

## Retrospective Study



## Criteria for the Appropriate Treatment of Osteoporotic Vertebral Compression Fractures

Giovanni C. Anselmetti, MD<sup>1</sup>, Jason Bernard, FRCS (Orth)<sup>2</sup>, Thomas Blattert, MD, PhD<sup>3</sup>, Charles Court, MD<sup>4</sup>, Daniel Fagan, FRCS<sup>5</sup>, Hendrik Fransen, MD<sup>6</sup>, Patrick Fransen, MD<sup>7</sup>, Tarun Sabharwal, FRCR<sup>8</sup>, Frédéric Schils, MD<sup>9</sup>, Rupert Schupfner, MD<sup>10</sup>, Mashood Ali Siddiqi, MD<sup>11</sup>, Herman Stoevelaar, PhD<sup>12</sup>, and Christian Kasperk, MD, PhD<sup>13</sup>

From: <sup>1</sup>Interventional Radiology, Villa Maria Hospital, Turin, Italy; <sup>2</sup>St Georges Hospital, London, United Kingdom; <sup>3</sup>Department for Spine Surgery and Traumatology, Orthopaedische Fachklinik Schwarzach, Schwarzach/Munich, Germany; <sup>4</sup>Bicetre University Hospital, AP-HP Paris, F-94270; JE 2494 Univ Paris-Sud ORSAY, F-91405, France; <sup>5</sup>BMI Woodlands Hospital Darlington, Morton Park, Darlington, County Durham, United Kingdom; <sup>6</sup>Interventional Department, University Hospital St. Lucas, Ghent, Belgium; <sup>7</sup>Clinique du Parc Léopold, Brussels, Belgium; <sup>8</sup>Guys and St Thomas' hospital, London, United Kingdom; <sup>9</sup>Clinique Générale Beaulieu and Clinique La Colline, Geneva, Switzerland; <sup>10</sup>Klinikum Bayreuth, Bayreuth, Germany; <sup>11</sup>University Hospital Aintree, Liverpool, United Kingdom; <sup>12</sup>Centre for Decision Analysis and Support, Ismar Healthcare, Lier, Belgium; <sup>13</sup>University of Heidelberg, Department of Internal Medicine I and Clinical Chemistry, Heidelberg, Germany

Address Correspondence:  
Giovanni Carlo Anselmetti, MD  
Interventional Radiology  
Villa Maria Hospital  
Strada Comunale di Mongreno  
180,  
Turin, 10132, Italy  
E-mail:  
gc.anselmettifastwebnet.itt

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**Background:** The heterogeneity of patients with osteoporotic vertebral compression fractures (VCF) necessitates a tailored approach of balancing the benefits and limitations of available treatments. Current guidelines are divergent, sometimes contradictory, and often insufficiently detailed to guide practice decisions.

**Objectives:** This study aimed at establishing treatment recommendations at the patient-specific level.

**Study Design:** Using the RAND/UCLA Appropriateness Method (RAM), the appropriateness of different treatment options for osteoporotic VCFs was assessed.

**Setting:** The assessment was conducted by a European multidisciplinary panel of 12 experts.

**Methods:** The appropriateness of non-surgical management (NSM), vertebroplasty (VP), and balloon kyphoplasty (BKP) was determined for 128 hypothetical patient profiles. These were unique combinations of clinical factors considered relevant to treatment choice (time since fracture, MRI findings, impact and evolution of symptoms, spinal deformity, ongoing fracture process, and pulmonary dysfunction). After 2 individual rating rounds and plenary meetings, appropriateness statements (appropriate, inappropriate, and uncertain) were calculated for all clinical scenarios.

**Results:** Disagreement dropped from 31% in the first round to 7% in the second round. Appropriateness outcomes showed specific patterns for the 3 treatments. For three-quarters of the profiles, only one treatment was considered appropriate: NSM 25%, VP 6%, and BKP 45%. NSM was usually appropriate in patients with a negative MRI or a positive MRI without other unfavorable conditions (poor outcomes for the other variables). VP was usually appropriate in patients with a positive MRI, time since fracture  $\geq 6$  weeks, and no spinal deformity. BKP was recommended for all patients with an ongoing fracture process, and also in most patients with a positive MRI and  $\geq 1$  other unfavorable factor.

**Limitations:** The prevalence of the patient profiles in daily practice is yet unknown.

**Conclusion:** The panel results may help to support treatment choice in the heterogeneous population of patients with osteoporotic VCF.

**Key words:** Appropriateness criteria, balloon kyphoplasty, non-surgical management, osteoporosis, RAND/UCLA Appropriateness Method, treatment choice, vertebral compression fractures, vertebroplasty:

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**V**ertebral compression fractures (VCFs) are a commonly seen complication of primary or secondary osteoporosis. For Europe, their annual incidence has been estimated at 1% for women aged 50-79 years and at 0.6% for men in the same age category (1). A substantial part (almost two-thirds) of osteoporotic VCFs remains undetected (2), but those coming to clinical attention are often associated with considerable morbidity. Although pain is usually the most pronounced initial problem, VCFs can also lead to spinal deformity that may be associated with impaired mobility and physical functioning (3), decreased pulmonary function (4), and gastro-intestinal problems (5). These conditions may have a significant impact on quality of life (6) and may even contribute to a reduced life expectancy (7). Although the management of acute pain is usually the primary short-term treatment objective, prevention of longer term consequences is also important. Non-surgical management (NSM), consisting of bed rest, analgesics, and occasionally bracing, is the common initial treatment. Although NSM shows pain relief and mobility improvement in many patients, there is a substantial number of patients that insufficiently responds to this conservative approach. This is particularly true for patients with spinal deformity, as NSM does not allow restoration of the damaged vertebra and does not prevent kyphosis (8). In addition, (narcotic) analgesics are often less well tolerated by elderly patients, and their sedative effects may also increase the risk of falling and fractures. As VCFs are often seen in vulnerable elderly, prolonged bed rest may result in a compromised pulmonary function, poor physical condition, and increased mortality (9). Minimally invasive treatments aim at stabilization and/or correction of the fracture resulting in pain relief and restoration or conservation of the spinal curvature. Conventional open surgery is reserved for unstable fractures with or without a neurologic deficit. Minimally invasive treatments, vertebroplasty (VP) and balloon kyphoplasty (BKP), are increasingly used. Both techniques aim at stabilizing and strengthening the fractured vertebra by injecting cement. VP consists of direct injection of the cement into the vertebra, while with BKP initially a cavity is created using an inflatable balloon, targeting at stabilizing the fracture, restoring the vertebral body height, and correcting angular deformity. VP and BKP may be performed by orthopedic and neurosurgeons, or by interventional radiologists and pain management physicians.

Several randomized controlled trials (RCTs) have

shown that VP and BKP result in quicker pain relief and mobility improvement in comparison to NSM (10-12). Two RCTs comparing VP to a sham procedure found no significant difference in pain and function up to 6 months follow-up (13-14). However, these studies have been widely criticized for their inclusion criteria and other methodological issues (15). VP and BKP show generally similar outcomes for efficacy and safety (10-12,16,17), but there are differences between these techniques. Cement leakage is more frequently seen after VP (11-60% versus 10-27% for BKP) (18). In addition, the capability of BKP for restoring vertebral body height is superior to VP (16). However, it is currently unclear in which patients these advantages of BKP over VP outweigh its drawbacks, such as higher invasiveness, more extensive anesthesia, and higher costs (19).

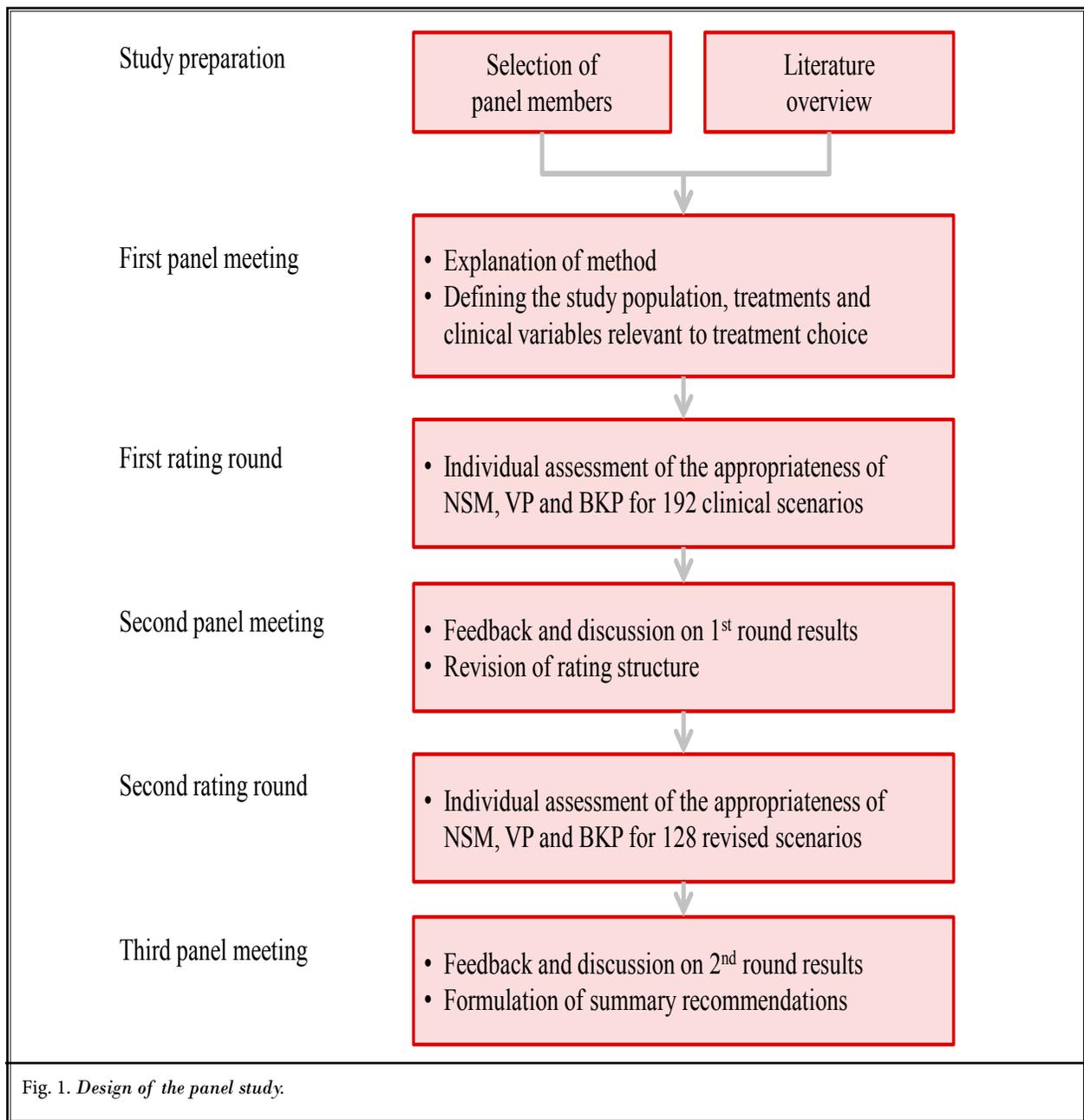
Despite the evidence on efficacy and safety of minimally invasive treatments for osteoporotic VCF, there remains much uncertainty about their precise indications, which is partly to be ascribed to the heterogeneity of the patient population. Currently available clinical guidelines and recommendations, established by different medical societies (20-26), reflect divergent perspectives, are sometimes contradictory, and often insufficiently detailed to the wide range of patients seen in day-to-day practice.

The aim of this European panel study was to establish criteria for individually tailored treatment choice in patients with osteoporotic VCFs, by combining the evidence from clinical studies with the judgment of a multidisciplinary team of experts.

## **METHODS**

### **Study Design**

To explore the indications and contra-indications of VCF treatments in light of relevant patient conditions, we used the RAND/UCLA Appropriateness Method (RAM) (27-28). This modified Delphi method has been used in various fields of medicine, and is particularly helpful when the evidence from clinical studies is insufficient or insufficiently detailed to apply to the wide range of patients seen in everyday clinical practice (28). The RAM encompasses a systematic approach to develop patient-specific recommendations (i.e., at the level of symptoms, medical history, and test results), by combining evidence from clinical studies with the collective judgment of experts (28). The RAM has been demonstrated to produce reliable, internally consistent, and clinically valid results (29). The design of



the study is depicted in Fig. 1. The panel was composed of 12 experts from 5 European countries, representing all relevant disciplines (interventional radiology, spinal surgery, orthopedic surgery, neurosurgery, trauma surgery, internal medicine; see Acknowledgments). Selection of experts was based on their specific expertise in the field of VCF. All but one performed VP and/or BKP themselves; one panelist (internist) was involved

in the pre-selection of these procedures. Selection of criteria and parameters was supported by a literature study on efficacy and safety of VCF treatments, and on factors related to treatment choice. The panel first met in May 2011 to discuss the study population, treatment options, and clinical variables to be considered in the appropriateness assessments. Consensus existed to restrict the study population to patients fulfilling

the following criteria: a). osteoporotic VCF type A (30), documented with an appropriate imaging technique, b). having at least moderate symptoms (visual analogue score (VAS)  $\geq 5$ ) correlating with the fracture, c). absence of neurological symptoms, d). age  $\geq 18$  years, and e). absence of absolute contra-indications for active treatment (not fit enough to undergo surgery, pregnancy, spine infection, coagulation disorder). These criteria are similar to the inclusion criteria used in the most recent RCTs on VCF treatment (10-12,16,17). Treatment choice was limited to NSM, VP, and BKP, all without further specification. Based on the available literature and their clinical experience, the panelists selected 7 clinical variables that they considered relevant to treatment choice (time since fracture, MRI findings, mobility limitation, severity of pain, spinal deformity, proof of ongoing fracture process, and presence of pulmonary and/or gastrointestinal dysfunction), all divided into 2-4 categories. By permutation of these clinical factors, and after exclusion of unrealistic combinations, a set of 192 mutually exclusive patient profiles was compiled. Using an electronic rating program, panelists individually assessed the appropriateness of the 3 therapeutic options for all these profiles on a 9-point scale (reference values: 1 = inappropriate, 5 = uncertain, 9 = appropriate). Following the RAND/UCLA definition, a treatment had to be considered appropriate if the expected benefits exceeded the potential negative consequences by a sufficient margin that the treatment is worth doing (27). Financial costs or other potential constraints had to be disregarded. The rating program was accompanied by a literature overview ensuring that panelists had access to the same body of evidence while doing the ratings. The results of the first rating round were discussed during a plenary meeting (September 2011). The aim of the discussion was not primarily to reach consensus, but to investigate whether disagreement was due to differences in the interpretation of the definitions and profiles used. After the meeting, a second individual rating round took place, using an adapted structure and refined definitions. A final meeting (December 2011) was organized to formulate recommendations based on the results of the second rating round.

### Statistical Analysis

To translate individual ratings into panel statements, we used the mathematical rules that are typically applied in RAND/UCLA studies (28). Indications were deemed appropriate if the median panel score was between 7 and 9, and inappropriate if the median was

between 1 and 3, both without disagreement between panelists. Disagreement was defined as the situation in which at least 4 panelists scored in each of the sections 1-3 and 7-9. All indications not assessed as "appropriate" or "inappropriate" were labeled "uncertain." Frequency tables and cross-tabulations were used to describe and analyze the appropriateness of indications by patient conditions.

## RESULTS

### Agreement

The first round showed substantial dispersion of opinions. Disagreement (see statistical analysis) was 31% with no extreme differences between the 3 treatments (27-34%). The panel discussion revealed that disagreement was largely due to different ways of rating the appropriateness of treatments. Some panel members had rated the first-choice treatment with a 9 and second best options with low scores; whereas others had used a more proportional approach (e.g., a 9 for the first choice and a 7 for the second best). In addition, it appeared that cases and definitions had not always been interpreted in a similar way. Finally, there were some pronounced differences between the specialties. The panel discussion led to adaptation of the rating structure, refinement of the definitions, exclusion of unrealistic cases, and better instructions to ensure uniformity in the way of rating the appropriateness of treatments. The adapted rating program included 128 different profiles (versus 192 in the first round). An overview of the clinical variables, categories, and definitions used in the second round is given in Table 1.

The second round showed substantial convergence of opinions. The overall percentage of disagreement dropped to 7%, with the best outcome for VP (2%) and similar figures for NSM (10%) and BKP (9%). As a consequence, the percentage of uncertain indications decreased from 63% in the first round to 35% in the second round.

### Appropriateness of Treatment

Results on appropriateness by treatment (second round) are shown in Fig. 2.

For two-thirds of the theoretical population BKP was considered appropriate, as opposed to one quarter for NSM and VP. The highest proportion of uncertainty was seen for VP. As the appropriateness of a treatment was rated independently from other treatments, more than one treatment could be appropriate for a certain

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Table 1. Overview of clinical variables, treatment options, and definitions used for the construction of clinical profiles in the second rating round

Variable	Categories	Definitions
Time since fracture	< 6 weeks 6 weeks – 3 months > 3 months	
MRI findings	Negative Positive	Positive MRI: edema visible
Impact of VCF on daily functioning	Moderate Severe	Impact of VCF on daily functioning due to mobility impairment and/or pain. It is assumed that pain medication has been optimized.
Evolution of symptoms	Stable Has worsened	Evolution of symptoms (mobility impairment, pain) since fracture
Spinal deformity	No Yes	≥ 15% kyphosis and/or ≥ 10% scoliosis and/or ≥ 10% dorsal wall height reduction and/or vertebral body height loss ≥ 20%
Proof of ongoing fracture process	No Yes	Increased height reduction on radiologic images at follow-up (≥ 20% in comparison to initial imaging)
Presence of pulmonary dysfunction	No Yes	Presence of pulmonary disorders likely to deteriorate due to kyphosis resulting from VCF (e.g. Chronic Obstructive Pulmonary Disease).

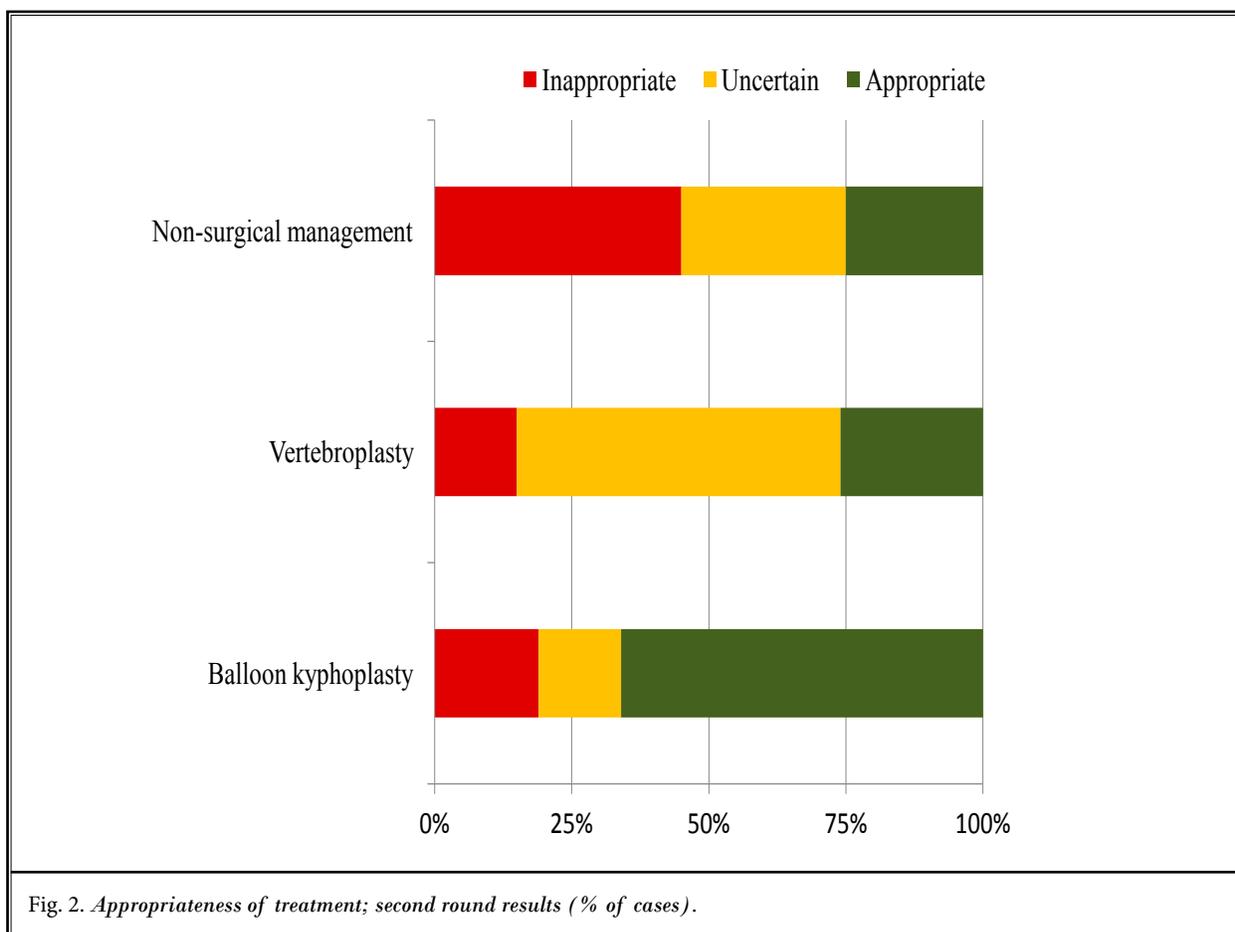


Fig. 2. Appropriateness of treatment; second round results (% of cases).

patient profile. In 4% of the profiles, none of the treatment options was deemed appropriate. For three-quarters of the profiles, only one of the treatments was considered appropriate. NSM was the only appropriate treatment in 25% of profiles, while the figures for VP and BKP were 6% and 45%, respectively. Profiles for which more than one treatment was appropriate concerned only the combination VP and BKP (21%). The appropriateness of treatments for different clinical factors is shown in Table 2.

For NSM, the most discriminative variable is magnetic resonance imaging (MRI) findings, followed by ongoing fracture process and time since fracture. Other (unfavorable) conditions had a modest impact on the appropriateness outcomes for NSM. VP and BKP were never considered appropriate if the outcomes of MRI were negative. However, this does not automatically imply that these indications are inappropriate since the outcome could also be uncertain. The presence of spinal deformity substantially lowered the appropriateness of VP, while the opposite was true for BKP. An ongoing fracture process increased the appropriateness of both treatments, and BKP was considered always appropriate if this condition was present. BKP was considered most appropriate in the first 6 weeks after the occurrence of the fracture, while the appropriateness of VP became higher if time since fracture was more than 6 weeks. Other (unfavorable) variables increased the appropriateness of both treatments, al-

beit to a modest extent. A detailed analysis of the appropriateness of NSM, VP, and BKP for the 128 different profiles showed pronounced patterns (Figs. 3-5). On the basis of these figures, the panel formulated a set of recommendations (Fig. 6), dichotomized into usually "recommended" (appropriate) and usually "not recommended" (inappropriate). All other situations that are not included in the recommendations were, by definition, deemed uncertain.

## DISCUSSION

This study produced consistent recommendations for the choice between NSM, VP, and BKP in patients with osteoporotic VCFs. The recommendations are very specific since in 75% of the clinical scenarios, the recommendation was exclusively in favor of one of the treatments (NSM, VP, or BKP), while there were only a few scenarios (4%) in which none of the treatments were considered appropriate. NSM was usually appropriate in patients with a negative MRI, or a positive MRI without other unfavorable conditions. VP was usually appropriate in patients with a positive MRI, time since fracture  $\geq 6$  weeks, and no spinal deformity. BKP was recommended for all patients with an ongoing fracture process, and also in most patients with a positive MRI and  $\geq 1$  other unfavorable factor.

We took into account that besides pain relief, restoring the vertebral shape may be a treatment goal, and that the opportunity to correct segmental kyphosis decreases

Table 2. *Appropriate treatments by clinical variables. Second round results.*

Variable	Category	% appropriate		
		NSM	VP	BKP
Time since fracture*	< 6 weeks	3	9	94
	6 weeks-3 months	31	31	60
	> 3 months	33	31	54
MRI findings	Negative	94	-	-
	Positive	2	34	89
Impact on daily functioning	Moderate	28	19	64
	Severe	22	33	69
Evolution of symptoms	Stable	28	23	63
	Has worsened	22	28	70
Spinal deformity	No	28	44	58
	Yes	22	8	75
Ongoing fracture process**	No	40	16	46
	Yes	-	42	100
Pulmonary dysfunction	No	27	23	64
	Yes	23	28	69

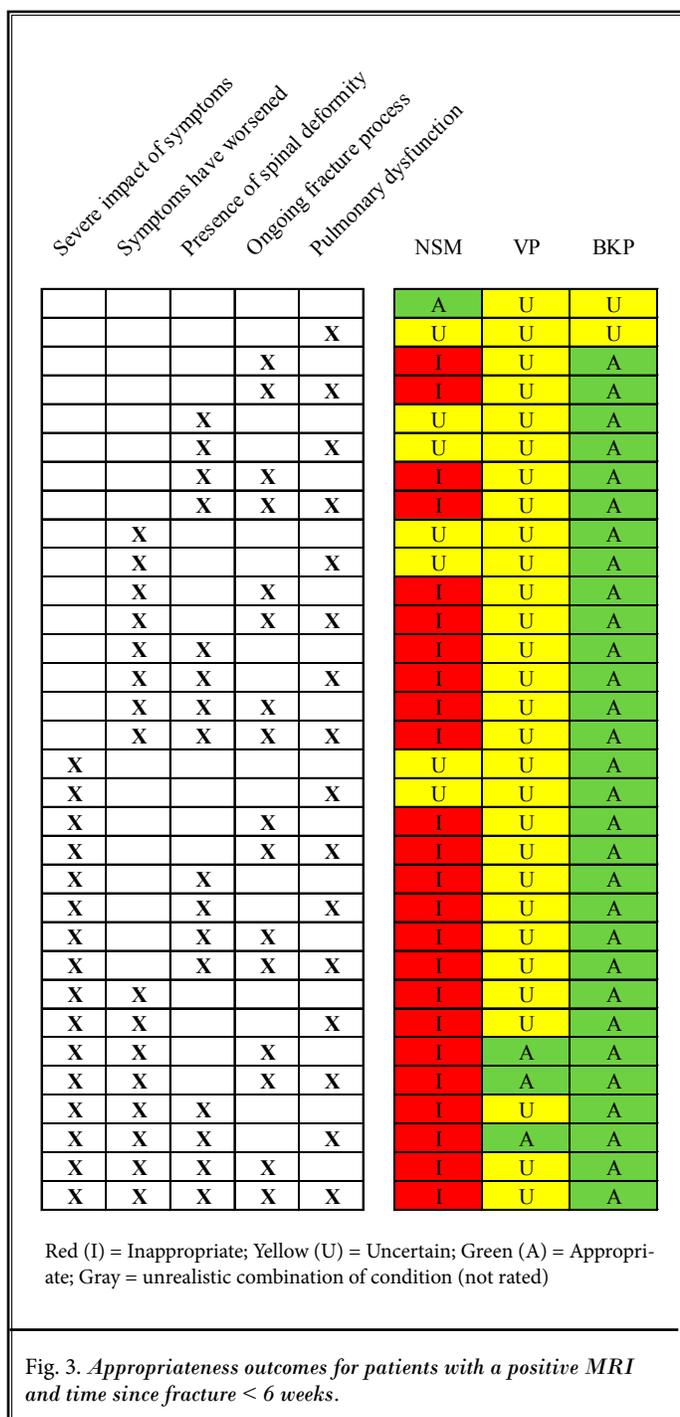
\* All patients with time since fracture < 6 weeks were assumed to have a positive MRI.

\*\* All patients with an ongoing fracture process were assumed to have a positive MRI.

with time. This may explain why the appropriateness of BKP was considered highest for patients with a fracture of less than 6 weeks. In that, the panel outcomes reflect the trade-off between trying to relieve the pain by NSM and the need of treating early to correct segmental kyphosis.

The recommendations, based on the balance of potential benefits and limitations of the 3 therapeutic options for various clinical scenarios, form the collective judgment of experts from different specialties, all with their own perspectives. The process of sequential individual ratings and in-depth group discussions showed growing convergence resulting in explicit recommendations.

Recent RCTs (10-12,16,17) have confirmed the efficacy and safety of VP and BKP for patient populations that are partly similar to the theoretical population we took into consideration in our panel study. We used similar absolute exclusion criteria (such as spine infection), but our inclusion criteria were broader and/or more specifically defined in comparison to most RCTs. For example, whereas the RCTs included only patients with a positive MRI, we considered also patients with a negative outcome. Most variables we used for the construction of clinical scenarios had not been considered in the RCTs (impact of symptoms on daily functioning, evolution of symptoms, spinal deformity, proof of ongoing fracture process, and presence of pulmonary dysfunction). Panelists had chosen these variables on the basis of their clinical experience, leading to a higher specificity of recommendations than is possible on the basis of the RCT outcomes. Where patient characteristics could be compared, the panel recommendations were never in conflict with the outcomes of the trials. Generally, no controversies were found when comparing the panel results with the available clinical guidelines. The guidelines of the National Institute for Health and Clinical Excellence (NICE) mention that these procedures should be limited to patients who are refractory to conservative treatment (20-21), that expert opinions on the benefits of VP versus NSM are divergent (21), and that there is uncertainty about the sustainability of the improvements following BKP (20). However, these guidelines were published in 2003 (VP) and 2006 (BKP), and did not consider the outcomes of the RCTs mentioned. Updates are underway. The guideline of the Cardiovascular



and Interventional Radiological Society of Europe (CIRSE, 2006) (22) includes recommendations for VP, focusing on the technical details of this procedure. Similar to NICE, CIRSE considers VP indicated in painful osteoporotic VCF refractory to conservative (medical) treatment. However, treatment failure is more explic-



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					Negative MRI			Positive MRI		
					NSM	VP	BKP	NSM	VP	BKP
					A	I	I	U	A	U
				X	A	I	I	U	U	U
			X					U	A	A
			X	X				U	A	A
		X			A	I	I	U	U	A
		X		X	A	I	I	U	U	A
		X	X					I	U	A
		X	X	X				I	U	A
	X				A	U	I	U	U	U
	X			X	A	I	I	U	U	A
	X		X					U	A	A
	X		X	X				U	A	A
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	X	X	X					I	A	A
	X	X	X	X				I	A	A
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X	X		X	X				U	A	A
X	X	X			A	U	I	U	U	A
X	X	X		X	A	U	I	U	U	A
X	X	X	X					I	U	A
X	X	X	X	X				I	U	A

Red (I) = Inappropriate, Yellow (U) = Uncertain, Green (A) = Appropriate, Gray = unrealistic combination of condition (not rated)

Fig. 5. Appropriateness outcomes for patients with time since fracture > 3 months.

	Usually <u>recommended</u> for patients with:	Usually <u>not recommended</u> for patients with:
NSM	<ul style="list-style-type: none"> <li>● Negative MRI</li> <li>● Positive MRI and no other unfavorable conditions</li> </ul>	<ul style="list-style-type: none"> <li>● Proof of ongoing fracture process</li> <li>● <math>\geq 2</math> other unfavorable factors</li> </ul>
VP	<ul style="list-style-type: none"> <li>● Positive MRI, time since fracture <math>\geq 6</math> weeks and no spinal deformity</li> </ul>	<ul style="list-style-type: none"> <li>● Negative MRI and presence of spinal deformity</li> </ul>
BKP	<ul style="list-style-type: none"> <li>● Ongoing fracture process</li> <li>● Positive MRI and <math>\geq 1</math> other unfavorable factors</li> </ul>	<ul style="list-style-type: none"> <li>● Negative MRI and time since fracture <math>\geq 3</math> months</li> <li>● Negative MRI, time since fracture 6 weeks – 3 months and moderate impact of symptoms</li> </ul>

\*Recommendations apply to patients with an osteoporotic VCF type A, having at least moderate symptoms, no neurological symptoms and no absolute contraindications for active treatment.

Fig. 6 . Panel recommendations after the second rating round.

itly formulated than in the NICE guidelines (insufficient response and/or intolerance following 3 weeks of medical treatment) (22). In addition, a list of absolute and relative contra-indications is provided (22). A position paper on vertebral augmentation by American societies for neuroradiology, interventional radiology, neurosurgery, and spine radiology (2007) includes a consensus statement that both VP and BKP are appropriate therapies for painful VCFs refractory to (optimized) medical therapy, and that the choice between the 2 options may merely be a matter of operator experience or preference (24). This is in contrast to the guideline and evidence report of the American Academy of Orthopaedic Surgeons (AAOS, 2010) (23). They recommend strongly against VP in patients with an osteoporotic VCF, while BKP is mentioned as an option for this indication (23). However, the recommendation on VP was primarily based on the 2 RCTs that compared VP to a sham procedure and that found no significant difference in pain and function up to 6 months follow-up (13,14). As mentioned, these studies have been subject to an extensive debate about their methodological properties (15). A similar RCT with

more appropriate inclusion criteria (i.e., VAS  $\geq 5$ , positive MRI findings) is now recruiting patients (31). For BKP, the AAOS found the evidence sufficient to merit its use as optional, though the strength of the recommendation was classified as weak (23). Indications and contraindications of BKP were not further specified. In their appropriateness criteria on the radiologic management of VCFs, the American College of Radiology (ACR) recommended conservative management as the first-line and gold standard management, and VP as a second-line procedure for patients who have failed or cannot tolerate conservative management (25). According to the ACR, BKP produces similar results as VP, but may have some advantages in complex cases where it could offer a better angular and fracture correction (25). Finally, the Dachverband Osteologie (DVO), a joint organization of scientific societies involved in bone research in Germany, Austria, and Switzerland established guideline recommendations on osteoporosis, including the treatment of VCFs (26). They state that both VP and BKP should only be considered after a conservative treatment attempt over 3 weeks, after exclusion of degenerative changes

of the spine as the reason for the complaints, and after an interdisciplinary discussion of the individual patient case (26). The majority of currently available guidelines consider VP and BKP to be appropriate options in patients refractory to conventional treatment (including analgesics), thereby assuming that (short-term) pain relief is the principal/only treatment goal for patients with osteoporotic VCF.

A limitation of the current study is that the outcomes relate to a theoretical population, and that the distribution of the clinical scenarios in real-life practice is yet unknown. Prospective studies to determine the validity and feasibility of these recommendations in daily clinical practice are in preparation.

To our knowledge, this study is the first that used the RAND/UCLA methodology (27,28) to establish appropriateness criteria for the treatment of osteoporotic VCF. The panel recommendations can be seen as a refinement of currently available guidelines (20-26), based on a combination of evidence from clinical trials (10-14,16,17) and the collective judgment of an international expert panel.

## CONCLUSION

Using the RAND/UCLA approach, a multidisciplinary expert panel formulated appropriateness criteria for the treatment of osteoporotic VCFs. These criteria may help physicians choose between non-surgical management, vertebroplasty, and balloon kyphoplasty.

## ACKNOWLEDGMENTS

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radiologist (London, UK); Frédéric Schils, neurosurgeon (Geneva, Switzerland); Rupert Schupfner, trauma surgeon (Bayreuth, Germany); and Mashood Ali Siddiqi, internist, bone metabolic specialist (Liverpool, UK).

Jason Bernard, Tarun Sabharwal, and Herman Stoevelaar were involved in the design of the study. The members of the expert panel (Giovanni Carlo Anselmetti, Jason Bernard, Thomas Blattert, Charles Court, Daniel Fagan, Hendrik Fransen, Patrick Fransen, Christian Kasperk, Tarun Sabharwal, Frédéric Schils, Rupert Schupfner, Mashood Ali Siddiqi) performed the appropriateness ratings, contributed to data interpretation, and critically reviewed the manuscript. Herman Stoevelaar performed the statistical analyses. Giovanni Carlo Anselmetti, Christian Kasperk, and Herman Stoevelaar drafted the manuscript.

## Conflict of interest

Panel members were financially compensated by Medtronic for their time in performing the ratings and attending the panel meetings, and were reimbursed for travel expenses related to the panel meetings. Giovanni Carlo Anselmetti is consultant to Medtronic. Jason Bernard received sponsorship for travel to conferences from Medtronic and received payment for an in-house training day of Medtronic. Thomas Blattert is medical consultant to Aesculap, AOSpine, Biomet, DePuySynthes, Integra, Medtronic, Spontech and Vexim. Charles Court is consultant to Medtronic, Spineguard and Spine art and he received payment for lectures from Medtronic, Spine art and Spineguard. His institution received a grant from Spineguard. Daniel Fagan received payment for BKP courses from Medtronic. Patrick Fransen is consultant to Medtronic and Covidien. Frédéric Schils has a consultancy agreement with Medtronic for cadaver training and teaching activities concerning balloon kyphoplasty. Rupert Schupfner received sponsorship for travel to conferences from Medtronic. Herman Stoevelaar received financial support from Medtronic for the design of the study, analysis of the data and writing of the draft manuscript. Christian Kasperk is member of a Medtronic advisory group and received honoraria for oral presentations on the topic of balloon kyphoplasty from Medtronic.

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