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Biological disease-modifying anti-rheumatic drugs and spinal fractures related to ankylosing spondylitis

National multi-registry cohort study from the Swedish Patient Registry and the Swedish Prescribed Drugs Registry

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Key Points

Question: Do biological disease-modifying anti-rheumatic drugs (bDMARD) reduce the spinal fracture risk related to ankylosing spondylitis (AS)?

Findings: In this national registry cohort study in 12,297 patients with AS 2005 to 2014 no significant effect of bDMARD treatment on the incidence of a spinal fracture 2011 to 2014 was found.

Meaning: bDMARD treatment did not reduce the spinal fracture risk for patients with AS. Therefore, the current activity restrictions for AS patients must remain despite improved medical treatment.

Abstract (≤300 words)

Objectives

Ankylosing spondylitis (AS) is associated with an increased spinal fracture risk due to loss of elasticity in spinal motion segments. With the introduction of biological disease modifying anti-rheumatic drugs (bDMARD) treatment for AS the individual course of the disease has been decelerated. This study aims to clarify whether the improved medical therapy reduced the spinal fracture incidence.

Design

Population based multi-registry study

Setting

Swedish Patient Registry 1987 to 2014 and Prescribed Drugs Registry 2005-2014

Participants

Included were all patients with the primary diagnosis of AS at an age between 40 and 70 years, receiving treatment at a healthcare facility between 2005 to 2014.

Interventions

From the Swedish Prescribed Drug Registry the Anatomical Therapeutic Chemical codes for bDMARD, non-steroidal anti-inflammatory drugs (NSAID), methotrexate (MTX) and sulfasalazine were extracted and numbers of prescriptions and years of treatment counted since 2005.

Results

12,297 patients with ankylosing spondylitis were treated between 2005 and 2014 (age 67±19, 67% male). Of these **294** had spinal fractures between 2011 and 2014. 59% were diagnosed with AS in conjunction to their first spinal fracture. The number of prescriptions of bDMARD increased during the last decade, but not of MTX, sulfasalazine and NSAID. 64% of all AS patients used NSAID, 13% used bDMARD, 13% used MTX, and 10% used sulfasalazine. **Spinal fractures occurred after a time from AS diagnosis of median of 9 years (95% C.I. 9-10) with bDMARD treatment (n=1289) and after 11 years (95% C.I. 10-11) without (n=5287). No relevant effect of years of bDMARD treatment on the fracture-free survival from diagnosis or birth was identified.**

Conclusion

Biological DMARD treatment did not reduce spinal fracture risk related to AS. Therefore, the activity restrictions for patients with AS should not be changed based on the medical bDMARD treatment.

Trial registration: ClinicalTrials.gov, Identifier NCT02840695.

Article summary: strengths and limitations of this study

- The national multi-registry approach provides nationwide coverage of prescriptions since 2005 and ankylosing spondylitis and spinal fracture incidence since 1987.
- Drugs administrated to in-patients or specialised hospital-bound clinics are not registered in the Prescribed Drugs Registry (PDR), where only out-patient prescriptions are registered.
- Most patients (59%) received their AS diagnosis in conjunction to their first spinal fracture. These patients could not benefit from bDMARD since ankylosis was already accomplished.
- Since a long-term effect of anti-rheumatic treatment is to be assumed, a longer observation period of this cohort could validate the presented results.

Introduction

Ankylosing spondylitis (AS) is a rheumatoid disease affecting all joints of the axial skeleton, leading to a progressive fusion of all spinal segments.[1] Due to the unfavourable biomechanics, risk of falls, and AS-related osteoporosis the spine in AS is prone to fractures even in minor trauma.[2]

Currently, there is no evidence for the efficacy of glucocorticoids, sulfasalazine and methotrexate for the treatment of axial AS.[3] NSAID are recommended as first-line drug treatment for AS patients with pain and stiffness. For patients with persistently high disease activity despite conventional treatments biological disease modifying anti-rheumatic drugs (bDMARD) therapy is recommended.

The bDMARD group consist mainly of anti-TNF-α pharmaceuticals which all have proven effect with regard to pain, function, quality of life and inflammation compared to placebo.[4] Beyond that, bDMARD increase bone density which is of great importance with regard to the spinal fracture risk.[5 6]

Given the beneficial effects of bDMARD treatment a reduced spinal fracture rate could be anticipated in patients receiving modern anti-rheumatic therapy.[7]

This study is designed to investigate whether bDMARD treatment reduces the spinal fracture risk related to AS.

Methods

Study Design

This national multi-registry cohort study uses prospectively collected electronic healthcare data from the Swedish National Patient Registry (NPR), the Swedish Cause of Death registry (CDR), and the Swedish Prescribed Drugs Registry (PDR) between 2005 and 2014. The study protocol was approved by the Institutional Ethical Review Board (no. 2015/147), registered with ClinicalTrials.gov (NCT02840695), and follows STROBE and RECORD statements.[8 9]

Setting

The Swedish National Patient Registry (NPR) is hosted by the Swedish National Board of Health and Welfare and contains all patient contacts within Sweden with a coverage of >90% for orthopaedic diagnoses.[10] Registered are main diagnosis and co-morbidity using ICD-9 until December 1996, and since then the ICD-10 code.[11] Treatment is coded since 1997 using the Swedish classification of surgical procedures.[12] Furthermore, information on hospitalisation time is available from the registry. **Since 2005 even outpatient / primary care contacts were included in the NPR.[13]**

Data collection for the Swedish Prescribed Drugs Registry (PDR) is administered by the National Corporation of Swedish Pharmacies, a governmental institution responsible for the provision of pharmaceutical services in the whole country. Since July 1st, 2005 information from all prescriptions dispensed is monthly transferred to the Centre for Epidemiology at the National Board of Health and Welfare, responsible for keeping the registry.[14] The PDR uses Anatomical Therapeutic Chemical (ATC) codes for identification of medication group.

In the Swedish Cause of Death registry (CDR) all incident deaths and cause of death are registered for all patients. A validation of death certificates and CDR registration document **found** 83% agreement for hospital and 46% agreement for non-hospital cause of death.[15]

Participants

All patients registered with the main diagnosis of ankylosing spondylitis treated between January 1st, 1987 to December 31st, 2014 were extracted from the NPR. A

second dataset was provided from the PDR including all prescriptions of anti-inflammatory drugs to patients in the dataset from the NPR between July 1st, 2005 to December 31st, 2014. Prior to data transmission, the Swedish National Board of Health and Welfare anonymised the individual personal identification numbers using a key which remained with the Agency. Since only patients with an active form of AS were of interest for this study, patients younger than 40 and older than 70 years in 2014 were excluded. An inclusion flow diagram according to CONSORT statements illustrated the inclusion protocol.[16]

Variables

The ICD-9 code "720" and **the ICD-10 code "M45"** were used to identify patients with AS in the NPR. From the NPR baseline values as age, gender, date of hospitalisation was collected for each included individual. Additionally, co-morbidity was collected by storing co-incident ICD-9 and ICD-10 codes in each patient's entry. Using ICD-codes the Charlson Comorbidity Index could be calculated for each patient using a previously validated algorithm. [17] Thereafter patients with spinal fractures 2011 to 2014 were identified in the NPR using ICD-10 codes S12.0, S12.1, S12.2, S12.7, S12.8, S12.9, S13.0, S13.1, S13.2, S13.3, S22.0, S22.1, S23.0, S23.1, S32.0, S32.1, S33.0, and S33.1. **Even ICD-10 codes for osteoporotic spinal fractures M80.0A, M80.0J, and M80.0K, and delayed/non-unions M84.0J, M84.0K, M84.1A, M84.1J, M84.1K, M84.2A, M84.2J, M84.2K were included.**

All dates of death of included patients were extracted from the CDR. This allowed censoring of the fracture-free survival analysis using the true dates of death.

To identify anti-inflammatory prescriptions, the PDR was searched for the ATC-codes for bDMARD (L04AA and L04AB), non-steroidal anti-inflammatory drugs (NSAID) (M01A), methotrexate (MTX) (L04AX), and sulfasalazine (A07EC01). Registered were number of prescriptions and years of treatment.

Statistical methods

The age distribution difference of AS patients with spinal fractures treated with and without bDMARD was visualised with a density distribution plot**. Logistic regression analyses identified predictors of bDMARD treatment and spinal fractures 2011-2014. Goodness-of-fit of the model was presented with pseudo-r^2 according to McFadden [18] and the p-value of the Hosmer-Lemeshow test.[19]. The effect of these**

predictors on spinal fracture-free survival was estimated using a Cox proportional hazards model.

The spinal fracture-free proportion by treatment with bDMARD was plotted using a Kaplan-Meier plot with 95% C.I. Proportional group differences were tested with the χ^2-test.

As relevant covariates for the occurrence of a spinal fracture besides years of bDMARD treatment, years of NSAID treatment[2 20], **osteoporosis[21]**, and male gender[22] were identified from systematic literature review.

All statistical calculations were programmed in R version 3.3.0 (R Foundation for Statistical Computing, Vienna, Austria). [23] Mean values were presented ± standard deviation if not indicated otherwise. Groups were compared with t-test for normally distributed variables, otherwise the Wilcoxon-test was applied. Group proportions were tested with the χ2-test. A probability of $p<0.05$ was regarded as statistically significant.

Data access and cleaning methods

The authors did not have direct access to the national registry databases in this study, but were provided a predefined extract from the national registries by the Swedish National Board of Health and Welfare (specification no. 13062/2015).

Even though a clean patient registry dataset was provided, duplicates (recurrent admissions of the same patient or continued treatment in a secondary facility) had to be identified and removed from the extract. Prior to removal of duplicates, comorbidity data from duplicate records was stored in the unique patient record.

From the Prescribed Drugs Registry for each included patient the number of prescriptions 2005 to 2014 was extracted, as well as the number of years 2005 to 2014 when the patient received anti-rheumatic treatment.

Linkage

Individual patients in all three registries were identifiable by unique identification numbers. By searching the patient registry for diagnosis of AS a duplicate-free dataset of all included patients was created. The Cause of Death Registry was linked with this dataset using the MERGE function in R. For each patient in the dataset the number and years of prescriptions were identified after splitting the Prescribed Drugs Registry according to identification number, and then searching for prescriptions. Due to the unique identification number used in all three registries, the linkage quality which was

controlled with 50 random samples was 100%.

Results

Participants

The original registry extract from the NPR contained 142,073 entries with patients with spinal fractures or AS. Of these 12,297 patients with AS were included. The inclusion flow diagram is depicted in figure 1.

Descriptive data

Demographics:

294 patients with AS had a fracture between 2011-2014. Patients with fractures were predominately male (ratio 4:1, p<0.001), slightly older (p=0.010), and more osteoporotic (p<0.004), but had a higher CCI (p<0.001) than those without fracture (Table 1). **For 172 patients (59%) AS was diagnosed within half a year from the first spinal fracture diagnosis**.

Exposures

About 13% of all patients with AS received bDMARD **(Table 2). Those receiving bDMARD were younger (OR=0.95, 95% C.I. 0.93-0.95, p<0.001), rather male (OR=1.13, 96% C.I. 1.00-1.28, p=0.046), osteoporotic (OR=2.00, 95% C.I. 1.23-3.12, p=0.003), had rheumatoid arthritis at a higher rate (OR=2.40, 95% C.I. 1.78-3.21, p<0.001), and received other anti-rheumatic treatment at a higher rate (p<0.01) in a weak logistic regression model (r^2=0.23, Hosmer-Lemeshow p<0.001), where CCI and the history of a spinal fracture had no significant effect.**

Confounders

The AS diagnosis of patients with bDMARD occurred 10±8 years ago, while for those without bDMARD treatment it is 13±9 years ago (p<0.001). Those with bDMARD had a CCI of 2.6±1.9 and those without DMARD had a CCI of 4.7±2.5 (p<0.001). (Table 2)

Outcome data

AS prevalence and Fracture rate

The prevalence of AS registered in the NPR in Sweden was **8587** in 2014 (0.88 ‰) with an annual incidence of 5.84 per 100,000 inhabitants in 2014. The annual spinal fracture

rate related to AS 2011 to 2014 was 73 patients, implying that every year 0.85 ‰ of patients with prevalent AS suffered from a spinal fracture.

Main results

Prescriptions of anti-rheumatic drugs during the last decade

The number of bDMARD prescriptions increased linearly during the last decade from 2% in 2005 to 7% in 2014 (r=0.84, p<0.001). Simultaneously the proportion of MTX- (r=0.56, p<0.001) and sulfasalazine-treated (r=0.77, p<0.001) decreased. The proportion of patients receiving more than 1 year of anti-rheumatic treatment 2005-2014 is presented in tables 1 and 2. Between 2005 and 2014 patients were receiving bDMARD for 4.3±2.9 years, MTX for 3.8±3.0 years, sulfasalazine for 4.0±3.3 years, and NSAID for 5.0±3.0 years.

Fracture free survival and years of bDMARD treatment

1.6% of patients with bDMARD-treatment had a spinal fracture 2011-2014, compared to 2.5% of those without bDMARD treatment (p=0.047) (Table 1). Osteoporosis was most predictive for a spinal fracture 2011-2014 (OR=2.98, 95% C.I.=1.54-5.26, p<0.001), followed by male gender (OR=2.07, 95% C.I.=1.55-2.80, p<0.001) and CCI (OR=1.10, 95% C.I.=1.03-1.17, p=0.003), while the amount of years with bDMARD-treatment had a non-significant trend reducing spinal fractures (OR=0.92, 95% C.I.=0.84-1.00, p=0.081) in the logistic regression model (McFadden pseudo r^2=0.019, Hosmer-Lemeshow p=0.99).

Patients between 40 and 70 years of age receiving bDMARD **(n=24)** had their fracture 2011 to 2014 at a median age of **57.5 years (95% C.I. 52-62),** while those without bDMARD treatment **(n=118)** had their fracture at the median age of 62 years (95% C.I. 60-63**) (Figure 2). The Cox proportional hazards regression model (r^2=0.254, p<0.001) including gender, osteoporosis, and CCI found no effect of years of anti-rheumatic treatment in this group, but of osteoporosis (HR=39.0, 95% C.I. 2.7-562.2, p=0.007) and CCI (HR=0.56, 95% C.I. 0.43-0.72, p<0.001).**

After exclusion of all patients which had their AS diagnosed in conjunction with the spinal fracture, the spinal fracture occurred after a median of 9 years (95% C.I. 9-10) with bDMARD treatment (n=1289) and after 11 years (95% C.I. 10-11) without (n=5287) (Figure 3). The Cox proportional hazards regression model

(r^2=0.06, p=0.43) including gender, osteoporosis, and CCI found no effect of years of anti-rheumatic treatment on the time from diagnosis to fracture.

Discussion

Principal findings

This study documented an increase in the prescriptions of bDMARD for patients with AS during the last decade. Furthermore, **we presented prevalence and incidence of AS and spinal fractures related to AS in a nationwide registry dataset until 2014. Despite the previously documented beneficial effect of bDMARD treatment on bone density, the incidence of spinal fractures was not affected.**

Strengths and weaknesses of this study

Even though registry studies have obvious advantages providing nationwide population data several limitations and sources of bias must be assumed:

One important limitation of this study is the relatively short observation time for the medication data, which is only available since 2005. Since a long-term effect of anti-rheumatic treatment is to be assumed, longer observation periods of this cohort could change the presented results. Therefore, it is mandatory to revisit this cohort in the future to audit our assumptions based on medium-term follow-up.

A major observational error is implicit with the design of the PDR registering only prescribed drugs picked up at pharmacies [14]. Drugs administrated to in-patients or specialised hospital-bound clinics are not registered in the PDR, implying a significant source of bias.[24]

Another limitation of this study is the fact that a prescription and expenditure registered in the PDR does not mean that the patient took his medication. There is abundant data that patients only take about 50% of their prescribed medication.[25] With regard to our study the actual treatment effect was most likely reduced due to this bias.

The changes in the **classification criteria for AS** during the last decade from the modified New York criteria to Assessment of Spondyloarthritis International Society (ASAS) criteria could have led to a gradual change in the demography of registered AS patients.[26] Interestingly, in our cohort most patients (59%) received their first AS diagnosis in conjunction to their first spinal fracture. These patients did not appear in the PDR despite their obvious disease, implying that more than half of our AS patients remain undetected even with the **updated classification criteria**.

One of the peculiarities with AS is the inflammatory interval between the late 20s and the 60s, followed by a rheumatologically asymptomatic but structurally vulnerable phase where an ankylosed spine remains, and the fracture risk is high.[27] Since for more than half of the patients AS was diagnosed at the time of the fracture, these patients would not have benefited from bDMARD since ankylosis was already accomplished. This again could have attenuated the measured effect of bDMARD on spinal fracture risk.

Regional differences in the accessibility of health care in Sweden could delay the primary diagnosis of AS. These data were not included in the registry extract of our study and could not be adjusted for.

The validation of the NPR using other quality registries confirms high validity of registered orthopaedic diagnoses.[10] Diagnoses as hip fractures are correctly identified in more than 95%. Since the NPR was started in the 1960s, a coding learning curve could explain an increasing incidence for most diagnosis groups. Instead, no increasing incidence of lumbar fractures was reported in the NPR during the last decades, which would have been expected if a systematic bias was present.[28] Obviously, the current registration quality is good, and registration bias cannot explain the findings in this study. Besides, the Swedish reimbursement policy requires complete diagnosis registration, an effective incitement to proper coding.

Beyond that, this study presents data from the geographically, health-economically and ethnically specific population in Sweden, which cannot be generalised to other countries' populations. Future studies from national prescription registries in other countries will have to validate our results in their unique setting.

As with most therapeutic registry studies, our results are prone to the selection of an inadequate reference group. It is very likely that those receiving bDMARD have greater access to high quality healthcare and were possibly screened for AS at an earlier age, thus receiving adequate physiotherapy and prevention, while those with less access were possibly diagnosed with AS together with their first spinal fracture when bDMARD treatment is not an option anymore. [29] Thus, bDMARD treatment possibly adds to best practice AS care, while the reference group implies more or less a natural history of disease progression.

In contrast, it would even be possible that patients with bDMARD treatment have a more therapy resistant form of AS and thus receive this still expensive treatment. Those without bDMARD were then relatively symptom free with NSAID treatment. Thus

bDMARD treatment could be associated with a more aggressive course of the disease, biasing the bDMARD group towards worse results. If baseline and outcome measures would have been included in the parametrically adjusted models this bias could be minimised. The growing availability of health related quality of life data will enable these study designs in the near future.

Strengths and weaknesses in relation to other studies

One of the most recognised complications of AS are spinal fractures, which are associated with multiple potentially hazardous complications.[2] Reason for the susceptibility of the ankylosed spine to fractures are long lever arms of the stiff spine,[30] as well as osteoporosis related to this rheumatic disease.[31]

Since the introduction of bDMARD for anti-rheumatic treatment expectations were high for a reduced disease activity, possibly delaying ankylosis. A radiographical study found reduced progression of spinal ankylosis if patients received bDMARD for more than 4 years.[32] The medium-term beneficial effects of bDMARD on the burden of disease of AS are well-documented, and bDMARD are nowadays an important pillar of anti-rheumatic therapy for AS.[4 33] The availability of national registries for disease, mortality and prescriptions allowed now for the first time an investigation of the anti-rheumatic prescription routine and spinal fracture risk of patients with AS with nationwide coverage. For countries like Germany,[34] an increase of prescriptions of bDMARD has been reported during the last decade. A similar trend was found for AS patients in Sweden, which documents adherence to current treatment recommendations.

8% of patients with spinal fracture 2011 to 2014 received bDMARD, compared to 13% of those without fracture (p=0.043). These differences were not found for any other anti-rheumatic medication (Table 1). **When adjusting for covariates as i.e. osteoporosis, this bDMARD treatment effect diminished. Obviously, the beneficial effects of bDMARD on radiographic progression of ankylosis only had a minor effect on the spinal fracture risk related to the unfavourable biomechanics of AS.[21 32]**

Interestingly, other authors found an effect of anti-rheumatic drugs on spinal fracture incidence related to AS. Muñoz-Ortego *et al.*[2] presented Spanish national population based registry data from 2006 in 6474 patients with AS, suggesting regular NSAID-treatment to reduce spinal fracture risk (p=0.02). Unfortunately, they did not include

bDMARD-treatment in their analysis. Vosse *et al.*[20] made similar conclusions from a UK General Practice Research Database extract from 1988 to 1999, where NSAID but not sulfasalazine was associated with a reduced spinal fracture rate related to AS (OR 0.65; 95% CI 0.50-0.84). Here, again bDMARD were not investigated, most likely due to the historical data, when bDMARD treatment was not common practice.

In a prospectively collected cohort of 173 AS patients treated with bDMARD, Maas *et al.*[21] found that during 4 years of bDMARD therapy 20% developed at least one new radiographic vertebral fracture. They found older age, smoking, and osteoporosis at baseline to be associated with the development of new spinal fractures.

In the NPR osteoporosis was registered in only 1.6% of all patients with AS. (n=12,297) In the context of the previously published prevalence of 6% for male and 21% for female between 50 and 84 years of age, we assume an under-reporting of osteoporosis in the NPR.[35]

The meaning of the study

This study suggests that bDMARD has no effect on the risk of spinal fractures related to AS. Therefore, recommendations for physiotherapy and activity restrictions for spinal injury prevention are valid even for patients receiving bDMARD.[36] Since 59% of AS patients with spinal fractures had no previous AS diagnosis registered, AS remains a public health issue, where screening for AS in populations-at-risk has to be weighed against the risks and cost-effectiveness of radiation and laboratory tests.

Unanswered questions and future research

The relatively short available follow-up of 10 years may have underestimated both beneficial and adverse effects of bDMARD. Therefore, follow-up studies on this unique national cohort are recommended to validate the findings in this study. Beyond that, long-term follow-up of available cohorts from randomised placebo-controlled trials on bDMARD treatment [4] could provide important *post hoc* data regarding the treatment effect on spinal fracture incidence and its health-economic implications.

Tables

Table 1: Baseline data of patients with ankylosing spondylitis with and without a spinal fracture between 2011 and 2014

		fracture 2011-2014	no fracture	all	p
	n	294	12003	12297	
age	mean	69	67	67	0.010
	sd	14	17	17	
CCI	mean	5.0	4.4	4.4	<0.001
	sd	2.4	2.5	2.5	
Years with AS	mean	6	13	13	<0.001
	sd	8	9	9	
male	%	80%	66%	67%	<0.001
female	%	20%	34%	33%	<0.001
SCI	%	7%	0%	1%	<0.001
RA	%	3%	3%	3%	0.75
osteoporosis	%	4%	2%	2%	0.004
malignancy	%	6%	8%	8%	0.35
bDMARD	%	9%	13%	13%	0.043
MTX	%	12%	13%	13%	0.84
Sulfasalazine	%	7%	11%	10%	0.11
NSAID	%	68%	64%	64%	0.54

Table 2: Baseline data of patients with and without bDMARD treatment. Presented with p-values of group differences.

		with bDMARD	w/o bDMARD	all	p
	n	1625	10672	12297	
age	mean	53	69	67	<0.001
	sd	13	17	17	
CCI	mean	2.6	4.7	4.4	<0.001
	sd	1.9	2.5	2.5	
Years with AS	mean	10	13	13	<0.001
	sd	8	9	9	
male	%	63%	67%	67%	0.006
female	%	37%	33%	33%	0.006
SCI	%	0.3%	0.7%	0.6%	0.25
RA	%	6%	2%	3%	<0.001
malignancy	%	3%	9%	8%	<0.001
fracture	%	1.6%	2.5%	2.4%	0.043
MTX	%	45%	8%	13%	<0.001
Sulfasalazine	%	27%	8%	10%	<0.001
NSAID	%	88%	61%	64%	<0.001

Figures

Figure 1: Inclusion flow chart

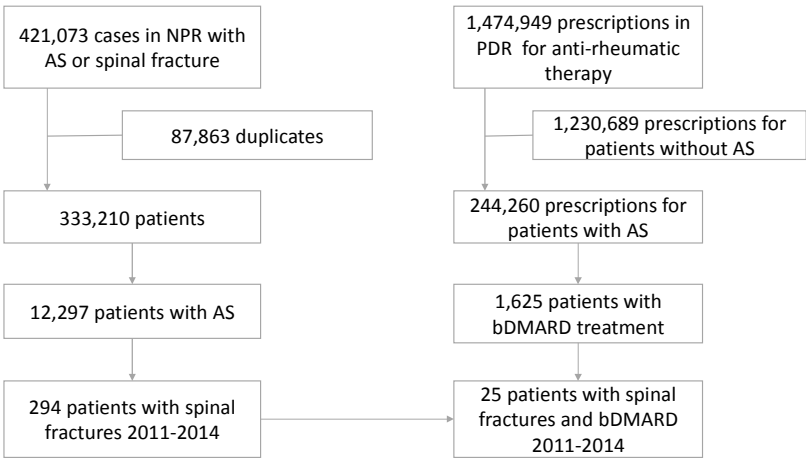
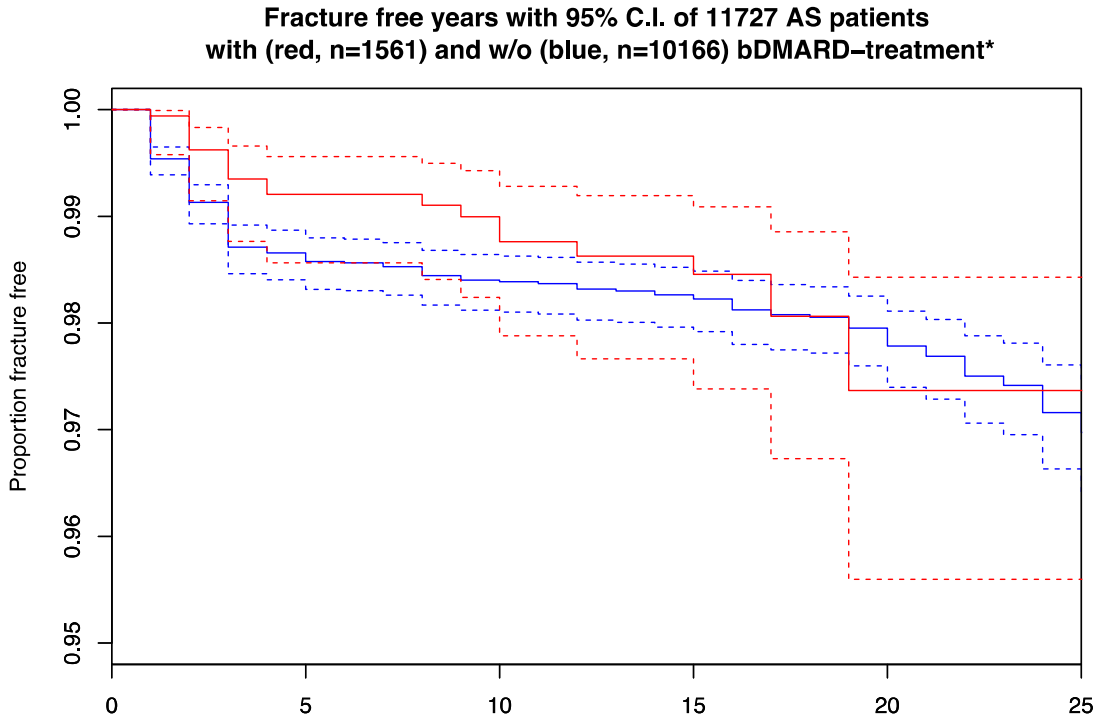


Figure 2: Adjusted survival curves of fracture free years after first AS diagnosis with (red) and without (blue) bDMARD treatment. Patients with AS diagnosis < 1 year ago were excluded. Presented with 95% C.I.



*adjusted for gender, age, osteoporosis, CCI, years of methotrexate–, sulfasalazin–, and NSAID–treatment
*570 patients with recent AS–diagnosis (<1 year) were excluded

Contributorship statement

YR designed the study, analysed the data, and wrote the manuscript. CO supervised the study and revised the final manuscript. JW critically revised the statistical methods and the final manuscript.

Competing interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; YR and CO have been paid for developing and delivering educational presentations for Medtronic Inc. and DePuy Synthes. No other relationships or activities that could appear to have influenced the submitted work.

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Data sharing statement

The Swedish National Patient Registry is hosted by the Swedish National Board of Health and Welfare. Data collection for the Swedish Prescribed Drugs Registry (PDR) is administered by the National Corporation of Swedish Pharmacies. National registry data is available to researchers from the Swedish National Board of Health and Welfare (http://www.socialstyrelsen.se/statistics) after institutional review board approval.

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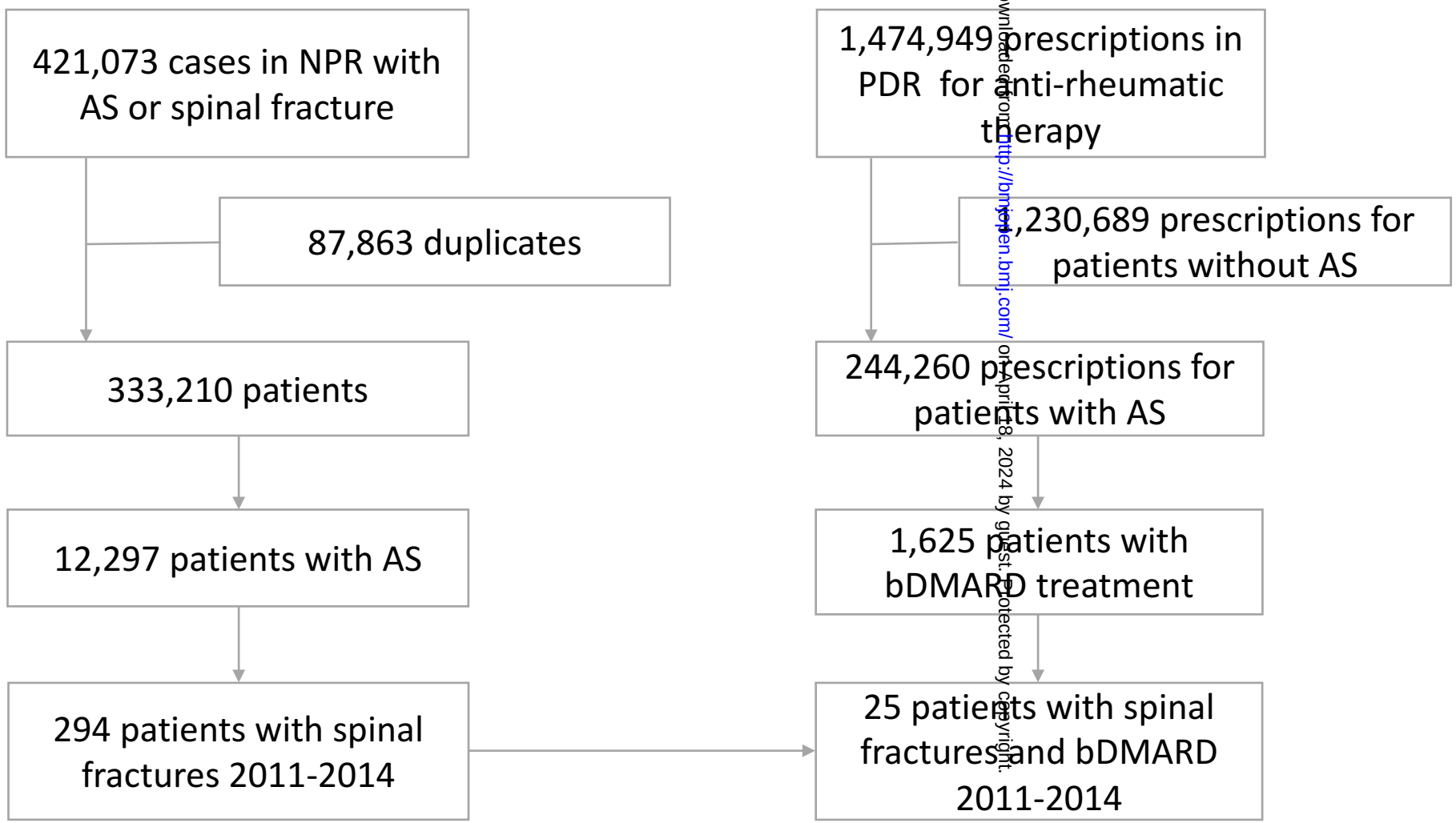
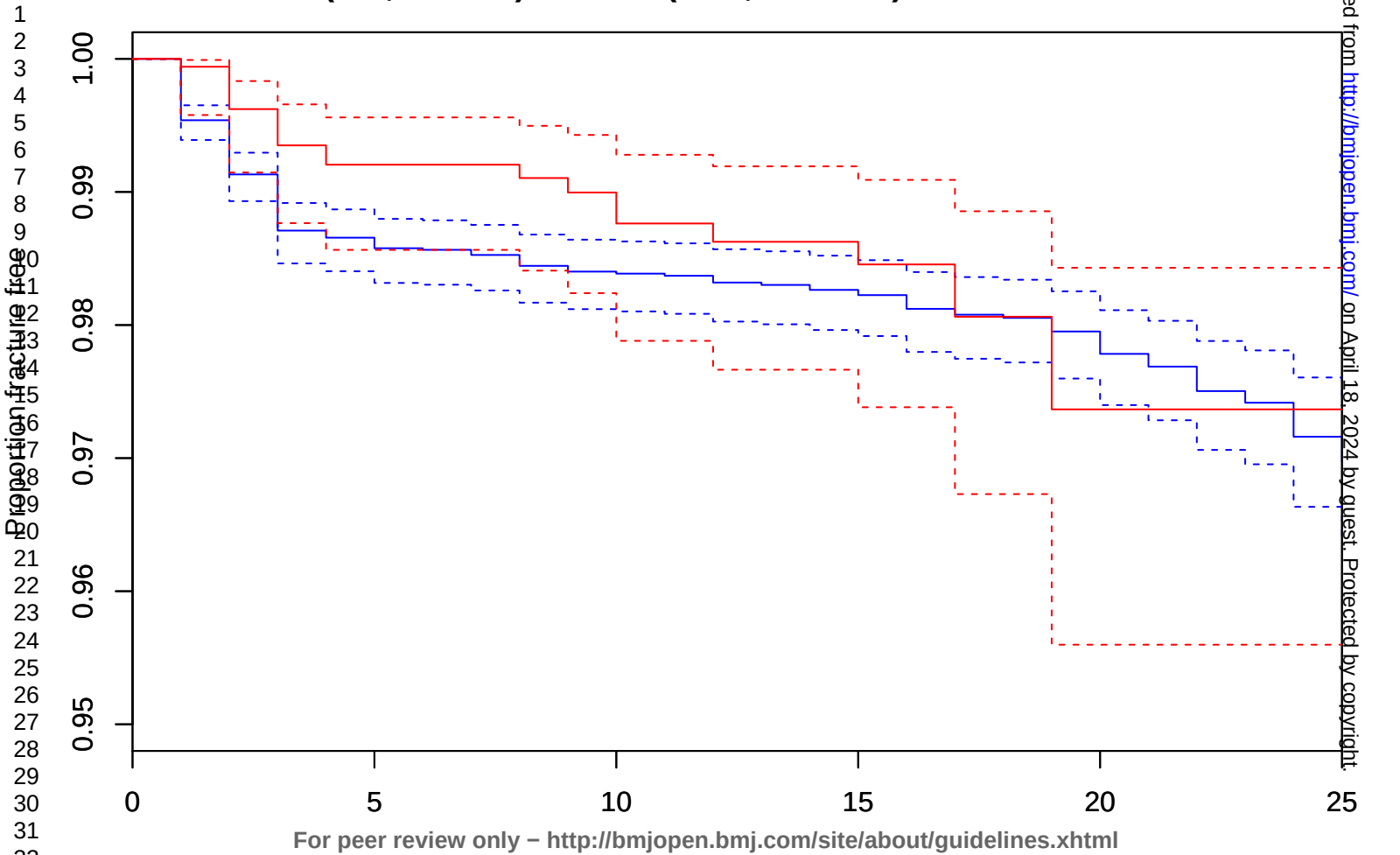


Fracture free years with 95% C.I. of 11727 AS patients with (red, n=1561) and w/o (blue, n=10166) bDMARD−treatment*



*adjusted for gender, age, osteoporosis, CCI, years of methotrexate−, sulfasalazin−, and NSAID−treatment

*570 patients with recent AS−diagnosis (<1 year) were excluded

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	6
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	7
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	7
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	8-9
Bias	9	Describe any efforts to address potential sources of bias	8-9
Study size	10	Explain how the study size was arrived at	
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8
		(*b*) Describe any methods used to examine subgroups and interactions	8
		(*c*) Explain how missing data were addressed	9
		(*d*) If applicable, explain how loss to follow-up was addressed	
		(*e*) Describe any sensitivity analyses	
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	10
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	10
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) Summarise follow-up time (eg, average and total amount)	10
Outcome data	15*	Report numbers of outcome events or summary measures over time	Table 2
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	11
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	11
Discussion			
Key results	18	Summarise key results with reference to study objectives	12
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12
Generalisability	21	Discuss the generalisability (external validity) of the study results	13
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	18

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Do biological disease-modifying anti-rheumatic drugs reduce the spinal fracture risk related to ankylosing spondylitis?

A longitudinal multi-registry matched cohort study

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Abstract (≤200 words)

Objectives

Ankylosing spondylitis (AS) is associated with an increased spinal fracture risk due to loss of elasticity in spinal motion segments. With the introduction of biological disease modifying anti-rheumatic drugs (bDMARD) treatment for AS the individual course of the disease has been ameliorated. This study aims to examine the association of bDMARD treatment and risk of spinal fracture.

Design

Longitudinal population-based multi-registry observational matched cohort study

Setting

Swedish Patient Registry 1987-2014 and Swedish Prescribed Drugs Registry 2005-2014

Participants

Included were patients ≥18 years of age receiving treatment at a healthcare facility for the primary diagnosis of AS. About 1,352 patients received more than one prescription of bDMARD from 2005 to 2014. An untreated control group was created by propensity score matching for age, sex, comorbidity, anti-rheumatic prescriptions, and years with AS (n=1,352).

Main outcome measures

Spinal fracture-free survival

Results

No bDMARD treatment-related effect on spinal fracture-free survival was observed in the matched cohorts. Male gender (HR=2.54, 95% C.I. 1.48-4.36) and Charlson Comorbidity Index score (HR=3.02, 95% C.I. 1.59-5.75) contributed significantly to spinal fracture risk.

Conclusion

Biological DMARD had no medium-term effect on the spinal fracture-free survival in patients with AS.

Trial registration: ClinicalTrials.gov, Identifier NCT02840695.

Article summary: strengths and limitations of this study

- The national multi-registry approach provides nationwide coverage of prescriptions since 2005 and ankylosing spondylitis and spinal fracture incidence since 1987.
- With propensity score matching of treatment and control groups, the bias of the confounders year of birth, sex, comorbidity, years with AS diagnosis, and co-medication was addressed.
- Drugs administrated to in-patients or specialised hospital-bound clinics are not registered in the Prescribed Drugs Registry (PDR), where only out-patient prescriptions are registered.
- Since a long-term effect of anti-rheumatic treatment is to be assumed, a longer observation period of this cohort could change our study results.

Introduction

Ankylosing spondylitis (AS) is a rheumatic disease affecting the axial skeleton, leading to a progressive ankylosis of all spinal segments.[1] Even though not all patients fuse, there is consensus on the end-stage of axial AS – the bamboo-spine – being a pathognomonic radiological feature for this disease.[2] Ankylosis often leads to a rigid kyphotic sagittal profile, where flexibility and segmental lever arm length are comparable to a long bone of the lower extremities.

Due to the unfavourable biomechanics, risk of falls, and AS-related osteoporosis, the spine in AS is prone to fractures even in minor trauma.[3] Spinal injury prevention of patients with an ankylosed spine nowadays comprises of improvement of balance and posture with physiotherapy and rehabilitation. While restriction of certain activities can reduce the risk of spinal fractures in end-stage AS, the proven benefit of training on pulmonary function and quality of life often outweighs these risks.[4]

Currently, there is no evidence for the efficacy of glucocorticoids, sulfasalazine and methotrexate for the treatment of axial AS.[5] NSAID are recommended as first-line drug treatment for AS patients with pain and stiffness. For patients with persistently high disease activity despite conventional treatments biological disease modifying anti-rheumatic drugs (bDMARD) therapy is recommended.

The bDMARD group consist mainly of anti-TNF-α pharmaceuticals which all have proven effect with regard to pain, function, quality of life and inflammation compared to placebo.[6 7] Recently, IL-17A inhibitors have been added to the bDMARD family for the treatment of AS.[8]

The long-term delay of spinal ankylosis and the risk reduction for spinal fractures has not been the primary goal of pharmacological therapy for AS, but several authors indicate that bDMARD treatment has the potential of reducing or delaying spinal ankylosis.[2 9] A radiographical study finds reduced progression of spinal ankylosis if patients receive bDMARD for more than 4 years.[10] Furthermore bDMARD increase bone density which is of great importance regarding the spinal fracture risk.[11 12] Given the beneficial effects of bDMARD treatment a reduced spinal fracture rate could be anticipated in patients receiving modern anti-rheumatic therapy.[13]

This study is designed to investigate whether bDMARD treatment reduces the spinal fracture risk related to AS in national registry-based observational matched cohorts.

Methods

Study Design

This national multi-registry matched cohort study uses prospectively collected electronic healthcare data from the Swedish National Patient Registry (NPR), the Swedish Cause of Death registry (CDR), and the Swedish Prescribed Drugs Registry (PDR) between 2005 and 2014. The study protocol was approved by the Institutional Ethical Review Board (no. 2015/147), registered with ClinicalTrials.gov (NCT02840695), and follows STROBE and RECORD statements.[14 15]

Setting

The Swedish National Patient Registry (NPR) is hosted by the Swedish National Board of Health and Welfare and contains all patient contacts within Sweden with a coverage of >90% for orthopaedic diagnoses.[16] Registered are main diagnosis and co-morbidity using ICD-9 until December 1996, and since then the ICD-10 code.[17] Treatment is coded since 1997 using the Swedish classification of surgical procedures.[18] Furthermore, information on hospitalisation time is available from the registry. Since 2005 even outpatient / primary care contacts were included in the NPR.[19]

Data collection for the Swedish Prescribed Drugs Registry (PDR) is administered by the National Corporation of Swedish Pharmacies, a governmental institution responsible for the provision of pharmaceutical services in the whole country. Since July 1st, 2005 information from all prescriptions dispensed is monthly transferred to the Centre for Epidemiology at the National Board of Health and Welfare, responsible for keeping the registry.[20] The PDR uses Anatomical Therapeutic Chemical (ATC) codes for identification of medication group.

In the Swedish Cause of Death registry (CDR) all incident deaths and cause of death are registered for all patients. A validation of death certificates and CDR registration document found 83% agreement for hospital and 46% agreement for non-hospital cause of death.[21]

Participants

After removal of 18,551 duplicate entries, the original registry extract from the NPR contained 13,112 patients registered with the main diagnosis of ankylosing spondylitis

(AS) treated between January 1st, 1987 to December 31st, 2014. A second dataset was provided from the PDR including 1,474,949 prescriptions of anti-inflammatory drugs to patients in the dataset from the NPR between July 1st, 2005 to December 31st, 2014. Prior to data transmission, the Swedish National Board of Health and Welfare anonymised the individual personal identification numbers using a key which remained with the Agency.

Variables

The ICD-9 code "720" and the ICD-10 code "M45" were used to identify patients with AS in the NPR. From the NPR baseline values as age, gender, date of hospitalisation was collected for each included individual. Additionally, co-morbidity was collected by storing co-incident ICD-9 and ICD-10 codes in each patient's entry. Using ICD-codes the Charlson Comorbidity Index (CCI) could be calculated for each patient using a previously validated algorithm. [22] The factor "CCI score" categorised the level of comorbidity in low (1-3), moderate (4-5), high (6-7), and very high comorbidity (≥8).

Patients with spinal fractures 2005 to 2014 were identified in the NPR using ICD-10 codes S12.0, S12.1, S12.2, S12.7, S12.8, S12.9, S13.0, S13.1, S13.2, S13.3, S22.0, S22.1, S23.0, S23.1, S32.0, S32.1, S33.0, and S33.1. Even ICD-10 codes for osteoporotic spinal fractures M80.0A, M80.0J, and M80.0K, and delayed/non-unions M84.0J, M84.0K, M84.1A, M84.1J, M84.1K, M84.2A, M84.2J, M84.2K were included. Patients with a history of rheumatoid arthritis (ICD-9: 714, ICD-10: M05 and M06) were excluded from the analysis, as they could have received bDMARD treatment for different reasons.

All dates of death of included patients were extracted from the CDR. This allowed censoring of the fracture-free survival analysis using the true dates of death.

To identify anti-inflammatory prescriptions, the PDR was searched for the ATC-codes for bDMARD (L04AA and L04AB), non-steroidal anti-inflammatory drugs (NSAID) (M01A), methotrexate (MTX) (L04AX), and sulfasalazine (A07EC01). Registered were number of prescriptions and years of treatment.

Statistical methods

All statistical calculations were programmed in R version 3.3.0 (R Foundation for Statistical Computing, Vienna, Austria).[23] Patients receiving bDMARD were matched against an untreated control group using the "MatchIT" package. Propensity score matching was performed 1:1 for year of birth, sex, CCI, and years with the diagnosis of

AS, with the hierarchical "nearest" neighbour matching method. Appendix 1 summarised the propensity scores of treatment, matched control, and unmatched control groups. The included participants were grouped according to bDMARD treatment in bDMARD and (untreated) control groups. An inclusion flow diagram according to CONSORT statements illustrated the inclusion protocol.[24]

As relevant covariates for the occurrence of a spinal fracture – besides years of bDMARD treatment, years of NSAID treatment[3 25], and male gender[26] were identified from systematic literature review. The effect of bDMARD on spinal fracture-free survival in the matched cohorts was estimated using a Cox proportional hazards model applying the right-censored type of the "Surv()"-function in the "survival" package in R. Both univariate and multivariate models were developed. Fracture free survival was visualised using a Kaplan-Meier plot adjusted for gender, CCI score and years of bDMARD treatment.

Mean values were presented ± standard deviation if not indicated otherwise. Groups were compared with t-test for normally distributed variables, otherwise the Wilcoxon-test was applied. Group proportions were tested with the χ^2-test. A probability of $p<0.05$ was considered as statistically significant.

Data access and cleaning methods

The authors did not have direct access to the national registry databases in this study, but were provided a predefined extract from the national registries by the Swedish National Board of Health and Welfare (specification no. 13062/2015).

Even though a clean patient registry dataset was provided, duplicates (recurrent admissions of the same patient or continued treatment in a secondary facility) had to be identified and removed from the extract. Prior to removal of duplicates, comorbidity data from duplicate records were stored in the unique patient record.

From the Prescribed Drugs Registry for each included patient the number of prescriptions 2005 to 2014 was extracted, as well as the number of years 2005 to 2014 when the patient received anti-rheumatic treatment.

Linkage

Individual patients in all three registries were identifiable by unique identification numbers. By searching the patient registry for diagnosis of AS a duplicate-free dataset of all included patients was created. The Cause of Death Registry was linked with this

dataset using the "merge()" function in R. For each patient in the dataset the number and years of prescriptions were identified after splitting the Prescribed Drugs Registry according to identification number, and then searching for prescriptions. Due to the unique identification number used in all three registries, the linkage quality which was controlled with 50 random samples was 100%.

Results

Participants

All 1,352 included patients with AS receiving bDMARD were matched with 1,352 controls with AS without bDMARD treatment. The CONSORT inclusion flow diagram is depicted in figure 1.

Descriptive data

All 1,352 patients in the treatment group received bDMARD treatment (6,166 person-years of treatment) and were followed for median 10 years after AS diagnosis (16,567 person-years of observation), while the 1,352 in the control group received no bDMARD treatment more than once (16 person-years of treatment) and were followed for median 8 years (16,189 person-years). Those receiving bDMARD were older (p<0.001), had a higher CCI (p=0.008) and received more methotrexate (p<0.001) than the control group. Of 2,704 patients with AS, 91 had a fracture. The baseline data of the matched cohorts are presented in table 1.

Main results

Patients with bDMARD had a spinal fracture after 12 years with the registered diagnosis AS (95% C.I. 6-12), and those without after 11 years (95% C.I. 5-12). Regarding fracture free survival, no bDMARD treatment effect was observed, neither in the univariate model (HR=1.05, 95% C.I. 0.70-1.59, p=0.80), nor in the multivariate model (HR=1.00, 95% C.I. 0.66-1.51, p=0.99). Instead, male gender (HR=2.54, 95% C.I. 1.48-4.36, p=<0.001) and Charlson Comorbidity Index score (HR=3.02, 95% C.I. 1.59-5.75, p<0.001) contributed significantly to fracture risk. Adjusted survival curves by treatment are presented in figure 2. Table 2 summarises the results from univariate and multivariate Cox proportional hazards regression models.

Discussion

Principal findings

This study analysed in a national multi-registry cohort the spinal fracture risk of all patients with AS treated with bDMARD. No effect of bDMARD treatment on the spinal fracture risk related to AS was found.

Strengths and weaknesses of this study

Even though registry studies have obvious advantages providing nationwide population data, several limitations and sources of bias must be assumed:

One important limitation of this study is the relatively short observation time for the medication data, which are only available since 2005. Since a long-term effect of anti-rheumatic treatment is to be assumed, longer observation periods of this cohort could change the presented results. We strongly recommend revisiting this cohort in the future to audit our assumptions based on medium-term follow-up.

A major observational error is implicit with the design of the PDR – registering only prescribed drugs picked up at pharmacies [20]. Drugs administrated to in-patients or specialised hospital-bound clinics are not registered in the PDR, implying a significant source of bias.[27]

Another limitation of this study is the fact that a prescription and expenditure registered in the PDR does not mean that the patient took his medication. There is abundant data that patients only take about 50% of their prescribed medication.[28] With regard to our study the actual treatment effect could have been reduced due to this bias.

One of the peculiarities with AS is the inflammatory interval between the late 20s and the 60s, followed by a rheumatologically asymptomatic but structurally vulnerable phase where an ankylosed and osteoporotic axial skeleton remains, with a high fracture risk.[29]

Regional differences in the accessibility of health care in Sweden could delay the primary diagnosis of AS. These data were not included in the registry extract of our study and could not be adjusted for.

The validation of the NPR using other quality registries confirms high validity of registered orthopaedic diagnoses.[16] Diagnoses as hip fractures are correctly identified in

more than 95%. Since the NPR was started in the 1960s, a coding learning curve could explain an increasing incidence for most diagnosis groups. Instead, no increasing incidence of lumbar fractures was reported in the NPR during the last decades, which would have been expected if a systematic bias was present.[30] Obviously, the current registration quality is good, and registration bias cannot explain the findings in this study. Besides, the Swedish reimbursement policy requires complete diagnosis registration, an effective incitement to proper coding.

Furthermore, this study presents data from the geographically, health-economically and ethnically specific population in Sweden, which cannot be generalised to other countries' populations. Future studies from national prescription registries in other countries will have to validate our results in their unique setting.

As with most therapeutic registry studies, our results are prone to the selection of an inadequate reference group. It is very likely that those receiving bDMARD have greater access to high quality healthcare and were possibly screened for AS at an earlier age, thus receiving adequate physiotherapy and prevention, while those with less access were possibly diagnosed with AS together with their first spinal fracture when bDMARD treatment is not an option anymore. [31] In contrast, it would even be possible that patients with bDMARD treatment have a more therapy resistant form of AS and thus receive this still expensive treatment. Those without bDMARD were then relatively symptom free with NSAID treatment. Thus, bDMARD treatment could be associated with a more aggressive course of the disease, biasing the bDMARD group towards worse results. We addressed this bias by matching the control group even for years with AS diagnosis.

Strengths and weaknesses in relation to other studies

One of the most recognised complications of AS are spinal fractures, which are associated with multiple potentially hazardous complications.[3] Reason for the susceptibility of the ankylosed spine to fractures are long lever arms of the stiff spine,[32] as well as osteoporosis related to this rheumatic disease.[33]

Interestingly, other authors found an effect of anti-rheumatic drugs on spinal fracture incidence related to AS. Muñoz-Ortego *et al.*[3] presented Spanish national population based registry data from 2006 in 6,474 patients with AS, suggesting regular NSAID-treatment to reduce spinal fracture risk (p=0.02). Unfortunately, they did not include

bDMARD-treatment in their analysis. Vosse *et al.*[25] made similar conclusions from a UK General Practice Research Database extract from 1988 to 1999, where NSAID but not sulfasalazine was associated with a reduced spinal fracture rate related to AS (OR 0.65; 95% CI 0.50-0.84). Here, again bDMARD were not investigated, most likely due to the historical data, when bDMARD treatment was not common practice.

In a prospectively collected cohort of 173 AS patients treated with bDMARD, Maas *et al.*[34] found that during 4 years of bDMARD therapy 20% developed at least one new radiographic vertebral fracture. They found older age, smoking, and osteoporosis at baseline to be associated with the development of new spinal fractures.

The meaning of the study

This study suggests that bDMARD has no medium-term effect on the risk of spinal fractures related to AS. Therefore, recommendations for physiotherapeutic guidance for spinal injury prevention are valid even for patients receiving bDMARD.[35]

Unanswered questions and future research

The follow-up of 10 years may have underestimated both beneficial and adverse effects of bDMARD. Therefore, studies revisiting this unique national cohort are recommended to validate the findings in this study. Beyond that, long-term follow-up of available cohorts from randomised placebo-controlled trials on bDMARD treatment [6] could provide important *post hoc* data regarding the treatment effect on spinal fracture incidence and its health-economic implications.

Tables

Table 1: Baseline data of matched cohorts with and without bDMARD treatment with p-values of group differences.

		bDMARD	Control	p
n		1,352	1,352	
age	years	55 ± 12	53 ± 12	<0.001
female proportion		36 %	36 %	0.689
Charlson Comorbidity Index		2.8 ± 1.8	2.6 ± 1.8	0.008
Time since AS diagnosis	years	12 ± 8	12 ± 8	0.831
Methotrexate	years	6 ± 18	4 ± 11	<0.001
Sulfasalazine	years	4 ± 13	4 ± 13	0.409
NSAID	years	20 ± 19	20 ± 24	0.833

AS: ankylosing spondylitis, bDMARD: biological disease modifying anti-rheumatic drugs, NSAID: non-steroidal anti-inflammatory drugs

Table 2: Fracture free survival of patients with and without bDMARD treatment. Results of univariate and multivariate Cox proportional hazards regression are presented with 95% C.I.

Covariate	categories	#Fractures/#Subjects	#Person-years bDMARD	Univariate HR (95%-C.I.)	p	Multivariate* HR (95%-C.I.)	p
Treatment							
	Control	44/1,352	17	1.00 (Ref)		1.00 (Ref)	
	bDMARD	47/1,352	6,166	1.05 (0.70-1.59)	0.804	1.00 (0.66-1.51)	0.999
Gender							
	Female	16/973	2,050	1.00 (Ref)		1.00 (Ref)	
	Male	75/1,731	4,133	2.54 (1.48-4.36)	<0.001	2.40 (1.40-4.13)	0.002
Charlson Comorbidity Index Score							
	Low (1-3)	51/1,981	4,481	1.00 (Ref)		1.00 (Ref)	
	Moderate (4-5)	28/585	1,430	1.68 (1.05-2.66)	0.028	1.61 (1.02-2.56)	0.043
	High (6-7)	7/94	194	2.70 (1.22-5.95)	0.014	2.55 (1.16-5.63)	0.020
	Very High (≥8)	5/44	78	4.44 (1.77-11.12)	0.001	3.91 (1.55-9.82)	0.004

HR: Hazard Ratio, C.I.: Confidence interval, bDMARD: biological disease modifying anti-rheumatic drugs, Ref: Reference category
*r^2=0.009 (Likelihood ratio test p<0.001, Wald test p<0.001, Score (logrank) test p<0.001)

Figures

Figure 1: CONSORT inclusion flow diagram

Figure 2: Adjusted survival curves of fracture free years after first AS diagnosis in matched cohorts according to bDMARD treatment.

Appendix

Appendix 1: Distribution of Propensity Scores in matched and unmatched bDMARD treatment and control units.

Contributorship statement

YR designed the study, analysed the data, and wrote the manuscript. CO supervised the study and revised the final manuscript. JW critically revised the statistical methods and the final manuscript.

Competing interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; YR and CO have been paid for developing and delivering educational presentations for Medtronic Inc. and DePuy Synthes. No other relationships or activities that could appear to have influenced the submitted work.

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Data sharing statement

The Swedish National Patient Registry is hosted by the Swedish National Board of Health and Welfare. Data collection for the Swedish Prescribed Drugs Registry (PDR) is administered by the National Corporation of Swedish Pharmacies. National registry data are available to researchers from the Swedish National Board of Health and Welfare (http://www.socialstyrelsen.se/statistics) after institutional review board approval.

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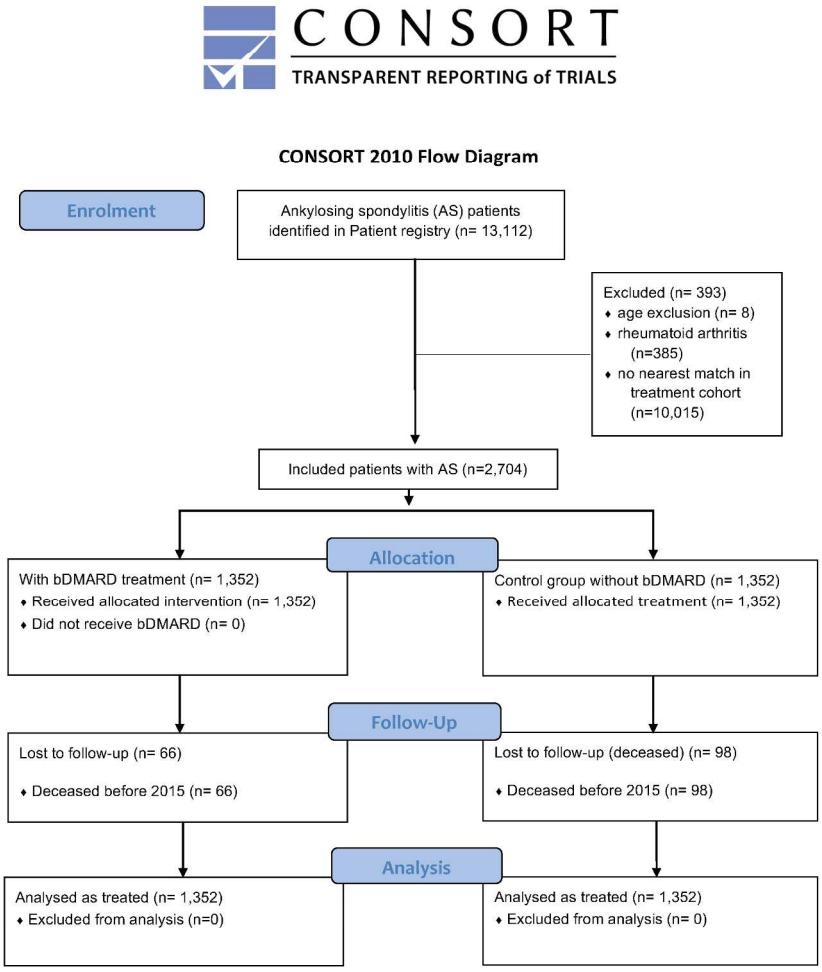
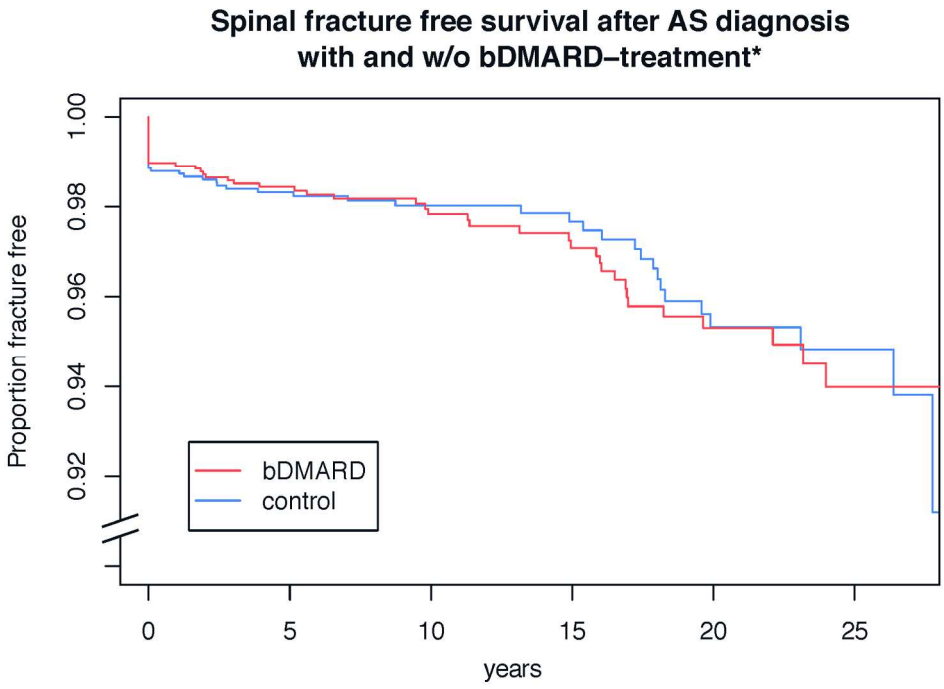


CONSORT inclusion flow diagram

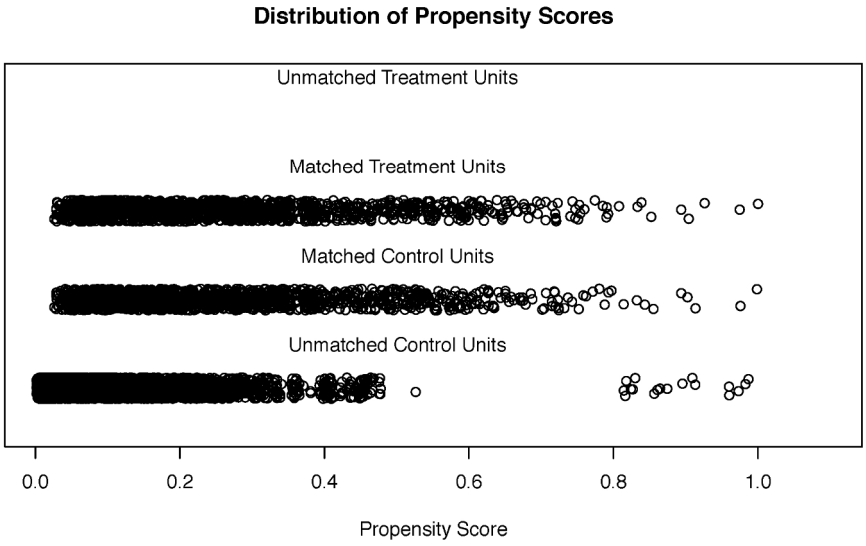
215x279mm (300 x 300 DPI)



*adjusted for sex, CCI score, and years of DMARD–treatment

Spinal fracture-free survival

171x130mm (300 x 300 DPI)



Distribution of propensity scores

217x130mm (300 x 300 DPI)

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	7-8
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7-8
Bias	9	Describe any efforts to address potential sources of bias	7
Study size	10	Explain how the study size was arrived at	7-8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7-8
		(*b*) Describe any methods used to examine subgroups and interactions	7-8
		(*c*) Explain how missing data were addressed	7-8
		(*d*) If applicable, explain how loss to follow-up was addressed	n.a.
		(*e*) Describe any sensitivity analyses	8
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	10
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	10, Table 1
		(b) Indicate number of participants with missing data for each variable of interest	n.a.
		(c) Summarise follow-up time (eg, average and total amount)	10
Outcome data	15*	Report numbers of outcome events or summary measures over time	Table 2
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Table 1
		(*b*) Report category boundaries when continuous variables were categorized	n.a.
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	n.a.
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10
Discussion			
Key results	18	Summarise key results with reference to study objectives	11
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11-12
Generalisability	21	Discuss the generalisability (external validity) of the study results	12
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	19

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.