex, race, comorbidities, and medications	Yes	No
Song, 2012, Korea	501,924 (35)	71*	18,599 (3.7)	Hip, vertebral, pelvic, other	HIRA database	HIRA database	Age, sex-specific comorbidities, and medications	Yes	Yes

βB β-blockers, *BMD* bone mineral density, *BMI* bone mass index, *DM* diabetes mellitus, *HIRA* health insurance review and assessment service, *HRT* hormone replacement therapy, *NR* not reported, *GPRD* UK General Practice Research Database, *PHARMO RLS* PHARMO Record Linkage System (including hospital discharge records) * for βB users, median, # approximately 60 % below 60 years old (relatively young population), § over 50 % above 80 years old (relatively aged population)

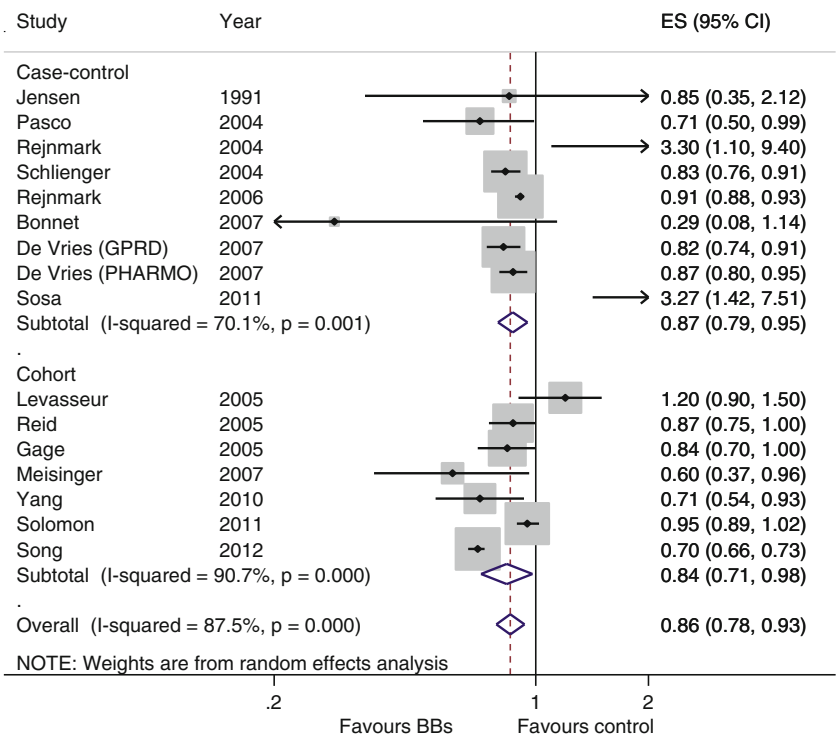

Fig. 1 Forest plot of the risk of any fracture comparing subjects treated with β-blockers to controls. *βBs* β-blockers, *ES* effect size (adjusted odds ratio for case–control studies and adjusted hazard ratio for cohort studies)

Secondary outcomes

Gender- and site-specific risk of fractures

Gender- and site-specific pooled estimates of the fracture risk are summarized in Table 2. In general, the magnitude of effect remained consistent in men, women, and mixed populations. The estimate of hip fracture risk was lower in both women and men receiving BBs compared to controls (Females: pooled ES= 0.86, 95 % CI 0.80–0.91; I^2=1 % and males: pooled ES=0.80, 95 % CI 0.71–0.90, I^2=0 %; Fig. 2). Exclusion of the two largest studies did not affect the results. Similar risk reductions were suggested for clinical vertebral and forearm fractures, although statistical significance was not reached (Table 2).

Dose-related effects

A potential dose-related effect, expressed in terms of either cumulative or current exposure, was explored in a subset of studies. Exposure was quantified on the basis of the sum of defined daily dose (12, 19), the sum of prescriptions (24), the last prescribed dose (16), dose group and sum of treatment days (17), and the midpoint of the recommended dose range (32). Two studies (one case–control and one cohort) did not support a dose-related pattern (16, 17), while in three studies, a dose–response relationship was evident (12, 19, 24). Another study in which patients were evaluated on duration of BB treatment risk was increased after 8 years (33). Extractable data (adjusted ES estimates across dose categories) were provided only in four case–control studies (including distinctly GPRD and PHARMO studies, reported in De Vries et al. (16)) (12, 16, 24) and one cohort study (19). Pooled effects stratified by dose level (low, medium, or high) revealed no significant difference between medium and high dose compared to low dose (*p* values 0.786 and 0.161, respectively, Fig. 3). Meta-regression analysis showed no significant differences among exposure categories, although a suggestion for a linear trend, compatible with a dose–response relationship, was noted (*p* value 0.150). By alternately excluding GPRD studies to inspect the effect of duplicate publication bias (37), findings remained unchanged with the exclusion of either Schlienger et al. (24) (*p* value 0.167) or de Vries et al. (16) (*p* value 0.156).

Selectivity

The potential effect of β1-selective blockers on fracture risk as compared to that of nonselective BBs was investigated in a subset of the studies included in the meta-analysis. In three cohort studies (13, 14, 19), the β1-selective agents were significantly more effective in reducing fracture risk than nonselective BBs, in line with a previous report (32). In contrast, no major difference on the basis of BB selectivity was detected in two studies (16, 24). A study in which β1-selective agents were not considered reported no significant difference in fracture between BBs users and controls (34). Using adjusted indirect comparison, it was estimated that β1-selective agents were significantly more effective than nonselective BBs in reducing the risk of any fracture (six

Table 2 Gender- and site-specific pooled estimates of fracture in subjects under β-blockers compared to controls

Outcome	Design and number	Pooled ES	95 % CI	*P* value	I^2 (%)
Females					
Case–control					
Any*	6	0.91	0.76–1.10	0.339	76
Hip	4	0.86	0.81–0.92	$<10^{-4}$	0
Vertebral	2	0.87	0.68–1.11	0.256	0
Forearm	3	0.94	0.83–1.06	0.285	26
Cohort					
Any	3	0.76	0.65–0.89	0.01	74
Hip	2	0.71	0.54–0.93	0.011	0
Vertebral	1	0.80	0.55–1.17	0.247	N/A
Forearm	1	0.76	0.54–1.06	0.111	N/A
Males					
Case–control					
Any	2	0.75	0.59–0.95	0.016	89
Hip	3	0.80	0.71–0.91	0.001	0
Vertebral*	1	0.74	0.47–1.17	0.200	N/A
Forearm	1	1.07	0.80–1.44	0.652	N/A
Cohort					
Any	2	0.64	0.58–0.70	$<10^{-4}$	0
Hip *	1	0.50	0.17–1.51	0.213	N/A
Vertebral*	1	0.47	0.23–0.97	0.040	N/A
Mixed populations					
Case–control					
Any	2	0.88	0.80–0.96	$<10^{-4}$	73
Hip	5	0.87	0.83–0.91	$<10^{-4}$	34
Vertebral	2	0.85	0.69–1.05	0.129	0
Forearm	2	0.88	0.81–0.95	0.002	N/A
Cohort					
Any*	3	0.87	0.74–1.02	0.095	59
Hip *	1	0.92	0.83–1.02	0.130	N/A
Forearm*	1	0.91	0.79–1.05	0.194	N/A

*Pooled effect size (*ES*) was significant when data synthesis included both cohort and case–control studies. *CI* confidence interval, *N/A* not applicable

studies, β1-selective blockers vs. nonselective BBs: RE pooled ES=0.82, 95 % CI 0.69–0.97). By alternately excluding GPRD studies to inspect the effect of duplicate publication bias (37), findings remained unchanged with the exclusion of either Schlienger et al. (24) (RE pooled ES=0.76, 95 % CI 0.62–0.93) or de Vries et al. (16) (RE pooled ES=0.79, 95 % CI 0.64–0.99).

Interaction with other antihypertensives

The protective effect of BBs was present only in patients who had received or were currently receiving other antihypertensive regimens in both GPRD and PHARMO-RLS analyses (16). On the other hand, the risk reduction (compared to controls) was rather similar in patients only on BB and those on concurrent use of BB and thiazides (24). Unfortunately, thiazide use was investigated as a covariate in the majority of studies, and no further analysis was feasible.

Discussion

The present study suggests that the risk of any fracture is approximately 15 % lower in patients treated with BBs compared to controls. This risk reduction appears to be seen in men and women and for all major fracture sites (hip, vertebral, and forearm) and remained robust in sensitivity analyses. Dose dependency was not established. Finally, it was demonstrated that the reduction in fracture risk was associated with the effects of β1-selective blockers rather than nonselective BBs.

A series of elegant preclinical experiments established the role of β2AR in skeletal biology (5, 38–43), and the reported clinical benefit in terms of fracture risk could be explained within this context. On the other hand, the role of β1AR signaling and its potential interaction with β2AR remain unclear (44). An "unexplored complexity" in the regulation of bone metabolism by sympathetic signaling has been suggested (6). Thus, the present finding that fracture risk reduction is possibly associated with the effects of β1AR rather than β2AR blockade could not have been anticipated intuitively. Such complexity may also explain the counterintuitive epidemiological report that β2-agonists had a rather neutral effect on fracture risk (45). An alternative explanation β1AR blockade's apparent superiority could be gleaned by an interesting study, in which the acute effects of β1AR blockade on parathyroid hormone (PTH) secretion were investigated (46). In this study, an increase in pulsatile PTH secretion was documented in response to intravenous infusion of a short-acting hydrophilic BB agent (esmolol). Thus, aside from a direct local action on the skeletal β1AR, the beneficial effect of selective β1-blockers on bone metabolism conceivable could be mediated by the osteoanabolic actions of PTH. This speculation will obviously require experimental confirmation.

Assuming the overall lifetime risk of any osteoporotic fracture at the age of 50 to be 30 % (36), 1 osteoporotic fracture is prevented over the life course of every 30 treated patients. This is not a negligible effect and may have important implications for clinical practice and/or health policy. However, the reported anti-fracture potential of BBs should be carefully weighed against the side-effects associated with their use, namely hypotension, dizziness, blurred vision (which collectively might be associated with an increased risk of falls), as well as cold extremities, bradycardia, nausea, insomnia, erectile dysfunction, and negative influence on glucose

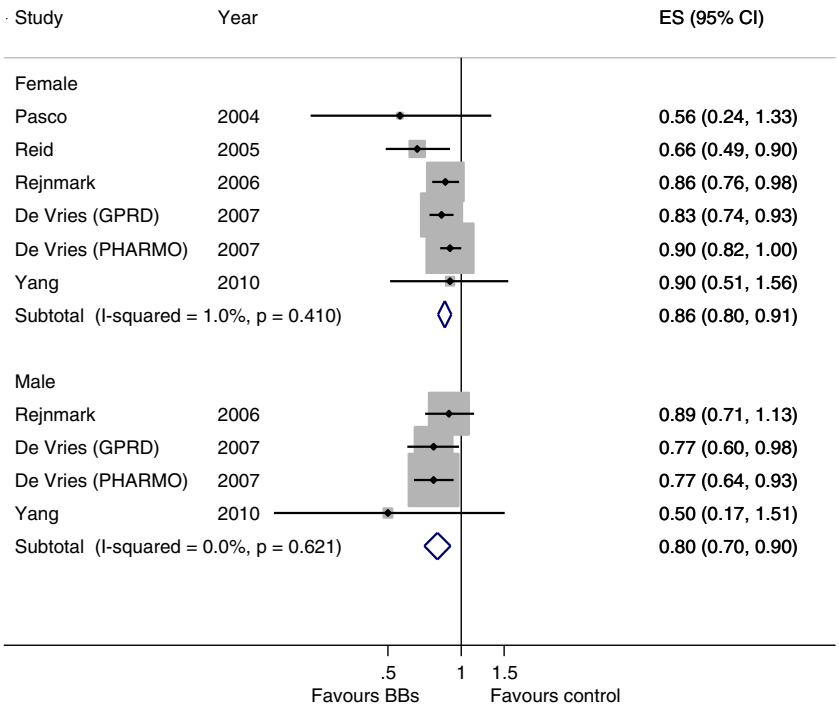

Fig. 2 Forest plot of the gender-specific risk of a hip fracture comparing subjects treated with β-blockers to controls. *βBs* β-blockers, *ES* effect size (adjusted odds ratio for case–control studies and adjusted hazard ratio for cohort studies)

and lipid metabolism. Moreover, the demonstrated superiority of β1-selective blockers over nonselective agents in terms of skeletal effects may provide additional impetus to explore further the "complex" role of β1AR in the central regulation of the skeleton.

The findings of the present study should be interpreted with caution because of the observational nature of the evidence and significant heterogeneity in the results, which was not explained in the sensitivity analysis. Diversity in study design, study populations, and use of beta-blockers (type, dose, and

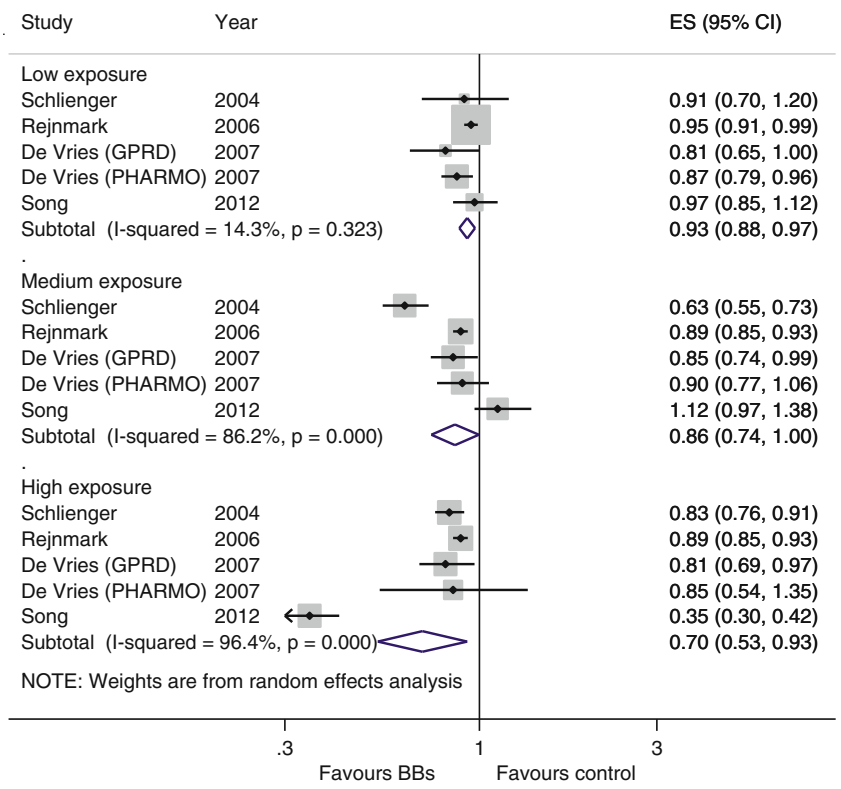

Fig. 3 Subgroup analysis of studies with extractable data on the basis of exposure. *βBs* β-blockers, *ES* effect size (adjusted odds ratio for case–control studies and adjusted hazard ratio for cohort studies)

duration) are plausible explanations for the observed statistical heterogeneity. Another potential source of heterogeneity may be the underlying disease. Heart failure, a treatment indication for BBs, is an established, clinically and densitometrically, independent risk factor for osteoporotic fractures (47). However, the extent to which this may have contributed to the observed heterogeneity could not be quantified. Finally, it should be noted that beta-adrenergic receptor selectivity is rather lost at higher doses (48), an observation that may have a potential confounding effect in the dose-response analysis. On the other hand, (1) the use of adjusted (rather than crude estimates), which has probably minimized the confounding effect of patient-level characteristics (imbalance between groups on a study level) and (2) the analysis of the best available evidence, which confirmed the robustness of the findings, supports the validity of the results. Some of our findings are also in accordance with a recently published meta-analysis by an independent group (49), despite the facts that a different methodology was applied, different populations were considered (18, 19, 34), and that dose and selectivity were not addressed. On the other hand, no difference in fracture risk between carvedilol-treated patients with congestive heart failure and controls could be documented in a report of a pooled analysis of nine relevant trials (22, 32). However, it should be noted that fractures were recorded only as adverse events, an imbalance between study groups in terms of baseline fracture risk could not be excluded, and that the duration of the trials may not have been long enough for the full skeletal effects to take place.

In summary, by this meta-analysis, the risk of any fracture is approximately 15 % lower in patients under treatment with BBs compared to controls independently of gender and site. This risk reduction may be mostly associated with β1-selective blockers.

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Conflicts of interest None

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