


POSITION ARTICLE AND GUIDELINES

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Brazilian recommendations for the use of nonsteroidal anti-inflammatory drugs in patients with axial spondyloarthritis

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Abstract

Spondyloarthritis (SpA) is a group of chronic inflammatory systemic diseases characterized by axial and/or peripheral joints inflammation, as well as extra-articular manifestations. Over some decades, nonsteroidal anti-inflammatory drugs (NSAIDs) have been the basis for the pharmacological treatment of patients with axial spondyloarthritis (axSpA). However, the emergence of the immunobiologic agents brought up the discussion about the role of NSAIDs in the management of these patients. The objective of this guideline is to provide recommendations for the use of NSAIDs for the treatment of axSpA. A panel of experts from the Brazilian Society of Rheumatology conducted a systematic review and meta-analysis of randomized clinical trials for 15 predefined questions. The Grading of Recommendations, Assessment, Development and Evaluation methodology to assess the quality of evidence and formulate recommendations were used, and at least 70% agreement of the voting panel was needed. Fourteen recommendations for the use of NSAIDs in the treatment of patients with axSpA were elaborated. The purpose of these recommendations is to support clinicians' decision making, without taking out his/her autonomy when prescribing for an individual patient.

Keywords: Spondyloarthritis, Ankylosing spondylitis, Nonsteroidal anti-inflammatory drugs, Systematic review, Meta-analysis, Guidelines

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Background

Spondyloarthritis (SpA) is a set of diseases that cause inflammation of the spine and peripheral joints and may have extra-articular manifestations, such as anterior uveitis, psoriasis, and inflammatory bowel disease. The main manifestation of SpA is the involvement of the entheses, attachment sites of the tendons, capsules, and ligaments to the bones, especially Achilles' tendon and plantar fascia. Frequently, axSpA patients have a genetic predisposition linked to human leukocyte antigen (HLA)-B27 and are usually seronegative for rheumatoid factor. The set of diseases consists of ankylosing spondylitis (AS), psoriatic arthritis, reactive arthritis, enteropathic arthritis and undifferentiated spondyloarthritis. Axial spondyloarthritis (axSpA) is defined as all cases involving the spine and/or sacroiliac joints, and peripheral spondyloarthritis is defined as cases involving only peripheral joints and/or peripheral entheses. When the same patient has both types of conditions, he/she should be classified by the predominant segment (predominantly axial involvement or predominantly peripheral involvement) [1–4].

AxSpA comprises the so-called radiographic form or AS, which includes patients who present sacroiliitis on simple radiography according to the modified New York criteria, and non-radiographic axial spondyloarthritis (nr-axSpA), which is diagnosed according to the presence of HLA-B27 (clinical arm) or positive sacroiliac MRI (imaging arm), according to the 2009 Assessment in Ankylosing Spondylitis (ASAS) classification criteria [1–4]. Although there is currently no consensus, the prevailing opinion is that axSpA is a single disease in which 20–30% of patients with nr-axSpA can develop radiographic changes over time (5 to 10 years) [5]. In fact, radiographic sacroiliitis artificially splits the axSpA spectrum into two groups, and it is unlikely that its presence alone is critical to the outcome [6]. Thus, the present recommendations will address axSpA as a single entity and combine all relevant data, since most of the available studies included patients with the radiographic form.

Over some decades, nonsteroidal anti-inflammatory drugs (NSAIDs) have been the basis for the pharmacological treatment of axSpA. However, with the emergence of biological agents which have brought great benefit to patients with axSpA, the discussion about the role of NSAIDs, as well as its cost/effectiveness and safety has gained attention.

Recently, the Brazilian Society of Rheumatology has published evidence based recommendations for the diagnosis and management of axSpA [7]. Our main goal in the present guideline was to specifically evaluate the role of NSAIDs for treating axSpA patients through a systematic review with meta-analysis and critical analysis of the published scientific data.

Methodology

Study design

This guideline was conducted in two phases. In the first phase, a systematic review and meta-analysis of randomized clinical trials (RCTs) were performed. In the second phase, an expert panel answered predefined questions and developed the recommendations.

Systematic review and meta-analysis

Inclusion criteria

We included RCTs, systematic reviews, and meta-analyses that have evaluated the efficacy and safety of NSAIDs, as monotherapy or in combination with TNFi or IL17i, in patients older than 18 years of age with axSpA.

Exclusion criteria

Non-randomized comparative studies, non-comparative studies, studies published only as conference abstracts, narrative reviews, animal studies, in vitro studies were excluded. Additionally, studies that evaluated the efficacy and safety of NSAIDs in populations with peripheral spondyloarthritis (psoriatic arthritis, reactive arthritis, inflammatory bowel disease) or rheumatoid arthritis were excluded.

Definition of therapeutic intervention

Studies that evaluated intervention with NSAIDs as a class (total or selective and nonselective COX-2 inhibitors), as well as studies that evaluated NSAID-specific molecules alone or in combination with TNFi or IL17i were considered.

Definition of controls

The included studies that evaluated the efficacy and safety of NSAIDs were compared to placebo or active treatment.

Efficacy outcomes

The outcomes used are shown in the Supplementary Material and included parameters of disease activity, functionality, and progression of axial and peripheral damage. Not all outcomes were reported in all comparisons, although most outcomes were included in each of them.

Safety outcomes

Any adverse events were considered, regardless of severity, causal relationship, and resolution, including renal, cardiovascular, gastrointestinal, neurological, dermatologic, hematologic and hepatic events.

Data sources

The search was conducted in the electronic databases MEDLINE (via PubMed), EMBASE, and the Cochrane Library. In addition, ongoing studies were searched in the Clinical Trials.gov and World Health Organization (WHO) trial registration databases. We searched for other potential studies not retrieved by the search strategies by checking the reference list of each eligible study, as well as in the electronic databases Health Technology Assessment (HTA), Database of Abstracts of Reviews of Effects (DARE), and National Institute for Health and Care Excellence (NICE), in addition to the guidelines of specialty societies.

Search strategies, eligibility assessment, data extraction and risk of bias assessment are shown in the [Supplementary Material](#).

References eligible for meta-analyses

Through the search strategies reported above, 1915 references were retrieved (369 in Medline, 1532 in EMBASE, and 14 in the Cochrane Library) that were published from January 1, 2014 until May 31, 2018 (update date since the review by Kroon et al., 2015) [8]. After removing duplicates, 1698 references were evaluated by reading titles and abstracts, of which 1666 were excluded. Thus, 32 references were evaluated by reading their complete texts. At this stage, 29 references were excluded: 18 according to the type of study [9–26] (non-comparative studies; observational, single-arm studies; systematic reviews without meta-analysis or with overlapping studies; language other than Portuguese, English, or Spanish; and abstracts); eight according to the type of intervention [27–34] (drugs not registered in the country and anti-inflammatory agents other than NSAIDs); two according to the type of outcome [35, 36] (indirect/incomplete analyses, ineligible outcome); and one according to the type of population [37] (not AS and not spondyloarthritis). Thus, three RCTs [38–40] were considered eligible. In addition, through the search of the reference list of the studies evaluated, one RCT was manually included [41]. Therefore, four new eligible references were added to those previously analyzed by Kroon et al. (2015) [8].

Also, additional searches were performed into ClinicalTrials.gov and WHO International Clinical Trials Registry Platform databases. At ClinicalTrials.gov, 19 records were found, of which 17 reported no results. The two trials with available data, presented results before the review of Kroon et al. [8], they were not eligible. In the WHO International Clinical Trials Registry Platform, 18 reports of 15 RCT registrations were found. However, as they did not have available results, they were not included in this meta-analysis (Fig. 1).

Meta-analyses

Meta-analyses were performed for outcomes commonly reported by at least two studies. Their results are presented in the form of forest plots and are described in the text. Outcomes reported by only one study were also presented in graphical form ([Supplementary Material](#)).

Measures of association

For dichotomous variables, the measure of association used was relative risk (RR) with its respective 95% confidence interval (CI). For continuous variables, the measure of association used was the mean difference (MD) with its respective 95% CI. If the studies evaluated the same outcome, but using different scales, the measure of association used was the standardized mean difference (SMD) with its respective 95% CI.

Statistical methods

For the outcomes of dichotomous variables, the method used for the meta-analysis was the Mantel-Haenszel method. For the outcomes of continuous variables, the method used for the meta-analysis was the inverse-variance weighting.

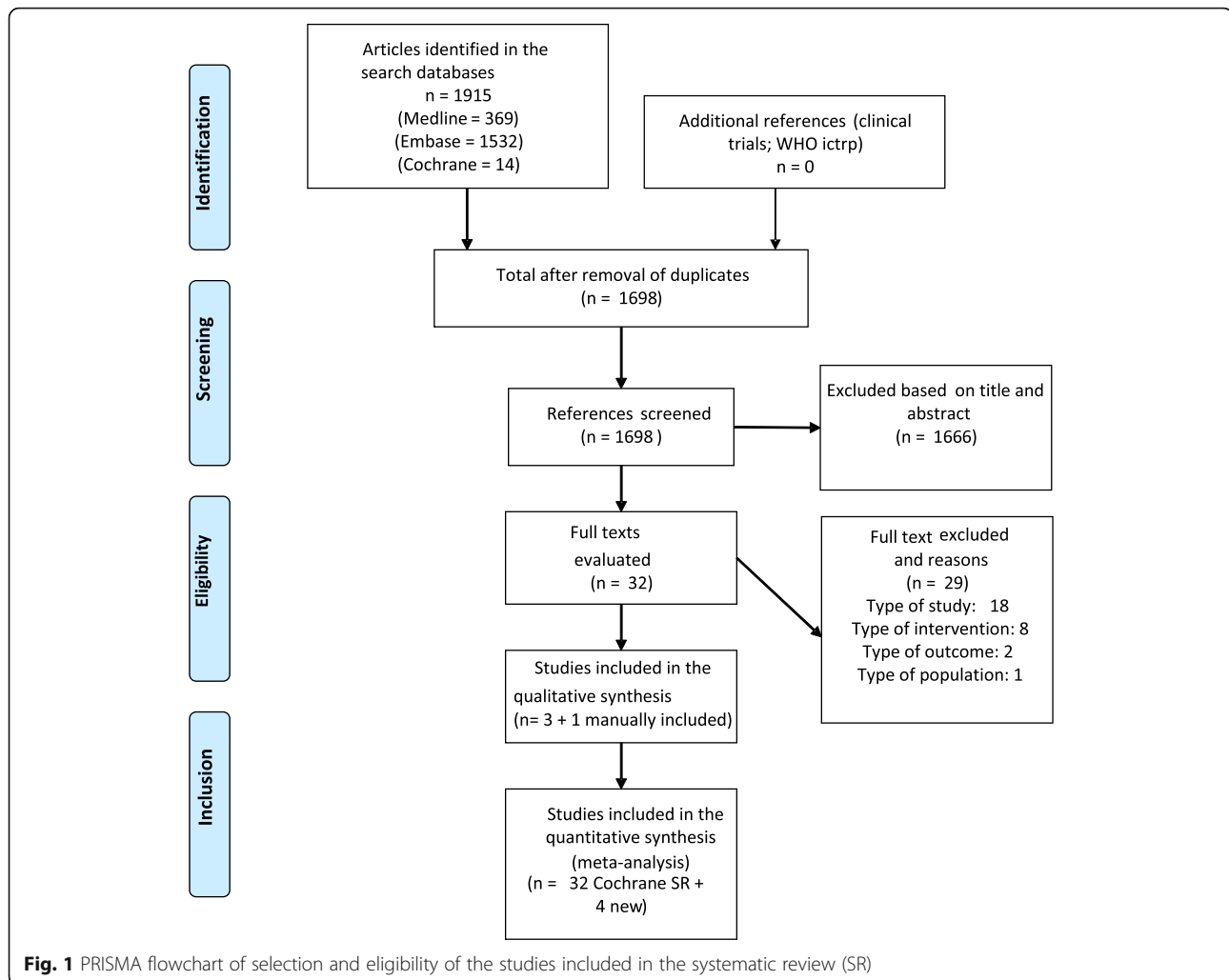
Analytical model

The random-effects model was used when the statistical heterogeneity was significant by the Cochrane chi-squared test ($p < 0.1$). However, if the statistical heterogeneity was not significant but was moderate or high ($I^2 \geq 30\%$), the results are presented according to the random-effects model. In cases of mild statistical heterogeneity ($I^2 < 30\%$) or lack of statistical heterogeneity, the fixed-effects model was preferably used to add greater weight to the estimates from studies with larger sample sizes.

Heterogeneity

In cases of statistical heterogeneity, such heterogeneity was explored based on 2 strategies: the clinical-demographic differences of the participants among studies or study design differences and subgroup analyses. Some subgroup analyses were defined in advance because they were of clinical interest. These subgroup divisions were present or absent HLA-B27, normal or elevated C-reactive protein (CRP), normal or elevated erythrocyte sedimentation rate (ESR), present or absent syndesmophyte, and male or female sex.

The description of each included RCT, the risk of bias analyses, the evaluation of the quality of the evidence according to Grading of Recommendations Assessment, Development and Evaluation (GRADE) [42, 43] and the meta-analyses with all the forest plots are available in the [Supplementary Material](#).



Development of recommendations

A panel of 28 rheumatologists with expertise in SpA elaborated 15 questions divided into 6 sections: efficacy and effect size, window of opportunity and treatment strategy, continuous or on demand use, radiographic progression, comparison of different NSAIDs, safety and adverse reactions. Regarding not answered questions according to the current evidence, the data from individual RCTs were reported. If necessary, a manual search for available evidences, including observational studies, was performed to support the recommendations. There was a hierarchic and standardized sequence to report available evidence: meta-analysis, individual RCTs, and finally observational studies. Observational studies were always reported as very low-quality evidence and supported conditional recommendations.

These recommendations followed the GRADE methodology. Strength of recommendation was determined by the balance between desirable and undesirable

consequences of alternative management strategies, quality of evidence, variability in values and preferences, and resource use. Strong recommendations mean that most informed patients would choose the recommended management and that clinicians can structure their interactions with patients accordingly. Weak or conditional recommendations mean that patients' choices will vary according to their values and preferences, and clinicians must ensure that patients' care is in keeping with their values and preferences. The quality of evidence was assessed using GRADE for predefined key outcomes ([Supplementary Material](#)) [42, 43].

The degree of expert agreement (inter-rater reliability) was determined by the Delphi method through an online anonymous survey, and a minimum 70% agreement was needed for each recommendation.

Table 1 summarizes the Brazilian recommendations for the use of NSAIDs in patients with axSpA.

Table 1 Brazilian recommendations for the use of nonsteroidal anti-inflammatory drugs in patients with axial spondyloarthritis

Recommendations	QoE	DoA
1. EFFICACY		
Recommendation 1. In patients with active axSpA, we strongly recommend treatment with NSAIDs over no treatment, because they are effective for mitigating disease activity measures and improving functional status.	low	9.8
Recommendation 2. In patients with persistent active axSpA, we strongly recommend long-term over short-term use of NSAIDs, because they exhibit sustained symptomatic efficacy. We conditionally recommend that disease activity and adverse events should be regularly monitored, evaluating long-term risks versus benefits.	low	9.3
Recommendation 3. In patients with active axSpA, we conditionally recommend treatment with NSAIDs over no treatment for alleviate symptoms of peripheral arthritis and enthesitis, since few data have shown moderate efficacy in these clinical manifestations.	very low	8.8
2. WINDOW OF OPPORTUNITY AND TREATMENT STRATEGY		
Recommendation 4. In patients with active axSpA, we strongly recommend NSAIDs as the first-line treatment over an immunobiologic agent, considering its low cost and satisfactory efficacy. The benefit of starting an immunobiologic agent in NSAIDs-naïve patients, even in those with poor prognostic criteria, is not proven.	low	8.6
Recommendation 5. In patients with active axSpA, we strongly recommend to immediately start a NSAID after the diagnosis because early treatment may increase the response rate.	very low	8.8
Recommendation 6. In patients with active axSpA, we strongly recommend to initiate NSAIDs at full dosage over low dosage, because they exhibit a tendency for greater efficacy in achieving ASAS 20, reduction of morning stiffness, BASDAI, pain, patient global assessment of disease activity, and BASFI. We conditionally recommend that the full dosages of NSAIDs should be maintained, with adequate monitoring, until good disease control is achieved.	low	9.4
Recommendation 7. In patients with active axSpA, in the absence of a response to the first NSAID at 4 weeks, we conditionally recommend switching to a second traditional NSAID or iCOX2. If the therapeutic target is not reached with the use of NSAIDs for 12 weeks, we strongly recommend to start an immunobiologic agent.	low to high	8.6
3. CONTINUOUS OR ON-DEMAND USE		
Recommendation 8. In patients with active axSpA, we conditionally recommend to start continuous over on-demand NSAIDs until symptoms relief is achieved. After clinical improvement or the clinical target (low disease activity or remission) has been achieved, the full dosage can be reduced or switched to on-demand strategy. Before prescribing continuous NSAIDs, it is important to take into account: the patient's opinion, comorbidities and risk factors.	very low to moderate	9.4
4. RADIOGRAPHIC PROGRESSION		
Recommendation 9. Regarding radiographic progression, in patients with active axSpA, we conditionally recommend continuous over on demand use of NSAIDs. Considering controversial results among the studies, we conditionally recommend switching to on demand strategy in inactive disease. We conditionally recommend against switching NSAIDs to immunobiological therapy when there is radiographic progression without evidence of disease activity, because the risk/benefit ratio of starting an immunobiologic agent in this scenario is not clear.	Very low	8.2
5. COMPARISON AMONG NSAIDS		
Recommendation 10. In patients with active axSpA, we conditionally recommend that the choice of specific NSAID should be based on patient's profile (age, prior toxicity, comorbidities) and on shared decision making. To date, there is no consistent evidence of efficacy and safety differences among the NSAIDs (non-selective or iCOX2) in axSpA.	low	9.6
6. SAFETY AND ADVERSE REACTIONS		
Recommendation 11. Regarding safety, in patients with active axSpA, we strongly recommend treatment with NSAIDs over no treatment, because the available evidence showed an overall good safety profile of these drugs in axSpA. We conditionally recommend that NSAIDs should be used with caution in individuals with risk factors (age > 65 years, diabetes mellitus, use of aspirin, corticosteroids and other platelet antiaggregants, renal or liver diseases). The risks and benefits of starting them should be shared and individualized according to the patient's risk profile.	low	9.0
Gastrointestinal		
Recommendation 12. In patients with active axSpA, we conditionally recommend to avoid NSAIDs (non-selective or iCOX2) and to start an immunobiologic agent in those with current or previous peptic ulcer or gastrointestinal bleeding. We conditionally recommend the use of an iCOX2 agent over a traditional NSAID in patients with gastrointestinal risk factors. We strongly recommend the use of concomitant gastroprotective drugs in symptomatic or high-risk patients.	low	8.9
Cardiovascular		
Recommendation 13. In patients with active axSpA, we conditionally recommend to avoid NSAID therapy and to start an immunobiologic agent in those with cardiovascular risk factors, mainly in those with previous acute myocardial infarction or stroke, especially if recent (past 12 months).	very low (observational studies)	8.4

Table 1 Brazilian recommendations for the use of nonsteroidal anti-inflammatory drugs in patients with axial spondyloarthritis (Continued)

Recommendations	QoE	DoA
Renal		
Recommendation 14. In patients with active axSpA, we conditionally recommend to avoid NSAIDs and to start an immunobiologic agent in those with increased risk of renal adverse events. The decision should be individualized and risk/benefits shared with the patient. We strongly recommend caution and regular monitoring of renal function, especially in high-risk individuals (elderly, hypertension, diabetes, kidney dysfunction).	very low (observational studies)	9.4

NSAIDs nonsteroidal anti-inflammatory drugs, iCOX2 selective COX-2 inhibitor, axSpA axial spondyloarthritis, QoE quality of evidence, DoA degree of agreement

Recommendations

Efficacy and effect size

Are NSAIDs effective for treating patients with axSpA?

Five RCTs evaluated the efficacy of conventional NSAIDs, and three evaluated cyclooxygenase 2-selective inhibitors (iCOX2) compared to placebo. A total of 2002 patients with active AS, with a mean age between 40 and 45 years and a predominance of men (60%), were included in these studies and were followed up for 2 to 52 weeks [44–48].

There was a superiority of traditional NSAIDs over placebo for the following outcomes: pain by VAS (0–100 mm), patient global assessment (PGA) of disease activity by VAS (0–100 mm), duration of morning stiffness in minutes, C-reactive protein concentration, at least 20% improvement according to the ASAS group response criteria (ASAS 20), at least 50% improvement in pain, and the Bath Ankylosing Spondylitis Function Index (BASFI) (Table 2).

Regarding iCOX2, the meta-analyses showed superiority over placebo in the following outcomes: pain VAS, PGA, ASAS 20, and BASFI (Table 2). Individual studies showed superiority of iCOX2 over placebo in the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) [–2.2 (–2.74 to –1.66)] [48], at least 50% improvement in pain [iCOX2: 47.5% vs placebo: 20%, RR: 2.41 (1.45 to 4.00)] [45], and ASAS partial remission [iCOX2: 15% vs

placebo: 3%, RR: 4.65 (1.39 to 15.55)] [48]. Fig. 2 shows the subgroup analysis for pain VAS by comparing traditional NSAIDs, iCOX2, or both versus placebo.

Recommendation 1

In patients with active axSpA, we strongly recommend treatment with NSAIDs over no treatment, because they are effective for mitigating disease activity measures and improving functional status. **Quality of evidence: low; Degree of agreement: 9.8**

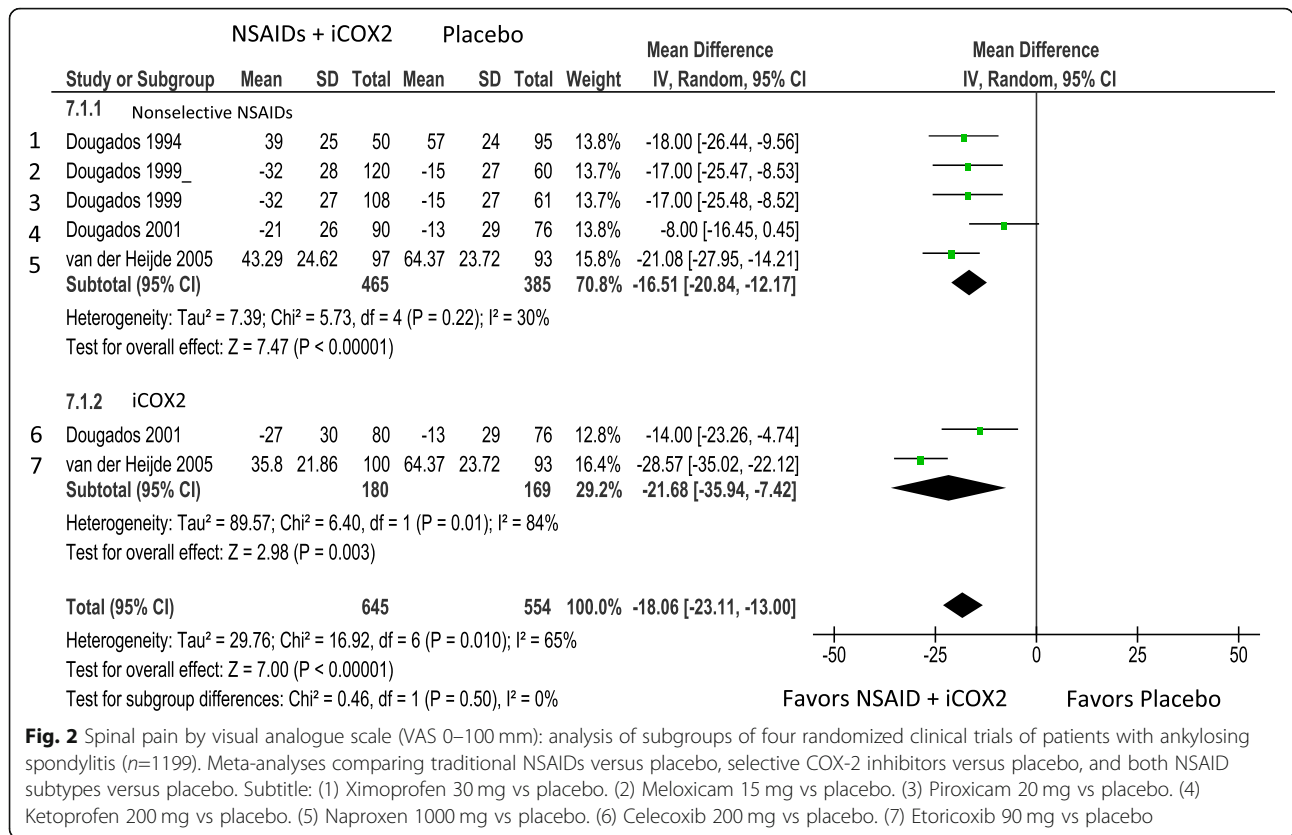
Do NSAIDs have sustained symptomatic efficacy in axSpA?

Most RCTs that evaluated the efficacy of NSAIDs, compared to both placebo and other NSAIDs, had a short duration (8 to 12 weeks) [13, 29, 31, 38, 40, 44, 47, 49–53]. In two long-term RCTs involving patients with AS, the sustained efficacy of NSAIDs was shown in 12 months. Van der Heijde et al. found an ASAS20 response of 52.5% with naproxen and 65% with etoricoxib compared to 20% in placebo group. The 1-year maintenance rate was 90% with etoricoxib and 79% with naproxen [48]. In another RCT, Dougados et al. evaluated the efficacy of NSAIDs in 473 patients with short- and long-term AS. At 6 weeks, 43, 50, and 47% of patients who received 20 mg of piroxicam, 15 mg of meloxicam, or 22.5 mg of meloxicam, respectively, had ≥ 50% improvement in PGA, compared to 21% for the placebo,

Table 2 Efficacy of traditional NSAIDs or iCOX2 vs. placebo in patients with axial spondyloarthritis: meta-analyses of randomized clinical trials

	TRADITIONAL NSAIDs n=1289	iCOX2 n=669
PAIN VAS (95% CI)	–16.75 (–20.28 to –13.07)	–21.68 (–35.94 to –7.42)
PGA	–17.75 (–24.39 to –11.10)	–20.82 (–39.88 to –11.75)
ASAS20	60% vs. 23% (PbO) RR=2.49 (1.94 to 3.19)	57% vs. 20% (PbO) RR=2.51 (1.66 to 3.79)
BASFI	–9 (–13 to –5)	–13.4 (–17.3 to –5)
MS - SMD	–0.4 (–0.58 to –0.22)	NA
CRP mg/L	–3.37 (–6.11 to –0.62)	NA
PAIN50%	48% vs 21% 2.25 (1.75 to 2.89)	NA

NSAIDs nonsteroidal anti-inflammatory drugs, iCOX2 COX-2-selective inhibitors, PAIN VAS pain by visual analog scale 0–100 mm, PGA Patient Global Assessment 0–100 mm, BASFI Bath Ankylosing Spondylitis Function Index 0–100 mm, MS-SMD standardized mean difference in the duration of morning stiffness, CRP C-reactive protein, PAIN50% ≥ 50% improvement in pain, RR relative risk, PbO placebo, N/A meta-analysis not feasible



with sustained response at 12 months. The discontinuation rate due to lack/ loss of efficacy was between 10 and 20%. Only 16% of the responders at 6 weeks had a 1-year loss of response [46].

In a German population-based cohort, almost 80% of 1080 patients with AS were on NSAIDs, of whom 71% had been taking it for more than 4 years. The NSAIDs were effective for complete or partial resolution (> 50%) of pain in 19.1 and 61.2% of patients, respectively [54]. In a Swedish cohort, 21, 108 patients with AS were analyzed for 3 years. Approximately 80% of patients used iCOX2, and 63.8% used non-selective NSAIDs for more than 50% of the follow-up time, with a good initial response rate as well as a good response rate over time [17]. In the Netherlands, Carbo et al. followed up 393 patients with AS who were anti-TNF naïve, of whom 254 were prescribed some TNF inhibitors (BASDAI=6.1 and ASDAS=3.8), while 139 were kept under conventional treatment (BASDAI=3.9 and ASDAS=2.4; 74% with NSAIDs). After 12 months of follow-up, both groups had similar activity scores (BASDAI=3.4 and ASDAS=2.2 vs. BASDAI=3.7 and ASDAS=2.3, respectively). Among patients who received conventional treatment, 82% maintained a sustained response with NSAIDs after 52 weeks [55]. Despite being observational studies whose primary objective was not to evaluate the response to treatment, the high rate of drug retention observed over time suggested a sustained efficacy of NSAIDs.

Recommendation 2

In patients with persistent active axSpA, we strongly recommend long-term over short-term use of NSAIDs, because they exhibit sustained symptomatic efficacy. We conditionally recommend that disease activity and adverse events should be regularly monitored, evaluating long-term risks versus benefits.

Quality of evidence: low; Degree of agreement: 9.3

Are NSAIDs effective for treating the peripheral manifestations of axSpA?

Four of the five RCTs of NSAIDs versus placebo did not evaluate the efficacy of these drugs on peripheral arthritis or enthesitis in axSpA. One RCT compared the effect of ximoprofen on peripheral arthritis at several doses with placebo as secondary outcome, and there was a significant improvement in peripheral arthritis with a moderate effect size (standardized mean difference, SMD=0.62 [95%CI: 0.26 to 0.97]) [47, 56]. From the three trials that assessed iCOX2 versus placebo, two of them excluded patients with peripheral manifestations. A *post-hoc* analysis of a study of etoricoxib and naproxen versus placebo in axSpA suggested NSAIDs were effective for treating peripheral arthritis, as assessed by question 3 of BASDAI, with an improvement on the VAS 0–100 mm of -16.4 (-20.3 to -12.6) compared to 0.9 (-5.9 to 7.6) for placebo, as well as in enthesitis (question 4 of BASDAI), with a shift of -21.3 (-25.2 to -

17.5) with NSAID versus -6.5 (-13.3 to 0.4) with placebo in patients with concomitant peripheral arthritis, and of -27.6 (-30.8 to -24.5) versus -7.3 (-12.9 to -1.8) in those without concomitant peripheral arthritis [48, 50].

The effect of NSAIDs on enthesitis was not specifically evaluated in RCTs of patients with axSpA. The current recommendations suggest that they are effective in a subsample of patients, but that conclusion was extrapolated from studies on psoriatic arthritis or based on expert opinions [57, 58].

Recommendation 3

In patients with active axSpA, we conditionally recommend treatment with NSAIDs over no treatment to alleviate symptoms of peripheral arthritis and enthesitis, since few data have shown moderate efficacy in these clinical manifestations. **Quality of evidence: very low; Degree of agreement: 8.8**

Window of opportunity and treatment strategy

Should NSAIDs be considered first-line treatment in axSpA?

In the INFAST study, 158 patients with axSpA were randomized to receive infliximab + naproxen or placebo + naproxen for 28 weeks. The interesting aspect of this study was that the patients were not refractory to NSAIDs, as in other immunobiologic RCTs (they were NSAID naïve or used low dose of NSAIDs). At week 28, 62% of the Infliximab + naproxen group had ASAS partial remission versus 35% of the placebo + naproxen group [59]. Later, infliximab was discontinued, and patients who achieved remission were monitored until week 52 under continuous naproxen use or no treatment. A similar percentage maintained remission in both the group using naproxen (47.5%) and the group without any treatment (40%) and independent of the initial therapeutic regimen, despite small sample for the latter analysis. The response rate was higher with anti-TNF, but NSAIDs (with placebo) led to remission in more than 1/3 of the cases [60].

In an open-label follow-up study, 39 of the 40 patients with very early axSpA from the RCT conducted by Barkham *et al* [61] (who had received infliximab or placebo for 16 weeks) were monitored for 5 years. There was no difference in current disease activity or radiographic progression by mSASSS among participants receiving infliximab or placebo in the randomized phase. However, approximately 60% (7/12) of patients who initially received infliximab still needed an anti-TNF after 5 years, while 100% (13/13) of those who received placebo remained on anti-TNF treatment [62].

There are not available data to define whether NSAIDs should remain the first-line treatment in patients with poor prognostic criteria (smokers, with elevated CRP and syndesmophytes on baseline) or whether immunobiologics should be the first choice in these cases. Indeed, the long-term benefit of initiating an immunobiologic agent as first line treatment was not proven, as the data suggesting this benefit

originated from a small sample size [62]. In addition, early starting of the NSAID led to a highly significant ASAS partial remission rate (35%) [59].

Considering the low cost, long term experience, and satisfactory response in early disease showed in the INFAST trial [59], the expert panel stated that NSAIDs should still be the first-line treatment in axSpA.

Recommendation 4

In patients with active axSpA, we strongly recommend NSAIDs as the first-line treatment over an immunobiologic agent, considering its low cost and satisfactory efficacy. To date, the benefit of starting an immunobiologic agent in NSAIDs-naïve patients, even in those with poor prognostic criteria, is not proven. **Quality of evidence: low; Degree of agreement: 8.6**

Should NSAIDs be started immediately after the diagnosis of axSpA?

Several studies suggest that the response rates are higher with an earlier onset of treatment [39, 63–65]. In the INFAST study [59], approximately 35% of patients with very early (<2 years of disease on average) axSpA (AS + nr-axSpA) achieved ASAS partial remission with naproxen versus 9% with placebo (only 15% of patients with AS, with longer disease duration, had achieved this target with etoricoxib in the study by van der Heijde *et al*) [48]. Barkham *et al.* achieved 56% ASAS partial remission with infliximab in patients with early axSpA (average of 1 year and 3 months of symptom duration) compared to 22% in the pivotal study of infliximab [61]. Other RCTs found a 70 to 75% ASAS40 response rate after TNF inhibitors in patients with axSpA and disease duration below 3 years, compared to around 40–45% of ASAS40 response rate in those with established AS [59, 66, 67]. Haroon *et al.* reinforced the importance of early treatment by demonstrating that the delay in the onset of anti-TNF treatment increases the rate of radiographic progression [68]. These results reinforce the idea of a “window of opportunity” during the treatment of axSpA and the importance of effective early onset treatment.

Despite the few available data, the panelists considered important to immediately start an NSAID as soon as the diagnosis of axSpA is confirmed.

Recommendation 5

In patients with active axSpA, we strongly recommend to immediately start an NSAID after the diagnosis, because early treatment may increase the response rate. **Quality of evidence: very low; Degree of agreement: 8.8**

When NSAIDs are prescribed for the treatment of patients with axSpA, should they be used in full dosages or at the lowest possible dosage for symptomatic control?

Six RCTs compared full-dosage versus low-dosage of NSAIDs in almost 2000 patients with active axial SpA. In two of

them the mean disease duration was long (10 to 13 years) [46, 47]. The comparisons were: 1) celecoxib 200 mg x celecoxib 400 mg [44, 49]; 2) ximoprofen 5 mg x ximoprofen 30 mg [47]; 3) meloxicam 15 mg x meloxicam 22.5 mg [46]; 4) etoricoxib 90 mg x etoricoxib 120 mg [48]; and 5) etoricoxib 60 mg x etoricoxib 90 mg [41]. The meta-analyses showed a slight superiority of the higher dosages of NSAIDs in reducing the duration of morning stiffness [SMD: 0.14 (0.02; 0.27)] and the proportion of patients who achieved ASAS 20 [RR: 0.87 (0.77; 0.99)], at the limit of statistical significance. However, there was uncertain risk of bias in four studies [44, 46, 47, 49] and high risk in one study [41]. Regarding the BASDAI and BASFI, the meta-analyses did not demonstrate a significant difference between full- and low-dosage NSAIDs, but the results of the individual studies were consistent in favoring higher dosage. Regarding pain outcomes, including pain VAS and 50% improvement, CRP serum levels and PGA, the data were inconsistent, sometimes favoring high doses and other times favoring lower doses of NSAIDs. ASAS partial remission [48] and BASMI [49] were reported in only one RCT each, with no difference between doses. Also, the results of the RCTs cited above should be interpreted with caution, as the 120 mg dose of etoricoxib and 22.5 mg of meloxicam are not currently in use.

Regarding safety, the meta-analyses showed no differences among NSAIDs dosages on the occurrence of any adverse event, serious adverse event, or adverse events per specific system (cardiovascular, gastrointestinal, neurological, respiratory, or dermatologic). There was also no difference in the proportion of patients who discontinued treatment due to unexpected adverse events. Given the low accuracy of the findings, the results were considered inconclusive.

Recommendation 6

In patients with active axSpA, we strongly recommend to initiate NSAIDs at full dosage over low dosage, because they exhibit a tendency for greater efficacy in achieving ASAS 20, reduction of morning stiffness, BASDAI, pain, patient global assessment of disease activity, and BASFI. We conditionally recommend that the full dosages of NSAIDs should be maintained, with adequate monitoring, until good disease control is achieved. **Quality of evidence: low; Degree of agreement: 9.4**

For how long should we wait for initial response to NSAIDs in axSpA?

The traditional NSAIDs and iCOX2 trials have shown that pain and stiffness measures differed from placebo in the first week and the maximum effect was achieved from 2 to 4 weeks. The majority of the studies had a short duration of 2 to 6 weeks [44–48]. The two trials with an extension phase from 6 to 52 weeks did not show any additional effect size with the use of NSAIDs after 6 weeks [46, 48].

The panelists considered a period of 2 weeks too short to evaluate efficacy and recommended a 4-week period as a reasonable time to change treatment, if no response is observed. Based on the previous guidelines for the

treatment of axSpA and the clinical experience, despite lack of evidence, the panel recommended a second NSAID, regardless therapeutic class (selective COX-2 or not), could be used if the first one failed after 4 weeks. The total treatment period with NSAIDs should not exceed 12 weeks, if the predefined target is not achieved [6, 7].

Recommendation 7

In patients with active axSpA, in the absence of a response to the first NSAID at 4 weeks, we conditionally recommend switching to a second traditional NSAID or iCOX2. If the therapeutic target is not reached with the use of NSAIDs for 12 weeks, we strongly recommend to start an immunobiologic agent. **Quality of evidence: low to high; Degree of agreement: 8.6**

Continuous or on-demand use

Is there any significant difference in the reduction of disease activity or safety of NSAIDs when comparing the on-demand versus continuous use for the treatment of axSpA?

Only two RCTs compared continuous and on-demand use of NSAIDs in AS patients. In both studies, the primary outcome was radiographic progression. Wanders et al. [69] evaluated celecoxib continuously or on demand in 215 patients with AS, and disease activity rates were reported as a secondary outcome. After 2 years, there was no significant difference of BASDAI, PGA, overall pain, or C-reactive protein serum levels between two ways of prescribing NSAIDs. More recently, Sieper et al. evaluated 167 patients with AS and compared the continuous or on-demand use of diclofenac. Although not significant, the BASDAI decreased from 4.1 to 2.7, in continuous group, and from 4.2 to 3.2 in on-demand group [70]. Regarding adverse events, there was no difference between continuous and on-demand use in either study.

Despite the lack of evidence, the panel recommended continuous use of NSAIDs in active disease until symptoms relief is achieved, based on the previous guidelines and the clinical experience [6, 7, 71].

Recommendation 8

In patients with active axSpA, we conditionally recommend to start continuous over on-demand NSAIDs until symptoms relief is achieved. After clinical improvement or the clinical target (low disease activity or remission) has been achieved, the treatment regimen can be switched to on-demand strategy. Before prescribing continuous NSAIDs, it is important to take into account patient's opinion, comorbidities and risk factors. **Quality of evidence: very low to moderate; Degree of agreement: 9.4**

Radiographic progression

Is there evidence that NSAIDs can delay or minimize the progression of axial damage in axSpA? Should we switch to an immunobiologic agent in asymptomatic patients with radiographic progression?

Only the two previously cited RCTs had the reduction of radiographic progression through modified Stoke

Ankylosing Spondylitis Spine Score (mSASSS) as the primary outcome. Over a two-year follow-up, Wanders et al. observed higher progression in the on-demand group ($+1.5 \pm 2.5$) compared to the continuous-use group ($+0.4 \pm 1.7$) ($p=0.002$) [69]. This result was similarly found in previous retrospective studies [72, 73]. However, a *post-hoc* analysis of the Wanders et al. trial showed a significant difference only in those with elevated CRP, which brought into discussion if celecoxib reduced the radiographic progression due to the reduction of inflammation instead of a specific drug class effect [74].

On the other hand, Sieper et al. did not find any significant difference on radiographic progression between the continuous and on-demand use of diclofenac over 2 years using mSASSS as outcome [70]. Numerically, the progression was higher in continuous group compared to on-demand group ($+1.3$; 95% CI 0.7 to 1.9 vs $+0.8$; 95% CI 0.2 to 1.4, respectively), but there was no statistical significance, even when considering subgroups with the worst prognosis, such as those with higher CRP and previous syndesmophytes. Therefore, the efficacy of NSAIDs in preventing radiographic damage remains an open question. Nowadays, there is growing evidence that immunobiologic agents may reduce long-term radiographic progression, especially after 4 years of treatment. However to date, the benefit of starting an immunobiologic agent in patients with radiographic progression measured by mSASSS, but with a good symptom control with NSAID was not addressed [75–77].

Recommendation 9

Regarding the radiographic progression, we conditionally recommend continuous over on demand use of NSAIDs in patients with active axSpA. Considering controversial results among the studies, we conditionally recommend switching to on demand strategy in inactive disease. We conditionally recommend against switching NSAIDs to immunobiological therapy when there is radiographic progression without evidence of disease activity, because the risk/benefit ratio of starting an immunobiologic agent in this scenario is not clear. **Quality of evidence: very low; Degree of agreement: 8.2**

Comparison among NSAIDs

Is there any difference regarding the efficacy of traditional NSAID versus another traditional NSAID or versus iCOX2 in patients with axSpA? Is there any difference among NSAIDs regarding adverse events in patients with axSpA?

Twenty-six RCTs compared different traditional NSAIDs in patients with axSpA. A total of 2176 participants aged 35 to 46 years were evaluated. The overall risk of bias in these studies was considered high due to lack of information on randomization, allocation concealment, blinding, and loss to follow-up. Given the data heterogeneity, a meta-analysis was not possible [46, 51–53, 78–95].

Seven trials compared traditional NSAIDs on pain reduction (VAS 0–100 mm) and some statistically significant differences were observed [46, 51, 78, 86, 96–98]: aceclofenac was inferior to indomethacin [SMD: 1.23; (95% CI: 0.98 to 1.47)], piroxicam was superior to naproxen [SMD: -1.25 ; (95% CI: -1.98 to -0.51)], and diclofenac was superior to sulindac [SMD: -0.54 ; (95% CI: -1.06 to -0.03)]. However, no significant difference was observed using a Likert pain scale. Two studies [46, 93, 99] measured the PGA, and only one [93] evaluated the proportion of patients with $\geq 50\%$ pain improvement. However, none of them found significant differences in comparison among traditional NSAIDs (piroxicam vs. meloxicam and ketoprofen vs. phenylbutazone, respectively).

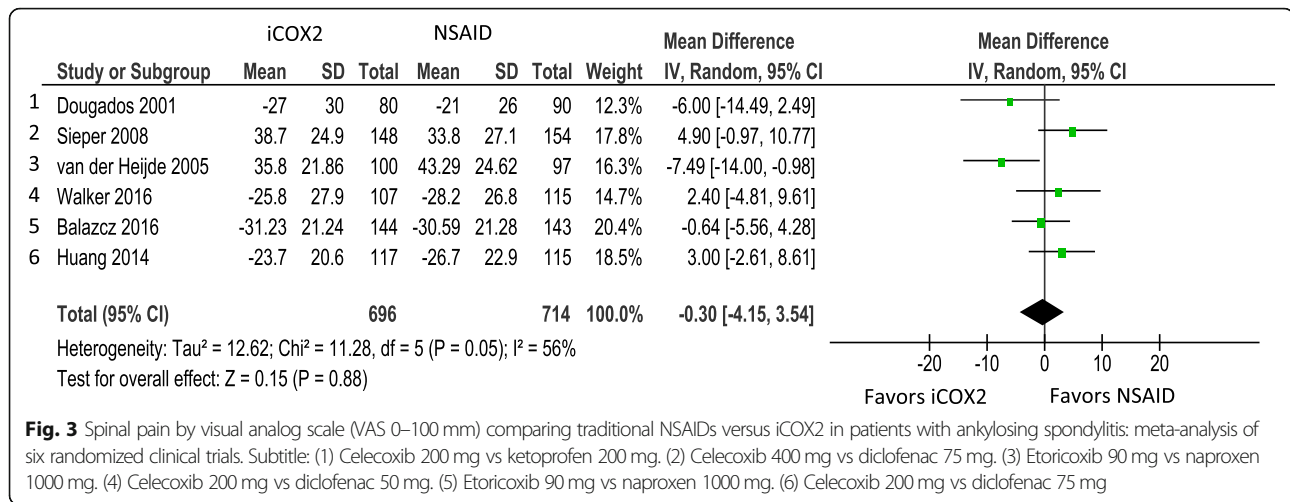
A network meta-analysis, that included 26 RCTs and 3410 patients with AS, did not find any significant difference among 18 different traditional NSAIDs in short-term (between 2 and 12 weeks) [25].

To compare coxibs and nonselective NSAIDs, seven studies were evaluated [38, 40, 41, 44, 45, 48, 49]. Two RCTs used etoricoxib [41, 48], and the others with celecoxib [38, 40, 44, 45, 49]. Three RCTs used diclofenac as comparator, another three used naproxen, and the last used ketoprofen. The meta-analyses did not show significant differences between iCOX2 and traditional NSAIDs for pain VAS 0–100 mm score (Fig. 3), BASDAI, PGA, the proportion of patients who achieved ASAS20, or BASFI. Only the study by van der Heijde et al. found a slight superiority of etoricoxib 90 mg/day over naproxen 1000 mg/day for the outcomes pain VAS 0–100 mm and PGA. This same study found no significant difference regarding BASDAI, BASFI, or ASAS partial remission [48].

In the network meta-analysis by Wang et al., 18 traditional NSAIDs and two iCOX2 agents were compared to each other in treatment of AS. Etoricoxib was superior to celecoxib, ketoprofen, and tenoxicam with regard to pain reduction, but without a significant difference in the duration of morning stiffness. The superiority of etoricoxib should be interpreted with caution because it was based on only one RCT [25, 48].

Regarding any adverse events, there was no significant difference among traditional NSAIDs. In only one of the 19 studies, indomethacin caused more adverse events than oxaprozin [80]. In the analysis by organ system, indomethacin was also associated with a higher rate of neurological adverse events than aceclofenac, oxaprozin, and diclofenac [80, 83, 86]. No difference was observed in adverse events rate (renal, cardiovascular, hepatic, hematological, respiratory, or dermatologic) in patients with axSpA.

In comparison between iCOX2 and traditional NSAIDs, the meta-analysis did not detect differences for any adverse events. In the evaluation by organ system (Fig. 4a and b), there were also no significant differences, except for



increased hepatic toxicity for iCOX2. However, this finding was highly imprecise and at the limit of statistical significance. Regarding discontinuation of treatment due to adverse events, there were no differences in the comparison of traditional NSAIDs or in the comparison between these and iCOX2. Systematic reviews that included several diseases showed greater gastrointestinal safety of iCOX2 compared to traditional NSAIDs and suggested a greater cardiovascular safety of naproxen compared to other NSAIDs [100, 101]. However, we did not observe any significant difference in the present meta-analysis (see [supplementary material](#)).

Recommendation 10

In patients with active axSpA, we conditionally recommend that the choice of a specific NSAID should be based on patient's profile (age, prior toxicity, comorbidities) and on shared decision making. To date, there is no consistent evidence of efficacy and safety differences among the NSAIDs (non-selective or iCOX2) in axSpA. **Quality of evidence: low; Degree of agreement: 9.6**

Safety and adverse reactions

Is there any evidence that NSAIDs carry an increased risk of adverse events in patients with axSpA?

Five studies compared non-selective NSAIDs versus placebo regarding adverse events, totaling 1289 patients evaluated [44–48]. The meta-analysis showed no significant adverse events differences compared to placebo. Furthermore, there was no significant serious adverse events difference or in the discontinuation rate due to adverse events in short-term (6–12 weeks) (Table 3 and Fig. 5). Another 52-week study found no significant adverse event difference among piroxicam 20 mg, meloxicam 15 mg, and meloxicam 22.5 mg compared to placebo in 473 patients with AS (26, 38, 34, and 36%, respectively) [46].

Considering iCOX2, three studies compared the incidence of any adverse events versus placebo in 700 patients with axSpA [44, 45, 48]. Our meta-analysis did not show any

significant short-term differences (incidence of any adverse events, serious adverse events, or discontinuation of treatment due to adverse events for iCOX2 compared to placebo) (Table 3 and Fig. 6). In the single RCT with a longer follow-up period (52 weeks), the placebo group was blindly reallocated to receive etoricoxib 90 mg, etoricoxib 120 mg, or naproxen 1000 mg after 6-week follow-up. In the first 6 weeks, the rates of any adverse events were 39.8, 47.6, 48.9, and 41.4% for placebo, etoricoxib 90 mg, etoricoxib 120 mg, and naproxen, respectively. At the end of 1 year, there were no significant differences in any of the adverse events among the three groups (43.5%, 36.1, and 38.5%, respectively), nor in severe adverse events (7.6, 7.2, and 7.7%, respectively) or discontinuation rate due to adverse events (8.7, 4.8, and 7.7%, respectively) [48].

Therefore comparing NSAIDs versus placebo, we did not find statistical differences in the overall incidence of adverse events, which suggests a good safety profile. However, considering specific organ system analyses showed in the following sections, caution is recommended when using NSAIDs, especially regarding gastrointestinal events.

Recommendation 11

Regarding safety, in patients with active axSpA, we strongly recommend treatment with NSAIDs over no treatment, because the available evidence showed an overall good safety profile of these drugs in axSpA. We conditionally recommend that NSAIDs should be used with caution in individuals with risk factors (age > 65 years old, diabetes mellitus, use of aspirin, corticosteroids and other platelet antiaggregants, renal or liver diseases). The risks and benefits of starting them should be shared and individualized according to the patient's risk profile. **Quality of evidence: low, Degree of agreement: 9.0**

Is the use of NSAIDs associated with increased gastrointestinal risk in patients with axSpA?

Five studies compared traditional NSAIDs versus placebo regarding gastrointestinal adverse events in 1289 patients [44–48]. The frequency of gastrointestinal

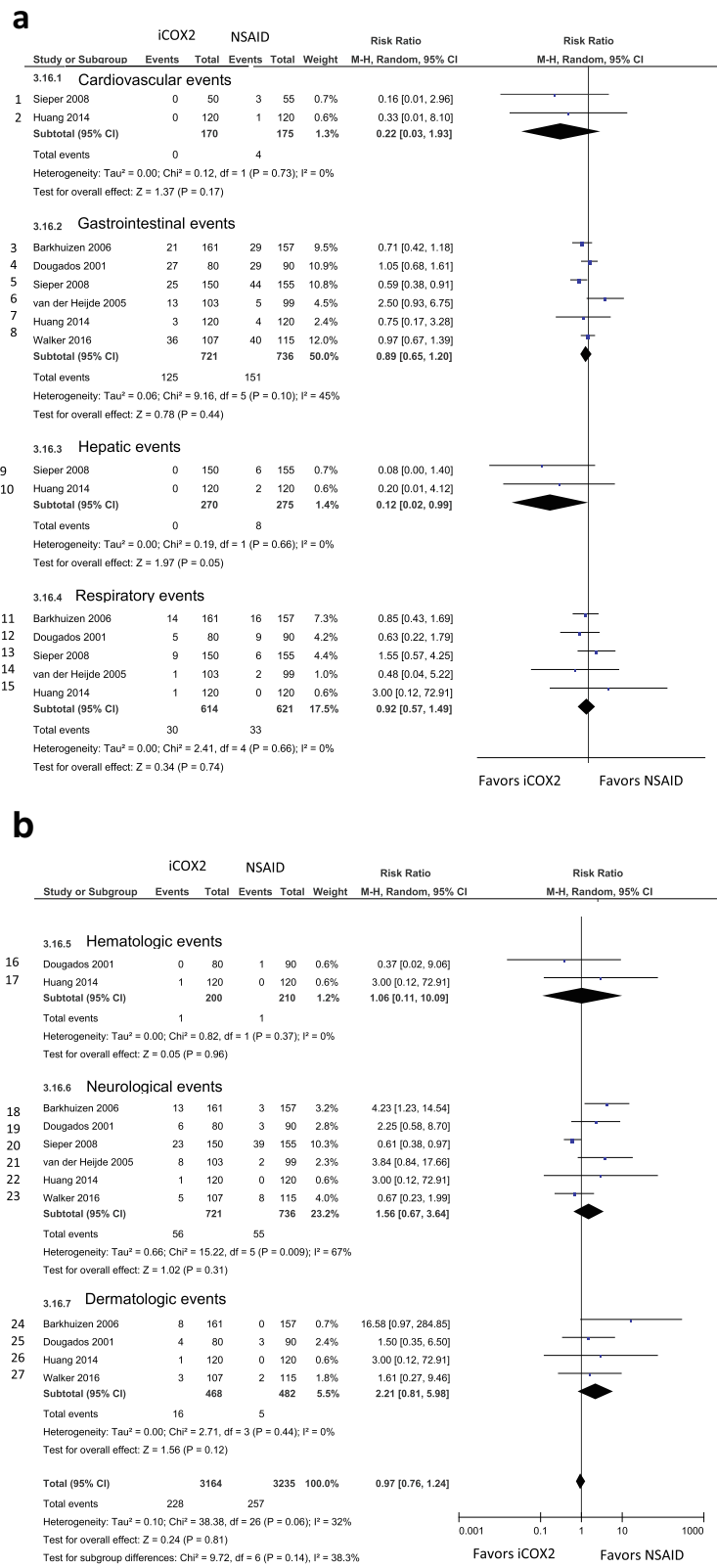


Fig. 4 (See legend on next page.)

(See figure on previous page.)

Fig. 4 a and b Incidence of adverse events per organ system in the comparison of COX2 selective inhibitors versus traditional NSAIDs in patients with ankylosing spondylitis: meta-analyses of seven randomized clinical trials. Subtitle: (1) Celecoxib 400 mg vs diclofenac 75 mg. (2) Celecoxib 200 mg vs diclofenac 75 mg (3) Celecoxib 400 mg vs naproxen 500 mg. (4) Celecoxib 200 mg vs ketoprofen 200 mg. (5) Celecoxib 400 mg vs diclofenac 75 mg. (6) Etoricoxib 90 mg vs naproxen 1000 mg. (7) Celecoxib 200 mg vs diclofenac 75 mg. (8) Celecoxib 200 mg vs diclofenac 50 mg (9) Celecoxib 400 mg vs diclofenac 75 mg. (10) Celecoxib 200 mg vs diclofenac 75 mg. (11) Celecoxib 400 mg vs naproxen 500 mg. (12) Celecoxib 200 mg vs ketoprofen 200 mg. (13) Celecoxib 400 mg vs diclofenac 75 mg. (14) Etoricoxib 90 mg vs naproxen 1000 mg. (15) Celecoxib 200 mg vs diclofenac 75 mg (16) Celecoxib 200 mg vs ketoprofen 200 mg. (17) Celecoxib 200 mg vs diclofenac 75 mg. (18) Celecoxib 400 mg vs naproxen 500 mg. (19) Celecoxib 200 mg vs ketoprofen 200 mg. (20) Celecoxib 400 mg vs diclofenac 75 mg. (21) Etoricoxib 90 mg vs naproxen 1000 mg. (22) Celecoxib 200 mg vs diclofenac 75 mg. (23) Celecoxib 200 mg vs diclofenac 50 mg (24) Celecoxib 400 mg vs naproxen 500 mg. (25) Celecoxib 200 mg vs ketoprofen 200 mg (26) Celecoxib 200 mg vs diclofenac 75 mg. (27) Celecoxib 200 mg vs diclofenac 50 mg

events was higher with traditional NSAIDs than placebo. A similar result was observed with iCOX2 in 769 patients when compared to placebo (Table 3, Figs. 7 and 8) [44, 45, 48]. There was no significant difference in the meta-analysis of six RCTs that compared iCOX2 versus traditional NSAIDs (RR=0.89; 0.65–1.2). Most RCTs were short-term (2–12 weeks) [38, 40, 44, 45, 48, 49].

In the Dougados' study (1999), the extension phase lasted from 6th to 52nd week. In the first 6 weeks, the authors showed 14% gastrointestinal events with traditional NSAIDs versus 7% in placebo group. A total of six (1.7%) individuals from NSAID group had gastroduodenal ulcers, and no patients were diagnosed in placebo group by week 52 [46]. Regarding iCOX2, only the RCT by van der Heijde et al. (2005) analyzed adverse events from week 6 to week 52 in the extension phase, not controlled by placebo. The incidence of pyrosis after 1 year of use was 9.8, 7.2, and 7.7% for etoricoxib 90 mg, etoricoxib 120 mg, and naproxen 1000 mg, respectively. Three (2.4%) patients who received etoricoxib 120 mg and 4 (3.2%) who received naproxen had gastroduodenal ulcers at 1 year of follow-up [48].

Most data on gastrointestinal risk were from studies in other populations (osteoarthritis, rheumatoid arthritis, etc.) and there is no evidence that the risk is different in axSpA. Factors considered high-risk for gastrointestinal complications with NSAIDs are age above 65 years, comorbidities (diabetes, COPD, coronary disease, coagulopathies), alcoholism, concomitant medication (corticosteroids, anticoagulants, aspirin, other antiplatelet

aggregation drugs), history of peptic ulcer, and *Helicobacter pylori* infection. An observational study that evaluated 4144 individuals with osteoarthritis (85%), rheumatoid arthritis (11%), or AS (3%) and at least one gastrointestinal risk factor, with a mean follow-up of 6 months, showed an incidence of 0.7 severe events per 100 patients-year after the initiation of NSAIDs. The associated use of gastroprotective drugs, such as proton pump inhibitors, reduced the risk in approximately 30% of patients [100, 102, 103]. Systematic reviews that included several diseases, not restricted to the population with SpA, showed greater gastrointestinal safety of iCOX2 [100, 101], but we did not find any significant difference between iCOX2 and traditional NSAIDs in the present meta-analysis (see Fig. 4a and Supplementary Material).

Recommendation 12

In patients with active axSpA, we conditionally recommend to avoid NSAIDs (non-selective or iCOX2) and to start an immunobiologic agent in those with current or previous peptic ulcer or gastrointestinal bleeding.

We conditionally recommend the use of an iCOX2 agent over a traditional NSAID in patients with gastrointestinal risk factors.

We strongly recommend the use of concomitant gastroprotective drugs in symptomatic or high-risk patients. **Quality of evidence: low; Degree of agreement: 8.9**

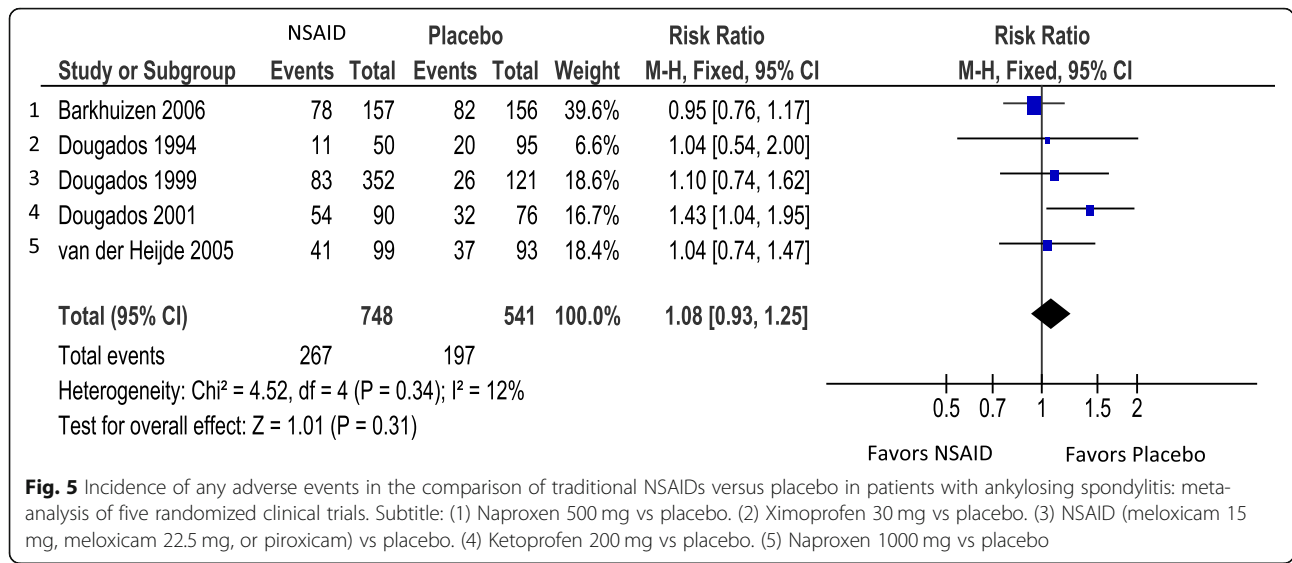
Is the use of NSAIDs associated with increased cardiovascular risk in axSpA?

There is growing evidence that SpA is associated with increased mortality, especially for cardiovascular diseases,

Table 3 Incidence of adverse events associated with traditional NSAIDs or iCOX2 compared to placebo in patients with axSpA: meta-analysis of randomized clinical trials

	TRADITIONAL NSAIDs N=1289	iCOX2 N=669
Adverse events	35.6% vs 36.4% (PbO) RR=1.08 (0.93 to 1.25)	54.6% vs 46.4% (PbO) RR=1.22 (0.93 to 1.62)
Severe adverse events	1% vs 0.6% (PbO) RR=1.71 (0.37 to 8.01)	0.6% vs 0.6% (PbO) RR=0.96 (0.17 to 5.53)
Gastrointestinal adverse events	18% vs 9.5% (PbO) RR=1.92 (1.41 to 2.61)	17.7% vs 7.5% (PbO) RR=2.55 (1.92 to 4.95)
Discontinuation due to adverse events	5% vs 5.5% (PbO) RR=0.76 (0.48 to 1.22)	4.6% vs 3.4% (PbO) RR=2.14 (0.36 to 12.56)

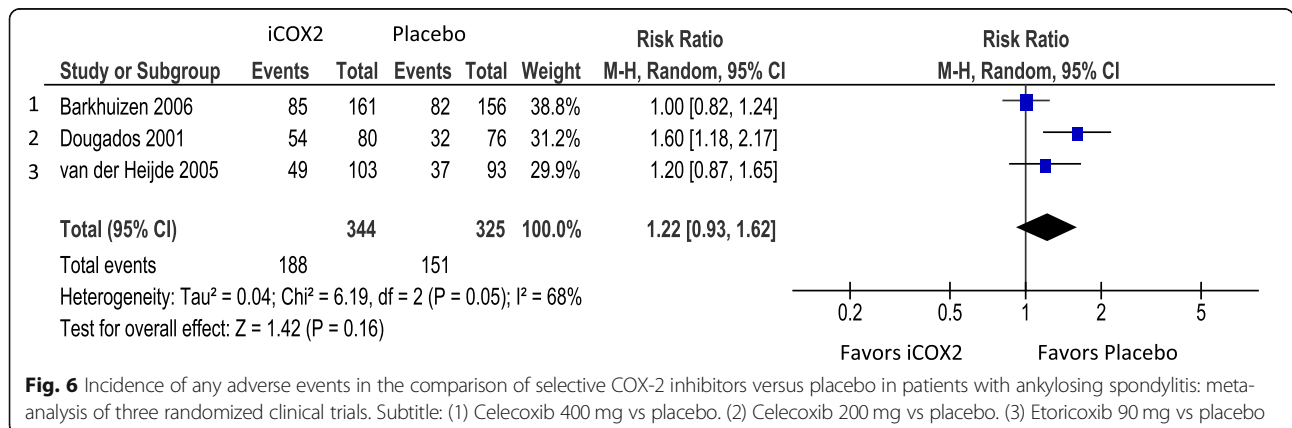
NSAIDs nonsteroidal anti-inflammatory drugs, iCOX2 selective cyclooxygenase 2 inhibitors, PbO placebo, RR relative risk

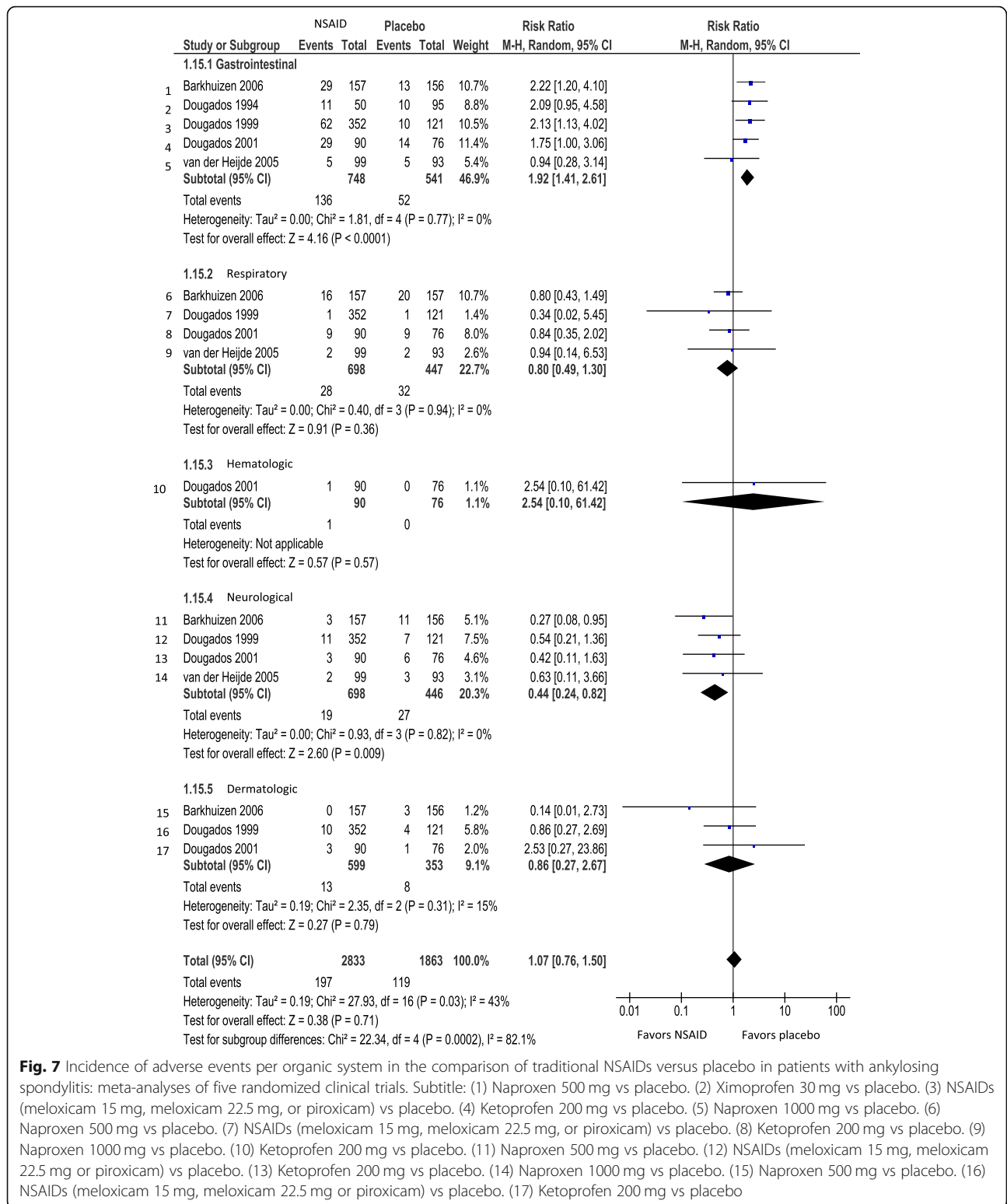


due to multiple factors such as chronic inflammation, associated comorbidities and maybe the drugs used to treat these patients [104–107]. Regarding NSAIDs, large population studies, including a Danish cohort of more than 1 million individuals, suggested 2 to 3-fold increase regarding cardiovascular risk (acute myocardial infarction, stroke, and death from cardiovascular disease) with the chronic use of iCOX2 or nonselective NSAIDs, except for naproxen. Meta-analysis of observational studies estimates an absolute risk of major adverse cardiovascular events (MACE) of approximately 3 per 1000 patients-year with the use of NSAIDs [100, 101, 108, 109]. Furthermore, NSAIDs have been shown to increase mortality in the first 3 to 6 months after acute cardiovascular events [110, 111].

However, in the population with SpA, the relationship of NSAIDs with cardiovascular mortality risk is less clear. Debreuil et al., in a case-control study using a large British database, compared the incidence of acute myocardial infarction (AMI) between a cohort of SpA patients with a

cohort of osteoarthritis (OA) patients. Current use of diclofenac (0–180 days prior to index date) compared to remote use (more than 365 days prior to index date) was associated with an increased risk of AMI both in SpA group [adjusted OR=3.32 (95% CI 1.57 to 7.03)] and OA group [(ORa=1.26 (95% CI 1.14 to 1.39)]. Additionally, the risk was different between the two groups [ORa ratio=2.64 (95% CI 1.24 to 5.58, OA as reference)], whereas there was no increased risk of AMI when naproxen was analyzed, either in patients with SpA [(ORa=1.19 (95% CI 0.53 to 2.68)] or in those with OA [112]. Interestingly, other authors have observed a protective effect of NSAIDs against cardiovascular events in patients with axSpA. Haroon et al. studied 21,143 patients with AS compared to 86,606 controls, based on Canadian database, observed a hazard ratio (HR) of 1.36 (95% CI 1.13 to 1.65) for a composite outcome of cardiovascular death. A subgroup analysis of patients older than 65 years demonstrated a protective effect of conventional NSAIDs for





cardiovascular death [HR=0.1 (95% CI 0.01 to 0.61)] [105]. Tsai et al., using data from the Taiwan Health Insurance, observed a reduced risk of MACE after 12 months in patients with AS who had prolonged use of NSAIDs (> 80% of

the observation time) [23]. Another Taiwan case-control study found negative association between the use of celecoxib (versus non-users) and coronary events [OR=0.34 (95% CI 0.13 to 0.89)] in AS patients [26]. Other publications

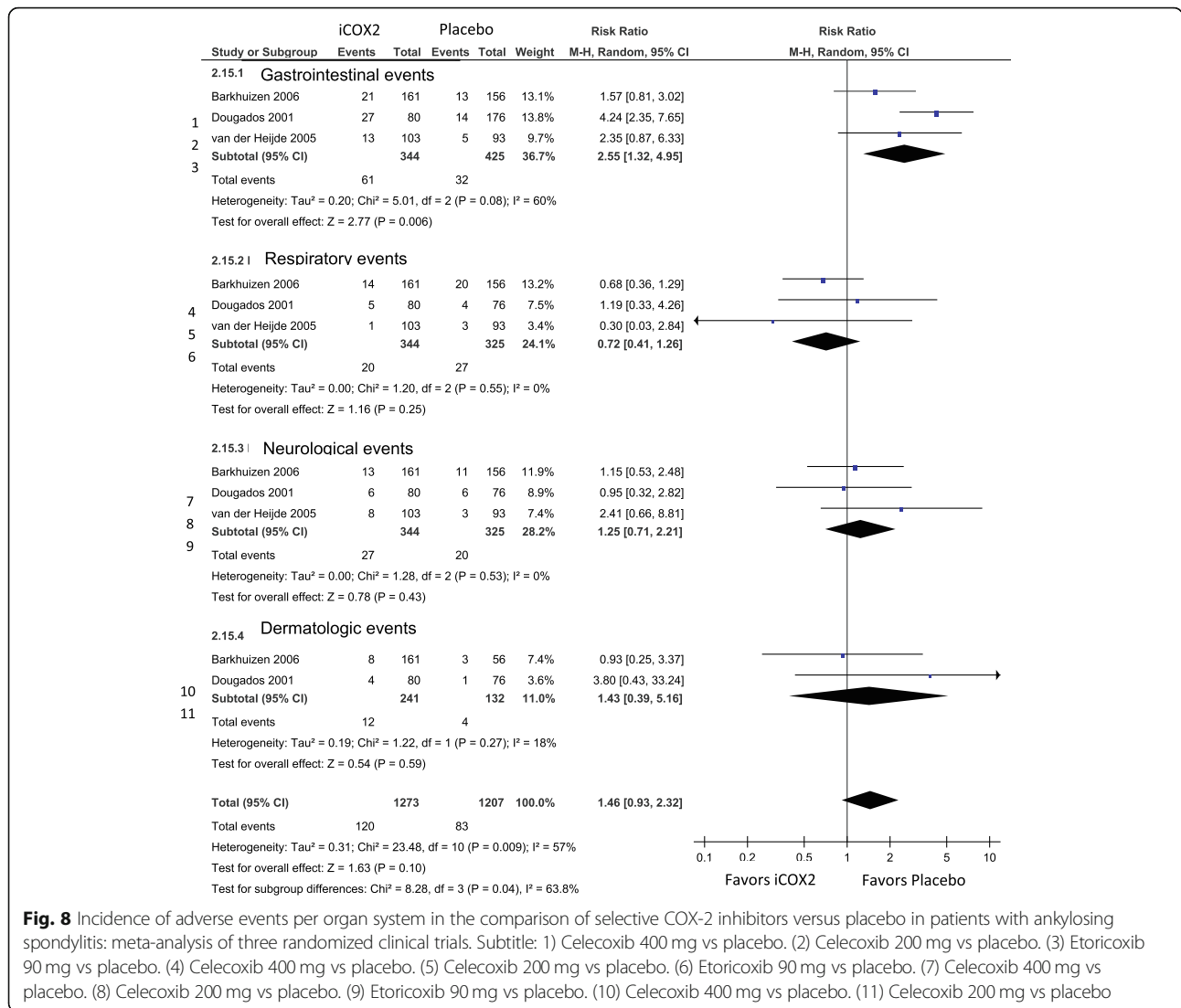


Fig. 8 Incidence of adverse events per organ system in the comparison of selective COX-2 inhibitors versus placebo in patients with ankylosing spondylitis: meta-analysis of three randomized clinical trials. Subtitle: 1) Celecoxib 400 mg vs placebo. (2) Celecoxib 200 mg vs placebo. (3) Etoricoxib 90 mg vs placebo. (4) Celecoxib 400 mg vs placebo. (5) Celecoxib 200 mg vs placebo. (6) Etoricoxib 90 mg vs placebo. (7) Celecoxib 400 mg vs placebo. (8) Celecoxib 200 mg vs placebo. (9) Etoricoxib 90 mg vs placebo. (10) Celecoxib 400 mg vs placebo. (11) Celecoxib 200 mg vs placebo

also suggest the protective effect of NSAIDs against cardiovascular events, but the data should be interpreted with caution because patients with more comorbidities and risk factors tend to be less exposed to NSAIDs [17, 106]. In summary, it is still controversial whether the beneficial effect of reducing inflammation would outweigh the negative effects of NSAIDs per se regarding cardiovascular risk.

The present systematic review, which included only RCTs and not observational studies, did not find higher cardiovascular risk when comparing traditional NSAIDs or iCOX2 versus placebo. Two RCTs compared traditional NSAIDs versus iCOX2 on cardiovascular events incidence [2% (4/175) and 0% (0/170), respectively] and no significant difference in meta-analysis [RR=0.22 (95% CI 0.03 to 1.93)] was observed [38, 49].

Furthermore, the panel decided to conditionally recommend caution when prescribing NSAIDs in

patients with cardiovascular risks factors, specially in those with a recent myocardial infarction or stroke.

Recommendation 13

In patients with active axSpA, we conditionally recommend to avoid NSAID therapy and to start an immunobiologic agent in those with cardiovascular risk factors, mainly in those with previous acute myocardial infarction or stroke, especially if recent (past 12 months).

Quality of evidence: very low; Degree of agreement: 8.4

Are NSAIDs associated with increased renal risk in patients with axSpA?

The RCTs selected for this systematic review did not report renal toxicity from NSAIDs in patients with axSpA. Similarly to the cardiovascular toxicity, the renal adverse events evidences were obtained from data including other populations. A large cohort study (183,

446 patients; 80% women; mean age of 78 years) found an incidence of 0.5% (1 in 200 new treatments) of acute kidney injury (AKI), requiring hospitalization, in a period of up to 45 days after the onset of NSAIDs [113]. A meta-analysis evaluated 28,992 patients and demonstrated a RR of AKI associated with NSAIDs ranging from 1.25 to 2.21 that was statistically significant for several NSAIDs [114]. Regarding the possibility of progression to chronic kidney disease, a prospective study with 10,184 patients (57% women; mean age 76 years) found RR=1.26 (95% CI 1.04 to 1.53) for a reduction of glomerular filtration rate of at least 15 ml/min/1.73 m² among NSAID users when compared with non-users during a median follow-up of 2.75 years [115].

Does the use of NSAIDs increase the risk of adverse events in other organs/systems in axSpA?

Considering five RCTs of non-selective NSAIDs versus placebo and three of iCOX2 versus placebo, neither the meta-analysis nor individual studies found an increase in respiratory, hematological, dermatologic, or neurological adverse events [44–48]. Additionally, no significant differences were found in the comparison of iCOX2 versus traditional NSAIDs [38, 40, 44, 45, 48, 49]. In the comparison of NSAIDs with other NSAIDs, selective or not for COX-2, only indomethacin was associated with a greater number of neurological adverse events [80, 83, 86]. Despite data from general population have suggested some hepatotoxic effect of NSAIDs, no specific RCTs were found for NSAIDs versus placebo in patients with axSpA [116]. The current meta-analysis found greater hepatic toxicity for iCOX2 compared to non-selective NSAIDs, but with high imprecision data and at the limit of statistical significance (Figs. 7 and 8).

Recommendation 14

In patients with active axSpA, we conditionally recommend to avoid NSAIDs and to start an immunobiologic agent in those with increased risk of renal adverse events. The decision should be individualized and risk/benefits shared with the patient.

We strongly recommend caution and regular monitoring of renal function, especially in high-risk individuals (elderly, hypertension, diabetes, kidney dysfunction). **Quality of evidence: very low; Degree of agreement: 9.4**

Conclusions

The most recently published guidelines for the management of axSpA recommended NSAIDs as the first line treatment, but none of them has addressed specifically the current role of NSAIDs in the treatment of patients with axSpA regarding efficacy, safety and therapeutic strategy [6, 7, 71]. The present systematic review and critical analysis of the available evidences have confirmed that NSAIDs are still the basis for the

treatment of patients with axSpA, as they are effective in most part of those patients.

There is no doubt that the immunobiologic agents are quite effective and brought great benefit for the management of axSpA, but they carry a high cost which demands the best rationale for prescribing them. Our recommendations, in consonance with the most important guidelines, strengthen the statement that NSAIDs are the first line treatment in patients with axSpA and they should be started as soon as the diagnosis is confirmed.

The benefit of NSAIDs in delaying radiographic progression in axSpA and if immunobiologics should be the first line treatment in patients with poor prognostic criteria (elevated CRP, smokers and those with previous syndesmophytes) remain an open question.

This review has also shown that NSAIDs have a good safety profile and are usually well tolerated for the long-term use. The concerns about the cardiovascular and renal side effects are based mostly in data from other populations, but not in patients with axSpA that are usually younger and have less comorbidities and risk factors than other NSAID's long-term or frequently users, like patients with osteoarthritis for example.

One possible limitation of these recommendations is that we did not include a patient representative in the voting panel. This strategy could be used in future guidelines.

The purpose of these guidelines was to provide recommendations elaborated by a panel of rheumatologists with expertise in the field of SpA, mainly to support clinician's decision making, without taking out his/her autonomy to choose the best therapeutic option for an individual patient.

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s42358-020-00160-6>.

Additional file 1.

Abbreviations

AxSpA: Axial Spondyloarthritis; AS: Ankylosing Spondylitis; PsA: Psoriatic Arthritis; ASAS: Ankylosing Spondylitis Assessment Study Group; RCT: Randomized Clinical Trial; TNFi: Tumor Necrosis Factor inhibitor; IL17i: Interleukin-17 inhibitor; NSAID: Nonsteroidal Anti-inflammatory Drug; iCOX2: Specific Cyclooxygenase-2 inhibitor; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; ASDAS: Ankylosing Spondylitis Disease Activity Score; BASFI: Bath Ankylosing Spondylitis Disease Functional Index; PAIN50%: ≥ 50% improvement in pain; MD: Mean Difference; SMD: Standard Mean Difference; CRP: C Reactive Protein; ESR: Erythrocyte Sedimentation Rate; PAIN-VAS: Pain by Visual Analogue Scale; PGA: Patient Global Assessment of disease activity; ASAS20: At least 20% improvement according to ASAS response criteria; ASAS40: At least 40% improvement according to ASAS response criteria; mSASSS: modified Stoke Ankylosing Spondylitis Spine Score

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Authors' contributions

All authors made contributions to the acquisition of data, have been involved in drafting the manuscript or revising it critically for important intellectual content, participated in the voting rounds, gave final approval of the version to be published and have participated sufficiently in the work to take public responsibility for appropriate portions of the content.

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