# A simple score for estimating the long-term risk of fracture in patients with multiple sclerosis

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## ABSTRACT

**Objective:** To derive a simple score for estimating the long-term risk of osteoporotic and hip fracture in individual patients with MS.

**Methods:** Using the UK General Practice Research Database linked to the National Hospital Registry (1997–2008), we identified patients with incident MS (n = 5,494). They were matched 1:6 by year of birth, sex, and practice with patients without MS (control subjects). Cox proportional hazards models were used to calculate the long-term risk of osteoporotic and hip fracture. We fitted the regression model with general and specific risk factors, and the final Cox model was converted into integer risk scores.

**Results:** In comparison with the FRAX calculator, our risk score contains several new risk factors that have been linked with fracture, which include MS, use of antidepressants, use of anticonvulsants, history of falling, and history of fatigue. We estimated the 5- and 10-year risks of osteoporotic and hip fracture in relation to the risk score. The C-statistic was moderate (0.67) for the prediction of osteoporotic fracture and excellent (0.89) for the prediction of hip fracture.

**Conclusion:** This is the first clinical risk score for fracture risk estimation involving MS as a risk factor. *Neurology*® 2012;79:922–928

## GLOSSARY

**BMD** = bone mineral density; **BMI** = body mass index; **GC** = glucocorticoid; **GPRD** = General Practice Research Database; **MS** = multiple sclerosis.

Multiple sclerosis (MS) is a chronic inflammatory disorder of the brain and spinal cord characterized by damage to myelin and axons. MS is one of the most common causes of neurologic disability in young adults.[1] Previous epidemiologic studies have shown that patients with MS are at risk of fractures, especially fractures of the hip.[2,3] This risk may be caused by different underlying mechanisms, which include low bone mineral density (BMD)[4–9] and increased risk of falling.[10–12] Explanations for low BMD in MS include immobility,[6,7] vitamin D deficiency,[6,9] and use of glucocorticoids (GCs).[4,7] The increased risk of falling may be explained by poorer postural balance, impaired vision, disability, or spasticity.[10,12] We have shown that absolute risks of fracture were substantial when patients with MS were older than 60 years.[2] It is currently possible to estimate an individual's risk of fracture with FRAX[13] or the Garvan calculator.[14]

The FRAX tool has been developed by the World Health Organization to evaluate fracture risk of patients.[13] FRAX uses easily obtainable clinical risk factors, with or without femoral

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neck BMD, to estimate a 10-year probability of hip fracture and osteoporotic fracture. The FRAX model uses data derived from 9 cohorts from around the world, including centers from North America, Europe, Asia, and Australia and has been validated in 11 independent cohorts with a similar geographic distribution.[15] For fracture prediction without BMD, the C-statistic for hip fracture was 0.66 in the validation cohorts, and for osteoporotic fracture, it was 0.60. FRAX models have been calibrated to the epidemiology of many countries, including the United Kingdom, and are available through the Web.[16] Risk factors that are incorporated in FRAX include age, sex, body mass index (BMI), history of fracture, parental history of fracture, smoking, use of GCs, history of rheumatoid arthritis, secondary osteoporosis, and high alcohol consumption. Many clinicians have a wish list of risk factors not considered in FRAX, including many other risk factors for secondary osteoporosis and the inclusion of risk of falls.[17]

MS is one of the risk factors for fracture that is not incorporated in FRAX. To our knowledge, there is currently no clinical risk score available for the calculation of the long-term risk of fracture in patients with MS. Such a score might be a useful tool to identify those patients with MS who would be candidates for BMD screening or pharmacologic interventions. In patients with low BMD, the use of bisphosphonates, strontium ranelate, or raloxifene has been approved for the prevention of fractures.[18] The aim of this study was to derive a simple score for estimating the long-term risk of osteoporotic and hip fracture in patients with MS.

## METHODS

**Data source.** Information for this study was obtained from the General Practice Research Database (GPRD). The GPRD comprises prospectively collected computerized medical records for more than 10 million patients under the care of general practitioners in the United Kingdom. It has been the source for numerous epidemiologic studies, and the accuracy and completeness of these data have been well-validated and documented.[19] Previous studies of GPRD data have shown a high level of data validity with respect to the reporting of fracture.[20] GPRD data have been linked to the national Hospital Episode Statistics in England for approximately 45% of all practices.[21] In this study, data were linked from April 1997 until March 2008.

**Study population.** The study population has been described previously and is available under an open access license.[2] In short, we identified all patients aged 18 years or older with at least one recorded diagnosis of MS during the period of GPRD (January 1987–August 2009) or Hospital Episode Statistics data collection (April 1997–March 2008). Patients with a history of MS before the start of valid data collection were excluded. Each patient with MS was matched by year of birth, sex, and practice to 6 control subjects. The index date of MS diagnosis was the date of the first record of MS, after start of valid data collection. Control patients were assigned the same index date as their matched case patient. Each patient was followed from index date to the end of data collection, the date of transfer of the patient out of the practice area, or the patient's death, whichever came first. For the development of the prediction model, we followed FRAX in the decision to exclude patients who were currently treated with osteoporosis medication or who had previously taken medicines against osteoporosis. Therefore, we excluded all patients who had ever used osteoporosis treatment at baseline, which included prescriptions of bisphosphonates, raloxifene, strontium ranelate, and parathyroid hormone.

**Study outcomes.** All patients were followed up for the occurrence of fractures. The types of fracture were classified according to the International Classification of Diseases (ICD-10) categories. These included skull (S02), neck (S12), ribs (S22), pelvis (S32), shoulder (S42), forearm (S52), hand (S62), hip/femur (S72), ankle (S82), foot (S92), or unspecified fractures (T02, T08, T10, and T12). A clinical osteoporotic fracture was defined as a fracture of the radius/ulna, vertebrae, femur, hip, humerus, pelvis, or ribs.

**Risk factors.** The presence of risk factors was assessed by reviewing the computerized medical records at baseline. Potential risk factors included older age, female sex, low BMI, being a smoker, drinking alcohol, history of falling 3 months–1 year before, history of fracture, and history of chronic diseases (congestive heart failure, rheumatoid arthritis, cerebrovascular disease, inflammatory bowel disease, dementia, depression, epilepsy, and chronic obstructive pulmonary disease). In addition, evidence of fatigue, visual disturbances, vertigo, dizziness, imbalance, disturbance of sensation, spasticity, sexual dysfunction, paroxysmal symptoms, cognitive dysfunction, vitamin D deficiency, and proxy indicators of increased disability (home visits by the general practitioner, nursing care, patient receiving residential care/living in a care home, or patient using a wheelchair or walking aid) 6 months before the index date were considered. Further, prescriptions for PO or IV administered GCs, statins, antiarrhythmics, antidiabetics, antidepressants, antipsychotics, hypnotics/anxiolytics, asthma medication, anticonvulsants, hormone replacement therapy, vitamin D, levothyroxine, baclofen, opioids (potencies equivalent to tramadol or higher), nonsteroidal anti-inflammatory drugs, meprobamate, tizanidine, dantrolene, modafinil, methylphenidate, or amantadine 6 months before the index date were also considered potential risk factors.

**Statistical analysis.** Cox proportional hazards models were used to calculate the long-term risk of osteoporotic and hip fracture. The Cox model allows calculation of an individual's probability of fracture (i.e., survivor function) for each set of patient characteristics. For the analysis of long-term risk, we first fitted the regression model with all possible risk factors, which were determined at baseline. All characteristics, except age, were included as categorical variables in the regression models. For


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BMI, we used categories <20 kg/m$^2$, 20–25 kg/m$^2$ (reference), >25 kg/m$^2$, and unknown. Smoking status was divided over current smoking, ex-smoking, never smoking (reference), and unknown smoking status. Alcohol consumption was similarly categorized as current, ex, never (reference), and unknown. All other variables addressing medical history and the prescription of drugs were separately added and were categorized as yes or no. We used the PHREG procedure in SAS with forward selection and a significance level of 0.05. This resulted in a list of variables that were possible candidates for our prediction model.

For osteoporotic fracture, the following variables came out of the forward selection. MS, sex, age, use of GCs in the prior 6 months, use of anticonvulsants in the prior 6 months, history of fracture, current smoking, and BMI >25 kg/m$^2$. Because of clinical importance, we decided to add BMI <20 kg/m$^2$, use of antidepressants in the prior 6 months, and history of falling 3 months–1 year before. For the prediction of hip fracture, forward selection resulted in the variables MS, age, use of antidiabetics, baclofen, and amantadine in the prior 6 months, history of fatigue in the prior 6 months, BMI <20 kg/m$^2$ and BMI >25 kg/m$^2$. In this case, we considered sex, use of GCs in the prior 6 months, use of antidepressants in the prior 6 months, history of falling 3 months–1 year before, history of fracture, and current smoking important variables to add. However, because there were only 104 hip fractures among the patients with MS and control subjects, we were restricted to 10 predictors. Therefore, we dropped the use of antidiabetics, baclofen, and amantadine in the prior 6 months. We also dropped a history of fracture, because this variable led to $\beta$ of 0. Next, we investigated possible statistical interactions of these selected variables with MS. To account for multiple comparisons, we applied a Bonferroni correction. None of the interaction terms was subsequently added to the model.

The $\beta$ coefficients in the final Cox model were converted into integer risk scores. The value of each integer was calculated as the rounded sum of the Cox model predictor scores, multiplied by 10. The 5- and 10-year risks of fracture were then estimated using these scores, conditional on patient survival. Various methods were used to test the fitting of the Cox models, including a test of the proportional hazards assumption. We also compared the observed 5-year probability of fracture (based on the Kaplan-Meier estimate) with the probability predicted by the Cox model. To assess the internal validity of the model further, the C-statistic was calculated, and we performed a 10-fold cross-validation. We applied the shrinkage factor that we found to the $\beta$ coefficients of the model, and we adjusted the C-statistic for overestimation. We compared 10-year risks of osteoporotic and hip fracture as predicted by FRAX and by the present risk score.

As a sensitivity analysis, we also evaluated backward selection and stepwise selection instead of forward selection. Both methods resulted in exactly the same set of predictors, both for osteoporotic and for hip fracture. All data management and statistical analyses were conducted using SAS 9.1/9.2 software.

**Standard protocol approvals, registrations, and patient consents.** The study was approved by the Independent Scientific Advisory Committee of the GPRD.

**RESULTS** The study population consisted of 5,494 patients with MS and 32,669 population-based control subjects.

Of all patients with MS, 70% were female and the mean age at the index date (first recorded diagnosis of MS) was 44.5 years. The median duration of follow-up after the index date was 4.5 years. There were more current smokers among patients with MS than among control subjects, and there were more patients with MS with BMI <20 kg/m$^2$. Six months before the index date, patients with MS had used significantly more antidepressants (17.7%), anticonvulsants (6.6%), and GCs (5.7%) than the control subjects (8.3%, 1.2%, and 1.4%, respectively). Further descriptive details of the study participants are shown in table 1. Among all patients with MS, 163 experienced an osteoporotic fracture during follow-up, and 36 patients sustained a hip fracture. In the control group, there were 668 osteoporotic fractures and 68 hip fractures. The most common osteoporotic fractures were fractures of the radius/ulna: there were 61 patients with MS with these types of fractures and 298 control subjects.

Table 2 presents the risk score for osteoporotic and hip fracture in relation to various patient characteristics. The overall score for a patient is the cumulative score of the various risk factors. For example, a woman with MS aged 60 years, with a history of fracture and antidepressant use in the previous 6 months, had a risk score for osteoporotic fracture of 42 (+4 points for having MS, +3 points for being female, +30 points for her age, +4 points for history of fracture, and +1 point for the use of antidepressants). The figure displays the 5- and 10-year risks of fracture (percentages) in relation to the risk score. The corresponding 5-year risk of osteoporotic fracture for the patient described is 7.2%. To provide some risk level landmarks: the predicted 5-year risk of osteoporotic fracture for a 70-year-old woman without any other risk factors was 4.9% (score = 38). If the woman also had a history of fracture, her risk changed to 7.2% (score = 42). A female patient with MS of the same age and with a history of fracture had a 5-year risk of 10.5% (score = 46). The C-statistic was moderate (0.67) for the prediction of osteoporotic fracture and excellent (0.89) for the prediction of hip fracture.

Table 3 shows that FRAX underestimated risks of fracture for patients with MS, especially risks of hip fracture.

**DISCUSSION** In this study, we developed a simple score for estimating the long-term risk of osteoporotic and hip fracture in patients with MS. In comparison with the FRAX calculator,[13] our risk score contains several new risk factors that have been linked with fracture. These include MS, the use of antidepressants, the use of anticonvulsants, history of falling, and history of fatigue. The score was developed in a cohort of patients with MS and population-based control subjects, and the presence


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**Table 1** Baseline characteristics of patients with MS and control subjects

| Characteristic | Patients with MS (n = 5,494) | Control subjects (n = 32,669) |
|---|---|---|
| Female sex, n (%) | 3,833 (69.8) | 22,738 (69.6) |
| Age at index date | | |
| Mean | 44.5 | 44.3 |
| By category, n (%) | | |
| 18–29 y | 670 (12.2) | 4,016 (12.3) |
| 30–39 y | 1,443 (26.3) | 8,649 (26.5) |
| 40–49 y | 1,614 (29.4) | 9,661 (29.6) |
| 50–59 y | 1,044 (19.0) | 6,184 (18.9) |
| 60+ y | 723 (13.2) | 4,159 (12.7) |
| Duration of follow-up, y, median (range) | 4.5 (0–20.6) | 5.0 (0–20.6) |
| Smoking, n (%) | | |
| Never | 2,114 (38.5) | 14,805 (45.3)[a] |
| Current | 1,521 (27.7) | 7,062 (21.6)[a] |
| Ex | 790 (14.4) | 4,134 (12.7)[a] |
| Unknown | 1,069 (19.5) | 6,668 (20.4) |
| BMI, n (%) | | |
| <20 kg/m$^2$ | 443 (7.9) | 1,919 (5.9)[a] |
| 20–25 kg/m$^2$ | 1,904 (34.7) | 11,146 (34.1) |
| 25–30 kg/m$^2$ | 1,295 (23.6) | 8,591 (26.3)[a] |
| >30 kg/m$^2$ | 878 (16.0) | 5,347 (16.4) |
| Unknown | 984 (17.9) | 5,666 (17.3) |
| History of comorbidity, n (%) | | |
| Fracture | 801 (14.6) | 4,354 (13.3)[a] |
| Falling | 343 (6.2) | 928 (2.8)[a] |
| Fatigue | 425 (7.7) | 1,682 (5.1)[a] |
| Asthma | 568 (10.3) | 3,378 (10.3) |
| COPD | 53 (1.0) | 281 (0.9) |
| Congestive heart failure | 31 (0.6) | 146 (0.4) |
| Diabetes mellitus | 151 (2.7) | 804 (2.5) |
| Rheumatoid arthritis | 28 (0.5) | 207 (0.6) |
| Cerebrovascular incident | 147 (2.7) | 361 (1.1)[a] |
| Epilepsy | 129 (2.3) | 435 (1.3)[a] |
| History of drug use 6 mo before, n (%) | | |
| Statins | 220 (4.0) | 977 (3.0)[a] |
| Antidepressants | 974 (17.7) | 2,709 (8.3)[a] |
| Antipsychotics | 72 (1.3) | 294 (0.9)[a] |
| Anxiolytics/hypnotics | 456 (8.3) | 1,290 (3.9)[a] |
| Anticonvulsants | 364 (6.6) | 408 (1.2)[a] |
| Opioids | 156 (2.8) | 320 (1.0)[a] |
| PO/IV glucocorticoids | 311 (5.7) | 445 (1.4)[a] |
| Vitamin D | 35 (0.6) | 128 (0.4)[a] |

Abbreviations: BMI = body mass index; COPD = chronic obstructive pulmonary disease; MS = multiple sclerosis.
[a] Statistically significant difference ($p < 0.05$) between patients with MS and control subjects, based on $\chi^2$ test.

**Table 2** Risk score of fracture

| Characteristic | Score osteoporotic fracture | Score hip fracture |
|---|---|---|
| Patient with MS | 4 | 13 |
| Female sex | 3 | 2 |
| Age (for every 10 y) | 5 | 11 |
| Use of PO/IV glucocorticoids in the prior 6 mo | 1 | 3 |
| Use of antidepressants in the prior 6 mo | 1 | 3 |
| Use of anticonvulsants in the prior 6 mo | 6 | |
| History of falling 3 mo–1 y before | 4 | 6 |
| History of fracture ever before | 4 | |
| History of fatigue in the prior 6 mo | | 18 |
| Current smoker | 2 | 4 |
| BMI <20 kg/m$^2$ | 2 | 7 |
| BMI >25 kg/m$^2$ | −1 | −6 |

Abbreviations: BMI = body mass index; MS = multiple sclerosis.

of MS proved to be a useful characteristic in the prediction of osteoporotic and hip fracture.

There are various explanations for the association between MS and fracture, which include fall- and bone-related mechanisms. Previous studies have shown that patients with MS have an increased risk of osteoporosis,[4–9] which may result from immobilization,[6,7] vitamin D deficiency,[6,9] exposure to GCs,[4,7,22] and the inflammatory nature of the disease.[23] The decrease in bone formation with immobility is probably caused by the reduction of mechanical stress, which results in disruption of the osteocyte network.[24] GC-induced osteoporosis can be explained by apoptosis in osteoblasts and osteocytes or suppression of their differentiation.[25] In the present study, we investigated the predictive value of GC use as a risk factor for osteoporotic and hip fracture, and the recent use of GCs was indeed incorporated in our models. Further, it has been recognized that patients with MS are at increased risk of falling,[10–12] which may be explained by poorer postural balance, impaired vision, disability, or spasticity. Although we had information on the occurrence of falls, and history of falling was indeed selected as a risk factor in our models, there may have been an underrecording of falling in our study. The true contribution of falling may therefore be greater than represented in our risk scores. However, because we additionally incorporated MS as a risk factor, this probably has captured risk of falling in an indirect way. Recent use of GCs may also be a proxy for risk of falling, because treatment with GCs may be initiated because of a worsening of neurologic problems.


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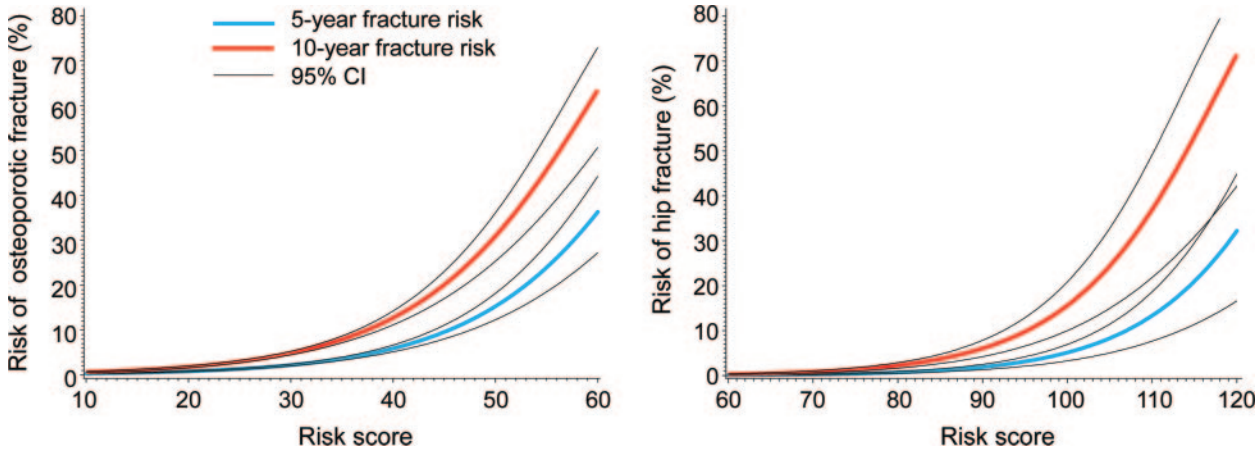
**Figure** Risk (percentage) of osteoporotic or hip fracture in relation to risk score




CI = confidence interval.

In addition to the presence of MS, the recent use of antidepressants and anticonvulsants were also covered in our risk score. One of the possible mechanisms by which antidepressant use may contribute to fracture risk is through an increased risk of falling.[26] Moreover, the microarchitecture of bone may be altered,[27] and depression itself might also increase risk of fracture.[28] The mechanisms by which anticonvulsants weaken the skeleton are not fully understood. One theory is that they accelerate vitamin D hydroxylation to polar inactive metabolites, resulting in hypocalcemia, secondary hyperparathyroidism, increased bone turnover, and higher rates of bone loss.[29]

**Table 3** Ten-year probability of fracture as predicted by FRAX and the present risk score by sex and age

| | Osteoporotic fracture | | Hip fracture | |
|---|---|---|---|---|
| | FRAX[a] | Present risk score[b] | FRAX[a] | Present risk score[b] |
| **Men** | | | | |
| **40** | 2.5 | 2.4 | 0.1 | 0.2 |
| **50** | 2.7 | 3.9 | 0.2 | 0.7 |
| **60** | 3.9 | 6.1 | 0.6 | 2.2 |
| **70** | 5.6 | 9.6 | 1.6 | 6.5 |
| **80** | 7.2 | 14.8 | 3.9 | 18.6 |
| **Women** | | | | |
| **40** | 2.6 | 3.3 | 0.2 | 0.3 |
| **50** | 3.5 | 5.2 | 0.3 | 0.9 |
| **60** | 6.1 | 8.2 | 1.0 | 2.8 |
| **70** | 11.0 | 12.9 | 3.1 | 8.2 |
| **80** | 18.0 | 19.6 | 8.6 | 22.8 |

[a] Using http://www.shef.ac.uk/FRAX[16] for the UK (accessed 5 March 2012), incorporating age, sex, and a body mass index of 22.5 kg/m$^2$.
[b] Incorporating age, sex, and multiple sclerosis as risk factors.

We tested the accuracy of our models in various ways. In terms of the ability to discriminate between patients who did and who did not sustain a fracture, both models performed reasonably well with a C-statistic of 0.67 for the prediction of osteoporotic fracture and 0.89 for the prediction of hip fracture. In addition, we investigated the concordance between predicted and actual probabilities, i.e., the calibration of the model. This was done by a 10-fold cross-validation; the shrinkage factors were close to 1. Overall, the predictive accuracy of our models was good, as tested by internal validation.

Our study has many advantages. As far as we know, we are the first to provide a clinical risk score for fracture risk estimation involving MS as a risk factor. Our data are representative of the total UK population, and we had detailed longitudinal information on drug prescribing and other risk factors for fracture, such as history of falling, low BMI, and smoking status.

There are some limitations, however. The predicted long-term risks of fracture vary between 0 and 1. This raises the issue of selecting an optimal cutoff point to determine which patients would, for example, be candidates for BMD screening or pharmacologic treatment. This cutoff value depends on a complex benefit-risk assessment and on individual perception of risk and was not investigated in the present study. The first symptoms of MS can arise several years before MS is diagnosed, and, therefore, the date of diagnosis as recorded on the GPRD is not entirely reliable. We did not have routinely collected information on the degree of disability in patients with MS. Vitamin D levels were not routinely col-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lected. Moreover, GPRD does not routinely collect BMD measurements, and we had no information on parental history of fracture (which is included in FRAX as a risk factor). The number of vertebral and rib fractures recorded in this study is probably underreported. The true risks of osteoporotic fracture may therefore be greater than reported in our study. The risk score that we developed is preliminary in the sense that it should be validated in an external population.[30] Another limitation is that the predicted risks are based on a single measurement of risk factors, with the underlying assumption that risk factors do not change over time. Obviously, this assumption is not true for many risk factors. Because of a relatively low number of osteoporotic and hip fractures among patients with MS, we built our model with data from patients with MS and their control subjects. A score that would be based on data from only patients with MS would be a valuable addition to this field, but a larger group of patients would then be needed. From all 5,494 patients with MS, there were 1,011 patients with more than 10 years of follow-up. Therefore, the predicted 10-year fracture risks are based on a subset of our cohort.

Overall, this is the first clinical risk score for fracture risk estimation involving MS as a risk factor. Our score may be a starting point for the communication of an individual's fracture risk in patients with MS.

## AUTHOR CONTRIBUTIONS

Marloes T. Bazelier: study concept/design, analysis/interpretation of data, statistical analysis, drafting/revising the manuscript for content. Tjeerd-Pieter van Staa: study concept/design, analysis/interpretation of data, statistical analysis, drafting/revising the manuscript for content, study supervision or coordination. Bernard M.J. Uitdehaag: study concept/design, drafting/revising the manuscript for content. Cyrus Cooper: study concept/design, drafting/revising the manuscript for content. Hubert G.M. Leufkens: study concept/design, drafting/revising the manuscript for content, study supervision or coordination Peter Vestergaard: study concept/design, drafting/revising the manuscript for content. Joan Bentzen: study concept/design, drafting/revising the manuscript for content. Frank de Vries: study concept/design, analysis/interpretation of data, statistical analysis, drafting/revising the manuscript for content, study supervision or coordination, obtaining funding.

## DISCLOSURE

M. Bazelier reports no disclosures. T.-P. van Staa also works for the General Practice Research Database (GPRD), UK. The GPRD is owned by the UK Department of Health and operates within the Medicines and Healthcare Products Regulatory Agency (MHRA). GPRD is funded by the MHRA, Medical Research Council, various universities, contract research organizations, and pharmaceutical companies. B.M.J. Uitdehaag has received honoraria for consultancy from Novartis, Merck Serono, and Synthon. C. Cooper, H.G.M. Leufkens, P. Vestergaard, J. Bentzen, and F. de Vries reports no disclosures. **Go to Neurology.org for full disclosures.**

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