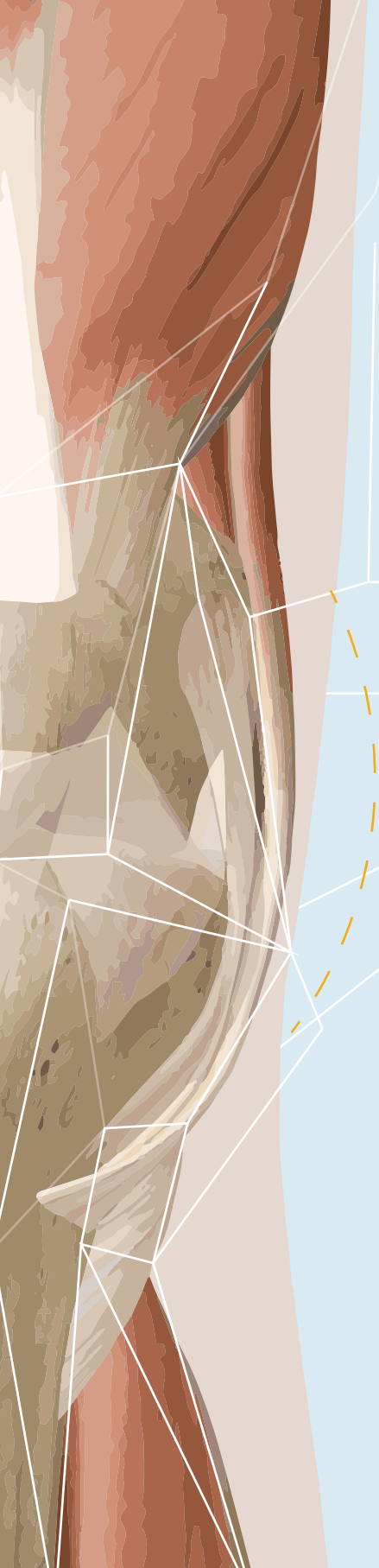


HYALURONIC ACID IN KNEE OSTEOARTHRITIS

effectiveness and efficiency

Job Hermans

Hyaluronic Acid in Knee Osteoarthritis effectiveness and efficiency

Job Hermans

Part of the research described in this thesis was supported by a grant from ZonMW.

Financial support for the publication of this thesis was kindly provided by:

- Erasmus MC Department of Orthopaedics and Sports Medicine
- Nederlandse Orthopaedische Vereniging
- Anna Fonds | NOREF
- Apotheekgroep Breda
- Össur Eindhoven
- Bioventus

The e-book version of this thesis is available at
www.orthopeden.org/downloads/proefschriften

ISBN 978-94-6416-168-7
Coverdesign and layout: Publiss.nl
Printing: Ridderprint | www.ridderprint.nl

© Job Hermans 2020
All rights reserved. No part of this publication may be reproduced or transmitted in any form or by any means, electronic or mechanical, including photocopy, recording, or any other information storage or retrieval system, without the prior written permission of the holder of the copyright.

Hyaluronic Acid in Knee Osteoarthritis
effectiveness and efficiency

Hyaluronzuur bij Knieartrose
effectiviteit en efficiëntie

Thesis
to obtain the degree of Doctor from the
Erasmus University Rotterdam
by command of the rector magnificus

Prof.dr. R.C.M.E. Engels

and in accordance with the decision of the Doctorate Board.

The public defense shall be held on
November 24 2020 at 13:30hrs

by

Job Hermans
Born in Boxmeer, the Netherlands

ERASMUS UNIVERSITY ROTTERDAM

Doctoral Committee

Promotors

Prof.dr. S.M.A. Bierma-Zeinstra
Prof.dr. J.A.N. Verhaar

Other members

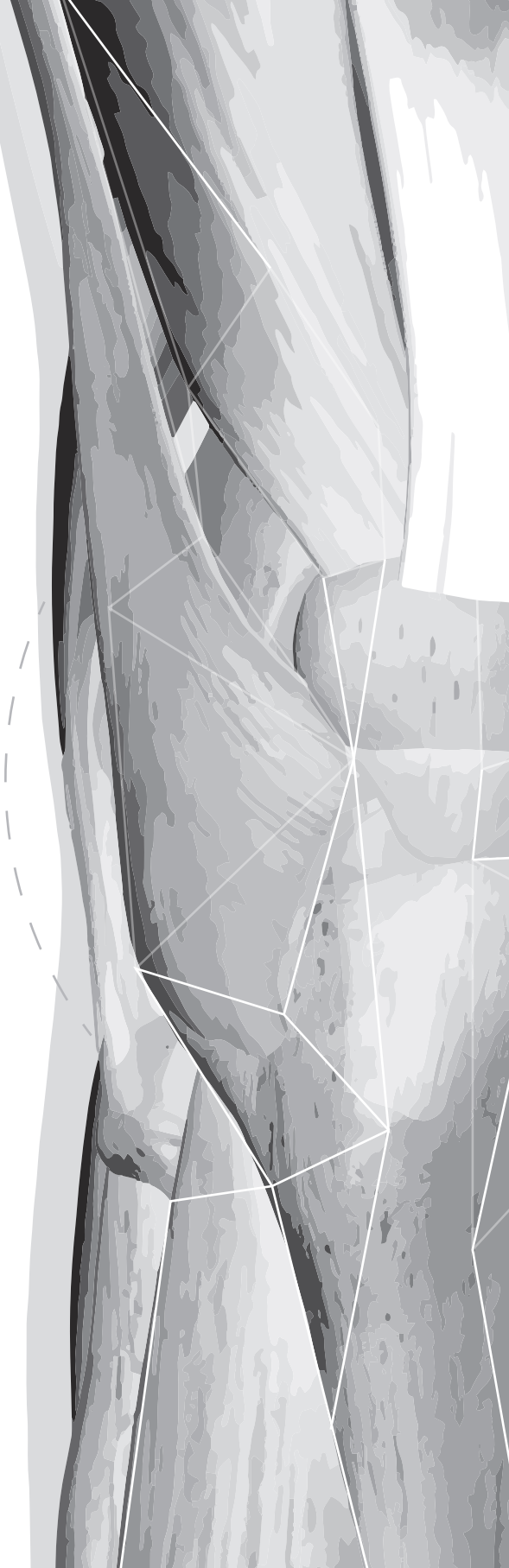
Prof.dr. S.K. Bulstra
Prof.dr. J.M.W. Hazes
Prof.dr. B.W. Koes

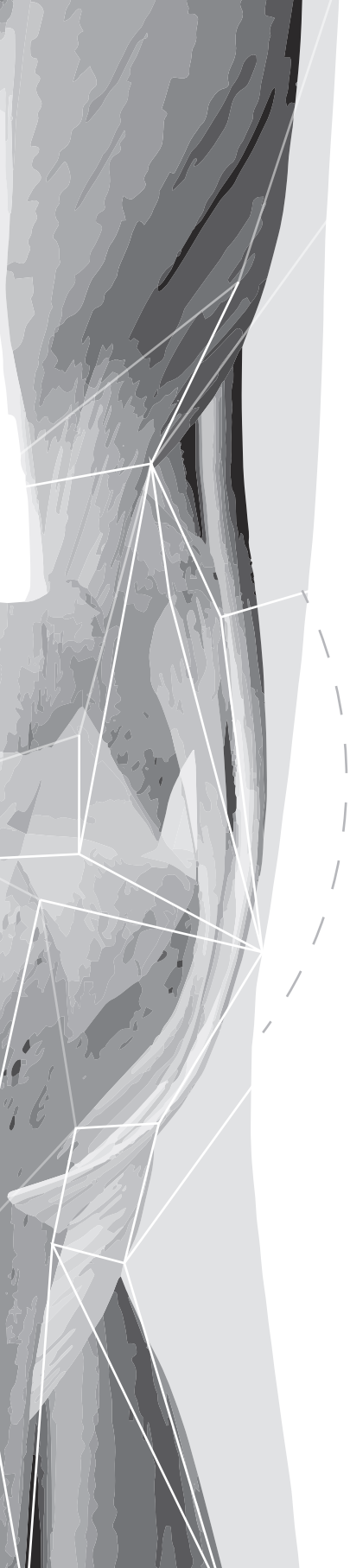
Copromotor

Dr. M. Reijman

Contents

Chapter 1	General introduction	**7**
Chapter 2	The most accurate approach for intra-articular needle placement in the knee joint: a systematic review	**19**
Chapter 3	Productivity costs and medical costs among working patients with knee osteoarthritis	**43**
Chapter 4	The effectiveness of high molecular weight hyaluronic acid for knee osteoarthritis in everyday clinical care: a randomized controlled trial	**65**
Chapter 5	Cost-utility analysis of high molecular weight hyaluronic acid for knee osteoarthritis in everyday clinical care in patients in the working age: an economic evaluation of a randomized clinical trial	**87**
Chapter 6	Product characteristic play a role in adverse events after hyaluronic acid therapy in knee osteoarthritis: a systematic review and meta-analysis.	**115**
Chapter 7	General discussion	**143**
	Summary	162
	Nederlandse samenvatting (summary, in Dutch)	166
	Dankwoord (acknowledgments, in Dutch)	171
	Curriculum Vitae	175
	PhD portfolio	176
	List of publications	179





Chapter 1
General introduction

Osteoarthritis

Osteoarthritis (OA) is a chronic disease of the knee joint, causing pain, joint stiffness and functional impairment.[1, 2] The incidence and prevalence of OA has risen in recent decades, including increasing numbers of younger patients suffering from OA.[3, 4] In 2010, together with hip OA, knee OA was ranked as the 11th highest contributor to global disability among the 291 investigated conditions.[5] Worldwide, knee OA was estimated to account for approximately 85% of the burden of disease for OA.[6] In The Netherlands, the prevalence of OA was estimated around 1.4 million patients in 2017, on a total population of around 17 million inhabitants at that time. Of these patients, 0.6 million patients suffered from knee OA which makes knee OA the most prevalent type of OA in The Netherlands.[7]

Although often referred to as a local degenerative disorder due to what is popularly denominated as wear of the cartilage, OA is a disease of the whole joint involving all joint tissues.[8, 9] Not only the intra-articular cartilage is affected, but also bone, menisci, ligaments and synovium are involved in several biological processes leading to structural changes throughout the joint.[8, 9] These changes comprehend loss of intra-articular hyaline cartilage, meniscal damage, subchondral bone sclerosis and osteophyte formation, but also inflammation of the synovium, degradation of the synovial fluid, laxity of the ligaments and muscle weakness of the surrounding muscles.[8-11]

Several biochemical and biomechanical factors contribute to the development of OA. These factors include age, gender, genetic predisposition, obesity, previous joint damage and specific injurious activities.[9, 10] For knee OA, evidence indicates a variety of moderate to strong specific risk factors like female sex, obesity, previous knee injury and knee malalignment.[12]

Occupational factors also play a role in the etiology of knee OA. For example, occupations that require physical activities like knee bending, kneeling, squatting and heavy lifting are associated with an increased risk for knee OA.[13, 14]

Economic consequences

Osteoarthritis has serious economic consequences. The rising prevalence and incidence of the disease in recent years has led to much higher overall spending for OA.[3, 15] The economic burden of OA consists of medical and

productivity costs.[16-18] Medical costs, or direct costs, refer to the costs from all resources consumed in the health care sector and patients' out of pocket expenses due to the disease.[16-19] Productivity costs, or indirect costs, are mainly subdivided in costs due to lost productivity while being present at work (presenteeism),[20-22] or costs due to absence from work (absenteeism).[23, 24] Costs related to the unpaid labor from caregivers in informal care or community care are generally also considered part of the productivity costs.[16, 25]

In the Netherlands, the total medical costs related to OA in 2015 were 1.3 billion euro. This equals 1.6% of the overall healthcare costs at that time.[26] The total medical costs related to knee OA in 2015 were estimated at 0.4 billion euro.[26] No studies on productivity costs related to knee OA for the Dutch situation were available before the onset of the investigations in this thesis. A systematic review on studies from nations worldwide reported that productivity costs for lower limb OA are lower than the medical cost.[27] Heterogeneity and lack of methodologic consensus between the included studies prohibited reliable estimates of the cost-of-illness in this study.[27]

Diagnosis

Knee OA can be diagnosed based on clinical findings, sometimes in combination with additional radiological investigations.[28-30] Typical symptoms of knee OA include persistent knee pain, short-term morning stiffness and functional impairments. During physical examination of the knee, crepitus, restricted movement and bony enlargements can be found.[30] The guideline from the Dutch Federation of Medical Specialists states that knee OA can be diagnosed based on the presence of clinical findings only. Routine imaging procedures are not recommended in the diagnostic work-up in knee OA.[28, 29] If radiographic imaging is needed, plain radiography (X-ray) should be made in weight-baring position and additional weight-bearing position with the knee flexed in 45° (the Rosenberg view).[31-33] Radiographic signs of knee OA seen on plain radiographs are joint space narrowing, osteophyte formation, sclerosis of the subchondral bone and the presence of cysts.[34] To further investigate soft tissue, bony and/or cartilage pathology, other imaging modalities like ultra sound (US), computed tomography (CT) and magnetic resonance imaging (MRI) are available.[29]

Radiographic knee OA is graded with the Kellgren and Lawrence (K&L) score. This score grades radiographic findings from 0 (no radiographic features of OA) to 4 (severe radiographic features of OA).[35] Although widely used, the K&L score has its limitations. The results of plain radiographs should not be used in isolation when assessing individual patients with suspected knee OA.[36-39]

Non-surgical treatment

The non-surgical treatment of knee OA is purely symptomatic. Disease modifying drugs with the ability to slow down, stop or even reverse disease progression are in a developmental stage and currently unapproved for therapeutic purposes.[12] The guidelines of stakeholder organizations in the field of knee OA mostly agree upon several recommendations concerning the non-surgical treatment of knee OA.[40] Treatment modalities like exercise therapy (land- or water-based), weight reduction in case of overweight and self-management and education are generally recommended for the non-surgical treatment of knee OA.[12, 40, 41] Biomechanical interventions like walking aids are recommended in appropriate circumstances, as are topical and/or oral non-steroidal anti-inflammatory drugs (NSAIDs) and intra-articular corticosteroids. Controversy exists about the use of knee braces and heel wedges, whereas acupuncture and glucosamine or chondroitin are mostly not recommended in the non-surgical treatment of knee OA.[12, 40, 41]

Hyaluronic acid as a treatment modality

An alternative treatment for symptomatic knee OA is intra-articular injection therapy with hyaluronic acid (HA, or hyaluronan), also known as viscosupplementation therapy.[42-44]

HA is a glycosaminoglycan molecule naturally found in the synovial fluid of joints. In the healthy knee joint, the synovial fluid contains HA macromolecules with a molecular weight (MW) ranging between 4-10 mega Daltons (mDa).[45] HA is constantly secreted into the joint and removed by the synovium in a natural turn-over process, with a half-life time of endogenous HA in the joint of around 12 hours.[45-47] Due to its shear-dependent viscosity, HA acts as a lubricant and shock absorber, protecting the articular cartilage from

compressive and shear forces. During joint loading, a gel structure of micrometric thickness is formed by which HA contributes to the protection of the cartilage surfaces from frictional damage. The synovial fluid supplies oxygen and nutrients to the surrounding tissues and removes carbon dioxide and metabolic wastes. The HA molecules act as a filter by restricting the entrance of large plasma proteins into the synovial fluid, while facilitating the passage of small molecules into the joint for maintenance of nutrition.[45-47] In the osteoarthritic knee, acceleration of the natural turn-over process of HA occurs under inflammation and oxidative stress. This pathological process results in a breakdown of the intact HA molecule into low molecular weight HA-fragments, which leads to an impairment of the viscoelastic properties of the HA molecules in the synovial fluid.[47]

Viscosupplementation therapy is based on the rationale that the degraded synovial fluid in the osteoarthritic knee is replaced or supplemented with an exogenous elastoviscous fluid. This fluid is composed of an HA derivative that has similar rheological properties compared to healthy synovial fluid.[42, 48, 49] The decreased rheological properties of the original pathological synovial fluid are recovered, resulting in restoration of shock absorption during movement and protection of the extracellular matrix of the cartilage.[42, 45, 48, 49] Research on the possible therapeutic effects of viscosupplementation in the human osteoarthritic knee started in the late 1960s and early 1970s.[49, 50] Initially, the clinical beneficial effects were attributed to the direct intra-articular administration of the HA-derivative and the following restoration of fluid elasticity and viscosity.[42] Nevertheless, the half-life time of exogenous administered HA appeared to be short, varying from 48 hours to about 7 days depending on the MW and structure of the derivative.[45] Over time, other biochemical mechanisms of action were found including effects of the administered HA-derivative on the extracellular matrix, immune cells, inflammatory mediators and the nociception of the arthritic joint.[45]

HA products for clinical use in knee OA are mostly produced by either bacterial fermentation or extracted from avian tissue like rooster combs.[51] In order to increase molecular weight and prolong the half-life time in the knee joint the molecular structure of HA can be chemically crosslinked to form so-called Hylans.[52]

In clinically manifest knee OA intra-articular HA results in pain reduction and improvement of knee function.[44] Several approaches are available to establish the intra-articular needle placement in the knee joint for the eventual administration of the HA derivative.[53, 54]

The beneficial effects on pain reduction are similar to NSAID use and larger than intra-articular corticosteroids on the longer term.[55-57] Treatment with NSAIDs is related to an increased risk of serious gastrointestinal and cardiovascular side effects, indicating limited use of NSAIDs only.[58, 59]

The peak effectiveness of a series of intra-articular injections with HA is reached between 1 and 2 months with residual effects up to 6 months.[43, 44, 60]

Intra-articular HA for knee OA is generally considered being safe. Adverse effects mostly consist of transient local reactions like pain, effusion or flare like symptoms.[44, 61] Within the spectrum of available HA derivatives, there is increasing evidence that the efficacy of HA products with a high molecular weight (HMW) is superior to the efficacy of derivatives with a low molecular weight.[61, 62]

Overall, treatment with intra-articular HA appears to result in a favorable benefit-risk balance in the treatment of knee OA compared to other pharmacological treatments.[63]

Nevertheless, controversy on the use of HA in knee OA exists. The clinical relevance of the effect size of HA in knee OA has been questioned in a systematic review and meta-analysis on the topic.[64] National and international OA management guidelines are ambiguous in their recommendation concerning intra-articular HA as a treatment modality for symptomatic knee OA.[28, 40]

Aims and outline of this thesis

This thesis focuses on various aspects of intra-articular HA as a non-surgical treatment modality for patients with knee OA.

In **chapter 2** we describe a systematic review on the accuracy of different approaches for intra-articular injections in the knee joint.

In **chapter 3** we identified and quantified the productivity costs and medical costs in knee OA patients with a paid employment. We also investigated the associations between productivity losses and relevant patient, health, and work characteristics.

A randomized clinical trial was designed to investigate the effectiveness as well as the cost-effectiveness of intra-articular HA added to the usual non-surgical care for symptomatic knee OA: the VISK study. Patients between 18 and 65 with symptomatic knee OA were randomized in either the intervention group who received 3 weekly injections with a HMW HA derivative added to the usual care, or in the control group who received usual care only. In **chapter 4** we report on the clinical effectiveness results of the VISK study. The primary clinical outcome was defined as response to therapy at 52 weeks follow-up according to OMERACT-OARSI criteria. This variable presents the results of changes after treatment in three symptomatic domains (pain, function, and patient global assessment (PGA)) as a single variable. **Chapter 5** presents the economic evaluation results of the VISK study. A cost-utility analysis was performed in order to determine the cost-effectiveness of intra-articular HA added to the usual non-surgical care for knee OA patients. The primary health economic outcome was determined by the between group difference in quality-adjusted life years (QALYs) and the between group difference in costs. The differences in mean adjusted QALYs and costs between the 2 treatment groups were expressed in a so-called incremental cost-effectiveness ratio (ICER), which is interpreted as the additional costs per QALY gained due to the intervention. Given various thresholds for the maximum willingness to pay for 1 QALY gained, the probability of cost-effectiveness of intra-articular HA therapy in knee OA was then indicated on an acceptability curve.

In **chapter 6** we present the results of a systematic review on the adverse effects of intra-articular treatment with HA in the knee. We describe the association of these adverse events with several product characteristics of different HA derivatives available.

Chapter 7 discusses the main findings of the research in this thesis. Limitations are addressed. Implications from a clinical as well as from a health-economic point of view are discussed as well as possible directions for future research.

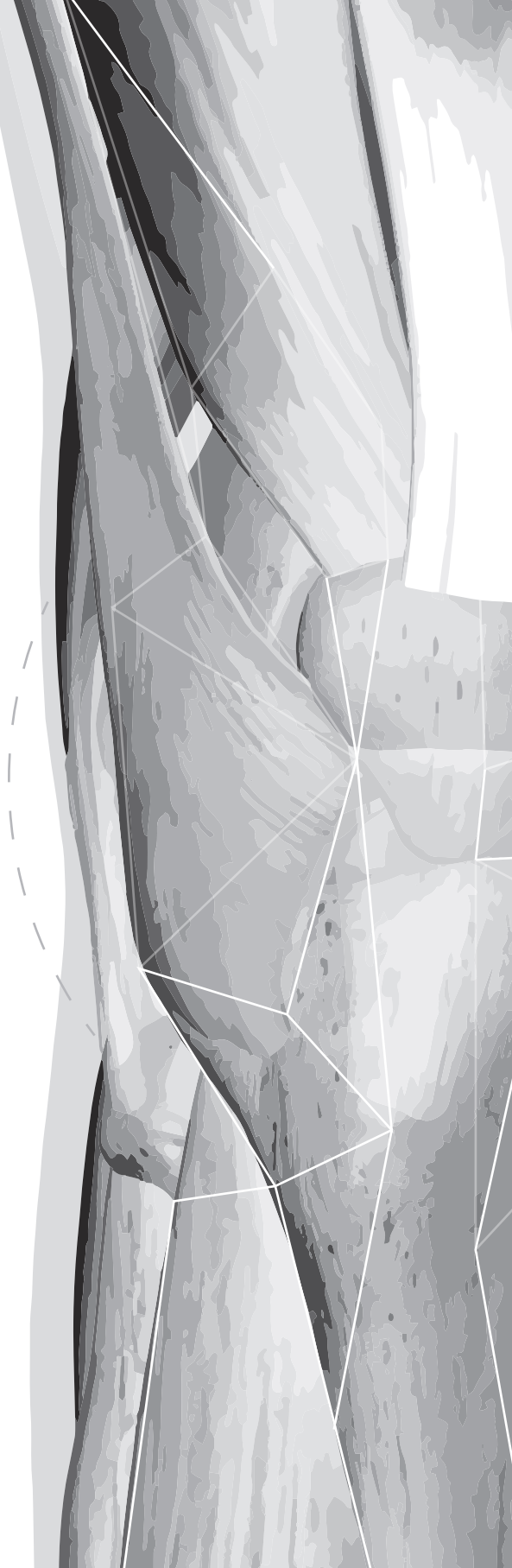
References

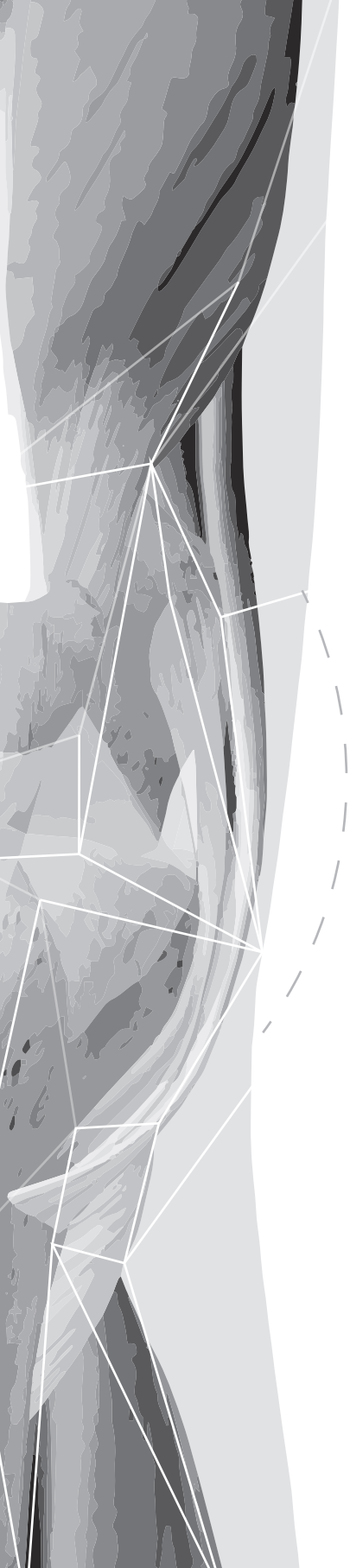
1. Lawrence RC, Felson DT, Helmick CG, et al. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part II. Arthritis Rheum 2008; 58(1): 26-35.
2. Vos T, Flaxman AD, Naghavi M, et al. Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet 2012; 380(9859): 2163-96.
3. Kiadaliri AA, Lohmander LS, Moradi-Lakeh M, Petersson IF, Englund M. High and rising burden of hip and knee osteoarthritis in the Nordic region, 1990-2015. Acta orthopaedica 2018; 89(2): 177-83.
4. Yu D, Peat G, Bedson J, Jordan KP. Annual consultation incidence of osteoarthritis estimated from population-based health care data in England. Rheumatology (Oxford) 2015; 54(11): 2051-60.
5. Cross M, Smith E, Hoy D, et al. The global burden of hip and knee osteoarthritis: estimates from the global burden of disease 2010 study. Ann Rheum Dis 2014; 73(7): 1323-30.
6. GBD Disease Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet 2016; 388(10053): 1545-602.
7. Prevalentie en aantal nieuwe gevallen van artrose (prevalence and incidence of osteoartritis). 2018. https://www.volksgezondheidenzorg.info/onderwerp/artrose/cijfers-context/huidige-situatie#node-prevalentie-en-aantal-nieuwe-gevallen-van-artrose (accessed 8-8-2019 2019).
8. Loeser RF, Goldring SR, Scanzello CR, Goldring MB. Osteoarthritis: a disease of the joint as an organ. Arthritis Rheum 2012; 64(6): 1697-707.
9. Felson DT. An update on the pathogenesis and epidemiology of osteoarthritis. Radiol Clin North Am 2004; 42(1): 1-9, v.
10. Felson DT, Lawrence RC, Dieppe PA, et al. Osteoarthritis: new insights. Part 1: the disease and its risk factors. Ann Intern Med 2000; 133(8): 635-46.
11. Glyn-Jones S, Palmer AJ, Agricola R, et al. Osteoarthritis. Lancet 2015; 386(9991): 376-87.
12. Hunter DJ, Bierma-Zeinstra S. Osteoarthritis. Lancet 2019; 393(10182): 1745-59.
13. Felson DT, Hannan MT, Naimark A, et al. Occupational physical demands, knee bending, and knee osteoarthritis: results from the Framingham Study. J Rheumatol 1991; 18(10): 1587-92.
14. Jensen LK. Knee osteoarthritis: influence of work involving heavy lifting, kneeling, climbing stairs or ladders, or kneeling/squatting combined with heavy lifting. Occup Environ Med 2008; 65(2): 72-89.
15. Bitton R. The economic burden of osteoarthritis. Am J Manag Care 2009; 15(8 Suppl): S230-5.
16. Drummond MF, Sculpher JM, Torrance GW, O'Brien BJ, Stoddart GL. Cost analysis. Methods for the Economic Evaluation of Health Care Programmes. 3 ed. Oxford: Oxford University Press; 2005: 55-102.
17. Maetzel A, Li LC, Pencharz J, Tomlinson G, Bombardier C. The economic burden associated with osteoarthritis, rheumatoid arthritis, and hypertension: a comparative study. Ann Rheum Dis 2004; 63(4): 395-401.

18. Rabenda V, Manette C, Lemmens R, Mariani AM, Struvay N, Reginster JY. Direct and indirect costs attributable to osteoarthritis in active subjects. J Rheumatol 2006; 33(6): 1152-8.
19. Kramer JS, Yelin EH, Epstein WV. Social and economic impacts of four musculoskeletal conditions. A study using national community-based data. Arthritis Rheum 1983; 26(7): 901-7.
20. Aronsson G, Gustafsson K. Sickness presenteeism: prevalence, attendance-pressure factors, and an outline of a model for research. Journal of occupational and environmental medicine / American College of Occupational and Environmental Medicine 2005; 47(9): 958-66.
21. Brouwer WB, Koopmanschap MA, Rutten FF. Productivity losses without absence: measurement validation and empirical evidence. Health Policy 1999; 48(1): 13-27.
22. Schultz AB, Edington DW. Employee health and presenteeism: a systematic review. J Occup Rehabil 2007; 17(3): 547-79.
23. Gabriel SE, Crowson CS, Campion ME, O'Fallon WM. Indirect and nonmedical costs among people with rheumatoid arthritis and osteoarthritis compared with nonarthritic controls. J Rheumatol 1997; 24(1): 43-8.
24. Li X, Gignac MA, Anis AH. The indirect costs of arthritis resulting from unemployment, reduced performance, and occupational changes while at work. Med Care 2006; 44(4): 304-10.
25. Ernst R. Indirect costs and cost-effectiveness analysis. Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research 2006; 9(4): 253-61.
26. Kosten van zorg naar vorm van artrose (costs of care diveded per osteoartritis type). 2015. https://www.volksgezondheidenzorg.info/onderwerp/artrose/kosten/kosten#node-kosten-van-zorg-naar-vorm-van-artrose (accessed 19-8-2019 2019).
27. Salmon JH, Rat AC, Sellam J, et al. Economic impact of lower-limb osteoarthritis worldwide: a systematic review of cost-of-illness studies. Osteoarthritis Cartilage 2016; 24(9): 1500-8.
28. FMS (Federation of Medical Specialists). Richtlijn conservatieve behandeling van artrose in heup of knie (guideline for non-operative treatment of ostoarthritis of hip or knee). 2018.
29. Sakellariou G, Conaghan PG, Zhang W, et al. EULAR recommendations for the use of imaging in the clinical management of peripheral joint osteoarthritis. Ann Rheum Dis 2017; 76(9): 1484-94.
30. Zhang W, Doherty M, Peat G, et al. EULAR evidence-based recommendations for the diagnosis of knee osteoarthritis. Ann Rheum Dis 2010; 69(3): 483-9.
31. Rosenberg TD, Paulos LE, Parker RD, Coward DB, Scott SM. The forty-five-degree posteroanterior flexion weight-bearing radiograph of the knee. J Bone Joint Surg Am 1988; 70(10): 1479-83.
32. Leach RE, Gregg T, Siber FJ. Weight-bearing radiography in osteoarthritis of the knee. Radiology 1970; 97(2): 265-8.
33. Brandt KD, Fife RS, Braunstein EM, Katz B. Radiographic grading of the severity of knee osteoarthritis: relation of the Kellgren and Lawrence grade to a grade based on joint space narrowing, and correlation with arthroscopic evidence of articular cartilage degeneration. Arthritis Rheum 1991; 34(11): 1381-6.
34. Jacobson JA, Girish G, Jiang Y, Sabb BJ. Radiographic evaluation of arthritis: degenerative joint disease and variations. Radiology 2008; 248(3): 737-47.
35. Kellgren JH, Lawrence JS. Radiological assessment of osteo-arthrosis. Ann Rheum Dis 1957; 16(4): 494-502.

36. Bedson J, Croft PR. The discordance between clinical and radiographic knee osteoarthritis: a systematic search and summary of the literature. BMC Musculoskelet Disord 2008; 9: 116.
37. Hannan MT, Felson DT, Pincus T. Analysis of the discordance between radiographic changes and knee pain in osteoarthritis of the knee. J Rheumatol 2000; 27(6): 1513-7.
38. Kohn MD, Sassoon AA, Fernando ND. Classifications in Brief: Kellgren-Lawrence Classification of Osteoarthritis. Clin Orthop Relat Res 2016; 474(8): 1886-93.
39. Schiphof D, Boers M, Bierma-Zeinstra SM. Differences in descriptions of Kellgren and Lawrence grades of knee osteoarthritis. Ann Rheum Dis 2008; 67(7): 1034-6.
40. Nelson AE, Allen KD, Golightly YM, Goode AP, Jordan JM. A systematic review of recommendations and guidelines for the management of osteoarthritis: The chronic osteoarthritis management initiative of the U.S. bone and joint initiative. Semin Arthritis Rheum 2014; 43(6): 701-12.
41. Block JA. Osteoarthritis: OA guidelines: improving care or merely codifying practice? Nature reviews Rheumatology 2014; 10(6): 324-6.
42. Balazs EA. Viscosupplementation for treatment of osteoarthritis: from initial discovery to current status and results. Surgical technology international 2004; 12: 278-89.
43. Bannuru RR, Natov NS, Dasi UR, Schmid CH, McAlindon TE. Therapeutic trajectory following intra-articular hyaluronic acid injection in knee osteoarthritis--meta-analysis. Osteoarthritis Cartilage 2011; 19(6): 611-9.
44. Maheu E, Rannou F, Reginster JY. Efficacy and safety of hyaluronic acid in the management of osteoarthritis: Evidence from real-life setting trials and surveys. Semin Arthritis Rheum 2016; 45(4 Suppl): S28-33.
45. Webb D, Naidoo P. Viscosupplementation for knee osteoarthritis: a focus on Hylan G-F 20. Orthopedic research and reviews 2018; 10: 73-81.
46. Laurent TC, Laurent UB, Fraser JR. The structure and function of hyaluronan: An overview. Immunology and cell biology 1996; 74(2): A1-7.
47. Tamer TM. Hyaluronan and synovial joint: function, distribution and healing. Interdisciplinary toxicology 2013; 6(3): 111-25.
48. Balazs EA, Denlinger JL. Clinical uses of hyaluronan. Ciba Foundation symposium 1989; 143: 265-75; discussion 75-80, 81-5.
49. Balazs EA, Watson D, Duff IF, Roseman S. Hyaluronic acid in synovial fluid. I. Molecular parameters of hyaluronic acid in normal and arthritis human fluids. Arthritis Rheum 1967; 10(4): 357-76.
50. Balazs EA. The pysical properties of synovial fluid and the special role of hyaluronic acid. In: Helfet AJ, ed. Disorders of the Knee. Philadelphia: J.B. Lippincott Company; 1974: 61-75.
51. Boeriu CG, Springer J, Kooy FKL, Van den Broek LAM, Eggink G. Production Methods for Hyaluronan. International Journal of Carbohydrate Chemistry 2013: 14.
52. Reichenbach S, Blank S, Rutjes AW, et al. Hylan versus hyaluronic acid for osteoarthritis of the knee: a systematic review and meta-analysis. Arthritis Rheum 2007; 57(8): 1410-8.
53. Courtney P, Doherty M. Joint aspiration and injection. Best Pract Res Clin Rheumatol 2005; 19(3): 345-69.
54. Malfair D. Therapeutic and diagnostic joint injections. Radiol Clin North Am 2008; 46(3): 439-53, v.

55. Bannuru RR, Natov NS, Obadan IE, Price LL, Schmid CH, McAlindon TE. Therapeutic trajectory of hyaluronic acid versus corticosteroids in the treatment of knee osteoarthritis: a systematic review and meta-analysis. Arthritis Rheum 2009; 61(12): 1704-11.
56. Bannuru RR, Vaysbrot EE, Sullivan MC, McAlindon TE. Relative efficacy of hyaluronic acid in comparison with NSAIDs for knee osteoarthritis: a systematic review and meta-analysis. Semin Arthritis Rheum 2014; 43(5): 593-9.
57. Ishijima M, Nakamura T, Shimizu K, et al. Intra-articular hyaluronic acid injection versus oral non-steroidal anti-inflammatory drug for the treatment of knee osteoarthritis: a multi-center, randomized, open-label, non-inferiority trial. Arthritis Res Ther 2014; 16(1): R18.
58. Sostres C, Gargallo CJ, Lanas A. Nonsteroidal anti-inflammatory drugs and upper and lower gastrointestinal mucosal damage. Arthritis Res Ther 2013; 15 Suppl 3: S3.
59. Bhala N, Emberson J, Merhi A, et al. Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: meta-analyses of individual participant data from randomised trials. Lancet 2013; 382(9894): 769-79.
60. Bellamy N, Campbell J, Robinson V, Gee T, Bourne R, Wells G. Viscosupplementation for the treatment of osteoarthritis of the knee. Cochrane Database Syst Rev 2006; (2): CD005321.
61. Johal H, Devji T, Schemitsch EH, Bhandari M. Viscosupplementation in Knee Osteoarthritis: Evidence Revisited. JBJS reviews 2016; 4(4): e11-e111.
62. Altman RD, Bedi A, Karlsson J, Sancheti P, Schemitsch E. Product Differences in Intra-articular Hyaluronic Acids for Osteoarthritis of the Knee. Am J Sports Med 2015.
63. Maheu E, Bannuru RR, Herrero-Beaumont G, Allali F, Bard H, Migliore A. Why we should definitely include intra-articular hyaluronic acid as a therapeutic option in the management of knee osteoarthritis: Results of an extensive critical literature review. Semin Arthritis Rheum 2019; 48(4): 563-72.
64. Rutjes AW, Juni P, da Costa BR, Trelle S, Nuesch E, Reichenbach S. Viscosupplementation for osteoarthritis of the knee: a systematic review and meta-analysis. Ann Intern Med 2012; 157(3): 180-91.





Chapter 2

The most accurate approach for intra-articular needle placement in the knee joint:
a systematic review

J. Hermans
S.M.A. Bierma-Zeinstra
P.K. Bos
J.A.N. Verhaar
M. Reijman

Semin Arthritis Rheum. 2011;41(2):106-115.

Abstract

Introduction

Intra-articular needle placement in the knee joint such as injection or aspirations are commonly used for therapeutic, diagnostic and research purposes concerning knee pathology. Although several approaches can be used to establish an intra-articular injection or aspiration of the knee joint, the accuracy differs per approach.

Objective

To summarize the evidence concerning the accuracy of different approaches for intra-articular needle placements in the knee. Additionally, to assess whether the accuracy of different approaches is related to factors such as underlying disease, severity of underlying disease, approach-related factors and/or to the rate of local reactions.

Methods

The literature was systemically reviewed until July 2010. Risk of bias of the included studies was assessed by the QUADAS tool. Study characteristics were extracted, accuracy results were pooled per approach.

Results

Nine studies were included. The superolateral approach with the leg in extension was studied most (230 injections) and resulted in the highest pooled accuracy of 91% (95% CI 84-99%). The lateral midpatellar approach, the anterolateral approach and the anteromedial approach resulted in the lowest pooled accuracy rates, 85% (95% CI 68-100%), 67% (95% CI 43-91%) and 72% (95% CI 65-78%), respectively.

Conclusions

The superolateral approach was investigated most and resulted in the highest pooled accuracy rate of 91% (95% CI 84-99%). Nevertheless, this approach still results in a substantial amount of extra-articular needle placements. Guidance of intra articular needle placements by imaging techniques may enhance the accuracy. The costs and extra time associated with these techniques should be taken in consideration.

Introduction

Intra-articular needle placements such as injections or aspiration of the knee joint are commonly used in clinical practice by physicians like rheumatologists, orthopaedic surgeons and general practitioners. In treatment modalities for knee joint disorders such as rheumatoid artritis (RA) and osteoarthritis (OA), intra-articular injections, eg, with corticosteroids can be required. Treatment guidelines for knee OA[1] furthermore include intra-articular therapy with hyaluronic acid (HA) based on increasing evidence of their efficacy.[2-7] HA is assumed to give the optimal result when injected directly into the cavity of the knee joint.[8-10] In the diagnostic process of gout, pseudo gout and bacterial arthritis, an intra-articular procedure such as knee joint aspiration can be necessary.[11] Furthermore, when severe swelling or a bacterial arthritis is present, knee joint aspiration may be required. For research purposes of e.g. synovial fluid, aspiration of the knee can also be performed.[11] In all the aforementioned, an accurate intra-articular localisation of the needle is of considerable importance.

Although several approaches to establish an accurate intra-articular needle placement in the knee joint are available,[12, 13] success rates of the different approaches are not optimal[14] and accuracy rates differ per approach.[10, 15, 16] Moreover, in the treatment of OA with intra-articular HA the rate of local reactions seems to be associated with the approach used.[4]

To date, no systematic review on the accuracy of different approaches of intra-articular needle placements in the knee joint has been published. A structured overview of this topic will be helpful to physicians performing intra-articular injections or aspiration of the knee in their practice.

Therefore, this systematic review summarizes the evidence regarding the accuracy of different approaches for intra-articular needle placements such as injections or aspiration of the knee joint. Additional objectives are to assess whether the accuracy of different approaches is related to factors such as underlying disease, severity of underlying disease, approach-related factors and/or to the rate of local reactions.

Methods

Identification of studies

To identify all studies addressing the accuracy of approaches for intra-articular needle placements in the knee joint, a systematic search was conducted in Pubmed and Embase since their inception up to July 2010. The search strategy is shown in Appendix 1. Reference tracking was performed to identify additional suitable studies not identified by the conducted search strategy.

The result of the search strategy was independently analysed for suitable articles by 2 of the reviewers (JH, MR). If both reviewers failed to achieve consensus the opinion of a third reviewer (JV) was available for final judgment, but was in fact not required.

A study was included when it met the following inclusion criteria:

- Study subjects were human or human cadavers;
- The study addressed the accuracy of a certain approach of intra-articular injection or intra-articular needle placement in the knee joint;
- An adequate reference method was used to ascertain intra-articular injection or needle placement in the knee joint;
- The article presented original data, or original data could be obtained from the authors;
- The article was written in Dutch, Spanish, French, German, English, Polish, Swedish, Danish or Norwegian; and
- Full text of the article was available.

Studies were excluded when concerning a review, systematic review or meta-analysis.

Risk of bias assessment

Risk of bias of the included studies was assessed by the QUADAS tool[17] (Table 1). This tool provides a standardised approach of quality assessment in diagnostic accuracy studies and has demonstrated good interrater reliability.[17, 18] It consists of 14 items[17, 18] and can be extended with 9 potential additional items[19] which all can be scored by 'yes', 'no' or 'unclear'. The 14 items refer to the spectrum of patients, reference standard, disease progression bias, verification bias, review bias, clinical review bias, incorporation bias,

test execution, study withdrawals and indeterminate results. The 9 potential additional items refer to technology development, observer and instrument variation, specification of objectives, definitions and cut-off values, skills level of test operators, treatment during testing and commercial funding. All studies were scored independently by 2 of the reviewers (JH, SBZ). In case of disagreement, both reviewers tried to achieve consensus. If not achieved, a third reviewer (JV) was available to make a final judgment but, again, this proved unnecessary.

Table 1 Items in the QUADAS tool

	Item	Yes	No	Unclear
1.	Was the spectrum of patients representative of the patients who will receive the test in practice?	☐	☐	☐
2.	Were selection criteria clearly described?	☐	☐	☐
3.	Is the reference standard likely to correctly classify the target condition?	☐	☐	☐
4.	Is the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests?	☐	☐	☐
5.	Did the whole sample or a random selection of the sample, receive verification using a reference standard of diagnosis?	☐	☐	☐
6.	Did patients receive the same reference standard regardless of the index test result?	☐	☐	☐
7.	Was the reference standard independent of the index test (i.e. the index test did not form part of the reference standard)?	☐	☐	☐
8.	Was the execution of the index test described in sufficient detail to permit replication of the test?	☐	☐	☐
9.	Was the execution of the reference standard described in sufficient detail to permit its replication?	☐	☐	☐
10.	Were the index test results interpreted without knowledge of the results of the reference standard?	☐	☐	☐
11.	Were the reference standard results interpreted without knowledge of the results of the index test?	☐	☐	☐
12.	Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?	☐	☐	☐
13.	Were uninterpretable/intermediate test results reported?	☐	☐	☐
14.	Were withdrawals from the study explained?	☐	☐	☐
15.	Were cut-off values established before the study was started?	☐	☐	☐
16.	Is the technology of the test unchanged since the study was carried out	☐	☐	☐
17.	Did the study provide a clear definition of what was considered a positive result?	☐	☐	☐
18.	Had test operators had appropriate training	☐	☐	☐
19.	Was treatment withheld until both the index test and reference standard were performed?	☐	☐	☐
20.	Were data on observer variation reported and within acceptable range?	☐	☐	☐
21.	Were data on instrument variation reported and within acceptable range?	☐	☐	☐
22.	Were objectives pre-specified?	☐	☐	☐
23.	Was the study free of commercial funding?	☐	☐	☐

Data extraction

Study characteristics (design, study population characteristics), accuracy data, other outcome measures, results and conclusions were extracted from the included articles by two of the reviewers (JH, KB). Agreement on data extraction was reached by consensus.

Data analysis

A trained statistician performed the meta-analysis using R 2.11. Accuracy rates of the included studies were pooled per used approach when approaches were investigated more than once. In these cases a random effects model was applied in the pooling procedure. An intra-articular needle placement was considered accurate when intra-articular presence of the needle or injected fluid was confirmed by an adequate reference test. In the meta-analysis, 95% confidence intervals (CI) for all (pooled) accuracy rates were calculated according to Wilson.

Results

Studies included

Our search strategy resulted in 1939 identified abstracts. The authors of 2 articles[20, 21] were contacted to provide further data concerning the number of injections per used approach and the used approach respectively. Subsequently, 8 studies met the inclusion criteria. Reference tracking of potentially relevant articles resulted in 1 suitable article. Therefore, a total of 9 articles were included (Figure 1); their characteristics are presented in table 2.

Figure 1 Search strategy

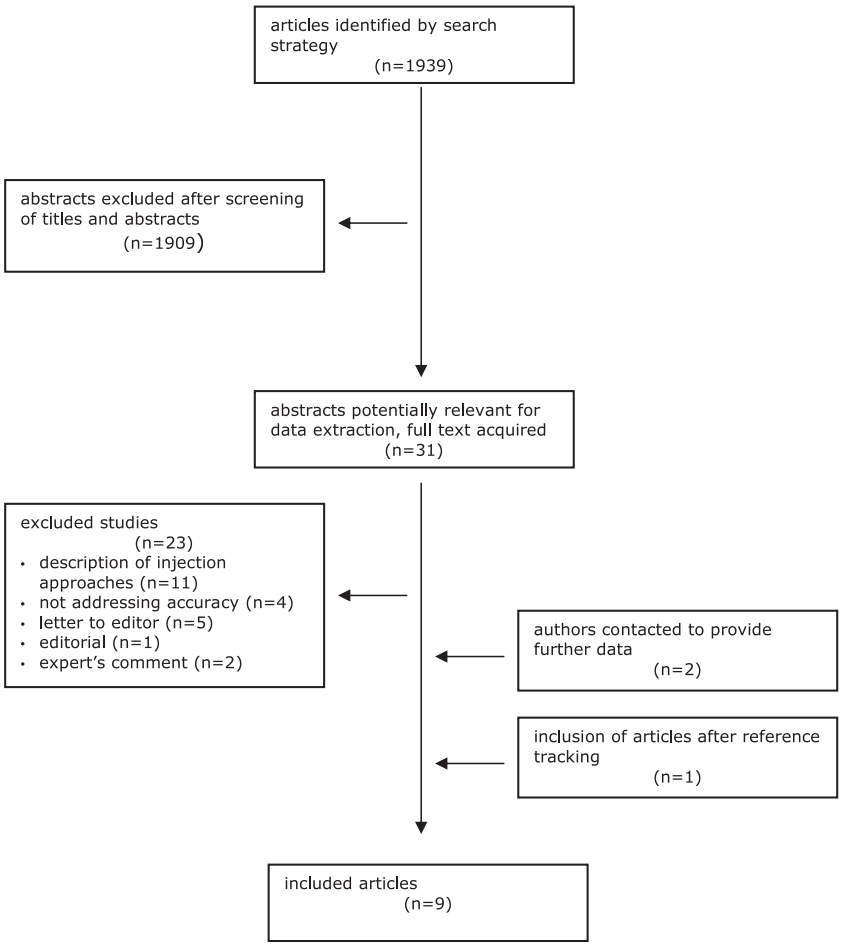


Table 2 Characteristics of the 9 included studies

First author, year of publication	Study population	No. of subjects (no. of injections)	Approach (no. of injections)	Index test	Reference test
Bliddall[22] 1999	OA; K&L ≥ II; no effusion	38 (56)[a]	SL (56)	Air injection	Air & radiograph
Esenyel[16] 2007	Cadavers	78 (312)[b]	LMP (78); MMP (78); AL (78); AM (78)	Needle placement and methylene blue injection	Methylene blue and needle detection after surgical dissection
Glattes[20] 2004	Clinical indication for knee injection; effusion	10 (10)	SL (10)	Contrast solution injection	Contrast & radiograph
Jackson[15] 2002	Symptomatic degenerative joint disease; no effusion	80 (240)[c]	LMP (80); AL (80); AM (80)	Contrast solution injection	Contrast & radiograph
Lopes[21] 2008	RA; synovitis	32 (37)	SL (37)	Contrast solution injection	Contrast & radiograph
Luc[23] 2006	Symptomatic OA; no effusion	33 (33)	SL (33)	Lidocaine + contrast solution injection	Contrast & radiograph
Toda[10] 2008	Medial OA > lateral OA; K&L ≥ II; no effusion	50 (150)[c]	SL (50); AM (50); MWA (50)	Hyaluronan + contrast solution injection	Contrast & radiograph
Waddell[24] 2001	History of knee problems (6 knees); no effusion	11 (20)	WA (20)	Contrast solution injection	Contrast & radiograph
Wind [25] 2004	Presenting for routine arthroscopy; effusion not excluded	131 (131)	SL (44); SM (43); AL (44)	Methylene blue injection	Methylene blue detection through arthroscopy

SL, superolateral approach, leg in extension; SM, superomedial approach, leg in extension; LMP, lateral midpatellar approach, leg in extension; MMP, medial midpatellar approach, leg in extension; AL, anterolateral approach, leg in 90^0 flexion; AM, anteromedial approach, leg in 900 flexion; WA, Waddell's approach, anterolateral with leg in 30^o-40^o flexion; MWA, modified Waddell's approach, anteromedial with leg in 30^o flexion and ankle traction towards lateral; OA, osteoarthritis; RA, rheumatoid arthritis; K&L, Kellgren and Lawrence scale. [a]One or two knees per subject, one injection per knee. [b]Two knees per subject, two injections per knee. [c]One knee per subject, three injections per knee.

The number of patients enrolled in the included studies ranged from 11-131 and the number of knees examined ranged from 20-240. The study population of the studies consisted of patients with degenerative joint disease or OA (4 studies[10, 15, 22, 23]), RA (1 study[21]), a clinical indication for knee injections (1 study[20]), a range of knee problems in 6 out of 20 injected knees (1 study[24]) and an indication for routine arthroscopy (1 study[25]). One study investigated cadaver subjects (1 study[16]). In 7 studies, radiographic verification of intra-articular location of an injected contrast agent[10, 15, 20, 21, 23, 24] or injected air[22] was used. In 1 study[25] the amount of visible injected intra-articular methylene blue was classified during arthroscopy. The study which investigated cadaver subjects[16] also injected methylene blue in the knee; thereafter, the knee joint was dissected and the actual position of the needle and the amount of intra-articular staining of methylene blue was visualized.

Risk of bias assessment

Table 3 presents the final results of the risk of bias assessment. The 2 reviewers (JH, SBZ) had 10 unique disagreements which were resolved in a single consensus meeting. Overall, the QUADAS tool showed little distinction between the included studies.

Table 3 Risk of bias assessment

	First author, Year of publication								
QUADAS item	**Bliddall[22] 1999**	**Esenyel[16] 2007**	**Glattes[20] 2004**	**Jackson[15] 2002**	**Lopes[21] 2008**	**Luc[23] 2006**	**Toda[10] 2008**	**Waddell[24] 2001**	**Wind[25] 2004**
1.	yes	yes	unclear	no	yes	yes	yes	no	no
2.	yes	no	yes	no	yes	yes	yes	unclear	yes
3.	yes	unclear	yes	unclear	yes	yes	yes	yes	yes
4.	yes	yes	yes	yes	unclear	yes	yes	yes	yes
5.	yes	yes	yes	yes	yes	yes	yes	yes	yes
6.	yes	yes	yes	yes	yes	yes	yes	yes	yes
7.	yes	yes	yes	yes	yes	yes	yes	yes	yes
8.	yes	yes	yes	yes	yes	yes	yes	yes	yes
9.	yes	yes	yes	yes	yes	yes	yes	yes	yes
10.	yes	yes	yes	yes	yes	yes	yes	yes	yes
11.	no	no	yes	no	yes	no	no	yes	no
12.	na	na	na	na	n.a	na	na	na	na
13.	yes	yes	yes	yes	yes	yes	yes	yes	yes
14.	yes	yes	yes	yes	yes	yes	yes	yes	yes
15.	na	na	na	na	n.a	na	na	na	na
16.	na	na	na	na	n.a	na	na	na	na
17.	unclear	no	yes	yes	yes	yes	yes	yes	yes
18.	unclear	unclear	unclear	yes	yes	unclear	yes	unclear	yes
19.	na	na	na	na	n.a	na	na	na	na
20.	no	no	no	no	unclear	no	unclear	no	unclear
21.	na	na	na	na	n.a	na	na	na	na
22.	yes	yes	yes	yes	yes	yes	yes	yes	yes
23.	yes	unclear	yes	yes	yes	unclear	yes	unclear	yes

Question 1 was scored 'yes' when one of the following conditions applied to the study population: RA, OA, synovitis, bursitis, swollen knee or any other well-defined condition that requires intra-articular therapy. Question 2 was scored 'yes' when at least 2 of the following were well described in the reviewed article: setting in which the study took place, age of the study population and underlying condition of the study population. Question 3 was scored 'yes' when the reference standard consisted of ultrasonography, computed tomography (CT), magnetic resonance imaging (MRI), fluoroscopy, arthrography or arthroscopy. Question 4 was scored 'yes' when elapsed time between reference standard and index test did not exceed 2 hours. Question 18 was scored 'yes' when injections were performed by an orthopaedic surgean, rheumatologist, sports doctor or trained other person. Question 22 was scored 'yes' when the objective was accuracy of an intra articular injection or needle placement in the knee. Questions 12, 15, 16, 19 and 21 were considered not applicable (n.a) for all included studies.

Study results

The different approaches used in the included studies are shown in Figure 2. Table 4 presents an overview of the accuracy results per used approach. Due to the practical performance of the injection procedure, the so-called lateral patellar approach studied by Toda and coworkers[10] was categorized in the superolateral approach group. The lateral joint line approach studied by Wind and coworkers[25] was categorized in the anterolateral approach group. In the latter study, the amount of detectable MB during arthroscopy was classified as poor, fair or good; procedures classified as 'good' by the authors were considered accurate.[26] The superolateral approach was investigated in 6 studies (230 knees). Accuracy rates ranged from 70 to 100%[10, 20-23, 25] and pooled accuracy was 91% (95% CI 84-99%).

Two studies in the superolateral approach group included patients with synovitis[21] or clinical effusion.[20] The pooled accuracy rate for these studies was 98% (95% CI 95-100%). The pooled accuracy rate of the superolateral approach group without these studies was 88% (95% CI 77-98%).

The superomedial approach was investigated in the study of Wind and coworkers[25] and resulted in an accuracy rate of 93%. This was significantly lower than the anterolateral approach used in that same study (p=0.001). Accuracy rates from the lateral midpatellar approach were examined in two studies and resulted in accuracy rates of 76%[16] and 93%[15], respectively, with a pooled accuracy of 85% (95% CI 68-100%). The accuracy of the medial midpatellar approach was studied once by Jackson and coworkers[16] and resulted in an accuracy rate of 56%. This was significantly lower than the investigated lateral midpatellar (p<0.0001), the anterolateral (p<0.0001) and the anteromedial approach (p<0.0001) in that study. The anterolateral approach was investigated in 3 studies.[15, 16, 25] Accuracy rates of the anterolateral approach ranged from 43 to 85% with a pooled accuracy of 67% (95% CI 43-91%). The 43% accuracy rate of the anterolateral approach in the study of Wind and coworkers[25] was significantly lower (p<0.001) than the accuracy rates from the superolateral and superomedial approach in the same study. The anteromedial approach was also investigated in 3 studies[10, 15, 16] and accuracy rates ranged from 62-73% with a pooled accuracy of 72% (95% CI 65-78%). In the study of Waddell and coworkers[24], 30°-40° flexion was applied while injecting lateral from the patellar tendon, which resulted in a 100% accuracy rate. This approach was

modified in the study of Toda et el.[10], where traction at the ankle joint was added while injecting from the medial side in the 30°-40° flexed knee; this modified approach resulted in an accuracy rate of 86%.

In 2 studies, the superolateral approach resulted in 100% accuracy in patients with synovitis[21] or effusion of the knee joint.[20] In the study of Wind and coworkers[25], patients with or without clinical knee effusion were also injected in the knee through the superolateral approah. This resulted in an 89% accuracy rate, whereas the anterolateral approach in this study reached a significantly lower accuracy rate of 43% ($p<0.001$).

The severity of underlying disease related to accuracy rates of intra-articular injections was explored in the study of Toda and coworkers[10] Accuracy rates of subgroups with different Kellgren and Lawrence (K&L) grade OA were presented. In the K&L grade II and III groups, no significant differences were found between the superolateral approach, anteromedial approach and modified approach by Waddell. In the K&L grade IV group the modified approach by Waddell reached 100% accuracy, which was significantly higher than the superolateral and anteromedial approach (both 55%, $p=0.035$).

In 2 studies[10, 23] approach-related factors were identified. In the study of Luc and coworkers[23] A 97% accuracy rate using the superolateral approach was reported applying the so-called backflow technique, ie, lidocaine is injected (1 mL at a time) until backflow of the injected lidocaine occurs, then contrast is injected and radiographs are taken to determine accuracy. In the study of Toda and coworkers[10] traction at the ankle joint was applied while injecting the affected knee joint at the medial side of the patellar tendon. This approach is a modification of the approach used in the study of Waddell and coworkers[24], and the overall accuracy rate was 86% with a 100% accuracy rate in the K&L grade IV subgroup.

Most studies did not report any local reactions related to the used approach.[10, 15, 16, 20, 23-25] In 1 study[22] a patient suffered from a quadriceps bleeding 1 week after extra-articular needle placement. Another study investigated intra-articular injections in several peripheral joints. Hypotrophy and/or hypochromia of the skin was found in 10% of the group injected extra-articularly compared to 4.7% injected intra-articularly.[21]

Figure 2 Approaches of knee injections

Superomedial approach
knee in extension, injection under superomedial patella margin

Superolateral approach
knee in extension, injection under superolateral patella margin

Medial midpatellar approach
knee in extension, injection medial under horizontal patella midline

Lateral midpatellar approach
knee in extension, injection lateral under horizontal patella midline

Anteromedial approach
knee in 90° flexion, injection medial from patellar tendon towards intercondylar notch

Anterolateral approach
knee in 90° flexion, injection lateral from patellar tendon towards intercondylar notch

Modified Waddell's approach
knee in 30° flexion, traction at ankle, injection 1-1,5 cm above anteromedial injection site towards anterior contact point femoral condyle

Waddell's approach
knee in 30°-40° flexion, injection 1-1,5 cm proximal from anterolateral arthroscopy portal towards anterior contact point femoral condyle-tibial plateau

all pictures show the left knee

Table 4 Accuracy results

First author, Year of publication	Accuracy percentage per approach (no. of intra-articular needle placements/no. of needle placements)							
	SL	SM	LMP	MMP	AL	AM	WA	MWA
Bliddall[22], 1999	91 (51/56)							
Esenyel[16], 2007			76 (59/78)	56 (44/78)	85 (66/78)	73 (57/78)		
Glattes[20], 2004	100 (10/10)							
Jackson[15], 2002			93 (74/80)		71 (57/80)	75 (60/80)		
Lopes[21], 2008	100 (37/37)							
Luc[23], 2006	97 (32/33)							
Toda[10], 2008*	70 (35/50)					62 (31/50)		86 (43/50)
K&L II	86 (18/28)					71 (15/28)		86 (18/28)
K&L III	61 (11/18)					56 (10/18)		78 (14/18)
K&L IV	55 (6/11)					55 (6/11)		***100 (11/11)***
Waddell[24], 2001							100 (20/20)	
Wind[25], 2004**	89 (39/44)	93 (40/43)			43 (19/44)			
Pooled accuracy percentage (95% CI)	89 (84-92)	93 (81-98)	85 (78-89)	56 (45-66)	67 (43-91)	72 (65-78)	100 (84-100)	86 (74-93)

SL: superolateral approach, leg in extension; SM: superomedial approach, leg in extension; LMP: lateral midpatellar approach, leg in extension; MMP: medial midpatellar approach, leg in extension; AL: anterolateral approach, leg in 90^0 flexion; AM: anteromedial approach, leg in 90^0 flexion; WA: Waddell's approach, anterolateral with leg in 30^0-40^0 flexion; MWA: modified Waddell's approach, anteromedial with leg in 30^o flexion and ankle traction towards lateral; K&L: Kellgren and Lawrence scale, *accuracy results also per K&L score,**intra-articular staining of injected methylene blue classified as 'good' during arthroscopy.

Discussion

An accurate intra-articular needle placement in the knee joint is important for intra-articular treatment, diagnosis and research purposes of diseases such as RA and OA.

Our systematic review of different approaches for intra-articular needle placements such as injections or aspiration in the knee joint revealed that the superolateral approach resulted in high accuracy rates[10, 20-23, 25], with the highest pooled accuracy of 91% (95% CI 84-99%). Furthermore, the superolateral approach was studied most (6 studies, 230 knees). Pooled accuracy rates for the lateral midpatellar approach, anterolateral approach and anteromedial approach were 85% (95% CI 68-100%), 67% (95% CI 43-91%) and 72% (95% CI 65-78%), respectively. Local reactions related to a certain approach are reported occasionally and appear to be related to extra-articular needle placement.[22, 23]

Intra-articular injections or aspiration of knees with effusion are believed to be less challenging. In 2 studies in the superolateral approach group only patients with synovitis[21] or clinical effusion[20] were injected in the knee joint. Both studies reported 100%[20, 21] accuracy. The pooled accuracy rate of the superolateral approach group without these 2 latter studies shows only a minor difference, i.e. 88% (95% CI 77-98%) compared to the original pooled accuracy rate, ie, 91% (95% CI 84-99%). Furthermore, in a third study investigating the superolateral approach, patients with knee effusion were not explicitly excluded[25]; these authors reported a significantly higher accuracy rate in the superolateral approach group compared to the anterolateral approach, ie, 89% and 43%, respectively ($p<0.001$). This suggests that even when effusion could be present, the superolateral approach still results in significantly higher accuracy rates.

A contributing factor to lower accuracy rates might be the length of the needle used for the procedure. The lowest accuracy rates in the superolateral group were reported by Toda and coworkers (70%[10]) and Wind and coworkers (89%[25]) both using a needle only 1.25 inch long. In the other included studies, in the superolateral approach group 1.5 or 2.0 inch needles were used; higher accuracy rates (91-100%) were reported using these longer needles.

In a pilot study reported by Jackson and coworkers[15] the distance from skin edge to femoral condyle was measured by MRI, ranging from 4.4-5.5 cm

(1.8-2.2 inches). Looking at the anterolateral approach group, only 1.5-2.0 inch needles were used.[15, 16, 25] Pooled accuracy rate in this group was 67% (95% CI 43-91%) and extra-articular injections were mainly reported in Hoffa's fat pad. This suggests that a needle longer than 2 inches should be used for intra-articular injections via the anterolateral approach.

The results from the study of Toda and coworkers[10] suggest that applying traction at the ankle during injection can contribute to a high accuracy rate in patients with K&L grade IV OA. Toda and coworkers[10] reported a significant difference in accuracy rate (100%) in the K&L grade IV group in favour of the modified approach by Waddell, compared to the superolateral and anteromedial approach (both 55%, p=0.035) in which no traction is applied during injection. Although only investigated in 1 study, the K&L grade of the knee might be important in the choice of injection approach and the appliance of traction.

However, in the K&L grade IV subgroup, the clinical implication of the high accuracy rate might be less extensive. In treated OA patients, the mechanism of HA is reported to be through suppressed cartilage degeneration [26] and improved superficial cartilage compactness and thickness.[27] However, severe OA patients with K&L grade IV show less response to treatment with HA than patients with K&L grades I, II or III.[4] It is therefore questionable whether HA should be used in patients with K&L grade IV OA.

The results of the risk of bias assessment using the QUADAS tool[17-19] (Table 3) show minor differences between the included studies. In assessing pooled accuracy rates, the sample size of the included studies is of great importance. Although this is a discriminating factor between the included studies in the present review, it is not part of the scored items in the QUADAS tool. In our review the QUADAS tool did not contribute to an obvious distinction between the included studies included.

To our knowledge the present study is the first systematic review of the available literature on this topic. The present review shows that the superolateral approach resulted in the highest pooled accuracy rate of 91% (95% CI 84-99%) and was investigated most in the included articles. The lateral midpatellar, anterolateral and anteromedial approach result in lesser pooled accuracy rates. Sufficient needle length should be considered before performing any intra-articular needle placement procedure in the knee joint.

Conclusion

We conclude that for a blindly performed intra-articular needle placement in the knee joint, the superolateral approach should be the approach of choice. Nevertheless, it is shown that the superolateral approach still results in a substantial amount of extra-articular needle placements in blindly performed procedures. Guidance of intra articular needle placements by the means of imaging techniques may enhance the accuracy. The costs and extra time associated with the implementation and use of imaging guided procedures in daily practice should be taken in consideration.

References

1. NOV DOS. Richtlijn diagnostiek en behandeling van heup- en knie artrose (Guidelines in diagnostics and treatment of hip- and knee ostoarthritis). 2007.
2. Bellamy N, Campbell J, Robinson V, Gee T, Bourne R, Wells G. Viscosupplementation for the treatment of osteoarthritis of the knee. Cochrane Database Syst Rev 2006; (2): CD005321.
3. Karlsson J, Sjogren LS, Lohmander LS. Comparison of two hyaluronan drugs and placebo in patients with knee osteoarthritis. A controlled, randomized, double-blind, parallel-design multicentre study. Rheumatology (Oxford) 2002; 41(11): 1240-8.
4. Lussier A, Cividino AA, McFarlane CA, Olszynski WP, Potashner WJ, De Medicis R. Viscosupplementation with hylan for the treatment of osteoarthritis: findings from clinical practice in Canada. The Journal of rheumatology 1996; 23(9): 1579-85.
5. Raynauld JP, Torrance GW, Band PA, et al. A prospective, randomized, pragmatic, health outcomes trial evaluating the incorporation of hylan G-F 20 into the treatment paradigm for patients with knee osteoarthritis (Part 1 of 2): clinical results. Osteoarthritis Cartilage 2002; 10(7): 506-17.
6. Wang CT, Lin J, Chang CJ, Lin YT, Hou SM. Therapeutic effects of hyaluronic acid on osteoarthritis of the knee. A meta-analysis of randomized controlled trials. J Bone Joint Surg Am 2004; 86-A(3): 538-45.
7. Aggarwal A, Sempowski IP. Hyaluronic acid injections for knee osteoarthritis. Systematic review of the literature. Canadian family physician Medecin de famille canadien 2004; 50: 249-56.
8. Genzyme Biosurgery RU. Hylan G-F 20 (Synvisc) package insert. Genzyme Biosurgery; 2006.
9. Fidia Farmaceutici S.p.A. Padua Italy. Sodium Hyaluronate (Hyalgan) package insert.
10. Toda Y, Tsukimura N. A comparison of intra-articular hyaluronan injection accuracy rates between three approaches based on radiographic severity of knee osteoarthritis. Osteoarthritis Cartilage 2008; 16(9): 980-5.
11. Pascual E, Doherty M. Aspiration of normal or asymptomatic pathological joints for diagnosis and research: indications, technique and success rate. Annals of the rheumatic diseases 2009; 68(1): 3-7.
12. Courtney P, Doherty M. Joint aspiration and injection. Best Pract Res Clin Rheumatol 2005; 19(3): 345-69.
13. Malfair D. Therapeutic and diagnostic joint injections. Radiol Clin North Am 2008; 46(3): 439-53, v.
14. Jones A, Regan M, Ledingham J, Pattrick M, Manhire A, Doherty M. Importance of placement of intra-articular steroid injections. BMJ (Clinical research ed 1993; 307(6915): 1329-30.
15. Jackson DW, Evans NA, Thomas BM. Accuracy of needle placement into the intra-articular space of the knee. The Journal of bone and joint surgery 2002; 84-A(9): 1522-7.
16. Esenyel C, Demirhan M, Esenyel M, et al. Comparison of four different intra-articular injection sites in the knee: a cadaver study. Knee Surg Sports Traumatol Arthrosc 2007; 15(5): 573-7.
17. Whiting P, Rutjes AW, Reitsma JB, Bossuyt PM, Kleijnen J. The development of QUADAS: a tool for the quality assessment of studies of diagnostic accuracy included in systematic reviews. BMC medical research methodology 2003; 3: 25.

18. Whiting PF, Weswood ME, Rutjes AW, Reitsma JB, Bossuyt PN, Kleijnen J. Evaluation of QUADAS, a tool for the quality assessment of diagnostic accuracy studies. BMC medical research methodology 2006; 6: 9.
19. Reitsma JB RA, Whiting P, Vlassov VV, Leeflang MMG, Deeks JJ. Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy Version 1.0.0. Chapter 9: Assessing methodological quality: The Cochrane Collaboration; 2009.
20. Glattes RC, Spindler KP, Blanchard GM, Rohmiller MT, McCarty EC, Block J. A simple, accurate method to confirm placement of intra-articular knee injection. Am J Sports Med 2004; 32(4): 1029-31.
21. Lopes RV, Furtado RN, Parmigiani L, Rosenfeld A, Fernandes AR, Natour J. Accuracy of intra-articular injections in peripheral joints performed blindly in patients with rheumatoid arthritis. Rheumatology (Oxford) 2008; 47(12): 1792-4.
22. Bliddal H. Placement of intra-articular injections verified by mini air-arthrography. Ann Rheum Dis 1999; 58(10): 641-3.
23. Luc M, Pham T, Chagnaud C, Lafforgue P, Legre V. Placement of intra-articular injection verified by the backflow technique. Osteoarthritis Cartilage 2006; 14(7): 714-6.
24. Waddell D, Estey D, DeWayne C, Bricker P, Marsala A. Viscosupplementation under fluoroscopic control. Am J Med Sports 2001; 4(July/August): 237-41.
25. Wind WM, Jr., Smolinski RJ. Reliability of common knee injection sites with low-volume injections. The Journal of arthroplasty 2004; 19(7): 858-61.
26. Listrat V, Ayral X, Patarnello F, et al. Arthroscopic evaluation of potential structure modifying activity of hyaluronan (Hyalgan) in osteoarthritis of the knee. Osteoarthritis Cartilage 1997; 5(3): 153-60.
27. Guidolin DD, Ronchetti IP, Lini E, Guerra D, Frizziero L. Morphological analysis of articular cartilage biopsies from a randomized, clinical study comparing the effects of 500-730 kDa sodium hyaluronate (Hyalgan) and methylprednisolone acetate on primary osteoarthritis of the knee. Osteoarthritis Cartilage 2001; 9(4): 371-81.

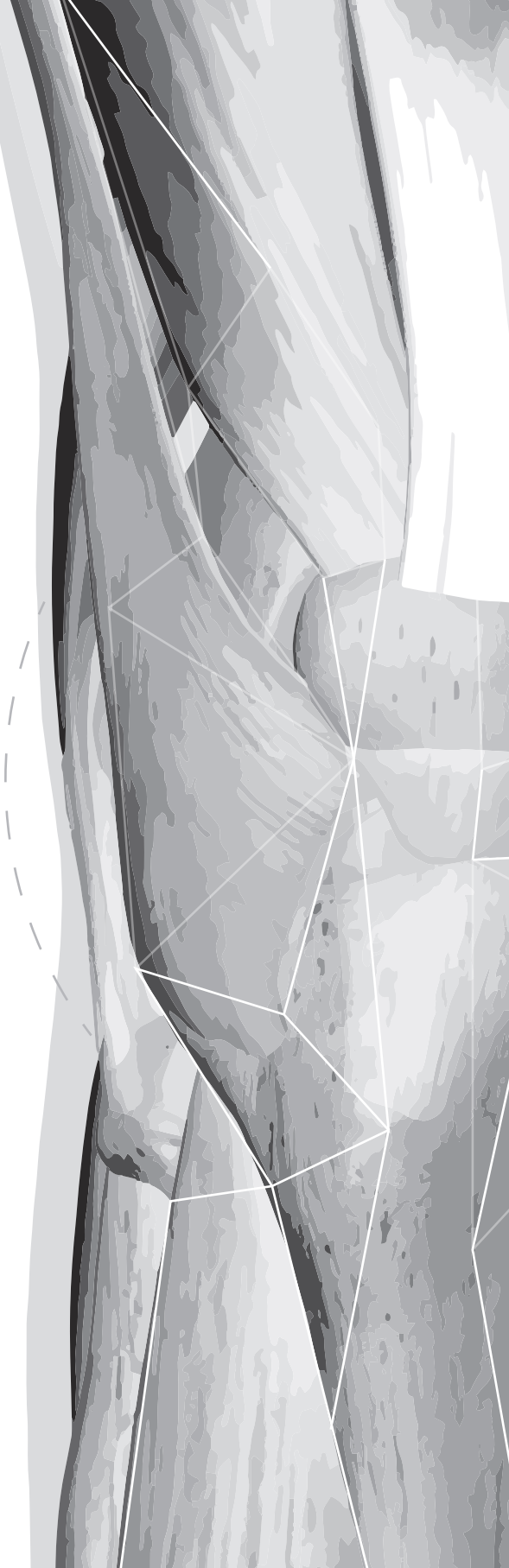
Appendix 1 Used search strategy

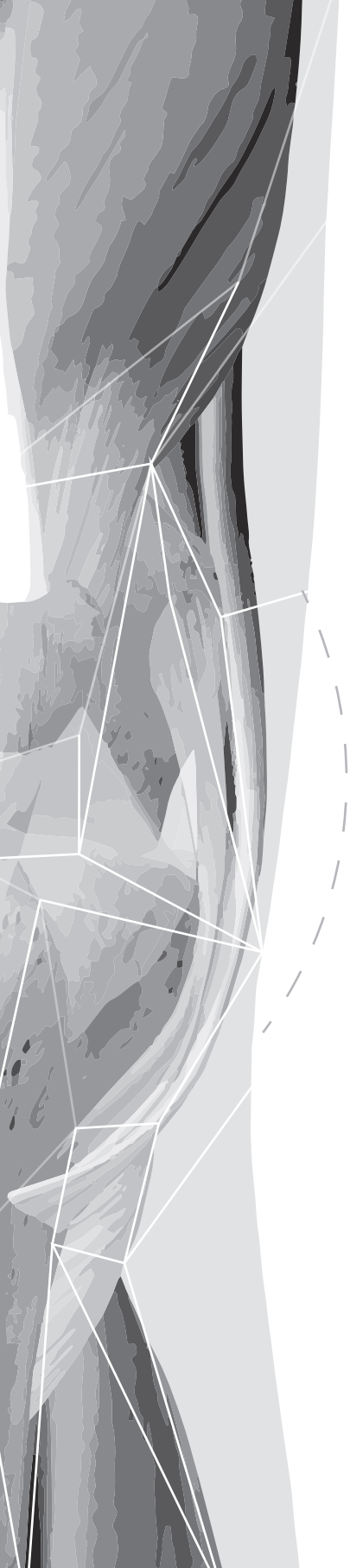
Embase

(knee/exp OR ((genu:ti,ab OR knee:ti,ab OR femorotibial: ti,ab OR tibiofemoral:ti,ab OR femoral-tibial:ti,ab OR tibial-femoral:ti,ab) AND (joint*:ti,ab OR arthros*: ti,ab))) AND ('intraarticular drug administration'/exp OR ((intraarticular:ti,ab OR intraarticular:ti,ab) AND (injection*:ti,ab OR administration*:ti,ab)) OR 'needle placement':ti,abOR'needle placements':ti,ab)NOT(animal* NOT human*).

PubMed

(knee[mesh] OR knee joint[mesh] OR ((genu[tiab] OR knee[tiab] OR femorotibial[tiab] OR tibiofemoral[tiab] OR femoral-tibial[tiab] OR tibial-femoral[tiab]) AND (joint*[tiab] OR arthros*[tiab]))) AND (injections, intraarticular[mesh] OR intraarticular injection*[tiab] OR intraarticular injection*[tiab] OR (intraarticular[tiab] AND administration[tiab]) OR needle placement*[tiab]) NOT (animal*[tw] NOT human*[tw]).





Chapter 3

Productivity costs and medical costs among working patients with knee osteoarthritis

J. Hermans
M. A. Koopmanschap
S.M.A. Bierma-Zeinstra
J.H. van Linge
J.A.N. Verhaar
M. Reijman
A. Burdorf

Arthritis Care Res (Hoboken). 2012 Jun;64(6):853-61.

Abstract

Objective

Although the knee joint is one the most affected joints by osteoarthritis (OA), research on economic implications focussed merely on OA in general. The goal of this study was to identify and quantify knee-related productivity and medical costs in knee OA patients in paid employment. Furthermore, we evaluated associations between productivity loss and relevant patient, health and work characteristics.

Methods

Consecutive knee OA patients with mild to moderate knee OA who were 18-65 years of age, had conservative treatment ≥ 6 months and had paid employment were included. Productivity loss and health care consumption were measured by questionnaires. Associations between productivity loss and patient, health and work characteristics were explored with regression analyses.

Results

In total, 117 knee OA patients with a mean age of 53.2 years and a body mass index of 28.8 kg/m^2 were included. Total knee-related productivity costs and medical costs were €871 (median €411, interquartile range (IQR) €107-1200) per patient per month, with total productivity costs of €722 (median €217, IQR €0-1041) and total medical costs of €149 (median €137, IQR €72-198). More pain during activity and performing physically intensive work were significantly associated with productivity loss.

Conclusion

The total knee-related productivity costs and medical costs of conservatively treated symptomatic knee OA patients with paid employment in The Netherlands are €871 per patient per month, with productivity costs accounting for 83% and medical costs for 17%. Productivity loss is associated with having more pain during activity and performing physically intensive work. Developing adequate treatment strategies for knee OA may be cost beneficial.

Introduction

Osteoarthritis (OA) is a chronic joint disease frequently affecting middle aged and older people [1]. The prevalence of clinical OA is about 12% in persons aged 25-74.[2] Due to aging and increasing life expectancy, OA is expected to become the worlds fourth leading cause of disability in 2020.[3] OA accounts for the majority of the economic burden of arthritis, estimated at 1 to 2.5% of the gross national product in western countries.[4-6]

The economic burden of OA consists of productivity and medical costs.[7-9] Productivity costs are subdivided in costs due to lost productivity while being present at work[10-12], costs due to absence from work[13, 14], and costs for compensation of household work by others.[7] Studies investigating musculoskeletal disorders show that the majority of the productivity costs are subscribed to lost productivity while being present at work.[14-16] Medical costs comprehend the costs of all resources consumed in the health care sector and patients' out of pocket expenses.[7-9, 17]

Productivity costs are influenced by several factors. Patient characteristics like increased body mass index (BMI)[18-21] and disease characteristics like pain[15] are frequently associated with productivity loss. The same applies to several work-related physical factors such as frequently using force[22] and bending or twisting the upper body.[23] Although kneeling, squatting and heavy lifting are known for their relation to knee OA[24], their associations to productivity loss have yet to be determined. Work-related psychosocial factors like low job autonomy, high job demands and emotionally demanding work[14, 22, 23, 25, 26] are furthermore often associated with productivity loss.

The knee joint is one of the joints most frequently affected by OA.[27, 28] Nevertheless, research on the economic implications of joint disease has focussed merely on arthritis or OA in general.[4, 6, 8, 9, 17, 29-31] The main goal of this study was to identify and quantify knee-related productivity and medical costs in conservatively treated knee OA patients with paid employment in The Netherlands. The secondary goal was to evaluate the associations between knee-related productivity loss and individual, disease and work characteristics.

Patients and methods

Study sample

The study subjects participated in a randomised controlled trial (RCT) investigating the cost-effectiveness of intra articular hyaluronic acid in addition to usual care, registered at the Dutch trial register (www.trialregister.nl). Inclusion took place between May 2009 and May 2010 in the Erasmus MC University Medical Center in Rotterdam (The Netherlands) and the Reinier de Graaf Hospital in Delft, The Netherlands. The RCT focussed on patients with mild to moderate knee OA receiving conservative treatment and who were not scheduled for knee OA-related surgery in the near future. Consecutive patients with knee OA consulting an orthopaedic surgeon at the outpatient clinic of one of the 2 participating hospitals were included. Patients with a Kellgren/Lawrence (K/L) grade of 1-3 and with a minimum numeric rating scale (NRS) for pain of 2 were eligible. At the time of inclusion, subjects were 18-65 years of age and had to be treated conservatively for their knee OA for ≥ 6 months prior to inclusion. Patients with K/L grade IV or patients scheduled for knee OA related surgery within 1 year were not considered eligible for participation. The local Medical Ethics Committee approved the study and all patients signed an informed consent. For the aim of this study, we performed a cross-sectional analysis on patients from abovementioned study sample who were involved in a paid employment at the baseline measurement. Only data acquired from the baseline measurement and therefore before onset of any trial intervention were used.

Productivity and medical costs

The Productivity and Disease Questionnaire (PRODISQ)[32] was used for the measurement of productivity costs due to knee symptoms. This questionnaire covers relevant aspects of the relationship between health and productivity including knee-related absence from work during the past 3 months. It includes the measurement of lost productivity due to knee symptoms while being present at work by the quality and quantity method.[11, 32] Subjects are asked to rate the quality and quantity of work performed on their last work day compared to a regular workday on a 10-point NRS. Zero represents no quantity or quality and 10 represents normal quantity or quality. The quantity scale was used for the calculations on productivity loss due to

the high correlation[33] between the both scales. To assess compensational mechanisms for productivity loss in the household, subjects were asked to indicate the amount of work in the household taken over by others.

Knee-related health care consumption in the prior 3 months was obtained through patient questionnaires. This included physician and paramedical therapist visits in primary and secondary care, use of aids (braces, inlay soles, crutches, etc.), use of home care, and medication use. Medication costs included the prescription fees pharmacists receive per prescription.[34]

Resources were valuated according to Dutch guideline prices and tariffs[34] (Table 1). If no prices were available (e.g. homeopath tariffs), the tariff was calculated based on mean tariffs charged by different practices. Tariffs for diagnostic imaging were obtained from the 2 participating hospitals. Tariffs for mobility aids were obtained from qualified homecare companies specialized in mobility aids reimbursed by health insurance companies. The depreciation time for sustainable aids like crutches, orthopaedic soles and braces was set on 2 years. Costs made solely for the participation of this study were omitted from the cost analyses.

Table 1 Prices used in the productivity and medical costs analyses

Item	Costs
Productivity costs (per hour)*	
Paid work	€ 30,02
Unpaid work	€ 12,50
Medical costs (per visit)*	
Primary care	
Physical therapist	€ 36,00
General practitioner	€ 28,00
Company physician	€ 62,50
Other†	€ 24,00 - 35,00
*Secondary care (visit)**	
Orthopaedic surgeon	€ 72,00
Rheumatologist	€ 72,00
Other‡	€ 72,00
Medication (per unit)§	
Acetaminophen§	€ 0,02
Nonsteroidal antiinflammatory drugs¶	€ 0,37
Glucosamine¶	€ 0,28
Gastro protective agents¶	€ 0,50
Other#	€ 0,13 - 0,84
Prescription fee	€ 5,99
Imaging (unit) **	
Radiographs	€ 19,28
Magnetic resonance imaging	€ 300,00
Other††	€ 105,89 - 250,00
Aids (unit)¶	
Cold/warm compresses	€ 1,95
Elastic bandage	€ 22,50
Knee braces	€ 75,00
Orthopaedic sole	€ 126,00
Other‡‡	€ 1,50 - 3.200,00

*According to published Dutch guidelines [34] † Price range of sports massage, homeopath, home care, practice therapist, and sports physician. Mean price of different practices. ‡ Price range of revalidation physician, neurologist, and surgeon. § According to the Health Care Insurance Counsel. ¶ Mean price of different products within the same product type. # Price range of aspirin, chondroitin, and nonsteroidal antiinflammatory drug gel. Mean price of different products within the same product type. ** Price is based on charges from the 2 participating hospitals. †† Price range of ultrasound, scintigraphy, and single-photon–emission computed tomography. ‡‡ Price range of crutches, tape, walking stick, shower chair, wheel chair, and bicycle adaption.

Patient, health and work characteristics

Patient characteristics enclosed age, gender, BMI and the level of education. Health characteristics included the NRS for pain[35] during rest and during activity and the presence of concomitant back pain. Quality of life (QOL) was assessed by the EuroQol 5-domain questionnaire (EQ-5D)[36, 37] resulting in a score between 0 (death) and 1 (perfect health). Knee-related function was assessed by the Knee injury and Osteoarthritis Outcome Score (KOOS).[38, 39] This questionnaire consists of 5 subscales (pain, other symptoms, functioning in activities of daily living (ADL), functioning in sport and recreation and knee-related QOL). A normalized score was calculated for each subscale, in which 100 indicates no symptoms and 0 indicates extreme symptoms. Work characteristics were separated into physical and psychosocial factors. Physical factors concerned the items known for their relation to knee (regular presence of kneeling or squatting, moving heavy loads and performing physically intensive work) OA.[24] These items were assessed using a 4-point scale containing "rarely or never", "now and then", "often" and "always". The latter 2 answers were considered high exposure to the physical factor of interest.[23, 25]

The psychosocial workload was assessed by questions based on the demand control support model of Karasek et al.[40] This included the dimensions job control, skills discretion, work demands and psychosocial work environment. Job control questions concerned influence on the planning of work and ability to postpone work if necessary. Skills discretion covered variety in work, involvement in complex matters and learning new matters. Work demands items included insufficient time to complete work, excessive work and working overtime. Questions on the psychosocial work environment concerned social interaction and loyalty between co-workers, support from supervisor in personal development and encouragement from supervisor in autonomy of work planning. Four or 5-point scales were used for these questions and for each dimension a sum score was calculated. Patients with median sum scores or higher were regarded as exposed.[23, 41]

Statistical analyses

Descriptive statistics were used to describe the study sample characteristics. All investigated costs were proportionally converted to costs per month.

The associations between quantity of work while being present at work and patient, health and work characteristics were explored with univariate linear regression analyses. For the exploration of absence from work and aforementioned characteristics we used univariate logistic regression analysis. Variables reaching a ***P*** value less than 0.20 in the univariate model were investigated in the multivariate regression model. Age and sex were considered potential confounding variables and were included in the multivariate regression analyses. A variable was retained in the multivariate model when statistically significant at a ***P*** value below 0.05. To identify interactions, correlations between investigated in the multivariate model were explored. If necessary, the model was adjusted for interacting variables. Given the size of the study sample, the number of independent variables in 1 model was limited. Analyses were performed using Statistical Package for Social Sciences, version 17.0.[42]

Results

Study sample

Patient characteristics are presented in Table 2. In total, 117 patients were included in this study, of which 50 (43%) were women. The mean age ± SD was 53.2 ± 7.4 years, mean ± SD BMI was 28.8 ± 5.1 kg/m^2. More than half of the sample (n=62, 53%) experienced knee symptoms >12 months at the time of inclusion. The mean ± SD NRS score for pain during rest was 4.4 ± 2.6 and for pain during activity 6.1 ± 2.4. The KOOS average subscale scores did not exceed 58.1 (function in ADL scale). The mean ± SD score on the KOOS pain scale was 50.0 ± 20.8). The lowest mean ± SD score was 28.2 ± 25.5) for the function in sports and recreation scale.

In total, 47 patients (40%) reported productivity loss (quantity) due to knee symptoms, compared to a regular work day. The mean ± SD score on the quantity scale was 8.6 ± 2.3, indicating an average productivity loss of 14% while being present at work. Twenty-three patients (20%) reported ≥1 episode of absence from work in the last 3 months due to knee symptoms. High exposure to work related physical determinants was present in 14-26 of the patients (12-22%), of which performing physically intensive work was the physical determinant most present (n=26, 22%). High exposure to work

related psychosocial determinants were present in 44-52 patients (38-44%), of which lack of job control was the psychosocial determinant most present (n=52, 44%).

Table 2 Baseline characteristics (n=117)

Individual characteristics	
Age, mean ± SD years	53.2 ± 7.4
Female, no. (%)	50 (43)
BMI mean ± SD kg/m^2	28.8 ± 5.1
Education, no. (%)	
Lower level	13 (11)
Intermediate level	70 (60)
Higher level	34 (29)
Job type, no. (%)	
Agriculture	4 (3.4)
Industry	14 (12.0)
Commercial services	61 (52.1)
Non-commercial services	30 (25.6)
Government	8 (6.8)
Health related characteristics	
Duration knee symptoms for 3-12 months, no. (%)	55 (47)
Duration knee symptoms for 12 months, no. (%)	62 (53)
NRS knee pain during rest (0-10), mean (sd)	4.4 ± 2.6
NRS knee pain during activity (0-10), mean (sd)	6.1 ± 2.4
Concomitant back pain, n (%)	35 (30)
K/L grade, no. (%)	
1	10 (9)
2	58 (49)
3	49 (42)
Quality of life, EQ-5D (range 0-1), mean ± SD	0.70 ± 0.23
KOOS subscales range (0-100), mean ± SD†	
Pain	50.0 ± 20.8
Other symptoms	58.0 ± 20.1
Function in activities of daily living	58.1 ± 22.2
Function sports and recreation	28.2 ± 25.5
Knee-related quality of life	33.3 ± 18.6

Work related characteristics	
Hours per week, mean ± SD	31.8 ± 11.7
Hindrance in work due to knee complaints, no. (%)	94 (80)
Quantity (range 0-10) due to knee complaints, mean ± SD	8.6 ± 2.3
Quality (range 0-10) due to knee complaints, mean ± SD	9.3 ± 1.6
Absence in the past 3 months due to knee symptoms, no. (%)	23 (20)
Physical factors, no.(%)	
Prolonged kneeling or squatting	17 (15)
Moving heavy loads >25 kg often	14 (12)
Performing physically intensive work	26 (22)
Psychosocial factors, no. (%)	
Lack of job control	52 (44)
Poor skills discretion	46 (39)
High work demands	44 (38)
Poor psychosocial environment‡	46 (41)

* BMI=body mass index; NRS=numerical rating scale; K/L=Kellgren/Lawrence; EQ-5D= EuroQol 5-domain questionnaire; KOOS=Knee injury and Osteoarthritis Outcome Score; NRS=Numeric Rating Scale. † N = 116 in the subscales function of all day life, function in sports and recreation and knee-related quality of life. ‡ N= 113, item includes relation to supervisor, 4 patient without supervisor

Productivity costs and medical costs

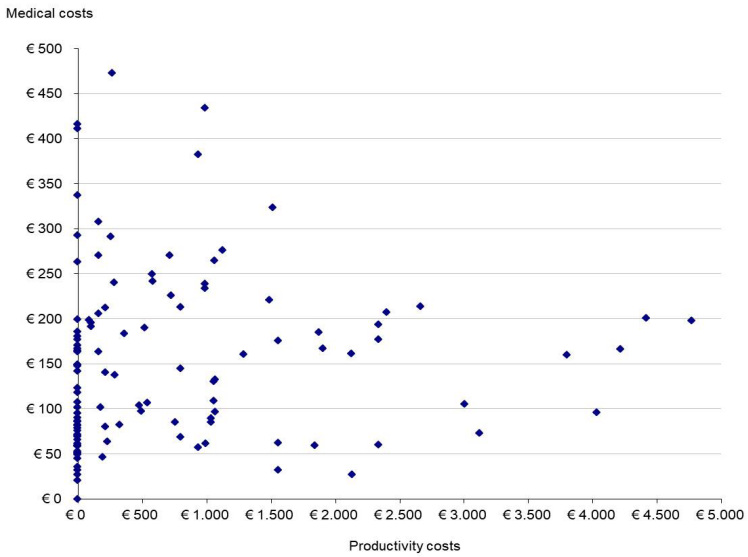
The prices used for the cost analyses are listed in Table 1. The average total monthly knee-related productivity costs were €722 (median €217, interquartile range (IQR) €0 - 1041) per patient per month. Knee-related lost productivity while being present at work accounted for the largest part of productivity loss (14.9 hours). The costs associated with this productivity loss were €448 per patient per month (median €0, IQR €0 -608) and accounted for 62% of the total productivity costs. Knee-related absence from work was responsible for 6.6 hours, corresponding to €197 (median €0, IQR €0 - 0). Compensation for work in the household was responsible for 6.2 hours and €77 (median €0, IQR €0 - 54).

The average total knee-related medical costs were €149 (median €137, IQR €72 - 198) per patient per month (Table 3). In primary care, the physical therapist and general practitioner were visited most frequent with on average 1.37 and 0.28 visits per patient per month, respectively. The mean total costs for primary care comprised €62 (median €31, IQR€9 - 96) per patient per month, being the main component of the total medical costs. In secondary care, the orthopaedic surgeon was visited on average 0.42

times per patient per month. The mean total costs for secondary care were €33 (median €24, IQR€24 - 48) per patient per month. Acetaminophen and nonsteroidal antiinflammatory drugs were the most used medications, with an average use of 14.95 and 11.73 units per patient per month, respectively. The average amount of glucosamine taken was 3.59 tablets per patient per month. The mean medication costs were €8 (median €0, IQR €0 - 13) per patient per month. Most aids most often used were compresses, bandages, braces and orthopaedic soles, with 39, 34, 26 and 22 patients using these aids in the last month. The mean total costs for aids were €6 (median €2, IQR €2 - 5) per patient per month. On average, patients underwent 1.29 x-rays for their knee symptoms per month. The mean total costs for diagnostic imaging were €40 (median €26, IQR €19 - €40) per patient per month.

The mean total of productivity costs and medical costs was €871 (median €411, IQR €107 - 1200) per patient per month. Figure 1 shows the productivity costs and medical costs for each subject in the study. Productivity costs accounted for €722 (median €217, IQR €0 - 1041), corresponding to 83% of the total costs, and medical cost accounted for €149 (median €137, IQR €72 - 198) corresponding to 17% of the total costs.

Figure 1 Productivity costs and medical costs for individual subjects



Associations with productivity loss

Loss of productivity due to knee symptoms was measured with the quantity scale (correlation quality scale Pearson's ρ=0.66). Univariate regression analyses (Table 4) showed that a higher BMI was significantly associated with lower quantity while being present at work. Furthermore, more pain during rest as well as during activity and QOL were significantly associated with lower quantity on a regular work day. Of the work characteristics, performing physically intensive work, poor skills discretion and a poor psychosocial work environment was significantly associated with lower quantity of work. In the multivariate linear regression model, only pain during activity (b -0.28 (95% confidence interval (95% CI) -0.47, -0.09) and performing physically intensive work (b -1.73, (95% CI -2.62, -0.84) showed significant associations with lower quantity of work.

A higher BMI was significant associated with absence from work due to knee symptoms (Table 5). Furthermore, more pain during rest and during activity and lower QOL resulted in significant associations with absence from work. Within the work characteristics, physical factors like moving heavy loads often and performing physically intensive work were significantly associated with absence from work. Of the psychosocial factors, lack of job control, poor skills discretion and high work demands were all significantly associated with absence from work. Due to mutual correlations between the work characteristics, we included the variables with the strongest univariate association (BMI and QOL) in the multivariate model. Age and gender were thus not corrected for. Significant work characteristics were then added separately to the model. This resulted in a significant independent association from performing physically intensive work with absence from work (adjusted odds ratio 4.2 (95% CI 1.48 - 11.93)).

Overall, having more pain during activity and performing physically intensive work are associated with productivity loss. In the multivariate analysis, other patient, health or work characteristics did not contribute significantly and when added to the final models the regression coefficients remained unchanged.

Table 4 Univariate and multivariate linear regression analysis and 95% CIs for quantity while being present at work (n=117)*

	Univariate analyses		Multivariate analyses	
	b	**(95% CI)**	**b**	**95% CI†**
Individual characteristics				
Age	-0.04	(-0.10, 0.02)‡		
Gender (man->vrouw)	-0.36	(-1.21, 0.49)		
BMI	-0.07	(-0.16, 0.01)‡		
Health characteristics				
NRS[a] knee pain during rest	-0.33	(-0.48, -0.17)‡		
NRS[a] knee pain during activity	-0.39	(-0.55, -0.23)‡	-0.28	(-0.47, -0.09)§
Concomitant back pain	-0.34	(-1.35, 0.68)		
Quality of life (EQ-5D)	3.28	(1.57, 4.99)‡		
Work characteristics				
Physical factors				
Prolonged kneeling or squatting	-0.30	(-1.49, 0.90)		
Moving heavy loads (>25kg) often	-0.28	(-1.58, 1.02)		
Performing physically intensive work	-1.92	(-2.87, -0.97)‡	-1.73	(-2.62, -0.84)§
Psychosocial factors				
Lack of job control	-0.37	(-1.21, 0.48)		
Poor skills discretion	-0.93	(-1.78, -0.08)‡		
High work demands	-0.17	(-1.04, 0.70)		
Poor psychosocial work environment	-0.73	(-1.60, 0.14)‡		

* 95% CI=95% confidence interval; BMI= body mass index; NRS=numerical rating scale; EQ-5D=EuroQol 5-domain questionnaire. † Adjusted for age and sex. ‡ Significant at P <0.20. § Significant at P <0.05.

Table 5 Univariate and multivariate logistic regression analysis and 95% CIs for sickness absence (n=117)*

	Univariate analyses		Multivariate analyses[b]	
	OR	(95% CI)	OR	(95% CI)†
Individual characteristics				
Age	1.04	(0.97 - 1.11)		
Gender	0.77	(0.31 - 1.93)		
BMI	1.12	(1.03 - 1.22)‡		
Health characteristics				
NRS knee pain in rest	1.17	(0.98 - 1.41)‡		
NRS knee pain during activity	1.17	(0.94 - 1.44)‡		
Concomitant back pain	0.46	(0.13 - 1.70)		
Quality of life (EQ-5D)	0.23	(0.04 - 1.32)‡		
Work characteristics				
Physical factors				
Prolonged kneeling or squatting	1.90	(0.59 - 6.06)		
Moving heavy loads (>25kg) often	3.80	(1.17 - 12.34)‡		
Performing physically intensive work	3.75	(1.40 - 3.04) ‡	4.20	(1.48 - 11.93)§
Psychosocial factors				
Lack of job control	1.83	(0.73 - 4.60)‡		
Poor skills discretion	2.40	(0.95 - 6.07)‡		
High work demands	2.11	(0.84 - 5.32)‡		
Poor psychosocial work environment	1.80	(0.71 - 4.52)		

* 95% CI=95% confidence interval; BMI= body mass index; NRS=numerical rating scale; EQ-5D=EuroQol 5-domain questionnaire. † Adjusted for age and sex. ‡ Significant at P <0.20. § Significant at P <0.05.

Discussion

In this study we investigated the productivity and medical costs due to knee symptoms in conservatively treated knee OA patients in paid employment. The productivity and medical costs of knee OA have been investigated once in a retrospective study examining 254 patients in Italy by Leardini et al.[43] In this study, 27% of the costs were medical costs and 73% were productivity costs. In our study, 17% medical costs and 83% productivity costs were reported. The difference in the cost ratios can be explained by the age and employment level of both study samples. The mean age in the study of Leardini was 65.8 years and 21.3% had paid employment. In our study the mean age was 52.3 years and 100% had paid employment; therefore the contribution of productivity costs is higher due to our restriction to a

working population. The difference in medical costs could be subscribed to the inclusion of conservatively treated patients as well as surgically treated patients and the inclusion of patients with K/L grade 4 (10,3%). These findings suggest higher disease severity in the population of Leardini, explaining the rise of medical costs.[3, 44]

Another study of Rabenda et al investigated direct (medical) and indirect (productivity) costs of OA in a large community-based population in Belgium[9]. Productivity loss due to knee OA related absence from work was reported to be 0.8 sick days per patient per month. In our study we found an average of 6.6 hours absence per patient per month, which is similar to approximately 0.8 days, based on an 8-hour work day. Productivity costs due to productivity loss while being present at work were not accounted for in the study of Rabenda et al. Still, these costs predominated the medical costs, which is in line with the results of our study.

Our findings are in concordance with the results of other studies investigating musculoskeletal disorders.[13-16, 30] Productivity costs in these studies are also reported to exceed medical costs and the magnitude of the productivity costs was mainly driven by costs due to decreased productivity while being present at work.[14-16]

It must be noted that this cross-sectional investigation of productivity and medical costs due to knee OA has some limitations. The sample size of our study is 117 patients. This sample was recruited from a population of knee OA patients participating in a RCT investigating the cost-effectiveness of intraarticular hyaluronic acid in addition to usual care. Patients were screened for eligibility and asked to participate in the RCT after visiting the orthopaedic outpatient clinic of one of the 2 participating hospitals. For the aim of this particular study, we performed a cross-sectional analysis on the baseline data of patients from the abovementioned RCT who had paid employment at the moment of inclusion. Due to the sample size, this study has a limited discriminatory power to identify all relevant determinants of productivity loss.

The aforementioned community based study of Rabenda[9] investigated 617 OA patients who were employed. Another study investigating the economic impact of OA-related pain included 2173 patients who were employed.[44] Although these studies present larger samples, the prevalence of OA was

self-reported and only assessed through questionnaires. In our study we included patients with clinical as well as radiological confirmed knee OA by a physician. Also, we collected data on a more detailed level compared to these 2 larger studies. This ensured us to perform a complete survey of the productivity costs and medical costs in OA patients in paid employment seeking medical treatment in a hospital.

Our study sample consists of patients consulting an orthopaedic surgeon for their knee symptoms and comprised secondary care patients only. It must be noted that this is a selected sample within the whole population of patients with knee OA. We stress the fact that our study results represent the medical and productivity costs of a conservatively treated group of working people with mild to moderate knee OA who are treated in secondary care. Mild to moderate knee OA was defined by our criteria of radiological knee OA with K/L grade of 1-3 and a minimum score on the NRS for pain of 2. Including patients with less severity of clinical or radiological knee OA would probably have led to lower productivity and medical costs. Also, including patients from a primary care setting could have led to cost differences, possibly due to differences in disease severity and management strategies compared to secondary care. Furthermore, previous research shows that medical and productivity costs are higher in patients experiencing pain due to arthritis.[15, 45] Since the course of OA is characterized with intermittent periods of pain increase, it is plausible that measuring over a longer time span would have included periods in which patients experienced less pain. Therefore, an overestimation of productivity and medical costs cannot be excluded in our study.

The total productivity costs are attributable to only 47% of the study sample, resulting in a difference between mean total productivity costs (€722) and median total productivity costs (€217). The medical costs were also not evenly distributed between study subjects (Table 3), although some medical costs were reported by all but 1 subject. Skewness of the distribution of productivity costs as well as medical costs is a phenomenon regularly seen in studies investigating costs in musculoskeletal and non-musculoskeletal disorders.[46-50] In these studies, the majority of the productivity costs were also attributable to a limited part of the study sample.

Comparing the patients reporting any productivity loss to the patients not reporting productivity loss shows several differences. Patients indicating

knee-related productivity loss have a higher mean BMI and report higher mean pain scores compared to patients not reporting any productivity loss. Furthermore, lower scores on all KOOS function scales and on the quality of life scale are reported by this group. Finally, the presence of all physical and psychosocial work factors was higher in the group reporting productivity loss compared to the group not reporting productivity loss. Ultimately, these differences resulted in a statistical significant relation between performing physically intensive work and having more pain during activity with productivity loss in the multivariate regression model.

Research on precision and accuracy in measuring absence from work in calculating productivity costs in The Netherlands reported a very good accuracy of a recall period of 2 months, which decreases considerably when applying a recall period of 6 months.[51] In our study, absence from work was the only item assessed with a recall period >2 months (3 months). As this recall period of 3 months is quite close to 2 months, we expect the recall bias to be limited. Nevertheless, there is possibility that the amount of productivity costs due to absence from work was subject to underestimation. It is possible that the amount of productivity costs due to absence from work was underestimated. In this investigation we presented an overview of the medical costs in patients with knee OA. Some out-of-pocket expenses like parking tickets and gasoline made for transfers to the hospital were not accounted for in the calculation of the medical costs. This could be compensated for by the fact that some patients visited a resident in orthopaedic surgery instead of the orthopaedic surgeon. In our costs calculations, we only used the specialist tariff.

The present study shows that the total of knee-related productivity and medical costs for knee OA patients on average is €871 (median €411, IQR €107 - 1200) per patient per month, of which productivity costs account for 83% (€722, median €217, IQR €0 - 1041) and medical costs account for 17% (€149, median €137, IQR €72 - 198). It also shows that reduced productivity while being present at work is responsible for the majority (62%) of the productivity costs. More pain during activity and performing physically intensive work were significantly related to productivity loss. The monthly costs of knee OA are substantial, illustrating the necessity of developing adequate treatment strategies whereby intensive treatment regimens for knee OA may be cost-beneficial.

References

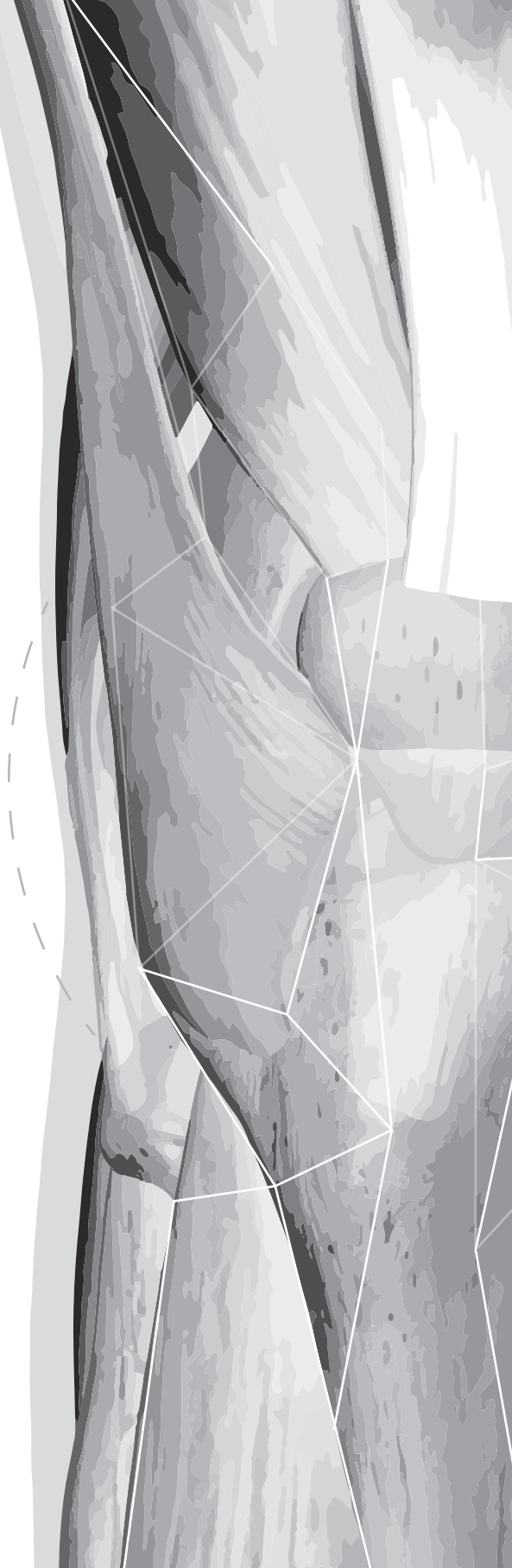
1. Buckwalter JA, Saltzman C, Brown T. The impact of osteoarthritis: implications for research. Clin Orthop Relat Res 2004; (427 Suppl): S6-15.
2. Estimated number of US population with physican-diagnosed osteoarthritis. Atlanta: Centers for disease control and preventions, 1990.
3. Woolf AD, Pfleger B. Burden of major musculoskeletal conditions. Bull World Health Organ 2003; 81(9): 646-56.
4. Dunlop DD, Manheim LM, Yelin EH, Song J, Chang RW. The costs of arthritis. Arthritis Rheum 2003; 49(1): 101-13.
5. March LM, Bachmeier CJ. Economics of osteoarthritis: a global perspective. Baillieres Clin Rheumatol 1997; 11(4): 817-34.
6. Reginster JY. The prevalence and burden of arthritis. Rheumatology (Oxford) 2002; 41 Supp 1: 3-6.
7. Drummond MF, Sculpher JM, Torrance GW, O'Brien BJ, Stoddart GL. Cost analysis. Methods for the Economic Evaluation of Health Care Programmes. 3 ed. Oxford: Oxford University Press; 2005: 55-102.
8. Maetzel A, Li LC, Pencharz J, Tomlinson G, Bombardier C. The economic burden associated with osteoarthritis, rheumatoid arthritis, and hypertension: a comparative study. Annals of the rheumatic diseases 2004; 63(4): 395-401.
9. Rabenda V, Manette C, Lemmens R, Mariani AM, Struvay N, Reginster JY. Direct and indirect costs attributable to osteoarthritis in active subjects. J Rheumatol 2006; 33(6): 1152-8.
10. Aronsson G, Gustafsson K. Sickness presenteeism: prevalence, attendance-pressure factors, and an outline of a model for research. Journal of occupational and environmental medicine / American College of Occupational and Environmental Medicine 2005; 47(9): 958-66.
11. Brouwer WB, Koopmanschap MA, Rutten FF. Productivity losses without absence: measurement validation and empirical evidence. Health Policy 1999; 48(1): 13-27.
12. Schultz AB, Edington DW. Employee health and presenteeism: a systematic review. J Occup Rehabil 2007; 17(3): 547-79.
13. Gabriel SE, Crowson CS, Campion ME, O'Fallon WM. Indirect and nonmedical costs among people with rheumatoid arthritis and osteoarthritis compared with nonarthritic controls. J Rheumatol 1997; 24(1): 43-8.
14. Li X, Gignac MA, Anis AH. The indirect costs of arthritis resulting from unemployment, reduced performance, and occupational changes while at work. Med Care 2006; 44(4): 304-10.
15. Stewart WF, Ricci JA, Chee E, Morganstein D, Lipton R. Lost productive time and cost due to common pain conditions in the US workforce. Jama 2003; 290(18): 2443-54.
16. van den Heuvel SG, Ijmker S, Blatter BM, de Korte EM. Loss of productivity due to neck/shoulder symptoms and hand/arm symptoms: results from the PROMO-study. J Occup Rehabil 2007; 17(3): 370-82.
17. Kramer JS, Yelin EH, Epstein WV. Social and economic impacts of four musculoskeletal conditions. A study using national community-based data. Arthritis Rheum 1983; 26(7): 901-7.
18. Bernaards CM, Proper KI, Hildebrandt VH. Physical activity, cardiorespiratory fitness, and

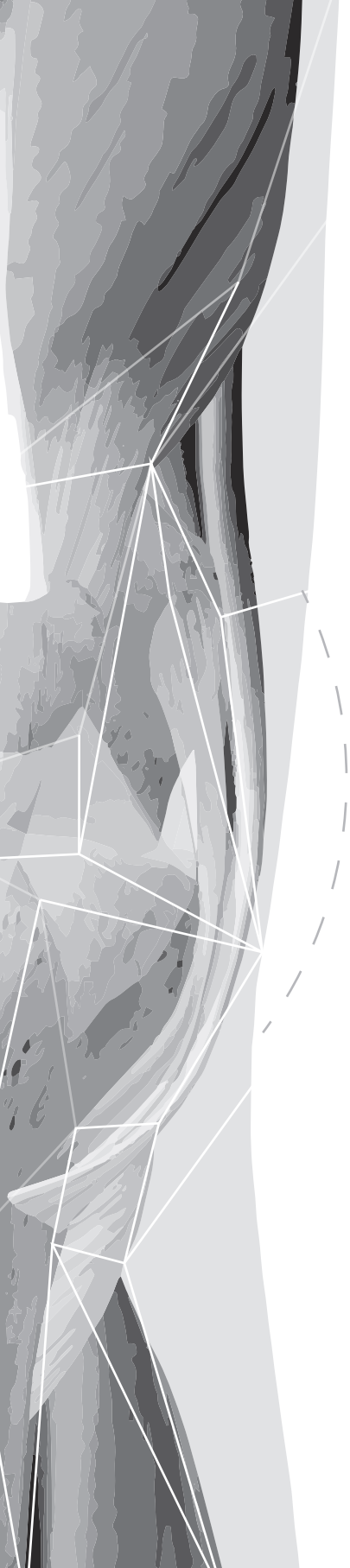
body mass index in relationship to work productivity and sickness absence in computer workers with preexisting neck and upper limb symptoms. Journal of occupational and environmental medicine / American College of Occupational and Environmental Medicine 2007; 49(6): 633-40.

19. Burton WN, Chen CY, Schultz AB, Edington DW. The economic costs associated with body mass index in a workplace. Journal of occupational and environmental medicine / American College of Occupational and Environmental Medicine 1998; 40(9): 786-92.
20. Burton WN, Conti DJ, Chen CY, Schultz AB, Edington DW. The role of health risk factors and disease on worker productivity. Journal of occupational and environmental medicine / American College of Occupational and Environmental Medicine 1999; 41(10): 863-77.
21. Gates DM, Succop P, Brehm BJ, Gillespie GL, Sommers BD. Obesity and presenteeism: the impact of body mass index on workplace productivity. Journal of occupational and environmental medicine / American College of Occupational and Environmental Medicine 2008; 50(1): 39-45.
22. van den Heuvel SG, Geuskens GA, Hooftman WE, Koppes LL, van den Bossche SN. Productivity loss at work; health-related and work-related factors. Journal of occupational rehabilitation 2010; 20(3): 331-9.
23. Alavinia SM, de Boer AG, van Duivenbooden JC, Frings-Dresen MH, Burdorf A. Determinants of work ability and its predictive value for disability. Occupational medicine (Oxford, England) 2009; 59(1): 32-7.
24. Jensen LK. Knee osteoarthritis: influence of work involving heavy lifting, kneeling, climbing stairs or ladders, or kneeling/squatting combined with heavy lifting. Occup Environ Med 2008; 65(2): 72-89.
25. Elders LA, Burdorf A. Interrelations of risk factors and low back pain in scaffolders. Occup Environ Med 2001; 58(9): 597-603.
26. IJzelenberg W, Burdorf A. Risk factors for musculoskeletal symptoms and ensuing health care use and sick leave. Spine (Phila Pa 1976) 2005; 30(13): 1550-6.
27. Lawrence RC, Helmick CG, Arnett FC, et al. Estimates of the prevalence of arthritis and selected musculoskeletal disorders in the United States. Arthritis and rheumatism 1998; 41(5): 778-99.
28. Van Meurs JBJ, Bierma-Zeinstra SMA, Uitterlinden AG. Osteoarthritis. National Compass Public Health. Bilthoven: RIVM (Dutch State Institute of Public Health and Environment); 2009.
29. Brooks PM. Impact of osteoarthritis on individuals and society: how much disability? Social consequences and health economic implications. Curr Opin Rheumatol 2002; 14(5): 573-7.
30. Gabriel SE, Crowson CS, Campion ME, O'Fallon WM. Direct medical costs unique to people with arthritis. The Journal of rheumatology 1997; 24(4): 719-25.
31. Pincus T, Mitchell JM, Burkhauser RV. Substantial work disability and earnings losses in individuals less than age 65 with osteoarthritis: comparisons with rheumatoid arthritis. Journal of clinical epidemiology 1989; 42(5): 449-57.
32. Koopmanschap MA. PRODISQ: a modular questionnaire on productivity and disease for economic evaluation studies. Expert Rev Pharmacoecon Outcomes Res 2005; 5(1): 23-8.

33. Meerding WJ, W I, Koopmanschap MA, Severens JL, Burdorf A. Health problems lead to considerable productivity loss at work among workers with high physical load jobs. Journal of clinical epidemiology 2005; 58(5): 517-23.
34. Hakkaart-Van Rooijen L, Tan SS, Bouwmans CAM. Handleiding voor kostenonderzoek, methoden en standaardprijzen voor ecenomische valuaties in de gezondheidszorg [Manual for costing research, methods and standard prices for economic evaluatons in healthcare]. Amstelveen; 2010.
35. Ferraz MB, Quaresma MR, Aquino LR, Atra E, Tugwell P, Goldsmith CH. Reliability of pain scales in the assessment of literate and illiterate patients with rheumatoid arthritis. J Rheumatol 1990; 17(8): 1022-4.
36. EuroQol--a new facility for the measurement of health-related quality of life. The EuroQol Group. Health policy (Amsterdam, Netherlands) 1990; 16(3): 199-208.
37. Dolan P. Modeling valuations for EuroQol health states. Med Care 1997; 35(11): 1095-108.
38. de Groot IB, Favejee MM, Reijman M, Verhaar JA, Terwee CB. The Dutch version of the Knee Injury and Osteoarthritis Outcome Score: a validation study. Health Qual Life Outcomes 2008; 6: 16.
39. Roos EM, Roos HP, Lohmander LS, Ekdahl C, Beynnon BD. Knee Injury and Osteoarthritis Outcome Score (KOOS)--development of a self-administered outcome measure. J Orthop Sports Phys Ther 1998; 28(2): 88-96.
40. Karasek R, Baker D, Marxer F, Ahlbom A, Theorell T. Job decision latitude, job demands, and cardiovascular disease: a prospective study of Swedish men. Am J Public Health 1981; 71(7): 694-705.
41. van den Berg TI, Robroek SJ, Plat JF, Koopmanschap MA, Burdorf A. The importance of job control for workers with decreased work ability to remain productive at work. Int Arch Occup Environ Health 2010.
42. Statistical package for Social Sciences (SPSS). 2009, IBM, New York, USA.
43. Leardini G, Salaffi F, Caporali R, Canesi B, Rovati L, Montanelli R. Direct and indirect costs of osteoarthritis of the knee. Clin Exp Rheumatol 2004; 22(6): 699-706.
44. Dibonaventura MD, Gupta S, McDonald M, Sadosky A. Evaluating the health and economic impact of osteoarthritis pain in the workforce: results from the National Health and Wellness Survey. BMC Musculoskelet Disord 2011; 12: 83.
45. Ricci JA, Stewart WF, Chee E, Leotta C, Foley K, Hochberg MC. Pain exacerbation as a major source of lost productive time in US workers with arthritis. Arthritis and rheumatism 2005; 53(5): 673-81.
46. Hoeijenbos M, Bekkering T, Lamers L, Hendriks E, van Tulder M, Koopmanschap M. Cost-effectiveness of an active implementation strategy for the Dutch physiotherapy guideline for low back pain. Health policy (Amsterdam, Netherlands) 2005; 75(1): 85-98.
47. Kobelt G, Berg J, Lindgren P, et al. Costs and quality of life in multiple sclerosis in The Netherlands. Eur J Health Econ 2006; 7 Suppl 2: S55-64.
48. Rutten-van Molken MP, van Nooten FE, Lindemann M, Caeser M, Calverley PM. A 1-year prospective cost-effectiveness analysis of roflumilast for the treatment of patients with severe chronic obstructive pulmonary disease. PharmacoEconomics 2007; 25(8): 695-711.

49. van den Hout WB, Goekoop-Ruiterman YP, Allaart CF, et al. Cost-utility analysis of treatment strategies in patients with recent-onset rheumatoid arthritis. Arthritis and rheumatism 2009; 61(3): 291-9.
50. van den Hout WB, Peul WC, Koes BW, et al. Prolonged conservative care versus early surgery in patients with sciatica from lumbar disc herniation: cost utility analysis alongside a randomised controlled trial. BMJ 2008; 336(7657): 1351-4.
51. Severens JL, Mulder J, Laheij RJ, Verbeek AL. Precision and accuracy in measuring absence from work as a basis for calculating productivity costs in The Netherlands. Soc Sci Med 2000; 51(2): 243-9.





Chapter 4

The effectiveness of high molecular weight hyaluronic acid for knee osteoarthritis in everyday clinical care: a randomised clinical trial

J. Hermans
S.M.A. Bierma-Zeinstra
P.K. Bos
D.D. Niesten
J.A.N. Verhaar
M. Reijman

BMC Musculoskelet Disord. 2019 May 7;20(1):196.

Abstract

Background

High molecular weight (HMW) hyaluronic acid (HA) is a treatment option for knee osteoarthritis (OA). The efficacy of HMW-HA in knee OA is investigated extensively, but the effectiveness in patients in the working age is unknown. Nevertheless, the number knee OA patients in the working age is increasing. Surgical treatment options are less eligible in these patients and productivity losses are high. In this study the effectiveness of intra-articular HMW-HA added to regular non-surgical usual care in everyday clinical practice (UC) compared to UC over 52 weeks in symptomatic knee OA patients in the working age was investigated.

Methods

In this open labelled randomized controlled trial, subjects aged between 18 and 65 years with symptomatic knee OA (Kellgren and Lawrence I-III) were enrolled and randomized to UC + 3 weekly injections with HMW-HA (intervention) or UC only (control). The primary outcome was the between group difference in responders to therapy according to OMERACT-OARSI criteria after 52 weeks. These criteria include the domains pain, knee related function and patient's global assessment (PGA). Function was evaluated with the KOOS questionnaire. Pain was assessed with the Numeric Rating Scale. Secondary outcome comprised the between group difference on the individual responder domains, as analysed with a random effects model. Odds Ratios (OR) were calculated by logistic regression analysis. Sensitivity analyses were performed.

Results

In total, 156 subjects were included (intervention group 77, control group 79). Subjects in the intervention group (HMW-HA+UC) were more often responder compared to the controls (UC). Depending on whether pain during rest or pain during activity was included in the responder domains, 57.1% versus 34.2% (p=0.006) and 54.5% versus 34.2% (p=0.015) was responder to

therapy respectively. The results of the secondary outcome analyses show that scores on individual responder domains over all follow-up moments were statistically significant in favour of the intervention group in the domains pain during rest (δ 0.8, 95%CI 0.2; 1.4, p=0.010), knee related function (δ -6.8, 95%CI -11.9; -1.7, p=0.010) and PGA (δ -0.7, 95%CI -0.9; -0.4, p<0.0001).

Conclusions

Intra-articular HMW-HA added to usual care is effective for knee OA in patients in the working age.

Background

Knee osteoarthritis (OA) is a chronic degenerative disease of the knee joint, causing pain, joint stiffness and functional impairment.[1-3] The lifetime risk on symptomatic knee OA is over 40%.[4] Next to health impairment and disability, knee OA is associated with substantial healthcare consumption and costs.[1, 5, 6]

The initial pharmacological treatment for patients with symptomatic knee OA generally includes rapid-acting pain medication like acetaminophen or non-steroidal anti-inflammatory drugs (NSAIDs). NSAIDs have shown to be effective in pain reduction and functional improvement in the symptomatic treatment of knee OA.[7-9]

Treatment with NSAIDs is related to an increased risk of serious gastrointestinal and cardiovascular side effects, indicating limited use of NSAIDs only.[10, 11] The safety profile of NSAIDs contradicts with the chronic character of knee OA in which prolonged symptomatic treatment is often required. Additionally, non-pharmacological interventions such as strength training, exercise and weight management are added to the treatment regime.[12-14]

An alternative treatment for knee OA patients is intra-articular injection therapy with hyaluronic acid (HA) [15]. Intra-articular HA results in similar effects on pain reduction and improvement of function compared to NSAID use, without the aforementioned side effects.[8, 16, 17] The efficacy of intra-articular HA has been investigated extensively in randomized controlled trials (RCTs) and subsequently in various systematic reviews and meta-analyses.[14, 15] Peak effectiveness of a series of intra-articular HA is reached between 1 and 2 months and residual effects exist up to 6 months.[15, 16, 18]

Limiting the results of meta-analyses to high quality trials only, the effect on pain is still clinically relevant in favour of intra-articular HA.[14, 18] There is increasing evidence that within the spectrum of available HA derivatives the efficacy of HA products with a high molecular weight (HMW) is superior to the efficacy of derivatives with a low molecular weight.[19, 20]

The effectiveness of HMW-HA in knee OA patients in the working age has not been evaluated yet. Relevance lies in the fact that the number patients with knee OA in the working age is increasing and surgical treatment options like unicompartmental or total knee arthroplasty (TKA) are less eligible in these patients, especially when they are involved in a physically demanding occupation.[21, 22] The revision rate of knee arthroplasty in these patients is high

and the life span of the prosthesis is limited.[23] Furthermore, the costs from loss of productivity at work due to symptomatic knee OA are high in patients in the working age.[24] In this population, the availability of an effective local therapy in everyday clinical care could thus offer important healthcare benefits next to possible economic benefits.

The aim of this study was to assess the effectiveness of intra-articular HMW-HA added to usual care (UC) compared to UC over a period of 52 weeks in symptomatic knee OA patients in the working age. We hypothesized that adding HMW-HA in patients with knee OA has a clinical relevant effect.

Alongside this effectiveness analysis, a parallel economic evaluation was performed which was published previously.[25] In this article we report that adding HMW-HA to the usual care results in an increase in quality of life. The increase is accompanied with an increase in costs. Ultimately this leads to a cost-effectiveness ratio of €9.100/ quality adjusted life years (QALY). Given the maximum willingness to pay for similar conditions to knee OA we conclude that intra-articular HMW-HA added to usual care for knee OA is probably cost-effective in the treatment of knee OA.

Methods

The current effectiveness evaluation and the previously published cost-effectiveness evaluation are both part of the VIScosupplementation for Knee osteoarthritis (VISK) study. The VISK study is registered at the Dutch trial register (www.trialregister.nl, NTR1651). The study protocol is available from the corresponding author on request.

The VISK study does not include a placebo group. In light of the evidence on the efficacy of HMW-HA in knee OA, we specifically sought to investigate the actual effectiveness of this intervention. Such a study design, in which the intervention is compared to what is considered regular care that is provided in an everyday clinical setting (without a placebo), is required to facilitate the parallel economic evaluation of the VISK study.[26, 27]

Study sample

Inclusion of eligible subjects took place between May 2009 and May 2010 in 2 hospitals (1 academic, 1 non-academic) in The Netherlands. Consecutive knee

OA patients at the outpatient orthopaedic department meeting the inclusion criteria were considered eligible. Patient's age was set between 18 and 65 years, the latter being the pensionable age in The Netherlands at the inclusion period. Inclusion criteria were: pain >3 months, mean pain severity ≥2 on the numeric rating scale (NRS), Kellgren & Lawrence (K&L) grade I to III in medial and/or lateral compartment.

Exclusion criteria were: intra-articular HA injections <1 year, intra-articular steroid injection <3 months, arthroscopy <6 months, tibial osteotomy <1 year, synovectomy, scheduled knee surgery <1 year, varus/valgus deformity >12 degrees, chondrocalcinosis, dermatologic knee disorders, allergy to HMW-HA components, (planned) pregnancy or lactation, inflammatory arthritis, severe hip OA, non-knee related regular analgesic use, daily oral steroid therapy, poor general health, conditions interfering with functional assessments, alcoholism, patients unable to attend follow-up and insufficient command of the Dutch language.

Sample size, randomization and masking

The sample size was calculated to detect a between group difference of 20% in the primary outcome parameter which was defined as response to therapy at 52 weeks according to OMERACT-OARSI criteria.[28] A power of 80% and an alpha of 0.05 resulted in a required sample size of 64 subjects per group (128 subjects in total). Anticipating a 20% dropout over 52 weeks, the final required sample size was set at 154 subjects.

Randomization took place after informed consent was signed. Concealed randomization was performed by computer generated lists with randomly assigned blocs of 2, 4, 6, 8 or 10 subjects. An independent employee not involved in any other part of the study performed the randomization. Stratification took place for radiologic degree of knee AO (K&L grade I/II versus grade III) and per orthopedic surgeons responsible for injections (2 per hospital, 4 in total).

The statistician and investigator responsible for assessment and analyses of the data were blinded for the treatment allocation. Due to the study design included subjects and orthopedic surgeons administering the study intervention could not be blinded.

Interventions

Subjects in the intervention group received 3 weekly intra-articular injections with Hylan G-F 20 (Sanofi S.A, Paris, France) added to usual care or usual care only. Hylan G-F 20 is the HMW-HA derivative with the highest molecular weight available for clinical use (6000 kiloDalton. The injections were performed through the superolateral approach.[29] Usual care was defined accordingly to the guidelines on the treatment of knee OA of the Dutch Orthopedic Association. This guideline recommends several non-surgical treatment modalities including pain medication (eg acetaminophen or NSAIDs), physical therapy and lifestyle recommendations.[12] Treating physicians were encouraged to follow these guidelines, but no treatment restraints were imposed. Other treatments were allowed when deemed appropriate in order to maintain the pragmatic character of the trial.

Questionnaires

The follow-up was 52 weeks and data was collected through questionnaires by mail at baseline, 6, 13, 26, 39 and 52 weeks. Knee related function was assessed by the functioning in daily living scale of the Knee injury and Osteoarthritis Outcome Score (KOOS).[30, 31] A normalized score from 0 (extreme symptoms) to 100 (no symptoms) was calculated for this subscale. Pain during rest and pain during activity was evaluated by the NRS, resulting in a score between 0 (no pain) and 10 (most severe pain).[32] Patient's global assessment (PGA) was assessed on a 5-point Likert scale on which subjects indicate the amount of improvement of their knee complaints compared to baseline (1. fair improvement, 2. moderate improvement, 3. no change, 4. moderate deterioration, 5. fair deterioration). Medication use and patient reported adverse events were monitored at all follow-up moments.

Outcomes

The primary outcome was defined as response to therapy at 52 weeks follow-up according to OMERACT-OARSI criteria. This variable presents the results of changes after treatment in three symptomatic domains (pain, function, and PGA) as a single variable.[28] Response to therapy according to the OMERACT-OARSI criteria is defined as ≥10% absolute improvement and ≥20% overall improvement at final follow-up in at least 2 of the 3 responder

domains (pain, function and/or PGA); or ≥20% absolute improvement and ≥50% overall improvement in either the pain or function domain.
The secondary outcome comprised the between group difference over the whole follow-up period of the 3 individual primary outcome responder domains: pain, function, and PGA.

Statistical analyses
For the primary outcome, the difference in percentage of responders according to OMERACT-OARSI criteria between study groups after 52 weeks follow-up was calculated.[28] In the base case analyses two responder sets were investigated: 1. with pain during rest was included in the responder domains, next to function and PGA; and 2. with pain during activity included. In order to minimize bias in favor of the intervention group, drop-outs and subjects lost to follow up were (regardless of their study results) considered non-responders in the intervention group, and (vice versa) responders in the control group in the final analyses.
Logistic regression analysis with responder as dependent variable and the intervention as independent variable were performed to calculate odds ratios (OR) including 95% confidence intervals (95%CI) after 52 weeks follow-up. The number needed to treat (NNT) to attain 1 responder was calculated (PASW statistics 17.0).
For the secondary outcome, scores on individual responder domains (pain during rest, pain during activity, knee related functioning in daily life, PGA) were analyzed over all follow-up moments by means of a random effects model with random intercept and slope. The baseline values of the variables and the treatment group were included in the model. In this way we obtained for each outcome an estimate for the between group difference in score on the relevant questionnaires (KOOS, NRS, Likert scale) over the whole follow-up period, including associated 95% CI (SAS 9.2, SAS Company).
Sixteen subjects divided over both study groups received knee related surgery during follow-up. This number was not foreseen and we therefore performed 2 additional sensitivity analyses to assess possible beneficial clinical effects on pain and function as a result of the surgery. These analyses were not specified in the VISK study protocol a priori. In these sensitivity analyses, subject receiving knee related were considered non-responder

irrespective of their study results.[33] In the first additional analysis, subjects who received major knee related surgery (e.g. knee prosthesis implantation, high tibial osteotomy) during follow-up were considered non-responders. In the second additional analysis subjects receiving any knee surgery (major knee surgery plus minor knee surgery like arthroscopy or knee manipulation under general anesthesia) were considered non-responders (PASW statistics 17.0). All analyses were performed according to the intention to treat principle. In order to generate unbiased estimates of the difference in effectiveness parameters across both treatment groups, we adjusted for baseline imbalances in and, if necessary, for unbalanced covariates.

Results

Study population

In total, 156 patients were included of which 77 subjects (mean age 53.6, standard deviation (SD) 8.6, range 20.9-64.6) in the intervention group and 79 subjects (mean age 54.8, SD 6.4, range 32.9-64.9) in the control group. The study flowchart is shown in Figure 1. Additional characteristics of included subjects are shown in Table 1. One subject in the intervention group received only 1 out of 3 planned injections with HA due to a painful first injection and 1 subject refused the injections of HMW-HA after allocation to the intervention group. In the control group, 3 subjects were not motivated for further study participation after baseline measurements and randomization, and 1 subject was lost to follow-up. All subjects were retained in the analyses of their randomization groups. We adjusted for the baseline imbalances on pain and functioning in all analyses.

Figure 1 Flowchart

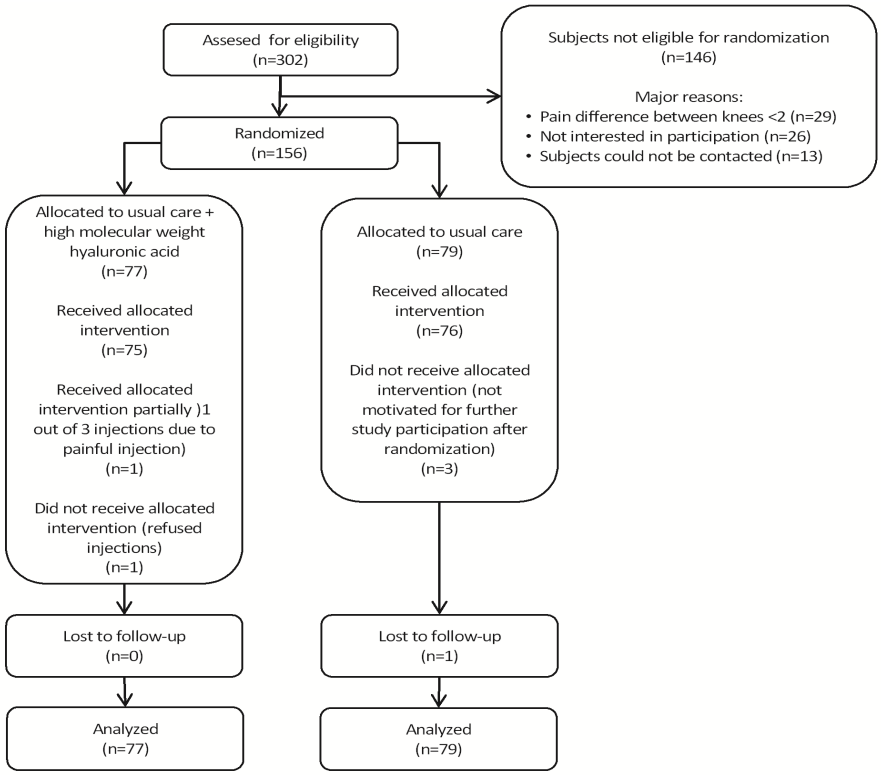


Table 1 Population characteristics (n=156)

	intervention (n=77)	**control (n=79)**
Mean age, years (sd, range)	53.6 (8.6, 20.9-64.6)	54.8 (6,4, 32.9-64.9)
Female, n (%)	37 (48)	40 (51)
BMI, kg/m^2 mean (sd, range)	28.9 (5.2, 20.4-44.8)	29.2 (5.4, 19.4-43.5)
K&L I-II, n (%)	44 (57)	47 (59)
K&L III, n (%)	33 (43)	32 (41)
Duration knee complaints 3-12M, n (%)	34 (44)	43 (54)
Duration knee complaints >12M, n (%)	43 (56)	36 (46)
Pain during rest (0-10)[1], mean (sd, range)	4.8 (2.5, 0-8.0)	4.1 (2.6, 0-10)
Pain during activity (0-10)[1], mean (sd, range)	6.5 (2.4, 0-10)	5.8 (2.4, 0-10)
Quality of life (0-1)[2], mean (sd, range)	0.68 (0.23, -0.05-1)	0.71 (0.24, -0.11-1)
KOOS subscales (0-100), mean (sd, range)		
Pain	46.6 (20.6, 5.6-100)	52.5 (21.1, 11.1-100)
Other symptoms	55.7 (18.3, 17.9-100)	61.3 (21.8, 3.6-100)
Function in daily life	53.2 (20.2, 7.4-100)	60.2 (24.0, 10.3-100)
Function in sports & recreation	24.0 (25.7, 0-95.0)	31.1 (30.9, 0-100)
Knee related quality of life	30.8 (18.5, 0-68.8)	35.9 (18.7, 0-81.3)

[1]on Numeric Rating Scale, [2]on EQ-5D questionnaire, K&L: Kellgren&Lawrence scale

Primary outcome

In Table 2 the results on the primary outcome and the results of the sensitivity analyses are shown. Subjects in the intervention group were statistically significant more often responder to treatment arm they were randomized to compared to the control group. When pain during rest was included in the responder domains, 57.1% of the subjects in the intervention group were responder to therapy, against 34.2% in the control group (p=0.006). With pain during activity included, 54.5% of the subjects was responders to therapy in the intervention group versus 34.2% of the controls (p=0.015).

Table 2 Percentage responders at 52 weeks follow-up (n=156)

	Intervention (n=77)	Control (n=79)	NNT	OR (95% CI)	p
All subjects analysed					
Responder set 1[a]	57.1%	34.2%	4.4	2.6 (1.3; 4.9)	0.006
Responder set 2[b]	54.5%	34.2%	4.9	2.3 (1.2; 4.4)	0.015
1st additional analysis[c]					
Responder set 1[a]	50.6%	31.6%	5.3	2.2 (1.2; 4.3)	0.022
Responder set 2[b]	48.1%	32.9%	6.6	1.9 (1.0; 3.6)	0.072
2nd additional analysis[d]					
Responder set 1[a]	50.6%	31.6%	5.3	2.2 (1.2; 4.3)	0.022
Responder set 2[b]	48.1%	31.6%	6.1	2.0 (1.0; 3.8)	0.049

[a]Pain during rest included in responder domains next to function and PGA , [b]Pain during activity included in responder domains next to function and PGA, [c]Subjects receiving major knee related surgery considered non-responder, [d]Subjects receiving any knee related surgery considered non-responder, OR: Odds ratio, CI: confidence interval, NNT: number needed to treat.

Secondary outcome

Over the whole follow-up period, we found statistically significant better scores in the intervention group in the domains pain during rest, knee related function, and PGA (Figures 2, 3 and 4). These results where statistically significant for pain during rest (**δ** 0.8, 95%CI 0.2; 1.4, p=0.010), knee related function (**δ** − 6.8, 95%CI -11.9; − 1.7, p=0.010) and PGA (**δ** − 0.7, 95%CI -0.9; − 0.4, p<0.0001). The intervention group also scored lower on the pain during activity score, but this difference was not statistically significant (**δ** 0.6, 95%CI 0; 1.2, p=0.060).

Sensitivity analyses

Nine surgical procedures related to the study knee were performed in the intervention group during follow-up, versus 7 in the control group. Despite a slight decrease in the between group differences in responder percentages, the results of both additional analyses are still statistically significant in favour of the intervention group (Table 2).

Figure 2 Results pain during rest and during activity

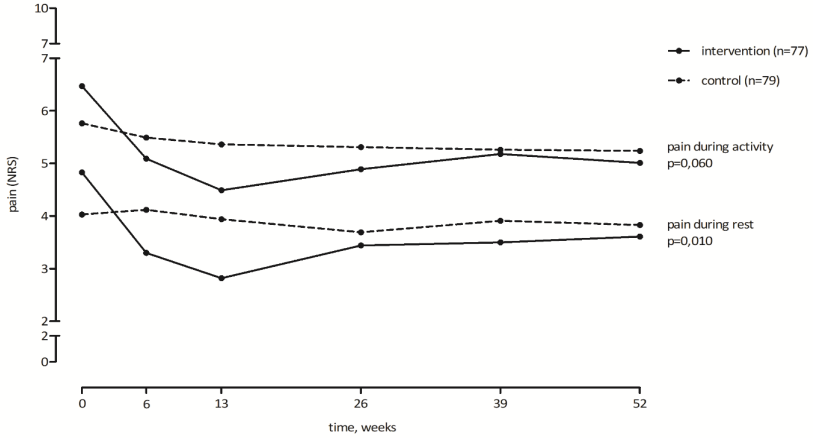
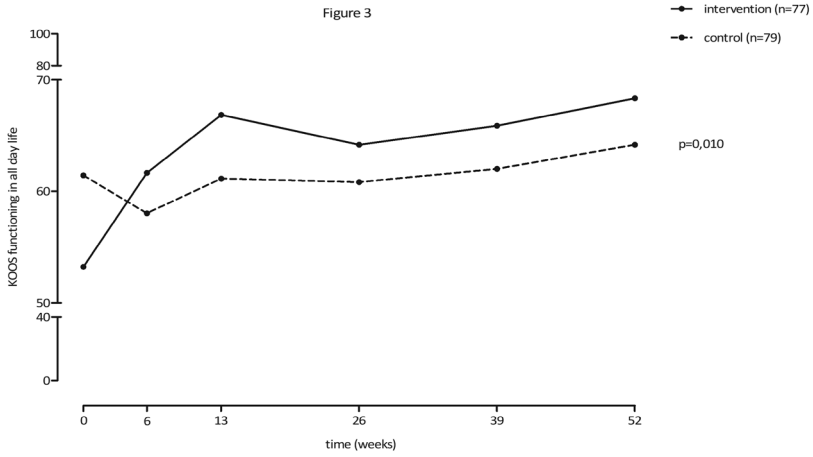


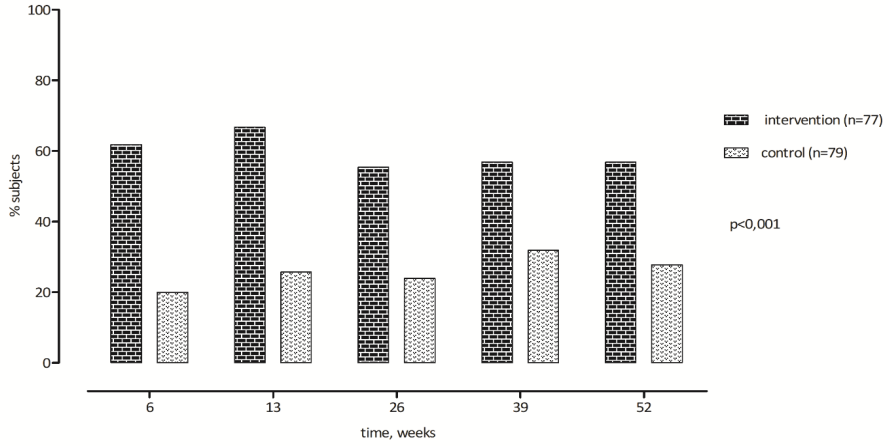
Figure 3 Results knee function



Medication use

At baseline, more subjects used pain medication because of knee complaints in the intervention group with (53%) compared to the control group (42%). This difference decreased over time, resulting in similar usage of pain medication for both groups at final follow-up. The difference in pain medication users was not statistically significant on any of the time points during follow-up.

Figure 4 Results patients' global assessment



Adverse events

In the intervention group, more subjects reported knee treatment related adverse events (AE) at 6 weeks (45% versus 18%), This difference was mainly due to flares or flare like symptoms of the study knee in this period (36% versus 10%, p>0.001, number needed to harm (NNH) 4.0). The difference decreased at 13 weeks, and at 26 weeks the percentage of subjects reporting flares was similar in both groups. None of the between group differences on the following time points after 6 weeks were statistically significant. No septic arthritis of the study knee occurred in any of the subjects during follow-up.
The amount of non-treatment related AEs was similar in both groups during follow-up. An additional file shows the percentage of patients experiencing treatment and non-treatment related adverse events per study group per time point during study follow-up (Additional file 1).

Discussion

This study is the first to investigate the effectiveness of HMW-HA added to usual care in subjects with clinical knee OA in the working age. We showed that adding intra-articular injections with a HMW-HA derivative to usual care treatment in an everyday clinical setting resulted in statistically significant more responders to therapy. It resulted in improvement of pain, function and PGA in these patients. The between group difference on 3 out of 4 of

the individual responder domains (pain during rest, pain during activity, knee related function, PGA) was statistically significant and in favour of the intervention group. Subjects in the intervention group experienced more episodes of transient knee pain and/or swelling during the first 6 weeks.

In our study we specifically choose to include subjects in the working age (mean age 54) with a higher involvement in paid work (75%).[25] By doing so we were able to investigate the effectiveness of HMW-HA in a population in which knee OA levels are rising and in which surgical treatments like arthroplasty are less eligible due to high revision rate and limited life span of the prosthesis.[21-23] We showed that in this population, intra-articular HMW-HA leads to clinically relevant improvement in pain, function and PGA. Since the costs from loss of productivity at work due to knee OA are high in patients in the working age, the treatment with HMW-HA could also result in certain economic benefits.[24] This was investigated in the parallel economic evaluation of the VISK study, in which we report that intra-articular HMW-HA in knee OA is probably cost-effective in this population.[25]

To date, 2 other studies compared HMW-HA added to usual care to usual care only.[34, 35] The same HMW-HA derivative as in our study was investigated. Both studies imposed no limitation on maximum age at time of inclusion, which probably contributed to the relatively low proportion of subjects involved in a paid occupation (19 to 34%).[34, 35] In the first study statistically significant more patients in the intervention group were responder to therapy at final follow-up of 9 months.[35] The percentage of responders was higher in both study groups compared to our study. Also no restriction on the radiologic degree of OA was imposed in this study and the minimal pain score at entry was higher (4 against 2).[35] The inclusion of clinically more severe OA patients may have resulted in a larger percentage of responders in both groups since these patients are more likely to benefit from their treatment for knee OA. The second study reported statistically significant differences on pain, function and stiffness (WOMAC questionnaire), and on PGA in favour of the intervention group.[34] A decrease of 38% in the pain scale in the intervention group was reported, compared to a 13% decrease in the control group. K&L grade IV was excluded but multiple series of intra-articular injections with HMW-HA were allowed, in contrast to 1 series of HMW-HA in our study. The effectiveness results of our study are in line with the results of both

aforementioned studies. Including our study, the results of the 3 studies showed that the primary effectiveness outcome parameters improve at least 20% when HMW-HA is added to the usual care treatment.

Intra-articular injections with HMW-HA are frequently accompanied by transient pain or swelling of the knee. The procedure itself also includes a risk of inducing septic arthritis.[16, 17] At 6 weeks, a statistically significant difference of subjects receiving HMW-HA in our study reported flares or flare-like symptoms of the study knee compared to the control group (35% vs 10%, p=>0.001) in the control group. No septic arthritis occurred. These results on local adverse events (AE) are similar compared to other studies.[34, 35] In our opinion the reduction of knee pain and the improvement of function outweigh the increase of transient flare like symptoms.

The follow up of the VISK study was 52 weeks. Optimal pain decrease after administration of intra-articular HMW-HA is seen at about 3 months though.[16, 18] A shorter follow-up period, closer to the peak effectiveness, encloses the risk of underestimation of possible health effects. Effects on pain function and PGA can occur during a longer period than the peak effectiveness. A longer follow-up also allows for assessment of the course of these effects. To ensure that these matters were accounted for, the current follow-up period of 52 weeks was chosen.

This study has limitations that need to be addressed. The study design of the VISK study did not include a placebo group. Previous research showed that placebo effects in intra-articular HA studies are above average.[36] It is thus likely that part of the beneficial effect in the intervention group is explained by the placebo effect. There were 2 main reasons to opt for this specific study design without a placebo group. First, evidence from high quality studies in meta-analyses showed that HMW-HA is efficacious for knee OA.[18-20] The next logical step was to investigate the actual effectiveness of HMW-HA, thereby accepting the fact that part of the possible beneficial effects is probably explained by the placebo effect. Second, a study design in which the intervention (HMW-HA) is compared to the usual care treatment (and not to placebo) in an everyday clinical setting is required to be able to facilitate a parallel economic evaluation which was also part of the VISK study project.[25-27]

The target population of our study can be described as secondary care patients with symptomatic and mild to moderate knee OA. We therefore

included subjects with K&L grade I-III and a minimal VAS pain score of 2. Patients who were more likely to benefit from surgical therapy like TKA or osteotomy, or from rheumatologic treatment where excluded in this study (e.g. K&L grade IV, substantial varus/valgus deformation, inflammatory arthritis). We aimed to avoid measuring effects strongly related to other factors than the intervention itself (e.g. recent or planned knee surgery, daily steroid use) and to avoid possible harm due to the intervention (e.g. allergies, pregnancy). Applying these criteria may have consequences for the generalizability of the results. It is for example uncertain if the effectiveness results also extend to other patient groups who might benefit from HMW-HA treatment, like knee OA patients not fit for surgery who are in need of surgical therapy.

Conclusion

We conclude that intra-articular injections with HMW-HA added to usual care is effective in patients in the working age. It results in more responders to therapy and improvement in pain, function and PGA.

References

1. Bitton R. The economic burden of osteoarthritis. Am J Manag Care 2009; 15(8 Suppl): S230-5.
2. Lawrence RC, Felson DT, Helmick CG, et al. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part II. Arthritis Rheum 2008; 58(1): 26-35.
3. Vos T, Flaxman AD, Naghavi M, et al. Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet 2012; 380(9859): 2163-96.
4. Murphy L, Schwartz TA, Helmick CG, et al. Lifetime risk of symptomatic knee osteoarthritis. Arthritis Rheum 2008; 59(9): 1207-13.
5. Dunlop DD, Manheim LM, Yelin EH, Song J, Chang RW. The costs of arthritis. Arthritis Rheum 2003; 49(1): 101-13.
6. Gupta S, Hawker GA, Laporte A, Croxford R, Coyte PC. The economic burden of disabling hip and knee osteoarthritis (OA) from the perspective of individuals living with this condition. Rheumatology (Oxford) 2005; 44(12): 1531-7.
7. Bannuru RR, Schmid CH, Kent DM, Vaysbrot EE, Wong JB, McAlindon TE. Comparative effectiveness of pharmacologic interventions for knee osteoarthritis: a systematic review and network meta-analysis. Ann Intern Med 2015; 162(1): 46-54.
8. Bannuru RR, Vaysbrot EE, Sullivan MC, McAlindon TE. Relative efficacy of hyaluronic acid in comparison with NSAIDs for knee osteoarthritis: a systematic review and meta-analysis. Seminars in arthritis and rheumatism 2014; 43(5): 593-9.
9. Bruyere O, Cooper C, Pelletier JP, et al. An algorithm recommendation for the management of knee osteoarthritis in Europe and internationally: a report from a task force of the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO). Seminars in arthritis and rheumatism 2014; 44(3): 253-63.
10. Bhala N, Emberson J, Merhi A, et al. Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: meta-analyses of individual participant data from randomised trials. Lancet 2013; 382(9894): 769-79.
11. Sostres C, Gargallo CJ, Lanas A. Nonsteroidal anti-inflammatory drugs and upper and lower gastrointestinal mucosal damage. Arthritis Res Ther 2013; 15 Suppl 3: S3.
12. NOV (Dutch Orthopaedic Society). Richtlijn diagnostiek en behandeling van heup- en knie artrose (Guidelines in diagnostics and treatment of hip- and knee ostoarthritis). 2007.
13. McAlindon TE, Bannuru RR, Sullivan MC, et al. OARSI guidelines for the non-surgical management of knee osteoarthritis. Osteoarthritis Cartilage 2014; 22(3): 363-88.
14. Cooper C, Rannou F, Richette P, et al. Use of Intraarticular Hyaluronic Acid in the Management of Knee Osteoarthritis in Clinical Practice. Arthritis Care Res (Hoboken) 2017; 69(9): 1287-96.
15. Maheu E, Rannou F, Reginster JY. Efficacy and safety of hyaluronic acid in the management of osteoarthritis: Evidence from real-life setting trials and surveys. Seminars in arthritis and rheumatism 2016; 45(4 Suppl): S28-33.
16. Bellamy N, Campbell J, Robinson V, Gee T, Bourne R, Wells G. Viscosupplementation for the treatment of osteoarthritis of the knee. Cochrane Database Syst Rev 2006; (2): CD005321.
17. Ishijima M, Nakamura T, Shimizu K, et al. Intra-articular hyaluronic acid injection versus oral non-steroidal anti-inflammatory drug for the treatment of knee osteoarthritis: a multi-center, randomized, open-label, non-inferiority trial. Arthritis Res Ther 2014; 16(1): R18.

18. Bannuru RR, Natov NS, Dasi UR, Schmid CH, McAlindon TE. Therapeutic trajectory following intra-articular hyaluronic acid injection in knee osteoarthritis--meta-analysis. Osteoarthritis Cartilage 2011; 19(6): 611-9.
19. Altman RD, Bedi A, Karlsson J, Sancheti P, Schemitsch E. Product Differences in Intra-articular Hyaluronic Acids for Osteoarthritis of the Knee. The American journal of sports medicine 2015.
20. Rutjes AW, Juni P, da Costa BR, Trelle S, Nuesch E, Reichenbach S. Viscosupplementation for osteoarthritis of the knee: a systematic review and meta-analysis. Ann Intern Med 2012; 157(3): 180-91.
21. Ackerman IN, Kemp JL, Crossley KM, Culvenor AG, Hinman RS. Hip and Knee Osteoarthritis Affects Younger People, Too. J Orthop Sports Phys Ther 2017; 47(2): 67-79.
22. Sutton PM, Holloway ES. The young osteoarthritic knee: dilemmas in management. BMC medicine 2013; 11: 14.
23. Julin J, Jamsen E, Puolakka T, Konttinen YT, Moilanen T. Younger age increases the risk of early prosthesis failure following primary total knee replacement for osteoarthritis. A follow-up study of 32,019 total knee replacements in the Finnish Arthroplasty Register. Acta Orthop 2010; 81(4): 413-9.
24. Hermans J, Koopmanschap MA, Bierma-Zeinstra SM, et al. Productivity costs and medical costs among working patients with knee osteoarthritis. Arthritis Care Res (Hoboken) 2012; 64(6): 853-61.
25. Hermans J, Reijman M, Goossens LM, Verburg H, Bierma-Zeinstra SM, Koopmanschap MA. A cost utility analysis of high molecular weight hyaluronic acid for knee osteoarthritis in everyday clinical care in patients in the working age. An economic evaluation of a randomized clinical trial. Arthritis Care Res (Hoboken) 2017.
26. Drummond MF, Sculpher MJ, Claxton K, Stoddart GL, Torrance GW. Methods for the Economic Evaluation of Health Care Programmes. 4 ed. Oxford: Oxford University Press; 2015.
27. Ramsey SD, Willke RJ, Glick H, et al. Cost-effectiveness analysis alongside clinical trials II-An ISPOR Good Research Practices Task Force report. Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research 2015; 18(2): 161-72.
28. Pham T, van der Heijde D, Altman RD, et al. OMERACT-OARSI initiative: Osteoarthritis Research Society International set of responder criteria for osteoarthritis clinical trials revisited. Osteoarthritis Cartilage 2004; 12(5): 389-99.
29. Hermans J, Bierma-Zeinstra SM, Bos PK, Verhaar JA, Reijman M. The most accurate approach for intra-articular needle placement in the knee joint: a systematic review. Seminars in arthritis and rheumatism 2011; 41(2): 106-15.
30. de Groot IB, Favejee MM, Reijman M, Verhaar JA, Terwee CB. The Dutch version of the Knee Injury and Osteoarthritis Outcome Score: a validation study. Health Qual Life Outcomes 2008; 6: 16.
31. Roos EM, Roos HP, Lohmander LS, Ekdahl C, Beynnon BD. Knee Injury and Osteoarthritis Outcome Score (KOOS)--development of a self-administered outcome measure. J Orthop Sports Phys Ther 1998; 28(2): 88-96.

32. Ferraz MB, Quaresma MR, Aquino LR, Atra E, Tugwell P, Goldsmith CH. Reliability of pain scales in the assessment of literate and illiterate patients with rheumatoid arthritis. J Rheumatol 1990; 17(8): 1022-4.

33. Thabane L, Mbuagbaw L, Zhang S, et al. A tutorial on sensitivity analyses in clinical trials: the what, why, when and how. BMC Med Res Methodol 2013; 13: 92.

34. Raynauld JP, Torrance GW, Band PA, et al. A prospective, randomized, pragmatic, health outcomes trial evaluating the incorporation of hylan G-F 20 into the treatment paradigm for patients with knee osteoarthritis (Part 1 of 2): clinical results. Osteoarthritis Cartilage 2002; 10(7): 506-17.

35. Kahan A, Lleu PL, Salin L. Prospective randomized study comparing the medicoeconomic benefits of Hylan GF-20 vs. conventional treatment in knee osteoarthritis. Joint Bone Spine 2003; 70(4): 276-81.

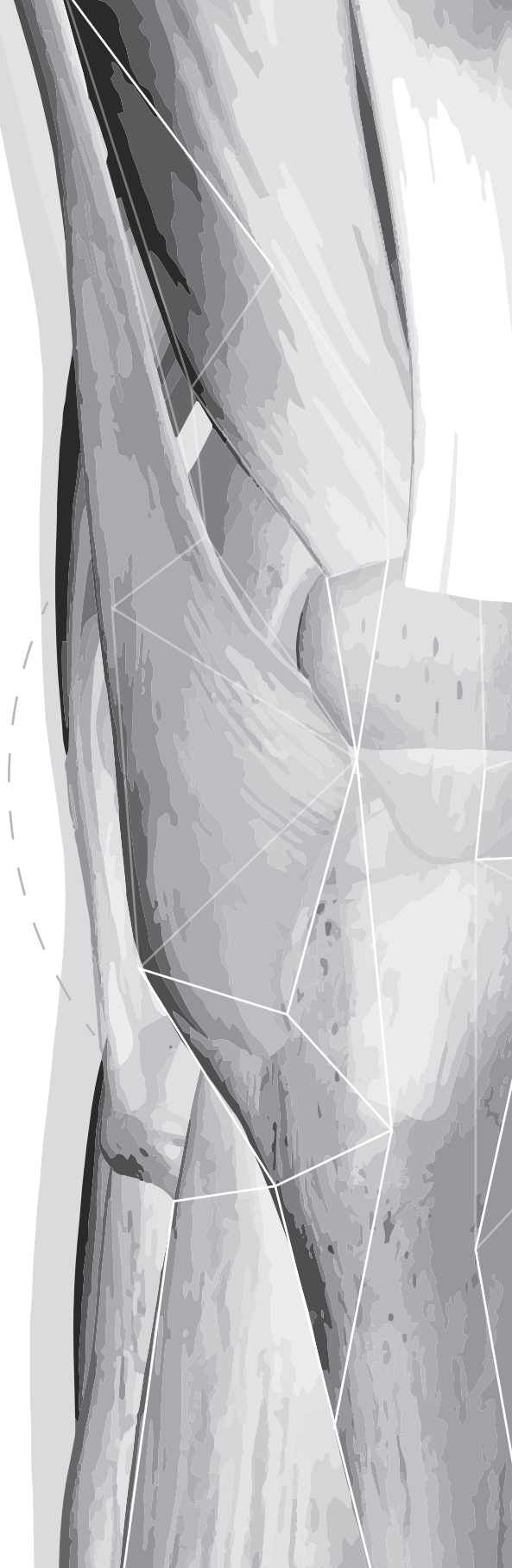
36. Zhang W, Robertson J, Jones AC, Dieppe PA, Doherty M. The placebo effect and its determinants in osteoarthritis: meta-analysis of randomised controlled trials. Annals of the rheumatic diseases 2008; 67(12): 1716-23.

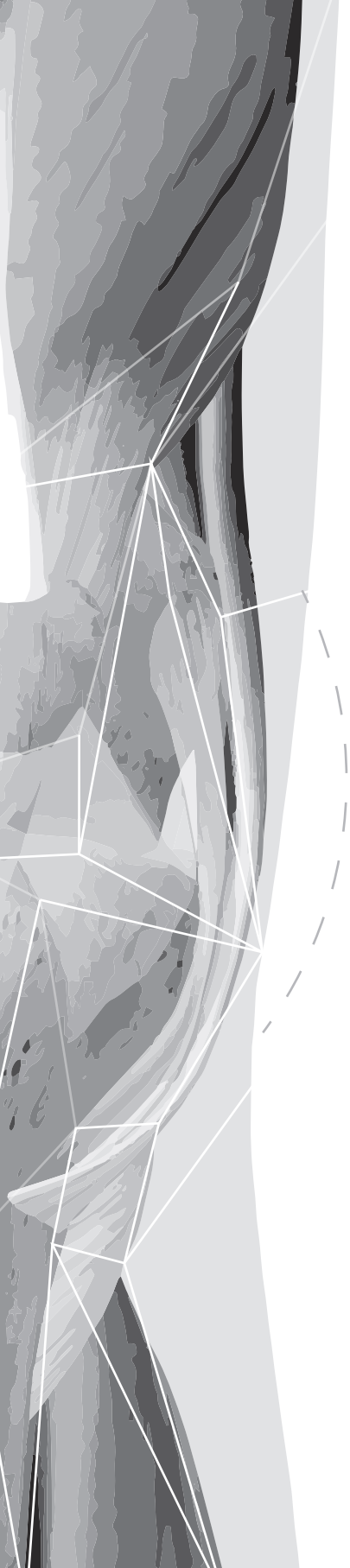
Additional file 1

Patients experiencing knee treatment related adverse events (n=156)										
	6	(n)	13	(n)	26	(n)	39	(n)	52	(n)
	intervention group (n=77)									
Flare knee	36%	(27)	8%	(6)	8%	(6)	8%	(6)	6%	(5)
Gastro-intestinal complaints	7%	(5)	3%	(2)	5%	(4)	5%	(6)	4%	(4)
Other	11%	(8)	8%	(8)	5%	(5)	4%	(3)	4%	(3)
Total	45%	(40)	15%	(16)	16%	(15)	13%	(15)	12%	(12)
	control group (n=79)									
Flare knee	10%	(7)	16%	(11)	8%	(6)	7%	(5)	11%	(8)
Gastro-intestinal complaints	6%	(7)	12%	(11)	3%	(3)	4%	(3)	3%	(3)
Other	10%	(9)	9%	(6)	7%	(5)	1%	(1)	16%	(12)
Total	18%	(23)	27%	(28)	15%	(14)	11%	(9)	20%	(23)

Patients experiencing other adverse events (n=156)			
Intervention group (n=77)	n	Control group (n=79)	n
Removal of staple from tibia	1	Gout	1
Radius fracture	1	Spondylolisthesis	1
Fibroadenoma	1	Removal of seborrheic verruca	1
Abducens nerve paresis	1	Partial parotidectomy due to Whartin tumor	1
Peroneal tendon ganglion	1	Dermatological flebectomy	1
Ribfracture	1	Actinic keratosis	1
Neurofibromatosis	1		

4





Chapter 5

A cost utility analysis of high molecular weight hyaluronic acid for knee osteoarthritis in everyday clinical care in patients in the working age: an economic evaluation of a randomized clinical trial

J. Hermans
M. Reijman
L.M.A. Goossens
H. Verburg
S.M.A. Bierma-Zeinstra
M.A. Koopmanschap

Arthritis Care Res (Hoboken). 2018 Jan;70(1):89-97.

Abstract

Objectives

Knee osteoarthritis (OA) is associated with high medical costs and especially with high productivity costs, in particular in patients in their working years. High molecular weight (HMW) hyaluronic acid (HA) is an alternative treatment for non-steroidal anti-inflammatory drugs, which are known for their serious side-effects. The cost-utility of intraarticular HMW-HA treatment in these patients is unknown, however, and was assessed in this study.

Methods

Secondary care patients ages 18 and 65 years with knee OA were randomized to usual care + HMW-HA (intervention group) or usual care only (control group). A cost-utility analysis over 52 weeks from the societal and health care perspective was performed. Uncertainty for costs, effects and cost-utility ratio was analysed by non-parametric bootstrapping. Baseline imbalance adjustment was done by inversed probability of treatment weighting.

Results

In total, 156 subjects were included (intervention group n=77, control group n=79). The total of productivity and medical costs was €475 higher in the intervention group (€7.754, 95% Confidence Interval (95% CI) 5.426, 10.436 versus €7.270 (€95%CI 5.453, 9.262). The amount of quality-adjusted life years (QALYs) gained during followup was also higher in the intervention group (0.779 versus 0.727**).** This resulted in an incremental cost-effectiveness ratio of €9.100/QALY from a societal perspective and €8.700/QALY from a health care perspective. When the maximum willingness to pay for conditions similar to knee OA is considered, the probability on cost-effectiveness is 64% and 86% respectively.

Conclusion

Intraarticular HMW-HA added to usual care for knee OA is probably cost-effective in the treatment of knee OA.

Introduction

Knee osteoarthritis (OA) is the most common type of OA. It results in high disability, high healthcare use and high associated costs.[1-3] The initial treatment for patients with knee OA consists of pain medication including acetaminophen, nonsteroidal antiinflammatory drugs (NSAIDs), physical therapy and lifestyle recommendations.[4] Oral NSAIDs may cause serious gastrointestinal and cardiovascular side effects, warranting limited use only.[5-7] An alternative treatment option is the use of intra articular injections with hyaluronic acid (HA).[8] Secondary care physicians like orthopaedic surgeons and rheumatologists can opt for such treatment, especially when contra indications to NSAIDs exist, or when a knee prosthesis is not indicated for example in younger patients. Within the spectrum of HA products, the use of HA derivatives with a high molecular weight (HMW) results in more favourable effects on clinical parameters like pain and function.[8-10]

To inform decision making on reimbursements and implementation of treatments, economic evaluations of treatments are useful and sometimes even mandatory. They provide insight in the effects and associated costs of the treatment and supply policy and decision makers in health care with useful information to support their decisions.[11, 12] Until this point two economic evaluations investigated the value of HMW-HA for knee OA in a real world clinical setting.[13, 14] Favourable cost-effectiveness results of HMW-HA were reported, but both studies included subjects of higher age and subjects were often not involved in a paid occupation.[13, 14] A study in subjects in their working years who are more likely to be employed and relatively younger than the general OA population, will extend the knowledge on the cost-effectiveness of HMW-HA. Since productivity costs account for the vast majority of the total costs in this population, the availability of a safe and effective local therapy could also offer important economic benefits alongside health care benefits.[15] We therefore determined the cost-effectiveness of intra articular HMW-HA added to usual care compared to usual care only in secondary care patients with symptomatic knee OA in their working years.

Patients and methods

This cost-utility analysis was performed alongside a randomized controlled trial (RCT) in which intraarticular HMW-HA added to usual care was compared to usual care only in the treatment of symptomatic knee OA subjects. The primary effectiveness outcome parameters included knee pain, function and patient-rated improvement. The effectiveness results were positive and predominantly statistically significant favouring the HMW-HA treated group, and will be presented in a forthcoming publication. The current paper focusses on the cost-utility analysis only.

Both analyses are part of the VIScosupplementation for Knee osteoarthritis (VISK) study, approved by the local Medical Ethics Committee and performed in compliance with the Declaration of Helsinki and Good Clinical Practice guidelines. The followup was 52 weeks and data on productivity costs, medical costs and quality of life was collected through questionnaires at baseline, 6, 13, 26, 39 and 52 weeks.

Study sample

Inclusion of eligible subjects took place between May 2009 and May 2010 in 2 hospitals (1 academic, 1 non-academic) in The Netherlands. Consecutive knee OA patients at the outpatient orthopaedic department meeting the inclusion criteria were eligible. Patient's age was set between 18 and 65 since this was the pensionable age in The Netherlands at time of study. Inclusion criteria were: pain >3 months, pain severity >2 on numeric rating scale (NRS), Kellgren/Lawrence (K/L) grade I to III. Exclusion criteria were intraarticular HA injections <1 year, steroid injection <3 months, arthroscopy <6 months, synovectomy, tibial osteotomy <12 months, scheduled knee surgery <12 months, varus/valgus deformity >12°, chondrocalcinosis, dermatologic knee disorders, allergy on HMW-HA components, (planned) pregnancy or lactation, inflammatory arthritis, severe hip OA, non-knee related regular analgesic use, daily steroid therapy, poor general health, conditions interfering with functional assessments (bed ridden, wheelchair, unable to walk 50 steps unaided), alcoholism, patients unable to attend followup and insufficient command of the Dutch language.

Sample size, randomization and masking

The sample size was calculated to detect a between group difference of 20% on the primary clinical effectiveness parameter (responder to therapy as defined by Outcome Measures in Rheumatology–Osteoarthritis Research Society International criteria) at 52 weeks.[13, 16] A power of 80% and an alpha of 0.05 resulted in a required sample size of 128 subjects in total. Anticipating 20% potential dropout rate over 1 year, the final required sample size was set at 154 subjects. Randomization took place after informed consent was signed. Concealed randomization was performed by computer generated lists with randomly assigned blocs of 2, 4, 6, 8 or 10 subjects. An independent employee performed the randomization. Stratification took place for the radiologic degree of OA and per orthopedic surgeon responsible for injections (2 per hospital, 4 in total). The investigator responsible for assessment and analyses of the data was blinded for the treatment allocation. Due to the study design, subjects and orthopedic surgeons could not be blinded.

Interventions

Subjects received 3 weekly intraarticular injections with Hylan G-F 20 (Sanofi) added to usual care (intervention) or they received usual care only (control). Hylan G-F 20 is the HMW-HA derivative with the highest molecular weight available for clinical use (6000 kilodaltons). The injections were performed by 2 experienced knee pathology orthopedic surgeons per hospital through the superolateral approach.[17]

Usual care was defined accordingly to guidelines of the Dutch Orthopedic Association, which includes pain medication including acetaminophen or NSAIDs when necessary; physical therapy and lifestyle recommendations.[4] No treatment restraints to the treating orthopedic surgeons were imposed in order to maintain the pragmatic character of the trial.

Productivity and medical costs

Productivity costs involved costs due to lost productivity while being present at work, costs due to absence from work and costs for unpaid work like household work by others.[18-23]

The Productivity and Disease Questionnaire (PRODISQ) was used for the measurement of knee-related productivity costs.[24] It includes knee-related

absence from work and knee-related lost productivity while being present at work.[22, 24] Subjects were asked to rate the quality and quantity of work performed on their last work day compared to a regular workday on a 10-point numeric rating scale (where 0=no quantity/quality and 10=normal quantity/quality). Due to the high correlation between both scales only the quantity scale was used for the productivity loss analyses.[25] To assess compensational mechanisms for productivity loss in unpaid activities (e.g., household) due to knee OA, subjects were asked to indicate the amount of work taken over by others. Productivity costs were valued according to the Dutch guideline tariffs.[26]

Medical costs included knee-related physician and paramedical therapist visits, use of aids (e.g., braces, inlay soles), home care use, knee-related surgery and medication use. Medication costs included prescription fees pharmacists receive per prescription.[26] Resources were valuated according to Dutch guideline tariffs.[26] If prices were unavailable (e.g., homeopath tariffs), the tariff was calculated based on mean tariffs charged by different practices. The consumption of diagnostic imaging was retrieved from the hospitals patient information systems and its tariffs were obtained from the Dutch Health Care Authority.[27] Tariffs for knee OA-related surgery were obtained from the participating hospitals. Tariffs for mobility aids were obtained from qualified mobility aids homecare suppliers. Costs from sustainable aids (crutches, etc) were calculated with respect to the depreciation time (2 years).

QoL assessment

QoL was assessed by the 3-level EuroQol questionnaire (EQ-5D).[28, 29] This questionnaire contains 5 dimensions (mobility, self-care, activity, pain and anxiety) and each domain can be scored at 3 levels (no problems, some problems, serious problems). The utility values derived from the EQ-5D can range from -0.329 (worst situation) to 1 (perfect health) in the Dutch situation.[30] The between group difference in the area under the curve of the QoL scores over 52 weeks was calculated to assess the QoL gain per year in quality-adjusted life years (QALYs).

Analyses

Patients were analyzed according to the intention-to-treat principle. The cost-utility analyses were conducted from a societal perspective (medical and productivity costs) and from a health care perspective (medical costs only) using the friction cost method. This method accounts for the ability of organizations to restore productivity within certain timespan in case of productivity loss.[31] Missing values were imputed by means of linear intrapolation. In few cases, only the baseline data were available (n=4, control group). In these cases the baseline observations were carried forward.

Cost utility analyses are sensitive for utility imbalances present at baseline.[32, 33] To generate unbiased estimates of the difference in QALYs and costs across both treatment groups, inverse probability of treatment weighting (IPTW) was used to adjust for baseline differences in QoL and pain.[34, 35] First, a logistic regression model was estimated to analyse the relationship between treatment assignment and baseline characteristics (QoL, pain scores, radiologic degree of OA). The regression results were then used to calculate how likely each patient was to receive the assigned treatment, based on their baseline characteristics. These probabilities were stabilized by multiplying them with 0.5, which is the average probability of being assigned to a certain treatment group.[36] Covariate balance before and after weighting was assessed based on standardized bias. The standardized bias for continuous covariates is calculated by dividing the difference in means of the covariate between the intervention and control group by the SD.[37] A standardized bias of <0.10 was considered acceptable. Ordinary least squares regression was applied on the weighted sample in order to estimate the difference in QALYs across both treatment groups and to calculate adjusted mean QALYs per treatment group. In this model, we adjusted again for the same baseline characteristics. Since adjustment for baseline unbalances was not necessary, this was done only to make the estimates more precise.[38] The costs were analyzed in a generalized linear model with a log link. Given the sensitivity of cost models for the specification of the link function when non-categorical covariates are used, we did not include baseline characteristics in this mode (Stata softwarere, version 14).

The differences in mean adjusted QALYs and costs between treatment groups are expressed in the so-called incremental cost-effectiveness ratio (ICER),

which is interpreted as the additional costs per QALY gained. We present the ICER from the societal perspective and from the health care perspective (Microsoft Excel, version 97-2003).

The uncertainty for costs and health effects was assessed by means of non-parametric bootstrapping, in which 5000 observations were randomly drawn from the available study.[39] For each bootstrap sample, stabilized weights were calculated and the average (incremental) cost and health effects were estimated. The 95% confidence intervals (95% CIs) around the point estimates for costs and effects were determined by taking the 2.5th and 97.5th percentiles of these bootstrap replications. The incremental costs and effects for each bootstrap sample were displayed on a cost-effectiveness plane.[40] An acceptability curve was drawn to indicate the probability that the cost-effectiveness ratio for HMW-HA is acceptable, given various thresholds for the maximum willingness to pay for 1 QALY gained (Microsoft Excel, version 97-2003).[41]

Results

Study population

In total, 156 subjects were included, with 77 patients in the intervention group and 79 subjects in the control group (Table 1). Mean age, percentage of female subjects and BMI were similar in both groups. Despite normal randomization, subjects in the intervention group showed slightly lower scores on QoL (0.68 versus 0.71) and higher scores on pain (pain during rest 4.8 versus 4.1, pain during activity 6.5 versus 5.8). IPTW resulted in balanced pain and QoL scores in both groups (Table 1). The standardized bias for all adjusted scores was <0.10.

One subject in the intervention group received only 1 out of 3 injections with HMW-HA due to a painful first injection and 1 subject refused the intervention after allocation to this group. In the control group, 3 subjects were not motivated for further study participation after baseline measurements and randomization and 1 subject was lost to followup (see Supplementary Figure 1). All subjects were retained in the analyses of their randomization groups.

Table 1 Population characteristics (n=156)*

	Intervention (n=77)	Control (n=79)
Age, yr	53.6 ± 8,6	54,8 ± 6,4
Women, no (%)	37 (48)	40 (51)
BMI, kg/m^2	28.9 ± 5,2	29.2 ± 5,4
Quality of life†	0.68 ± 0,23	0,71 ± 0,24
After IPTW	*0.69 ± 0,24*	*0.69 ± 0,24*
Pain rest‡	4.8 ± 2,5	4.1 ± 2,6
After IPTW	*4.4 ± 2.6*	*4.5 ± 2.6*
Pain activity‡,	6.5 ± 2,4	5.8 ± 2,4
After IPTW	*6.4 ± 2.5*	*6.1 ± 2.5*
Paid work, n (%)	58 (75)	59 (74)
Hours/week	30.7 ± 11,3	32.8 ± 12,1
Job type, no (% in paid work)		
Agriculture	2 (3)	2 (3)
Industry	9 (12)	5 (6)
Commercial services§	29 (38)	32 (41)
Noncommercial services¶	13 (17)	17 (22)
Government	5 (7)	3 (4)

* Values are the mean ± SD unless indicated otherwise. IPTW = inverse probability of treatment weighting. † On the EuroQol questionnaire (where -0.329 = worst, 1 = best). ‡ On a numeric rating scale (where 0 = no pain, 10 = worst pain). § E.g., bank, company, store.¶ E.g., health care, education.

5

Productivity and medical costs

Table 2 shows the unadjusted (before IPTW) mean annual knee-related productivity losses, medical resource use and their associated costs including the largest cost drivers over 52 weeks followup. Supplementary Tables 1 and 2 show the unadjusted subdivisions per time point of these items. Supplementary Table 3 shows the prices and tariffs used.

At final followup, the unadjusted mean productivity costs as well as the unadjusted mean medical costs were both higher in the intervention group. Concerning the productivity costs, decreased productivity while being present at work was the largest cost driver in both groups, accounting for 51% (intervention group) and 60% (control group). The costs associated with knee-related surgery were the main cost drivers within the medical costs. Although only 9 knee surgery procedures in the intervention group and 7 in the control group were performed, these surgical procedures did account for 36% and 32% of the medical costs in both groups, respectively.

After adjustment of baseline imbalances by means of IPTW, the total adjusted costs at final followup were higher in the intervention group (€7.745 (95%CI 5.426, 10.436)) compared to the control group (€7.270 (95%CI 5.453, 9.262)). This resulted in an adjusted annual cost difference of €475 (95%CI -2.686, 3.636) associated with the use of HMW-HA.

This cost difference was mainly due to higher adjusted medical costs in the intervention group (€1.586 (95%CI 1.125, 2.112)) compared to the control group (€1.130 (95%CI 713, 1.667)). The adjusted productivity costs were similar in both groups, with €6.160 (95%CI 4.134, 8.462) compared to €6.141 (95%CI 4.457, 7.977) in the control group.

Table 2 Annual unadjusted costs and largest contributors (n=156)*

	Intervention (n=77)		Control (n=79)	
	No.	**Costs**	**No.**	**Costs**
Productivity losses and costs, hours				
Unpaid work	107 ± 219	€1.340 ± €2.742	132 ± 241	€1.655 ± €3.013
Work absence	62 ± 185	€1.847 ± €5.557	21 ± 73	€638 ± €2.152
Present at work	110 ± 191	€3.315 ± €5.739	117 ± 196	€3.500 ± €5.876
Total productivity costs†		€6.502 ± €9.744		€5.792 ± €7.442
Medical consumption and costs‡				
Physician, visits				
General practioner	1 ± 2	€19 ± €62	0 ± 1	€8 ± €24
Orthopaedic surgeon	2 ± 3	€0 ± €3	1 ± 2	€120 ± €165
Total	3 ± 4	€218 ± €284	2 ± 3	€175 ± €241
Therapist, visits				
Physical therapist	8 ± 13	€285 ± €465	7 ± 11	€248 ± €379
Total	9 ± 14	€303 ± €482	8 ± 12	€267 ± €395
Homecare, hrs				
Total	5 ± 24	€57±€301	4 ± 23	€45 ± €288
medical aids, units§				
Inlay soles	0 ± 0	€33 ±€56	0 ± 0	€32 ± €55
Braces	0 ± 0	€15 ±€30	0 ± 0	€21 ± €34
Total	1 ± 2	€71 ±€85	2 ± 2	€72 ± €75
Medication, (units				
Acetaminophen	271 ± 577	€6 ±€13	214 ± 435	€5 ± €10
NSAID	121 ± 193	€45 ±€71	92 ±175	€34 ± €65
Gastroprotective	49 ± 118	€25 ±€60	47 ±123	€24 ± €62
Total	516± 732	€117 ±€194	464 ±621	€134 ± €220
Study medication				
Total	1 ± 0	€240 ±€0	-	- -
Imaging, units				
X-ray	1 ± 1	€30 ±€50	0 ± 1	€14 ± €25
Total	1 ± 1	€45 ±€72	0 ± 1	€21 ± €46
Surgery, procedures				
Total	0 ± 0	€595 ±€2.045	0 ± 0	€344 ± €1.591
Total medical costs		€1.647 ± €2.349		€1.059 ± €2.012
Total annual costs[a]		€8.148 ± €11.325		€6.851 ± €8.133

* Values are the mean ± SD. NSAID = nonsteroidal antiinflammatory drug. † Totals using friction costs method.
‡ Largest contributors are displayed; categories do not add up to total. § Adjusted for depreciation time.

Quality of life

From randomization to study end, the intervention group accrued more QALYs than the control group. The unadjusted data show an increase of the proportion of subjects who indicate no problems in the domains activities, mobility and anxiety/depression of the EQ-5D in both groups. This increase was highest in the intervention group. In the pain/discomfort domain an increase was seen in both groups and this increase reduced towards the end of the followup period in the intervention group. In the self-care domain the proportion of subjects indicating no problems remained about the same in both group throughout followup.

The average adjusted values were 0.779 QALY (95%CI 0.721, 0.793) in the intervention group and 0.727 (95%CI 0.668, 0.742) in the control group. This resulted in a difference of 0.052 (95%CI 0.014, 0.092).

Table 3 Total adjusted costs, adjusted effects, differences and cost-utility analysis at final followup*

	Intervention (n=77)	**Control (n=79)**	**Difference**
Costs (95%CI) †			
Productivity costs	6.160 (4.134, 8.462)	6.141 (4.457, 7.977)	19 (-2.752, 2.841)
Medical costs	1.586 (1.125, 2.112)	1.130 (713, 1.667)	456 (-252, 1.147)
Total costs	7.745 (5.426, 10.436)	7.270 (5.453, 9.262)	475 (-2.686, 3.636)
QALYs (95% CI)	0,779 (0,721, 0,793)	0,727 (0,668, 0,742)	0,052 (0,014, 0,092)
Perspective			
Societal			€9.061‡
Healthcare			€8.701‡

* QALY = quality-adjusted life year. † Values are in € (95% confidence interval). ‡ Incremental cost-utility ratio (€/QALY).

Cost-utility analysis

From the societal perspective, the gain of 0.052 QALY's in the intervention group along with its associated cost increase of €475 led to in an ICER of €9.061/QALY gained as a result of use of HMW-HA (Table 3). From the health care perspective (medical costs only), the ICER was €8.701 per QALY gained

As shown in the cost-effectiveness planes from the societal and medical perspective (Figures 1 and 2), over 99% of the bootstrap replications resulted in positive estimates of incremental health effects due to the use of HMW-HA. From the societal perspective, the probability that the intervention

is associated with additional costs is 60% as is represented in the upper half of the cost-effectiveness plane. The probability that the intervention is dominant, with HMW-HA resulting in better health effects and cost-savings, is 39% (Figure 1, south-east quadrant). From a health care perspective, the probability that the intervention leads to a cost increase is 90%, and the probability of dominance of the intervention from this perspective is 9% (Figure 2).

Figure 1 Cost-effectiveness plane from the societal perspective

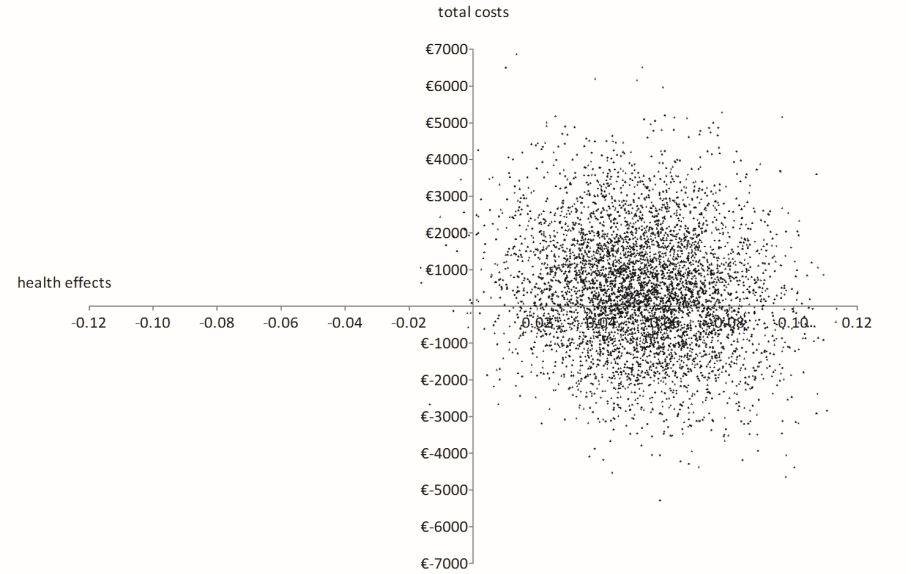
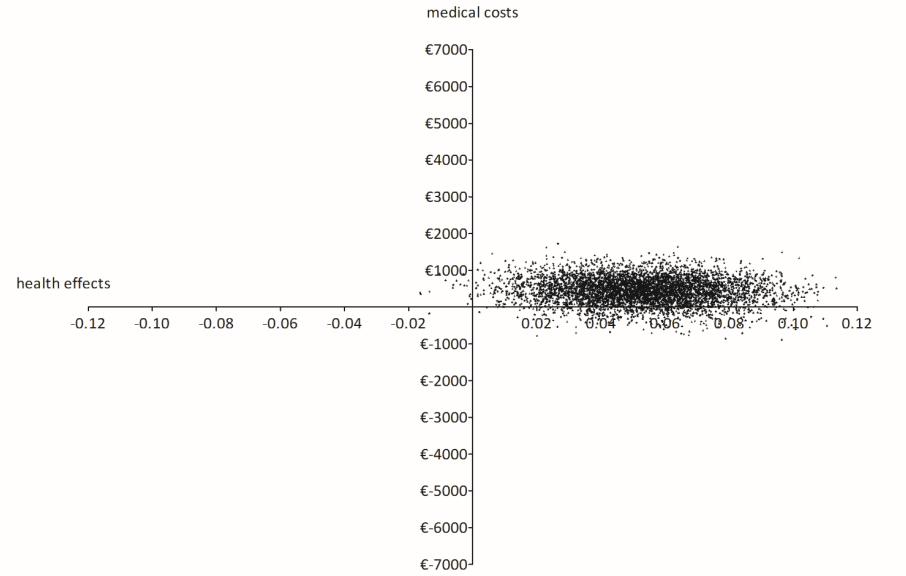
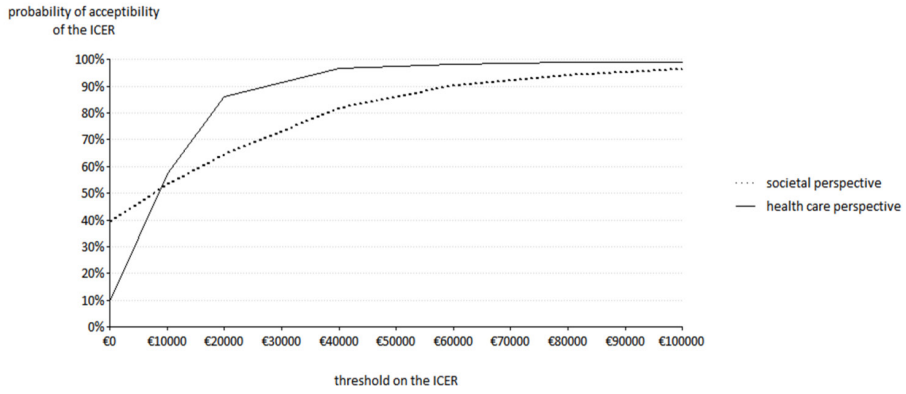


Figure 2 Cost-effectiveness plane from the health care perspective



According to the latest report of the Dutch Health Care Institute, the maximum willingness to pay for conditions with a disease burden similar to knee OA would be up to €20.000/QALY.[42] Considering this upper threshold of €20.000/QALY, the probability that HMW-HA is cost-effective is 64% from the societal perspective and 86% from the medical perspective (Figure 3).

Figure 3 Acceptability curves from the societal and health care perspective. ICER = incremental cost-effectiveness ratio.



Discussion

This health-economic evaluation is the first to our knowledge to study the cost-effectiveness of intraarticular HMW-HA added to usual care in knee OA patients in their working years. We found that adding HMW-HA to usual care for knee OA resulted in a gain in QoL of 0.052 (95%CI 0.014, 0.092) over 52 weeks. The gain in QoL was accompanied with a cost increase, resulting in a cost-utility ratio of approximately €9.100/QALY gained from the societal perspective and approximately €8.700/QALY gained from the health care perspective. The uncertainty analyses indicate a probability of 99% that HMW-HA in knee OA will result in positive health effects. Considering the maximum willingness to pay of €20.000/QALY for conditions similar to knee OA, the probability on cost-effectiveness of HMW-HA is 64% from the societal perspective and 86% from the medical perspective.[42]

To date, only 2 (commercially funded) studies compared HMW-HA added to usual care to usual care.[13, 14] In a Canadian study, a greater increase in QoL and in costs was found after 12 months followup in the intervention group.[14] The ICER equalled about €7.100/QALY (exchange rate at current study inclusion) from the societal perspective, which is less than the ICER we found. The included population was of higher age (63 years) and more subjects were not involved in a paid occupation was also higher (68%). Productivity loss when present at work was not accounted for in that study. Together, these factors may have contributed to the reported lower ICER than we found in our population in their working years.

A French study reported an ICER of -€1,78 favouring the intervention group after 9 months of followup.[13] The cost-effectiveness ratio was based on a clinical effectiveness parameter (Lequesne index). At final followup, total costs were similar in both groups, but HMW-HA was found to be 18% more effective. Uncertainty analyses showed a probability of 91% that the intervention was dominant (positive health effects, lower costs). No age restriction was imposed and productivity loss while being present at work, productivity loss in unpaid work and compensation for household work by others were not accounted for, which may have contributed in the differences in outcome compared to our study.

Furthermore, a cost-effectiveness analysis was performed instead of a cost-utility analysis. The Lequesne index measures knee-related pain/discomfort,

impairments in walking distance and activities in daily life, whereas the EQ-5D (as used in the current cost-utility analysis) also comprehends the domains self-care and anxiety. Thus all health effects due to HMW-HA may not have been accounted for.

In contrast to the aforementioned studies, the study subjects in the current investigation were more often involved in a paid occupation. This fact is represented in the relatively large portion of productivity costs in both groups (approximately 80% of the total costs) and these findings are in line with previous research.[15, 19, 43] It remains uncertain how possible differences in health care systems and reimbursement politics in different countries may have influenced the comparability of study results between both aforementioned studies and our study.

Several factors contributed to the favorable cost-utility ratio we found. Where the unadjusted data show that decreased productivity while being present at work was the largest cost driver in both groups, the higher costs related to being absent from work in the intervention group were mainly responsible for the between-group difference in productivity costs. The unadjusted medical costs in both groups were mainly driven by cost associated with knee-related surgery. These costs were higher in the intervention group. Together with the costs of the HMW-HA product itself, these were the costs mainly responsible for the higher medical costs in the intervention group. The unadjusted data also show that QoL was gained in both groups during followup and that more QoL was gained by the intervention group. Especially the domains activities, mobility and anxiety/depression of the EQ-5D were responsible for this difference in QoL gain. Altogether, despite the increase in costs in the intervention group, the relatively higher gain in QoL led to the current favorable cost-utility ratio.

As is customary in clinical cost-effectiveness analyses, the sample size of our VISK study was based on power calculations on clinical outcome parameter of the clinical effectiveness part of the trial.[14, 44, 45] This calculation is not optimal, since costs generally show larger variances and a more skewed distribution than clinical outcome parameters.[14, 44-48] Under ideal circumstances, sample size calculation would also be based on expected costs and QoL differences. In practice, sample sizes in the order of thousands instead of hundreds are then required. Such numbers are difficult to include in clinical practice and such a study is unlikely to be funded for. Nevertheless, the results of this cost-utility

analysis would have been more robust when derived from a larger sample. Therefore, the current results need to be interpreted with some reservations and in light of the sample size discussion.

After randomization, some variables, including utility, were imbalanced. Since baseline utility values are strongly correlated with QALY's at final followup, this issue was addressed.[32, 33] In order to generate unbiased estimates of the difference in QALY's and costs we adjusted for baseline differences in QoL and pain by means of IPTW.[34, 35] Failure to do so would have generated incorrect results that, at the end, could be misleading in decision making by health care professionals and reimbursement policy makers.[33]

The target population of our study can be described as patients with symptomatic and mild to moderate knee OA. For this reason, patients with K/L grade I-III and a minimal pain score of 2 were included. Patients who were more likely to benefit from different kinds of therapy were excluded in this study (e.g., K/L grade IV, substantial varus/valgus deformation, inflammatory arthritis). We also aimed to avoid measuring effects strongly related to other factors than the intervention itself (e.g., recent or planned knee surgery, daily steroid use). We avoided possible harm due to the intervention (e.g., allergies, pregnancy). The use of these criteria may have consequences for the generalizability of the results. It is for example uncertain if the current cost-utility results also extend to other patient groups who might benefit from HMW-HA treatment, like older patient with more severe knee OA or patients not fit for surgery who are in need of surgical therapy.

This study is the first economic analysis on the value of intraarticular HMW-HA in subjects in their working years. All relevant cost items were assessed. We found that adding HMW-HA to usual care is likely to result in an increase in QoL, which is accompanied by a cost increase. The probability on cost-effectiveness of HMW-HA is 64% from the societal perspective and 86% from the medical perspective, considering the maximum willingness to pay of €20.000/QALY for similar conditions to knee OA.[42]

We conclude that the treatment with intraarticular HMW-HA in knee OA patients in their working years is probably cost-effective for the Dutch health care situation. The current results support patients and physicians in the decision concerning treatment with HMW-HA in knee OA. It provides useful information in the matter of reimbursement of HMW-HA.

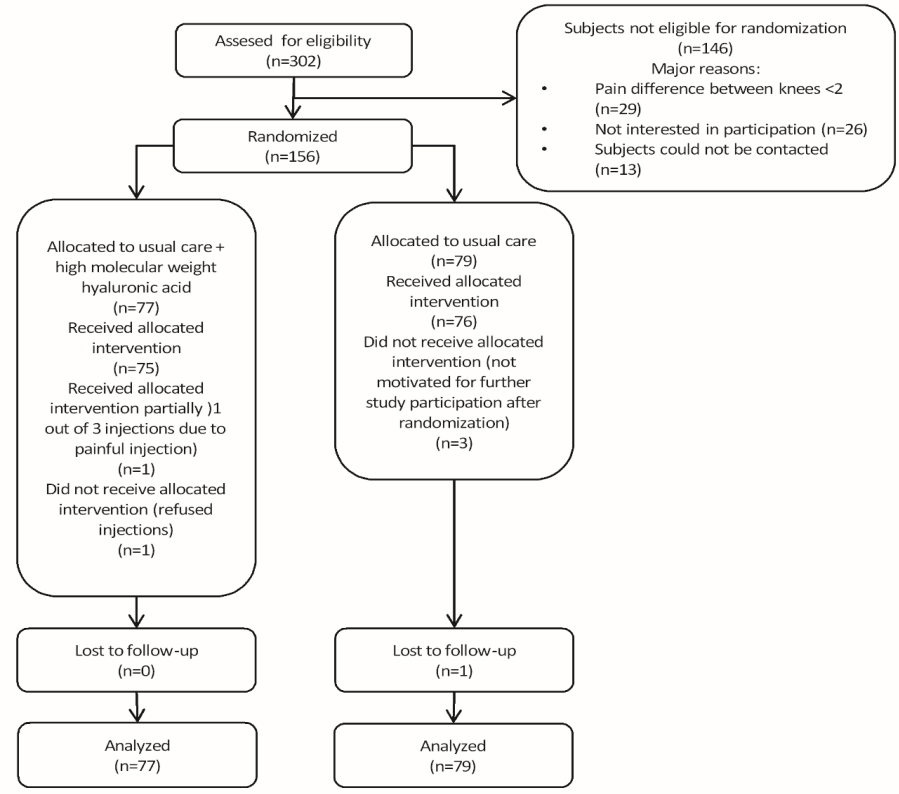
References

1. Bitton R. The economic burden of osteoarthritis. Am J Manag Care 2009; 15(8 Suppl): S230-5.
2. Lawrence RC, Felson DT, Helmick CG, et al. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part II. Arthritis Rheum 2008; 58(1): 26-35.
3. Vos T, Flaxman AD, Naghavi M, et al. Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet 2012; 380(9859): 2163-96.
4. NOV (Dutch Orthopaedic Society). Richtlijn diagnostiek en behandeling van heup- en knie artrose (Guidelines in diagnostics and treatment of hip- and knee ostoarthritis). 2007.
5. Bjordal JM, Ljunggren AE, Klovning A, Slordal L. Non-steroidal anti-inflammatory drugs, including cyclo-oxygenase-2 inhibitors, in osteoarthritic knee pain: meta-analysis of randomised placebo controlled trials. BMJ 2004; 329(7478): 1317.
6. Hawkey CJ, Langman MJ. Non-steroidal anti-inflammatory drugs: overall risks and management. Complementary roles for COX-2 inhibitors and proton pump inhibitors. Gut 2003; 52(4): 600-8.
7. Sostres C, Gargallo CJ, Lanas A. Nonsteroidal anti-inflammatory drugs and upper and lower gastrointestinal mucosal damage. Arthritis Res Ther 2013; 15 Suppl 3: S3.
8. Bannuru RR, Natov NS, Dasi UR, Schmid CH, McAlindon TE. Therapeutic trajectory following intra-articular hyaluronic acid injection in knee osteoarthritis--meta-analysis. Osteoarthritis Cartilage 2011; 19(6): 611-9.
9. Rutjes AW, Juni P, da Costa BR, Trelle S, Nuesch E, Reichenbach S. Viscosupplementation for osteoarthritis of the knee: a systematic review and meta-analysis. Ann Intern Med 2012; 157(3): 180-91.
10. Altman RD, Bedi A, Karlsson J, Sancheti P, Schemitsch E. Product Differences in Intra-articular Hyaluronic Acids for Osteoarthritis of the Knee. The American journal of sports medicine 2015.
11. Tan SS, Rutten FF, van Ineveld BM, Redekop WK, Hakkaart-van Roijen L. Comparing methodologies for the cost estimation of hospital services. The European journal of health economics : HEPAC : health economics in prevention and care 2009; 10(1): 39-45.
12. Marsh JD, Birmingham TB, Giffin JR, et al. Cost-effectiveness analysis of arthroscopic surgery compared with non-operative management for osteoarthritis of the knee. BMJ Open 2016; 6(1): e009949.
13. Kahan A, Lleu PL, Salin L. Prospective randomized study comparing the medicoeconomic benefits of Hylan GF-20 vs. conventional treatment in knee osteoarthritis. Joint Bone Spine 2003; 70(4): 276-81.
14. Torrance GW, Raynauld JP, Walker V, et al. A prospective, randomized, pragmatic, health outcomes trial evaluating the incorporation of hylan G-F 20 into the treatment paradigm for patients with knee osteoarthritis (Part 2 of 2): economic results. Osteoarthritis Cartilage 2002; 10(7): 518-27.
15. Hermans J, Koopmanschap MA, Bierma-Zeinstra SM, et al. Productivity costs and medical costs among working patients with knee osteoarthritis. Arthritis Care Res (Hoboken) 2012; 64(6): 853-61.

16. Pham T, van der Heijde D, Altman RD, et al. OMERACT-OARSI initiative: Osteoarthritis Research Society International set of responder criteria for osteoarthritis clinical trials revisited. Osteoarthritis Cartilage 2004; 12(5): 389-99.
17. Hermans J, Bierma-Zeinstra SM, Bos PK, Verhaar JA, Reijman M. The most accurate approach for intra-articular needle placement in the knee joint: a systematic review. Seminars in arthritis and rheumatism 2011; 41(2): 106-15.
18. Gabriel SE, Crowson CS, Campion ME, O'Fallon WM. Indirect and nonmedical costs among people with rheumatoid arthritis and osteoarthritis compared with nonarthritic controls. J Rheumatol 1997; 24(1): 43-8.
19. Li X, Gignac MA, Anis AH. The indirect costs of arthritis resulting from unemployment, reduced performance, and occupational changes while at work. Med Care 2006; 44(4): 304-10.
20. Aronsson G, Gustafsson K. Sickness presenteeism: prevalence, attendance-pressure factors, and an outline of a model for research. Journal of occupational and environmental medicine / American College of Occupational and Environmental Medicine 2005; 47(9): 958-66.
21. Schultz AB, Edington DW. Employee health and presenteeism: a systematic review. J Occup Rehabil 2007; 17(3): 547-79.
22. Brouwer WB, Koopmanschap MA, Rutten FF. Productivity losses without absence: measurement validation and empirical evidence. Health Policy 1999; 48(1): 13-27.
23. Drummond MF SJ, Torrance GW, O'Brien BJ, Stoddart GL. Cost Analysis. Methods for the Economic Evaluation of Health Care Programmes. 3 ed. Oxford: Oxforf University Press; 2005: 55-102.
24. Koopmanschap MA. PRODISQ: a modular questionnaire on productivity and disease for economic evaluation studies. Expert Rev Pharmacoecon Outcomes Res 2005; 5(1): 23-8.
25. Meerding WJ, W I, Koopmanschap MA, Severens JL, Burdorf A. Health problems lead to considerable productivity loss at work among workers with high physical load jobs. Journal of clinical epidemiology 2005; 58(5): 517-23.
26. Hakkaart-Van Rooijen L, Tan SS, Bouwmans CAM. Handleiding voor kostenonderzoek, methoden en standaardprijzen voor ecenomische valuaties in de gezondheidszorg [Manual for costing research, methods and standard prices for economic evaluatons in healthcare]. Amstelveen; 2010.
27. Dutch Healtcare Authority (Nederlandse Zorg Autoriteit), Tarieflijst Instellingen, gecorrigeerde versie februari 2010. 2010. http://www.nza.nl/regelgeving/tarieven/ (accessed january 13 2013.
28. EuroQol--a new facility for the measurement of health-related quality of life. The EuroQol Group. Health Policy 1990 dec; 16(3): 199-208.
29. Dolan P. Modeling valuations for EuroQol health states. Med Care 1997; 35(11): 1095-108.
30. Lamers LM, McDonnell J, Stalmeier PF, Krabbe PF, Busschbach JJ. The Dutch tariff: results and arguments for an effective design for national EQ-5D valuation studies. Health Econ 2006; 15(10): 1121-32.
31. Koopmanschap MA, Rutten FF, van Ineveld BM, van Roijen L. The friction cost method for measuring indirect costs of disease. J Health Econ 1995; 14(2): 171-89.
32. Richardson G, Manca A. Calculation of quality adjusted life years in the published literature: a review of methodology and transparency. Health Econ 2004; 13(12): 1203-10.

33. Manca A, Hawkins N, Sculpher MJ. Estimating mean QALYs in trial-based cost-effectiveness analysis: the importance of controlling for baseline utility. Health Econ 2005; 14(5): 487-96.
34. Williamson EJ, Morley R, Lucas A, Carpenter JR. Variance estimation for stratified propensity score estimators. Stat Med 2012; 31(15): 1617-32.
35. Austin PC, Stuart EA. Moving towards best practice when using inverse probability of treatment weighting (IPTW) using the propensity score to estimate causal treatment effects in observational studies. Stat Med 2015; 34(28): 3661-79.
36. Cole SR, Hernan MA. Constructing inverse probability weights for marginal structural models. Am J Epidemiol 2008; 168(6): 656-64.
37. Harder VS, Stuart EA, Anthony JC. Propensity score techniques and the assessment of measured covariate balance to test causal associations in psychological research. Psychol Methods 2010; 15(3): 234-49.
38. Senn S. Controversies concerning randomization and additivity in clinical trials. Stat Med 2004; 23(24): 3729-53.
39. Briggs AH, Wonderling DE, Mooney CZ. Pulling cost-effectiveness analysis up by its bootstraps: a non-parametric approach to confidence interval estimation. Health Econ 1997; 6(4): 327-40.
40. Briggs A, Fenn P. Confidence intervals or surfaces? Uncertainty on the cost-effectiveness plane. Health Econ 1998; 7(8): 723-40.
41. van Hout BA, Al MJ, Gordon GS, Rutten FF. Costs, effects and C/E-ratios alongside a clinical trial. Health Econ 1994; 3(5): 309-19.
42. Zwaap J, Knies S, Van der Meijden C, Staal P, Van der Heiden L. Kosteneffectiviteit in praktijk [cost-effectiveness in practice]: Zorginstituut Nederland [Dutch Healthcare Institute], 2015.
43. Stewart WF, Ricci JA, Chee E, Morganstein D, Lipton R. Lost productive time and cost due to common pain conditions in the US workforce. Jama 2003; 290(18): 2443-54.
44. Tan SS, van Linschoten RL, van Middelkoop M, Koes BW, Bierma-Zeinstra SM, Koopmanschap MA. Cost-utility of exercise therapy in adolescents and young adults suffering from the patellofemoral pain syndrome. Scand J Med Sci Sports 2010; 20(4): 568-79.
45. Tan SS, Teirlinck CH, Dekker J, et al. Cost-utility of exercise therapy in patients with hip osteoarthritis in primary care. Osteoarthritis Cartilage 2015.
46. Raynauld JP, Torrance GW, Band PA, et al. A prospective, randomized, pragmatic, health outcomes trial evaluating the incorporation of hylan G-F 20 into the treatment paradigm for patients with knee osteoarthritis (Part 1 of 2): clinical results. Osteoarthritis Cartilage 2002; 10(7): 506-17.
47. van Linschoten R, van Middelkoop M, Berger MY, et al. The PEX study - Exercise therapy for patellofemoral pain syndrome: design of a randomized clinical trial in general practice and sports medicine [ISRCTN83938749]. BMC Musculoskelet Disord 2006; 7: 31.
48. Teirlinck CH, Luijsterburg PA, Dekker J, et al. Effectiveness of exercise therapy added to general practitioner care in patients with hip osteoarthritis: a pragmatic randomized controlled trial. Osteoarthritis Cartilage 2016; 24(1): 82-90.

Supplementary Figure 1 Flowchart



Supplementary table 1 Mean unadjusted productivity loss and medical consumption per time point per subject (n=156)

	Intervention (n=77)									
	6	**sd**	**13**	**sd**	**26**	**sd**	**39**	**sd**	**52**	**sd**
Productivity loss hrs										
Unpaid work	12	33	11	39	33	76	27	67	24	52
Absence from work	14	55	7	30	14	64	13	60	13	67
Present at work	12	26	13	32	28	76	35	94	23	59
Total productivity loss	**38**	**63**	**31**	**70**	**75**	**116**	**75**	**134**	**60**	**99**
Medical consumption[a]										
Physician visits										
General practioner	0	0	0	0	0	1	0	1	0	1
Orthopaedic surgeon	0	1	0	1	0	1	0	1	1	1
Total	0	1	0	1	1	1	1	2	1	2
Therapist visits										
Physical therapist	1	3	1	3	2	4	2	5	2	4
Total	2	3	1	3	2	4	2	5	2	4
Homecare hours										
Total	2	14	0	2	2	8	1	4	1	4
Medical aids units[b]										
Inlay soles	0	0	0	0	0	0	0	0	0	0
Braces	0	0	0	0	0	0	0	0	0	0
Total	1	1	1	1	1	1	1	1	1	1
Medication units										
Acetominophen	30	69	39	91	72	174	64	169	67	180
NSAID	17	34	18	38	42	102	25	57	18	48
Gastroprotective agents	7	15	6	16	10	32	14	36	12	34
Total	60	94	69	117	147	234	124	198	116	222
Study medication[c]										
Total	1	0	-	-	-	-	-	-	-	-
Imaging units										
X-ray	0	0	0	0	0	0	0	1	0	1
Total	0	0	0	0	0	0	0	1	0	1
Surgery procedures										
Total	0	0	0	0	0	0	0	0	0	0
	Control (n=79)									
	6	**sd**	**13**	**sd**	**26**	**sd**	**39**	**sd**	**52**	**sd**
Productivity loss hrs										
Unpaid work	11	23	11	26	36	75	39	79	36	79
Absence from work	7	39	7	41	1	9	3	20	3	20
Present at work	16	42	15	32	27	67	28	65	31	92
Total productivity loss	**34**	**55**	**33**	**57**	**64**	**98**	**71**	**106**	**70**	**117**

Medical consumption[a]										
Physician visits										
General practioner	0	0	0	0	0	0	0	0	0	0
Orthopaedic surgeon	0	1	0	0	0	1	0	1	0	0
Total	0	1	0	1	0	1	0	1	0	1
Therapist visits										
Physical therapist	2	3	1	3	1	4	1	4	1	2
Total	2	3	2	3	2	4	2	4	1	4
Homecare hours										
Total	0	2	0	3	0	4	1	6	1	10
Medical aids units[b]										
Inlay soles	0	0	0	0	0	0	0	0	0	0
Braces	0	0	0	0	0	0	0	0	0	0
Total	1	1	1	1	1	1	1	1	1	1
Medication units										
Acetominophen	32	71	25	71	52	139	59	144	47	145
NSAID	12	32	18	43	10	37	22	64	30	79
Gastroprotective agents	5	15	8	21	10	36	10	35	14	35
Total	74	120	66	96	103	193	107	190	113	205
Study medication[c]										
Total	0	0	-	-	-	-	-	-	-	-
Imaging units										
X-ray	0	0	0	0	0	0	0	0	0	0
Total	0	0	0	0	0	0	0	0	0	0
Surgery procedures										
Total	0	0	0	0	0	0	0	0	0	0

[a]Largest contributors are displayed, categories do not add up to total, [b]Adjusted for depreciation time, [c]Series of 3 intra articular injections of HMW-HA

Supplementary table 2 Mean unadjusted productivity costs and medical costs per timepoint (€, n=156)

	Intervention (n=77)									
	6	**sd**	**13**	**sd**	**26**	**sd**	**39**	**sd**	**52**	**sd**
Productivity costs										
Unpaid	151	416	140	492	418	954	334	835	298	656
Absent	413	1.666	214	921	415	1.945	402	1.805	402	2.028
Present	364	788	384	969	836	2.283	1.045	2.833	685	1.759
Total productivity costs[a]	**928**	**1.719**	**738**	**1.618**	**1.669**	**2.904**	**1.781**	**3.444**	**1.385**	**2.521**
Medical costs[b]										
Physican visits										
General practioner	1	8	2	7	3	16	8	25	5	17
Orth. surgeon	0	0	0	3	0	0	0	0	0	0
Total	33	63	35	72	44	77	45	103	61	135
Therapist visits										
Physical therapist	54	118	41	98	58	149	67	164	66	155
Total	54	118	45	100	59	149	77	177	68	155
Homecare	22	173	3	30	19	105	6	56	6	56
Total	22	173	3	30	19	105	6	56	6	56
Medical aids[c]										
Inlay soles	8	38	8	37	5	19	7	38	5	18
Braces	3	21	3	21	3	21	3	25	2	19
Total	16	31	15	28	15	44	15	28	10	18
Medication										
Acetominophen	1	2	1	2	2	4	1	4	2	4
NSAID	6	13	7	14	16	38	9	21	7	18
Gastroprotective	3	8	3	8	5	16	7	18	6	17
Total	14	23	16	30	32	72	30	55	24	47
Study medication[d]	240	0								
Imaging										
X-ray	6	17	1	7	7	16	10	30	6	22
Total	6	17	1	7	14	39	14	43	9	30
Operations										
Total	0	0	12	107	12	107	235	1.209	336	1.646
Total medical costs	**385**	**424**	**128**	**266**	**195**	**594**	**423**	**1.671**	**515**	**2.087**
Total costs	**1.314**	**1.746**	**866**	**1.606**	**1.865**	**2.932**	**2.204**	**3.729**	**1.900**	**3.249**

	Control (n=79)									
	6	**sd**	**13**	**sd**	**26**	**sd**	**39**	**sd**	**52**	**sd**
Productivity costs										
Unpaid	135	285	137	326	446	933	489	987	448	987
Absent	204	1.153	213	1.207	43	278	100	593	78	600
Present	488	1.259	436	969	796	2.014	848	1.947	932	2.775
Total productivity costs[a]	**827**	**1.502**	**785**	**1.502**	**1.285**	**2.072**	**1.436**	**2.228**	**1.459**	**2.766**
Medical costs[b]										
Physican visits										
General practioner	2	10	2	7	0	3	1	4	2	12
Orth. surgeon	22	61	18	37	37	74	24	58	20	47
Total	40	101	27	51	43	86	33	73	31	74
Therapist visits										
Physical therapist	66	111	51	105	54	137	51	126	26	79
Total	69	113	52	105	60	150	55	126	31	83
Homecare										
Total	3	25	6	35	6	55	12	77	19	122
Medical aids[c]										
Inlay soles	6	15	7	28	5	16	7	15	6	16
Braces	3	12	3	13	5	23	5	19	6	26
Total	12	16	15	25	15	22	15	20	16	22
Medication										
Acetominophen	1	2	1	2	1	3	1	3	1	3
NSAID	5	12	7	16	4	14	8	24	11	29
Gastroprotective	2	8	4	11	5	18	5	18	7	18
Total	22	58	23	36	33	80	22	45	34	58
Study medication[d]										
Imaging										
X-ray	5	14	1	7	3	13	3	11	3	14
Total	5	14	1	7	10	38	3	11	3	14
Operations										
Total	0	0	89	802	12	107	111	894	132	995
Total medical costs	**151**	**328**	**213**	**1.061**	**179**	**538**	**251**	**1.246**	**265**	**1.368**
Total costs	**978**	**1.533**	**998**	**2.090**	**1.464**	**2.110**	**1.687**	**2.476**	**1.724**	**3.252**

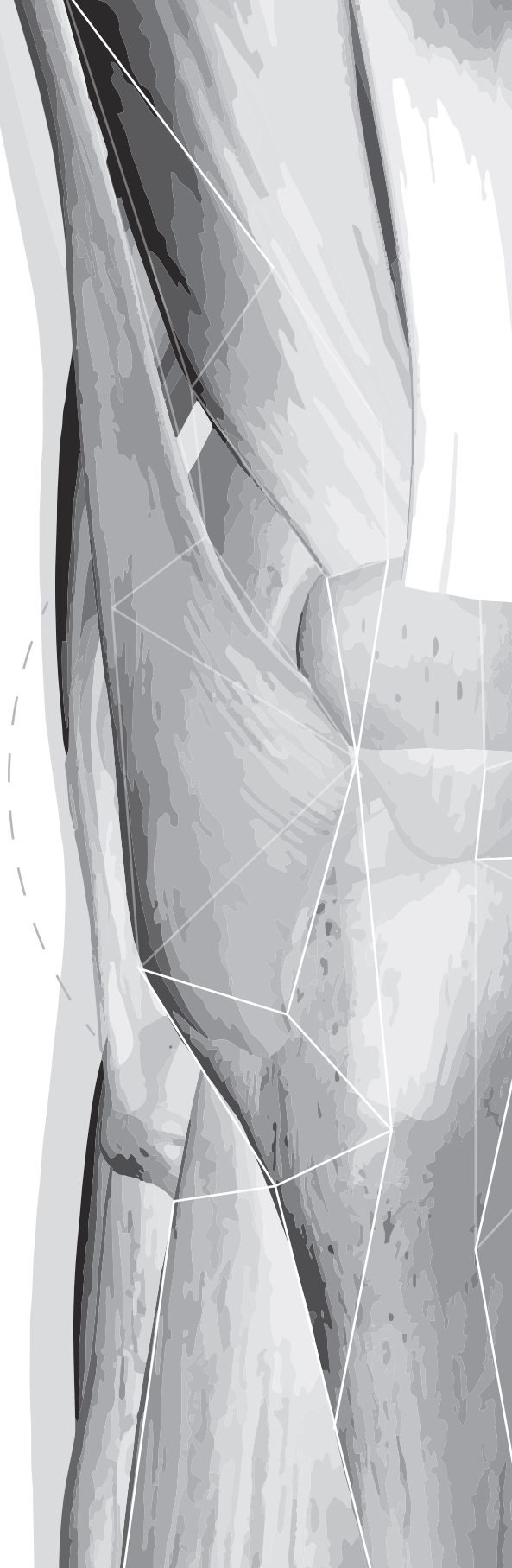
[a] Totals using friction costs method, [b] Largest contributors are displayed, categories do not add up to total, [c] Adjusted for depreciation time, [d] Series of 3 intra articular injections of HMW-HA

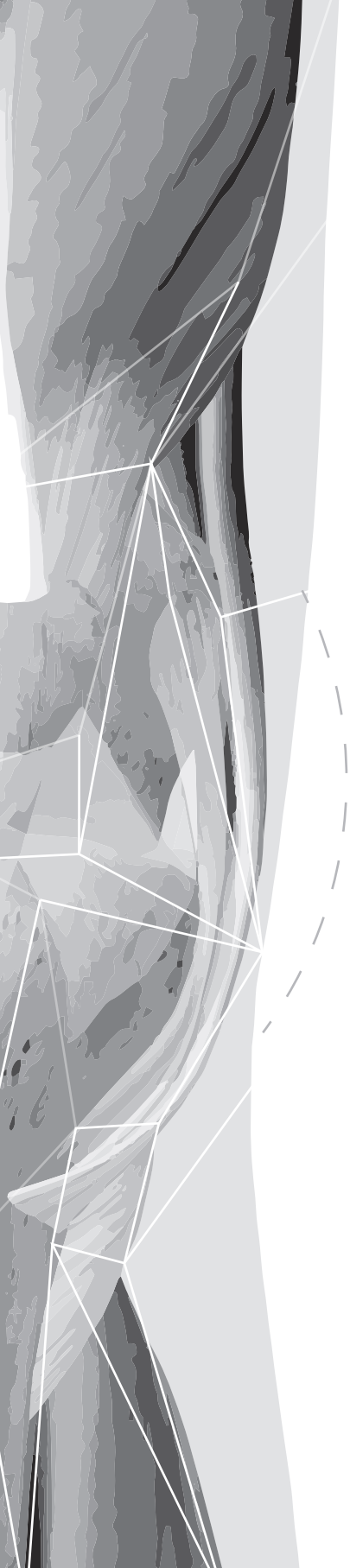
Supplemental Table 3 Unit prices productivity and medical costs (€)

Productivity costs (hour)			
Paid work	30,02		
Unpaid work	12,50		
Medical costs			
Physician / therapist (consult)		*Medication (unit)*	
General physician	28,00	*Pharmacists prescription fee*	*5,99*
Sports physician	30,00	*Pain medication*	
Physical therapist	36,00	Acetominophen	0,02
Practice therapist	35,00	Brufen 400	0,17
Medical specialist		Diclofenac 75	0,11
Non-academic hospital	64,00	Arthrotec 75/0,2	0,37
Medical specialist		Celebrex 200	0,79
Academic hospital	129,00	Tramadol 50	0,13
Company physician	62,50	Oramorph	0,29
Emergency room visit	151,00	Prednisolon	1,20
Homeopath	36,00	*Antacids*	
Podiatrist	36,00	Esomeprazol 20	0,64
Physical therapist fitness	8,00	Esomeprazol 40	0,91
Dietician	27,00	Pantoprozol 20	0,51
Sports masseuse	26,00	Pantoprozol 40	0,20
Aids (unit)		Pantopac	1,76
Cold compress	1,95	Omeprazol 20	0,31
Hot compress	1,95	Omeprazol 40	0,89
Crutches	39,75	Ranitidine 150	0,06
Walking stick	19,95	*Gels*	
Orthopaedic inlay	126,00	Voltaren	0,84
Bandage	22,50	Artrosilium	0,89
Brace	75,00	Tantum	1,42
Tape	1,50	IJslander	0,50
Orthopaedic shoes	125,00	Perozin	0,85
Shower chair	450,00	Spiroflor	0,60
Adjusted bicycle	3.200,00		
Wheelchair	358,00		

Surgery (procedure)		Tigerbalm	1,96
Non-academic hospital		Symphosan	0,65
Total knee prosthesis	6.072,07	Vacol ointment	0,50
Inilateral knee prosthesis	6.072,07	Biofreeze	0,59
High tibial osteotomy	1.430,84	Traumeel	1,08
Arthroscopy	622,45	Perskindol	0,50
Bending knee under anaesthesia	524,14	Reflex	1,20
Hospital day	320,42	*Miscellaneous*	
Academic hospital		Acetominophen+coffein	0,10
Total knee prosthesis	5.787,87	Acetominophen+codein	0,24
High tibial osteotomy	2.325,90	Zaldiar	0,41
Hospital day	575,00	Morfine	0,52
Imaging (unit)		Amytriptilline	0,99
X-ray	43,38	Glucosamine	0,28
Ultrasound	49,09	Chondroitine	0,65
CAT scan	152,96		
MRI scan	187,21		
Scintigraphy	126,71		
SPECT scan	126,71		

Abbreviations: CAT: Computerize Axial Tomography, MRI: Magnetic Resonance Imaging, SPECT: Single Photon Computed Tomography.





Chapter 6

Product characteristic play a role in adverse events after hyaluronic acid therapy in knee osteoarthritis: a systematic review and meta-analysis

J. Hermans
H.M. de Visser
P.K. Bos
E.H. Waarsing
J.A.N Verhaar
S.M.A. Bierma-Zeinstra
M. Reijman

Submitted.

Abstract

Introduction

Intra-articular haluronic acid (HA) in the treatment of knee osteoarthritis (OA) can lead to local adverse events (AE). The relation between HA and non-local AEs is unknown. Product differences and injection frequency might be related to the presence of local AEs. The primary goal was to assess the risk on local AEs, non-local AEs and study withdrawal in HA-treated subjects with knee OA compared to placebo. The secondary goal was to assess the association between local AEs and product characteristics and injection frequency.

Methods

A systematic review and meta-analysis was conducted. Risk of bias of the included studies was assessed. Data was pooled and analyzed per treatment group. The association with product characteristics and injection frequency was assessed.

Results

Thirty-three placebo controlled trials were included. The risk on local AEs was statistically significant higher in HA-treated subjects mainly due to flares or flare like symptoms (risk ratio (RR) 1.26, p=0.001). The higher risk on non-local AEs was not statistically significant. HA-treated subjects have a statistically significant higher risk on study withdrawal due to AEs. Multivariate analyses show an association between the higher risk on local AEs and the use of non-crosslinked derivatives (RR 3.93, P<0.001) and products with a lower molecular weight (RR 1.08, P<0.001).

Conclusion

Intra-articular HA for knee OA results in a higher risk on local AEs and in a higher risk in study withdrawal due to AEs. Non-crosslinked HA-derivatives and derivatives with a lower molecular weight are associated with a higher risk on local AEs.

Introduction

Hyaluronic acid or hyaluronan (HA) is known as a therapeutic agent for non-surgical treatment of symptomatic knee osteoarthritis (OA).[1] Intra-articular administered HA results in the reduction of knee pain and the improvement of function in knee OA patients up to 6 months after injections.[2, 3] In the long term, HA therapy for knee OA is associated with a delay of total knee replacement surgery.[4]

In general HA is considered to be safe in the treatment of knee OA.[1] Mostly, transient local reactions like flares or flare like symptoms like pain or effusion of the knee are reported after intra-articular HA therapy.[5, 6] Occasional local dermatological reactions or episodes of chondrocalcinosis have been reported.[7-11]

Initially, the intra-articularly administered HA-derivative acts as a supplement to the synovial fluid in the knee joint, adding to the viscosity of the degraded synovial fluid and providing both shock absorption and joint lubrication.[12] After injection, several biochemical mechanisms of action are initiated including effects on inflammatory mediators, immune cells and nociception.[13-15] The half-life time of exogenous administered HA is short, in which the knee joint is cleared from exogenous HA in a period of time between 48 hours to about 7 days. Nevertheless, the clinical effects of injections with HA last up to 6 months.[2, 3]

It is unclear whether or not the systemic uptake of the administered HA results in other AEs than the well-known local AEs like flares or flare like symptoms.[15] Serious systemic reactions after treatment with intra-articular HA have been reported in case reports.[16] One meta-analysis reporting an increased risk of serious AEs (SAE) in HA treated subjects compared to placebo.[17] The most frequently reported SAEs in this study were of cardiovascular, musculoskeletal or oncogenic origin.

Available HA products for the treatment of knee OA differ from each other in several ways. HA-derivatives for clinical are produced by either bacterial fermentation or by extraction from avian tissue like rooster combs.[18] The molecular weight of HA varies, generally between 500 to 6000 kiloDalton (kDa).[13, 19] In order to increase molecular weight and prolong the half-life time in the knee joint the molecular structure of HA can be chemically crosslinked to form so-called Hylans.[20]

These product differences can have clinical consequences on efficacy and safety. HA derivatives with a high molecular weight (HMW) appear to be more efficacious then products with a low molecular weight (LMW).[6, 17, 21] Results from several studies suggests an increased risk on local AEs like pain, effusion or flare like symptoms when HA products derived from avian tissue, crosslinked derivatives or derivatives with a high molecular weight are used.[20-23] Next to these product characteristics, the number of administered injections of HA is reported to play a role in the number of local AEs. Higher rates of local adverse reactions are reported after multiple courses of intra-articular injection therapy for knee OA.[24, 25]

More detailed information on the safety profile of intra-articular HA therapy will be helpful in choosing the optimal treatment for the individual knee OA patient. The primary goal of this study was to investigate the difference in local AEs, non-local AEs and study withdrawal in subjects treated with intra-articular HA for knee OA compared to subjects receiving placebo injections. In order to further indicate possible between group differences we only included studies providing a sufficient description of the nature of reported AEs.

The secondary goal was to investigate, in case of a significantly higher risk on local AEs in the HA group, the association with specific product characteristics of the HA-derivatives (origin, cross-linking and molecular weight) and the number of HA injections administered.

Methods

Identification and eligibility of studies

The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines were followed during the search and reporting phase.

A health science librarian of our institution with experience in the conduct of literature searching for systematic reviews assisted in designing and performing the search. To identify eligible studies, the electronic databases Medline, Embase, Web of Science, Scopus, Cochrane, Pubmed Publisher and Google Scolar were systematically searched since their inception until September 2018. The search strategy is shown in Appendix 1.

A study was included when meeting the following criteria: original data was presented; the study subjects were human; the study design was a placebo

controlled randomised controlled trial (RCT); the study presented numeric data on either local AEs, non-local AEs, study withdrawals or subjects excluded from final analyses; the nature of the reported AEs or the reason for study withdrawal/exclusion from final analyses was specified; the article was written in English.

Study selection and data extraction

Titles and abstracts from the search results were independently screened for eligibility by two reviewers (JH, HdV). Full-text reports of potential studies were acquired and examined on eligibility for final inclusion. Disagreements on eligibility or inclusion of the studies were solved by consensus. Authors of eligible articles were contacted to provide additional information when necessary. Relevant data concerning study characteristics, AEs, study withdrawal, exclusion from final analyses and specific product characteristics of the HA-derivatives were extracted from the included articles by two reviewers (JH, HdV). A third reviewer (MR) was available for final judgment in case of disagreement.

Risk of bias assessment

Risk of bias was assessed by the RCT assessment form from the Dutch Cochrane Center (Table 1, items 1-5).[26] Relevanty items on methods, conduct, reporting and follow-up according to Cochrane recommendations were added to the risk of bias assessment (items 6-10).[27] Each risk of bias item was scored as 'yes', 'no' or 'unable to determine'. Risk of bias of the included studies was independently assessed by the reviewers (JH/SBZ, MR/PB). A third reviewer (JV) was available for final judgment if consensus was not achieved.

Table 1 Risk of bias assessment

Item		Judgement
1	Where patients allocated by randomization?	yes/no/unable to determine
2	Was the person including the patients blinded for the allocation sequence?	yes/no/unable to determine
3	Where patients blinded for the treatment?	yes/no/unable to determine
4	Where treating physicians blinded for the treatment?	yes/no/unable to determine
5	Where assessors of effects or outcome blinded for the treatment?	yes/no/unable to determine
6	Was the evaluation of adverse events included in the methods section?	yes/no/unable to determine
7	Were the methods used for monitoring adverse effects adequate? [a]	yes/no/unable to determine
8	Were patients excluded from the adverse events analysis because of an adverse event?	yes/no/unable to determine
9	Were all categories of adverse events adequately reported on, even when no adverse event occurred in a category? [b]	yes/no/unable to determine
10	Were adverse events evaluated at least up to 3 months after final injection?	yes/no/unable to determine

[a]Yes when prospective or routine monitoring was used e.g by patient checklist, questionnaire or diary; No when only spontaneous reporting was recorded or no active inquiries of adverse events was done. [b]yes when a distinction was made in categories of AEs like local and non-local, serious and non-serious or treatment related and non-treatment related AEs and when presence or absence of AEs was reported on in these categories

Primary analyses

The primary statistical analyses were undertaken using RevMan (version 5.3, the Cochrane Collaboration). Data from included studies where pooled per treatment group (HA or placebo). A meta-analysis was performed to calculate relative risks (RR) with their 95% confidence intervals (CI). Included studies were weighted according to the sample size of included studies. The level of statistical heterogeneity for pooled data was determined using I^2 statistics. Random effects were used due to the variation in study methods and populations.

We assessed the between group differences of reported local AEs, non-local AEs and study withdrawals. The between group difference in overall study withdrawals in general was determined. We also examined the difference in withdrawals due to AEs as defined by the authors of the included papers. Additionally, we examined the number of withdrawals due to events that qualify as an AEs according to Good Clinical Practice (GCP) criteria, but were not qualified as such by the authors of the included studies.[28]

Secondary analyses

When the primary analyses resulted in a RR >1 and an accompanying 95% CI not including 1, the association with specific product characteristics (origin, crosslinking, MW) and the number of administered injections was assessed. This was done by means of univariate logistic regression analysis with generalized linear models. Possible correlations were investigated with multivariate analyses. Crosslinking and origin were entered into the models as categorical covariates and MW and number of injection were entered as continuous covariates.

Results

Included studies

The search strategy yielded 5072 unique results (Figure 1). Finally, 33 articles were included in the meta-analysis[29-61] (Table 2). Three studies investigated more than 1 intervention group, in which either different numbers of injections or HA derivatives with differing MWs where compared to placebo.[35, 52, 56] One study investigated 2 control groups, one arthrocentesis group and one group in which arthrocentesis was followed by placebo injection.[35] Both were considered control groups in this meta-analysis.

The median follow-up of included studies was 26 weeks (range 6-173). In total, 3282 subjects were included in the intervention groups and 2959 subjects in the control groups. Per study, the median number of subjects in the intervention group was 54 (range 15-293) and 72 (range 17-295) in the control group.

Figure 1 Flowchart

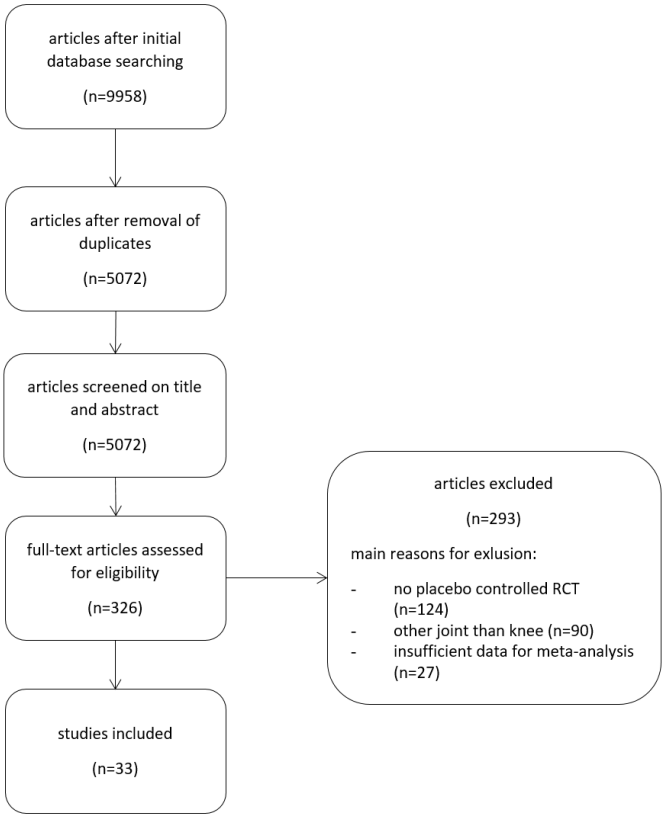


Table 2 Characteristics of included studies (n=33)

Author, year of publication	Injections/ weeks	N (HA)	N (placebo)	Origin	Cross-linking	MW (kDa)
Altman, 1998[30]	5/5	14	168	avian	no	500-730
Altman, 2004[29]	1/1	173	174	bacterial	yes	1000
Altman, 2009[31]	3/3	293	295	bacterial	no	2400-3600
Arden, 2014[32]	1/1	108	110	bacterial	yes	1000
Baltzer, 2009[33]	3/3	135	107	bacterial	no	1400
Brandt, 2001[34]	3/3	114	112	avian	no	1000-2900
Carabba, 1995[35]	1/1	20	20	avian	no	500-730
	3/3	20	20	avian	no	500-730
	5/5	20		avian	no	500-730
Chevalier, 2010[36]	1/1	124	129	avian	yes	6000
Dahlberg, 1994[37]	5/5	28	24	avian	no	600-1200
Day, 2004[38]	5/5	116	124	avian	no	620-1170
Diracoglu, 2009[39]	3/3	42	21	avian	yes	6000
Dixon, 1988[40]	11/23	30	33	NA	NA	NA
Dougados, 1993[41]	4/4	55	55	avian	no	500-730
Formiguera, 1995[42]	1/1	20	20	avian	no	500-730
Gormelli, 2015[43]	3/3	46	45	NA	no	1500
Grecomoro, 1987[44]	3/3	17[a]	17[a]	avian	no	500-750
Henderson, 1994[45]	1/1	45	46	avian	no	750
Huang, 2011[46]	5/5	100	100	avian	no	500-730
Huskisson, 1999[47]	5/5	50	50	avian	no	500-730
Jubb, 2003[48]	3/3	208	200	avian	no	500-730
Kul-Panza, 2010[49]	3/3	25	23	NA	no	1500
Lundsgaard, 2008[50]	4/4	84	84	avian	no	500-730
Navarro, 2011[51]	5/4	153	153	bacterial	no	900
Petterson, 2018[61]	1/1	184	185	bacterial	yes	1000-2900
Petrella, 2006[53]	6/6	53	53	NA	NA	NA
Petrella, 2008[52]	3/3	50	50	NA	NA	500-730
	3/3	50		NA	NA	6000
	3/3	50		NA	NA	580-2000
Pham, 2004[54]	1/1	131	85	bacterial	no	1900
Puhl, 1993[55]	5/5	102	107	avian	NA	600-1200
Scale, 1994[56]	2/2	25	40	avian	yes	6000
	3/4	15		avian	yes	6000
Strand, 2012[57]	1/1	251	128	avian	yes	NA
Tamir, 2001[58]	5/5	25	24	bacterial	NA	3000
Van der Weegen, 2015[59]	3/3	99	97	bacterial	no	2200
Wobig, 1998[60]	1/1	57	60	avian	yes	6000

[a]n=knees. HA=hyaluronic acid, MW-molecular weight, kDa=kilodalton, NA=data not available.

Risk of bias

Blinding of the person including study subjects resulted in an unclear risk of bias in 48% of the studies (table 3, item 2). The risk of bias of the blinding of the treating physician was high in 64% of the studies (item 4). In 35% of the included studies the methods used for monitoring AE were qualified as adequate (item 7). In 48% of the studies it was unclear whether or not subjects were excluded from the final study analyses due to AEs (item 8).

Table 3 Risk of bias of included studies per risk of bias item (n=33)

Author, year of publication	1	2	3	4	5	6	7	8	9	10
Altman, 1998[30]	y	u	y	n	y	y	u	u	u	y
Altman, 2004[29]	y	y	y	n	y	y	y	u	y	y
Altman, 2009[31]	y	y	y	n	y	y	y	n	y	y
Arden, 2014[32]	y	y	y	n	y	y	y	u	y	n
Baltzer, 2009[33]	y	y	y	n	y	y	u	u	u	y
Brandt, 2001[34]	y	u	y	u	y	y	y	n	y	y
Carabba, 1995[35]	y	u	y	n	y	y	u	n	y	y
Chevalier, 2010[36]	y	y	y	n	y	y	u	n	y	y
Dahlberg, 1994[37]	y	y	y	y	y	y	u	n	u	y
Day, 2004[38]	y	u	y	n	y	y	u	n	u	y
Diracoglu, 2009[39]	y	y	y	n	y	n	u	n	u	n
Dixon, 1988[40]	y	u	y	n	y	y	u	u	u	y
Dougados, 1993[41]	y	u	y	n	u	n	u	u	u	y
Formiguera, 1995[42]	y	u	y	u	y	y	u	n	n	n
Gormelli, 2015[43]	y	u	y	u	y	y	u	u	u	n
Grecomoro, 1987[44]	y	y	y	n	y	y	u	y	n	y
Henderson, 1994[45]	y	u	y	n	y	y	u	u	u	y
Huang, 2011[46]	y	u	y	u	y	y	u	n	y	y
Huskisson, 1999[47]	y	u	y	n	y	y	u	u	y	y
Jubb, 2003[48]	y	u	y	n	y	y	y	u	y	y
Kul-Panza, 2010[49]	y	y	y	n	y	n	u	u	u	y
Lundsgaard, 2008[50]	y	y	y	y	y	y	y	n	y	y
Navarro, 2011[51]	y	y	y	n	y	y	y	u	n	y
Petterson, 2018[61]	y	y	y	y	y	y	y	n	y	y
Petrella, 2006[53]	y	n	y	y	y	y	u	n	y	y
Petrella, 2008[52]	y	y	y	y	y	n	u	u	n	n
Pham, 2004[54]	y	u	y	n	y	y	y	n	y	y
Puhl, 1993[55]	y	y	y	y	y	y	y	n	y	y
Scale, 1994[56]	y	u	y	n	y	y	u	u	y	n
Strand, 2012[57]	y	y	y	n	y	y	y	n	y	y
Tamir, 2001[58]	y	u	y	n	y	n	u	u	y	y
Van der Weegen, 2015[59]	y	y	y	y	y	y	y	u	n	y
Wobig, 1998[60]	y	u	y	y	y	y	u	n	u	y

For the description of risk of bias items see Table 1. y=yes, n=no, u=unclear.

Primary outcome

Of the included studies, 28 studies reported in accordance with the inclusion criteria on the presence or absence of local AEs. More subjects experienced local AEs in the HA group (18.5%), compared to placebo (14%), resulting in a RR of 1.26 (95%CI 1.10-1.44, I^2=14%, p=0.001) (Figure 2). Flares or flare like symptoms like pain, effusion or a combination of these symptoms comprised the vast majority of local AEs in both groups. These symptoms were more present in the HA group (16.7%) than in the control group (11.7%). Local dermatological symptoms (1.3% versus 1.3%) and stiffness of the knee joint (0.1% versus 0.2%) were evenly present in both groups.

Fifteen out of 33 included studies reported on the presence or absence of non-local AEs. Non-local AEs were reported more often in the intervention group (35.9% versus 34.0%), but this difference was not statistically significant (RR 1.12 (95%CI 0.79-1.58), I^2=48%, p=0.53).

Thirty-one studies reported on study withdrawal, whether or not due to AEs. Study withdrawal occurred more often in the intervention group (13.6%) compared to placebo (13.4%), but this was not statistically significant (RR 1.05 (95%CI 0.92-1.18), I^2=0%, p=0.48).

The analyses show that statistically significant more study withdrawals occur in the HA group due to AEs as defined by the authors of included studies (2.2% versus 1.5%), as well as due to AEs as defined by GCP guideline criteria that were not qualified as such by the authors of included studies (4.5% versus 3.4%). The RR of study withdrawal due an AE according to the authors was 1.48 (95%CI 1.01-2.18, I^2=0%, p=0.05) and 1.38 (95%CI 1.08-1.77, I^2=6%, p=0.009) when GCP criteria were applied. Evidently more studies contributed to the risk estimate in the latter analysis (Appendices 2, 3).

Figure 2 Risk ratio local adverse events

Secondary outcome

The univariate analyses show that HA-derivatives of avian origin and non-crosslinked derivatives are associated with a higher risk on local AEs. The lower the molecular weight, the higher the risk on local AEs. The administration of more injections is also associated with a higher risk on local AEs (Table 4).

In the multivariate linear regression model, non-crosslinked derivatives and derivatives with a lower MW showed a significant association with the presence of local AEs after intra-articular HA therapy (both p<0.001). The association of local AEs with the administration of HA derivatives of avian origin was borderline significant (p=0.067), where the amount of administered injections was not associated with the presence of local AEs after intra-articular HA therapy for knee OA (p=0.13).

Table 4 Univariate and multivariate logistic regression analyses

	Univariate analyses, RR (95% CI), p-value	**Multivariate analyses, RR (95% CI)**
Origin (avian – bacterial)	1.67 (1.41-1.99), p<0.001	1.29 (0.98-1.68), p=0.067
Crosslinking (non-crosslinked–crosslinked)	1.54 (1.29-1.85), p<0.001	3.93 (2.57-6.01), p<0.001
Molecular weight (lower – higher)	1.08 (1.05-1.10), p<0.001	1.08 (1.04-1.11), p<0.001
Injections (less – more)	1.05 (1.01-1.09), p=0.011	0.93 (0.85-1.02), p=0.131

Discussion

In this systematic review and meta-analysis we investigated the possible differences in local AEs, non-local AEs and study withdrawals between HA-treated subjects with knee OA and their controls in studies providing a sufficient description of the nature of the reported AEs. We investigated the association between local AEs, several product characteristics of the HA derivatives used and the amount of injections administered.

We found that treatment with intra-articular HA results in a statistically significant higher risk on local AEs (RR 1.26) and that flares or flare like symptoms were mainly responsible for this results. The higher risk on non-local AEs was not statistically significant. The analyses show the higher risk on study withdrawal in general in the HA group was also not significant. When focussed on AEs though, the risk on study withdrawal after treatment with intra-articular HA was statistically significant. This was the case when study

withdrawal due to an AE according to the authors of the included studies was analysed (RR 1.48), as well as when GCP criteria for the definition of AEs were applied even when the authors did not indicate the event as AE (RR 1.38).
The multivariate regression analyses showed that the higher risk on local AEs after intra-articular HA therapy is associated with the administration of non-crosslinked derivatives and derivatives with a lower MW.
The results on the risk on local AEs and the use of intra-articular HA for knee OA are in line with previous systematic reviews and meta-analyses.[3, 19] As in our study, flares or flare like symptoms where the largest contributors to the difference in local AEs between HA-treated subjects and the controls.
We found no statistically significant between group differences in sufficiently described non-local AEs. The relation between intra-articular HA and serious systemic reactions or cardiovascular, musculoskeletal or oncogenic events as suggested in previous research was not confirmed in this meta-analysis.[16, 17]
The evidence from an earlier review that indicated a possible relation between cross-linked HA-derivatives (Hylans) with local AEs was also not confirmed by this meta-analysis.[20] Contrarily, the multivariate regression analyses showed that non-crosslinked HA-derivatives are associated with a higher risk on local AEs instead of cross-linked derivatives ($p<0.001$). This difference might be explained by the fact that in the previous review, studies performing a head-to-head comparison of HA to Hylan were included, where in our study we focussed on placebo controlled studies only.[20]
We also did not find a relation between HMW HA-derivatives and the risk on local AEs after intra-articular injection as suggested in an earlier meta-analysis.[21] In this meta-analysis of Altman et al, a statistically significant higher incidence of injections site flare-ups was reported for HMW derivatives compared to moderate molecular weight (MMW) derivatives and LMW derivatives, and also for MMW derivatives compared to LMW derivatives.[21] The results of our study show that a lower MW (instead of a higher MW) is associated with more local AEs ($p<0.001$). The study of Altman et al analysed MW as a categorical variable (LMW ≤1500kDa, moderate molecular weight (MMW) >1500-<3000 kDa, HMW ≥3000 kDa), where MW was entered as a continuous variable in our study. We therefore performed an additional analysis with MW entered as a categorical covariate according to the definitions of this study. The result of this additional analysis showed a statistically significant higher RR on local

AEs in the use of LMW versus HMW derivatives. A possible explanation may be that in the study of Altman et al specifically analysed injection site flare ups. In our study, all reported local AEs were analysed in relation to MW, including flares, but also individual flare like symptoms such as effusion or pain, and other local symptoms like stiffness or dermatological symptoms after injection.

Although the univariate analyses in our study indicated a possible relation between local AEs and the use of HA-derivatives of avian origin, the multivariate analyses did not show a robust association between these parameters. Where other studies reported statistically significant associations between HA derivatives of avian origin and the presence of local AEs, we only found a borderline statistically significant association (p=0.067).[21, 23] In one of these studies, patients were treated with intra-articular AH therapy per their request and no randomization was applied.[23] Another explanation may be that in the systematic review of Altman et al, again the number of flare-ups of the injection site was analysed, where we investigated the relation of any local AE with the use of intra-articular HA.

Two retrospective individual studies reported that multiple series of treatment are related to higher rates of local AEs.[24, 25] We found no statistical significant association between increasing numbers of injections administered and the incidence of local AEs. In all but 1 of the included studies in the current investigation, subjects in the intervention groups received a single series of treatment, mostly consisting of several weekly injections within a maximum time span of 6 weeks. In the aforementioned studies, multiple series of injections with several injections per series were administered over a longer time span.[24, 25] The injected HA derivative in these studies was a cross-linked HMW derivative of avian origin.[21, 22] It is possible that an immune-mediated response to avian components of the administered product over time led to sensitization, thereby enhancing the physical response against the injected substance in the repeated treatment cycles.

Some limitations from this study need to be addressed. The risk of bias analysis results show that the included studies in this systematic review and meta-analysis have methodologically shortcomings on several points. Especially blinding and the chosen methods for monitoring AEs resulted in unclear and high risk of bias in the majority of included studies.

Despite the inclusion criterion that sufficient description of the actual nature of reported AEs was required, there are indications that AEs were not reported adequately in the included studies. For example, only 12 of the 33 included studies reported on the presence (or absence) of local AEs, as well as possible non-local AEs and on study withdrawal (whether or not due to AEs). It is likely that the presence of such methodological shortcomings of included studies may have influenced the presented results.[62, 63] These findings support earlier published recommendations, emphasizing that treatment-emergent AEs and withdrawals due to AEs should always be taken into account in the reporting of harms in RCTs.[64]

In this study we only included RCTs that sufficiently described the nature of the reported AEs and that supplied sufficient numerical data for meta-analyses. The main contributors to the higher risk on local AEs were local reactions like flares or flare like symptoms. Less common symptoms like local skin reactions or episodes of chondrocalcinosis did not evidently contribute to the between group difference. Although these AEs are relatively uncommon, they may have serious clinical consequences and should be taken into account when considering treatment with intra-articular HA.[7-9]

Conclusion

Treatment with intra-articular HA for knee OA results in a higher risk on local AEs like flares or flare like symptoms and in a higher risk in study withdrawal due to AEs. We found no statistically higher risk on non-local AEs. The use of non-crosslinked HA derivatives or a derivative with a lower molecular weight is associated with a higher risk on the local AEs.

References

1. Maheu E, Rannou F, Reginster JY. Efficacy and safety of hyaluronic acid in the management of osteoarthritis: Evidence from real-life setting trials and surveys. Semin Arthritis Rheum 2016; 45(4 Suppl): S28-33.
2. Bannuru RR, Natov NS, Dasi UR, Schmid CH, McAlindon TE. Therapeutic trajectory following intra-articular hyaluronic acid injection in knee osteoarthritis--meta-analysis. Osteoarthritis Cartilage 2011; 19(6): 611-9.
3. Bellamy N, Campbell J, Robinson V, Gee T, Bourne R, Wells G. Viscosupplementation for the treatment of osteoarthritis of the knee. Cochrane Database Syst Rev 2006; (2): CD005321.
4. Altman R, Lim S, Steen RG, Dasa V. Hyaluronic Acid Injections Are Associated with Delay of Total Knee Replacement Surgery in Patients with Knee Osteoarthritis: Evidence from a Large U.S. Health Claims Database. PLoS One 2015; 10(12): e0145776.
5. Wang CT, Lin J, Chang CJ, Lin YT, Hou SM. Therapeutic effects of hyaluronic acid on osteoarthritis of the knee. A meta-analysis of randomized controlled trials. J Bone Joint Surg Am 2004; 86-A(3): 538-45.
6. Johal H, Devji T, Schemitsch EH, Bhandari M. Viscosupplementation in Knee Osteoarthritis: Evidence Revisited. JBJS Rev 2016; 4(4): e11-e111.
7. Ali Y, Weinstein M, Jokl P. Acute pseudogout following intra-articular injection of high molecular weight hyaluronic acid. Am J Med 1999; 107(6): 641-2.
8. Disla E, Infante R, Fahmy A, Karten I, Cuppari GG. Recurrent acute calcium pyrophosphate dihydrate arthritis following intraarticular hyaluronate injection. Arthritis Rheum 1999; 42(6): 1302-3.
9. Maillefert JF, Hirschhorn P, Pascaud F, Piroth C, Tavernier C. Acute attack of chondrocalcinosis after an intraarticular injection of hyaluronan. Rev Rhum Engl Ed 1997; 64(10): 593-4.
10. Kim WB, Alhusayen RO. Skin Necrosis from Intra-articular Hyaluronic Acid Injection. Journal of cutaneous medicine and surgery 2015; 19(2): 182-4.
11. Chung HC, Bak H, Lee JW, Ahn SK. A Rare Cutaneous Adverse Reaction after Intra-Articular Injection of Hyaluronic Acid. Annals of dermatology 2016; 28(4): 529-31.
12. Bagga H, Burkhardt D, Sambrook P, March L. Longterm effects of intraarticular hyaluronan on synovial fluid in osteoarthritis of the knee. J Rheumatol 2006; 33(5): 946-50.
13. Altman RD, Manjoo A, Fierlinger A, Niazi F, Nicholls M. The mechanism of action for hyaluronic acid treatment in the osteoarthritic knee: a systematic review. BMC musculoskeletal disorders 2015; 16: 321.
14. Moreland LW. Intra-articular hyaluronan (hyaluronic acid) and hylans for the treatment of osteoarthritis: mechanisms of action. Arthritis Res Ther 2003; 5(2): 54-67.
15. Webb D, Naidoo P. Viscosupplementation for knee osteoarthritis: a focus on Hylan G-F 20. Orthopedic research and reviews 2018; 10: 73-81.
16. Calvo M, Tornero P, De Barrio M, et al. Erytema multiform due to hyaluronic acid (go-on). Journal of investigational allergology & clinical immunology 2007; 17(2): 127-8.

17. Rutjes AW, Juni P, da Costa BR, Trelle S, Nuesch E, Reichenbach S. Viscosupplementation for osteoarthritis of the knee: a systematic review and meta-analysis. Ann Intern Med 2012; 157(3): 180-91.
18. Boeriu CG, Springer J, Kooy FKL, Van den Broek LAM, Eggink G. Production Methods for Hyaluronan. International Journal of Carbohydrate Chemistry 2013: 14.
19. Bannuru RR, Osani M, Vaysbrot EE, McAlindon TE. Comparative safety profile of hyaluronic acid products for knee osteoarthritis: a systematic review and network meta-analysis. Osteoarthritis Cartilage 2016; 24(12): 2022-41.
20. Reichenbach S, Blank S, Rutjes AW, et al. Hylan versus hyaluronic acid for osteoarthritis of the knee: a systematic review and meta-analysis. Arthritis Rheum 2007; 57(8): 1410-8.
21. Altman RD, Bedi A, Karlsson J, Sancheti P, Schemitsch E. Product Differences in Intra-articular Hyaluronic Acids for Osteoarthritis of the Knee. Am J Sports Med 2015.
22. Chen AL, Desai P, Adler EM, Di Cesare PE. Granulomatous inflammation after Hylan G-F 20 viscosupplementation of the knee : a report of six cases. J Bone Joint Surg Am 2002; 84-A(7): 1142-7.
23. Petrella AJ, Cogliano A, Decaria J. Comparison af avian and non-avian hyaluronic acid in osteoarthritis of the knee. Orthopedic Res Rev 2010; january(2): 5-9.
24. Leopold SS, Warme WJ, Pettis PD, Shott S. Increased frequency of acute local reaction to intra-articular hylan GF-20 (synvisc) in patients receiving more than one course of treatment. J Bone Joint Surg Am 2002; 84-A(9): 1619-23.
25. Webber TA, Webber AE, Matzkin E. Rate of adverse reactions to more than 1 series of viscosupplementation. Orthopedics 2012; 35(4): e514-9.
26. Assendelft WJ, Scholten RJ, van Eijk JT, Bouter LM. [The practice of systematic reviews. III. Evaluation of methodological quality of research studies]. Ned Tijdschr Geneeskd 1999; 143(14): 714-9.
27. Higgins JPT, Altman DG, Sterne JAC. Chapter 8: Assessing risk of bias in included studies. In: Higgins JPT, Green S, eds. Cochrane Handbook for Systematic Reviews of Interventions Version 510 [updated March 2011]: The Cochrane Collaboration; 2011.
28. ICH. Integrated addendum to ICH E6(R1): Guideline for Good Clinical Practice. 2016. p. 2.
29. Altman RD, Akermark C, Beaulieu AD, Schnitzer T, Durolane International Study G. Efficacy and safety of a single intra-articular injection of non-animal stabilized hyaluronic acid (NASHA) in patients with osteoarthritis of the knee. Osteoarthritis Cartilage 2004; 12(8): 642-9.
30. Altman RD, Moskowitz R. Intraarticular sodium hyaluronate (Hyalgan) in the treatment of patients with osteoarthritis of the knee: a randomized clinical trial. Hyalgan Study Group. J Rheumatol 1998; 25(11): 2203-12.
31. Altman RD, Rosen JE, Bloch DA, Hatoum HT, Korner P. A double-blind, randomized, saline-controlled study of the efficacy and safety of EUFLEXXA for treatment of painful osteoarthritis of the knee, with an open-label safety extension (the FLEXX trial). Semin Arthritis Rheum 2009; 39(1): 1-9.
32. Arden NK, Akermark C, Andersson M, Todman MG, Altman RD. A randomized saline-controlled trial of NASHA hyaluronic acid for knee osteoarthritis. Curr Med Res Opin 2014; 30(2): 279-86.

33. Baltzer AW, Moser C, Jansen SA, Krauspe R. Autologous conditioned serum (Orthokine) is an effective treatment for knee osteoarthritis. Osteoarthritis Cartilage 2009; 17(2): 152-60.
34. Brandt KD, Block JA, Michalski JP, Moreland LW, Caldwell JR, Lavin PT. Efficacy and safety of intraarticular sodium hyaluronate in knee osteoarthritis. ORTHOVISC Study Group. Clin Orthop Relat Res 2001; (385): 130-43.
35. Carrabba M, Paresce E, Angelini M, Re KA, Torchiana EEM, Perbellini A. The safety and efficacy of different dose schedules of hyaluronic acid in the treatment of painful osteoarthritis of the knee with joint effusion. Eur J Rheumatol Inflamm 1995; 15(1): 25-31.
36. Chevalier X, Jerosch J, Goupille P, et al. Single, intra-articular treatment with 6 ml hylan G-F 20 in patients with symptomatic primary osteoarthritis of the knee: a randomised, multicentre, double-blind, placebo controlled trial. Ann Rheum Dis 2010; 69(1): 113-9.
37. Dahlberg L, Lohmander LS, Ryd L. Intraarticular injections of hyaluronan in patients with cartilage abnormalities and knee pain. A one-year double-blind, placebo-controlled study. Arthritis Rheum 1994; 37(4): 521-8.
38. Day R, Brooks P, Conaghan PG, Petersen M, Multicenter Trial G. A double blind, randomized, multicenter, parallel group study of the effectiveness and tolerance of intraarticular hyaluronan in osteoarthritis of the knee. J Rheumatol 2004; 31(4): 775-82.
39. Diracoglu D, Vural M, Baskent A, Dikici F, Aksoy C. The effect of viscosupplementation on neuromuscular control of the knee in patients with osteoarthritis. J Back Musculoskelet Rehabil 2009; 22(1): 1-9.
40. Dixon AS, Jacoby RK, Berry H, Hamilton EB. Clinical trial of intra-articular injection of sodium hyaluronate in patients with osteoarthritis of the knee. Curr Med Res Opin 1988; 11(4): 205-13.
41. Dougados M, Nguyen M, Listrat V, Amor B. High molecular weight sodium hyaluronate (hyalectin) in osteoarthritis of the knee: a 1 year placebo-controlled trial. Osteoarthritis Cartilage 1993; 1(2): 97-103.
42. Formiguera Sala S, Esteve de Miguel R. Intra-articular hyaluronic acid in the treatment osteoarthritis of the knee: A short term study. Eur J Rheumatol Inflamm 1995; 15(1): 33-8.
43. Gormeli G, Gormeli CA, Ataoglu B, Colak C, Aslanturk O, Ertem K. Multiple PRP injections are more effective than single injections and hyaluronic acid in knees with early osteoarthritis: a randomized, double-blind, placebo-controlled trial. Knee Surg Sports Traumatol Arthrosc 2015; 25(3): 958-65.
44. Grecomoro G, Martorana U, Di Marco C. Intra-articular treatment with sodium hyaluronate in gonarthrosis: a controlled clinical trial versus placebo. Pharmatherapeutica 1987; 5(2): 137-41.
45. Henderson EB, Smith EC, Pegley F, Blake DR. Intra-articular injections of 750 kD hyaluronan in the treatment of osteoarthritis: a randomised single centre double-blind placebo-controlled trial of 91 patients demonstrating lack of efficacy. Ann Rheum Dis 1994; 53(8): 529-34.
46. Huang TL, Chang CC, Lee CH, Chen SC, Lai CH, Tsai CL. Intra-articular injections of sodium hyaluronate (Hyalgan(R)) in osteoarthritis of the knee. a randomized, controlled, double-blind, multicenter trial in the Asian population. BMC musculoskeletal disorders 2011; 12: 221.
47. Huskisson EC, Donnelly S. Hyaluronic acid in the treatment of osteoarthritis of the knee. Rheumatology (Oxford) 1999; 38(7): 602-7.

48. Jubb RW, Piva S, Beinat L, Dacre J, Gishen P. A one-year, randomised, placebo (saline) controlled clinical trial of 500-730 KDA sodium hyaluronate (hyalgan(registered trademark)) on the radiological change in osteoarthritis of the knee. Int J Clin Pract 2003; 57(6): 467-74.
49. Kul-Panza E, Berker N. Is hyaluronate sodium effective in the management of knee osteoarthritis? A placebo-controlled double-blind study. Minerva medica 2010; 101(2): 63-72.
50. Lundsgaard C, Dufour N, Fallentin E, Winkel P, Gluud C. Intra-articular sodium hyaluronate 2 mL versus physiological saline 20 mL versus physiological saline 2 mL for painful knee osteoarthritis: a randomized clinical trial. Scand J Rheumatol 2008; 37(2): 142-50.
51. Navarro-Sarabia F, Coronel P, Collantes E, et al. A 40-month multicentre, randomised placebo-controlled study to assess the efficacy and carry-over effect of repeated intra-articular injections of hyaluronic acid in knee osteoarthritis: the AMELIA project. Ann Rheum Dis 2011; 70(11): 1957-62.
52. Petrella RJ, Cogliano A, Decaria J. Combining two hyaluronic acids in osteoarthritis of the knee: a randomized, double-blind, placebo-controlled trial. Clin Rheumatol 2008; 27(8): 975-81.
53. Petrella RJ, Petrella M. A prospective, randomized, double-blind, placebo controlled study to evaluate the efficacy of intraarticular hyaluronic acid for osteoarthritis of the knee. J Rheumatol 2006; 33(5): 951-6.
54. Pham T, Le Henanff A, Ravaud P, Dieppe P, Paolozzi L, Dougados M. Evaluation of the symptomatic and structural efficacy of a new hyaluronic acid compound, NRD101, in comparison with diacerein and placebo in a 1 year randomised controlled study in symptomatic knee osteoarthritis. Ann Rheum Dis 2004; 63(12): 1611-7.
55. Puhl W, Bernau A, Greiling H, et al. Intra-articular sodium hyaluronate in osteoarthritis of the knee: a multicenter, double-blind study. Osteoarthritis Cartilage 1993; 1(4): 233-41.
56. Scale D, Wobig M, Wolpert W. Viscosupplementation of osteoarthritic knees with hylan: A treatment schedule study. CURR THER RES CLIN EXP 1994; 55(3): 220-32.
57. Strand V, Baraf HS, Lavin PT, Lim S, Hosokawa H. A multicenter, randomized controlled trial comparing a single intra-articular injection of Gel-200, a new cross-linked formulation of hyaluronic acid, to phosphate buffered saline for treatment of osteoarthritis of the knee. Osteoarthritis Cartilage 2012; 20(5): 350-6.
58. Tamir E, Robinson D, Koren R, Agar G, Halperin N. Intra-articular hyaluronan injections for the treatment of osteoarthritis of the knee: a randomized, double blind, placebo controlled study. Clin Exp Rheumatol 2001; 19(3): 265-70.
59. van der Weegen W, Wullems JA, Bos E, Noten H, van Drumpt RA. No difference between intra-articular injection of hyaluronic acid and placebo for mild to moderate knee osteoarthritis: a randomized, controlled, double-blind trial. The Journal of arthroplasty 2015; 30(5): 754-7.
60. Wobig M, Dickhut A, Maier R, Vetter G. Viscosupplementation with hylan G-F 20: a 26-week controlled trial of efficacy and safety in the osteoarthritic knee. Clin Ther 1998; 20(3): 410-23.
61. Petterson SC, Plancher KD. Single intra-articular injection of lightly cross-linked hyaluronic acid reduces knee pain in symptomatic knee osteoarthritis: a multicenter, double-blind, randomized, placebo-controlled trial. Knee Surg Sports Traumatol Arthrosc 2018.

62. Golder S, Loke YK, Wright K, Norman G. Reporting of Adverse Events in Published and Unpublished Studies of Health Care Interventions: A Systematic Review. PLoS medicine 2016; 13(9): e1002127.

63. Ioannidis JP, Lau J. Completeness of safety reporting in randomized trials: an evaluation of 7 medical areas. JAMA 2001; 285(4): 437-43.

64. Honvo G, Bannuru RR, Bruyere O, et al. Recommendations for the Reporting of Harms in Manuscripts on Clinical Trials Assessing Osteoarthritis Drugs: A Consensus Statement from the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO). Drugs & aging 2019; 36(Suppl 1): 145-59.

Appendix 1 search strategy

Embase.com

(viscosupplementation/de OR viscosupplement*:ab,ti OR (('hyaluronic acid'/de OR 'hyaluronic acid derivative'/de OR (adant OR amo-vitrax OR amvisc OR artz OR biolon OR etamucin* OR healon* OR hyalcon OR hyalga* OR hyalovet OR hyaluron* OR hialuron* OR hyladerm OR hylan* OR hylaform OR hylartin OR hylumed OR hyvisc OR ialugen OR luronit OR me3710 OR me-3710 OR na-hylan OR nrd101 OR nrd-101 OR orthovisc OR perlane OR provisc OR restylane OR si4402 OR si-4402 OR sl1010 OR sl-1010 OR sperm-select OR supartz OR synvisc OR sinovial):ab,ti) AND (joint/exp OR 'intraarticular drug administration'/exp OR 'hip disease'/exp OR 'knee disease'/exp OR 'shoulder disease'/exp OR 'elbow disease'/exp OR 'jaw disease'/exp OR 'hand disease'/exp OR osteoarthritis/exp OR (joint* OR acetabul* OR ankle* OR carpal OR carpometacarpal OR elbow* OR finger* OR hand* OR hip OR cox* OR gon* OR genu* OR knee* OR metacarpophalangeal OR metatarsophalangeal OR patellofemoral OR interphalangeal OR radioulnar OR sacroiliac OR shoulder OR sternoclavicular OR sternocostal OR subtalar OR tarsal OR tarsometatarsal OR temporomandibular OR toe OR wrist OR zygapophyseal OR shoulder OR hand OR (intra NEXT/1 articul*) OR intraarticul* OR intracox* OR spondylosis OR osteoarthr* OR 'degenerative arthritis' OR 'rheumatoid arthrosis' OR periarthrit*):ab,ti))) AND ('adverse drug reaction'/exp OR 'adverse outcome'/de OR 'side effect'/exp OR 'drug tolerability'/exp OR 'drug safety'/exp OR 'patient safety'/de OR safety/exp OR adverse:lnk OR 'drug efficacy'/de OR placebo/de OR 'Placebo Effect'/de OR complication/exp OR 'clinical effectiveness'/exp OR (adverse* OR ((side OR injurious) NEAR/3 (effect* OR react* OR event*)) OR undesir* OR safe* OR tolera* OR poison* OR toxic* OR 'chemically induced' OR complic* OR harm* OR effectiv* OR efficac* OR placebo* OR complication*):ab,ti) NOT ([animals]/lim NOT [humans]/lim)

Medline (OvidSP)

(viscosupplementation/ OR viscosupplement*.ab,ti. OR (("hyaluronic acid"/ OR "hyaluronic acid derivative"/ OR (adant OR amo-vitrax OR amvisc OR artz OR biolon OR etamucin* OR healon* OR hyalcon OR hyalga* OR hyalovet OR hyaluron* OR hialuron* OR hyladerm OR hylan* OR hylaform OR hylartin OR hylumed OR hyvisc OR ialugen OR luronit OR me3710 OR me-3710 OR na-

hylan OR nrd101 OR nrd-101 OR orthovisc OR perlane OR provisc OR restylane OR si4402 OR si-4402 OR sl1010 OR sl-1010 OR sperm-select OR supartz OR synvisc OR sinovial).ab,ti.) AND (exp joints/ OR "Injections, Intra-Articular"/ OR exp "joint diseases"/ OR exp osteoarthritis/ OR (joint* OR acetabul* OR ankle* OR carpal OR carpometacarpal OR elbow* OR finger* OR hand* OR hip OR cox* OR gon* OR genu* OR knee* OR metacarpophalangeal OR metatarsophalangeal OR patellofemoral OR interphalangeal OR radioulnar OR sacroiliac OR shoulder OR sternoclavicular OR sternocostal OR subtalar OR tarsal OR tarsometatarsal OR temporomandibular OR toe OR wrist OR zygapophyseal OR shoulder OR hand OR (intra ADJ articul*) OR intraarticul* OR intracox* OR spondylosis OR osteoarthr* OR "degenerative arthritis" OR "rheumatoid arthrosis" OR periarthrit*).ab,ti.))) AND (exp "Drug-Related Side Effects and Adverse Reactions"/ OR exp "safety"/ OR adverse effects.xs. OR placebos/ OR "Placebo Effect"/ OR complication/ OR "clinical effectiveness"/ OR (adverse* OR ((side OR injurious) ADJ3 (effect* OR react* OR event*)) OR undesir* OR safe* OR tolera* OR poison* OR toxic* OR "chemically induced" OR complic* OR harm* OR effectiv* OR efficac* OR placebo* OR complication*).ab,ti.) NOT (exp animals/ NOT humans/)

cochrane CENTRAL

(viscosupplement*:ab,ti OR (((adant OR amo-vitrax OR amvisc OR artz OR biolon OR etamucin* OR healon* OR hyalcon OR hyalga* OR hyalovet OR hyaluron* OR hialuron* OR hyladerm OR hylan* OR hylaform OR hylartin OR hylumed OR hyvisc OR ialugen OR luronit OR me3710 OR me-3710 OR na-hylan OR nrd101 OR nrd-101 OR orthovisc OR perlane OR provisc OR restylane OR si4402 OR si-4402 OR sl1010 OR sl-1010 OR sperm-select OR supartz OR synvisc OR sinovial):ab,ti) AND ((joint* OR acetabul* OR ankle* OR carpal OR carpometacarpal OR elbow* OR finger* OR hand* OR hip OR cox* OR gon* OR genu* OR knee* OR metacarpophalangeal OR metatarsophalangeal OR patellofemoral OR interphalangeal OR radioulnar OR sacroiliac OR shoulder OR sternoclavicular OR sternocostal OR subtalar OR tarsal OR tarsometatarsal OR temporomandibular OR toe OR wrist OR zygapophyseal OR shoulder OR hand OR (intra NEXT/1 articul*) OR intraarticul* OR intracox* OR spondylosis OR osteoarthr* OR 'degenerative arthritis' OR 'rheumatoid arthrosis' OR periarthrit*):ab,ti))) AND ((adverse* OR

((side OR injurious) NEAR/3 (effect* OR react* OR event*)) OR undesir* OR safe* OR tolera* OR poison* OR toxic* OR 'chemically induced' OR complic* OR harm* OR effectiv* OR efficac* OR placebo* OR complication*):ab,ti)

Web-of-science

TS=((viscosupplement* OR (((adant OR amo-vitrax OR amvisc OR artz OR biolon OR etamucin* OR healon* OR hyalcon OR hyalga* OR hyalovet OR hyaluron* OR hialuron* OR hyladerm OR hylan* OR hylaform OR hylartin OR hylumed OR hyvisc OR ialugen OR luronit OR me3710 OR me-3710 OR na-hylan OR nrd101 OR nrd-101 OR orthovisc OR perlane OR provisc OR restylane OR si4402 OR si-4402 OR sl1010 OR sl-1010 OR sperm-select OR supartz OR synvisc OR sinovial)) AND ((joint* OR acetabul* OR ankle* OR carpal OR carpometacarpal OR elbow* OR finger* OR hand* OR hip OR cox* OR gon* OR genu* OR knee* OR metacarpophalangeal OR metatarsophalangeal OR patellofemoral OR interphalangeal OR radioulnar OR sacroiliac OR shoulder OR sternoclavicular OR sternocostal OR subtalar OR tarsal OR tarsometatarsal OR temporomandibular OR toe OR wrist OR zygapophyseal OR shoulder OR hand OR (intra NEAR/1 articul*) OR intraarticul* OR intracox* OR spondylosis OR osteoarthr* OR "degenerative arthritis" OR "rheumatoid arthrosis" OR periarthrit*)))) AND ((adverse* OR ((side OR injurious) NEAR/3 (effect* OR react* OR event*)) OR undesir* OR safe* OR tolera* OR poison* OR toxic* OR "chemically induced" OR complic* OR harm* OR effectiv* OR efficac* OR placebo* OR complication*)) NOT ((animal* OR rabbit* OR mouse OR mice OR rat OR rats OR rodent* OR dog OR equin* OR horse* OR bovine* OR chicken* OR sheep OR pig OR swine* OR monkey*) NOT (human* OR patient*))) AND DT=(Article)

Scopus

TITLE-ABS-KEY((viscosupplement* OR (((adant OR amo-vitrax OR amvisc OR artz OR biolon OR etamucin* OR healon* OR hyalcon OR hyalga* OR hyalovet OR hyaluron* OR hialuron* OR hyladerm OR hylan* OR hylaform OR hylartin OR hylumed OR hyvisc OR ialugen OR luronit OR me3710 OR me-3710 OR na-hylan OR nrd101 OR nrd-101 OR orthovisc OR perlane OR provisc OR restylane OR si4402 OR si-4402 OR sl1010 OR sl-1010 OR sperm-select OR supartz OR synvisc OR sinovial)) AND ((joint* OR acetabul*

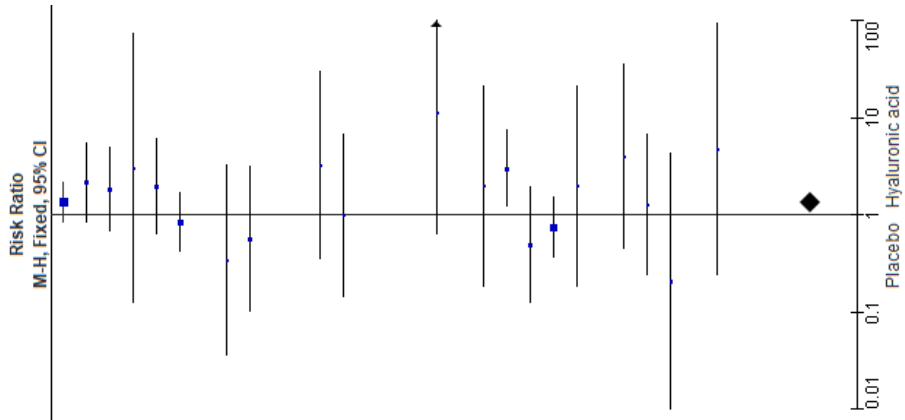
OR ankle* OR carpal OR carpometacarpal OR elbow* OR finger* OR hand* OR hip OR cox* OR gon* OR genu* OR knee* OR metacarpophalangeal OR metatarsophalangeal OR patellofemoral OR interphalangeal OR radioulnar OR sacroiliac OR shoulder OR sternoclavicular OR sternocostal OR subtalar OR tarsal OR tarsometatarsal OR temporomandibular OR toe OR wrist OR zygapophyseal OR shoulder OR hand OR (intra W/1 articul*) OR intraarticul* OR intracox* OR spondylosis OR osteoarthr* OR "degenerative arthritis" OR "rheumatoid arthrosis" OR periarthrit*)))) AND ((adverse* OR ((side OR injurious) W/3 (effect* OR react* OR event*)) OR undesir* OR safe* OR tolera* OR poison* OR toxic* OR "chemically induced" OR complic* OR harm* OR effectiv* OR efficac* OR placebo* OR complication*)) AND NOT ((animal* OR rabbit* OR mouse OR mice OR rat OR rats OR rodent* OR dog OR equin* OR horse* OR bovine* OR chicken* OR sheep OR pig OR swine* OR monkey*) AND NOT (human* OR patient*))) AND DOCTYPE(ar)

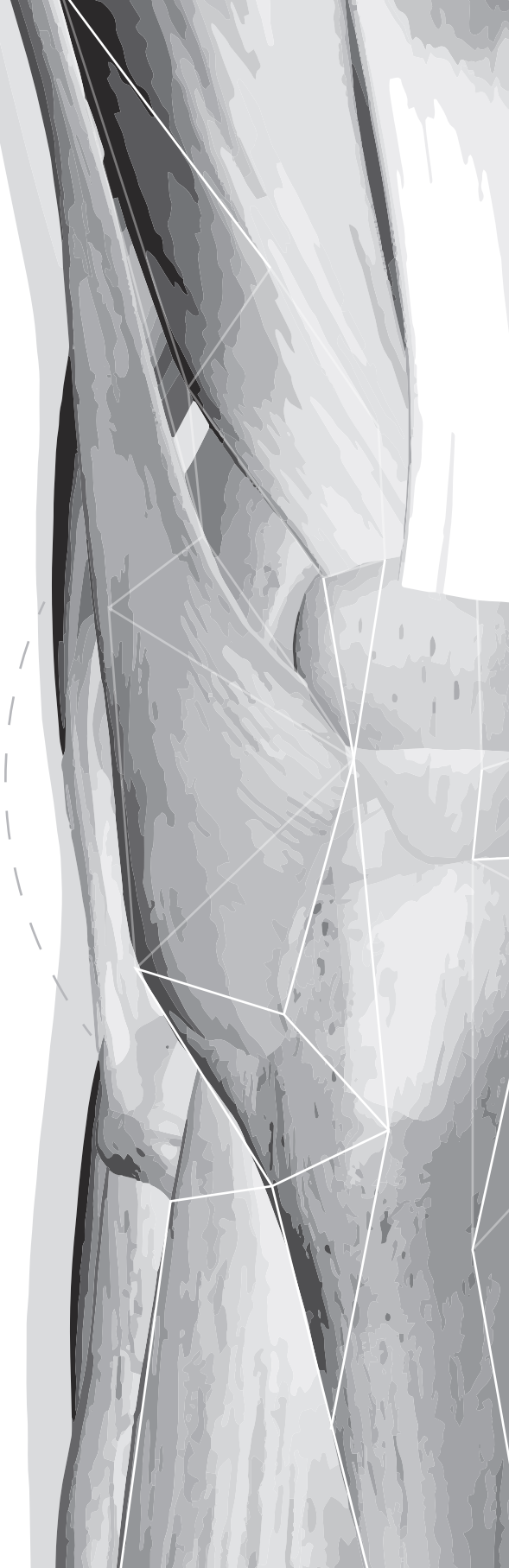
Google scholar

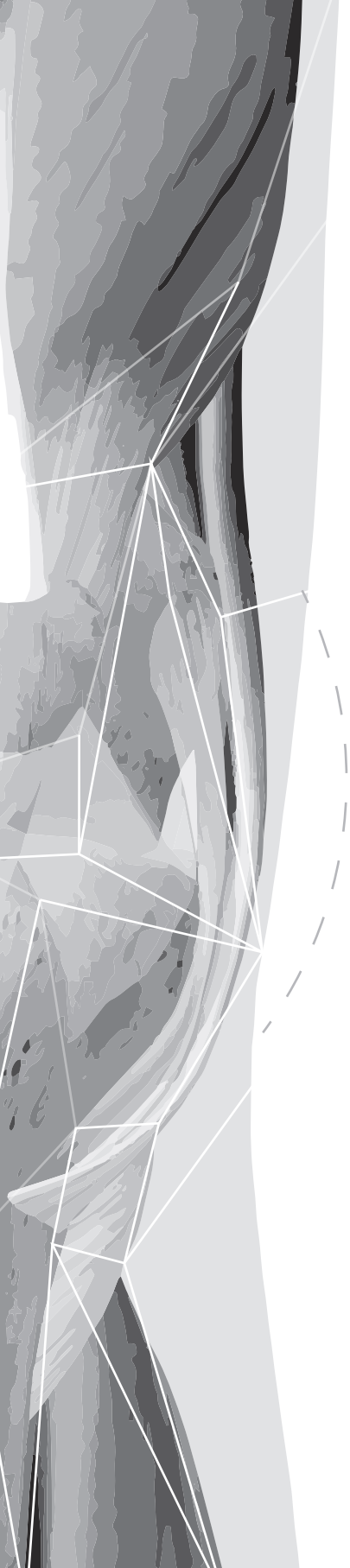
Viscosupplementation | hyaluronic joint | joints | intraarticular | "intra articular" | hip | knee | shoulder | elbow | osteoarthritis adverse | "side effect" | tolerability | safety | efficacy | placebo | complication | effectiveness

Appendix2Riskratiostudywithdrawalduetoadverseevents (author criteria)

Appendix3Riskratiostudywithdrawalduetoadverseevents (GCP criteria)







Chapter 7
General discussion

Intra-articular hyaluronic acid (HA) therapy as a treatment modality for symptomatic knee osteoarthritis (OA) has been investigated for decades. With this thesis, focusing on different aspects of HA therapy in relative young patients with symptomatic knee OA who are in their working years, we aimed to add to the discussion on its effectiveness and its economic consequences in clinical practice.

First, we conducted a systematic review to study the most accurate approach to administer HA into the knee joint. We examined the nature and extent of the productivity costs and the medical costs related to knee OA in non-surgically treated patients with a paid employment. The VISK study was conducted, which is a randomized controlled trial (RCT) to assess the effectiveness and cost-effectiveness of intra-articular HA therapy with a high molecular weight (HMW) derivative in symptomatic knee OA patients at the working age. Finally, we conducted a systematic review and meta-analysis to investigate the amount and nature of adverse events (AEs) related to the intra-articular administration of HA in the knee joint, and their possible relation with specific product characteristics of the HA derivative.

In this chapter the main results of this thesis are placed in a larger perspective. The limitations of the presented research are addressed and recommendations for future research are made.

Efficacy

The efficacy of intra-articular HA in the treatment of knee OA has been studied extensively. Dozens RCTs comparing HA to placebo have been performed since the first clinical experiments on HA as a treatment option for knee OA were conducted.[1]

Despite the numerous clinical studies, controversy concerning the efficacy of HA for the treatment of knee OA existed. The debate on the efficacy inevitably led to the publication of systematic reviews. To date, 17 systematic reviews and meta-analyses have been published on the topic, generally reporting positive efficacy results of intra-articular HA on pain and/or function compared to placebo.[2] These findings are not free of criticism. A meta-analysis investigating trial inconsistencies in HA studies for knee OA reported that intra-articular HA resulted in HADSFa better effect on pain reduction

compared to placebo, but the presence of publication bias and the risk of selective outcome reporting suggests that the clinical effect is only small.[3] In another systematic review poor methodological quality and reporting quality of the included trials were indicated as a major limitation. The authors conclude that trial size, blinded outcome assessment and publication status were associated with the effect size of intra-articular HA therapy for knee OA.[4]

Eventually, 2 systematic reviews were conducted, both investigating the already published meta-analyses on the efficacy of HA. These reviews report that the methodological quality between the included meta-analyses varies. The conclusions of the reviews both indicate HA as an effective intervention in the treatment of knee OA with moderate symptomatic benefit.[1, 2]

Most placebo controlled RCTs investigated the efficacy of a single series of intra-articular HA. More recently, the focus has shifted to the evaluation of efficacy and safety of repeated courses of intra-articular HA. A recent systematic review and meta-analysis on this topic showed that throughout repeated courses pain reduction was either sustained or further reduced. No further safety risks were found.[5]

Effectiveness

Based on the positive efficacy results from the Cochrane systematic review from 2006 the VISK study was designed.[6] One of the goals was to investigate the actual effectiveness intra-articular HA in the treatment of knee OA in a patient group in the working age. In **chapter 4** we report on the effectiveness results of the VISK study. We showed that intra-articular HA added to the usual (non-surgical) care for knee OA results in more responders to therapy according to the OMERACT-OARSI criteria after 12 months follow-up.[7] We conclude that intra-articular injections with HMW-HA added to usual care is effective. It results in more responders to therapy and in improvement in pain, function and patient global assessment. Based on these results we recommend intra-articular HMW-HA as a therapeutic option in the non-surgical management of symptomatic knee OA.

To date, 2 other RCTs have compared HMW-HA added to usual care to usual care only. Our effectiveness results are in line with these studies in which

beneficial clinical results on pain and function are reported when intra-articular HA is added to the usual care treatment for knee OA.[8, 9]

No long term follow-up RCTs on the effectiveness of intra-articular HA therapy for symptomatic knee OA have been published. The results of 2 studies investigating 2 different large healthcare claims databases in the United States (US) show that the time from the initial diagnosis of knee OA by an orthopedic surgeon to the date of total knee replacement (TKR) surgery is significantly longer in knee OA patients treated with intra-articular HA, compared to patients who were not treated with HA. Depending on the investigated database, the difference in delay varied from 0.7 years to 2.9 years.[14, 15] The increase in time to TKR is reported to be dose dependent and associated with the number of treatment series administered.[10] These results do need to be interpreted with reserve due the possibility of confounding by indication.

Efficiency

Efficiency measures the effect of an intervention in relation to the costs and the resources it consumes. Or in other words, is it worth it?[11, 12]

In **chapter 5** we present the cost-effectiveness results of the VISK-study. We show that adding HMW-HA to usual care for knee OA in a population in the working age results in an improvement of the quality of life (QoL). This gain in QoL was accompanied with a cost increase in the HMW-HA treated subjects. The gain in QoL and costs resulted in an incremental cost-effectiveness ratio (ICER) of approximately €9,100 per quality adjusted life year (QALY) gained from the societal perspective (productivity costs and medical costs included). From the health care perspective (medical costs only) the ICER was approximately €8,700/QALY gained. The uncertainty analyses indicated a probability of 99% that HMW-HA in knee OA will result in positive health effects. Considering a maximum willingness to pay of €20,000/QALY for the treatment of knee OA and similar conditions, the probability on cost-effectiveness of HMW-HA is 64% from the societal perspective and 86% from the health care perspective.[13-15]

To date, no other economic evaluations on the cost-effectiveness of HA in knee OA for the Dutch situation have been published. The economic results of the VISK study are in line with 2 other RCTs from France and Canada

investigating the cost-effectiveness of HMW-HA added to usual care for knee OA. Favorable ICERs were reported for the situation of the country in which the study was performed, both in a population with higher average age and in which a higher percentage of subjects was not involved in a paid occupation compared to our study.[9, 16]

A systematic review on the cost-effectiveness of intra-articular HA and disease-modifying drugs (DMOADs) in knee OA reported similar results. In the included RCT studies the authors report that the ICERs varied between €4390 and €13450 per QALY. This study included placebo controlled RCTs as well as RCTs with a head to head comparison of 2 or more HA derivatives.[17]

In the VISK study we included patients with mild to moderate knee OA aged between 18 and 65, the latter being the pensionable age in The Netherlands at time of the study. As a consequence 75% of the participants were involved in paid employment. In musculoskeletal disorders the productivity costs generally exceed the medical costs.[18-20] In **chapter 3** we show that the productivity costs of the working part of the VISK population prior to their participation in the study where 5 times higher than the medical costs. It is very well possible that the incremental costs associated with the addition of HMW-HA to usual care for mild to moderate knee OA in the general and older knee OA population are lower due to a smaller proportion of patients in paid employment, leading to a more favorable ICER than currently reported on in **chapter 5**.

In The Netherlands, the national Health Institute (Zorginstituut Nederland) advises the minister of Health, Welfare and Sports on the reimbursement of medical treatments by health insurance companies. Advises on reimbursement are based on 4 criteria: necessity (is there a health problem?); effectiveness (is there a treatment that can solve the health problem?); cost-effectiveness (is there an acceptable relation between health effects and costs?); and practicability (are the costs out of reach of the individual, and within reach of society?).[21]

Intra-articular therapy with HA for knee OA is currently not reimbursed in The Netherlands. [22] This decision is based on the most recent Dutch medical specialists guideline on the non-surgical treatment of knee and hip OA, which does not recommend intra-articular HA for reasons of limited efficacy and the absence of proven cost-effectiveness.[23, 24]

As we showed in **chapter 4 and 5**, intra-articular HA therapy results in beneficial

effectiveness results, a favorable ICER, a high probability of positive healthcare effects and a high probability on of cost-effectiveness. Based on these results, and given the decision tree used by the Health Institute to establish an advise on reimbursement, we believe that reasons exist to reconsider the current advise not to reimburse HA for the treatment of knee OA.[14, 21]

Guidelines and HA

Intra-articular HA as a treatment modality is not unambiguously recommended in the various clinical practice guidelines on the treatment of knee OA. Some guidelines recommend against its use in the treatment of knee OA, some guidelines regard intra-articular HA appropriate under certain circumstances, and some guidelines provide an uncertain recommendation or even no recommendation at all.[25-28] The most recent Dutch medical specialists guideline on the non-surgical treatment of knee and hip OA does not recommend intra-articular HA as a standard treatment option for knee OA for reasons of limited efficacy and absence of proven cost-effectiveness.[23, 24] The Dutch general practitioners association also does not recommend the intra-articular HA in the treatment of knee OA.[29]

Given the effectiveness and cost-effectiveness results of the VISK study (**chapter 4 and 5)** we advocate for the recommendation of intra-articular HMW-HA as treatment option in guidelines on the management of symptomatic knee OA.

Several methodological issues are held responsible for the variety in guideline recommendations on HA in knee OA. Inconsistency in work group composition and recommendation formation is reported to contribute to the difference in clinical practice guideline recommendations. Also, differences in the process of evidence assessment and evidence inclusion play an important role in the variation in the guideline recommendations.[25]

An important issue is that there is often a difference in the benefits observed in clinical practice and the treatment effects as assessed with placebo controlled RCTs. This is called the efficacy paradox.[30, 31] In clinical practice, when a patient receives a treatment the benefits experienced not only result just from the specific treatment effects but also from what are called contextual effects from receiving the treatment.[30, 31] These contextual effects

comprise the placebo effect, but also the Hawthorn effect (the effect due to being observed) and/or spontaneous effects (e.g. disease fluctuation or regression to the mean).[30, 32] Treatment effect and contextual effects may interact and influence the magnitude of the observed improvement seen.[30]
Treatment guidelines generally focus on specific treatment effects as assessed by means of placebo controlled RCTs. A certain treatment with a large effect due to strong nonspecific effects is generally considered less adequate in this matter, compared to a treatment with lesser total effects but with a stronger specific treatment effect.[30, 31] This results in a disconnect between guidelines, including the treatment guidelines on the non-surgical treatment of knee OA, and the actual clinical practice in everyday care.[30]
Another explanation for the variety in recommendations on the use of intra-articular HA for the treatment of knee OA is that in most studies and reviews on the efficacy, HA and available HA derivatives are considered as one treatment or one group. Nevertheless, HA-derivatives for therapeutic use in knee OA differ from each other in several ways. Intra-articular HA for clinical use can be produced by either bacterial fermentation or extraction from avian tissue.[33] The molecular weight of HA-derivatives varies (mostly between 500 to 6000 kiloDalton (kDa)). In order to further increase molecular weight the molecular structure can be chemically crosslinked to form so-called Hylans.[34-36] The volumes and frequency of injections varies and some derivatives include additives like mannitol or sorbitol.[37]
These differences result in clinical and also economic consequences. Subgroup analyses in previous meta-analyses on the efficacy of HA show that HMW-HA is more efficacious than LMW HA.[4, 38] A recent systematic review investigating the product differences between intra-articular HA derivatives concluded that product differences influence both efficacy and safety. The authors report that intra-articular HA products should not be treated as a group due to these differences. Based on their findings the authors conclude that HMW HA-derivatives and products derived from biological fermentation relate to superior efficacy and safety.[35] In **chapter 6** we show that the higher risk on local AEs after the administration of local intra-articular HA is associated with the use of non-crosslinked HA-products and products with a lower molecular weight.

Comparison with other non-surgical treatment modalities

Several treatment modalities for the non-surgical treatment of symptomatic knee OA are available.

A network meta-analysis compared common pharmacological interventions for knee OA.[39] Interventions and comparators were investigated, including oral acetaminophen, diclofenac, ibuprofen, naproxen and celecoxib, intra-articular corticosteroids and HA and oral and intra-articular placebo. Intra-articular HA was found to be the most efficacious treatment in pain reduction compared to the other interventions and the placebo comparators. On the improvement of function, intra-articular hyaluronic acid was statistically significantly better than intra-articular corticosteroids and oral or intra-articular placebo. No statistically significant differences in function were found in the comparison with oral treatments like acetaminophen, diclofenac, ibuprofen, naproxen or celecoxib.[39]

These results are in line with the results of a systematic review on overlapping meta-analyses on the comparison of HA versus other (non-surgical) therapies in the treatment of knee OA. This study reports that intra-articular corticosteroids are relatively more effective in pain relief than HA in the first 4 weeks after intra-articular administration. After this period, intra-articular HA results in greater efficacy with residual effects up to 26 weeks post-injection. Compared to oral non-steroidal anti-inflammatory drugs (NSAIDs), the efficacy of intra-articular HA on knee pain and function does not differ significantly. Intra-articular platelet-rich plasma (PRP) led to similar but more robust long term positive effects on knee function compared to intra-articular HA without a difference in AEs.[40]

Due to the risk of gastrointestinal side effects, the safety profile of intra-articular HA was considered more favorable than that of oral NSAIDs. Overall, the authors conclude that the current highest level of evidence suggests that IA-HA is a viable option for knee OA due to improvements in knee pain and function up to 26 weeks and a good safety profile.[40]

Economic evaluations of other non-surgical treatments for knee OA in the Dutch situation are scarce. One study from The Netherlands compared behavioral graded activity therapy to usual care as provided by physiotherapists in patients with hip or knee OA. At 65 weeks, no differences were found between the two groups in improvement with respect to baseline

on any of the outcome measures. The authors conclude that the study provides no evidence that behavioral graded activity is either more effective or less costly than usual care from physiotherapists for hip or knee OA.[41]

A study from New Zealand investigated the cost effectiveness of providing supervised physiotherapy in addition to usual medical care in patients with osteoarthritis of the hip or knee. After 2 years follow-up, the authors concluded that individually supervised exercise therapy is cost-effective and clinically effective in addition to usual medical care, and leads to cost savings for the health system and society.[42]

A systematic review on the cost-effectiveness of nonpharmacological nonsurgical interventions for hip and/or knee OA reported that there is only limited evidence for the cost-effectiveness of conservative treatments like exercise programs, acupuncture, rehabilitation programs, and lifestyle interventions for the management of hip and/or knee OA.[43] Another systematic review investigated the cost-effectiveness of adjunct non-pharmacological interventions for knee OA. Acupuncture, braces, heat treatment, insoles, interferential therapy, laser/light therapy, manual therapy, neuromuscular electrical stimulation, pulsed electrical stimulation, pulsed electromagnetic fields, static magnets and transcutaneous electrical nerve Stimulation (TENS) where all investigated. The authors conclude that TENS is cost-effective when a £20,000 per QALY threshold is used, with an ICER of £2,690 per QALY. If only higher quality trials are considered, acupuncture is cost-effective at this threshold with an ICER of £13,502 per QALY.[44]

Who will benefit?

An important matter in the decision making process on whether or not to opt for treatment with intra-articular HA is to know which patient will benefit most from the treatment. Nevertheless, the magnitude of the effect of treatment with intra-articular HA among different phenotypes of knee OA patients is unclear.[2] Subgroup analyses are generally not included in the individual studies and meta-analyses on the efficacy of HA in knee OA.

Evidence suggests that intra-articular treatment with HA is more effective in specific patient groups.[2, 45, 46] Results from individual studies show that patients with a mild radiological degree of OA (Kellgren & Lawrence (K&L)

grade II rather than III), patients under 60 years old, patients with a high level of symptoms, and the absence of effusion of the knee joint is related to more beneficial clinical results. The presence of crystals in the knee joint does not appear to prohibit the use of HA injections or reduce the level of response.[2, 45]

These results are in concordance with the findings we present in **chapter 4**. In this chapter we show that that HMW-HA added to the usual non-surgical care for knee OA is effective in a relatively younger patient group with an average age of 54, with K&L grade I to III and a mean pain score of 4.8 out of 10 during rest.

A recent post-hoc analysis of a non-inferiority randomized controlled trial comparing 2 different HA-derivatives showed that obesity and radiological severity were significantly associated with failure of treatment with intra-articular HA. Failure was defined in this study as not being responder to therapy at 6 months according to OMERACT-OARSI criteria.47 In a subsequent study the authors report that despite these results, evidence shows that particular subgroups of patients with obesity and advanced joint space narrowing still may benefit from intra-articular treatment with HA.[48]

It is very well possible that these results are subjected to bias, since both BMI and radiological severity of knee OA are also associated with progression of knee OA itself.[49]

Based on a systematic research of evidence, expert clinical opinion, and current evidence-based clinical practice guidelines a workgroup of clinical experts developed appropriate use criteria for HA therapy in the treatment of knee OA.[50] Intra-articular HA therapy was deemed appropriate for patients with confirmed radiological and clinical mild to moderate knee OA, who have not received other therapies for the knee, who have failed other non-pharmacologic or pharmacologic therapies, or who have incomplete response to other therapies for the knee. Treatment with HA in patients with severe knee OA was deemed uncertain, as was the treatment of patients with high risks to AEs or who are contraindicated for pharmacological agents for the knee.[50]

From an economic point of view the results if the VISK study (**chapter 5**) show that intra-articular HA added to UC in the treatment of knee OA results in a favorable ICER and a high probability on cost-effectiveness in relatively

younger patients with mild to moderate clinical knee OA.[13] No evidence from clinical studies is available on the costs or cost-effectiveness associated with HA treatment in certain patient subgroups.

Limitations

The backbone of this thesis is formed by the VISK study and its outcomes on effectiveness and cost-effectiveness as presented in **chapters 4 and 5**. With the VISK study we aimed to evaluate the effectiveness and cost-effectiveness of intra-articular HA for knee OA by means of a pragmatic RCT in which health and cost outcomes are measured in real life conditions.[51]

The target population of the VISK study can be described as patients in the working age with symptomatic and mild to moderate knee OA. For this reason, patients with K/L grade I to III and a minimal pain score of 2 were included and, for example, patients who were more likely to benefit from different kinds of therapy were excluded (e.g., K&L grade IV, substantial varus or valgus deformation). Other in- and exclusion criteria were applied to avoid measuring effects strongly related to other factors than the intervention itself (e.g. recent or planned knee surgery) or to avoid possible harm due to the intervention (e.g. pregnancy or allergies). Any characteristic of a patient or setting that impacts the benefit or risk of a treatment will inevitably affect generalizability if that characteristic differs between the trial population and the patient group where the results eventually are applied to.[12, 51] So whether the results of the VISK study also extend to other patient groups who might benefit from HMW-HA treatment (e.g. patients with more severe knee OA or patients not fit for surgery) remains uncertain.

As is common in cost-effectiveness analyses alongside RCTs, the sample size of the VISK study was based on the primary clinical outcomes.[8, 16, 52-55] Ideally, the sample size calculation would also be based on expected costs and QoL differences.[56] In practice this would result in large required sample sizes which are difficult to include. The economic results of the VISK study therefore must be interpreted in light of the sample size discussion.

In an economic evaluation of a certain interventions alongside a clinical trial the focus generally lies on the assessment of the associated medical costs and productivity costs.[16, 54, 55] Potentially long term personal costs

due to possible premature retirement, loss of income and/or subsequent reductions in personal savings are not accounted for in these types of studies, nor are national costs related to disability benefits, welfare benefits or lost tax revenues.[57, 58] Although these costs are estimated to be substantial and relevant to fully understand the economic consequences of an intervention, the design of the VISK study did not allow for the assessment of these costs.

Recommendations for future research

Most research on the efficacy (and effectiveness) of intra-articular HA in knee OA has focused on the administration of a single series of HA. The peak effectiveness of a series of intra-articular HA lies between 1 and 2 months and residual effects exist up to 6 months.[6, 45, 59] A recent systematic review on the topic reported that repeated courses were demonstrated to maintain or further improve pain reduction while introducing no increased safety risk.[5] Future research should investigate whether or not these positive health effects also result in beneficial economic results in terms of cost-effectiveness. The impact of intra-articular HA on long-term outcomes like delay of TKR has been studied in healthcare claims databases.[10, 46] These studies report that the time from initial diagnosis to the date of TKR surgery is significantly longer in knee OA patients treated with intra-articular HA, compared to patients who were not treated with HA.[10, 46] Due the possibility of confounding by indication these results need to be interpreted with reserve and prospective research in controlled studies is needed to investigate the influence of intra-articular HA on the delay of TKR surgery.

There is limited evidence on which knee OA patients might benefit more from intra-articular HA therapy and in which patients this therapy might fail[2]. A mild radiological degree of OA, age under 60 years, a high symptom level and the absence of knee effusion is reported to be associated with beneficial clinical outcomes and obesity and more advanced radiological OA appear to be associated with failure of treatment with intra-articular HA.[2, 45-47] The authors reporting on the latter findings in a following study show that particular subgroups of patients with obesity and advanced joint space narrowing still may benefit from intra-articular treatment with HA.[48] Since pain in knee OA can be from nociceptive as well as neuropathic origin, different

pain phenotypes might be the main reason for the success or failure of intra-articular therapy with HA.[48]

These results illustrate that more research is needed to answer the question on which knee OA patients, with which phenotypic pain characteristics, are more likely to benefit from treatment with intra-articular HA.[2] Given the availability of numerous studies on intra-articular HA in knee OA such subgroup analyses might be best performed by means of a meta-analysis of individual patient data, rather than by a meta-analysis using aggregate data only.[60]

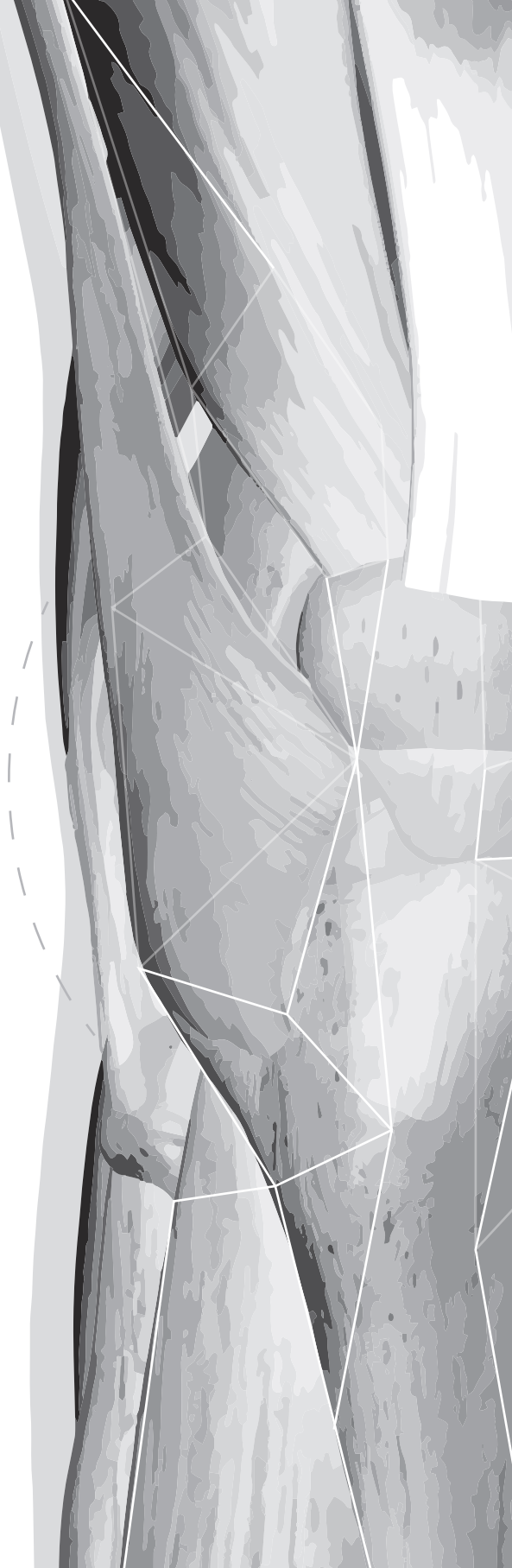
References

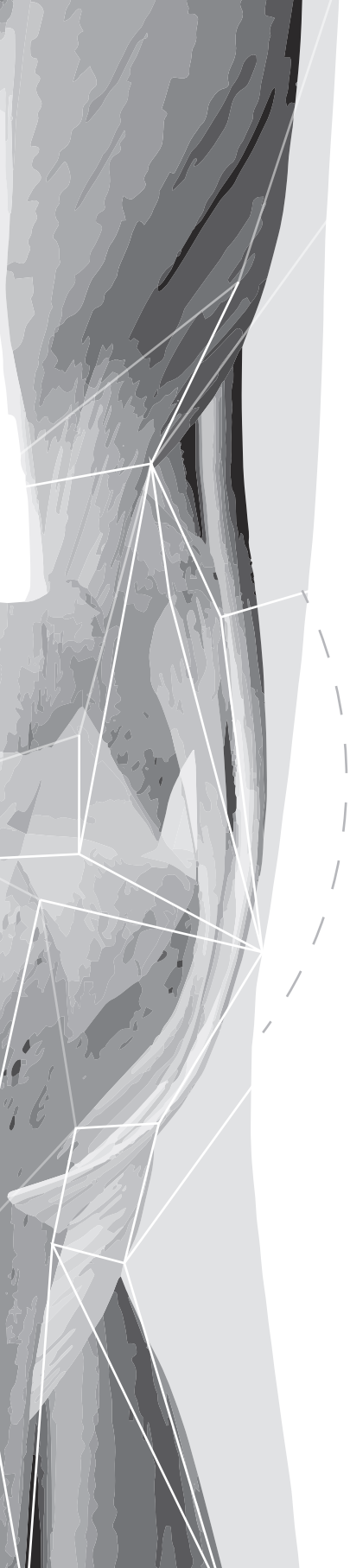
1. Xing D, Wang B, Liu Q, et al. Intra-articular Hyaluronic Acid in Treating Knee Osteoarthritis: a PRISMA-Compliant Systematic Review of Overlapping Meta-analysis. Scientific reports 2016; 6: 32790.
2. Maheu E, Bannuru RR, Herrero-Beaumont G, Allali F, Bard H, Migliore A. Why we should definitely include intra-articular hyaluronic acid as a therapeutic option in the management of knee osteoarthritis: Results of an extensive critical literature review. Semin Arthritis Rheum 2019; 48(4): 563-72.
3. Johansen M, Bahrt H, Altman RD, et al. Exploring reasons for the observed inconsistent trial reports on intra-articular injections with hyaluronic acid in the treatment of osteoarthritis: Meta-regression analyses of randomized trials. Semin Arthritis Rheum 2016; 46(1): 34-48.
4. Rutjes AW, Juni P, da Costa BR, Trelle S, Nuesch E, Reichenbach S. Viscosupplementation for osteoarthritis of the knee: a systematic review and meta-analysis. Ann Intern Med 2012; 157(3): 180-91.
5. Altman R, Hackel J, Niazi F, Shaw P, Nicholls M. Efficacy and safety of repeated courses of hyaluronic acid injections for knee osteoarthritis: A systematic review. Semin Arthritis Rheum 2018; 48(2): 168-75.
6. Bellamy N, Campbell J, Robinson V, Gee T, Bourne R, Wells G. Viscosupplementation for the treatment of osteoarthritis of the knee. Cochrane Database Syst Rev 2006; (2): CD005321.
7. Pham T, van der Heijde D, Altman RD, et al. OMERACT-OARSI initiative: Osteoarthritis Research Society International set of responder criteria for osteoarthritis clinical trials revisited. Osteoarthritis Cartilage 2004; 12(5): 389-99.
8. Raynauld JP, Torrance GW, Band PA, et al. A prospective, randomized, pragmatic, health outcomes trial evaluating the incorporation of hylan G-F 20 into the treatment paradigm for patients with knee osteoarthritis (Part 1 of 2): clinical results. Osteoarthritis Cartilage 2002; 10(7): 506-17.
9. Kahan A, Lleu PL, Salin L. Prospective randomized study comparing the medicoeconomic benefits of Hylan GF-20 vs. conventional treatment in knee osteoarthritis. Joint Bone Spine 2003; 70(4): 276-81.
10. Altman R, Lim S, Steen RG, Dasa V. Hyaluronic Acid Injections Are Associated with Delay of Total Knee Replacement Surgery in Patients with Knee Osteoarthritis: Evidence from a Large U.S. Health Claims Database. PloS one 2015; 10(12): e0145776.
11. Haynes B. Can it work? Does it work? Is it worth it? The testing of healthcareinterventions is evolving. BMJ 1999; 319(7211): 652-3.
12. Marley J. Efficacy, effectiveness, efficiency. Aust Prescr 2000; (23): 114-5.
13. Hermans J, Reijman M, Goossens LM, Verburg H, Bierma-Zeinstra SM, Koopmanschap MA. A cost utility analysis of high molecular weight hyaluronic acid for knee osteoarthritis in everyday clinical care in patients in the working age. An economic evaluation of a randomized clinical trial. Arthritis Care Res (Hoboken) 2017.
14. Zwaap J, Knies S, Van der Meijden C, Staal P, Van der Heiden L. Kosteneffectiviteit in praktijk [cost-effectiveness in practice]. Zorginstituut Nederland [Dutch Healthcare Institute]; 2015.
15. Mathers. C SS. WHO methods and data sources for global burden of disease estimates 2000-2011. In: Systems DoHSaI, editor. Geneva: World Health Organization; 2013.

16. Torrance GW, Raynauld JP, Walker V, et al. A prospective, randomized, pragmatic, health outcomes trial evaluating the incorporation of hylan G-F 20 into the treatment paradigm for patients with knee osteoarthritis (Part 2 of 2): economic results. Osteoarthritis Cartilage 2002; 10(7): 518-27.
17. Salmon JH, Rat AC, Charlot-Lambrecht I, Eschard JP, Jolly D, Fautrel B. Cost Effectiveness of Intra-Articular Hyaluronic Acid and Disease-Modifying Drugs in Knee Osteoarthritis. Pharmacoeconomics 2018; 36(11): 1321-31.
18. Li X, Gignac MA, Anis AH. The indirect costs of arthritis resulting from unemployment, reduced performance, and occupational changes while at work. Med Care 2006; 44(4): 304-10.
19. Stewart WF, Ricci JA, Chee E, Morganstein D, Lipton R. Lost productive time and cost due to common pain conditions in the US workforce. Jama 2003; 290(18): 2443-54.
20. van den Heuvel SG, Ijmker S, Blatter BM, de Korte EM. Loss of productivity due to neck/shoulder symptoms and hand/arm symptoms: results from the PROMO-study. J Occup Rehabil 2007; 17(3): 370-82.
21. Zwaap J. Pakketadvies in de praktijk. Wikken en wegen voor een rechtvaardig pakket. Zorginstituut Nederland; 2017.
22. Hyaluronzuur injecties bij artrose van de knie. Zorginstituut Nederland; 2018.
23. FMS (Federation of Medical Specialists). Richtlijn conservatieve behandeling van artrose in heup of knie (guideline for non-operative treatment of ostoarthritis of hip or knee). 2018.
24. Brouwer RWM, L.N. De Waal Malefijt, P.A. Nolte, P.A. Van Hellemondt, G.G. NOV standpunt: Hyaluronzuur injecties bij artrose van de knie. In: Society DK, editor.; 2013.
25. Altman RD, Schemitsch E, Bedi A. Assessment of clinical practice guideline methodology for the treatment of knee osteoarthritis with intra-articular hyaluronic acid. Semin Arthritis Rheum 2015; 45(2): 132-9.
26. Nelson AE, Allen KD, Golightly YM, Goode AP, Jordan JM. A systematic review of recommendations and guidelines for the management of osteoarthritis: The chronic osteoarthritis management initiative of the U.S. bone and joint initiative. Semin Arthritis Rheum 2014; 43(6): 701-12.
27. Bannuru RR, Osani MC, Vaysbrot EE, et al. OARSI guidelines for the non-surgical management of knee, hip, and polyarticular osteoarthritis. Osteoarthritis Cartilage 2019; 27(11): 1578-89.
28. Kolasinski SL, Neogi T, Hochberg MC, et al. 2019 American College of Rheumatology/Arthritis Foundation Guideline for the Management of Osteoarthritis of the Hand, Hip, and Knee. Arthritis & rheumatology 2020; 72(2): 220-33.
29. Belo JNB-Z, S.M.A. Kuijpers, T. Opstelten, W. Van den Donk, M. Weisscher P.J. Wildervanck-Dekker, C.M.J. NHG-Standaard Niet-traumatische knieklachten. In: Genootschap NH, editor.; 2016.
30. Zhang W, Doherty M. Efficacy paradox and proportional contextual effect (PCE). Clinical immunology 2018; 186: 82-6.

31. Walach H. The efficacy paradox in randomized controlled trials of CAM and elsewhere: beware of the placebo trap. Journal of alternative and complementary medicine 2001; 7(3): 213-8.
32. McCarney R, Warner J, Iliffe S, van Haselen R, Griffin M, Fisher P. The Hawthorne Effect: a randomised, controlled trial. BMC medical research methodology 2007; 7: 30.
33. Boeriu CG, Springer J, Kooy FKL, Van den Broek LAM, Eggink G. Production Methods for Hyaluronan. International Journal of Carbohydrate Chemistry 2013: 14.
34. Bannuru RR, Osani M, Vaysbrot EE, McAlindon TE. Comparative safety profile of hyaluronic acid products for knee osteoarthritis: a systematic review and network meta-analysis. Osteoarthritis Cartilage 2016; 24(12): 2022-41.
35. Altman RD, Bedi A, Karlsson J, Sancheti P, Schemitsch E. Product Differences in Intra-articular Hyaluronic Acids for Osteoarthritis of the Knee. Am J Sports Med 2015.
36. Reichenbach S, Blank S, Rutjes AW, et al. Hylan versus hyaluronic acid for osteoarthritis of the knee: a systematic review and meta-analysis. Arthritis Rheum 2007; 57(8): 1410-8.
37. Cooper C, Rannou F, Richette P, et al. Use of Intraarticular Hyaluronic Acid in the Management of Knee Osteoarthritis in Clinical Practice. Arthritis Care Res (Hoboken) 2017; 69(9): 1287-96.
38. Lo GH, LaValley M, McAlindon T, Felson DT. Intra-articular hyaluronic acid in treatment of knee osteoarthritis: a meta-analysis. Jama 2003; 290(23): 3115-21.
39. Bannuru RR, Schmid CH, Kent DM, Vaysbrot EE, Wong JB, McAlindon TE. Comparative effectiveness of pharmacologic interventions for knee osteoarthritis: a systematic review and network meta-analysis. Ann Intern Med 2015; 162(1): 46-54.
40. Campbell KA, Erickson BJ, Saltzman BM, et al. Is Local Viscosupplementation Injection Clinically Superior to Other Therapies in the Treatment of Osteoarthritis of the Knee: A Systematic Review of Overlapping Meta-analyses. Arthroscopy : the journal of arthroscopic & related surgery : official publication of the Arthroscopy Association of North America and the International Arthroscopy Association 2015; 31(10): 2036-45 e14.
41. Coupe VM, Veenhof C, van Tulder MW, Dekker J, Bijlsma JW, Van den Ende CH. The cost effectiveness of behavioural graded activity in patients with osteoarthritis of hip and/or knee. Ann Rheum Dis 2007; 66(2): 215-21.
42. Abbott JH, Wilson R, Pinto D, Chapple CM, Wright AA, team MOAT. Incremental clinical effectiveness and cost effectiveness of providing supervised physiotherapy in addition to usual medical care in patients with osteoarthritis of the hip or knee: 2-year results of the MOA randomised controlled trial. Osteoarthritis Cartilage 2019; 27(3): 424-34.
43. Pinto D, Robertson MC, Hansen P, Abbott JH. Cost-effectiveness of nonpharmacologic, nonsurgical interventions for hip and/or knee osteoarthritis: systematic review. Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research 2012; 15(1): 1-12.
44. Woods B, Manca A, Weatherly H, et al. Cost-effectiveness of adjunct non-pharmacological interventions for osteoarthritis of the knee. PloS one 2017; 12(3): e0172749.
45. Maheu E, Rannou F, Reginster JY. Efficacy and safety of hyaluronic acid in the management of osteoarthritis: Evidence from real-life setting trials and surveys. Semin Arthritis Rheum 2016; 45(4 Suppl): S28-33.

46. Altman RD, Farrokhyar F, Fierlinger A, Niazi F, Rosen J. Analysis for Prognostic Factors from a Database for the Intra-Articular Hyaluronic Acid (Euflexxa) Treatment for Osteoarthritis of the Knee. Cartilage 2016; 7(3): 229-37.
47. Eymard F, Chevalier X, Conrozier T. Obesity and radiological severity are associated with viscosupplementation failure in patients with knee osteoarthritis. Journal of orthopaedic research : official publication of the Orthopaedic Research Society 2017; 35(10): 2269-74.
48. Conrozier T, Eymard F, Chouk M, Chevalier X. Impact of obesity, structural severity and their combination on the efficacy of viscosupplementation in patients with knee osteoarthritis. BMC Musculoskelet Disord 2019; 20(1): 376.
49. Bastick AN, Runhaar J, Belo JN, Bierma-Zeinstra SM. Prognostic factors for progression of clinical osteoarthritis of the knee: a systematic review of observational studies. Arthritis Res Ther 2015; 17: 152.
50. Bhadra AK, Altman R, Dasa V, et al. Appropriate Use Criteria for Hyaluronic Acid in the Treatment of Knee Osteoarthritis in the United States. Cartilage 2017; 8(3): 234-54.
51. Zuidgeest MGP, Goetz I, Groenwold RHH, et al. Series: Pragmatic trials and real world evidence: Paper 1. Introduction. Journal of clinical epidemiology 2017; 88: 7-13.
52. van Linschoten R, van Middelkoop M, Berger MY, et al. The PEX study - Exercise therapy for patellofemoral pain syndrome: design of a randomized clinical trial in general practice and sports medicine [ISRCTN83938749]. BMC Musculoskelet Disord 2006; 7: 31.
53. Teirlinck CH, Luijsterburg PA, Dekker J, et al. Effectiveness of exercise therapy added to general practitioner care in patients with hip osteoarthritis: a pragmatic randomized controlled trial. Osteoarthritis Cartilage 2016; 24(1): 82-90.
54. Tan SS, van Linschoten RL, van Middelkoop M, Koes BW, Bierma-Zeinstra SM, Koopmanschap MA. Cost-utility of exercise therapy in adolescents and young adults suffering from the patellofemoral pain syndrome. Scand J Med Sci Sports 2010; 20(4): 568-79.
55. Tan SS, Teirlinck CH, Dekker J, et al. Cost-utility of exercise therapy in patients with hip osteoarthritis in primary care. Osteoarthritis Cartilage 2015.
56. Ramsey SD, Willke RJ, Glick H, et al. Cost-effectiveness analysis alongside clinical trials II-An ISPOR Good Research Practices Task Force report. Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research 2015; 18(2): 161-72.
57. Schofield D, Cunich M, Shrestha RN, et al. The long-term economic impacts of arthritis through lost productive life years: results from an Australian microsimulation model. BMC public health 2018; 18(1): 654.
58. Schofield DJ, Shrestha RN, Percival R, Passey ME, Callander EJ, Kelly SJ. The personal and national costs of lost labour force participation due to arthritis: an economic study. BMC public health 2013; 13: 188.
59. Bannuru RR, Natov NS, Dasi UR, Schmid CH, McAlindon TE. Therapeutic trajectory following intra-articular hyaluronic acid injection in knee osteoarthritis--meta-analysis. Osteoarthritis Cartilage 2011; 19(6): 611-9.
60. Riley RD, Lambert PC, Abo-Zaid G. Meta-analysis of individual participant data: rationale, conduct, and reporting. BMJ 2010; 340: c221.





Summary
Nederlandse samenvatting
(summary, in Dutch)
Dankwoord
(acknowledgments, in Dutch)
Curriculum Vitae
PhD portfolio
List of publications

Summary

Osteoarthritis (OA) is a chronic disease of the knee joint, causing pain, joint stiffness and functional impairment. Next to health impairment, OA results in serious economic consequences. Knee OA accounts for the vast majority of the burden of disease of OA. The treatment of knee OA is symptomatic. One of the non-surgical treatment modalities for knee OA is intra-articular injection therapy with hyaluronic acid (HA), which leads to pain reduction and improvement of knee function. This thesis focuses on various aspects of the effectiveness as well as the efficiency of intra-articular HA as a non-surgical treatment modality for patients with knee OA.

In **chapter 2** we present the results of a systematic review on the accuracy of different approaches for intra-articular injections in the knee joint. We systematically reviewed the literature and assessed the possible risk of bias of the 9 included studies. The analyses show that superolateral injection approach with the leg in extension was resulted in the highest pooled accuracy of 91%. Approaches like the lateral midpatellar approach, the anterolateral approach and the anteromedial approach resulted in the lowest pooled accuracy rates. We conclude that for a blindly performed intra-articular needle placement in the knee joint, the superolateral approach should be the approach of choice. Since this approach still results in a substantial amount of extra-articular needle placements, guidance by imaging techniques during the injection procedure may enhance the accuracy.

In **chapter 3** we present the results of a cross-sectional study in which aimed to identify and quantify the productivity costs and medical costs in knee OA patients with a paid employment. We investigated the possible associations between productivity losses and various patient, health, and work characteristics.

The investigated study subjects participated in a randomized controlled trial (RCT) investigating the effectiveness and cost-effectiveness of intra-articular hyaluronic acid in addition to usual care: the VISK study. Non-surgically treated patients with mild to moderate knee OA and aged 18-65 years were included in this RCT. The included study subjects in this cross-sectional study consisted of the patients of the RCT that were involved in paid employment. We analyzed the data acquired from the baseline measurement of this RCT that referred to the previous 3 months, before the onset of any trial

intervention. In total, 117 patients of the included patients of the VISK study were involved in paid employment at the time of inclusion. We show that the total knee-related productivity costs and medical costs were €871 per patient per month, of which the total productivity costs were €722 and the total medical costs were €149. The analyses show that reduced productivity while being present at work was responsible for the majority (of the productivity costs. Performing physically intensive work and experiencing more pain during activity were significantly associated with the productivity losses. We conclude that the total knee-related productivity costs and medical costs of conservatively treated symptomatic knee OA patients with paid employment in The Netherlands are €871 per patient per month, of which the productivity costs account for 83% and the medical costs for 17% of these total costs.

To investigate the effectiveness and the cost-effectiveness of intra-articular HA in the non-surgical treatment regime of knee OA the VISK study was designed. In this open-labelled RCT, patients between 18 and 65 with mild to moderate symptomatic knee OA were randomized to either the intervention group, who received 3 weekly injections with a high molecular weight (HMW) HA derivative added to the usual non-surgical care for knee OA, or in the control group who received the usual care only. In total, 156 study subjects were included in the VISK study, of which 77 were randomized to the intervention group and 79 to the control group.

In **chapter 4** the clinical effectiveness results of the VISK study are presented. The primary clinical outcome parameters were defined as response to therapy at 52 weeks follow-up according to OMERACT-OARSI criteria. This is a variable in which the results of changes after treatment in three symptomatic domains (pain, function, and patient global assessment (PGA)) are combined to a single variable. The secondary outcome comprised the between group difference on the individual responder domains pain, function and PGA. The results show that adding intra-articular HA to the usual care for knee OA leads to significantly more responders to therapy compared to usual care only. In the intervention group 57.1% was responder to therapy versus 34.2% in the control group when pain during activity included in the responder domains, and 54.5% versus 34.2% when pain during rest was included in the responder domains. The results of the secondary outcome analyses show that the scores on individual responder domains over all follow-up moments

were statistically significant in favour of the intervention group in the domains pain during rest, knee related function and PGA. Based on these results we conclude that intra-articular HMW-HA added to usual care is an effective treatment strategy for knee OA patients in the working age.

In **chapter 5** the results of the economic evaluation of the VISK study are presented. We performed a cost-utility analysis over 52 weeks follow-up in order to determine the cost-effectiveness of intra-articular HA added to the usual non-surgical care for knee OA patients. The primary health economic outcome was determined by the between group difference in quality-adjusted life years (QALYs) and costs. To determine the amount of QALYs the area under the curve of the quality of life scores as measured by the EuroQol questionnaire over 52 weeks was calculated. The between group differences in costs and QALYs were expressed in a so-called cost-effectiveness ratio (ICER). This ratio is interpreted as the additional costs per gained QALY due to the addition of intra-articular HA to the usual care. Given various thresholds for the maximum willingness to pay for 1 QALY gained, the probability of cost-effectiveness of intra-articular HA therapy for knee OA was indicated on an acceptability curve. The results show that the total of productivity and medical costs was €475 higher in the intervention group. The intervention group gained more QUALYs during follow-up compared to the control group (0.779 versus 0.727). This resulted in an ICER of €9.100/QALY from a societal perspective (productivity costs and medical costs included) and €8.700/QALY from a health care perspective (only medical costs included). When the maximum willingness to pay for conditions similar to knee OA is considered, the probability on cost-effectiveness of the addition of intra-articular HA to usual care is 64% from the societal perspective and 86% from the healthcare perspective. We conclude that the treatment with intraarticular HMW-HA in knee OA patients in their working years is probably cost-effective for the Dutch health care situation.

In **chapter 6** we report on the results of a systematic review and meta-analysis on the adverse events (AE) of intra-articular treatment with HA for knee OA. We investigated the difference in local AEs, non-local AEs and study withdrawal in subjects treated with intra-articular HA for knee OA compared to their controls. Subsequently, we investigated the association with specific HA-product characteristics and the number of injections administered in

case of a statistically significant difference. The analyses of the 33 included articles show that treatment with intra-articular HA for knee OA results in more local AEs like flares or flare like symptoms, compared to placebo. It does not result in more non-local AEs or more study withdrawals. The higher risk on local AEs is associated with the use of non-crosslinked HA-products and products with a lower molecular weight.

Chapter 7 discusses the main findings of the research in this thesis. We discuss the possible implications of the VISK study results in relation to current clinical treatment guidelines for knee OA the current advise on reimbursement of intra-articular HA for the treatment of knee OA. The limitations of the presented research in this thesis are addressed. Implications from a clinical as well as from a health-economic point of view are discussed as well as possible directions for future research.

Nederlandse samenvatting

Artrose is een chronische ziekte van het kniegewricht die pijn, stijfheid en belemmeringen in het functioneren veroorzaakt. Naast gezondheidsklachten heeft artrose ook forse economische consequenties. Van alle gewrichten geeft artrose van de knie de grootste ziektelast. De behandeling van knieartrose is symptomatisch. Eén van de conservatieve behandelopties voor artrose is intra-articulaire injecties met hyaluronzuur (HA). Deze behandeling wordt gegeven ter vermindering van pijn en verbetering van de functie van de knie. Dit proefschrift focust op diverse aspecten van zowel effectiviteit als doelmatigheid van intra-articulaire injecties met HA als behandelmodaliteit voor patiënten met knieartrose.

In **hoofdstuk 2** worden de resultaten van een systematische review gepresenteerd over de accuratesse van verschillende benaderingen van intra-articulaire injecties in het kniegewricht. Middels een systematische zoekactie werd in de verschillende databases gezocht naar geschikte wetenschappelijke publicaties. Het mogelijke risico op vertekening van de onderzoeksresultaten van de 9 geïncludeerde studies werd beoordeeld. De analyses laten zien dat de superolaterale injectie benadering met het been gestrekt de hoogste gepoolde accuratesse van 91% opleverde. Benaderingen zoals midpatellair, anterolateraal en anteromediaal resulteerden in de laagste gepoolde accuratesse. We hebben geconcludeerd dat de superolaterale benadering voor een intra-articulaire injectie in de knie de benadering van keuze is. Omdat bij deze benadering nog steeds 9% van de injecties buiten het kniegewricht terecht komt kan het gebruik van beeldvormende technieken tijdens de procedure mogelijk de accuratesse verhogen.

In **hoofdstuk 3** presenteren we de resultaten van een cross-sectionele studie waarin we productiviteitskosten en medische kosten van knieartrose patiënten hebben geïdentificeerd en gekwantificeerd. We onderzochten de mogelijke associaties tussen dit verlies van productiviteit en verschillende karakteristieken van de patiënten zelf, hun gezondheid en het werk. De onderzochte studiepopulatie was onderdeel van een gerandomiseerd en gecontroleerd onderzoek (RCT) waarin de effectiviteit en kosteneffectiviteit van intra-articulair HA toegevoegd aan de standaard zorg werd onderzocht: de VISK studie. Conservatief behandelde patiënten met milde tot matige knieartrose in de leeftijd van 18-65 jaar namen deel aan deze studie.

De geïncludeerde patiënten in het cross-sectionele onderzoek waren deelnemers aan de VISK-studie met een betaalde baan. We hebben de data van de nulmeting van de VISK-studie geanalyseerd in deze groep. Deze data gaf de situatie weer van de periode van 3 maanden vóór de nulmeting tot aan de nulmeting zelf. De geïncludeerde deelnemers namen in die periode nog niet actief deel aan de VISK studie. In totaal hadden 117 van de 156 deelnemers aan de VISK studie een betaalde baan en werden geïncludeerd in de huidige studie. Uit de metingen blijkt dat het totaal aan knie gerelateerde productiviteitskosten en medische kosten €871 per werkende deelnemer per maand bedraagt. De productiviteitskosten bedroegen €722 en de medische kosten bedroegen €149. Uit de analyses blijkt dat de verminderde productiviteit op het werk verantwoordelijk is voor de meerderheid van de productiviteitskosten. Het hebben van fysiek zwaar werk en het hebben van meer pijnklachten tijdens activiteiten waren statistisch significant geassocieerd met productiviteitsverlies. We hebben geconcludeerd dat het totaal aan knie gerelateerde productiviteitskosten en medische kosten van werkende conservatief behandelde knieartrose patiënten in Nederland €871 per patiënt per maand bedraagt. Deze kosten bestaan voor 83% uit productiviteitskosten en voor 17% uit medische kosten.

De VISK-studie is ontworpen om de effectiviteit en efficiëntie van intra-articulair hyaluronzuur in het niet-operatieve behandeltraject van knieartrose te onderzoeken. In dit open-label gerandomiseerde onderzoek werden patiënten tussen de 18 en 65 jaar met milde tot matige knieartrose gerandomiseerd in de interventie groep of de controle groep. De interventiegroep kreeg 3 wekelijkse injecties met een hoog moleculair gewicht (HMW) HA preparaat toegevoegd aan de gebruikelijke niet-operatieve zorg voor knieartrose. De controle groep kreeg alleen de gebruikelijke niet-operatieve zorg. In totaal werden 156 patiënten geïncludeerd in de VISK studie, waarvan 77 patiënten gerandomiseerd werden in de interventie groep en 79 patiënten in de controle groep.

In **hoofdstuk 4** worden de resultaten van de VISK studie gepresenteerd met betrekking tot de effectiviteit. De primaire klinische uitkomst parameter werd gedefinieerd als de zogeheten 'respons op behandeling' na de volgperiode van 52 weken, conform de OMERACT-OARSI criteria. In deze uitkomst parameter worden de resultaten van uitkomsten op 3 symptomatische domeinen (pijn,

functie, globale patiënten beoordeling (PGA)) gecombineerd tot 1 variabele. De secundaire klinische uitkomstmaten bestaan uit het verschil tussen de randomisatiegroepen in de individuele respons domeinen pijn, functie en PGA. Uit de resultaten blijkt dat het toevoegen van intra-articulair HA aan de gebruikelijke zorg voor knieartrose leidt tot statistisch significant meer respons op de behandeling. Wanneer pijn gedurende activiteit in de respons domeinen was opgenomen, was 57.1% van de patiënten in de interventiegroep respondent na de behandeling versus 34.2% van de patiënten in de controle groep. Wanneer pijn in rust in de respons domeinen was opgenomen was 54.4% van de patiënten in de interventiegroep respondent na de behandeling versus 34.2% in de controlegroep. De resultaten van de secundaire analyses laten zien dat de scores op de individuele respons domeinen op alle volg momenten statistisch significant waren ten faveure van de interventiegroep in de domeinen pijn tijdens rust, knie gerelateerde functie en PGA. Op basis van deze resultaten hebben we geconcludeerd dat intra-articulair HMW-HA toegevoegd aan de gebruikelijke zorg een effectieve behandeling is voor knieartrose patiënten in de werkende leeftijd.

In **hoofdstuk 5** worden de resultaten van het economisch deel van de VISK-studie gepresenteerd. Een kosten-utiliteitsanalyse werd uitgevoerd om de kosteneffectiviteit van het toevoegen van intra-articulair HA aan de conservatieve behandeling van knieartrose te bepalen. De primaire gezondheidseconomische uitkomstmaat werd bepaald door het verschil in voor kwaliteit van leven gecorrigeerde levensjaren (QALY) en kosten tussen beide studiegroepen. Om het aantal QALY's te bepalen werd de oppervlakte onder de kromme van de grafiek van de kwaliteit van leven scores, zoals gemeten met de EuroQol vragenlijst, over 52 weken berekend. De verschillen tussen beide groepen in kosten en QALY's werden uitgedrukt in een zogeheten kosten-batenverhouding (ICER). In deze ratio komen de additionele kosten per gewonnen QALY als gevolg van de toevoeging van intra-articulair HA aan de gebruikelijke behandeling tot uiting. Op basis van verschillende drempelwaardes van betalingsbereidheid voor 1 gewonnen QALY werd de mate van waarschijnlijkheid van kosteneffectiviteit van intra-articulaire therapie met HA uiteengezet in een aanvaardbaarheidscurve. Uit de resultaten blijkt dat het totaal van productiviteitskosten en medische kosten €475 hoger was in de interventiegroep. In de interventiegroep werden meer QALY's gewonnen

in vergelijking met de controlegroep (0.779 versus 0.727). Dit resulteerde in een ICER van €9.100/QALY vanuit het maatschappelijk perspectief (productiviteitskosten en medische kosten meegenomen) en €8.700/QALY vanuit het medisch perspectief (alleen medische kosten meegenomen). Wanneer de betalingsbereidheid voor aandoeningen vergelijkbaar met knieartrose wordt beschouwd dan is de waarschijnlijkheid van kosteneffectiviteit van de toevoeging van intra-articulair HA aan de gebruikelijke zorg vanuit een maatschappelijk perspectief 64% en vanuit een medisch perspectief 86%. We concludeerden dat de behandeling met intra-articulair HMW-HA in knieartrose patiënten in de werkende leeftijd waarschijnlijk kosteneffectief is binnen de Nederlandse gezondheidszorg situatie.

In **hoofdstuk 6** presenteren we de resultaten van een systematisch review en meta-analyse over de bijwerkingen van intra-articulaire behandeling van knieartrose met HA. Alleen placebo-gecontroleerde studies werden geïncludeerd. We onderzochten de verschillen in lokale bijwerkingen en systemische bijwerkingen in studiedeelnemers die behandeld werden met intra-articulair HA en vergeleken dit met de controlegroepen. We onderzochten tevens de verschillen tussen beide groepen in het aantal deelnemers dat de studiedeelname staakte. Wanneer een verschil statistisch significant was, onderzochten we vervolgens de associatie met specifieke productkarakteristieken van HA en het aantal toegediende injecties met HA. De analyses van de 33 geïncludeerde studies laten zien dat behandeling van knieartrose met intra-articulair HA resulteert in een statistisch significant hoger risico op meestal kortdurende opvlammingen van knieklachten zoals pijn, stijfheid en zwelling in vergelijking met placebo (risico ratio (RR) 1.26, p=0.001). Er is geen statistisch significant hoger risico op systemische bijwerkingen of op het vaker stoppen van studiedeelname door deelnemers. Uit de multivariate analyses blijkt dat het hogere risico op lokale bijwerkingen statistisch significant is geassocieerd met het gebruik van HA producten zonder moleculaire kruisverbinding (RR 3.93, P<0.001) en producten met een lager molecuulgewicht (RR 1.08, P<0.001). We concludeerden dat intra-articulair HA in de behandeling van knieartrose leidt tot een hoger risico op lokale bijwerkingen en dat dit risico geassocieerd is met het toedienen van HA producten zonder moleculaire kruisverbinding en producten met een lager molecuulgewicht.

In **hoofdstuk 7** worden de belangrijkste bevindingen van dit proefschrift besproken. De mogelijke implicaties van de VISK-studie resultaten voor de huidige behandelrichtlijnen voor knieartrose worden besproken evenals voor het huidige vergoedingsbeleid van intra-articulair HA voor de behandeling van knieartrose. De beperkingen van de gepresenteerde onderzoeksresultaten worden besproken. Implicaties vanuit klinisch en vanuit gezondheidseconomisch oogpunt worden aangegeven en tevens worden mogelijkheden voor toekomstig onderzoek besproken.

Dankwoord

Een proefschrift voltooien is teamwork, en de aanhouder wint (in dit geval). Dit proefschrift was er niet geweest zonder de hulp van velen die ik dankbaar ben voor hun bijdrage op welke manier dan ook. Een aantal van hen wil ik in het bijzonder hiervoor bedanken.

Mijn promotoren, prof. dr. J.A.N. Verhaar en prof. dr. S.M.A. Bierma-Zeinstra. Beste Jan, door een scherpe blik en een brede kennis van zaken op zowel wetenschappelijk als klinisch gebied heb ik veel van je kunnen leren. Dank voor de kansen en het vertrouwen tijdens het onderzoek en tijdens de opleiding. Dank ook voor de goede gesprekken en de adviezen bij de keuze om juist te stoppen met diezelfde opleiding. Opleiden is mensenwerk, ook in dat stuk. Ik heb dat zeer gewaardeerd.

Beste Sita, als er iemand inhoudsdeskundig is op het gebied van de conservatieve behandeling van artrose ben jij het. Dank voor je begeleiding, je kennis van zaken en de kunst van het pragmatisch omgaan met alles waar een promovendus zoal tegen aan loopt in onderzoeksland. Dank ook voor de gezelligheid en het laagdrempelige contact. Het is prettig om op deze manier te kunnen samenwerken.

Mijn co-promotor, dr. M. Reijman. Beste Max, waar het ooit begon met een afstudeeronderzoek werd het daarna een compleet promotietraject. Inmiddels kennen we elkaar al heel wat jaren. Je bent een betrokken begeleider en een betrokken co-promotor. Altijd op de hoogte van waar we (moeten) staan en altijd bereid tot advies en ondersteuning. Ik heb op wetenschappelijk gebied veel van je geleerd. Gezelligheid kent geen tijd en met z'n allen uit eten en wijntjes drinken maakte het werk een stuk leuker.

Mijn klinisch begeleider tijdens het onderzoek en destijds plaatsvervangend opleider, dr. P.K. Bos. Beste Koen, dank je wel voor de ondersteuning en de klinische blik op het reilen en zeilen van de VISK studie. Het was nooit een probleem om tussen de poli's door de hyaluronzuur injecties toe te dienen aan de VISK-studie deelnemers. Daar was geen discussie over, dat hoorde er gewoon bij. Tijdens de opleiding was er altijd tijd voor uitleg en bij het stoppen met de opleiding was er begrip en ondersteuning waar nodig. Dat heb ik gewaardeerd.

De VISK studie was niet van de grond gekomen zonder de orthopeden en de assistenten van het Erasmus MC en het Reinier de Graaf Gasthuis. Een

klinische studie starten is één ding, maar voldoende mensen includeren op 2 locaties is toch echt iets anders. Dank jullie wel voor het aandragen van alle potentiele deelnemers. Zonder jullie hulp had ik niet de benodigde aantallen kunnen halen binnen het jaar.
Rien, fijn dat je met Koen bereid was om de VISK-deelnemers in het Erasmus MC van hun injecties te voorzien. Hennie, Dieu Donne dank dat jullie dit in het Reinier wilden doen. Dat heeft de logistiek echt een stuk makkelijker gemaakt. Joost, soms ging de planning anders dan bedacht maar moesten de deelnemers toch een injectie krijgen. Fijn dat ik op die dagen kon aankloppen op de polideur.
Aan de orthopeden en assistenten van het Reinier: het was een warm welkom in Delft. Zoals gezegd, een multicenter trial is soms best uitdagend qua planning en organisatie. Jullie hebben er voor gezorgd dat de faciliteiten in orde waren, alles goed geregeld was en ik wekelijks met plezier op de racefiets naar Delft ging.
Dokters weten over het algemeen maar weinig van kosten in de gezondheidszorg. Behalve dat het allemaal te duur is. Dan is het prettig dat er mensen zijn die daar veel verstand van hebben, zeker als het hoofdonderwerp van het promotieonderzoek een doelmatigheidsstudie betreft.
In dit kader wil ik dan ook heel graag de mensen van het IMTA bedanken, met in het bijzonder Marc Koopmanschap en Lucas Goossens. Zonder hen hadden we niet tot deze resultaten kunnen komen.
Marc, dank je wel voor alle begeleiding tijdens het onderzoek, de overleggen, de uitleg, de colleges tijdens Health Technology Assessment (ik voelde me weer helemaal student) en je deskundige blik op het kosteneffectiviteitsdeel van de VISK studie. Het is uiteindelijk een prachtig artikel geworden. Lucas, Marc en ik hebben aardig zitten worstelen met hoe om te gaan met de verschillen op baseline die een enorme invloed op de resultaten bleken te hebben. Dank voor de hulp daarbij en voor de analyses waarmee we toch een passende oplossing hebben kunnen vinden.
Onderzoek doen en artikelen schrijven gaat niet vanzelf en doe je meestal ook niet alleen. Veel co-auteurs zijn in dit dankwoord al aan bod gekomen. Een daarvan is dat nog niet en die wil ik zeker niet onbenoemd laten. Prof. dr. ir. A. Burdorf, beste Lex, dank voor de goede ideeën, de begeleiding en de hulp bij de analyses in het artikel over de kosten bij mensen met knie artrose.

Veel dank ook aan de collega's met wie tijdens het onderzoek veel ben opgetrokken. De orthopaedie onderzoekers van Hs-104 en de bovenburen van het lab, Maaike, Belle, Vincent, Thijs, Desiree, Karin, Eline, Guus, Jasper, Michiel, Rintje. Dank voor de lol, de (slechte) grappen, de steun in barre onderzoekstijden en vooral voor de gezelligheid. Zo werd onderzoek doen een stuk leuker. De collega's van de huisartsgeneeskunde met wie het altijd goed koffiedrinken was. Dieuwke en Jos, dank voor de gezelligheid. Erwin, het waren altijd interessante gesprekken. Dank voor de hulp bij de laatste analyses van de laatste review. Pim, zonder de logistieke database had niemand van de VISK-studie zijn vragenlijst gekregen, en al helemaal niet ingevuld en terug gestuurd. Dank je wel voor het helpen bij het bouwen ervan. Marienke, vroeger werden ingevulde vragenlijsten nog gescand. Wat een klus om dat te programmeren. Dat was zonder je hulp niet gelukt. Fijn dat je ook wilde helpen met de analyses van de laatste review.

Een special thanks in dit dankwoord gaat uit naar Simone. De beste secretaresse die het ziekenhuis heeft. Altijd bereikbaar en altijd een vriendelijk antwoord op zo ongeveer alle vragen.

Promoveren gaat niet zonder mijn paranimfen, mijn goede en dierbare vrienden Selwyn en Arjan. Wat tof dat ik dit samen met jullie mag doen. Selwyn, goede gesprekken, samen eten, for good times and for worse. Ik hoop dat we dat nog heel lang zullen doen. Arjan, of we nou gaan skiën met de maten, oud en nieuw vieren in Hattem of een weekend op Eelerberg zitten met de family, het is altijd top om samen op pad te zijn.

Ik mag me verheugen in het gezelschap van vele vrienden en vriendinnen. Een aantal ken ik inmiddels langer wel dan niet. Was het vroeger tot laat in de kroeg, is het nu een drankje en op tijd naar bed. Bul, bruiloft, baby, begrafenis we hebben het allemaal wel een keer samen meegemaakt. Ik ben nog steeds dankbaar voor jullie vriendschap.

Mijn studievrienden en vriendinnen van het eerst uur, Tino, Alex, Titi en Teau. Van Maastricht naar Rotterdam naar Breda en alles wat daar bij kwam kijken. Jullie waren er altijd.

De mannen van Dolgedraaid, het zijn er velen, Van der Horst, Maasdam, Van L, Reitsma, Spitzen, Meenink, Van Wijk en alle anderen. Het leven in Rotterdam werd een stuk gezelliger met jullie. Wat mooi dat we elkaar nog vaak zien.

De mannen van de hockey, Guy, Pino, Björn, Nelis, Ab, Korsten en JM. Het

niveau op het veld was niet altijd even hoog, en aan de bar overigens ook niet, maar het blijft gezellig samen!
De mannen van RT21, door wie Breda veranderde van de stad waar mijn huis staat naar de plek waar mijn thuis is.
Mijn huidige werkgever UWV wil ik hier niet onbenoemd laten. Ik heb in de afgelopen jaren veel ruimte, faciliteiten en gelegenheid gekregen voor opleiding en persoonlijke ontwikkeling. Een aantal mensen heeft hier elk op hun eigen wijze aan bijgedragen, waaronder mijn huidige en vorige manager Petra en Esther, mijn opleider Karin en de collega's (verzekerings-)artsen. Veel dank daarvoor.
Het is fijn om te beseffen dat wat je ook doet, je familie achter je staat. Mam, fijn dat je met Ger altijd voor ons hebt gezorgd. Het Pietje Precies en het moet allemaal wel netjes heb ik toch echt niet van een vreemde. Pa, kwaliteit komt nooit vanzelf tot stand, het is meestal het gevolg van intelligente inspanning. Ik hoor het mezelf nog vaak denken. Dat we nog maar vaak samen mogen klussen. Corry, dank voor alle hartelijkheid en goede zorgen. Floor, lieve zus, bij wie de deur altijd open staat en bij wie ik altijd welkom ben, dank je wel.
Lieve Pam, het is er dan toch echt van gekomen. Het ging altijd wel ergens over het onderzoek of over de opleiding. De laptop op vakantie toch iedere keer maar weer mee in de tas. Je hebt alle fases van dit verhaal wel meegemaakt. Van co-schappen naar SEH, van onderzoek naar opleiding, van opleiding naar stoppen en kiezen voor een ander pad. Dank je wel voor je onvoorwaardelijke support, liefde en humor. En voor koffie bij persisterend ochtendhumeur.
Sepp, Flynn, Catootje wat is papa toch beretrots op jullie.

Curriculum Vitae

Job Hermans was born on the 15th of May in Boxmeer (The Netherlands). After high school graduation from the Kandinsky College in Nijmegen in 1999 he studied Law in Maastricht for one year, after which he began his Medicine study at the Erasmus University in Rotterdam in 2000. In 2003 he entered the board of the student association of the medical faculty (MFVR) for one year.
After receiving his Medical Degree in 2007, he started working as a physician at the Emergency Department of the Vlietland Hospital in Schiedam. In 2009 he began the PhD research project on the topic of hyaluronic acid in knee osteoarthritis at the Erasmus University Medical Center in Rotterdam, in close collaboration with the Reinier de Graaf Gasthuis in Delft. Eventually, this research project resulted in the current thesis.
Job started his specialty training in orthopaedic surgery in 2012 at the Department of General Surgery of the IJsselland Hopsital in Capelle aan den IJssel (supervisor dr. I. Dawson). He continued his training in 2013 at the Department of Orthopaedic surgery of the Erasmus University Medical Center in Rotterdam (supervisor prof. dr. J.A.N. Verhaar). In 2014 he made a career switch to the field of insurance medicine and started working as a physician at the Objection and Appeal department of UWV. He started his specialty training in insurance medicine in 2015 (supervisor drs. C.E.M. van Geest) and is now a registered insurance medicine physician since April 2020.
Job is married to Pam Hermans-Kool and together they have 3 children: Sepp, Flynn and Cato.

PhD portfolio

Name PhD student: J. Hermans
Erasmus MC Department: Orthopaedic Surgery
Promotoren: Prof. dr. S.M.A. Bierma-Zeinstra, Prof. dr. J.A.N. Verhaar
Copromotor: dr. M. Reijman

General courses / workshops	**Year**	**Workload (ECTS)**
Health Technology Assessment, EUR	2011	5
Clinical Decision Analysis, NIHES	2010	0.7
Health Economics, NIHES	2010	0.7
Basiscursus Regelgeving en Organisatie voor Klinisch onderzoekers / Good Clinical Practice	2010	1.5
Clinical trials, NIHES.	2009	0.7
Introduction to data analysis, NIHES	2009	0.7
Endnote course, Erasmus MC medical library	2009	0.1
Oral lectures		
The VISK study: effectiveness and cost-effectiveness of intra-articulair hyaluronic acid in knee osteoarthritis, a pragmatic RCT. Wetenschapsdag Orthopedie, Erasmus MC , Rotterdam, The Netherlands	2018	0.5
Methodologie van een kosteneffectiviteit studie. NOV najaarsvergadering, Veldhoven, The Netherlands	2013	1.0
The VISK study: effectiveness and cost utility of intra articular hyaluronic acid for knee osteoarthritis. NOV voorjaarsvergadering, Utrecht, The Netherlands.	2013	1.0
The VISK study: A cost utility analysis of intra articular hyaluronic acid for knee osteoarthritis. NOF congress, Talinn, Estonia	2012	1.0
The VISK study: A pragmatic randomized controlled trial for the effectiveness of intra articular hyaluronic acid for knee osteoarthritis. NOF congress, Talinn, Estonia	2012	1.0

The most accurate approach for intra-articular needle placement in the knee joint: a systematic review. EORS congress, Vienna, Austria	2011	1.0
Productivity costs and medical costs among working patients with knee osteoarthritis. NOV najaarsvergadering, Noordwijkerhout, The Netherlands,	2011	1.0
The diagnostic value of clinical tests in rotator cuff disease. Wetenschapsdag Orthopedie, Erasmus MC , Rotterdam, The Netherlands	2011	0.5
Productivity costs and medical costs in knee osteoarthritis. Opleidingsdag ROGO Rotterdam, Delft, The Netherlands	2010	0.5
Voortgang VISK studie. ZONMw projectleiders bijeenkomst doelmatigheidsonderzoek, Den Haag, 2010, The Netherlands	2010	1.0

Poster presentations

Effectiveness of hyaluronic acid in knee osteoarthritis patients using delayed gadolinium enhanced MRI of cartilage. OARSI International Workshop on Osteoarthritis Imaging, South Carolina, United States	2012	1.0
Productivity costs and medical costs among working patients with knee osteoarthritis. OARSI congress, San Diego, United States	2011	1.0
The most accurate approach for intra-articular needle placement in the knee joint: a systematic review. OARSI congress, Brussels, Belgium	2010	1.0

Teaching

The diagnostic value of clinical tests in rotator cuff disease. Teaching orthopedic surgeons and residents, Reinier de Graaf Hospital Delft, The Netherlands	2011	0.5

Accuracy of intra articular injection approaches of the knee joint: a systematic review. Teaching orthopedic surgeons, residents and researchers, Erasmus MC, Rotterdam, The Netherlands	2010	0.5
Accuracy of intra articular injection approaches of the knee joint: a systematic review. Teaching orthopedic surgeons and residents, Reinier de Graaf Hospital, Delft, The Netherlands	2010	0.5
The VISK study: cost-effectiveness of VIScosupplementation therapy for patients with osteoarthritis of the Knee, a randomized clinical trial. Teaching orthopedic surgeons, residents and researchers, Erasmus MC, Rotterdam, The Netherlands	2009	0.5
The VISK study: cost-effectiveness of VIScosupplementation therapy for patients with osteoarthritis of the Knee, a randomized clinical trial. Teaching orthopedic surgeons and residents, Reinier de Graaf Hospital, Delft, The Netherlands	2009	0.5

Other

Peer reviewing for various international medical journals	2011-2020	3.0
Interactive Module for JAMA: podcast on the clinical examination for rotator cuff disease.	2018	1.0

List of Publications

J. Hermans, H.M. de Visser, P.K. Bos, E.H. Waarsing, J.A.N. Verhaar, S.M.A. Bierma-Zeinstra, M. Reijman
The safety of hyaluronic acid in knee osteoarthritis. A systematic review and meta-analysis.
Submitted

J. Hermans, S.M.A Bierma-Zeinstra, P.K. Bos PK, D.D. Niesten DD, J.A.N. Verhaar, M Reijman
The effectiveness of high molecular weight hyaluronic acid for knee osteoarthritis in patients in the working age: a randomised controlled trial
BMC Muskuloskeletal disorders. (2019) 20:196.

J. Hermans, M. Reijman M, L.M.A. Goossens, H. Verburg H, S.M.A. Bierma-Zeinstra, M.A. Koopmanschap
Cost-utility analysis of high molecular weight hyaluronic acid for knee osteoarthritis in everyday clinical care in patients at a working age: an economic evaluation of a randomized clinical trial
Arthritis Care Res (Hoboken). 2018 Jan;70(1):89-97.

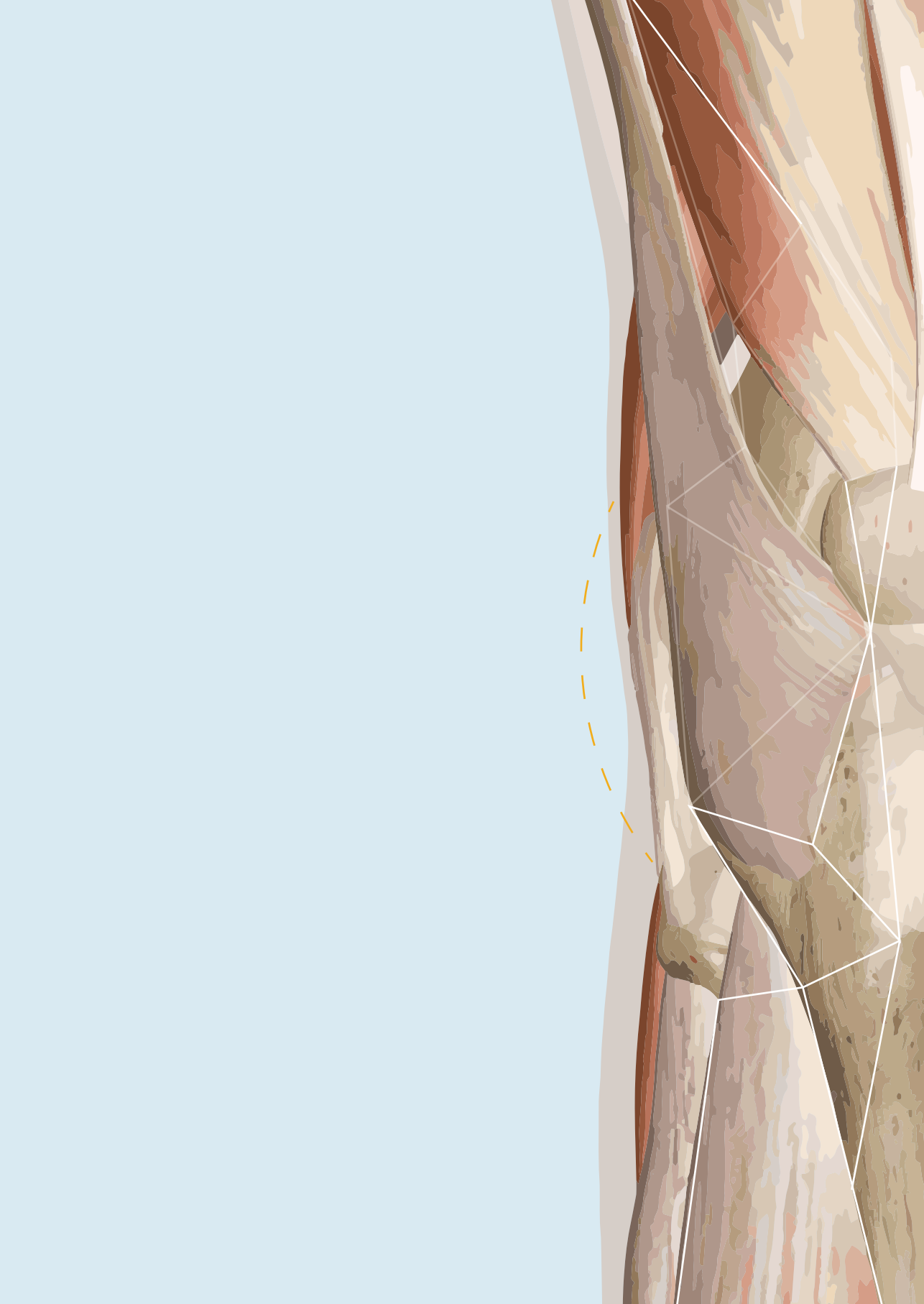
J. Hermans, J.J. Luime, D.E. Meuffels
Testing for shoulder disorders. Reply.
JAMA. 2014 Jan 1;311(1):94-5.

J. van Tiel, M. Reijman M, P.K. Bos, **J. Hermans**, G.M. van Buul, E.E. Bron, S. Klein, J.A.N. Verhaar, G.P. Krestin GP, S.M.A. Bierma-Zeinstra, H. Weinans, G. Kotek, E.H. Oei
Delayed Gadolinium-Enhanced MRI of Cartilage (dGEMRIC) shows no change in cartilage structural composition after viscosupplementation in patients with early-stage knee osteoarthritis.
PLoS One. 2013 Nov 6;8(11).

J. Hermans, J.J Luime, D.E. Meuffels, M. Reijman, D.L. Simel, S.M.A. Bierma-Zeinstra
Does this patient with shoulder pain have rotator cuff disease?: The Rational Clinical Examination systematic review.
JAMA. 2013 Aug 28;310(8):837-47.

J. Hermans, S.M.A. Bierma-Zeinstra, D.D Niesten, J.A.N. Verhaar, M. Reijman.
The VISK study: a pragmatic randomized clinical trial for the effectiveness of intra articular hyaluronic acid for knee osteoarthritis.
Osteoarthritis and Cartilage. 2013;21:S148-S149.

J. Hermans, M. Reijman M, H. Verburg H, S.M.A. Bierma-Zeinstra, M.A. Koopmanschap
The VISK study: a cost-utility analysis of intra articular hyaluronic acid for knee osteoarthritis.
Osteoarthritis and Cartilage. 2013;21:S148-S149.

J. Hermans, M.A. Koopmanschap, S.M.A Bierma-Zeinstra, J.H. van Linge, J.A.N. Verhaar, M. Reijman, A. Burdorf
Productivity costs and medical costs among working patients with knee osteoarthritis
Arthritis Care Res (Hoboken). 2012 Jun;64(6):853-61.

J. Hermans, S.M.A. Bierma-Zeinstra, P.K Bos, J.A.N. Verhaar, M. Reijman.
The most accurate approach for intra-articular needle placement in the knee joint: a systematic review.
Semin Arthritis Rheum. 2011 Oct;41(2):106-15.