Evaluation of 2 Screening Strategies for Early Identification of Patients with Axial Spondyloarthritis in Primary Care

DENIS PODDUBNYY, JANIS VAHLDIEK, INGE SPILLER, BEATE BUSS, JOACHIM LISTING, MARTIN RUDWALEIT, and JOACHIM SIEPER

ABSTRACT. ***Objective.*** To evaluate 2 referral strategies for axial spondyloarthritis (SpA) in patients with chronic low back pain at the primary care level.

Methods. Referral physicians (n = 259) were randomly assigned to either Strategy 1 or Strategy 2 in order to refer patients with chronic back pain (duration > 3 months), age at onset of back pain < 45 years, and no diagnosis of axial SpA, to a cooperating rheumatologist (n = 43). According to Strategy 1, suitable patients were referred if at least 1 of the following screening criteria was present: inflammatory back pain, HLA-B27, or sacroiliitis detected by imaging. According to Strategy 2, patients were referred if 2 out of 5 criteria were positive: the same 3 criteria from Strategy 1 and additionally a positive family history of ankylosing spondylitis (AS) or a good treatment response to nonsteroidal antiinflammatory drugs. The final diagnosis of the rheumatologist was used as the "gold standard."

Results. In total, 560 consecutively referred patients were included in the analysis. Among 318 patients referred by Strategy 1, 41.8% (95% CI 36.5%–47.3%) were diagnosed with definite axial SpA. Among 242 patients referred by the second strategy, definite axial SpA was diagnosed in 36.8% (95% CI 31.0%–43.0%) of the cases.

Conclusion. Both referral strategies demonstrated comparable performance in identification of patients with axial SpA. Strategy 1 might be preferred as an easy and reliable screening method for axial SpA at the primary care level. (J Rheumatol First Release Sept 15 2011; doi:10.3899/jrheum.110070)

Key Indexing Terms:
SPONDYLOARTHRITIS ANKYLOSING SPONDYLITIS SPONDYLOARTHROPATHY AXIAL NONRADIOGRAPHIC SCREENING PRIMARY CARE

The recently introduced term "axial spondyloarthritis" (SpA) covers all patients with SpA with predominant axial involvement and includes ankylosing spondylitis (AS), normally fulfilling the modified New York criteria[1] with definitive radiographic sacroiliitis, and nonradiographic axial SpA, previously also termed undifferentiated SpA[2,3]. Classification criteria for this whole group of axial SpA have recently been developed and published by the Assessment of SpondyloArthritis international Society (ASAS)[4,5].

AS — the prototype disease of the SpA group — has an estimated prevalence of about 0.5%[6,7], whereas the estimated prevalence for the whole group of SpA is about 1.5%[6,7]. Although the prevalence of SpA in the general population is high and is comparable with that of rheumatoid arthritis[7,8,9], there is a major problem with the early diagnosis of axial SpA. The delay between first symptoms and a final diagnosis has been reported in different surveys to be between 5 and 10 years in developed countries[10,11,12], often associated with a long history of futile diagnostic efforts. The question of early diagnosis of SpA has become even more important lately since the introduction of the highly effective tumor necrosis factor-α (TNF-α) blockers for the treatment of AS. Moreover, short disease duration seems to be the best predictor for a good response to TNF-α blockers[13,14].

A major reason for such a delay in the diagnosis is the difficulty in identifying patients for whom there is suspicion of axial SpA among the large group of patients with chronic back pain seen in primary care. Thus, there is urgent need

From the Department of Rheumatology, Charité – Campus Benjamin Franklin, Berlin; Department of Epidemiology, German Rheumatism Research Centre, Berlin; and Department of Rheumatology, Evangelisches Krankenhaus Hagen-Haspe, Hagen, Germany.

Supported by an unrestricted grant from Essex Pharma GmbH, Munich, Germany.

D. Poddubnyy, MD, Fellow; J. Vahldiek, MD, Fellow; I. Spiller, MD, Fellow; B. Buss, Study Nurse, Department of Rheumatology, Charité – Campus Benjamin Franklin; J. Listing, PhD, Department of Epidemiology, German Rheumatism Research Centre; M. Rudwaleit, MD, Professor, Department of Rheumatology, Evangelisches Krankenhaus Hagen-Haspe; J. Sieper, MD, Professor, Department of Rheumatology, Charité – Campus Benjamin Franklin.

Address correspondence to Dr. J. Sieper, Medicine Department I, Rheumatology, Charité – Campus Benjamin Franklin, Hindenburgdamm 30, 12203 Berlin, Germany. E-mail: joachim.sieper@charite.de

Accepted for publication July 8, 2011.

for a kind of filter at the primary care level, allowing preselection of patients with a relatively high probability of axial SpA from the large group of patients with chronic back pain, for further referral to the rheumatologist. In 2005 we proposed a set of criteria suitable for screening and early referral of patients with low back pain and suspicion of axial SpA by primary care physicians[15], which resulted in a diagnosis of axial SpA in 45.4% of the referred cases in a study at a specialized single center[16]. In patients with only 1 positive screening criterion, axial SpA was diagnosed in 34.2% of the patients, while in patients with at least 2 positive criteria in that study a diagnosis of axial SpA was made in 62.6%[16]. Thus, an important question resulted from this investigation: whether the performance of the referral strategy can be improved by increasing the number of referral criteria that are called for. Moreover, the good performance of the referral strategy had to be confirmed on the multicenter level with rheumatologists not specialized in SpA.

MATERIALS AND METHODS

Participating centers and referral strategies. This Multicenter Ankylosing Spondylitis survey Trial to Evaluate and compare Referral parameters in early SpA (MASTER) was conducted in 12 federal states of Germany. Initially, 54 rheumatologists distributed all over Germany and not specialized in SpA agreed to participate and provided lists of collaborating physicians (orthopedists and general practitioners) who normally see patients with chronic back pain on the primary care level. Thus, 43 rheumatologists participated actively in the study. Altogether, 1035 referral physicians designated by the rheumatologists were randomly assigned to 1 of the 2 screening strategies (Figure 1) in order to refer eligible patients: 516 (336 orthopedists and 180 general practitioners) were assigned to Strategy 1 and 519 (342 orthopedists, 177 general practitioners) to Strategy 2. Finally, 66 physicians assigned to Strategy 1 (58 orthopedists and 8 general practitioners) and 58 physicians assigned to Strategy 2 (56 orthopedists, 2 general practitioners) referred at least 1 patient to the cooperating rheumatologist.

Referral Strategy 1 required the presence of at least 1 of the following criteria: inflammatory back pain (IBP), HLA-B27 positivity, or sacroiliitis detected by imaging. The inflammatory character of back pain was described as morning stiffness in the lower part of the spine with duration > 30 min; improvement by exercise, not by rest; and/or awakening in the night because of back pain, with improvement by exercise, without further specification. Sacroiliitis could be present on any of the following imaging methods: radiographs, magnetic resonance imaging (MRI), computed tomography (CT), or scintigraphy. However, it was stressed that sacroiliac joint imaging was not obligatory at the level of the referral physician, but could be used if available.

Referral Strategy 2 required the presence of at least 2 out of the following 5 screening criteria: IBP, HLA-B27 positivity, sacroiliitis detected by imaging, positive family history for AS, and good response of the back pain to nonsteroidal antiinflammatory drugs (NSAID). Positive family history and good response to NSAID were chosen from the list of SpA manifestations on the basis of an optimal combination of sensitivity and specificity[17]. Other typical SpA manifestations (uveitis, enthesitis, peripheral arthritis, dactylitis, psoriasis, inflammatory bowel disease) may occur at any time in the course of the disease and are often not yet present in patients with short symptom duration.

Diagnostic examination at the level of the rheumatologist. At the level of the rheumatologist, diagnostic investigations required for confirmation/exclusion of SpA included clinical investigation, patient's symptoms and history, acute-phase reactants (C-reactive protein and erythrocyte sedimentation rate), HLA-B27 testing, and imaging of the sacroiliac joints (radiographs, MRI, and/or CT — whatever was required in the opinion of the rheumatologist). Finally, a decision on definite axial SpA, possible SpA, and non-SpA was made in all cases. Diagnosis of definite axial SpA was further subdivided into AS according to the modified New York crite-

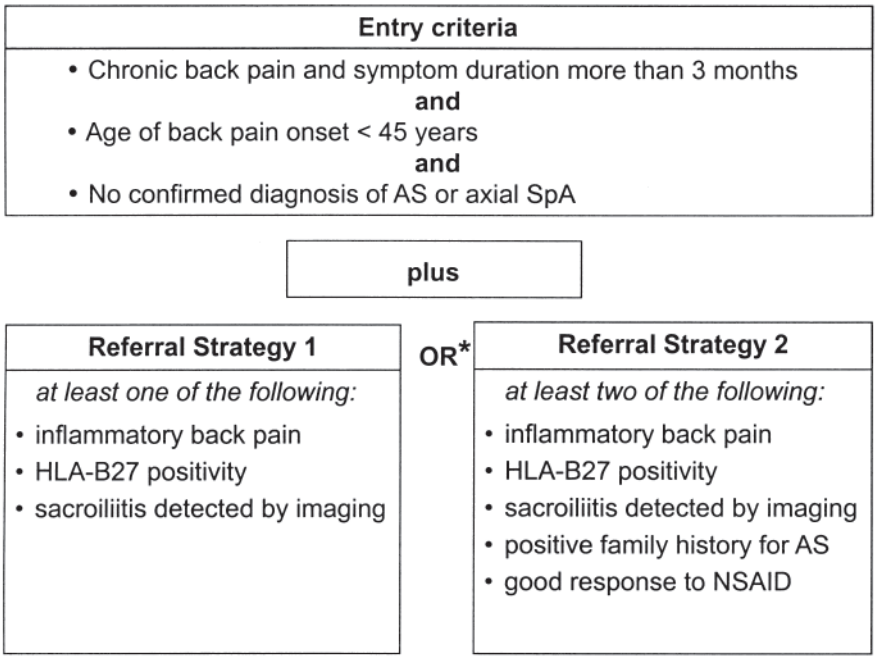

Figure 1. Entry criteria and measures of the referral strategies for primary care physicians in the MASTER study. *Each physician referred the patient using only 1 randomly assigned strategy. AS: ankylosing spondylitis, SpA: spondyloarthritis, NSAID: nonsteroidal antiinflammatory drugs.

ria and nonradiographic axial SpA[2,18]. The rheumatologist's decision on the diagnosis was used as a "gold standard."

Statistics. All clinical data were collected centrally, controlled for completeness and consistency, recorded in the database, and then analyzed. In order to compare 2 strategies, the 95% CI for the primary outcome (percentage of patients diagnosed with definite axial SpA) and the 95% CI for the absolute difference between 2 percentages was calculated. The difference was considered to be statistically significant if the lower bound of the 95% CI of this difference was above zero.

For comparison of patients' characteristics, the Mann-Whitney U test was used for the scale variables and the chi-square test for categorical variables. Agreement between the referral physicians and rheumatologists regarding the presence of SpA manifestations, assessed in all patients at both levels, was evaluated by means of the kappa value. The p value < 0.05 was considered to be statistically significant.

The study protocol was approved by the central ethical committee in Berlin and by all local ethical committees of the participating centers. Written informed consent was obtained from all patients.

RESULTS

In total, 560 cases referred to the rheumatologist by both strategies between June 2007 and August 2009 were available for analysis: 318 patients (57%) referred by Strategy 1 and 242 patients (43%) referred by Strategy 2.

Among the 318 patients referred by the first strategy, 41.8% (95% CI 36.5% to 47.3%) were diagnosed as having axial SpA: AS in 25.8% and nonradiographic axial SpA in 16.0% of the cases. Among 242 patients referred by the second strategy, axial SpA was diagnosed less often: 36.8% (95% CI 31.0% to 43.0%) of the referred patients were diagnosed as having axial SpA: AS in 22.7% and nonradiographic axial SpA in 14.1% (Figure 2). The difference in the proportion of patients with axial SpA between Strategy 1 and Strategy 2 was 5% (95% CI –3.1% to 13.1%). Therefore, Strategy 1 was at the 95% confidence level comparable to Strategy 2 regarding this outcome.

The principal characteristics of the referred patients are presented in Table 1. There were no major differences between the 2 referral strategies. Duration of symptoms at the time of referral was high in both referral strategies: a mean of 8.3 years (range 0.25–61) for referral Strategy 1, and a mean of 8.6 years (range 0.25–44) for referral Strategy 2, with no significant difference between patients with AS (mean 9.5 yrs) and patients with nonradiographic axial SpA (mean 8.6 yrs).

Performance of referral Strategy 1. The majority of patients (46.2%, n = 147) referred by Strategy 1 had 2 positive screening criteria, followed by 38.4% (n = 122) of the patients who had only 1 screening criterion, and 15.4% (n = 49) of patients with all 3 screening criteria positive (Figure 3A). Clearly, the probability of the axial SpA diagnosis was increased with the increase of the number of positive referral criteria.

The most common positive referral criterion in Strategy 1 was IBP: it was present in the opinion of the referring physician in 76.7% (n = 244) of patients referred by this strategy. The diagnosis of definite axial SpA was made in 41.8% (n = 102) of all patients referred because of the presence of IBP (Figure 4A). However, in patients with IBP as the single referral criterion (21.4%, n = 68), definite axial SpA was diagnosed in only 16.2% (n = 11). The strength of

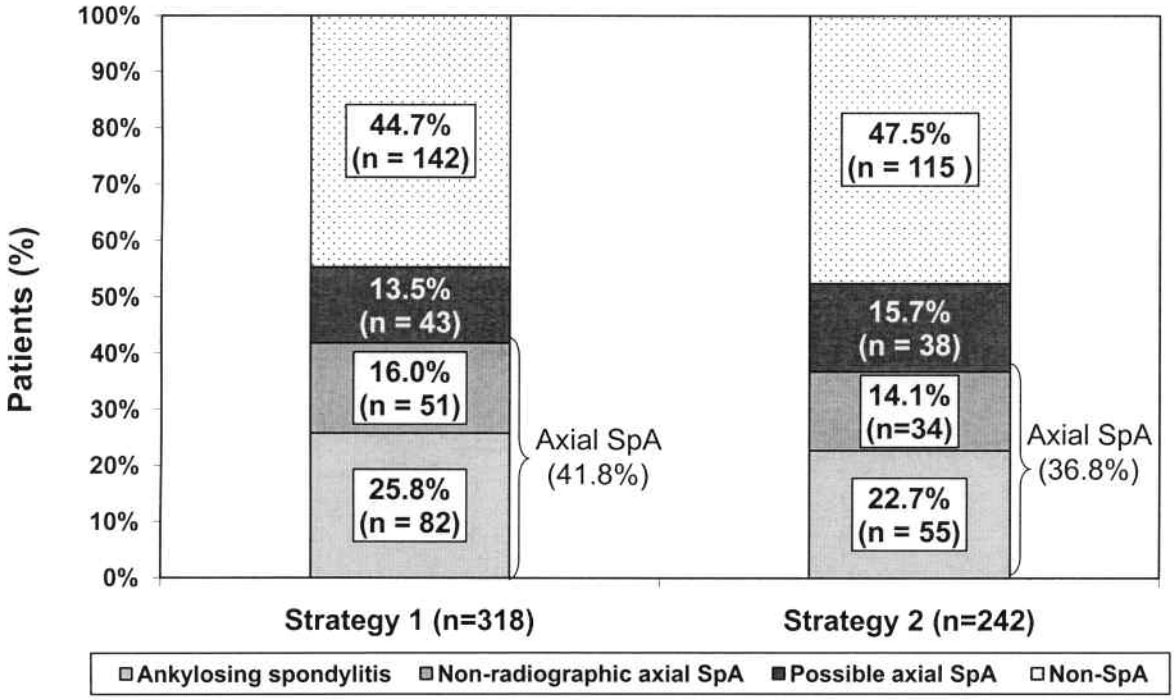

Figure 2. Distribution of the final diagnoses in patients referred by the 2 strategies (for definition see Figure 1). Definite axial SpA comprised ankylosing spondylitis according to modified New York criteria and nonradiographic axial SpA as judged by a rheumatologist. SpA: spondyloarthritis.

Table 1. Patient characteristics according to diagnosis and referral strategy.

Group		Age, yrs, mean ± SD	Age of Back Pain Onset, yrs, mean ± SD	Duration of Back Pain, yrs, mean ± SD	Males %	HLA-B27+, %
All patients	Strategy 1 (n = 318)	38.1 ± 11.3	28.7 ± 9.2	8.3 ± 9.5	53.1	55.2
	Strategy 2 (n = 242)	39.5 ± 10.9	29.2 ± 8.9	8.6 ± 9.3	55.4	56.1
Ankylosing spondylitis	Strategy 1 (n = 82)	37.4 ± 11.9	26.5 ± 8.3	9.3 ± 10.8	61.0	81.7
	Strategy 2 (n = 55)	38.2 ± 11.9	28.5 ± 10.1	9.8 ± 9.9	69.1	83.6
Nonradiographic axial SpA	Strategy 1 (n = 51)	39.4 ± 13.1	29.4 ± 9.2	9.1 ± 9.4	47.1	74.5
	Strategy 2 (n = 34)	37.0 ± 11.0	28.2 ± 7.7	7.9 ± 9.1	50.0	67.7
Possible SpA	Strategy 1 (n = 43)	35.1 ± 10.7	27.6 ± 9.2	6.5 ± 8.9	58.1	59.5
	Strategy 2 (n = 38)	39.5 ± 11.3	29.4 ± 9.9	8.4 ± 9.0	65.8	59.5
Non-SpA	Strategy 1 (n = 142)	38.9 ± 10.2	29.9 ± 9.6	8.0 ± 8.9	49.3	31.7
	Strategy 2 (n = 115)	40.9 ± 10.1	31.3 ± 8.3	8.4 ± 9.2	47.0	38.0

SpA: spondyloarthritis.

agreement between referral physicians and rheumatologists regarding the presence of IBP was rather low, with a kappa value of 0.198 ($p < 0.001$). In the opinion of the rheumatologists, IBP was present in 58.5% (n = 186) of the patients referred by Strategy 1. In this group, 62.9% (n = 117) of patients were diagnosed with definite axial SpA.

Sacroiliitis on imaging was used as a referral criterion in 55.7% (n = 177) of the patients referred by Strategy 1. Definite axial SpA was diagnosed in 50.3% (n = 89) of them (Figure 4A). Most often, referral physicians reported sacroiliitis on radiographs (88 patients), followed by MRI (82 patients), scintigraphy (20 patients), and CT (5 patients). At the same time, the highest sensitivity (evaluated by the percentage of patients diagnosed with axial SpA) was found for sacroiliitis noted by a referral physician on CT (80%, 4 of 5 patients), followed by MRI (64.6%, n = 53), radiographs (45.5%, n = 40), and scintigraphy (30%, n = 6).

HLA-B27 positivity was used as a referral criterion in 44.7% (n = 142) of patients referred by Strategy 1, 57.7% (n = 82) of whom were diagnosed with definite axial SpA (Figure 4A).

Performance of referral Strategy 2. As shown in Figure 2, fewer patients (36.8%, 89 out of 242) were diagnosed with definite axial SpA in Strategy 2 compared to Strategy 1, although the difference was not statistically significant. The probability of a diagnosis of definite axial SpA also increased with the increase of the number of positive referral criteria (Figure 3B).

Interestingly, 241 of the 242 patients referred by Strategy 2 would also have fulfilled Strategy 1, and only 1 patient had 2 referral criteria other than IBP, HLA-B27, or sacroiliitis detected by imaging.

The frequency and performance of IBP, HLA-B27, and sacroiliitis detected by imaging as referral criteria were similar to those found in Strategy 1 (Figure 4B). As in Strategy 1, the most frequent referral criterion (in 87.6%, n = 212, of the referred patients) was IBP. Definite axial SpA was diagnosed in 34.9% (n = 74) of these patients, but again the level of agreement between referral physicians and rheumatologists regarding the presence of IBP was low, with a kappa value of 0.035 ($p = 0.052$). The second most frequent positive referral criterion in Strategy 2 was the good response to NSAID, with a frequency of definite axial SpA of 34.6% (n = 54) in this group (Figure 4B). Agreement between referral physician and rheumatologist regarding this factor also was not high, with a kappa value of 0.211 ($p = 0.061$).

HLA-B27 positivity was noted as a referral criterion in 52.5% (n = 127) of all patients referred by Strategy 2, 48.8% (n = 62) of whom were diagnosed with definite axial SpA. Sacroiliitis detected by imaging was present as a referral criterion in 38.0% (n = 92; Figure 4B). Similarly to Strategy 1, sacroiliitis was most frequently reported on radiographs (49 patients), followed by MRI (33 cases), scintigraphy (18 cases), and CT (3 patients). However, the most sensitive imaging method with respect to the final SpA diagnosis was MRI (69.7%, n = 23, of the patients with sacroiliitis on MRI in the opinion of the referral physician received a diagnosis of definite axial SpA), followed by scintigraphy (55.6%, n = 10), radiographs (47.0%, n = 23), and CT scanning (33.3%, n = 1).

Family history of AS was noted as a referral criterion in 19.0% (n = 46) of the patients, and definite axial SpA was diagnosed in 45.6% (n = 21) of the cases (Figure 4B).

DISCUSSION

When assessing referral strategies for identifying patients with axial SpA by physicians, who are the first to see the patients with chronic back pain, 2 aspects are of relevance: first, which strategy results in a higher number of patients referred because of suspected axial SpA; and second, how many referred patients must the rheumatologist see to make a final diagnosis of axial SpA. In both aspects the simpler Strategy 1 (1 out of 3 referral criteria has to be positive) was slightly better than Strategy 2 (requiring 2 out of 5 positive

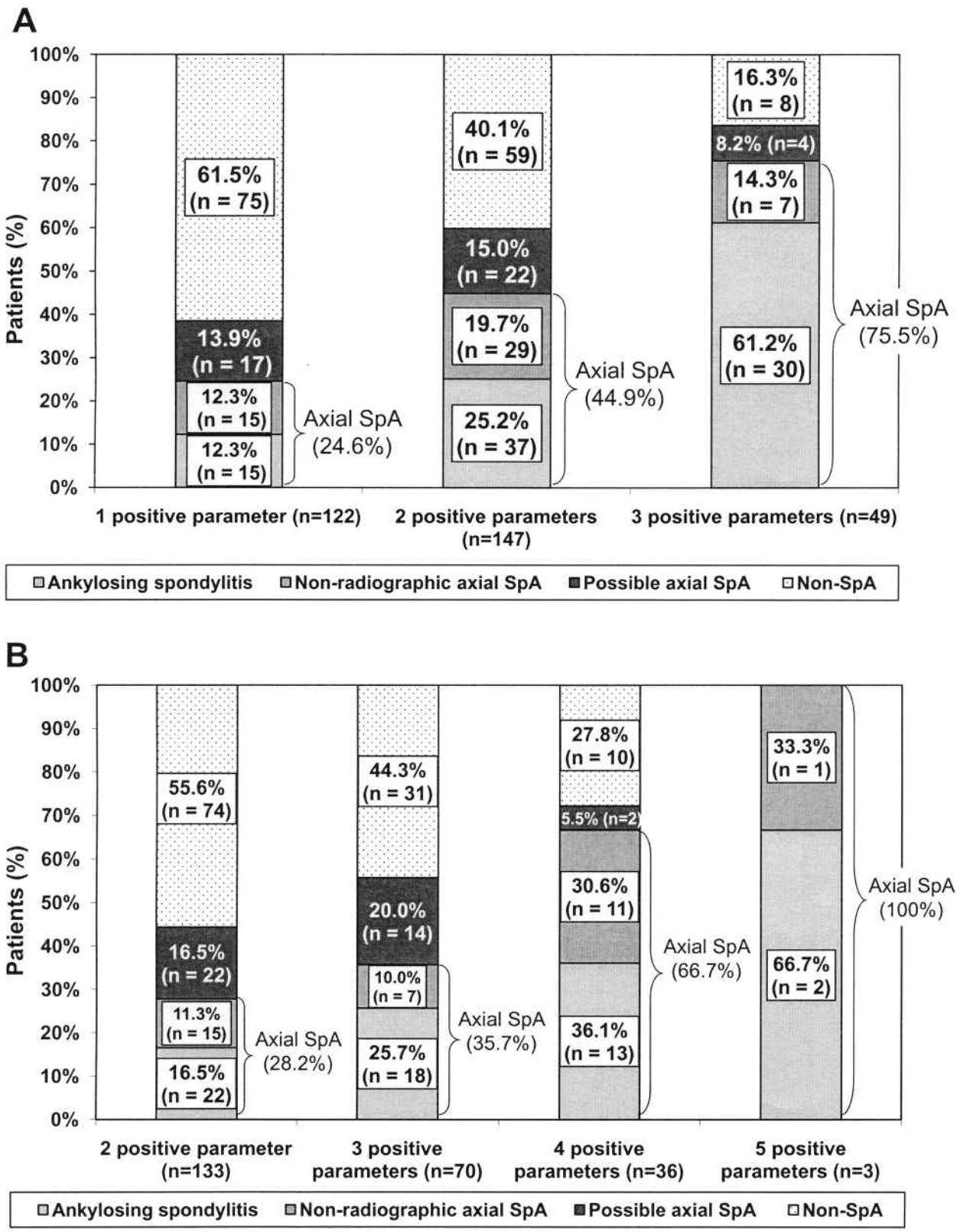

Figure 3. Probability of the diagnosis of axial SpA in relation to the number of positive screening criteria in the 2 referral strategies. A. Referral Strategy 1 (n = 318). B. Referral Strategy 2 (n = 242). SpA: spondyloarthritis.

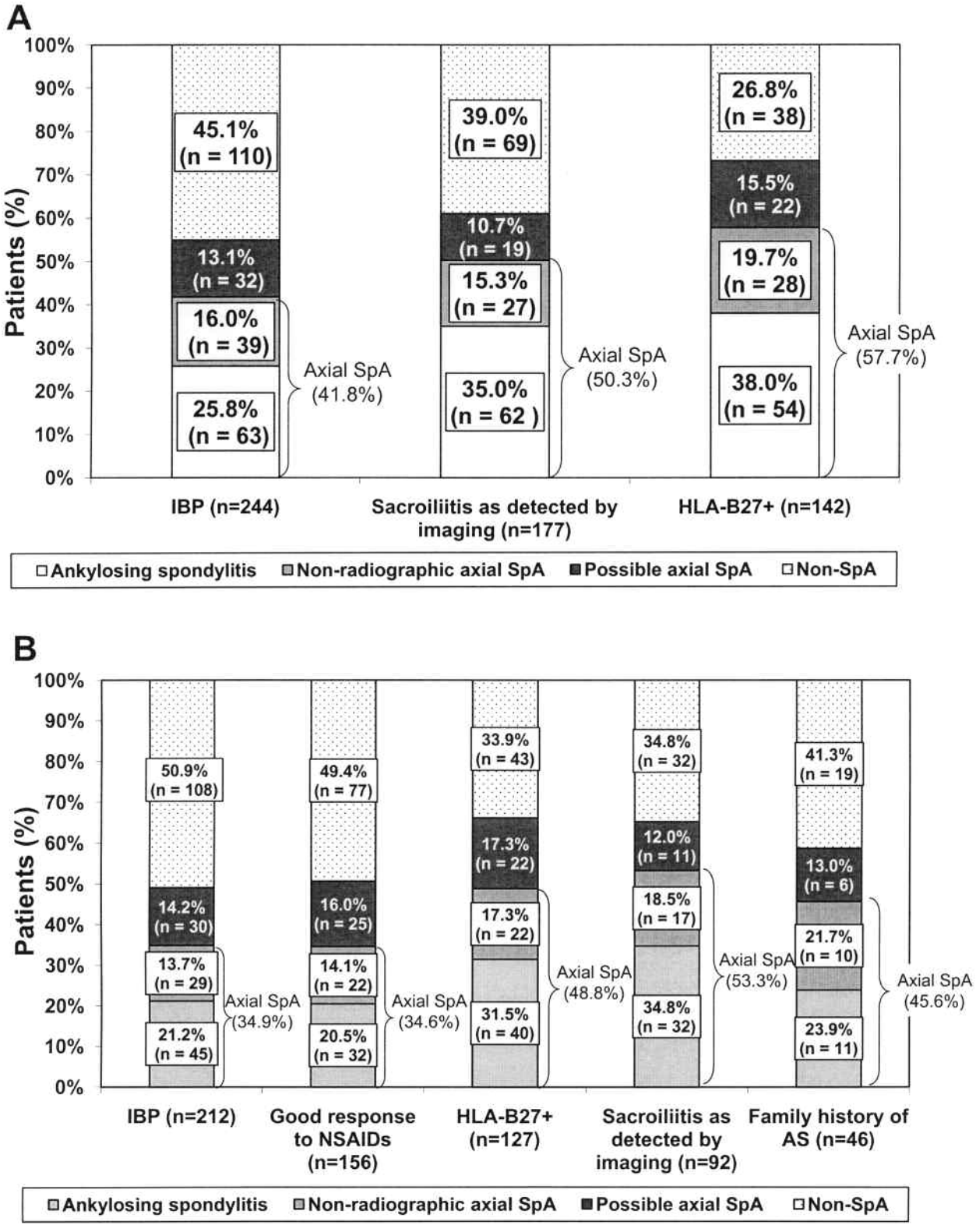

Figure 4. Fulfillment of the referral criteria indicated by percentage of patients diagnosed finally with definite axial SpA. A. Referral Strategy 1. B. Referral Strategy 2. Numbers of patients indicate all patients with a positive criterion in the corresponding strategy independent of the presence or absence of other referral criteria. SpA: spondyloarthritis, AS: ankylosing spondylitis, IBP: inflammatory back pain, NSAID: nonsteroidal antiinflammatory drugs.

criteria): more patients were referred, and among the referred patients an SpA diagnosis could be made in 41.8% compared to 36.8%, respectively, although the difference was not statistically significant. It is important to stress here that both strategies were tested in patients with chronic low back pain (in contrast to acute back pain) and in patients aged 45 years or younger when the first symptoms started. Such a preselection for criteria typical for SpA is necessary to reduce the huge number of patients with any back pain.

Most interestingly, in this prospective nationwide study in Germany we were able to confirm the outcome of our previous study performed in a tertiary SpA center in which only Strategy 1 was tested, resulting in a final diagnosis of SpA in 45.6% of patients[16]. Among all patients diagnosed with definite axial SpA in both arms of our present study, a diagnosis of AS was made in about 60% and diagnosis of nonradiographic axial SpA in about 40% of cases. Although the percentage of patients with nonradiographic axial SpA was slightly lower than the 49% in our previous investigation[16], these results underline the relevance of this subgroup for early diagnosis[2]. The kind of physician who is seeing patients with chronic back pain primarily differs from country to country. In Germany these patients are most often seen primarily by orthopedists, a situation that is reflected by the high percentage of orthopedists in comparison to general practitioners participating actively in our study. In other countries general practitioners, physiotherapists, or even neurologists might be the first and main contact for patients with chronic back pain. The proposed screening strategies are intended for unselected populations of patients with back pain, independent from which physician these patients are seen by first.

Strategy 1 is simple, feasible, and results in a high percentage of patients diagnosed with SpA, which is important if such a strategy should be accepted and applied by rheumatologists who are normally too busy to see many chronic back patients not having SpA. Strategy 2 was designed in the expectation that the percentage of patients diagnosed with SpA might be even higher when at least 2 positive criteria were required. Indeed, in both strategies there was a higher percentage of patients diagnosed with SpA the more referring indicators were positive. That Strategy 2 was not better and was even slightly less effective might be explained by the rather complex features of this strategy, which include the evaluation of 5 criteria. This might also be a reason why fewer of the contacted physicians initially randomized to Strategy 2 participated in our study and why fewer patients were referred by this strategy. Our results also confirm the assumption that any referral strategy used in primary care has to be as simple as possible, otherwise it will not be used or may not be used correctly[15].

The 3 referral criteria used in Strategy 1 — IBP, evidence of sacroiliitis by imaging, and a positive HLA-B27 test, either alone or in combination — performed more or less equally well. Patients were most often referred because of IBP, followed by sacroiliitis and positive HLA-B27. However, among these 3 criteria HLA-B27 performed best regarding a final diagnosis of SpA, either alone or in combination with 1 of the others, followed by sacroiliitis. This good performance of HLA-B27 as a referring criterion was also found in Strategy 2. If the best criterion, HLA-B27, had been used alone, a diagnosis of axial SpA would have been made in only 82 patients; and if the most often-used criterion, IBP, had been used alone such a diagnosis would have been made in only 102 patients referred by Strategy 1. This is quite in contrast to the larger number of 133 patients with axial SpA diagnosed by applying Strategy 1, suggesting that all 3 criteria should be used in a referral strategy. The effectiveness of Strategy 1 can even be increased when referring physicians are asked to send only patients who have 2 or 3 of these criteria positive (Figure 3A); however, this will result in a decrease in the sensitivity of this strategy for the identification of patients with axial SpA.

In addition to our own previous study[16], several related investigations have recently been published, mostly focusing on the presence of IBP. Recently, Weisman, *et al* described a case ascertainment tool for AS[19]. The authors developed a questionnaire for patients with chronic back pain with several questions related to IBP plus the presence of uveitis. The questionnaire is relatively simple, does not involve a physician at the stage of completion by a patient, and demonstrated a sensitivity of 67.4% and specificity of 94.6%. However, that tool was validated only for patients with AS and its sensitivity in the identification of patients with nonradiographic axial SpA is not known. More important, it was not determined how this tool would perform as a screening measure in primary care. Another study focused on clinical variables typical for IBP. Among referred patients, 32.7% were diagnosed with SpA (14.6% with AS, 15.1% with undifferentiated SpA, and 3% with other SpA)[20]. These data are similar to those published by Hermann, *et al* for patients referred with IBP according to the Calin criteria: 33% were diagnosed with SpA by the rheumatologist[21].

Our results demonstrate that interpretation of back pain as inflammatory or noninflammatory, as well as detection of sacroiliitis, is quite challenging for referral physicians. These findings are in accord with data from a recent study in Spain that showed low level of agreement between primary care physicians and rheumatologists regarding the presence of IBP and sacroiliitis, while variables such as HLA-B27, acute anterior uveitis, inflammatory bowel disease, and psoriasis showed a moderate to good agreement[22]. HLA-B27 is in fact the easiest test to interpret, as indicated by the 96.7% of patients in whom this referral criterion was positive in the opinion of referral physicians and rheumatologists in our study.

Performance of imaging procedures was not required by

the study protocol at the level of the referral physician; however, a substantial proportion of the patients in both strategies were referred because of sacroiliitis in imaging. While sacroiliitis as a referral measure performed relatively well in our study, the final rates of diagnosis of axial SpA (50% for Strategy 1, 53% for Strategy 2) in patients referred because of sacroiliitis upon imaging indicate that sacroiliitis cannot be used for diagnosis of axial SpA at the primary care level. These relatively low rates indicate substantial discrepancy between referral physicians and rheumatologists regarding interpretation of imaging relevant for the SpA diagnosis. Additionally, it might also indicate that not all patients with sacroiliitis on imaging do indeed have SpA.

MRI, a relatively new diagnostic tool for sacroiliitis, was used frequently in our study and only slightly less often than radiography as a referral measure in the 2 strategies. More interesting, if sacroiliitis on MRI was used as a referral measure, 65% of the patients in Strategy 1 and 70% in Strategy 2 were diagnosed finally as having axial SpA. In this regard, MRI performed best in relation to the other imaging methods. This indicates the increasingly important role of MRI in early identification of patients with axial SpA. Although we do not suggest use of MRI actively as a screening criterion in primary care because of the costs and the difficulties of interpretation[15], our data indicate that MRI is used quite often anyway for investigation of patients with chronic back pain. This also implies that not only rheumatologists but also radiologists, orthopedists, and probably primary care physicians should be trained in indications for and recognition of typical SpA findings on MRI[23,24].

A limitation of our study is related to its design: only patients with chronic back pain who fulfilled the requirements for the strategy were referred to the rheumatologist. Therefore it is not known how many patients with back pain were seen by referral physicians in total, and as a consequence how many patients with axial SpA were overlooked because they did not fulfill either strategy or because the presence of any of these referral criteria was not observed by the referral physician. Nonetheless, it can be assumed that the screening criteria were applied in only a proportion of suitable patients seen in a busy practice, and that continuous education on SpA is needed to raise interest in this disease and to improve early diagnosis in a higher number of patients. We intended to test an approach from the rheumatologist's point of view: how many patients are referred and in how many of these can a diagnosis of axial SpA be made? However, consecutively including all patients with chronic back pain seen at the primary care level would also be very interesting, but would require a different study design and would be more difficult.

Although the screening criteria applied in our study worked, the long periods between first symptoms and diagnosis of SpA that we observed consequently emphasize the need for more application of such a strategy.

Strategy 1 can be recommended as an effective and reliable method to screen patients with chronic back pain for the identification of axial SpA at the primary care level.

ACKNOWLEDGMENT

The authors thank all cooperating rheumatologists, orthopedists, and general practitioners who participated in the study, including K. Alliger, C. Baumann, W.A. Biewer, M. Bohl-Bühler, J. Brandt-Jürgens, W. Demary, R. Dockhorn, S. Ewerbeck, K.H. Göttl, A. Grässler, M. Hammer, B. Heilig, S. Jacki, A. Kapelle, K. Karberg, H. Kellner, P. Kern, T. Klopsch, I. Kötter, G. Kramer, C. Kühne, H-E. Langer, K. Manger, H. Markus, A. Melzer, F. Mielke, W. Ochs, D. Pick, N. Rinaldi, K. Rockwitz, J-A. Rump, M. Schneider, U. Schoo, H. Schwenke, E. Ständer, C. Stille, F. Striesow, J. Währisch, U. Walter, V. Waltz, S. Wassenberg, M. Zänker, and S. Zinke. The authors acknowledge also the work of Georg Heine on management of the study database.

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