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No decrease in fracture risk despite 15 years of treatment evolution for multiple myeloma patients: A Danish nationwide case-control study

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ABSTRACT

Rationale: While treatment strategies for multiple myeloma have evolved radically over the last decades, little is known about the risk of fractures for symptomatic multiple myeloma patients over time.
Objective: To determine the effect of different treatment periods (1996–2000, 2001–2006 and 2007–2011) on the risk of fractures in patients with multiple myeloma.
Methods: This retrospective case-control study included patients with multiple myeloma in Denmark, using the Danish National Health Service. Cases were defined as patients who had sustained a fracture between 1996 and 2011, and controls were those without a fracture. Exposure was defined as an ICD code for multiple myeloma. Vertebral fractures, gender, and age were considered in secondary analyses. Conditional logistic regression was used to estimate odd ratios (ORs) of fracture risk, and the analyses were adjusted for comorbidities and recent drug use.
Results: The study population consisted of 925,341 cases, and the same number of matched controls, of whom 1334 patients with multiple myeloma. Among cases, the risk of any fracture was higher in multiple myeloma patients compared to patients without multiple myeloma (any fracture: OR_{adj}[95% CI] 1996–2000: 1.7[1.3–2.3]; 2001–2006: 1.3[1.1–1.6]; 2007–2011: 1.7[1.4–2.2]). Although fractures were mainly non-vertebral, the risk of vertebral fractures in particular was higher in multiple myeloma patients (vertebral fracture: OR_{adj}[95% CI] 1996–2000: 3.5[1.4–8.6]; 2001–2006: 4.0[1.9–8.2]; 2007–2011: 3.0[1.6–5.7]).
Conclusions: Despite new treatment strategies and improved supportive care, this study showed no decreased fracture risk for multiple myeloma patients over time. New treatment strategies, even if they have a positive impact on overall survival, offer no guarantee for a corresponding reduction in bone lesions.

Abbreviation: MM, multiple myeloma

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1. Introduction

Bone lesions are one of the primary symptoms in multiple myeloma (MM), and it has been suggested that these lesions adversely impact overall survival (OS). [1–6] Approximately 80% of the patients experience a pathological fracture at initial presentation or during the course of the disease, [4,7] particularly axial fractures of the vertebrae. [7] While the risk of fractures in patients diagnosed with monoclonal gammopathy of undetermined significance (MGUS) has been investigated in several studies, [8–11] little is known about the risk of fractures in symptomatic MM patients. One study with 165 symptomatic patients found a 9-fold increase in overall fracture risk after the diagnosis of MM, compared to expected rates. [7]

Over the last decades, treatment strategies for MM have evolved radically, from melphalan-and anthracycline-based regimes before 2000, to combinations with more novel agents after 2000, such as the immunomodulatory agents (IMiDs) and the proteasome inhibitors (PI). Corticosteroids are still considered the backbone of every treatment schedule. However, corticosteroids reduce bone mineral density and can cause osteoporosis, thus increasing fracture risk. [12,13] In the late 1990s, bisphosphonates were introduced to prevent bone resorption by osteoclasts, and they have shown to be effective in reducing pathological vertebral fractures in MM patients. [4,14] Combinations with IMiDs and/or PI improve disease-free survival and OS in MM patients, [15,16] but their role in the prevention of pathological fractures has not yet been established. Bortezomib and the IMiDs may have the capacity to stimulate bone formation, [17–22] but reduction in skeletal morbidity has not been demonstrated yet. We hypothesized that the improved treatment strategies and supportive care, including the use of bisphosphonates, reduced the overall fracture risk in MM patients. The aim of this nation-wide population-based study was to determine time trends in the risk of any fracture in MM patients (1996–2011). Secondary objectives were to determine the risk of vertebral fractures, and the effects of gender and age on the occurrence of fractures.

2. Methods

2.1. Source population

A population-based case-control study was performed using the Danish National Health Service. This register covers all contacts to general practitioners, and includes approximately 5.2 million individuals in 1995 and 5.5 million in 2011. [23] The National Hospital Discharge Register, which was established in 1977, contains all inpatient contacts to hospitals. Since 1995, outpatient visits to hospitals, clinics and emergency rooms are incorporated into the register. It contains administrative data and clinical data, including diagnoses and surgical procedures, with high precision for diagnoses, particularly for fractures. [24] All diagnoses are coded using the International Classification of Diseases and Related Health Problems (ICD) version 8 ($<$ 1994) and 10 ($\geq$ 1994). The Danish Medicines Agency Register gathers information on prescriptions for refundable drugs by using the Anatomical Therapeutic Chemical Classification (ATC) system (from 1996 onward) in the Medicinal Product Statistics database. By using the civil registry number that is assigned to all Danish citizens, the registers can be linked. [25]

Ethical approval for this study was obtained from the National Data Protection Agency (project number 703381), and the study was approved by Statistics Denmark and the National Health Data Administration (Sundhedsdatastyrelsen).

2.2. Study population/endpoints

Cases were defined as patients aged 18 years and older, who had sustained a fracture between January 1996 and December 2011. For each case, one control patient (without a fracture) was matched by gender and year of birth using incidence-density sampling. [26] The date of the first fracture defined the index date for cases, and matched controls were assigned the same index date. Any fracture was determined by the following ICD-10 codes: S02, S12, S22, S32, S42, S52, S62, S72, S82, S92, T02, T08, T10 and T12. Fractures of the vertebrae were identified with the ICD-10 codes S12, S22.0-S22.1, S32.0-S32.2, S32.7, S32.8, and T08. Both according to the World Health Organization's (WHO) definition.

2.3. Exposure

According to the European Medicines Agency, thalidomide and lenalidomide received an orphan designation for the treatment of multiple myeloma in 2001 and 2003, respectively. The official EU marketing authorization of thalidomide, bortezomib, and lenalidomide was in 2008, 2004, and 2007, respectively [27–29]. Also, based on the information received by the Danish Myeloma Study Group, treatment of MM was, to the best of our knowledge, based on the first guideline from the UK in 2001, the UK/Nordic Myeloma Study Group guideline from 2005, and the Danish guideline from 2011 [30–32]. Therefore, we defined three time periods as exposure to different treatment strategies, and case-control pairs were classified by year of index date: 1996–2000, 2001–2006 and 2007–2011. Hereby, between 1996 and 2000 new treatment modalities were not yet available for MM, between 2001 and 2006 all agents were used in clinical trials and became part of regular treatment, and after 2006, all agents were available for the treatment of MM.

Individuals without an ICD code for MM (C.90.0) before the index date were used as the reference category in all analyses.

2.4. Covariates

Table 1 shows the identified comorbidities before the index date, and potential confounders including a dispensing within 6 months before the index date of the drugs listed.

2.5. Statistical analysis

Conditional logistic regression was used to estimate odds ratios (ORs) for fracture risk (SAS 9.4). In multivariable analyses, potential confounders were included if they independently changed the beta-coefficient for MM exposure by at least 5%, or when consensus about inclusion existed within the team of researchers, supported by clinical evidence from literature. No correction was performed for factors that were strongly linked to the disease itself, such as the use of oral corticosteroids. Analyses were performed for each time cohort, and diagnosis of MM. Separate models were run for any fracture (primary outcome), vertebral fractures, age, and gender. Between group differences were evaluated via a test for interaction estimating the ratio of the odds ratios. [33] All results were presented as OR with corresponding 95% confidence intervals (CIs).

3. Results

3.1. Study population

The study population consisted of 925,341 cases, and the same number of matched controls. The number of cases, and controls, in the treatment periods 1996–2000, 2001–2006, and 2007–2011 was 351,616; 327,612; and 246,113; respectively. The distribution of several risk factors between cases and controls is shown in Table 1. The mean age in each time cohort was 53 (SD 21.9), 54 (SD 21.1), and 55 (SD 20.6) years, and 53.0, 54.0, and 55.6% were women, respectively. The proportion of cases with a history of fractures before 1996 was higher compared to controls in each time cohort (27.0 vs. 9.1%, 22.8 vs. 7.5%, and 20.3 vs. 6.8%, respectively).

Table 1
Baseline characteristics of Danish citizens with a fracture (cases), and matched citizens without a fracture (controls).

Characteristic	1996–2000				2001–2006				2007–2011			
	Cases (n = 351,616)	(%)	Controls (*n* = 351,616)	(%)	Cases (n = 327,612)	(%)	Controls (*n* = 327,612)	(%)	Cases (*n* = 246,113)	(%)	Controls (n = 246,113)	(%)
Women	186,483	(53.0)	186,483	(53.0)	176,914	(54.0)	176,914	(54.0)	136,766	(55.6)	136,766	(55.6)
Mean age at index date (years, SD)	53	(21.9)	53	(21.9)	54	(21.1)	54	(21.1)	55	(20.6)	55	(20.6)
− 49 years	165,683	(47.1)	165,695	(47.1)	139,757	(42.7)	139,756	(42.7)	97,384	(39.6)	97,390	(39.6)
50–59 years	50,285	(14.3)	50,293	(14.3)	52,577	(16.0)	52,618	(16.1)	40,024	(16.3)	39,977	(16.2)
60–69 years	37,797	(10.7)	37,808	(10.8)	43,561	(13.3)	43,520	(13.3)	41,387	(16.8)	41,436	(16.8)
70–79 years	44,758	(12.7)	44,741	(12.7)	41,101	(12.5)	41,172	(12.6)	31,078	(12.6)	31,071	(12.6)
≥ 80 years	53,093	(15.1)	53,079	(15.1)	50,616	(15.4)	50,546	(15.4)	36,240	(14.7)	36,239	(14.7)
History of comorbidities												
Fractures (prior to 1996)	94,863	(27.0)	31,960	(9.1)	74,795	(22.8)	24,546	(7.5)	49,914	(20.3)	16,675	(6.8)
Rheumatoid arthritis	3922	(1,1)	3133	(0.9)	4489	(1.4)	3317	(1.0)	4223	(1.7)	3071	(1.2)
Inflammatory bowel disease	4705	(1,3)	3728	(1.1)	6704	(2.0)	5255	(1.6)	7089	(2.9)	5476	(2.2)
Secondary osteoporosis[a]	4237	(1.2)	2532	(0.7)	5900	(1.8)	3442	(1.1)	5643	(2.3)	3556	(1.4)
Dementia	4283	(1.2)	2744	(0.8)	5892	(1.8)	3081	(0.9)	5276	(2.1)	2603	(1.1)
Malignancies (excluding non-melanoma skin cancer)	21,517	(6.1)	19,467	(5.5)	25,113	(7.7)	21,816	(6.7)	23,343	(9.5)	19,650	(8.0)
Diabetes mellitus type 2	9488	(2.7)	7733	(2.2)	11,643	(3.6)	8924	(2.7)	10,671	(4.3)	8519	(3.5)
Cerebrovascular disease	17,476	(5.0)	14,028	(4.0)	19,199	(5.9)	13,616	(4.2)	15,789	(6.4)	11,054	(4.5)
Pneumonia	10,558	(3.0)	8200	(2.3)	9121	(2.8)	6866	(2.1)	7584	(3.1)	5766	(2.3)
Gout	804	(0.2)	689	(0.2)	1608	(0.5)	1163	(0.4)	1686	(0.7)	1190	(0.5)
Drug use within 6 months before index date												
Oral corticosteroids	13,438	(3.8)	10,691	(3.0)	14,004	(4.3)	9933	(3.0)	10,092	(4.1)	7303	(3.0)
Bisphosphonates	2660	(0.8)	1530	(0.4)	6349	(1.9)	3437	(1.0)	7803	(3.2)	5177	(2.1)
Vitamin D	4227	(1.2)	3032	(0.9)	4083	(1.2)	3136	(1.0)	3368	(1.4)	2711	(1.1)
Calcium	3690	(1.0)	2360	(0.7)	2967	(0.9)	2070	(0.6)	2029	(0.8)	1485	(0.6)
Selective estrogen receptor modulators	74	(0.0)	34	(0.0)	448	(0.1)	297	(0.0)	228	(0.0)	164	(0.0)
Strontium ranelate	NA		NA		46	(0.0)	17	(0.0)	206	(0.1)	107	(0.0)
Denosumab	NA		NA		NA		NA		NA		NA	
Thyroid therapy	7667	(1.1)	7934	(1.1)	10,131	(1.5)	10,090	(1.5)	9549	(1.9)	9352	(1.9)
Hormone replacement therapy	17,204	(4.9)	20,819	(5.9)	17,564	(5.4)	21,548	(6.6)	12,759	(5.2)	14,982	(6.1)
Antipsychotics	14,635	(4.2)	10,000	(2.8)	13,149	(4.0)	8205	(2.5)	8687	(3.5)	5261	(2.1)
Antiepileptics	8547	(2.4)	3867	(1.1)	9874	(3.0)	4701	(1.4)	8983	(3.6)	4769	(1.9)
Use of non-insulin diabetes mellitus drugs	5878	(1.7)	6371	(1.8)	8472	(2.6)	8358	(2.6)	9077	(3.7)	9210	(3.7)
Antithrombotics	29,753	(8.5)	28,807	(8.2)	44,456	(13.6)	41,127	(12.6)	41,507	(16.9)	38,107	(15.5)
Antiviral agents	1310	(0.4)	1128	(0.3)	2257	(0.7)	2011	(0.6)	2560	(1.0)	2374	(1.0)
Antidepressants	28,750	(8.2)	17,234	(4.9)	40,444	(12.3)	24,208	(7.4)	36,010	(14.6)	21,779	(8.8)
Anti-Parkinson drugs	4362	(1.2)	2754	(0.8)	3797	(1.2)	2091	(0.6)	3381	(1.4)	1941	(0.8)
Hypnotics/anxiolytics	38,090	(10.8)	28,789	(8.2)	34,422	(10.5)	25,732	(7.9)	20,842	(8.5)	15,603	(6.3)
Antihypertensives	74,108	(10.5)	75,224	(10.7)	88,455	(13.5)	86,520	(13.2)	78,641	(16.0)	77,189	(15.7)
Inhaled cromoglycates	30	(0.0)	35	(0.0)	7	(0.0)	21	(0.0)	NA		NA	
Inhaled corticosteroids	17,439	(5.0)	16,501	(4.7)	17,083	(5.2)	15,882	(4.8)	NA		NA	
PPI	12,524	(3.6)	9043	(2.6)	23,460	(7.2)	16,786	(5.1)	27,880	(11.3)	20,740	(8.4)
Xanthine derivatives	3406	(1.0)	3131	(0.9)	1748	(0.5)	1300	(0.4)	544	(0.2)	389	(0.2)

[a] Secondary osteoporosis defined as a diagnosis of diabetes type 1, hypogonadism or premature menopause.

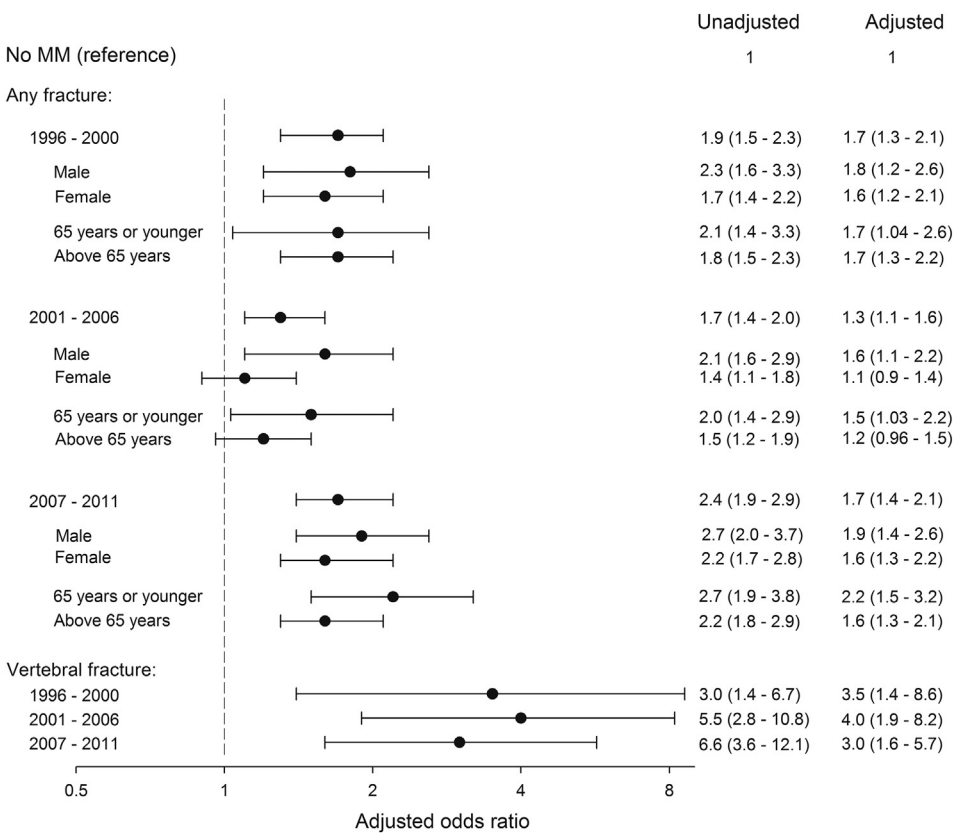

Fig. 1. Odds ratio of any fracture by treatment period, gender, and age, and vertebral fracture by treatment period. The ORs of any fracture were adjusted for the use of antidepressants, bisphosphonates, antiepileptics, hypnotics, proton pump inhibitors in the past 6 months, malignancies, and fractures prior to 1996. The ORs of vertebral fractures were adjusted for the use of antidepressants, antipsychotics, bisphosphonates, calcium, proton pump inhibitors in the past 6 months, malignancies, and fractures prior to 1996.

3.2. Risk of any fracture

A total of 1334 MM patients were enrolled in the study, of whom 881 patients with a fracture, and 453 MM patients without a fracture. For each study period, 268 and 142 (1996–2000), 284 and 171 (2001–2006), and 329 and 140 (2007–2011) cases and controls with MM were identified, respectively. Fig. 1 shows that the risk of any fracture was elevated in MM patients compared to patients without MM during the whole study period, especially in the first and last treatment period (OR_{adj} [95% CI] 1996–2000: 1.7 [1.3 to 2.1]; 2001–2006: 1.3 [1.1 to 1.6]; 2007–2011: 1.7 [1.4 to 2.2]).

3.3. Influence of sex and age on bone fractures

As expected, [34] the absolute numbers of fractures in female MM patients and patients aged > 65 years were higher than in male MM patients and younger patients (data not shown). However, the relative risk of any fracture was equally elevated for male or female MM patients in the three different time cohorts (male: OR_{adj} [95% CI] 1996–2000: 1.8 [1.2 to 2.6]; 2001–2006: 1.6 [1.1 to 2.2]; 2007–2011: 1.9 [1.4 to 2.6], and female: OR_{adj} [95% CI] 1996–2000: 1.6 [1.2 to 2.1]; 2001–2006: 1.1 [0.9 to 1.4]; 2007–2011: 1.6 [1.3 to 2.2]), as well as for MM patients aged ≤65 or > 65 years (≤65 years: OR_{adj} [95% CI] 1996–2000: 1.7 [1.04 to 2.6]; 2001–2006: 1.5 [1.03 to 2.2]; 2007–2011: 2.2 [1.5 to 3.2], and > 65 years: OR_{adj} [95% CI] 1996–2000: 1.7 [1.3 to 2.2]; 2001–2006: 1.2 [0.96 to 1.5]; 2007–2011: 1.6 [1.3 to 2.1], see Fig. 1).

3.4. Risk of vertebral fractures

For vertebral fractures (34,714 cases with 34,714 matched controls), the numbers of cases and controls with MM in each time cohort was 24 and 8 (1996–2000), 55 and 10 (2001–2006), and 80 and 13 (2007–2011), respectively. These numbers accumulated into an even higher risk in MM patients for vertebral fractures compared to patients without MM (OR_{adj} [95% CI] 1996–2000: 3.5 [1.4 to 8.6]; 2001–2006: 4.0 [1.9 to 8.2]; 2007–2011: 3.0 [1.6 to 5.7], see Fig. 1).

4. Discussion

This long-term study showed that fracture risk, especially of the vertebrae, was much higher in MM patients than in the general population. Although we hypothesized that improved treatment strategies might reduce fracture risk in MM patients, we did not observe a reduction in fractures. The risk of any fracture was equally high in male or female MM patients, and patients aged ≤65 or > 65 years.

The higher fracture risk in MM patients found in this study confirms previous results, [7] where a 9-fold increase in overall fracture risk was found compared to expected rates from 10 years before the diagnosis of MM. From experience in daily practice, supported by two studies, [4,7] we know that vertebral fractures are more common in MM patients than in the general population. Indeed, the relative risk of vertebral fractures in our study is much higher than the risk of non-vertebral fractures, but in absolute numbers, more non-vertebral fractures than vertebral fractures occur in MM patients. As most fracture studies in MM patients focus on vertebral fractures, [35–39] it is probable that non-vertebral fractures are underreported, and awareness of non-vertebral fractures in MM patients is warranted.

Although all treatment periods show a higher risk of any fracture in MM patients, it is possible that in the first treatment period patients did not yet receive bisphosphonates. Once bisphosphonate therapy became more common from the second treatment period onwards, improvement of fracture risk was expected. Indeed, there does appear to be at least a trend towards a reduction of any fracture risk, and it is tempting to speculate that this is a consequence of bisphosphonate therapy. However, from the third treatment period any fracture risk appears to have worsened again. Furthermore, even though the increase in absolute numbers of vertebral fractures could be explained by the use of

better imaging modalities, the relative risk of vertebral fractures remains uniformly high throughout the three treatment periods.

One explanation for the sustained fracture risk could paradoxically be the improved OS in MM patients, [15,16,40] due to being longer at risk of sustaining a fracture. In addition, the new treatment modalities provide options to use more cycles with different drugs, or maintenance therapy. For example, thalidomide and bortezomib are known to cause peripheral neuropathy. The more intense treatment strategies could induce tingling or numb feelings in the extremities, making patients more susceptible to falling. Another explanation could be the reduction of bone density due to the use of corticosteroids. Indeed, the use and dosage of corticosteroids has not changed markedly during the study period. [12,13] One study found that lower doses of dexamethasone are equally effective and decrease toxicity, [41] but further studies are needed to investigate optimal dosing regimens for corticosteroids, balancing efficacy and toxicity. Although bisphosphonates are nowadays given for a longer duration of time compared to the 90s, this apparently did not result in a decrease in fractures on population level over time. Also, the incidence of atypical femoral fractures is associated with prolonged bisphosphonate use [42]. In addition, treatment with bisphosphonates is often suboptimal, especially in patients with impaired renal function, or the elderly. [43,44]

Our findings imply that there is still a strong clinical need for new bone-sparing strategies in the treatment of MM, such as anti-resorptive therapies (e.g. denosumab), anabolic therapies (e.g. teriparatide, romosozumab), anti-DKK1 antibodies, or a combination of sequenced agents, demonstrating benefit in osteoporosis patients [45]. Therefore, in the effort to optimize treatment to control MM, and improve progression-free survival and OS, also other clinical challenges, including fractures should be taken into account.

The major strength of our study was the large number of cases and controls, and the long follow-up. By using this nationwide population-based register with approximately 5 million anonymized patient records from Denmark, this study provided a representative and complete overview of bone fractures in the Danish population. In addition, the data used to identify fractures have been validated, [26] and we were able to adjust for many potential confounders. However, some limitations need to be mentioned. First, exposure to chemotherapy and/or immunomodulatory agents, radiotherapy, stem cell transplantation, and intravenous bisphosphonates was unknown, as the administration of in-hospital drugs is not linked to the register. Therefore, the follow-up time was divided in three-time periods, based on treatment availability. Second, some potential confounders could not be taken into account, such as ISS stage, CRAB criteria, BMI, smoking, amount of exercise, or serum vitamin D levels, but we expect this to be equal for all groups. Last, diagnostic bias could have occurred, as MM patients are supervised more intensely by a physician than patients without MM.

In conclusion, despite new treatment strategies and improved supportive care, there was no decreased fracture risk for MM patients. It is thus crucial for physicians to be aware of the ever-elevated fracture risk in MM patients, especially of the vertebrae. Further steps are necessary to reduce fracture risk, and at the same time, to improve the OS of these patients. New treatment strategies, even if they have a positive impact on OS, offer no guarantee for a corresponding reduction in bone lesions.

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Author contribution

Berdien Oortgiesen: Conceptualization, Methodology, Validation, Investigation, Writing - Original draft, Visualization. **Johanna Driessen**: Methodology, Formal analysis, Writing - Review & Editing. **Mels Hoogendoorn**: Conceptualization, Validation, Writing - Review & Editing. **Robby Kibbelaar**: Conceptualization, Writing - Review & Editing. **Nic Veeger**: Methodology, Writing - Review & Editing, Visualization. **Joop van den Bergh**: Conceptualization, Resources. **Peter Vestergaard**: Conceptualization, Resources. **Frank de Vries**: Conceptualization, Methodology, Resources, Writing - Review & Editing. **Eric van Roon**: Conceptualization, Methodology, Validation, Writing - Review & Editing, Supervision.

Declaration of competing interest

BO, JD, MH, RK, NV, PV and ER declare that they have no conflicts of interest. JB reports grants and personal fees from Eli Lilly, grants and personal fees from Amgen, and personal fees from Sanofi, outside the submitted work. FV currently supervises a PhD student who is also employed with F. Hoffmann la Roche Ltd., Basel Switzerland. He has not received any reimbursements for this, and the student's research topics are not related to this publication.

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