Technology Assessment

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Systematic Review for Effectiveness of Hyaluronic Acid in the Treatment of Severe Degenerative Joint Disease (DJD) of the Knee

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Systematic Review for Effectiveness of Hyaluronic Acid in the Treatment of Severe Degenerative Joint Disease (DJD) of the Knee

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Systematic Review of Effectiveness of Hyaluronic Acid in the Treatment of Severe Degenerative Joint Disease (DJD) of the Knee

Structured Abstract

Purpose. The Coverage and Analysis Group at the Centers for Medicare and Medicaid Services (CMS) requested from The Technology Assessment Program (TAP) at the Agency for Healthcare Research and Quality (AHRQ), a review of the evidence that intraarticular injections of hyaluronic acid (HA) in individuals with degenerative joint disease (osteoarthritis [HA]) of the knee improve function and quality of life (QoL) and that they delay or prevent the need for total knee replacement (TKR), specifically for individuals age 65 and over.. AHRQ assigned this report to the following Evidence-based Practice Center: RAND Southern California Evidence –based Practice Center (Contract Number: HHSA290201200006I).

Data Sources. Searches of Medline, Cochrane Library, Web of Science, Clinicaltrials.gov, the FDA Premarket Approval database, and unpublished documents identified in grey literature searches or provided by manufacturers.

Review Methods. Randomized controlled trials (RCTs) or observational studies that reported on HA administration and delay or avoidance of TKR; double-blind placebo-controlled RCTs that reported on functional outcomes or QoL; RCTs, case reports, and large cohort studies and case series that assessed the safety of HA; and unpublished data identified through grey literature searches or provided by manufacturers for efficacy or safety outcomes, in human subjects of mean age 65 or older, were considered for inclusion, as were recent comprehensive systematic reviews that reported on the effects of HA injections on knee pain as an outcome. A standardized protocol with predefined criteria was used to extract details on study design, interventions, outcomes, and study quality and to analyze the data.

Results. Only one RCT reported on delay or avoidance of TKR as a pre-specified outcome of interest and found a non-statistically significantly longer delay of TKR compared with placebo; two RCTs reported TKR only as a secondary outcome; and 13 published observational studies reported on TKR as an outcome in HA-treated participants.

Eighteen RCTs that enrolled participants of average age 65 or older reported on functional outcomes of intra-articular HA injection: pooled analysis of ten sham-injection placebo-controlled, assessor-blinded trials showed a standardized mean difference of -0.23 (95% CI -0.34, -0.02) significantly favoring HA at 6 months' follow-up. Durability of effect could not be assessed because of the short duration of most studies. Too few head-to-head trials were available to assess superiority of one product over another. Three RCTs that compared changes in QoL/HRQoL between HA- and placebo-treated participants reported no differences between active treatment and placebo. Two recent large, good quality systematic reviews that conducted meta-analysis of the effects of HA on pain and function (pooling 71 and 52 RCTs for the outcome of pain, respectively) showed a significant and clinically important effect of HA on

both outcomes among adults of all ages, but a subgroup analysis that included only the largest double-blind placebo-controlled studies reduced the average effect of HA to less than the prespecified minimum clinically important difference. Studies of intra-articular HA reported few serious adverse events, with no statistically significant difference in the rates of serious or non-serious adverse events between HA- and placebo-treated groups.

Conclusions. Trials enrolling older participants show a small, statistically significant effect of HA on function and relatively few serious adverse events; however no studies limited participation to those 65 years or older. No conclusions can be drawn from the available literature on delay or avoidance of TKR through the use of HA. Studies that can compare large numbers of treated and untreated individuals, preferably with a randomized design, are needed to answer this question.

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Background

Condition

Degenerative joint disease (usually termed osteoarthritis [OA]) of the knee is a condition characterized by the progressive destruction of the articular cartilage that lines the knee joints, the subchondral bone surfaces, and synovium, accompanied by pain, immobility, and reduction in function and the ability to complete activities of daily living (ADL).

In 2005, the estimated prevalence of osteoarthritis among adults in the United States (US), the number of individuals who had ever been told by a doctor that they had the condition, was approximately 27 million cases.[1] Prevalence rates vary by the joint involved and the method of ascertainment (clinical vs. radiographic): symptomatically, the knee is the most frequently affected joint.[2] The prevalence of osteoarthritis of the knee is increasing rapidly because of shifting population demographics: The primary risk factors for osteoarthritis of the knee are aging, obesity, prior injury, repetitive use,[3] and female gender. The US Centers for Disease Control have estimated that the prevalence of symptomatic knee osteoarthritis may reach 50 percent by the age of 85.[4] From 2002 to 2012, the number of individuals in the US with a total knee replacement (TKR) doubled from some 2 million to approximately 4 million).[5] The increase in obesity has translated not only into an increase in incidence of osteoarthritis of the knee but also into a younger age of onset and need for treatment; as a result, by the time individuals with osteoarthritis of the knee reach the age of Medicare eligibility, the length of time they have had the condition has grown, their cases are more advanced,[6] and the risk that surgery will be needed has increased. Thus, the aging of the baby boomer population, along with the increased incidence and prevalence of obesity have increased the risk for this condition, all representing an increasing strain on Medicare resources.

Diagnostic Strategies

The clinical diagnosis of OA of the knee is typically based on presentation, including insidious onset of weight-bearing knee pain that is exacerbated by use of the joint and relieved by rest, and that tends to worsen over the course of the day. Radiographic evidence of OA may precede symptomatic OA but may not correlate with symptom severity. Radiologic severity can be estimated and expressed using the Kellgren and Lawrence criteria. However, a number of versions of the criteria exist: At low cutoff scores, correlation with symptoms is poor,[7] whereas at higher cutoff scores, agreement tends to be higher. The primary impact of these different versions of the criteria may be the challenge that they create in trying to assess, compare, and pool the findings of research studies:[7] Some longitudinal studies have even used different criteria at different time points within the same study. Because of the variation in scores for radiographic finding under various versions of the criteria (especially for individuals with less-advanced disease), stratification is important.

Some evidence suggests that among individuals with knee pain, MRI demonstrates physical signs of osteoarthritic changes in the knee before they are visible radiographically.[8] However, the

sensitivity and specificity of MRI in diagnosis and monitoring of progression have not yet been definitively demonstrated and is not used in routine clinical practice.

Treatment Strategies

The goals of treatment for osteoarthritis of the knee include relief of pain and inflammation, slowing of progression, and improvement in or maintenance of mobility, function (including activities of daily living [ADLs]), and health-related quality of life (HRQoL).

Treatment options for OA of the knee include analgesics (e.g., acetaminophen) and anti-inflammatory agents (non-steroidal anti-inflammatory agents [NSAIDs], intraarticular corticosteroids), physical therapy and exercise (both to strengthen muscles that support the affected joints and to increase range of motion), weight loss, and if patients fail to obtain satisfactory relief from pain and improved function from the aforementioned treatments, partial or total arthroplasty (an alternative term for knee replacement) may be recommended for advanced cases. More recent therapies include intraarticular viscosupplementation, which involves local injections of the natural joint lubricant, hyaluronic acid, among other treatments.[9]

Hyaluronic acid (hyaluronate or hyaluronan) is a high molecular weight glycosaminoglycan synthesized in plasma membranes of connective tissues and secreted into the synovial fluid surrounding joints, where it forms part of the extracellular matrix.[10] Intra-articular injection of HA was approved by the US Food and Drug Administration in 1997 as a medical device for the relief of pain due to osteoarthritis of the knee. Progressive osteoarthritis of the knee includes a decrease in, the concentration of hyaluronic acid by one half to two thirds of the normal value and a reduction the molecular size of the hyaluronic acid, lowering the viscoelastic properties of the synovial fluid.[11] Injecting hyaluronic acid intraarticularly was posited as a means to restore the viscosity of the synovial fluid; thus approval was sought for HA as a device rather than as a drug[12] (the distinction being that a device does not exert its effect via a chemical interaction with the body. A large number of trials have examined the efficacy and safety of supplemental hyaluronic acid injections, usually to relieve pain, but sometimes also to improve function in patients with OA of the knee, with varying efficacy results. Systematic reviews have attempted to resolve these conflicting findings. Some reviews have reported positive outcomes[13, 14] whereas some have reported mixed effects.[12, 15-17] A 2010 update of an earlier systematic review actually found a decrease in the effect size for hyaluronic acid on knee osteoarthritis from the previous review.[18] The discrepancies in outcomes are likely due to study heterogeneity both within and among reviews with respect to population characteristics, intervention modalities, treatment and followup duration, and the actual outcomes measured (e.g., pain, functionality, HRQoL), as well as the measures employed. Heterogeneity may also be attributable to how efficacy is expressed, i.e., the proportion of each treatment group that responds positively to treatment, vs. the mean change in that efficacy measure from baseline in the active treatment group vs. the comparison group, and whether participants are credibly blinded to treatment allocation (using an intraarticular placebo control). Table 1 in the main text describes the HA products currently approved for use in the US.

In the 2012 update to their 2000 guidelines for the treatment of osteoarthritis of the knee, hip, and hand, the American College of Rheumatology conditionally recommended hyaluronic acid injections for patients who had an inadequate response to initial therapy.[9] The 2013 American Academy of Orthopedic Surgeons guidelines for the treatment of osteoarthritis of the knee recommend against the use of hyaluronic acid to treat patients with symptomatic conditions.[19]

Assessment of Outcomes of Treatment

A number of assessment tools are used to assess pain, quality of life, and physical functioning in patients with osteoarthritis of the knee. These tools can be divided into those specifically developed for knee osteoarthritis and those that are used for a variety of conditions.

Tools specifically developed and validated to assess pain and functioning associated with osteoarthritis of the knee as well as treatment outcomes include the Western Ontario-McMaster Universities Arthritis Index (WOMAC[20]), the Lequesne Index[21], the Knee Injury and Osteoarthritis Outcomes Score (KOOS[22]), and the Animated Activity Questionnaire.[23] In 2004, the Osteoarthritis Research Society International (OARSI) developed a consensus set of guidelines to assess the outcomes of research trials on products intended to treat osteoarthritis; and under the International League of Rheumatologists, OMERACT (Outcome Measures in Rheumatology) has developed guidelines on outcome measures.[24]

General tools that have been adapted for use in assessing osteoarthritis of the knee include the Short form (SF)-36, developed at RAND for the Medical Outcomes Study[25] and the Activities of Daily Living (ADLs) and IADLs assessment.

The Kinemax Outcomes Group has used a combination of the WOMAC, the SF-36, and a series of questions addressing demographic characteristics to predict patient outcomes of total knee arthroplasty.[26]

Scope and Key Questions

The scope of work for this task order includes an assessment of the evidence that intraarticular HA injections prevent or delay the need for TKR among individuals 65 and over and that they improve function and quality of life. The Centers for Medicaid and Medicare Services (CMS) currently covers HA injections for elderly Medicare recipients under certain conditions.[27] If HA is effective, it is postulated that it might effectively prevent or delay the need for life-disrupting surgery and rehabilitation by relieving pain and improving function with minimal inconvenience or adverse effects; however, if the treatment delays arthroplasty but fails to halt progressive degeneration, patients could potentially experience worse outcomes, although thus far, evidence for such outcomes has been weak. In addition to assessing the evidence for a role of HA in delaying or preventing the need for TKR, and assessing the evidence to date on the efficacy of intra-articular injections of HA with respect to the outcomes of function, ADLs/IADS, and quality of life, the report aims to assess the evidence to date on the safety of intraarticular HA when used as indicated and to scan the literature on the evidence for a role of HA in controlling pain. The key questions were provided by the CMS Coverage Analysis Group. They are presented here along with a description of the participants, interventions, comparators, outcomes, and timeframes (PICOTs) of interest, which defined the inclusion and exclusion criteria of the review. An analytic framework that shows the interrelationships among the presenting problems, the interventions and the outcomes of interest appears below.

Key question 1. Does intra-articular injection of hyaluronic acid eliminate the need for knee replacement surgery? Is this outcome affected by the type of hyaluronic acid, the type of presentation, severity at study entry, or age at study entry?

Key Question 2. Does intra-articular injection of hyaluronic acid significantly postpone the need for knee replacement surgery?

Key Question 3. Does intra-articular injection of hyaluronic acid improve the ability to successfully perform activities of daily living (ADLs) or instrumental activities of daily living (IADLs)?

Key Question 4. Does intra-articular injection of hyaluronic acid improve quality of life? PICOTs for KQ1 through 4 are the same with the exception of outcomes.

The effects of hyaluronic acid injection on pain and adverse events associated with hyaluronic acid injection were not included in the key questions posed by CMS. However because pain is regarded as an important component of effectiveness for treatments for OA of the knee and because safety is also an important treatment consideration, we volunteered to appraise this literature.

Methods

Criteria for Inclusion/Exclusion of Studies in the Review

We sought randomized placebo-controlled trials, head-to-head trials, or quasi-randomized trials that reported results for individuals whose average age was 65 or older; that assessed the effects of intra-articular HA on function, quality of life, delay of TKR, and prevention of the need for TKR (as well as factors that might affect these outcomes, such as age, disease severity, or comorbidities); and were powered to see a clinically important difference. If no randomized controlled trials (RCTs) were identified that assessed an outcome of interest, we included observational studies that assessed the outcome in question. Studies were included that enrolled individuals with other comorbidities and that enrolled community dwelling or institutionalized participants. Acceptable comparators included placebo (sham injection) or other HA devices. Studies with followup times of 4 weeks or longer were accepted. Adverse effects were assessed in randomized placebo-controlled trials, case reports, and large observational studies. Although it was outside the original scope, we also assessed the effects of HA on pain because it is the sole treatment indication for which HA is approved and is the most frequently reported primary outcome in trials of intraarticular HA injection; for this outcome, we identified several recent, comprehensive, good to high quality systematic reviews as well as randomized placebo-controlled trials published after the reviews.

Figure A. Analytic framework of the effects of hyaluronic acid (HA) (vs. placebo or active comparator) on function, pain, adverse events, and delay/avoidance of total knee replacement

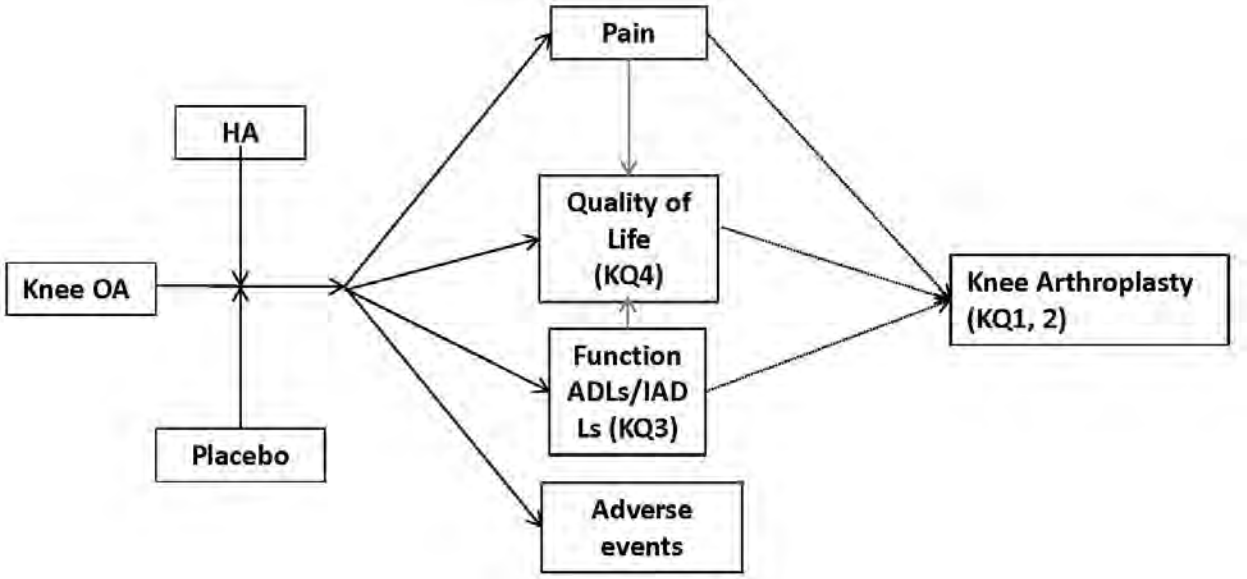


Figure notes: The framework shows potential outcomes of treatment with intraarticular HA (and placebo) the review sought to assess. These outcomes include a change in function, ADLs/IADLs (KQ3), a change in overall quality of life (KQ4), a change in pain, possible adverse events, and perhaps ultimately, a delay in TKR or decision not to undergo TKR, based potentially in part on some effect of treatment on pain, function, or quality of life.

ADL: Activities of Daily Living; DJD=Degenerative Joint Disease; HA=Hyaluronic Acid; IADLs=Instrumental Activities of Daily Living

Literature Search Strategy

The search strategy was based in part on a search conducted for a 2012 evidence review on HA,[16] with the addition of search terms for the additional outcomes of interest: arthroplasty/total knee replacement, functional outcomes (e.g., WOMAC, Lequesne Index), ADLs, IADLs (including terms for the tools commonly used to assess ADLs and IADLs, e.g., Lawton IADL scale, Katz Index), and quality of life (Appendix A of the full report).

PubMed, CINAHL, EMBASE, Web of Science, SCOPUS, and Cochrane were searched from 1990 to the present to identify original studies of HA. To capture unpublished or not-yet-published findings, we searched the New York Academy of Medicine database of grey literature, the database Grey Matter, a grey literature tool from the Canadian Agency for Drugs and Technologies in Health; clinicaltrials.gov; and the FDA Premarket Approval (PMA) database. The AHRQ Scientific Resource Center contacted the manufacturers of HA devices approved for use in the US to obtain scientific information packets (SIPs) on their products. Systematic reviews that reported on outcomes of interest were identified by searching the Cochrane Database, and original studies were obtained if not already identified among the results of the searches. Non-US studies were included if the intervention on which they reported was approved in the US for the indicated use, or if it was similar to a device approved for use in the US. Non-English language studies were not included; however we surveyed a random sample of the abstracts of non-English language studies to assess whether these studies differed in any apparently systematic way from English-language studies (the results are presented in Appendix E of the full report).

The titles and abstracts obtained from the literature searches were independently screened by two reviewers after being input into the systematic review database, DistillerSR; all selected articles were obtained. A second round of screening was then conducted with full text to exclude articles that provided no usable data on the outcomes of interest; reported duplicate data; were observational in design and reported only on adverse events and enrolled fewer than 500 participants; enrolled a population whose mean age was less than 65 years (unless the study outcomes were reported by age group and we could abstract outcomes for older individuals); or reported no outcomes of interest. When conference abstracts of interest were identified, we sought peer reviewed articles that reported the same data.

An update search was conducted on December 12, 2014, dating back to 6 months prior to the initial searches, while the draft report underwent peer review. Any new articles identified by the update search or suggested by peer reviewers were screened using the methods applied initially.

Data Abstraction, Management, and Synthesis

Study-level details and outcome data were dually abstracted in DistillerSR. Disagreements were reconciled with the input of the principal investigator. Data that were collected fell into two categories: PICOTs (study-level data) and outcomes (study findings). Study-level data included the population demographics (age, sex, weight status), fitness level (if reported), comorbidities, disease stage, methods of ascertainment, intervention protocols, comparators, outcomes assessed in the study, and time course of interventions.

Data were abstracted for the following outcomes, when reported: receipt of TKR, time elapsed between HA therapy and TKR, change in functional status (as measured using the WOMAC, Lequesne, or KOOS scales), range of motion, ADLs/IADLs, QoL/Health-related QoL, adverse events, (and for studies reporting on pain and published subsequent to the two most recent systematic reviews, pain).

If three or more studies were determined to be relatively homogeneous with respect to intervention, outcome, and follow-up times, we conducted a meta-analysis, estimating a pooled random-effects estimate of the overall effect size using the Hartung-Knapp-Sidik-Jonkman method for our random effects meta-analysis.[28] This method has been preferred when the number of pooled studies is small. It has been shown that the error rates are more acceptable than the previously used DerSimonian and Laird method.[29]

To obtain an estimate of the clinical importance of the pooled effect size for function (which represented a standardized mean difference), we compared it to the minimum clinically important difference (MCID) derived for large groups of patients with OA of the knee undergoing similar treatments and used in one of the two most recent comprehensive systematic reviews and the minimum clinically important improvement (MCII) used in the other recent review and recommended by OMERACT-OARSI, as well as MCII derived by Tubach and colleagues and used in a recent trial included in the report.[16, 30-34]

In addition to obtaining the standardized effect size for each trial, we attempted to abstract the proportion of participants who reported improvement in function; a subset of studies reported on global improvement only.

The RCTs that compared active treatments head to head were not pooled, as the numbers of studies comparing the same interventions were insufficient. Similarly, the numbers of studies that reported on ADLs or quality of life were insufficient to allow pooling. The results are reported narratively. RCTs reporting on total knee replacement/arthroplasty were also small in

number and are described narratively. Because only three RCTs reported on arthroplasty (and only one considered it as a treatment outcome), we included observational studies that assessed arthroplasty. The results of these studies are described narratively.

Publication bias was assessed for all pooled outcomes using the Begg adjusted rank correlation test[35] and Egger regression asymmetry test.[36] Heterogeneity was assessed using the I^2 test.[37] An effect-size or odds ratio was calculated for trials that reported data but did not contribute to a pooled analysis, and these studies were described narratively. All efficacy analyses were conducted with Stata statistical software, version 12.0 (Stata Corp., College Station, Texas).

Because we identified several large, recent, comprehensive systematic reviews on the outcome of pain, we selected the two most recent (and comprehensive) and described the results of these reviews as well as those of newer original trials that were not included in a prior meta-analysis.

Risk of Bias (Quality) Assessment of Individual Studies

Individual study quality/risk of bias (ROB) for randomized trials was assessed using a set of questions adapted from the Cochrane Risk of Bias Assessment Tool[38] and the EPC Methods Handbook (chapter 5).[39] The quality of observational studies included for assessment of efficacy was assessed using a modification of the Newcastle-Ottawa Scale.[40] The quality of RCTs included in the assessment of adverse events was assessed using the McHarms tool.[41] The quality of systematic reviews was assessed using the AMSTAR tool.[42]

Strength of the Body of Evidence

The strength of evidence was assessed for each conclusion within each key question using the EPC modification of the GRADE system (Table A).[43] The domains are defined in Appendix G of the full report.[44]

Applicability

The applicability of the findings was assessed based on age, study setting, and study design.

Results

We describe first the results of the literature searches, followed by the findings for effects of HA treatment on TKR, function, quality of life, pain, and adverse events.

Results of Literature Searches

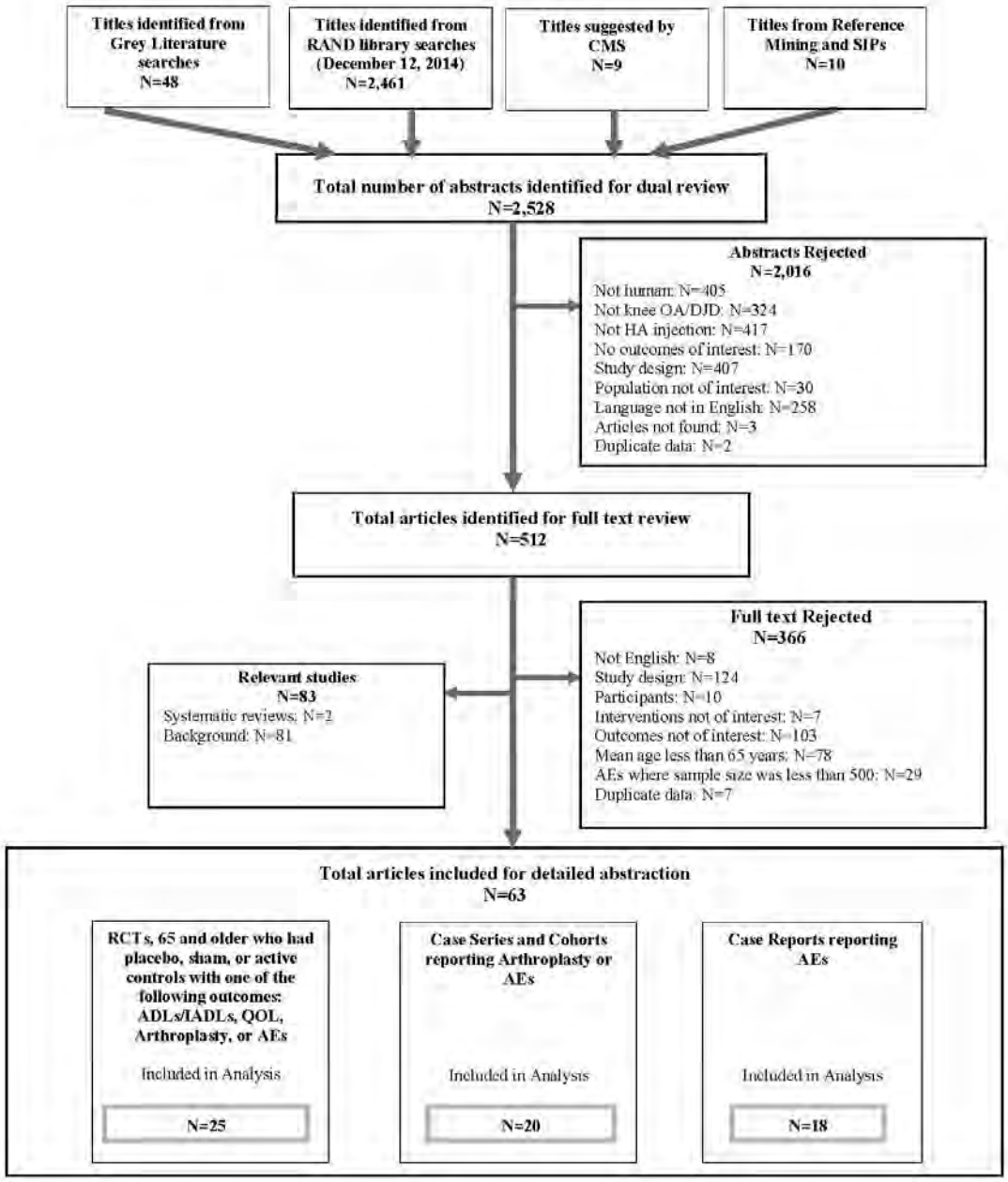
The searches of peer reviewed literature identified 2,461 unique titles. The partner, CMS, provided 84 titles, of which all but 9 were already included in the search results. Reference mining of those studies yielded an additional 10 titles. The searches of grey literature yielded 48 titles. Information provided by manufacturers (Scientific Information Packets (SIPs)) included two titles, of which two unique titles were accepted. Altogether, 2,528 titles and abstracts went on to dual screening.

Of the 2,528 titles, 512 were initially identified for full-text review. The remaining 2,016 titles and abstracts were rejected for being animal or in vitro studies (405), not reporting on OA

of the knee (324), not using intra-articular HA injections (417), not reporting any outcomes of interest (170), having an inappropriate study design (e.g., obvious commentaries or non-systematic reviews) (407), not enrolling a population of interest (30), or being written in a non-English language (258). Three articles could not be obtained and two had duplicate data.

A second level of screening was conducted on the 512 titles and abstracts initially identified for full-text review. Of the 512 titles, 366 were rejected: Studies were rejected at this stage for the following reasons: language not English (8), study design (124); participants excluded (10); interventions not of interest (7); outcomes not of interest (103); mean age less than 65 (78); adverse event (AE) reports with sample size less than 500 (29); or duplicate data (7). Of the remaining 83 studies, two systematic reviews were accepted, 81 were background articles, and 63 were original studies that underwent detailed abstraction. These included RCTs that reported function, ADLs/IDLs, QoL, TKR, and/or AEs (25); case series or prospective cohort studies reporting AEs or TKR (20); or case reports reporting AEs (18). Of the case series and cohort studies that reported AEs, only those that enrolled populations of 500 or greater were included, to ensure detection of rare AEs.

Figure B. Literature Flow Diagram



Footnotes: ADLs=Activities of Daily Living; IADLs=Instrumental Activities of Daily Living AEs=Adverse events; CMS=Center for Medicaid Services; SIPs: Scientific Information Packets

Table A. Strength of Evidence

Outcome	Strength of evidence Grade	Study Design	No. Studies (N)	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Other Issues	Finding
Arthroplasty	Insufficient	RCTs Observational	3 13	High	Direct	Consistent	Imprecise	Suspected	TKR not intended outcome in 2 trials	No pooled effect size
Function: HAs vs. placebo	Low	RCTs	10	Moderate	Direct	Inconsistent	Precise	None	2ndary outcome	-0.23 (-0.34, 0.02)
Function: HA vs. HA	Insufficient	RCTs	5	High	Direct	Inconsistent	Imprecise	unknown	2ndary outcome	No pooled effect size
Quality of Life	Insufficient	RCTs	2* 1	High	n/a	n/a	n/a	n/a	Different outcome measures	No pooled effect size
Adverse Events: total	Moderate	RCTs Observational cohort case reports	25 4 18	Moderate	Direct	Consistent	Precise	Unknown	Cohort studies included patients<65	Similar rates of AEs were reported in studies of HA and placebo
Adverse Events: serious (SAEs)	Moderate for the rarity of SAEs; Low for a difference between the intervention and placebo groups	RCTs	25	Moderate	Direct	Consistent	Imprecise	Unknown	Causal mechanism not proposed for some SAEs	Joint: 0.77(0.25, 2.31) Other: 0.62(0.23, 1.57)

*Two trials compared Synvisc® to Hyalgan;® one trial compared Hyalgan® to saline. Each used a different measure

Delay or avoidance of total knee replacement surgery

Three RCTs[45-47] and 13 observational studies (reported in 16 articles)[48-63] reported on total knee replacement (TKR) after administration of intra-articular HA injections. Of the three RCTs, only one assessed TKR as a prespecified outcome of interest: They reported it as a treatment failure.

Key Points

- Three RCTs enrolled small numbers of patients and reported on TKR: Two did not specify TKR as a prespecified outcome of interest but as a treatment failure, whereas the third reported it as the primary outcome. One study reported higher rates of TKR among HA-treated patients, whereas the other two reported higher rates among placebo-treated patients.
- Six case series and seven cohort studies reported on TKR as an outcome following HA treatment. Most studies reported delays in, or lower rates of, TKR with HA injections compared with the usual progression or the rate seen in an untreated cohort. Two studies that assessed risk factors for undergoing TKR over a 12 year follow-up among those treated with HA found that only baseline severity and age were factors: those in the 60 to 69-year old age range in one study and in the 65 to 79-year range in the other were significantly more likely than those younger or older to undergo TKR, and in the former study, the time from diagnosis to TKR was faster for the 60–69 year old age group. No study reported the criteria used by the treating physicians for recommending patients to undergo knee replacement surgery (although all patients enrolled in the largest and longest cohort study had Kellgren-Lawrence Stage IV OA and were considered candidates for TKR by the treating physicians) or the characteristics that distinguished those who underwent surgery.

Intra-articular injection of hyaluronic acid and measures of function

We identified 18 randomized trials that compared the effects of HA with another HA[64-69] or sham (intraarticular) placebo control[45, 47, 66, 70-76] or both using a validated measure of function, including the WOMAC, Lequesne, ADLs, or IADLs, in individuals with OA of the knee whose average age was 65 or older. Two studies compared an HA to other active treatment.[46, 77]

Key Points

- Our meta-analysis of 10 studies that compared the effect of an HA to that of a sham placebo control showed a statistically significant improvement in WOMAC-assessed function following HA treatment, compared to placebo (standardized effect size or standardized mean difference [SMD] -0.23, 95% CI -0.34, -0.02) that did not achieve the MCID of -0.37 applied in a systematic review by Rutjes and colleagues[16] but did exceed the MCII of -0.12 derived by Tubach and colleagues, as well as the MCII of -0.20 used in a recent network meta-analysis by Bannuru and colleagues[30] (based on the OMERACT-OARSI responder criteria); based on the pooled effect size, about 11 percent would have exceeded the MCID of 0.37 in improvement and about 33 percent would have exceeded the MCII of -0.12) at follow-up.[45, 47, 66, 70-76]

- The number of head-to-head trials is too small to be able to assess the relative superiority of one HA over another.
- One head-to-head study found that 69% of patients given an intermediate-weight HA and 56% of patients given a lower-molecular weight HA achieved the pre-specified MCII for function. Seven studies assessed the proportion of patients with patient- or investigator reported global improvement; of the four that were placebo-controlled, three reported significant increases in the proportion of HA-treated patients who improved, compared with the proportion of placebo-treated patients who improved.
- No studies assessed the effect of HA on range of motion.
- No studies assessed the durability of effect.

Intra-articular injection of hyaluronic acid and quality of life

Three randomized trials were identified that assessed quality of life. A 2008 saline-controlled randomized trial assessed quality of life using the KOOS quality-of-life component.[74] Two head-to-head trials that compared Genzyme Synvisc® with FIDIA Hyalgan® also assessed quality of life/health-related quality of life (HRQoL), one using the SF-36 mental component summary,[67] and one using the EuroQol-5D index (for HRQoL).[69]

Key Points

- Three trials that compared HA to saline or to another HA found no differences in quality of life between the two groups at 6 months follow-up.

Intra-articular injection of hyaluronic acid and pain

Pain is the most frequently assessed outcome for HA but was not within the scope of the present review. However, the studies that have assessed the effect of intraarticular HA on pain have been assessed in numerous recent systematic reviews with meta-analysis. We summarized the findings of two of the most recent, comprehensive, and good to high quality meta-analyses. One good quality 2012 review summarized the entire body of trials that compared the effects of HA with those of a sham or nonintervention control on pain; this review also included separate analysis for double-blind placebo control trials and stratified analyses for a number of potential effect modifiers.[15, 16, 78-81] A 2015 network meta-analysis compared the effects of pharmacological treatments (oral and intraarticular) for knee OA, intraarticular HA, and oral and intraarticular placebos for the treatment of knee OA.[30]

We identified no double-blind placebo controlled randomized trials that reported the effects of HA on pain and enrolled only individuals 65 and over, and no such studies in individuals of average age 65 and over that were published subsequent to these systematic reviews. We did identify and reviewed the results of two recent randomized head-to-head trials not included in the previous reviews that assessed the effects of HA on pain in individuals of average age 65 and over.[64, 67]

Key Points

- A large, comprehensive 2012 systematic review of RCTs that assessed the effects of HA on pain in 71 RCTs (with either sham or non-sham controls) reported that HA injections

significantly reduce pain when assessed at 3 months (-0.37, 95% CI -0.46, -0.28) and the effect met the criterion for a MCID (-0.37, which corresponded to 9mm on a VAS scale of 0 to 100mm); When the reviewers performed a subgroup analysis that included only the 18 sham-controlled, assessor-blinded studies with sample size of 100 or more per intervention group in the pooled analysis, the effect of HA was still statistically significant (-0.11, 95% CI -0.18, -0.04), but no longer met the criterion of clinical importance. A stratified analysis comparing the effect size for all 54 studies with a sham control (regardless of size) with that of the 18 studies with a non-sham comparison obtained a pooled effect size for the sham-controlled studies of -0.34 (95% CI -0.44, -0.24), nearly equal to that for the entire group of studies and to the MCID.

- A 2015 network meta-analysis of 129 RCTs that compared the effects of oral and intraarticular pharmacologic agents, HA, and placebo on pain (52 studies compared HA with placebo and 12 compared HA with steroids) reported a significant effect size of HA compared with placebo (-0.34; 95% CI -0.42, -0.26), exceeding the prespecified absolute MCII of -0.20, based on the OMERACT-OARSI responder criteria; sensitivity analysis showed that limiting study size to 50 or more did not change the effect size, but limiting the analysis to studies of 100 or more did reduce the effect size.
- No new placebo-controlled trials were identified that were not already included in the comprehensive 2012 systematic review on the effects of HA or that of Bannuru and colleagues, enrolled patients of average age 65 and older, and reported on pain outcomes.
- Two new head-to-head trials compared the effects of two different HAs on pain in individuals of average age 65 and over and were not included in prior SRs. One found that single injections of a high- and low-molecular weight were equally effective in reducing pain and improving function at 6 months (with no change in quality of life), whereas another found that three injections of an intermediate molecular weight HA might be superior to low molecular weight HA over 6 months (with respect to reducing pain and improving function). The latter study found that 70.5% of participants receiving the intermediate molecular weight product and 58.4% of participants receiving the lower molecular weight product exceeded the prespecified MCII for pain.

Intra-articular injection of hyaluronic acid and adverse events

Twenty four trials[45-47, 64-77, 82-89], four large cohort and case series studies,[90-93] and 18 case reports[94-111] were identified that reported on the incidence of adverse events among individuals 65 years of age and over.

Key Points

- In 24 placebo-controlled trials of HA, serious adverse events were small in number.
- Among four large cohort studies and case series, representing nearly 6,000 recipients of HA (some more than one series), one serious adverse event was reported: severe swelling and synovial fluid accumulation.
- Eighteen case reports provided reports of adverse events among 30 individuals 65 years of age or older, including five cases of sepsis (one case of staphylococcus scalded skin

syndrome), and one case each of saphenous nerve injury, eosinophiluria, erythema, and herpes zoster (new onset).

Discussion

Key Findings and Strength of Evidence

Intra-articular HA and TKR

Three randomized trials and 13 observational studies reported on TKR. Two of the trials did not regard receipt of TTKR as a prespecified outcome of interest, one of the two enrolled patients whose average was under 65, and none of the trials were adequately powered to compare the rates of TKR between HA and comparison groups. A number of observational studies reported rates of TKR among HA recipients; one study that followed over 1000 patients for as long as 12 years reported an overall incidence of TKR of 25% and an average delay of 2.8 years (compared with 3 months for a cohort that chose not to be treated). However, observational studies cannot control for the selection effect whereby patients who are more or less inclined to TKR are selected by their physicians for getting—or not getting—HA injections. Therefore, without randomized trials designed and adequately powered to assess the effect of HA on TKR, it is not possible to draw conclusions at this time regarding the effect of HA treatment on delay or avoidance of TKR.

The strength of evidence for this question is insufficient to draw any conclusions about the effect of HA on TKR.

Intra-articular HA and Function

Pooling of ten placebo-controlled studies that reported outcomes for the WOMAC or Lequesne revealed a small but significant increase in function in favor of HA (-0.23, 95% CI -0.34, -0.02); seven of the ten measured outcomes at 6 months. This difference did not achieve the MCID of -0.37 applied by Rutjes and colleagues but did exceed the MCII of -0.20 recommended by the OMERACT-OARSI guidelines (and applied by Bannuru and colleagues) and the MCII of -0.12 derived by Tubach and colleagues. Two studies reported no difference between HA and placebo. Based on the pooled effect size, approximately 11 percent of patients would have exceeded the MCII in improvement.

One trial reported on the effects of HA on ADLs. This study found no change from baseline in the HA or placebo group.

One head-to-head study found that 69% of patients given an intermediate-weight HA and 56% of patients given a lower-molecular weight HA achieved the pre-specified MCII for function Three of four placebo-controlled trials that assessed the effect of HA on global improvement reported statistically significant increases in the proportion of HA-treated patients who improved, compared with the proportion of placebo-treated patients who improved.

Too few head-to-head trials were identified to be able to draw any conclusions about the superiority of anyone product over another.

None of the identified studies stratified findings by age, sex, or any other outcome of interest.

The strength of evidence for the conclusion that HA, on average, modestly improves function in patients with knee OA based on placebo-controlled trials is low. The strength of evidence for the conclusion that one HA is better than another, based on head-to-head trials, is insufficient.

Intra-articular HA and QoL

Three randomized trials reported on the effects of HA on QoL with mixed results. No conclusions can be drawn about the effects of HA on QoL. As only three trials reported both QoL and functional outcomes, no conclusions can be drawn about the relationship between these two parameters.

The strength of evidence for any conclusions regarding an effect of HA on quality of life is insufficient.

Intra-articular HA and Pain

Two large, comprehensive, recent systematic reviews that assessed the literature on the effects of HA on reducing pain compared the effects of HA compared the effects of HA with sham or non- intervention controls or with placebo and all pharmacologic agents on pain reduction, and reported that HA injections significantly reduced pain, both statistically and clinically (that is, the effects reached the MCID/MCII) when measured at 3 months. A 2012 systematic review found that this effect was no longer clinically significant when only double-blind placebo-controlled trials enrolling at least 100 participants per treatment group were included in the analysis. A 2015 network meta-analysis compared the effects of oral and intraarticular pharmacologic agents, oral and intraarticular placebo, and HA on pain at 3 months among 129 RCTs (52 studies compared HA with intraarticular placebo).[30] This study reported a significant effect size of HA compared with placebo that exceeded the prespecified absolute MCII; sensitivity analysis showed that limiting study size to 50 or more did not change the effect size but limiting the analysis to studies of 100 or more did reduce the effect size to less than the MCII. In contrast to the 2012 review, the 2015 review found minimal evidence for reporting bias among the placebo-controlled HA studies.

Based on the findings of the two reviews, we believe that the strength of evidence is moderate that HA reduces pain, on average, by an amount about equivalent to the minimum clinically important difference.

Intra-articular HA and AEs

The findings of randomized trials, observational studies, and case reports suggest that the adverse events associated with intra-articular injections of HA are nearly all at the site of injection or within the joint, largely confined to pain or swelling, and as likely in the placebo-treated as in the actively treated individual. Serious adverse events are rare. In 24 placebo-controlled trials of HA, serious adverse events were small in number. Estimates are imprecise, and the magnitude of any increase in risk is very small, if present at all. The rate of non-serious AEs was higher but did not differ significantly between the HA-treated and placebo-control groups. The FDA PMA database revealed no post-marketing reports of unexpected adverse events. Information provided by manufacturers about five products was limited to already published data.

The strength of evidence for the conclusion that serious adverse events are rare is moderate. The strength of evidence for a statistically significant difference in SAEs and non-serious AEs between intervention and placebo groups is low.

Findings in Relation to What is Already Known

To our knowledge, this report represents the first systematic review to attempt to assess the effects of intra-articular HA injections on the combination of delay or avoidance of TKR, pain, function, quality of life, and adverse events.

No other systematic reviews have attempted to synthesize the effects of HA on TKR, and the present review found insufficient evidence to draw a conclusion about the effects of HA on those outcomes.

Regarding the effect of HA on function, we calculated an effect size of -0.23 (95% CI -0.45, -0.01), smaller than the MCID specified in the review by Rutjes but larger than the MCII used in the network meta-analysis by Bannuru (the Rutjes review reported an effect size of-0.33, [95% CI -0.43, -0.22]; the Bannuru review reported an effect size of -0.30 [95% CI -0.40, -0.20] for function).

The smaller effect size we calculated, compared with those of the Rutjes review and the Bannuru review may be attributable to two factors: the smaller number of studies we included and the fact that we sought to pool outcomes for 6 months of followup, whereas the two prior reviews sought to pool outcomes for 3 months of follow-up; thus we may have pooled outcomes when the effect of the HA on function was waning.

Also similar to the Bannuru network meta-analysis, our analysis of the effects of HA on function compared with intraarticular placebo showed no evidence of publication bias.

The moderate effect of HA on function that was identified in the review by Rutjes was no longer considered clinically significant when only large trials (100 or more participants per study arm, or at least 200 per trial) with assessor blinding were considered (-0.09, 95% CI -0.17, 0.00, based on 15 trials).[16] The review by Bannuru, which included only double-blind placebo-controlled trials, found no significant difference in effect size when they included only studies enrolling 50 or more participants but did see a decrease in the effect size when they included only studies of 100 or more participants. However study size is not typically a criterion in assessing study quality/risk of bias. Our meta-analysis on the outcome of function included only intraarticular placebo-controlled trials that incorporated assessor blinding; we did not find any studies that met our inclusion criteria that enrolled more than 100 participants per study arm.

The present review is the first to consider only studies of individuals of average age 65 or older. Approximately half of the trials included in the pooled analysis of the effects of HA on pain by Rutjes enrolled populations of average age less than 65; and of the 52 trials they included in their analysis of the effects of HA on function, nearly all included participants of average age less than 65.[16] No evidence exists that would suggest age would affect the ability to experience pain relief. Therefore, we believe the analyses in the prior reviews by Rutjes and by Bannuru, given the much larger number of included studies, were more adequately powered to assess the effects of HA on pain than would be an analysis limited to the smaller number of studies that enrolled only individuals of average age 65 and over.

The current review found only a small number of serious AEs and in pooling placebo-controlled RCTs, found no statistical differences between serious AEs in treatment and placebo conditions. The 2012 review pooled data on serious AEs from14 trials that reported on AEs and found an increased risk for serious AEs in the HA-treated groups,[16] whereas a 2013 review of 29 studies,[15] as well as the 2015 network meta-analysis by Bannuru and colleagues found no difference between HA and placebo for any AE, in agreement with the present study. To derive a potential explanation for the disparity in the apparent risk for serious AEs between the review by Rutjes and colleagues and ours, we re-abstracted the data on serious AEs (both those reported by

original study authors as being serious, those deemed serious by the criteria of the present study, and those deemed serious by the criteria of the 2012 review). We included only studies that would have met our inclusion criteria (making an exception for mean age); therefore we excluded studies in the Rutjes analysis that were not assessor blinded, studies in which patients served as their own controls, and conference abstracts. The reported increase in risk for serious AEs among patients who received HA compared with placebo in the 2012 review appears to be attributable to several factors. The methods use for the statistical analyses differed slightly between the two reviews. In addition, the criteria used to define serious AEs, the criteria for accepting original authors' definitions of serious AEs, and the criteria for plausible associations differed between the two reviews; fewer than half of the trials included in the serious AE analysis of the review by Rutjes and colleagues[16] actually described specific AEs, and a number of studies that did describe the specific AEs they observed had methodological limitations. The network meta-analysis by Bannuru and colleagues, as well as another recent (2014) meta-analysis by this group compared the efficacy and safety of intraarticular HA with NSAIDs for the treatment of knee OA: Although the small number of studies they were able to pool showed no differences in efficacy between HA and NSAIDs, NSAIDs were associated with a significantly increased risk for gastrointestinal AEs compared with HA We address the issue of adverse event reporting further below in our discussion of limitations.

Applicability

To increase potential applicability, we limited studies included in the current review with functional outcomes to those with an average age of 65 or older. Nevertheless, no studies excluded patients younger than 65. Given that the only study that assessed factors that might influence the likelihood of undergoing TKR found that age was the only influential factor, age of study participants is likely to be an important consideration for this outcome.

The larger trials included in the assessment of functional outcomes were mostly conducted in academic settings; this typical characteristic of randomized trials tends to limit their applicability to community settings. However a number of the observational studies that addressed the outcome of TKR were conducted in private medical practices.

Implications for Clinical and Policy Decision Making

The evidence identified for the current study is insufficient to support a decision either way about the efficacy of intra-articular HA injection based on the delay or avoidance of TKR. In addition, the strength of evidence is low regarding the efficacy of HA for improving function in a population 65 years of age or older.

Limitations of the Comparative Effectiveness Review Process

Given the key questions specified by the partner and specified in our study protocol, we did not attempt to review studies of populations of average age less than 65 years to determine whether they found improvements in function or quality of life. However, removing the exclusion criterion of age for studies that assessed the outcome of TKR, we still identified only three randomized trials that reported TKR, and it was considered a primary outcome in only one study. We also did not contact authors of original research studies to request raw data by patient age and did not attempt to do new pooling of the data on pain in the studies included in the

review by Rutjes and colleagues, to include only studies of older populations for reasons explained above.

In addition, as we discuss in the next paragraph (Limitations of the Evidence Base), in choosing the 6-month time point for pooling of effects on function, rather than a shorter follow-up time, we may have underestimated the effect of HA.

Limitations of the Evidence Base

The majority of trials identified for the current report did not meet the criteria for a low risk of bias, primarily the result of inadequate reporting: Few trials described their recruitment strategy or method for allocation concealment. A number of studies had dropout rates higher than 20% (no studies addressed differences between dropouts and completers), and although most excluded individuals who had recently received corticosteroids or other courses of an HA, most also did not bar participants from using other modes of pain relief, such as NSAIDs. Further, few or no studies attempted to determine whether response to HA differed between groups of patients stratified by characteristics such as baseline age, disease severity (stage) or type; or duration of treatment, few studies followed patients long enough to measure duration of effect, and adverse events were not assessed using any type of standard methodology.

Specific to the outcome of function, no trials measured the duration of effect. A 2011 meta-analysis by Bannuru and colleagues assessed the therapeutic trajectory of intraarticular HA in placebo-controlled trials among patients with knee OA.112 The review identified 54 studies and computed effect sizes for changes from baseline in pain from 4 to 24 weeks. A significant effect size was seen for HA by 4 weeks and this effect peaked at 8 weeks, decreasing thereafter so that only a small effect remained by 6 months. The studies we identified that reported on function at multiple time points were insufficient in number to estimate a trajectory of effect for function.

Specific to the outcome of TKR, only one small RCT measured knee replacement as a primary outcome, and only one trial reported the percentage of participants whose function improved (seven studies reported on the percent who achieved a prespecified level of global improvement, of which four were double-blind placebo-controlled trials).

Another challenging issue for studies of HA is that of the potential placebo effect inherent in the kinds of studies we reviewed. Although we limited our assessment to double-blind placebo-controlled trials (using only intraarticular placebos), the main analysis in the systematic review by Rutjes and colleagues included studies with various types of control groups, including both intraarticular and oral placebo. A 2012 meta-analysis by Colen and colleagues that included 74 studies specifically noted the large effect size for placebo alone (approximately 30%).[15] The network meta-analysis by Bannuru and colleagues found that the effect size for intraarticular placebo exceeded that of all active oral treatments for pain,[30] prompting a commentary on the role of placebo controls in studies of the treatment of knee OA.[113] Identifying the proper control for studies of interventions such as the injection of hyaluronic acid can be challenging, but at the same time, the existing trials, with intraarticular saline controls, are capable of assessing whether HA has any specific active effect over and above that of inexpensive saline.

A related but slightly different issue is that a number of studies allowed the use of rescue medications (acetaminophen, NSAIDs, and less often, CS or opioids) between treatments, which could have eliminated any observable difference between active treatment and placebo. The use of statistical significance vs. clinical significance in studies such as the ones included in this review (as well as the review itself) also needs to be mentioned. The attainment of both statistical significance and MCID or MCII is critical for demonstrating effectiveness of any clinical

treatment. However the threshold chosen for the MCID/MCII and how it is applied is controversial.[114] The evidence is limited as to what the MCID/MCII should be for an effect of HA on function, whether it should be the same as for pain, and whether it should be limited to the use of only certain outcome measures. In trying to interpret our results regarding HA and function, we used three levels of MICD that have been proposed and used by others: our observed effect size exceeded the lower MCIIs of 0.12 and 0.2 but did not meet the one used in the review by Rutjes, 0.37 (an effect size of 0.2-0.4 is normally considered small to moderate according to Cohen's classification). But we acknowledge as a limitation that additional research could improve estimates of the MCID/MCII. Perhaps more importantly, we identified almost no studies that reported the proportion of patients who achieved either a statistical or clinical improvement.

Finally an issue of possible concern is that many studies of HA show potential financial conflict of interest (FCOI), either direct industry funding of the research or employment of authors by manufacturers of the agents being tested.[78, 81] A 2013 systematic review examined 48 trials of intraarticular HA for the treatment of knee OA to determine whether industry sponsorship was associated with the likelihood of a positive finding. Of 33 trials that identified a sponsor, 30 were industry sponsored; therefore, determining whether industry sponsorship affected outcomes was impossible. However the study also assessed the association between industry authorship (compared with academic authorship) and outcomes. Of the 17 studies with industry authors, none reported unfavorable conclusions (all reported favorable or neutral conclusions); 11 of the 31 academic authored studies reported unfavorable conclusions and 9 reported neutral conclusions. Another 2013 systematic review assessed only studies of HA that employed US-approved HA products; this review, which identified 29 studies and was funded by a trade group representing the pharm industry, reported statistically and clinically significant pooled effects sizes for the outcomes of pain and function compared with saline controls and no difference in serious AEs.[78] However, the 2015 network meta-analysis by Bannuru and colleagues reported comparable effect sizes and was funded by the Agency for Healthcare Research and Quality.

Research Gaps

Many of the research gaps we identified were discussed in the previous section on the limitations of the evidence base. This section presents several specific research needs based on the outcomes of greatest interest.

Clear research gaps exist regarding studies of the effectiveness of HA among individuals 65 years of age and older and the effect of HA, if any, on delay or avoidance of TKR. Two searches for ongoing studies of HA and OA of the knee on Clinicaltrials.gov and review of entries provided by manufacturers revealed no completed, ongoing, or recruiting studies on older individuals with knee OA or with outcomes of TKR. The observational studies identified for this review could not definitively answer the question of whether HA delays or prevents the need for TKR. However, data from any of the large administrative databases maintained by commercial payers offer an alternate possibility. TKR Preliminary findings of three such studies have been presented at two recent meetings. An abstract presented at the 2013 meeting of the American College of Rheumatology reported using the Truven Marketscan database to match 7,000 HA recipients (66% female) with 19,627 non-recipients with OA of the knee (propensity score matching with the non-HA cohort was 98%).[115] With one episode of HA treatment, the median times from the initial specialist visit to TKR were 199 and 443 days for the non-HA cohort and

HA cohort, respectively. Additional treatment episodes increased the median gap by an average 202 days, suggesting true dose-response.

The findings of two similar audits of health plan claims were presented at the 2014 annual meeting of the Academy of Managed Care Pharmacy.[116] An industry-sponsored study identified 18,217 patients who initiated treatment between 2007 and 2010 and were followed for 3 years, some receiving 5 or more courses of treatment. Successive courses of HA led to greater proportions of patients without TKR at 3 years: 96.3% of those who received 5 or more courses avoided TKR compared with 72.7% who received 1 course (HR 0.113, $p<0.0001$). In a study funded by a major insurance provider, among 2,728 patients with confirmed diagnoses of OA of the knee who received a first dose of HA, 35% underwent knee surgery within the first year and another 34.2% underwent surgery the second year. However the study did not specify the type of surgery and included patients who had undergone prior knee surgery; thus the authors concluded that although 69% of patients underwent surgery (of some type) within two years of treatment, further research is needed that enrolls patients with appropriate eligibility criteria. [117]

The decision to undergo TKR is difficult to predict, as it is affected by a number of factors besides severity of osteoarthritis, such as age, comorbidities, pain tolerance, activity level, aversion to surgical intervention, and expectations about one's life expectancy; OMERACT has considered this issue and has suggested considering two alternative outcomes for assessing the effect of treatments for knee OA: "time to physician's decision to recommend surgery" and "time to fulfilling criterial for total joint replacement."[118] However, if the primary question of interest is whether or not intraarticular HA can delay joint replacement, a double-blind placebo controlled trial could be conducted that enrolls a group of people who have already been deemed "appropriate for surgery" and randomizes them to receive intraarticular HA or an intra-articular placebo. Comparison of the time to TKR could then be appropriately compared. We did identify one small pilot study that employed this design, the study conducted by Blanco and colleagues, which reported a delay in time to TKR in the HA group that did not achieve statistical significance.[47]

Research is also needed to confirm the suggestion that higher molecular weight, more cross-linked HA products are more effective than lower molecular weight products: a subgroup analysis in the review by Rutjes suggested a trend toward greater pain relief for very high molecular weight products but studies are needed to assess whether this observation generalizes to function and also to compare the newer, larger products with the smaller ones.

Another issue of concern is the effectiveness (and safety) of HA over time and with repeated treatment cycles. Given that most studies of HA have been 6 months or less in duration and that OA of the knee is a chronic condition, studies are needed to assess both the safety and effectiveness of repeated cycles of HA over time and whether HA decreases the need for pharmacotherapy (NSAIDS, corticosteroids, and opioids), which has its own safety concerns.

Finally, as discussed above, the way that AEs are recorded and reported merits concern. Although issues such as potential underreporting affect active interventions as well as placebo-treated controls within the same study, the disparity in that of Bannuru reinforces the need for standardization in the way that adverse events are documented. Based on a systematic review conducted in 2013, a group of researchers has developed an ACTTION (Analgesic, Anesthetic, and Addiction Clinical Trial Translations, Innovations, Opportunities, and Networks) AE checklist to improve the accuracy and completeness of AE data abstracted from reports of trials.[119]

We advocate analyzing data from any of the large administrative databases maintained by commercial payers, to answer the question as to whether beneficiaries who are treated with intra-articular HA proceed to TKR at a slower rate than do those who do not receive HA. We realize that a number of factors might affect the decision to undergo TKR, such as age, comorbidities, pain tolerance, activity level, aversion to surgical intervention, and expectations about one's life expectancy; at least some of these factors could be controlled for in a large, well-designed case control study, although an RCT would be needed to provide a definitive answer.

Conclusions

Trials enrolling older participants show a small, statistically significant effect of HA on function. Whether this effect is clinically meaningful is less clear: The research literature varies on its definition of minimum clinically important improvement. Based on our analyses, HA demonstrated clinically important improvements using two out of three of these definitions for this assessment. HA shows relatively few serious adverse events; however no studies limited participation to those 65 years or older. No conclusions can be drawn from the available literature on delay or avoidance of TKR through the use of HA. Studies that can compare large numbers of treated and untreated individuals, preferably with a randomized design, are needed to answer this question.

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Introduction

Background

Condition

Degenerative joint disease (usually called osteoarthritis [OA]) of the knee is a condition characterized by the progressive destruction of the articular cartilage that lines the knee joints, the subchondral bone surfaces, and synovium, accompanied by pain, immobility, and reduction in function and the ability to complete activities of daily living (ADL).

In 2005, the estimated prevalence of osteoarthritis among adults in the United States, the number of individuals who had ever been told by a doctor that they had the condition, was approximately 27 million cases.[1] Prevalence rates vary by the joint involved and the method of ascertainment (clinical vs. radiographic): symptomatically, the knee is the most frequently affected joint.[2] The prevalence of osteoarthritis of the knee is increasing rapidly because of shifting population demographics: The primary risk factors for osteoarthritis of the knee are aging, obesity, prior injury, repetitive use,[3] and female gender. The US Centers for Disease Control and Prevention have estimated that the prevalence of symptomatic knee osteoarthritis may reach 50 percent by the age of 85.[4] In the first decade of the 21st century, the number of individuals in the US with a total knee replacement doubled (from some 2 million to approximately 4 million).[5] The increase in obesity has translated not only into an increase in incidence of osteoarthritis of the knee but also into a younger age of onset and need for treatment; as a result, by the time individuals with osteoarthritis of the knee reach the age of Medicare eligibility, the length of time they have had the condition has grown, their cases are more advanced,[6] and the risk that surgery will be needed has increased. Thus, the aging of the baby boomer population, along with the increased incidence and prevalence of obesity have created a perfect storm for an increase in the number of cases and the proportion of the population at risk for this condition, all representing an increasing strain on Medicare resources.

Diagnosis Strategies

The clinical diagnosis of OA of the knee is typically based on presentation, including insidious onset of weight-bearing knee pain that is exacerbated by use of the joint and relieved by rest, and that tends to worsen over the course of the day. Radiographic evidence of osteoarthritis may precede symptomatic osteoarthritis but may not correlate with symptom severity. Radiologic severity can be estimated using the Kellgren and Lawrence criteria; however, a number of versions of the criteria exist: At low cutoff scores, correlation with symptoms is poor,[7] whereas at higher cutoff scores, agreement tends to be higher. The primary impact of these different versions of the criteria may be the challenge that they create in trying to use the different versions to assess, compare, and pool the findings of research studies:[7] Some longitudinal studies have even used different criteria at different time points within the same study. Because of the variation in scores for radiographic finding under various versions of the criteria (especially for individuals with less-advanced disease), stratification is important.

Some evidence suggests that among individuals with knee pain, MRI demonstrates physical signs of osteoarthritic changes in the knee before they are visible radiographically.[8]

Treatment Strategies

The goals of treatment for osteoarthritis of the knee include relief of pain and inflammation, slowing of progression, and improvement in or maintenance of mobility, function, and quality of life. Measures used to assess the achievement of these outcomes are described below.

Treatment options for osteoarthritis of the knee include analgesics (e.g., oral acetaminophen) and anti-inflammatory agents (non-steroidal anti-inflammatory agents [NSAIDs], intraarticular corticosteroids), , physical therapy and exercise (both to strengthen muscles that support the affected joints and to increase range of motion), weight loss to reduce stress on the joints, bracing to reduce lateral motion and friction, and if patients fail to obtain satisfactory relief from pain and improved function from the aforementioned treatments, partial or total arthroplasty (throughout this report, the terms arthroplasty and knee replacement are used interchangeably) may be recommended for advanced cases. More recent therapies include intraarticular viscosupplementation, involving local injections of the natural joint lubricant, hyaluronic acid, among other treatments.[9]

Hyaluronic acid (HA, hyaluronate or hyaluronan) , a high molecular weight glycosaminoglycan that is naturally synthesized in plasma membranes of connective tissues and secreted into the synovial fluid surrounding joints, where it forms part of the extracellular matrix.[10] Intra-articular injection of HA was approved by the US Food and Drug Administration in 1997 as a medical device for the relief of pain due to osteoarthritis of the knee. Progressive osteoarthritis of the knee includes a decrease in, the concentration of hyaluronic acid by one half to two thirds of the normal value and a reduction the molecular size of the hyaluronic acid, lowering the viscoelastic properties of the synovial fluid.[11] Injecting hyaluronic acid intraarticularly was posited as a means to restore the viscosity of the synovial fluid; thus approval was sought for HA as a device rather than as a drug[12] (the distinction being that a device does not exert its effect via a chemical interaction with the body. A large number of trials have examined the efficacy and safety of supplemental intra-articular injections of HA, usually to relieve pain, but sometimes also to improve function in patients with OA of the knee, with varying efficacy results. A number of systematic reviews have attempted to resolve these conflicting findings. Some reviews have reported positive outcomes[13-15] whereas some have reported mixed effects.[12, 16, 17] A 2010 update of an earlier systematic review actually found a decrease in the effect size for HA on knee osteoarthritis from the previous review.[18] The discrepancies in outcomes may be due to study heterogeneity both within and among reviews (and original studies, themselves) with respect to population characteristics (such as average age or body mass index), intervention modalities (the particular HA employed), treatment and followup duration (the number of treatments as well as how long after treatment initiation outcomes are measured), and the actual outcomes measured (e.g., pain, functionality, HRQoL), as well as the measures employed. Heterogeneity may also be attributable to how efficacy is expressed, i.e., the proportion of each treatment group that responds positively to treatment vs. the mean change in that efficacy measure from baseline in the active treatment group vs. the comparison group. Finally, whether or not a study reports a positive effect of HA has been shown to depend, at least in part, on study design: whether participants are credibly blinded to treatment allocation and the outcomes of active treatment are compared to that of a placebo control.[17]

Commercial preparations of HA differ in three respects: source, molecular size, and dosing. Whereas the older HA were all avian in origin (purified from chicken comb), some newer products are bioengineered in yeast cell cultures. The newer products also tend to be higher in

molecular weight, the result of greater cross-linking. Products may be packed to be delivered as a single dose or in multiple doses. The products included in this report are shown in Table 1, along with their indications and recommended dosages (HA devices not approved for use in the United States are described in Appendix F).

Table 1. Hyaluronic Acid Devices Approved for Use in the United States

Device **Source** **Approval Date** **Avian/Non-Avian** **Molecular Weight**	**Trade name(s)**	**Labeled indications**	**Dosing**	**Dose adjustments for special populations**
Sodium hyaluronate FIDIA Pharmaceutical Corp. May 1997 Avian 500-730 kD	Hyalgan®	Indicated for treatment of pain in osteoarthritis of the knee in patients who have failed to respond adequately to conservative non-pharmacologic therapy and simple analgesics, (e.g., acetaminophen)	Five* weekly injections into knee joint (20 mg/2 mL)	Safety/effectiveness not known in pregnant/lactating women or children
Hylan GF-20 Genzyme Corp. (Biomatrix, Inc.) August 1997 Avian 6,000 kD	Synvisc®	Indicated for treatment of pain in osteoarthritis of the knee in patients who have failed to respond adequately to conservative non-pharmacologic therapy and to simple analgesics (e.g., acetaminophen)	Three weekly injections into knee joint (16 mg/2 mL)	Safety/effectiveness not known in pregnant/lactating women or children
Sodium Hyaluronate Seikagaku Corp. January 2001 Avian 620-1170 kD	Supartz® *Marketed as* Artz® *or* Artzal® *outside U.S.*	Indicated for the treatment of pain in osteoarthritis of the knee in patient show have failed to respond adequately to conservative non-pharmacologic therapy and simple analgesics (e.g., acetaminophen)	Five weekly injections into knee joint (25 mg/2.5 mL)	Safety/effectiveness not known in pregnant/lactating women or children
Hyaluronan Anika Therapeutics, Inc. February 2004 Non-Avian 1000-2900 kD	Orthovisc®	Indicated for treatment of pain in osteoarthritis of the knee in patients who have failed to respond adequately to conservative non-pharmacologic therapy and to	Three or four weekly injections into knee joint (30 mg/2 mL)	Safety/effectiveness not known in pregnant/lactating women or children

Device **Source** **Approval Date** **Avian/Non-Avian** **Molecular Weight**	**Trade name(s)**	**Labeled indications**	**Dosing**	**Dose adjustments for special populations**
		simple analgesics (e.g., acetaminophen)		
Hylan GF-20 Genzyme Corp. February 2009 Avian 6,000 kD	Synvisc-One®	Indicated for treatment of pain in osteoarthritis of the knee in patients who have failed to respond adequately to conservative non-pharmacologic therapy and to simple analgesics (e.g., acetaminophen)	Single injection into knee joint (48 mg/6 mL)	Safety/effectiveness not known in pregnant/lactating women or children
Sodium hyaluronate Seikagaku Corp. March 2011 Avian Unknown MW (“high”)	Gel-One®	Indicated for the treatment of pain in osteoarthritis of the knee in patients who have failed to respond adequately to non-pharmacologic therapy, NSAIDs, or analgesics (e.g., acetaminophen).	Single injection into knee joint (30 mg/3 mL)	Safety/effectiveness not known in pregnant/lactating women or children
1% sodium hyaluronate Ferring Pharmaceuticals, Inc. October 2011 Non-Avian 2400-3600 kD	Euflexxa® *Formerly Nuflexxa®, (Savient) approved December 2004*	Indicated for treatment of pain in osteoarthritis of the knee in patients who have failed to respond adequately to conservative non-pharmacologic therapy and to simple analgesics (e.g., acetaminophen)	Three weekly injections into knee joint (20mg/2 mL)	Safety/effectiveness not known in pregnant/lactating women or children
Hyaluronan Anika Therapeutics, Inc. February 2014 Non-Avian Unknown MW (“high”)	Monovisc™	Indicated for treatment of pain in osteoarthritis of the knee in patients who have failed to respond adequately to conservative non-pharmacologic therapy (e.g., acetaminophen)	Single injection into knee joint (88 mg/4 mL)	Safety/effectiveness not known in pregnant/lactating women or children

Treatment Guidelines

In the 2012 update to their 2000 guidelines for the treatment of osteoarthritis of the knee, hip, and hand, the American College of Rheumatology conditionally recommended hyaluronic acid injections for patients who had an inadequate response to initial (standard or more conservative) therapy.[9] The 2013 American Academy of Orthopedic Surgeons guidelines for the treatment of osteoarthritis of the knee recommend against the use of hyaluronic acid to treat patients with symptomatic conditions.[19]

Assessment of Outcomes of Treatment

A number of assessment tools are used to assess pain, quality of life, and physical functioning in patients with osteoarthritis of the knee. These tools can be divided into those specifically developed for knee osteoarthritis and those that are used for a variety of conditions.

Tools specifically developed and validated to assess pain and functioning associated with osteoarthritis of the knee as well as treatment outcomes include the Western Ontario-McMaster Universities Arthritis Index (WOMAC[20]), the Lequesne Index[21], the Knee Injury and Osteoarthritis Outcomes Score (KOOS[22]), and the Animated Activity Questionnaire.[23] The Visual Analog Scale, which rates patient-reported responses on a scale from 0 to 100, is often used to quantify patient-reported outcomes for these scales as well as being used on its own. The WOMAC, probably the most widely used tool for assessing knee osteoarthritis, comprises three scales: pain, function, and stiffness; the function scale comprises 17 items that can be rated using a 5-item Likert scale (where 0=no difficulty and 4=extreme difficulty) or a 10 or 100-point Visual Analog Scale (VAS).[20] In 2004, the Osteoarthritis Research Society International (OARSI) developed a consensus set of guidelines to assess the outcomes of research trials on products intended to treat osteoarthritis; and under the International League of Rheumatologists, OMERACT (Outcome Measures in Rheumatology) has developed guidelines on outcome measures.[24]

Several tools have been adapted for use in assessing osteoarthritis of the knee. One such tool, the Short form (SF)-36, developed at RAND for the Medical Outcomes Study,[25] is generally used to measure quality of life. Assessment of health-related quality of life is an attempt to measure the impact of a health condition and its treatment on a patient's life; the Euroqol has been validated for use in patients with osteoarthritis of the knee.[26] The Activities of Daily Living scale (ADLs)[27] measures the ability to perform basic daily tasks such as dressing/bathing, eating, ambulating, toileting, and hygiene. The Instrumental Activities of Daily Living (IADLs) scale allows the assessment[28] of activities that are not needed for basic functioning but allow independent living.

The Kinemax Outcomes Group has used a combination of the WOMAC, the SF-36, and a series of questions addressing demographic characteristics to predict patient outcomes of total knee arthroplasty.[29]

Appendix H provides the WOMAC, Lequesne, and SF-36 instruments.

Scope and Key Questions

Scope of the Review

The purpose of this review is to assess, primarily, the evidence on the effects of intra-articular injections of HA in preventing or delaying the need for TKR among individuals 65 and

over, and on functional outcomes and quality of life/health-related quality of life. The Centers for Medicaid and Medicare Services (CMS) currently covers HA injections for elderly Medicare recipients under certain conditions.[30] Arthroplasty and the postoperative rehabilitation it requires can be life-disrupting. If HA can relieve pain and improve function with minimal adverse effects, it may prevent or delay the need for this surgery. However, if the treatment delays arthroplasty but fails to halt progressive degeneration, patients could potentially experience worse outcomes, although thus far, evidence for such outcomes has been weak. In addition to assessing the evidence for a role of HA in delaying or preventing the need for TKR, and affecting the outcomes of function, ADLs/IADS, and quality of life, this report aims to assess the evidence to date on the safety of intra-articular injections of HA when used as indicated and to scan the literature on the evidence for a role of HA in controlling pain. The Coverage and Analysis Group at the Centers for Medicare and Medicaid Services (CMS) requested this report from The Technology Assessment Program (TAP) at the Agency for Healthcare Research and Quality (AHRQ). AHRQ assigned this report to the Southern CA Evidence-based Practice Center (HHSA290201200006I). A protocol for the review was provided to, and approved by, the AHRQ TAP.

Key Questions

The key questions were provided by the CMS Coverage Analysis Group. Their inter-relationship and association with the topic are described in the analytic framework below (Figure 1).

Key Question 1. Does intra-articular injection of hyaluronic acid eliminate the need for knee replacement surgery? Is this outcome affected by the type of hyaluronic acid, the type of presentation, severity at study entry, or age at study entry?

Key Question 2. Does intra-articular injection of hyaluronic acid significantly postpone the need for knee replacement surgery?

Key Question 3. Does intra-articular injection of hyaluronic acid improve the ability to successfully perform activities of daily living (ADLs) or instrumental activities of daily living (IADLs)?

Key Question 4. Does intra-articular injection of hyaluronic acid improve quality of life? PICOTs are the same as for KQ1-3 with the exception of outcomes.

The effects of HA injection on pain and adverse events associated with HA injection were not included in the key questions posed by CMS. However because pain is regarded as an important component of effectiveness for treatments for OA of the knee and because safety is also an important treatment consideration, we volunteered to appraise this literature.

Figure 1. Analytic Framework

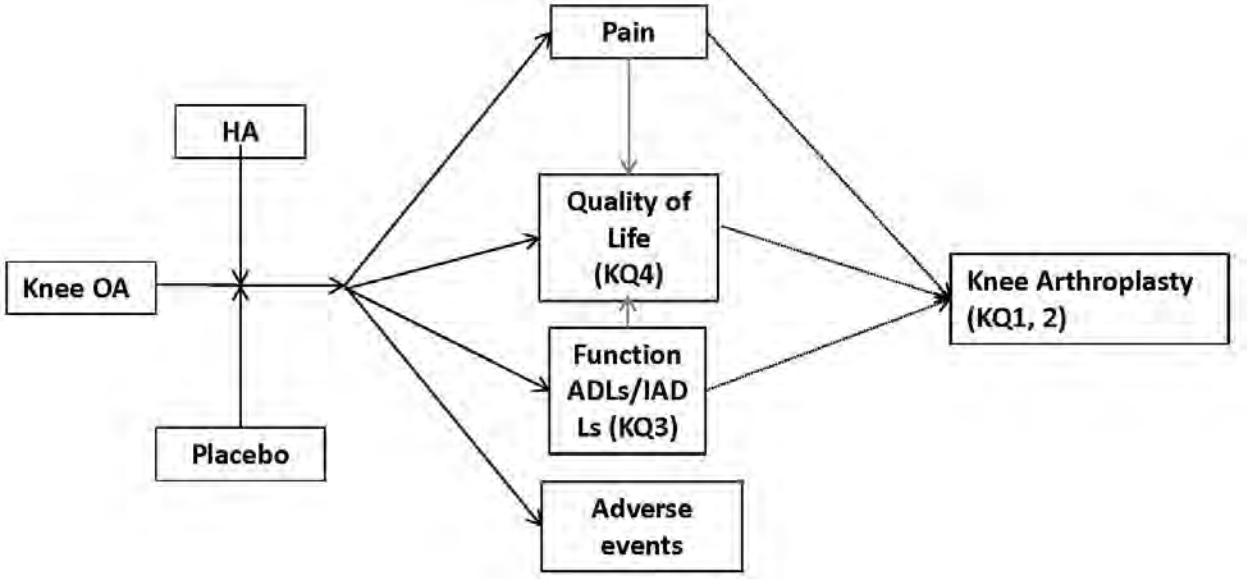


Figure notes: The framework shows potential outcomes of treatment with intraarticular HA (and placebo) the review sought to assess. These outcomes include a change in function, ADLs/IADLs (KQ3), a change in overall quality of life (KQ4), a change in pain, possible adverse events, and perhaps ultimately, a delay in TKR or decision not to undergo TKR, based potentially in part on some effect of treatment on pain, function, or quality of life.

ADL: Activities of Daily Living; DJD=Degenerative Joint Disease; HA=Hyaluronic Acid; IADLs=Instrumental Activities of Daily Living

Organization of this report

The remainder of this report presents the methods used to conduct the literature searches, data abstraction, and analysis for this review; the results of the literature searches; the conclusions; and a discussion of the limitations as well as suggestions for future research.

Methods

Criteria for Inclusion/Exclusion of Studies in the Review

This report is based on a systematic search for randomized placebo-controlled trials, head-to-head trials, or quasi-randomized trials that reported results for individuals whose average age was 65 or older; that assessed the effects of HA on function, quality of life, delay of TKR, prevention of the need for TKR, and adverse events (as well as factors that might affect these outcomes, such as age, disease severity, or comorbidities); and were powered to see a clinically important difference. If no randomized controlled trials were identified that assessed an outcome of interest, we included observational studies that assessed the outcome in question. Studies were included that enrolled individuals with other comorbidities and that enrolled community dwelling or institutionalized participants. The populations, interventions, comparators, outcomes, timeframes, and settings (PICOTs) of included studies are outlined below.

The efficacy of HA for pain relief has been reviewed in a large number of systematic reviews within the past two years, including a comprehensive 2012 systematic review and a 2015 network meta-analysis. Therefore, we addressed the outcome of pain, which is considered the primary outcome of HA treatment, by describing the findings of these two reviews in some detail, and reviewing any original studies published concurrently or subsequently and not included in those reviews.

To broaden our search for reports of rare adverse events, we included individual case reports and observational studies (prospective cohort studies and case series) that enrolled or followed more than 500 individuals' data.

PICOTs

- **Population(s):**
  - Individuals with severe OA of the knee (e.g., as characterized by a Kellgren-Lawrence grade of III, or a failure to respond to oral analgesics and anti-inflammatories) and no prior arthroplasty on the affected limb;
  - Comorbidities: studies that do not explicitly exclude individuals with any comorbidities that significantly and independently affect quality of life and activities of daily living (including involvement of the contralateral knee or of other joints) would be excluded or considered separately
  - Age 65 and over, male or female, community-dwelling or institutionalized (if studies enrolling only individuals 65 and over were not identified, we would broaden our inclusion criteria to include studies enrolling populations with mean age 65 and over)
- **Interventions:**
  Intraarticular Hyaluronan
- **Comparators:**
  - Placebo (sham treatment)
  - Non-steroidal anti-inflammatory drugs
  - Corticosteroids
  - Other forms/brands of hyaluronic acid

- **Outcome measures:**
  - Receipt of total arthroplasty surgery within follow-up time, length of time before undergoing surgery
  - Function and range of motion
    - WOMAC Index
    - Lequesne Functional Index
    - KOOS
    - Other validated functional scales
    - Range-of-motion assessment
  - Pain
    - WOMAC
    - VAS
    - Other tests included in prior systematic reviews
  - Activities of daily living/Instrumental activities of daily living
  - (Health-related) quality of life
    - Standard Form (SF)-36
    - EuroQol (EQ-5D)
  - Adverse effects of HA injection: physical effects, progression of disease (including flare ups)

- **Timing:**
  Surgical postponement outcomes: 12 months or longer
  Other efficacy outcomes: 3 months or longer

- **Settings:**
  All settings

Literature Search Strategies for Identification of Relevant Studies to Answer the Key Questions

The search strategy was based on one used for a 2012 evidence review on HA,[17] with the addition of search terms for the additional outcomes of interest: arthroplasty/total knee replacement, ADLs, IADLs (including terms for the tools commonly used to assess ADLs and IADLs, e.g., Lawton IADL scale, Katz Index), and quality of life (Appendix A). To test the search strategy, we checked for the inclusion of a set of 84 articles provided to us by the CMS.

PubMed, EMBASE, Web of Science, SCOPUS, and the Cochrane Collection were searched from January 1, 1990 to late November, 2013 to identify original studies of HA. An update search was conducted on December 12, 2014 dating back to six months prior to the initial searches, while the draft report underwent peer review. Any new articles identified by the update search or suggested by peer reviewers were screened using the methods applied initially. To capture unpublished or not-yet-published efficacy and adverse event findings, we searched the NY Academy of Sciences database of grey literature; Grey Matters, a grey literature tool from the Canadian Agency for Drugs and Technologies in Health; clinicaltrials.gov; and the FDA Pre-Market Approval (PMA) database. The AHRQ SRC contacted the manufacturers of HA devices approved for use in the United States to obtain scientific information packets (SIPS) on their products. Information obtained from the latter sources was checked against published data to ensure no duplicate data were included.

Systematic reviews of potential relevance were identified by searching the Cochrane Database. For the outcomes of function, ADLs/IADLs, quality of life, and prevention or delay of total knee replacement, systematic reviews were assessed for any original studies not already identified among the results of the searches. For the outcome of pain, we identified several recent comprehensive systematic reviews.

Only English-language studies were accepted for data abstraction. However, to ensure we were not systematically excluding studies that might report important outcomes, we screened the titles and English-language abstracts of a random selection of 30 non-English-language articles. Descriptions of these articles appear in Appendix E; none qualified for inclusion.

The output of the literature searches was transferred to DistillerSR™ for screening. Article titles and abstracts were independently screened by two reviewers with all selected articles obtained. A second round of screening was then conducted with full text to exclude articles that provided no usable data, reported duplicate data, enrolled participants whose mean age was less than 65 years of age, or reported no outcomes of interest. We searched accepted studies for additional references and screened any articles of apparent interest. For studies of potential interest reported in meeting abstracts (conference proceedings), we searched for peer-reviewed articles that reported the data; abstracts were not included as a source of original data.

Data Abstraction and Data Management

Articles accepted for inclusion were dually abstracted in DistillerSR, and any disagreements reconciled with the input of the project manager, SCEPC director, or local subject matter expert.

Study-level data (PICOTs) included the population demographics (average age, age range, sex, body mass index), comorbidities, disease stage, methods of ascertainment, intervention protocols, comparators, outcomes assessed in the study, and time course of interventions and follow-up.

Outcomes data were abstracted from original research studies for the following outcomes if reported: receipt of arthroplasty, time elapsed between HA therapy and surgery, change or improvement in ADLs/IADLs and other measures of function, QoL/Health-related QoL, and harms (adverse effects).

Assessment of Methodological Quality of Individual Studies

The quality/risk of bias (ROB) of trials that reported on efficacy outcomes was assessed using the Cochrane Risk of Bias tool[31] with the addition of several questions to assess elements of importance to this review. ROB was assessed in duplicate, with reconciliation of differences. A copy of the questions appears in Appendix D.

The quality of observational studies that reported on delay or avoidance of total knee replacement surgery was assessed using a modification of the Newcastle-Ottawa scale.[32] A copy of the criteria is included in Appendix D.

To assess the quality of included systematic reviews and meta-analyses, we used AMSTAR, a measurement tool for the assessment of multiple systematic reviews.[33] This tool contains eleven yes/ no items, such as whether the literature search was comprehensive, dual abstraction was used, and individual study characteristics are displayed. The tool has strong face and content validity, inter-rater reliability, and construct validity.[34] A copy is included in Appendix D.

We rated the quality of RCTs included in the assessment of adverse events (AEs) using the McHarms assessment tool.[35]

Data Synthesis

Studies Reporting on Efficacy. For the assessment of functional outcomes, we considered randomized placebo-controlled or head-to-head trials with blinded outcome assessment that reported changes in the score on a functional assessment scale (such as ADL/IADLS, WOMAC or Lequesne) or changes in a measure of quality of life. Trials might report more than one outcome.

For RCTs that compared the effects of interventions with HA with placebo for functional outcomes (WOMAC, Lequesne, or KOOS scales), most trials reported the WOMAC as the measure of function; followup times ranged from 4 to 52 weeks (all but three studies reported outcomes at 6 months). A standardized effect size was calculated for trials that reported a mean change from baseline by treatment group for a continuous outcome. In some cases, a mean change from baseline was not reported, but the mean outcome at baseline and at follow-up was reported. Using this information, we could estimate the mean change from baseline. Because various scales (or various ranges of the same scale) were reported, we calculated a standardized effect size. This provides a unit-less measure. For trials that did not report the standard deviation of the mean change, one was estimated using the standard deviations of the baseline and follow-up means. If a follow-up standard deviation was not reported, then we assumed that the standard deviation was one-fourth the theoretical range for the specific measure in the trial.

For each comparison of interest, an unbiased estimate of Hedges' g effect size[36] and its standard deviation were calculated. A negative effect size indicates that the treatment group is doing better than its comparator group (i.e. placebo group or other active comparator). For trials that reported the number of patients having total arthroplasty, a Peto's odds-ratio (OR) was estimated. An OR less than 1 indicates that the treatment group has fewer arthroplasty patients then the comparison group.

Three or more trials similar in outcome and treatment comparison were considered for meta-analytic pooling. Since some trials reported only the Lequesne score, we looked at trials that reported both the WOMAC and the Lequesne score to see if conclusions were the same. If so, then we felt justified in pooling the WOMAC and Lequesne score together. For trials that reported more than one follow-up time, the time closest to 26 weeks was used. Sensitivity analyses were conducted by excluding trials with follow-up times not close to 26 weeks. For comparisons that had at least three trials, we derived a pooled estimate of the overall effect size using the Hartung-Knapp-Sidik-Jonkman (HKSJ) method for our random effects meta-analysis.[37] This method has been preferred when the number of pooled studies is small. It has been shown that the error rates are more acceptable than the previously used DerSimonian and Laird method.[38] Publication bias was assessed for all pooled outcomes using the Begg adjusted rank correlation test[39] and Egger regression asymmetry test.[40] Heterogeneity was assessed using the I^2 test.[41] An effect-size or odds ratio was calculated for trials that reported data but did not contribute to a pooled analysis. All efficacy analyses were conducted with Stata statistical software, version 12.0 (Stata Corp., College Station, Texas).

To obtain an estimate of the clinical importance of the pooled effect size for function (which represented a standardized mean difference), we compared it to the minimum clinically important difference (MCID) or minimum clinically important improvement (MCII) derived for large groups of patients with OA of the knee undergoing similar treatments and used in the two most recent comprehensive systematic reviews (including the OMERACT-OARSI

recommendations) as well as the MCII derived by Tubach and colleagues and used in a recent trial included in the report.[17, 42-46]

In addition to obtaining the standardized effect size for each trial, we attempted to abstract the proportion of participants who reported improvement in function; a subset of studies reported on global improvement only.

The RCTs that compared active treatments head to head were not pooled, as the numbers of studies comparing the same interventions were insufficient. Similarly, the numbers of studies that reported on ADLs or quality of life were insufficient to allow pooling. The results are reported narratively. RCTs reporting on total knee replacement/arthroplasty were also small in number and are described narratively. Because only three RCTs reported on arthroplasty (and only one considered it as a treatment outcome), we included observational studies that assessed arthroplasty. The results of these studies are described narratively.

The effect of HA treatment on pain has been assessed in a number of recent systematic reviews, including one relatively high quality review published in 2012. This review pooled 71 RCTs that met their inclusion criteria of a minimum of 3 months follow up (without regard to type of control or mean age of participants); in addition, they pooled only the 18 trials that had both placebo (sham) controls and enrolled more than 100 participants per study arm. They also conducted stratified analysis on a number of potential effect modifiers, including use of a sham control intervention. We describe the findings of this review and subsequent studies that reported on pain as an outcome narratively.

Studies Reporting on Adverse Events. Trials of any length were considered for the safety analysis. The AHRQ EPC Scientific Resource Center (SRC) contacted manufacturers of all HA devices approved for use in the US; citations for published studies received from manufacturers were deduplicated with published studies already identified in the literature searches. No unpublished data were provided. We also accessed the Food and Drug Administration (FDA) PostMarketing Assessment (PMA) database for information posted about HA products (code MOZ) this database includes information for six products approved for use in the US. Finally, we accessed the FDA Manufacturer and User Device Experience (MAUDE) database; however, we did not include MAUDE data in the report because the ages of the individuals about which the reports were filed could not be determined and because we did not include single case reports of adverse events.

Adverse event data extracted from RCTs included the name of each trial group, the description of the adverse event from the original article, the number of subjects in each group, and the number of subjects with each adverse event. Each event was counted as if it represented a unique individual. Because a single individual might have experienced more than one event, this assumption may have overestimated the number of people having an adverse event. Events described as adverse events or harms (and reported as part of a safety assessment) were extracted regardless of whether the study authors described them as being unrelated or related to the interventions.

Adverse events reported in RCTs were grouped using clinical expertise into three categories: local, joint, and other. Within those categories, events were further categorized as serious or not serious. For groups of events that occurred in three or more trials, we performed a meta-analysis to estimate the pooled odds ratio and its associated 95% confidence interval. Given that many of the events were rare, we used exact conditional inference to perform the pooling rather than applying the usual asymptotic methods that assume normality. We conducted the meta-analyses using the statistical software package StatXact Procs v9.0 (Cytel Software, Cambridge, MA).

Any significant pooled odds ratio greater than one indicates the odds of the adverse event associated with HA are larger than the odds associated with the comparison (placebo or active control) group.

Adverse events were also abstracted from prospective cohort studies and case series of 500 or more patients, and case reports of individuals age 65 or older.

Grading the Evidence for Each Key Question

The overall strength of evidence (SOE) was assessed for each conclusion within each key question using the EPC modification of the GRADE system.[47] Domains included were study limitations (risk of bias), directness, consistency, precision, and reporting bias (definitions and criteria for these domains are provided in Appendix G).[48] This method classifies the evidence according to the following criteria:

High = High confidence that the evidence reflects the true effect. Further research is very unlikely to change our confidence in the estimate of effect.

Moderate = Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of effect and may change the estimate.

Low = Low confidence that the evidence reflects the true effect. Further research is likely to change our confidence in the estimate of effect and is likely to change the estimate.

Insufficient = Evidence either is unavailable or does not permit a conclusion.

The applicability of the findings was assessed based on age, community residence, comorbidities, weight status, and study size.

Peer Review and Public Commentary

A draft version of the report was posted for peer and public comment on December 9, 2014. The report was revised in response to those comments.

Results

Introduction

This chapter first describes the results of the literature searches and then provides the results for the outcomes of interest in the following order: delay or avoidance of total knee replacement; measures of function, including ADLs/IADLs; quality of life; pain; and adverse events.

Results of Literature Searches

The searches of peer reviewed literature identified 2,461 unique titles (Figure 2). The partner, CMS, provided 84 titles, of which all but 9 were already included in the search results. Reference mining of those studies yielded an additional 10 titles. The searches of grey literature yielded 48 titles. Information provided by manufacturers (Scientific Information Packets (SIPs)) included two titles, of which two unique titles were accepted. Altogether, 2,528 titles and abstracts went on to dual screening.

Of the 2,528 titles, 512 were initially identified for full-text review. The remaining 2,016 titles and abstracts were rejected for being animal or in vitro studies (405), not reporting on OA of the knee (324), not using intra-articular HA injections (417), not reporting any outcomes of interest (170), having an inappropriate study design (e.g., obvious commentaries or non-systematic reviews) (407), not enrolling a population of interest (30), or being written in a non-English language (258). Three articles could not be obtained and two had duplicate data.

A second level of screening was conducted on the 512 titles and abstracts initially identified for full-text review. Of the 512 titles, 366 were rejected: Studies were rejected at this stage for the following reasons: language not English (8), study design (124); participants excluded (10); interventions not of interest (7); outcomes not of interest (103); mean age less than 65 (78); AE reports with sample size less than 500 (29); or duplicate data (7). Of the remaining 83 studies, two systematic reviews were accepted, 81 were background articles, and 63 were original studies that underwent detailed abstraction. These included RCTs that reported function, ADLs/IDLs, QoL, arthroplasty, and/or AEs (25); case series or prospective cohort studies reporting AEs or arthroplasty (total knee replacement) (20); or case reports reporting AEs (18). Of the case series and cohort studies that reported AEs, only those that enrolled populations of 500 or greater were included, to ensure detection of rare AEs. Appendix B provides a list of excluded studies with the reasons for exclusion.

Figure 2. Literature Flow Diagram

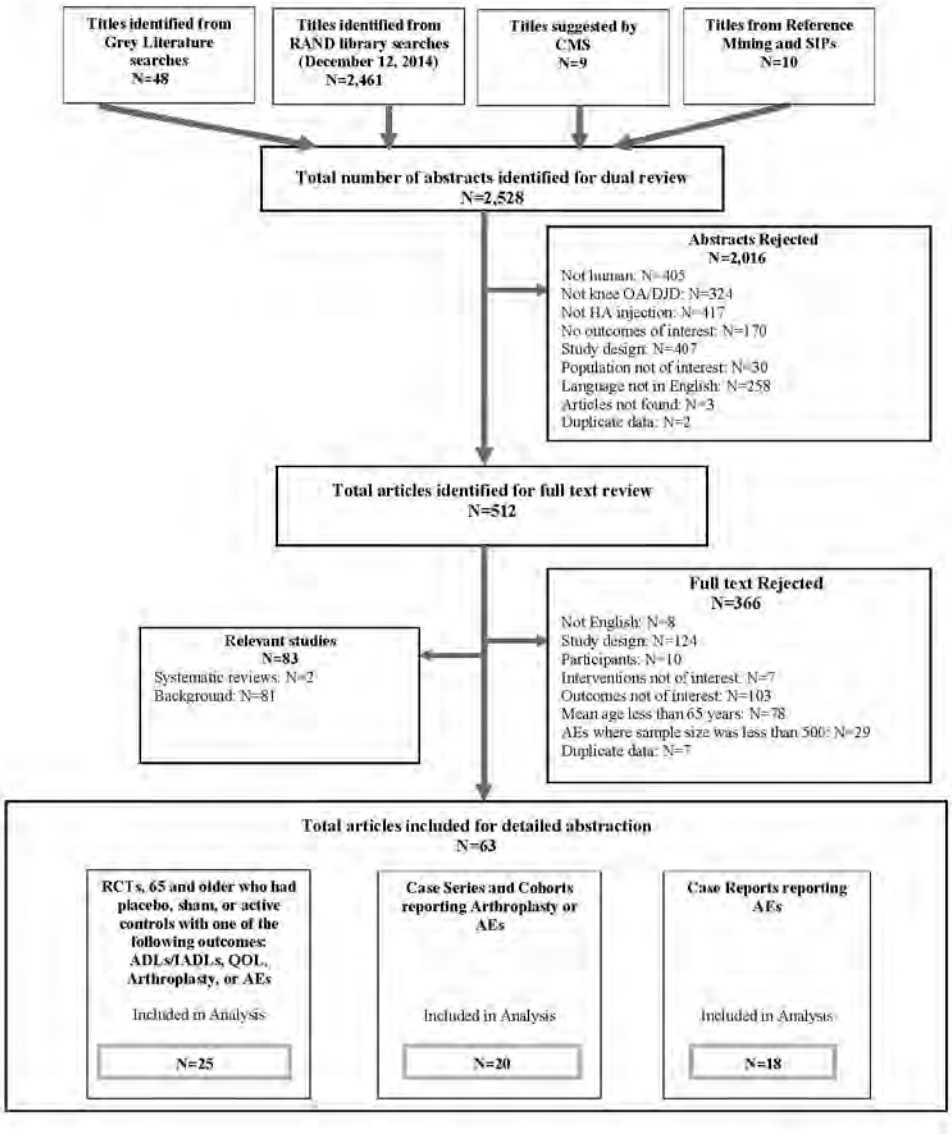


Figure Notes: ADLs=Activities of Daily Living; IADLs=Instrumental Activities of Daily Living; AEs=Adverse events; CMS=Center for Medicaid Services; SIPs: Scientific Information Packets

Table 2. Strength of Evidence

Outcome	Strength of evidence Grade	Study Design	No. Studies (N)	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Other Issues	Finding
Arthroplasty	Insufficient	RCTs Observational	2 13	High	Direct	Consistent	Imprecise	Suspected	TKR not intended outcome	No pooled effect size
Function: HAs vs. placebo	Low	RCTs	10	Moderate	Direct	Inconsistent	Precise	None	2ndary outcome	-0.23 (-0.34, 0.02)
Function: HA vs. HA	Insufficient	RCTs	5	High	Direct	Inconsistent	Imprecise	unknown	2ndary outcome	No pooled effect size
Quality of Life	Insufficient	RCTs	2* 1	High	n/a	n/a	n/a	n/a	Different outcome measures	No pooled effect size
Adverse Events: total	Moderate	RCTs Observational cohort case reports	25 4 18	Moderate	Direct	Consistent	Precise	Unknown	Cohort studies included patients<65	Similar rates of AEs were reported in studies of HA and placebo
Adverse Events: serious (SAEs)	Moderate for the rarity of SAEs; Low for a difference between the intervention and placebo groups	RCTs	25	Moderate	Direct	Consistent	Imprecise	Unknown	Causal mechanism not proposed for some SAEs	Joint: 0.77(0.25, 2.31) Other: 0.62(0.23, 1.57)

Table Notes: *Two trials compared Synvisc® to Hyalgan;® one trial compared Hyalgan® to saline. Each used a different measure

Delay or avoidance of knee replacement surgery

Three RCTs and 13 observational studies reported on knee replacement (TKR) after administration of intra-articular HA injections. Of the three RCTs, only one assessed TKR as a prespecified outcome; the other two reported it as a treatment failure.

Key Points

- Three RCTs enrolled small numbers of patients and reported on TKR, although it was not a prespecified outcome of interest in two of the studies: One reported higher rates of TKR among HA-treated patients, whereas the other two reported higher rates among placebo-treated patients.
- Six case series and seven cohort studies reported on TKR as an outcome following HA treatment. Most studies reported delays in TKR in patients who received HA injections compared with the usual progression among patients who did not receive TKR, or lower rates of TKR in patients receiving HA than usually seen in the absence of such treatment. Two studies that assessed risk factors for undergoing TKR among patients who received HA found that only baseline severity and age were factors: those in the 60 to 69 year old age range in one study and in the 65 to 79-year range in the other were significantly more likely than those younger or older to undergo TTKR, and in the former study, the time from diagnosis to TTKR was faster for this age group. No study reported the criteria for knee replacement surgery or the characteristics that distinguished those who underwent surgery.

Detailed Synthesis

No systematic reviews were identified that reported on studies assessing the rate of TKR among patients who were treated with HA.

Randomized Controlled Trials. We identified three randomized trials[49, 50,51] that reported the number of people who underwent arthroplasty. However, TKR was a pre-specified outcome of interest in only one of the studies, and the others showed indications of high risk of bias. Two of the three trials demonstrated non-significant trends, indicating that fewer people in the Hyalgan® group had arthroplasty than the placebo group.

A 1993 study by Dougados and colleagues was a 1-year trial of Hyalectin, a higher molecular weight avian product (four weekly doses) vs. saline placebo (quality assessed as moderate risk for bias).[49] A group of 110 patients (mean age 68, 71% women) were divided into two groups; the primary outcome was improvement in effusion and secondary outcomes were pain and function. Between week 7 and 52, two patients in the active intervention group and 5 in the placebo group underwent TKR (OR 0.41, 95% CI 0.09, 1.89).

A 2003 study by Forster and Straw was a 1-year trial of Hyalgan, a lower molecular weight avian product (5 weekly doses) vs. arthroscopic washout (quality assessed as moderate risk).[50] A group of 38 patients (mean age 62, proportion of women not reported) were randomized into the two groups. At 1 year, two patients from the active intervention and one patient from the arthroscopy group had undergone TKR; one patient from the active intervention and two patients from the arthroscopy group were on a waiting list for TKR; and two additional patients from the active intervention group had undergone arthroscopy and were on a waiting list for TKR (OR 0.54, 95% CI 0.08, 3.59).

A 2008 study by Blanco and colleagues was a 1-year trial of two cycles of Hyalgan (5 weekly doses each) vs. placebo control (quality assessed as low risk of bias).[51] A group of 42 patients (mean age 67.9, 76% women) on the waiting list for TKR were randomly assigned to the two treatment groups. The primary outcome was avoidance or delay of TKR; secondary outcomes included WOMAC pain, function, and stiffness, and adverse events. At one year, survival analysis showed a non-statistically significant higher survival time until knee replacement in the HA group compared with the placebo group (368.8 days vs. 253.9 days, p=0.249). The proportion who discontinued treatment at 24 weeks due to lack of efficacy was also non-statistically significantly higher in the placebo group (87% vs. 64%, p=0.06). Knee surgery was avoided in 9 HA-treated patients and 3 placebo-treated patients (OR 0.30, 95% C, 0.08, 1.10). The randomized trials are described in evidence tables included in Appendix C.

Observational Studies. Six retrospective case series (reported in 7 articles) reported on TKR as an outcome (Table 3).[52-58] Numbers of enrolled patients ranged from 69 (73 knees) to 1,342 (1,863 knees). Three of the studies administered Hylan GF-20 (Synvisc®, a higher molecular weight avian product), one administered Hyalgan, one administered Suplasyn, a lower molecular weight synthetic, and one administered Supartz™, a medium-high molecular weight avian hyaluronic acid. Follow-up times ranged from 6 months to 12 years. Rates of TKR in these studies of HA-treated patients varied from fewer than 1% for 310 patients treated with Suplasyn and followed for 6 months,[55] to 25% of 1,863 knees treated with Hylan GF-20 and followed over 12 years.[58] None of the studies specified the criteria used by the treating physicians for recommending patients to undergo surgery, although all 863 patients included in the study by Waddell and Bricker were classified as Kellgren-Lawrence stage IV[56], had failed to obtain relief from pharmacologic agents, and were considered candidates for TKR.

Two medium[52,54] and one large[56] case series on patients treated with HA assessed the effect of various factors on the likelihood of these patients undergoing TTKR and the time to TTKR by age group. One medium-size 2002 study[52] by Barrett and colleagues reported that those who underwent TTKR tended to be older than those who did not but that BMI did not differ between the groups. The other medium sized study, a 2001 study by Evanich and colleagues, reported that those with Grade IV (67%) and those 65-79 years of age (34%) were more likely than those with less severe disease or in older or younger age groups to get TKR. [54] The largest study, a 2007 study by Waddell and Bricker, found that the likelihood of stage IV patients undergoing TKR did not differ by sex, BMI, history of effusion, or baseline VAS for pain. Only age range was a factor: HA-treated patients 60 to 69 were significantly more likely to undergo TKR than patients under 50, patients 70 to 79, and those over 80, and patients in the younger age groups (50–79) were 2-3-fold more likely to get a TKR than those 80 and over. Median time to TKR for HA recipients was 1.8 years (range 14–2,147 days). Median followup time was 2.2 years (7–2,222 days). Seventy-five percent of knees had not had TKR by 3.8 years. Time to TKR was associated only with age: 60-69 year olds had a significantly shorter time to TKR than other age groups.[56]

A subsequent followup of the Waddell and Bricker study re-assessed the 863 patients who were treated between 1997 and 2003 as well as the full cohort of 1,342 patients who continued to be followed through 2010.[58] The number of treatment courses ranged from 1 to 7. For the original cohort, the mean observation period (time to TKR) for patients who underwent TKR was 3.1 years; patients who did not undergo TKR were observed for a mean of 10.9 years. The overall incidence of TKR was 28% in this group. For the full cohort, the mean observation period (time to TKR) for patients who underwent TKR was 2.8 years; patients who did not undergo TKR were followed for a mean of 8.7 years (mean for all patients 7.2 years). The rate of

TKR for the full cohort was 25%. A comparison group of stage IV patients who did not elect HA underwent TKR within 3 months. Survival analysis demonstrated that HA treatment delayed the need for TKR in 75% of patients by 7.3 years. As in the original analysis, age was the only factor associated with tendency to undergo TKR.

Several other case series also reported on the average or longest time to TKR in treated patients. For example, the case series by Barrett and by Evanich reported mean lag times of more than 6 months in those who underwent the procedure,[52,54] and a large 2010 multi-site study of Supartz™ by Whitman reported that the mean time to TKR was 1.99 years and time to TKR was as long as 4 years.[57]

Nine articles reported on seven cohort studies that assessed TKR as an outcome (Table 4).[59-67] Numbers of enrolled patients ranged from 76 (92 knees) to 1,047 (1,489 knees). All studies enrolled patients with mean ages over 65, except one.[66] Three studies administered Hylan GF-20 (Synvisc); two administered Hyalgan; one administered Durolane, a non-avian product of medium molecular weight administered as a single injection; and one administered Adant, a non-avian medium molecular weight product administered in three to five weekly doses. Follow up times ranged from 6 months to 4.5 years. Rates of TKR varied among studies as did the methods of reporting. One study that administered Hyalgan reported that over two years, 12 of 15 patients originally scheduled for TKR cancelled the procedure.[59] The study that reported its findings in three articles reported that over a followup of 24 months, 20% of patients underwent TKR;[62] over 54 months, 28.4% of patients had undergone TTKR, with a mean time to surgery of 15.4 months.[61] When they stratified patients by Ahlback Grade, 4% of patients in the lowest severity group (Ahlback Grades of 1 or 2) underwent TKR, 32.9% of patients in the medium severity group underwent TKR, and 13.4% of patients in the highest severity group underwent TKR.[63] Hylan GF-20 was associated with lower rates of TKR in two studies by the same group,[64, 65] but with a 22% rate of TKR in another study.[66] As with the retrospective studies, no study specified the criteria used to recommend patients proceed to TKR.

A modification of the Newcastle-Ottawa instrument was used to assess the risk of bias of the included observational studies (Table 5). Risk of bias varied, with most studies indicating scoring on the moderate to high risk of bias side. Few studies attempted to control for baseline differences in comorbidities, few reported financial conflicts of interest, and patients were aware of their treatment in every instance.

Table 3. Case Series Reporting on Knee Replacement as an Outcome

Author, Year Country	# patients/ mean age (SD)/age range/ % female/ mean BMI/ mediating factors	Inclusion criteria/ exclusion criteria	Intervention/ dosing schedule/ follow-up times	Outcomes reported	Efficacy results	AEs results	Conclusions and comments
Evanich, 2001[54] US	84 patients /66±14 years/age range NR/61% women/BMI NR	First 100 knees to receive HA at authors' clinic	Hylan GF-20 (Synvisc) 3 injections FU 12 months	Pain, function, TKR, other procedures (CS injection, arthroscopy) over 12 months	Loss to followup 14 patients; 80 knees in 70 patients followed over 12 months 20 of 80 (25%) knees underwent TTKR (20 patients) at an average of 6.7 months Those with Grade IV (67%) and those 65-79 years of age (34%) were more likely than those with less severe disease or in other age groups to get TKR. 2 more had arthroscopy.	12 knees experienced AEs: 1 case of staph septic arthritis (2 weeks post initial injection), 11 cases of pain and swelling	Higher and lower age (compared with 65-79 years) and lesser severity decreased likelihood of undergoing TTKR. Outcomes assessed by clinic nurse, not patient's own provider
Barrett, 2002[52]	249 patients (363 knees) treated Mean age 72 years /range 30-97 years/ 51.2% female/ BMI 29 Non-participants (those unavailable to be assessed): 127	Inclusion: ACR OA diagnosis and radiogram within prior 6 months, completion of 5-injection course Exclusion: receipt of 2nd course within 12 months (to study effects of single treatment	Hyalgan 5 injections/ 1 per week 6 months	Lack of TTKR or other significant intervention therapy; secondary outcomes assessed in patients who avoided TKR: QOL, pain (reported as improvement ,	60.1% of knees (61.8% of patients) were considered clinically improved at 6 mos. 39.9% were judged as failures (20.3% underwent TTKR); Risk for TKR depended	"Excellent safety profile"	Single-course Hyalgan delayed or avoided TTKR for at least 6 months in the majority of knees. Successes tended to be younger but did not differ on BMI Comment: 1. Unclear

Author, Year Country	# patients/ mean age (SD)/age range/ % female/ mean BMI/ mediating factors	Inclusion criteria/ exclusion criteria	Intervention/ dosing schedule/ follow-up times	Outcomes reported	Efficacy results	AEs results	Conclusions and comments
	(176 knees)	course); significant alteration in exercise routine within 6 months		non-improvement)	somewhat on compartmental involvement		whether comparison group received treatments or what their success rate was 2. one of the 2 authors is employed by the manufacturer
Campbell, 2004[53]	69 (73 knees)/ 62.2 years /range 37-90/ 44% women	Inclusion: Confirmation with plain x-rays or arthroscopy; Exclusion: none	Hylan GF-20 (Synvisc) 3 injections immediately after arthrocentesis Mean FU 8 months	Subjective improvement, total knee replacement, other treatments	61 patients identified for followup (90%) 51% of respondents reported a range of improvement; 11 patients underwent surgery including 7 knee replacements	Swelling/redness (6 patients) Pain at injection site (12) Apparent sepsis (3)	Patients were allowed to continue other methods of management; HA provided short-term relief for about half of patients but authors had largely discontinued use
Mazieres, 2007[55] France MESSAGE Study	310 patients, 296 of whom were assessed for outcomes:/69± 10 years/age range 36-88; 65% women/BMI 28±5 (30% obese) 36.5% of patients had both knees affected	Inclusion:>18 years; knee OA meeting ACR criteria; inadequate self- or MD-reported response to level 1 or 2 analgesics or NSAIDS within last 3 months Exclusion: effusion; history of intra-articular CS therapy within past 3 months,	Suplasyn 3 injections FU 3 months, 6 months	Kellgren Lawrence, Lequesne; WOMAC pain and function, QoL (SF-12); costs (including procedures)	Of the 310, 14 were withdrawn early; 296 patients were assessed for outcomes: 1 partial TKR and 1 TKR were performed; significant improvements in WOMAC, Lequesne, SF-12	NR	<1% TTKR after at least 2 injections Suplasyn

Author, Year Country	# patients/ mean age (SD)/age range/ % female/ mean BMI/ mediating factors	Inclusion criteria/ exclusion criteria	Intervention/ dosing schedule/ follow-up times	Outcomes reported	Efficacy results	AEs results	Conclusions and comments
		history of HA therapy within last year; scheduled surgery on target knee; contraindications to intra-articular injections; known hypersensitivity to HA; pregnancy					
Waddell, 2007[56] Waddell, 2014[58] US	1,187 knees (863 patients)/mean age of patients who underwent TKR: 66.8±10.02(36-89), patients without TKR: 67.5±13.3 (28-98); 60% Female for both groups	Inclusion criteria: Any grade OA; unsuccessful treatment with NSAIDs and analgesics (WOMAC or pain VAS score of 50 or more) Exclusion criteria: mechanical problems, deformities due to OA, contraindications to HA (hypersensitivity, target knee joint infections, skin diseases, infections in area of injection site) (inclusion criteria for TKR: K-L Grade IV and VAS pain score ≥60)	Hylan GF-20 (Synvisc) 3 injections (1997-2003) administered using a fluoroscopic technique to ensure accurate needle placement; repeat courses for some patients; prescription pain killers allowed for post injection pain and swelling FU 5 years	Primary outcome time to TTKR	19% of knees treated with HA underwent TKR. Undergoing TTKR did not differ by sex, mean age, BMI, history of effusion, or baseline VAS for pain. Only age range was a factor. Patients 60-69 were significantly more likely than patients under 50, patients 70-79, and those over 80 to undergo TKR, and patients in the younger age groups (50-79) were 2-3 fold more likely to get a TTKR than	NR	Retrospective case series review; TKR candidates who are not candidates for HA in this clinic typically undergo surgery within 3 months of first visit; in comparison, median time to TKR in HA recipients was 638 days (median followup 810 days). Authors acknowledge lack of information on patients who did not receive TKR within the followup time and other limitations.

Author, Year Country	# patients/ mean age (SD)/age range/ % female/ mean BMI/ mediating factors	Inclusion criteria/ exclusion criteria	Intervention/ dosing schedule/ follow-up times	Outcomes reported	Efficacy results	AEs results	Conclusions and comments
					those 80 and over. Median time to TKR for HA recipients was 1.8 years (14-2,147 days). Median followup time was 2.2 years (7-2,222 days). 75% of knees had not had TKR by 3.8 years. Time to TKR was associated only with age: 60-69 year olds had a significantly shorter time to TKR than other age groups.		
Whitman, 2010[57] US	220 patients (303 knees); average age 70.9; range 35-99; 74.5% female	Inclusion: age≥18 years, confirmed diagnosis of OA, at least one repeat treatment with Supartz™ Exclusion: NR	5 weekly injections, follow-up 5 years	Pain, TKR, AEs	Overall rate of TKR: 23/303 (7.6%) Local site rates (5 sites) ranged from 1.8% to 24.0%. Mean time to TKR 1.99 years (0.5 to 4 years)	26 total AEs none severe	Supartz was thought to delay or prevent need for TKR. 92 percent of patients reported improvement in pain

Table Notes: CS corticosteroids; FU follow-up; HA hyaluronic acid; OA osteoarthritis; TKR total knee replacement

Table 4. Cohort Studies Reporting on Total Knee Replacement as an Outcome

Author, Year Country	# patients/ mean age (SD)/age range/ % female/ mean BMI/ mediating factors	Inclusion criteria/ exclusion criteria	Intervention/ dosing schedule	Outcomes reported/Follow-up times	Efficacy results	AEs results	Conclusions and comments
Neustadt, 2003[59] US	76 patients (92 knees)/64±7.4 years/40-80 years/60% > 65 years/21% female	Authors did not specify inclusion or exclusion criteria but all patients had moderate-severe OA, Kellgren-Lawrence II-IV, pain unresponsive to conventional treatments	Hyalgan 5 weekly injections	Physical exam, radiographs, AEs, ADLs/QoL, TKR/ weekly and then at 6, 12, and 24 months	72% of patients achieved >50% improvement in in pain for ≥1 year 12 of 15 patients scheduled for TKR no longer considered procedure necessary at 1 year; 15 of 19 avoided or delayed TKR at 2 years.	No systemic AEs Minor AEs were infrequent and included injection site bruising and pain, rare headache, nausea; no pseudoseptic reactions	HA seemed to be associated with reduced need for TKR. Improvement decreased with increasing Kellgren-Lawrence score, but this was not determined for TKR
Waddell, 2005[65] US	85 patients (66 completed 26 weeks, 24 completed 104 weeks;)/65.5±11.1 years/64.8% female	Inclusion criteria: healthy, ambulatory men or women aged _40 years; diagnosed with OA (at least 3 months earlier, ACR criteria); WOMAC score ≥2 on pain while walking on a flat surface; a score of 50-90 mm VAS; failure to obtain OA knee pain relief with previous therapy of analgesics or NSAIDs; having received a clinical	Hylan GF-20: 3 weekly injections	Pain, mobility, medication, AEs, TKR (counted as reason for loss to followup), 104 weeks follow-up	At 52 weeks, of 59 remaining patients, 1 patient had undergone TKR. No more TKRs were reported through 104 weeks.	AEs were reported only as possibly, probably, or definitely treatment-related. 1 patient experienced severe arthrosis. No AE-related discontinuations	Repeated course of HA provided continued pain relief

Author, Year Country	# patients/ mean age (SD)/age range/ % female/ mean BMI/ mediating factors	Inclusion criteria/ exclusion criteria	Intervention/ dosing schedule	Outcomes reported/Follow-up times	Efficacy results	AEs results	Conclusions and comments
		benefit from an initial course given at least 3 months prior. Exclusion: any serious systemic disease or significant psychiatric or neurological disorder; pregnant or nursing women, or women of childbearing age not using reliable birth control; known allergy to avian products, any components of hyaluronan-based injection devices, or corticosteroid injections; acetaminophen hypersensitivity; or use of an investigational drug or device within 90 days prior to the study; other joint diseases or conditions; patella femoral knee pain; acute synovitis; palpable effusion at screening or					

Author, Year Country	# patients/ mean age (SD)/age range/ % female/ mean BMI/ mediating factors	Inclusion criteria/ exclusion criteria	Intervention/ dosing schedule	Outcomes reported/Follow-up times	Efficacy results	AEs results	Conclusions and comments
		baseline; local AE with first course of hylan G-F 20; history of any joint sepsis; major surgery or arthroscopy in either knee within 6 months before screening or planned during the study; arthroplasty at the target joint; oral or intra-articular corticosteroid or any other intra-articular injection at the target joint within 3 months, or at a non-target joint within 4 weeks of screening; or use of glucosamine or chondroitin sulfate within 30 days prior to study entry					
Waddell, 2006[64] US	1,047 patients (1,489 knees)/mean age 65.3/60% female 71% grade IV Kellgren-Lawrence	Inclusion criteria: OA diagnosis, lack of response to NSAIDS and analgesics Exclusion criteria: mechanical symptoms or deformities due to OA, contraindications to	Hylan GF-20: 3 weekly injections	Pain, mobility, medication, AEs, TKR, 26 weeks follow-up	21 patients (2%) underwent TKR before the end of the 26-week followup period	49 patients experienced 54 local AEs (pain and swelling) 12 patients experienced severe local pain and swelling. All resolved spontaneously or with aspiration and	Proportion of patients who underwent TKR was low

Author, Year Country	# patients/ mean age (SD)/age range/ % female/ mean BMI/ mediating factors	Inclusion criteria/ exclusion criteria	Intervention/ dosing schedule	Outcomes reported/Follow-up times	Efficacy results	AEs results	Conclusions and comments
		HA				corticosteroids. AEs did not affect efficacy.	
Turajane, 2007a,[62] Turajane, 2007b[63] Turajane, 2009[61] Thailand	195 patients (220 knees) /68.74 years/ range 50-84 years/75% female/BMI 25.21	Inclusion criteria: Primary knee OA by ACR criteria, failure of conservative treatment more than 6 months (anti-inflammatories), no contraindication for surgery Exclusion criteria: other degenerative arthritis or other joint disease, previous surgery, allergy to avian protein or sodium hyaluronate, any intra-articular treatment within prior 6 months	Hyalgan: 3 weekly injections, at least 1 course Patients who responded well received additional courses at 12-month intervals	Cost analysis of HA after ≥2 years follow-up WOMAC, delay or cancellation of surgery, AEs Follow-up >24 months (24-48 months) Time to TKR over 54-month follow-up	183 patients (206 knees) completed treatment; 146 patients (164 knees) responded to HA; 37 patients required surgery by 24 months (20%). Of the responders, 83 patients received a second course of tx and 14 received a third course. WOMAC improved in all groups. Group 1 (Ahlback grades 1,2):89.1% of patients delayed or cancelled knee surgery; 10.9% underwent surgery: 2 underwent TKR, 3 arthroscopy Group 2: 67.1% delayed/cancelled surgery; 23 patients (32.9%) underwent TKR Group 3: 86.5% delayed surgery; 13.4% underwent TKR	NR	Retrospective cohort study enrolled 2001-2004 HA is cost effective Repeated courses of HA were efficacious in delaying TKR in patients who responded to tx

Author, Year Country	# patients/ mean age (SD)/age range/ % female/ mean BMI/ mediating factors	Inclusion criteria/ exclusion criteria	Intervention/ dosing schedule	Outcomes reported/Follow-up times	Efficacy results	AEs results	Conclusions and comments
					Incidence of TKR: 28.4% Mean time to TKR: 15.4 months (0.7-51.7 months) Mean follow-up time for patients who did not undergo TKR was 45.6 months (19.0-53.1 months)		
Anand, 2010[66] US	167 patients/ mean age 59.4 (range 15-92)/57% female Ahlbeck classification used: 1 Grade 1, 20 Grade 2, 104 Grade 3, 5 Grade 4	Inclusion criteria (for analysis): 1 completed course of HA, failure at previous protocol (NSAIDS, strength training, weight reduction, shoe modification, bracing, topical anesthetics, intra-articular CS) 119 patients had undergone prior arthroscopy.	Patients offered HA or TKR; all opted to try HA: Synvisc (1999-2003)	Self-reported satisfaction, TKR, AEs/6 months—5 years FU	130 patients underwent chart evaluation. Average number of courses HA: 1.6, 6-36 months between intervals. 45 patients were advised to proceed to surgery (including 17 who responded poorly at 6 months). 29/45 underwent surgery, including 24 TKR and 5 partial (22%). All TKR patients were Grade 3-4 at baseline. Of 109 patients seen at 5-year followup, 58.7% had not had surgery and were doing well.	3 patients developed toxic synovitis	Authors conclude HA can delay need for TKR
Korkmaz, 2013[67] Turkey	705 patients/ mean ages and sex ratios reported by	Inclusion criteria: ACR diagnosis Exclusion criteria: intra-articular	218 patients received Adant once weekly for 3	Surgical intervention at 1-year follow-up	197 patients received all HA treatments. Of those patients, 20 surgical procedures	NR	Rates of total surgical procedures did not differ

Author, Year Country	# patients/ mean age (SD)/age range/ % female/ mean BMI/ mediating factors	Inclusion criteria/ exclusion criteria	Intervention/ dosing schedule	Outcomes reported/Follow-up times	Efficacy results	AEs results	Conclusions and comments
	diagnostic group and treatment group; only Grade 4 patients in the HA group had mean age>65 (68±13.3)	injection within prior 3 months; arthroscopic intervention within prior year; history of pain with intra-articular injection	weeks; 487 patients received only NSAIDs and exercise prescriptions (2007-2009)		were done, including 7 TKR (3 were done in patients with grade 3 OA and 4 in patients with grade 4 OA). Of 487 patients who received NSAIDs, 62 had surgery, including 26 TKR		between groups but there was a non-significant decrease in procedures among those with the most advanced OA treated with HA (compared with NSAIDS) and in TKR among the HA-treated groups
Jurado, 2013[60] Spain	224 patients/65.7 years/age range 34-89/67.9% female/	Inclusion criteria: diagnosis of OA according to Spanish Society of Rheumatology criteria; no other mechanical joint problems; no contraindications to HA; consistent use of same HA product; minimum 1-year followup Criteria for referral for TKR were grade IV OA and age<75 or Grade III and age >60	Durolane (NASHA HA) 22 patients (9.2%) did not receive HA	Referral and time to referral for TKR/mean follow up 374 days (95% CI, 323, 425) (range 0-1547 days) Effects of gender, age, comorbidity, number of joints affected, severity at last follow-up, progression, pain, HA on time to TKR	40 patients (17.9%) were referred for TKR. Mean follow-up was 328 days (95% CI, 232, 424). 20 of the 40 referred received TKR. 9.1% of these patients were referred for surgery (these patients had lower average Kellgren-Lawrence classifications than those treated with HA) Viscosupplementation increased the time between referral until surgery but not significantly.	NR	Age over 65, involvement of both knees, severity of OA, lower pain intensity, and HA were each associated with longer time to TKR; HA was associated with 1093 days to TKR (95% CI. 980, 1206) vs. 694 with no treatment (95%CI, 548, 839) (p=.064)

Table 5. Risk of Bias Assessment for Observational Studies Included in Assessment of Total Knee Replacement*

Author, Year	Representativeness	Control for differences	Loss to follow-up	Masking exposures	Ascertainment**	Other treatment modalities	Valid outcomes**	AE collection	Financial COI	Author COI
Evanich, 2001[54]	Y	Y	N	Y	Y	N	Y	N	N	NR
Barrett, 2002[52]	N	NR	Y	Y	Y	Y	Y	NA	N	N
Neustadt, 2003[59]	Y	Y	Y	N	Y	N	Y	Y	N	Y
Campbell, 2004[53]	N	NR	N	Y	Y	N	Y	N	Y	Y
Waddell, 2005[65]	N	Y	Y	N	Y	Y	Y	Y	N	NR
Waddell, 2006[64]	Y	Y	Y	N	N	Y	Y	Y	N	Y
Waddell, 2007[56]	Y	Y	Y	N	Y	Y	Y	N	N	N
Mazieres, 2007[55]	Y	N	Y	Y	Y	Y	Y	NA	NR	NR
Turajane, 2007[62]	N	Y	Y	N	Y	N	Y	NA	NR	NR
Anand, 2010[66]	N	N	Y	N	Y	Y	Y	NA	Y	Y
Jurado, 2013[60]	N	Y	Y	N	Y	Y	Y	NA	Y	Y
Korkmaz, 2013[67]	NR	N	Y	N	Y	N	Y	NA	NR	NR
Waddell, 2014[58]	Y	Y	Y	N	Y	Y	Y	Y	Y	Y
Whitman, 2010[57]	Y	N	Y	N	Y	N	Y	N	N	N

Table Notes: *See Appendix D for assessment tool. Y=yes (low risk); N=no (high risk); NR=not reported; NA=not applicable; COI conflict of interest; #also includes Turajan, 2007[63] and 2009;[61] ;**Ascertainment: Yes indicates the diagnosis and/or treatment outcome were validated by medical report; Validity of outcomes: Yes indicates the outcome measure(s) have been validated for the condition and treatment of interest.

Intra-articular injection of hyaluronic acid and measures of function

We identified 18 randomized trials that compared the effects of HA with placebo or another HA using a validated assessment of function that included the WOMAC and/or Lequesne Index, or ADLs/ IADLs, in individuals with OA of the knee whose average age was 65 or older.

Description of included studies

Of the 18 trials that reported on function as an outcome, sample sizes ranged from 32 to 495.[49-51, 68-82] Only a small proportion were US studies; the rest were conducted in Canada, the UK, Germany, France, Denmark, Sweden, Thailand, and Taiwan, and one was a multinational European trial. Of the trials, 11 were compared to a placebo,[49, 51, 69, 71-74, 76, 79, 81, 82] six compared two HA devices head to head (one study had both a head-to-head comparison and a placebo group),[68, 70, 76-78, 80] and two studies compared an HA to another active treatment.[50, 75] Two studies conducted followup at 52 weeks[49, 82], one conducted followup at 4 weeks,[79] one ran for 12 weeks,[78] and the remainder conducted follow-up at 6 months (26 weeks).[50, 51, 68-77, 80, 81]Most studies included Hyalgan, five included Synvisc, and one each included Adant, NRD101 (a medium molecular weight non-avian HA), Orthovisc, Supartz, Suplasyn, and GO-ON.

Nearly all studies reported functional outcomes using either the WOMAC functional domain or Lequesne functional index; one study measured KOOS activities, and one measured ADLs. In order to decide if the Lequesne index was similar enough to the WOMAC for pooling, we looked at 4 trials[70, 75, 76, 78] that reported both outcomes to see if the conclusions based on these two indices agreed (within trial). Conclusions for three of the four trials were the same for WOMAC and Lequesne. The one the differed[78] had different follow-up times for the WOMAC and Lequesne Index. Thus, we believed that the results of trials that only reported the Lequesne Index could be pooled with those of WOMAC trials. The one trial[68] that reported on ADL/IADLs was deemed different enough from the other function outcomes to preclude pooling. These studies are described in Table 6 and in the evidence table in Appendix C.

The risk of bias for these RCTs varied widely from 0 to 12 (of 12) indicators of unclear or high risk of bias (Figure 4). The characteristics most often not reported or clearly not considered were allocation concealment and blinding of providers. In addition, although not considered in assessment for risk of bias, almost no studies reported the proportion of participants who responded (reporting only the mean difference in response from baseline).

Key Points

- Our meta-analysis of ten studies that compared the effects of an HA to those of a placebo control showed a significant improvement in WOMAC-assessed function following HA treatment compared to placebo (standardized effect size or standardized mean difference [SMD] -0.23, 95% CI -0.45, -0.01) that did not achieve the MCID of -0.37 applied by Rutjes but did exceed the MCII of -0.20 utilized in the recent network meta-analysis by Bannuru and colleagues and the MCII of -0.12 used in one of the included trials (based on the pooled effect size, about 11 percent would have exceeded the MCID of 0.37 in improvement and about 33% would have exceeded the MCII of -0.12).
- The number of head-to-head trials is too small to be able to assess the relative superiority of one HA over another.

- Although most studies reported findings at 6 months' follow-up, one study with 4 weeks follow-up and two studies with 52 weeks' follow-up also reported a positive effect of the device on functional outcomes.
- One study, a head-to-head trial comparing two types of HA, assessed the proportion of patients who achieved a minimum clinically important improvement in function: 69% of patients given an intermediate-weight HA and 56% of patients given a lower-molecular weight HA. Seven studies assessed the proportion of patients with patient- or investigator reported global improvement; of the four that were placebo-controlled, three reported significant increases in the proportion of HA-treated patients who improved, compared with the proportion of placebo-treated patients who improved.
- No studies assessed the effect of HA on range of motion.
- No studies assessed the durability of effect.

Detailed Synthesis

Placebo-controlled trials. Eleven trials[49, 51, 69, 71-74, 76, 79, 81, 82] presented data comparing the effect of HA on function to that of a sham-injected placebo group with blinded assessment (Table 6). All but one[69] reported a mean change from baseline or a baseline and follow-up mean by treatment group. Four trials[71, 74, 79, 81] did not report the standard deviation of the mean change, so we estimated it using the standard deviations of the baseline and follow-up mean change. One of these trials[71] also did not report a follow-up standard deviation so it was imputed. We included the WOMAC function scale from 4 trials[71-73, 79], Lequesne index from 3 trials[49, 74, 76] and KOOS activities from one trial.[81] One trial[76] reported both the WOMAC and the Lequesne Index. In this case, we used the Lequesne Index, as it provided more data.

Pooled analysis of ten placebo-controlled trials showed a small increase in function for the HA-treated group (standardized effect size or standardized mean difference [SMD] -0.23, 95% CI -0.45, -0.01) at follow-up using the HKSJ method (Figure 3).[49, 51, 71-74, 76, 79, 81, 82] This finding indicates that those in the HA group had statistically significantly better functioning than those in the placebo group. We calculated that the effect size corresponded to an improvement of 8.28 units (on a 0-100 VAS scale) which was smaller than the MCID used in the systematic review of the effects of HA conducted by Rutjes[17] but exceeded the MCII of -0.20 recommended by OARSI-OMERACT[24] as well as that derived by Tubach and colleagues.[45]

The I^2 is 54.0%, indicating low to moderate heterogeneity. Both the Begg's and Egger's test showed no evidence of publication bias (p=0.245 and p=0.418, respectively). One of the included studies reported a stronger effect for placebo than for the active treatment,[76] and one study showed no effect for either.[81] All but three of the studies reported follow-up at 6 months; sensitivity analyses that excluded all of the studies that reported follow-up sooner (4 weeks)[79] or later (52 weeks)[49] individually did not result in a large difference from our main result (SMD=-0.23 and SMD=-0.25, respectively) (Figure 3). Among the comparisons not included in the meta-analysis, one study compared the effect of Hyalgan to that of placebo using a standard assessment for ADLs.[68] This study found no significant improvement in ADLs at 6 months among the Hyalgan-treated group (SMD -0.08 95% CI -0.57, 0.42)

A 1998 study by Altman that compared Hyalgan (5 weekly treatments) to placebo as well as to NSAIDs found that Hyalgan significantly improved WOMAC function at 6 months over placebo but no differences were seen between Hyalgan and NSAIDs.[69] This study had a large sample size but a high dropout rate.

Head-to-Head Comparisons of HA. Five trials reported function data and compared one HA to another[70, 76, 77 , 78, 80] at 26 weeks. Three of these trials had standard deviations imputed.[77, 78, 80] Since the comparisons were quite heterogeneous, we did not do a meta-analytic pooling.

A 2012 multi-site study by Berenbaum and colleagues that compared the lower-molecular weight Hyalgan to a medium-molecular weight device, GO-ON, reported greater improvement in WOMAC-assessed function at 6 months for the GO-ON treated group than for the Hyalgan group (SMD -0.326, 95% CI -0.52, -0.13).[70]

Two studies compared Hyalgan to the high-molecular-weight HA, Synvisc.[77, 80] One very small 2012 Thai study by Khanasuk reported a significant improvement in WOMAC function for single injections of both devices at 6 months, with no difference between the two (SMD 0.053, 95% CI -0.66, 0.77).[77] A much larger 2008 UK study by Raman that compared five weekly treatments with Hyalgan (the standard dosing schedule) to three weekly treatments with Synvisc reported a significant and much larger effect for Synvisc than for Hyalgan (SMD -0.882, 95%CI -1.09,-0.68) at 6 months.[80]

One 2011 study by Pavelka and colleagues compared Synvisc to Sinovial, a medium-molecular weight (800-1200kD) HA of non-avian origin.[78] At 12 weeks follow-up, both groups of patients showed the same degree of improvement on the Lequesne index (SMD 0.100, 95%CI -0.11, 0.30). At 6 months' follow-up, both groups showed a larger improvement in function, this time assessed by the WOMAC function scale, and again, no difference was seen between groups (SMD -0.009 95% CI -0.21, 0.19).

Non-pharmacologic comparisons. Two studies compared the effects of a HA to that of another active treatment. One small UK study that compared Hyalgan to arthroscopic washout of the affected knee found comparable improvement in function (as assessed by the Lequesne index) for both groups at 6 and 12 months (SMD -0.028 95% CI -0.66, 0.61).[50]

One large 2003 trial in France by Kahan and colleagues compared the effects of a standard dosing schedule of Synvisc with that of conventional treatment (which was not defined by this study, but often indicates a series of treatments of increasing intensity, e.g., NSAIDs and exercise, physical therapy, orthotics, and bracing.[75] At 6 months' follow-up, Synvisc improved function significantly compared with conventional treatment, as assessed with both the WOMAC (SMD -0.567, 95% CI -0.75, -0.39) and the Lequesne index (SMD -0.494, 95% CI -0.67, -0.32).

Percent of Patients Showing Improvement. One of the studies that met inclusion criteria reported the percentage of participants who met prespecified criteria for improvement in function. The 2012 study by Berenbaum and colleagues, which compared the intermediate molecular weight Go-On with the lower molecular weight Hyalgan (see above), assessed the proportion of patients who achieved a minimum clinically important improvement (MCII) in function: 69% of patients who received Go-On and 56% of patients given Hyalgan demonstrated a MCII.[70] Seven studies assessed the proportion of patients with patient- or investigator reported global improvement (according to prespecified criteria).[70, 73, 75, 76, 78, 81, 82] Four were placebo-controlled (two others were head-to-head comparisons only, and the remaining study compared HA to conventional treatment);[73, 76, 81, 82] Of the four placebo-controlled trials (26-52 weeks in duration), three reported increases in the proportion of HA-treated patients who improved (according to themselves or the investigator), compared with the proportion of placebo-treated patients who improved.[73, 76, 81]

Effect Duration. Effect duration could not be derived from the identified studies. As described above, the longest followup point for most of the included studies was 6 months; three studies assessed function at 52 weeks. One study that compared the effects of a course of

Hyalgan with that of arthroscopic washout through 52 weeks on Lequesne Index score reported that function at 52 weeks was improved over function at baseline in both groups, that function appeared to be continuing to improve at 52 weeks in both groups, and that improvement was not significantly different in the HA-treated group than in the group that underwent washout.[50] A study that compared the effect of Hyalectin to that of a saline placebo at 7 weeks and 52 weeks after initiation of treatment, showed that Lequesne Index scores continued to improve through 12 months in both groups but that improvement was significantly greater in the Hyalectin group ($p=0.03$).[49] Finally, a third study compared the effects of Hylan G-F 20 (Synvisc) with that of a lower molecular weight preparation of HA on WOMAC function scores over 52 weeks: Hylan-G-F 20 recipients showed comparable improvement in WOMAC scores from 3 months through 12 months, whereas HA showed a significant improvement only at 3 months.[80]

Table 6. Summary of studies reporting functional outcomes

Author, Year Location	# Patients (Knees)/ Mean Age (SD)/ Age Range/% Female	Comorbidities	Study Arms	Relevant Outcomes Reported/ Follow Up Times
Grecomoro et al., 1987[83] Italy	34(40) Mean age: 64.88 (10.94) % Female: 19/34	Involvement of both knees: 6/34	Arm 1: N = 20 knees Mean age: NR Placebo/sham Arm 2: N = 20 knees Mean age: NR Hyalgan Molecular weight: 500K-750K Total treatments: 3 Time between treatment: 1 week	
Dixon et al., 1988[68] UK	63(NR) Mean age: 68.5 (NR) % Female: 54	NR	Arm 1: N = 33 Mean age: nr Hyalgan 0.2mg/2 ml Molecular weight: NR Placebo/sham Arm 2: N = 30 Mean age: nr Hyalgan 20mg/2 ml Molecular weight: NR Paracetamol was permitted but NSAIDS, corticosteroids, and strong analgesics were not Total treatments: Varied 1 for first 3 weeks and then 2	<u>ADL/IDLS</u> (Follow up time: 25 weeks) Arm 1: Hyalgan 0.2mg/2 ml, N=33 Mean change from baseline: -1 (10.5) * Arm 2: Hyalgan 20mg/2 ml, N=30 Mean change from baseline: -1.8 (10.5) * <u>Study-level:</u> ADL/IDLS Standard mean difference: -0.076 (-0.57, 0.42)

Author, Year Location	# Patients (Knees)/ Mean Age (SD)/ Age Range/% Female	Comorbidities	Study Arms	Relevant Outcomes Reported/ Follow Up Times
Dougados et al., 1993[49] France	110 Mean age: 69.0 (10.6) % Female: 71.0	NR	Arm 1: N=55 Placebo/sham Arm 2: N=55 Hyalectin (Hyalgan) Molecular weight: 500-730 kDa Total treatments: 4 Time between treatment: 1 week	Lequesne index (Follow up time: 52 weeks) Arm 1: Placebo, N=48 Mean change from baseline: -2.7 (4.1) Arm 2: Hyalgan 500-730 kDa, N=47 Mean change from baseline: -4.4 (5.1) Number of patients with arthroscopy (Follow up time: 52 weeks) Arm 1: Placebo, N=48 Count = 5 (10.4%) Arm 2: Hyalgan 500-730 kDa, N=47 Count = 2 (4.3%) Study-level: Lequesne index Standard mean difference: -0.360 (-0.77, 0.04) Number of patients with arthroscopy OR: 0.409 (0.09, 1.89)

Author, Year Location	# Patients (Knees)/ Mean Age (SD)/ Age Range/% Female	Comorbidities	Study Arms	Relevant Outcomes Reported/ Follow Up Times
Henderson et al., 1994[84] UK	91(NR) Mean age: NR (NR) % Female: 69	Involvement of both knees: >99%	Arm 1: N = 20 (Severity group I) Mean age: 60.0(1.9) Placebo/sham Arm 2: N = 26 Severity Group 2 Second placebo group Arm 3: N = 18 Severity Group 1 Mean age: 63.9(1.9) Hyalgan (20mg/2mL) Molecular weight: NR Arm 4: N = 26 Severity Group 2 Mean age: 67.0(1.7) Hyalgan Total treatments: 5 Time between treatment: 1 week	

Author, Year Location	# Patients (Knees)/ Mean Age (SD)/ Age Range/% Female	Comorbidities	Study Arms	Relevant Outcomes Reported/ Follow Up Times
Altman et al., 1998[69] US	495(NR) Mean age: 64 (10 (whole group)) % Female: 57	NR	Arm 1: N = 115 Mean age: 65 (10) Placebo/sham Acetaminophen up to 4000mg /day permitted as rescue Arm 2: N = 105 Mean age: 62(10) Hyalgan 20mg/2ml Molecular weight: 500-730kD Oral placebo for naproxen twice daily and Acetaminophen up to 4000mg /day permitted as rescue Arm 3: N = 113 Mean age: 63(9) NSAID Total treatments: 5 Time between treatment: 1 week	<u>WOMAC physical function</u> (Follow up time: 26 weeks) Arm 1: Placebo, N=115 Arm 2: Hyalgan 20mg/2ml 500-730kD, N=105 Arm 3: NSAIDs, N=113 <u>Study-level:</u> WOMAC physical function HA group improvement more than placebo group p=0.047
Huskisson et al., 1999[74] United Kingdom	100(NR) Mean age: nr (nr) % Female: 67		Arm 1: N = 50 Mean age: 64.8 (9.3) Placebo/sham Arm 2: N = 50 Mean age: 65.8 (8.8) Hyalgan Molecular weight: 500-730 kDa Total treatments: 5 Time between treatment: 1 week	<u>Lequesne functional index</u> (Follow up time: 26 weeks) Arm 1: Placebo, N=41 Mean change from baseline: -1.4 (7.8) Arm 2: Hyalgan 500-730 kDa, N=40 Mean change from baseline: -2.2 (7.9) <u>Study-level:</u> Lequesne functional index Standard mean difference: -0.101 (-0.54, 0.34)

Author, Year Location	# Patients (Knees)/ Mean Age (SD)/ Age Range/% Female	Comorbidities	Study Arms	Relevant Outcomes Reported/ Follow Up Times
Roman et al., 2000[85] Spain	49 Mean age: 65.14 (9.77) % Female: 83.7	NR	Arm 1: N = 30 Mean age: NR Adant Molecular weight: 900 kD Arm 2: N = 19 Mean age: NR Hyalgan Molecular weight: 800 kD Total treatments: 5 Time between treatment: 1 week	
Brandt et al., 2001[71] US	226(NR) Mean age: NR (NR) % Female: 63	Involvement of both knees: HA: 78% Saline: 88%	Arm 1: N = 112 Mean age: 67(8.4) Placebo/sham Arm 2: N = 114 Mean age: 65(8.4) Orthovisc (2 mL, 15mg/mL) Molecular weight: 1000-2900 kD (considered high MW) Total treatments: 3 Time between treatment: 1 week	<u>WOMAC function</u> (Follow up time: 27 weeks) Arm 1: Placebo, N=69 Mean change from baseline: -9.8 (15.1) * Arm 2: Orthovisc (2 mL, 15mg/mL) 1000-2900 kD (considered high MW), N=66 Mean change from baseline: -14.7 (15.1) * <u>Study-level:</u> WOMAC function Standard mean difference: -0.323 (-0.66, 0.02)

Author, Year Location	# Patients (Knees)/ Mean Age (SD)/ Age Range/% Female	Comorbidities	Study Arms	Relevant Outcomes Reported/ Follow Up Times
Tamir et al., 2001[86] Israel	49 Mean age: 71 (NR) % Female: 73.5	NR	Arm 1: N = 24 Mean age: 70 Placebo/sham Arm 2: N = 25 Mean age: 71 Bio-Hy Molecular weight: 3000 kDa Total treatments: 5 Time between treatment: 1 week	

Author, Year Location	# Patients (Knees)/ Mean Age (SD)/ Age Range/% Female	Comorbidities	Study Arms	Relevant Outcomes Reported/ Follow Up Times
Karlsson et al., 2002[76] Sweden	246(NR) Mean age: reported by arm below (reported by arm below) % Female: 61	NR	Arm 1: N = 66 (57 PP) Mean age: 71(6) Placebo/sham Arm 2: N = 92 (76 PP) Mean age: 72(7) Artzal (2.5 ml 1% hyaluronan) Molecular weight: 1,000 kDa Arm 3: N = 88 (77 PP) Mean age: 70(7) Synvisc (2 ml 0.8%) Molecular weight: 7,000 kDa Total treatments: 3 Time between treatment: 1 day	Lequesne algofunctional index (Follow up time: 26 weeks) Arm 1: Placebo, N=57 Mean change from baseline: -4.7 (4.4) Arm 2: Artzal (2.5 ml 1% hyaluronan) 1,000 kDa, N=76 Mean change from baseline: -3.9 (4.6) Arm 3: Synvisc (2 ml 0.8%) 7,000 kDa, N=77 Mean change from baseline: -4.4 (4.1) WOMAC physical function (Follow up time: 26 weeks) Arm 1: Placebo, N=57 Mean change from baseline: -11.1 (14.8) * Arm 2: Artzal (2.5 ml 1% hyaluronan) 1,000 kDa, N=76 Mean change from baseline: -7.3 (14.9) * Arm 3: Synvisc (2 ml 0.8%) 7,000 kDa, N=77 Mean change from baseline: -11.7 (14.7) * Study-level: WOMAC physical function Standard mean difference: 0.260 (-0.09, 0.60) Arms 2 vs 1 WOMAC physical function Standard mean difference: -0.297 (-0.62, 0.02) Arms 3 vs 2 Lequesne algofunctional index Standard mean difference: 0.176 (-0.17, 0.52) Arms 2 vs 1 Lequesne algofunctional index Standard mean difference: -0.115 (-0.43, 0.20) Arms 3 vs 2

Author, Year Location	# Patients (Knees)/ Mean Age (SD)/ Age Range/% Female	Comorbidities	Study Arms	Relevant Outcomes Reported/ Follow Up Times
Petrella et al., 2002[79] Canada	120 Mean age: 65.5 (9.5) % Female: 45.8	Involvement of both knees: 0%	Arm 1: N = 28 Mean age: 62.6 (9.5) Placebo/sham Arm 2: N = 25 Mean age: 67.3 (8.9) Suplasyn Molecular weight: NR Placebo pill Arm 3: N = 29 Mean age: 65.0 (9.7) Suplasyn Molecular weight: NR NSAID Arm 4: N = 26 Mean age: 66.3 (8.8) NSAID Total treatments: 3 Time between treatment: 1 week	<u>WOMAC disability</u> (Follow up time: 4 weeks) Arm 1: Placebo, N=28 Mean change from baseline: -0.99 (3) Arm 2: Suplasyn NR, N=25 Mean change from baseline: -1.65 (2.5) Arm 3: Suplasyn+NSAIDs NR, N=29 Mean change from baseline: -1.17 (2.7) Arm 4: NSAIDs, N=26 Mean change from baseline: -1.56 (2.8) <u>Study-level:</u> WOMAC disability Standard mean difference: -0.234 (-0.77, 0.31)

Author, Year Location	# Patients (Knees)/ Mean Age (SD)/ Age Range/% Female	Comorbidities	Study Arms	Relevant Outcomes Reported/ Follow Up Times
Forster et al., 2003[50] UK	38 Mean age: 61.5 (NR) % Female: NR	NR	Arm 1: N = 19 Mean age: 63 Arthroscopic washout Arm 2: N = 19 Mean age: 60 Hyalgan Molecular weight: 500-730 kD Total treatments: 5 Time between treatment: 1 week	Lequesne index (Follow up time: 26 weeks) Arm 1: Arthroscopic washout, N=19 Mean change from baseline: -1 (25) * Arm 2: Hyalgan 500-730 kD, N=19 Mean change from baseline: -1.5 (6) * Number of patients with arthroscopy (Follow up time: 52 weeks) Arm 1: Arthroscopic washout, N=15 Count = 3 (20%) Arm 2: Hyalgan 500-730 kD, N=17 Count = 2 (11.8%) Study-level: Lequesne index Standard mean difference: -0.028 (-0.66, 0.61) Number of patients with arthroscopy OR: 0.546 (0.08, 3.59)

Author, Year Location	# Patients (Knees)/ Mean Age (SD)/ Age Range/% Female	Comorbidities	Study Arms	Relevant Outcomes Reported/ Follow Up Times
Kahan et al., 2003[75] France	506 Mean age: 66 (10) % Female: 67.5	Involvement of both knees: 74	Arm 1: N = 253 Mean age: 66 (10) Conventional treatment Arm 2: N = 253 Mean age: 66 (10) Synvisc Molecular weight: NR Total treatments: 3 Time between treatment: 1 week	<u>Lequesne index</u> (Follow up time: 26 weeks) Arm 1: Conventional treatment, N=253 Mean change from baseline: -1.6 (4) Arm 2: Synvisc, N=253 Mean change from baseline: -3.6 (4.1) <u>WOMAC function</u> (Follow up time: 26 weeks) Arm 1: Conventional treatment, N=247 Mean change from baseline: -7 (20.6) Arm 2: Synvisc, N=251 Mean change from baseline: -18.4 (19.6) <u>Study-level:</u> Lequesne index Standard mean difference: -0.494 (-0.67, -0.32) WOMAC function Standard mean difference: -0.567 (-0.75, -0.39)
Leopold et al., 2003[87] US	100(NR) Mean age: NR (NR) % Female: CS: 56 HA: 52	NR	Arm 1: N = 42 Mean age: 64 Arm 2: N = 38 Mean age: 66 Hylan G-F 20 (16mg/2ml) Total treatments: 3 HA 1CS Time between treatment: 1 week	

Author, Year Location	# Patients (Knees)/ Mean Age (SD)/ Age Range/% Female	Comorbidities	Study Arms	Relevant Outcomes Reported/ Follow Up Times
Pham et al., 2004[82] France	301 Mean age: 64.9 (7.7) % Female: 65 average	NR	Arm 1: N = 85 Mean age: 64.9 (7.7) Placebo/sham Arm 2: N = 131 Mean age: 71.0 NRD101 Molecular weight: 1.900 kDa Arm 3: N = 85 Mean age: 64.5 Diacerein Total treatments: 12? (3 course every 3 months for a year) Time between treatment: 1 week	Lequesne's algofunctional index (Follow up time: 52 weeks) Arm 1: Oral placebo+saline, N=85 Mean change from baseline: 10.5 (3.1) Arm 3: NRD101 1.900 kDa, N=131 Mean change from baseline: 11.1 (2.8) Study-level: Lequesne's algofunctional index Standard mean difference: -0.070 (-0.34, 0.21)
Blanco et al., 2008[51] Spain	42 Mean age: 68.3 ((9.1)) % Female: 76	NR	Arm 1: N = 20 Mean age: 68.3(9.1) Placebo/sham Paracetamol and/or diclofenac as rescue analgesics Arm 2: N = 22 Mean age: 67.5(8.1) Adant Molecular weight: 900 kDa Total treatments: 10 (2 cycles of 5 weekly injections, separated by 24 weeks) Time between treatment: 1 week	Number of patients with knee surgery (Follow up time: 24 weeks) Arm 1: Placebo, N=23 Count = 20 (87%) Arm 2: Adant 900 kDa, N=25 Count = 16 (64%) Physical function WOMAC (Follow up time: 24 weeks) Arm 1: Placebo, N=20 Mean change from baseline: -4.4 (18.8) Arm 2: Adant 900 kDa, N=22 Mean change from baseline: -24.7 (18) Study-level: Physical function WOMAC Standard mean difference: -1.080 (-1.74, -0.43) Number of patients with knee surgery OR: 0.300 (0.08, 1.10)

Author, Year Location	# Patients (Knees)/ Mean Age (SD)/ Age Range/% Female	Comorbidities	Study Arms	Relevant Outcomes Reported/ Follow Up Times
Lundsgaard et al., 2008[81] Denmark	251 Mean age: 69.6 (7.27) % Female: 52.4	NR	Arm 1: N=84 Saline 2ml Arm 2: N=83 Saline 20 mL, no hyaluronate Arm 3: N=84 Hyalgan Molecular weight: NR Total treatments: 4 Time between treatment: 1 week	<u>KOOS activities</u> (Follow up time: 26 weeks) Arm 1: Saline 2ml, N=84 Mean change from baseline: -5 (16.3) Arm 2: Saline 20 mL, no hyaluronate, N=83 Mean change from baseline: -5.2 (15.1) Arm 3: Hyalgan 500 - 730 kD, N=84 Mean change from baseline: -4.4 (15.7) <u>KOOS quality of life</u> (Follow up time: 26 weeks) Arm 1: Saline 2ml, N=84 Mean change from baseline: -6.4 (15.7) Arm 2: Saline 20 mL, no hyaluronate, N=83 Mean change from baseline: -7.1 (12.1) Arm 3: Hyalgan 500 - 730 kD, N=84 Mean change from baseline: -3.4 (15.4) <u>Study-level:</u> KOOS activities Standard mean difference: 0.037 (-0.27, 0.34) KOOS quality of life Standard mean difference: -0.193 (-0.50, 0.11)

Author, Year Location	# Patients (Knees)/ Mean Age (SD)/ Age Range/% Female	Comorbidities	Study Arms	Relevant Outcomes Reported/ Follow Up Times
Petrella et al., 2008[88] Canada	200 Mean age: 71 (8) % Female: 30	NR	Arm 1: N = 50 Mean age: 71+/-8 Placebo/sham Arm 2: N = 50 Mean age: 68+/-6 HA dual molecular weight Molecular weight: 580–780 kDa+1.2 to 2.0 million kDa Arm 3: N = 50 Mean age: 69+/-5 HA low molecular weight Molecular weight: 500–730 kDa Arm 4: N = 50 Mean age: 71+/9 HA high molecular weight Molecular weight: 6 million kDa Total treatments: 3 Time between treatment: 1 week	

Author, Year Location	# Patients (Knees)/ Mean Age (SD)/ Age Range/% Female	Comorbidities	Study Arms	Relevant Outcomes Reported/ Follow Up Times
Raman et al., 2008[80] UK	392 Mean age: 67.2 (NR) % Female: 68	NR	Arm 1: N = 199 Mean age: NR Synvisc (Hylan GF 20) Molecular weight: 6000 kD Arm 2: N = 193 Mean age: NR Hyalgan Molecular weight: 500 - 730 kD Total treatments: 3 for Synvisc, 5 for Hyalgan Time between treatment: 1 week	EQ-5D (Follow up time: 26 weeks) Arm 1: Synvisc (Hylan GF 20) 6000 kD, N=199 Mean change from baseline: -12 (25) * Arm 2: Hyalgan 500 - 730 kD, N=193 Mean change from baseline: 1 (25) * WOMAC physical activity (Follow up time: 26 weeks) Arm 1: Synvisc (Hylan GF 20) 6000 kD, N=199 Mean change from baseline: -21.8 (17) * Arm 2: Hyalgan 500 - 730 kD, N=193 Mean change from baseline: -6.8 (17) * Study-level: WOMAC physical activity Standard mean difference: -0.882 (-1.09, -0.68) EQ-5D Standard mean difference: -0.520 (-0.72, -0.32)
Huang et al., 2011[73] Taiwan	200(NR) Mean age: 65.0 (8.3) % Female: 76	NR	Arm 1: N = 100 Mean age: 64.2(8.4) Placebo/sham Arm 2: N = 100 Mean age: 65.9(8.1) Hyalgan (20mg/2ml) Total treatments: 5 Time between treatment: 1 week	WOMAC function (Follow up time: 25 weeks) Arm 1: Placebo, N=98 Mean change from baseline: -18.2 (16.7) Arm 2: Hyalgan (20mg/2ml), N=100 Mean change from baseline: -25.16 (16.7) Study-level: WOMAC function Standard mean difference: -0.415 (-0.70, -0.13)

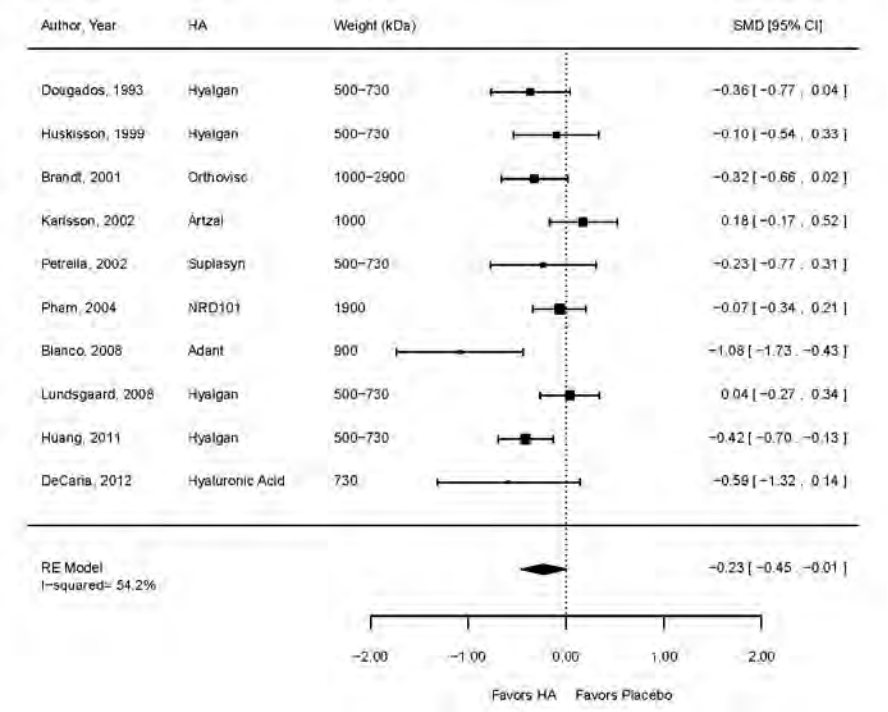
Author, Year Location	# Patients (Knees)/ Mean Age (SD)/ Age Range/% Female	Comorbidities	Study Arms	Relevant Outcomes Reported/ Follow Up Times
Pavelka et al., 2011[78] Czech Republic, France, Italy, Switzerland, the Slovak Republic and Germany	381 Mean age: 65 (9) % Female: 72.9	Involvement of both knees: 66%	Arm 1: N = 192 Mean age: 65.1 (9.1) Synovial Molecular weight: 800 - 1,200 kD Arm 2: N = 188 Mean age: 64.9 Synvisc Molecular weight: 6,000 kD Total treatments: 3 Time between treatment: 1 week	Lequesne algofunctional index (Follow up time: 12 weeks) Arm 1: Synovial 800 - 1,200 kD, N=192 Mean change from baseline: -3.9 (5.2) Arm 2: Synvisc 6,000 kD, N=188 Mean change from baseline: -3.4 (5.2) WOMAC function (Follow up time: 26 weeks) Arm 1: Sinovial 800 - 1,200 kD, N=192 Mean change from baseline: -28 (21.8) * Arm 2: Synvisc 6,000 kD, N=188 Mean change from baseline: -28.2 (21.7) * Study-level: WOMAC function Standard mean difference: -0.009 (-0.21, 0.19) Lequesne algofunctional index Standard mean difference: 0.100 (-0.11, 0.30)

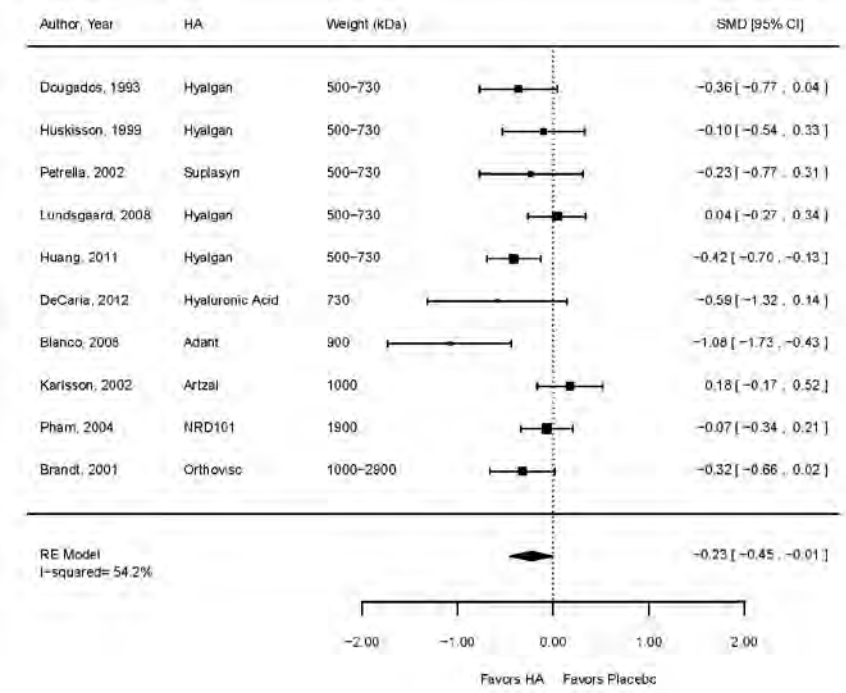
Author, Year Location	# Patients (Knees)/ Mean Age (SD)/ Age Range/% Female	Comorbidities	Study Arms	Relevant Outcomes Reported/ Follow Up Times
Petrella et al., 2011[89] Canada	200 Mean age: 70 (8) % Female: 57	NR	Arm 1: N = 50 Mean age: 71 (8) Placebo/sham Arm 2: N = 50 Mean age: 68 (6) sodium hyaluronate Molecular weight: Combined high & low weight Arm 3: N = 50 Mean age: 69 (5) sodium hyaluronate - low weight Molecular weight: 500-730 KDa Arm 4: N = 50 Mean age: 71 (9) sodium hyaluronate - high weight Molecular weight: 6000 KDa Total treatments: 3 Time between treatment: 1 week	

Author, Year Location	# Patients (Knees)/ Mean Age (SD)/ Age Range/% Female	Comorbidities	Study Arms	Relevant Outcomes Reported/ Follow Up Times
Berenbaum et al., 2012[70] France, Germany	426(NR) Mean age: 67 (NR) % Female: 63		Arm 1: N = 209 Mean age: 66.1 (8.1) Hyalgan Molecular weight: 500 kD-730 kD NSAID or paracetamol up to 4g/d as permitted as rescue medication Arm 2: N = 217 Mean age: 67.2 (7.8) GO-ON (2.5 ml, 10mg/ml) Molecular weight: 800 kD-1500 kD NSAID or paracetamol up to 4g/d as permitted as rescue medication Total treatments: 3 Time between treatment: 3 weeks	Lequesne index (Follow up time: 26 weeks) Arm 1: Hyalgan 500 kD-730 kD, N=209 Mean change from baseline: -3 (3.7) Arm 2: GO-ON (2.5 ml, 10mg/ml) 800 kD-1500 kD, N=217 Mean change from baseline: -4.2 (3.8) WOMAC function (Follow up time: 26 weeks) Arm 1: Hyalgan 500 kD-730 kD, N=209 Mean change from baseline: -15.4 (19.9) Arm 2: GO-ON (2.5 ml, 10mg/ml) 800 kD-1500 kD, N=217 Mean change from baseline: -22.2 (21.8) Study-level: WOMAC function Standard mean difference: -0.326 (-0.52, -0.13) Lequesne index Standard mean difference: -0.320 (-0.51, -0.13)
DeCaria et al., 2012[72] Ontario Canada	30(na) Mean age: NR (NR) % Female: 47	NR	Arm 1: N = 15 Mean age: 72.93 (5.48) 500 mg acetaminophen to be taken up to 4g/day as rescue medication Placebo/sham 1.2 ml 0.001 mg/ml inert HA Arm 2: N=15 Hyaluronic acid (2 ml, 20 mg/ml) Molecular weight: 730 kD 500 mg acetaminophen to be taken up to 4g/day as rescue medication Total treatments: 3 Time between treatment: 1 week	WOMAC function (Follow up time: 26 weeks) Arm 1: Placebo, N=15 Mean change from baseline: -3.53 (10.15) Arm 2: Hyaluronic Acid 730 kD, N=15 Mean change from baseline: -9.07 (8.14) Study-level: WOMAC function Standard mean difference: -0.586 (-1.32, 0.15)

Author, Year Location	# Patients (Knees)/ Mean Age (SD)/ Age Range/% Female	Comorbidities	Study Arms	Relevant Outcomes Reported/ Follow Up Times
Khanasuk et al., 2012[77] Thailand	32(NR) Mean age: NR (NR) % Female: 80	NR	Arm 1: N = 15 Mean age: 65.1(9.6) Hylan GF-20 (Synvisc)(single 6 ml injection) Molecular weight: Reported as High Arm 2: N = 15 Mean age: 67.0(9.5) Hyalgan (single injection Molecular weight: Reported as Low Total treatments: 1	<u>SF-36 PCS</u> (Follow up time: 26 weeks) Arm 1: Synvisc (single 6 ml injection), N=15 Mean change from baseline: -6 (25) * Arm 2: Hyalgan (single injection, N=15 Mean change from baseline: -4 (25) * <u>WOMAC function</u> (Follow up time: 26 weeks) Arm 1: Synvisc (single 6 ml injection) Reported as High, N=15 Mean change from baseline: -20 (37.5) * Arm 2: Hyalgan (single injection Reported as Low, N=15 Mean change from baseline: -22 (37.5) * <u>Study-level:</u> WOMAC function Standard mean difference: 0.053 (-0.66, 0.77) SF-36 PCS Standard mean difference: -0.080 (-0.80, 0.64)

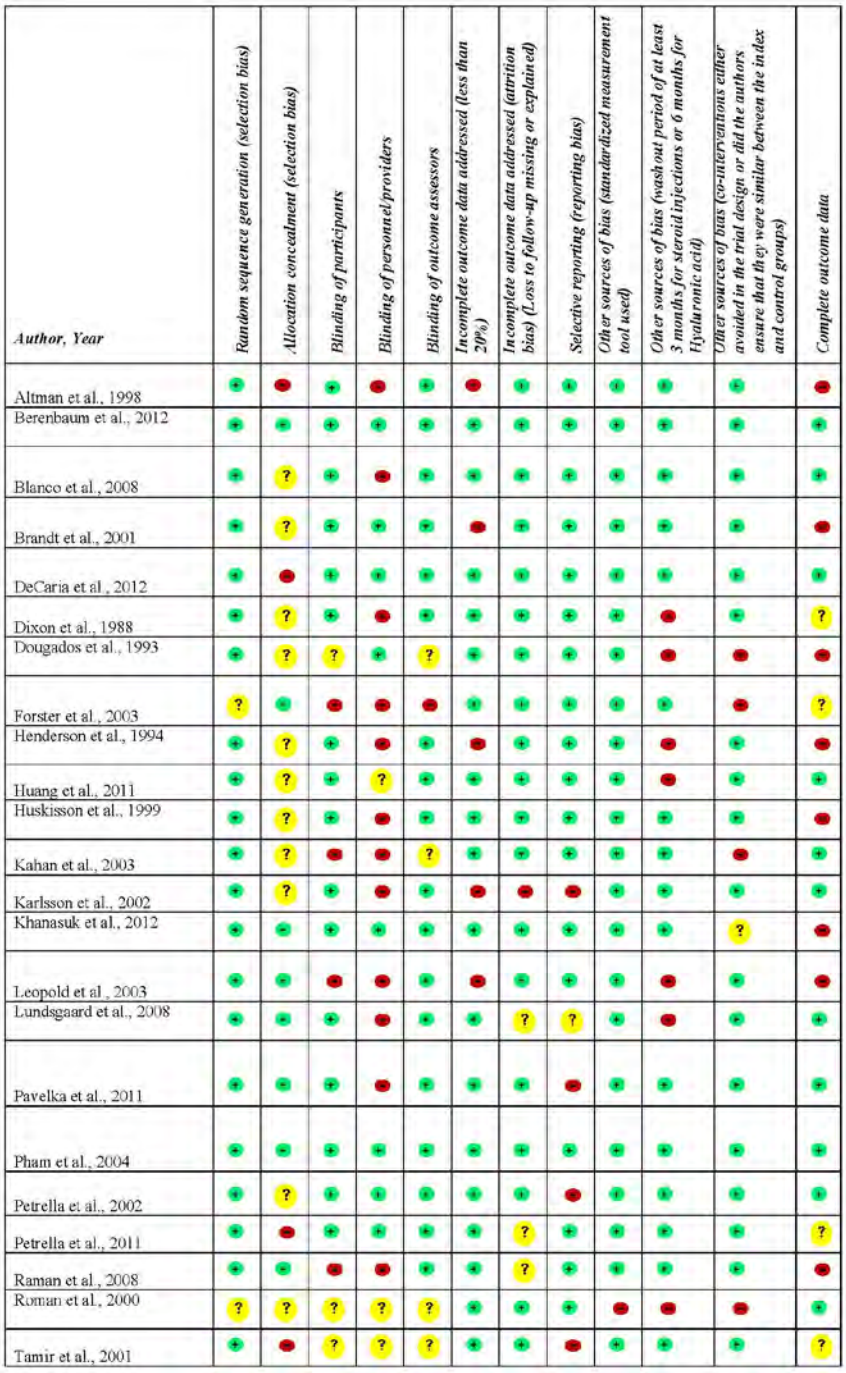
Figure 3. Forest Plots for Comparisons of the Effect of Hyaluronic Acid Treatment with Placebo on function (WOMAC, Lequesne, or KOOS) at 26 Weeks Follow-up:* a. studies arranged chronologically, b. studies arranged by product molecular weight





*Follow-up time for Petrella is 4 weeks and for Dougados and Pham it is 52 weeks

Figure 4. Risk of Bias Assessment on Randomized Controlled Trials



Legend:

Unclear= ?

Low risk of bias= +

High risk of bias= −

Intra-articular injection of hyaluronic acid and quality of life

Three randomized trials were identified that assessed quality of life.

Description of included studies

A 2008 randomized trial that compared treatment with Hyalgan to treatment with two different volumes of saline assessed quality of life using the KOOS quality-of-life component.[81] A head-to-head trial that compared Synvisc with Hyalgan assessed quality of life using the SF-36 mental component summary,[77] and a second head-to-head trial that compared Synvisc with Hyalgan assessed health-related quality of life using the EuroQol-5D index[80]

Key Points

- Three trials that compared HA to saline or to another HA found no differences in quality of life or health-related quality of life between the two groups at 6 months follow-up.
- In one head to head trial of Synvisc and Hyalgan, health-related quality of life was improved in the Synvisc group from 3 weeks through the final follow-up at 12 months post-treatment.

Detailed Synthesis

Two trials[77, 80] that compared Hyalgan to Synvisc and one trial[81] that compared Hyalgan to saline reported on quality of life or health-related quality of life.[69] All three needed to have standard deviations imputed. A meta-analytic pooling was not done since we did not have three trials with similar comparisons.

A 2008 randomized placebo-controlled trial of Hyalgan in 251 Danish adults (mean age 69, minimum age 59) assessed quality of life with the KOOS measure.[81] No significant improvement was seen at 6 months compared with baseline, and there was no difference among the groups (-0.193 95% CI -0.496, 0.110), as was seen for the assessment of KOOS function.

A 2008 UK head-to-head trial comparing Hyalgan with Hylan GF-20 (Synvisc) in 393 OA patients found a significant increase in health-related quality of life at 3 months, as measured by the EuroQol EQ-5D, which was greater for the Hylan GF-20 group (-0.52 95% CI -0.72, -0.32), paralleling the WOMAC physical activity subscores, as reported above; the effect on EQ-5D score was sustained until 12 months in the Synvisc group but not the Hyalgan group.[80] However a small 2012 trial in Thailand that compared the same devices among 32 patients found no improvement in quality of life in either group, as measured by the SF-36, (-0.08 95% CI -0.80, 0.64) (compared with WOMAC physical function scores, which improved equally in both groups).[77]

None of the three studies conducted subgroup analysis to assess possible contributing factors (such as age, disease severity, or comorbidities) to the response of quality of life to treatment with HA.

Intra-articular injection of hyaluronic acid and pain

Description of included studies

We identified a number of articles described as systematic reviews that summarized trials of the effects of HA on pain. One good quality 2012 review summarized the entire body of trials that compared the effects of HA with those of a sham or nonintervention control on pain; this review also included separate analysis for double-blind placebo control trials and stratified analyses for a number of potential effect modifiers. We summarize the results of this review below.[17] We then identified a 2015 network meta-analysis comparing the effectiveness of pharmacological interventions and HA for knee OA.[42] We summarize the results of this review as well. Many of the remaining systematic reviews are summarized in the Discussion chapter.[16, 17, 90-93] We identified no double-blind placebo controlled randomized trials that reported the effects of HA on pain only in individuals 65 and over, and no such studies in individuals of average age 65 and over that were published subsequent to these systematic reviews; however we did identify two randomized head-to-head trials that compared the effects of two different HA products on pain in individuals of average 65 or over. These two studies are summarized below.

Key Points

- A large, 2012 comprehensive systematic review of RCTs that assessed the effects of HA on pain in 71 RCTs (with either sham or non-sham controls) reported that HA injections significantly reduce pain when assessed at 3 months (-0.37, 95% CI -0.46, -0.28) and the effect met the criterion for a minimum clinically important difference (MCID, -0.37, which corresponds to 9 mm on a VAS scale of 0 to 100mm). When the reviewers performed a subgroup analysis that included only the 18 sham-controlled, assessor-blinded studies with sample size of 100 or more per intervention group in the pooled analysis, the effect of HA was still statistically significant (-0.11, 95% CI -0.18, -0.04), but no longer met the criterion of clinical importance. A stratified analysis comparing the effect size for all 54 studies with a sham control (regardless of size) with that of the 18 studies with a non-sham comparison obtained a pooled effect size for the sham-controlled studies of -0.34 (95% CI -0.44, -0.24), nearly equal to that for the entire group of studies and to the MCID.
- A 2015 network meta-analysis of 129 RCTs that compared the effects of oral and intraarticular pharmacologic agents, HA, and placebo on pain (52 studies compared HA with placebo and 12 compared HA with steroids) reported a significant effect size of HA compared with placebo (-0.34; 95% CI -0.42, -0.26), exceeding the prespecified absolute MCID of -0.20, based on the OMERACT-OARSI responder criteria; sensitivity analysis showed that limiting study size to 50 or more did not change the effect size but limiting the analysis to studies of 100 or more did reduce the effect size.

- No new placebo-controlled trials were identified that were not already included in the systematic review by Rutjes and colleagues or that of Bannuru and colleagues, enrolled patients of average age 65 and older, and reported on pain outcomes.

- Two new head-to-head trials compared the effects of two different HAs on pain in individuals of average age 65 or over and were not included in prior SRs. One found that single injections of a high- and low-molecular weight were equally effective in reducing pain and improving function at 6 months (with no change in quality of life), whereas another found that three injections of an intermediate molecular weight might be superior to low molecular weight HA over 6 months (with respect to reducing pain and improving function).

Detailed Synthesis

Systematic review

Two systematic reviews of good to high quality, published in 2012 and 2015, were identified that compared the effects of intra-articular HA with some other intervention on pain; the quality of the reviews was assessed with AMSTAR (Table 7).[17, 42]

The 2012 systematic review and meta-analysis by Rutjes and colleagues, which identified 89 published and unpublished randomized trials of HA with any control, assessed the effects on pain intensity.[17] Of the 89 trials, the authors were able to pool 71 sham or non-intervention controlled trials (9,617 patients), obtaining an effect size of -0.37 (95%CI -0.46, -0.28), which just met their prespecified minimal clinically important difference. Pooling 18 of the larger (sample size greater than 100 per intervention group) assessor-blinded trials showed a statistically significant but clinically irrelevant effect size of -0.11(95%CI -0.18, -0.04). A stratified analysis that compared the pooled effect size for the 54 studies with a sham control with that of 18 studies with a non-sham intervention found a pooled effect size for studies with a sham control of -0.34 (95% CI -0.44, -0.24).

A 2015 network meta-analysis of 129 RCTs by Bannuru and colleagues[42] compared the effects of oral and intraarticular pharmacologic agents, intraarticular HA, and placebo (oral and intraarticular) on pain. Pooling 52 studies that compared HA with placebo at 3 months' follow-up showed a significant effect size of HA compared with placebo (-0.34; 95% CI -0.42, -0.26). This effect size was the highest for any agent assessed (all but CS were oral agents, and exceeded the prespecified absolute MCID of -0.20, based on the OARSI-OMERACT responder criteria. Sensitivity analysis showed that limiting study size to 50 or more did not change the effect size but limiting the analysis to studies of 100 or more did reduce the effect size.

Table 7. AMSTAR Assessment for Systematic Reviews of HA and Pain*

Study	A priori design	Duplicate screening and extraction	Comprehensive search	Grey literature inclusions	Included/excluded studies listed	Study characteristics	Quality assessment	Quality considered	Pooling appropriate	Publication bias	COI assessment
Rutjes, 2012[17]	C#	Y	Y	Y	Y	N	Y	C	Y	Y	C
Bannuru, 2015[42]	C	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y

*See Appendix D for assessment tool. Y=yes (low risk); N=no (high risk);C=can't respond; NA=not applicable; COI conflict of interest; #need to access supplemental files

Original studies

No new placebo-controlled trials were identified that enrolled patients of average age 65 and older, and reported on pain outcomes and were not already included in the systematic reviews by Rutjes and colleagues or Bannuru and colleagues. Two randomized trials were identified that were not included in either review, enrolled populations of OA patients of average age 65 or over, and assessed the effects of two different HA products head-to-head on pain.

A multi-center trial in France and Germany compared the effects of three weekly injections of GO-ON, a non-avian medium-molecular weight HA (1800-1500kD) with those of Hyalgan, a low molecular weight product on pain in 426 patients.[70] Mean differences in WOMAC pain change were 5.2(95% CI 0.9, 9.6) per protocol and 4.5 (95% CI 0.5, 8.5) (intention to treat) at 6 months, favoring GO-ON. Also, a higher proportion of patients responded to GO-ON than to Hyalgan: 70.5% of participants receiving GO-ON and 58.4% of participants receiving Hyalgan exceeded the prespecified MCII for pain. These differences paralleled the effects of the two devices on function as assessed by both the WOMAC (difference in effect size: -6.8, 95% CI -10.7, -2.8) and Lequesne indices (-1.2, 95% CI -2.0, -0.6), as described earlier in this report.

A Thai study compared the effects of a single injection of Hylan G-F 20 (Synvisc) and a single injection of Hyalgan on pain at 6 months in 30 patients. The WOMAC pain and function subscales showed significant improvement with no differences between the treatments at 6 months. QoL, as assessed by the SF-36, did not change over the same 6-month period.[77]

Intra-articular injection of hyaluronic acid and adverse events

Description of included studies

Twenty four trials, four large cohort and case series studies, and 18 case reports were identified that reported on the incidence of adverse events among individuals 65 years of age and over.

Key Points

- In 24 placebo-controlled trials of HA, serious adverse events were small in number. Estimates are imprecise, and the magnitude of any increase in risk is very small, if present at all. The rate of non-serious AEs was higher but did not differ significantly between the HA-treated and placebo-control groups.
- Among four large cohort studies and case series, representing nearly 6,000 recipients of HA (some more than one series), one serious adverse event was reported: severe swelling and synovial fluid accumulation.
- Eighteen case reports provided reports of adverse events among 30 individuals 65 years of age or older, including five cases of sepsis (one case of staphylococcus scalded skin syndrome), and one case each of saphenous nerve injury, eosinophiluria, erythema, and herpes zoster (new onset).

Detailed Synthesis

Adverse events reported in trials. Twenty four trials reported data on adverse events (AEs).[49, 51, 68-89] Thirteen trials[49, 51, 71-74, 80-84, 86, 88] compared Hyalgan to placebo, and seven[68, 70, 75, 77, 78, 85, 87] compared Hyalgan to an active comparator. Four trials[69, 76, 79, 89] reported data on both comparison types.

Only the placebo comparisons had enough trials within adverse event categories to pool. The results are presented in Table 8. With the assistance of a rheumatologist, we grouped the adverse events into three groups based on their site (injection site, joint [intra-articular], or other [including systemic]) and within each of the three groups, we further divided events according to whether they were serious or not serious. Examples of each type of event are also provided in Table 8.

The RCTs included in the AE analyses were assessed using items from the McHarm scale (Table 10).[35] Out of 24 RCTs, four described a protocol for collecting AEs or a predefined set of AEs; the remaining 20 were unclear or indicated no predefined list of AEs. To elaborate, these 20 studies did not describe whether assessors asked patients about specific AEs on a list. Four of 24 studies described an active form of AE collection; the remainder used a passive form of AE assessment (e.g., they asked patients something more generic such as "have you experienced any adverse reactions?") or did not describe how AEs were assessed. Fourteen of the 24 RCTs did describe assessing AEs at prespecified intervals (e.g., at follow-up appointments). In addition, eight studies reported that no serious adverse events occurred, without defining the term "serious adverse events." However, as these weaknesses apply to both the active and placebo arms (assessors were blinded to study arm), any systematic undercounting of AEs would apply to both arms and have little effect on the relative difference.

Table 8. Pooled adverse events reported in trials, according to category

AE Group	# studies	# event HA	sample size HA	# events placebo	sample size placebo	OR	95% CI
local, not serious (e.g., erythema)	6	79	493	98	492	0.70	(0.48, 1.03)
joint, serious (e.g., synovitis)	5	8	447	10	442	0.77	(0.25, 2.31)
joint, not serious (e.g., pain)	7	97	518	121	559	0.83	(0.60, 1.15)
other, serious (e.g., Herpes zoster)	6	8	570	17	614	0.62	(0.23, 1,57)
other, not serious (e.g., headache)	6	199	553	196	594	1.26	(0.94, 1.68)

Adverse Events reported in observational studies. In order to further investigate rare adverse events that may not have occurred during clinical trials, we searched for cohort studies that reported AEs and cases reported post-licensure.

We identified four observational studies with at least 500 subjects each that reported adverse events in patients receiving hyaluronic acid for knee osteoarthritis. Due to heterogeneity, the results are described narratively.

Petrella[94] published on a cohort of 537 hyaluronic acid-naïve patients who received at least one series of three injections of Suplasyn (500 – 730 kD) in a primary care center in Ontario, Canada. All had unilateral osteoarthritis of the knee with Kellgren-Lawrence grade 1 to 3; mean age was 68 years. All but 21 patients returned for a second series of three injections. Patients

were followed for a mean of 6.7 years. The study was supported by the Canadian Institutes of Health; Suplaysn was purchased by the patients and was not subsidized by the manufacturer. The primary outcome studied was pain in walking, as measured using the VAS. No serious AEs were reported, and there were no systemic (not local or intra-articular) AEs. Local AEs were observed following 1.48% and 1.32% of injections with the first and second series respectively. The authors provided no information on whether AEs were assessed passively or actively.

Kemper and colleagues[95] reported on 4,253 patients of 840 orthopedic surgeons in Germany. Patients received injection of Synvisc (6000 kD) at three visits; Kellgren-Lawrence grades were not reported; 8.1% of patients had previously received hyaluronic acid injections. Mean age of the patients was 63.9 years, 60.8% were female, and 23.7% had bilateral osteoarthritis. AEs were actively elicited, serious AEs were clearly defined, and MEDRA coding was used. Adverse events were reported in 5.3% of patients and 2.9% of injections. Only one serious AE was reported; this event involved severe swelling and synovial fluid accumulation. The most commonly reported AEs were joint effusion (2.4% of patients), joint swelling (1.3%), arthralgia (1.2%), joint warmth (0.6%) and injection site erythema (0.3%). Secondary analyses were performed; surprisingly, patients younger than 70 years old were more likely to experience an AE than were older patients. Those with a longer time since diagnosis and those previously treated with viscosupplementation were also more likely to experience an AE. The product manufacturer sponsored the study; two of their scientists were co-authors.

In a large retrospective cohort study Petrella[96] compared the safety of avian and non-avian hyaluronic acid for osteoarthritis of the knee. They included 1,726 patients who received avian HA and 1,971 who received non-avian HA at a large center in Canada from 1997 to 2007. Patients had Kellgren-Lawrence grade 1 to 3 evidence of knee OA; mean age was 65 years. There were no significant differences in baseline demographic characteristics or severity between groups. The group receiving avian HA had a significantly higher rate of adverse events (4.8% versus 1.7%) between the second and 10th series than the group receiving non-avian HA. Rates of specific events were not reported; pain, effusion, and erythema were noted as most common. No serious adverse events were reported.

Finally, Waddell and Bricker[97] published a case series of 1,158 patients in a large orthopedic practice in the US. The primary goal of the study was to assess AEs. The patients received at least one series of three injections of Synvisc. The mean age (65.8 years) and gender composition (60.6% female) were similar to the other two studies. However, the patients' osteoarthritis of the knee was more severe; 70.9% of knees were grade four on the Kellgren-Lawrence scale, and 44.6% of patients had bilateral OA. The authors provided details on treatment method that were not reported in the other studies. A fluoroscopic technique that confirms accurate needle placement was used. To avoid local AEs, they instructed patients to rest the afternoon of the injection and use an ice pack for two to three hours. In addition, they provided patients with a prescription opioid to use if needed. Finally, they prophylactically administered an intramuscular steroid in patients who had previously experienced knee pain and swelling with injection. Local AEs were reported in 4.7% of patients (1.3% of injections) during Course 1, 13.8% of patients (4.5% of injections) during Course 2, and 17.3% of patients (5.6% of injections) during Course 3. Non-local AEs were not reported. Both authors had received previous funding from the product manufacturer, who provided support for statistical analysis and a medical writer for the manuscript. In a 2014 followup to this study, Waddell and Joseph tracked the incidence of synovitis (knee pain and swelling) over multiple treatment courses.[58] The incidence was 3.5% (65/1,863 patients) following course 1, 9.5% (81/849) following course

2, 12.9% (46/356) following course 3, 12.1% (19/157) following course 4, 23.8% (15/63) following course 5, and 6.7% (2/30) following course 6. Nearly all cases were considered mild or moderate, and none were considered serious enough to require hospitalization.

Data from the 19 identified AE case reports that included patients age 65 or over are displayed in Table 9. Thirty patients were represented; 77% were female. Over half had received injections of Synvisc, which is considered a high molecular-weight product.

The most commonly reported adverse events involved joint reactions. Pullman-Mooar[98] reported inflammatory knee effusions in eight patients, ranging in age from 31 to 67 years. Each of three physicians reported cases of pseudo-septic arthritis.[99-101] Acute arthritis, and gout or pseudo-gout were also reported.

Importantly, five cases of sepsis were reported in three articles; one of these patients suffered from staphylococcal scalded skin syndrome.

Other adverse events included systemic reactions in two patients, granulomatous synovitis in two patients, and one case each of saphenous nerve injury, eosinophiluria, erythema, and one case of new-onset herpes zoster.

Table 9. Adverse events described in case reports

Author, Year	AE	N	Age	Sex	Co-morbidities	Brand
Joint Reaction (crystals, etc.)						
Bernardeau, et al., 2001[102]	Acute Arthritis	2	59, 73	F	NR	Synvisc
Idrissi et al., 2012[101]	Pseudo-septic arthritis	1	70	F	NR	Ostenil
Maillefert et al., 1997[103]	Pseud- gout (Chondrocalcinosis)	2	62, 83	F	NR	Hyaluron, unspecified
Pullman-Mooar et al., 2002[98]	Inflammatory knee effusions	8	31 to 67	3 M, 5 F	NR	Synvisc
Roos et al., 2004[99]	Pseudo-septic arthritis	1	70	F	Chondrocalcinosis 2 years earlier	Ostenil
Tahiri et al., 2007[100]	Pseudo-septic arthritis	1	70	F	Diabetes	Curavisc
Wendling et al., 2007[104]	Acute gouty arthritis	1	72	F	Overweight, hypertension	Sinovial
Ali et al., 1999[105]	Pseudo-gout	1	74	M	NR	Synvisc
Infections						
Kunugiza et al., 2011[106]	Staphylococcal scaled skin syndrome (sepsis)	1	68	F	NR	NR
Lequerre et al., 2002[107]	Septic arthritis	1	70	M	NR	Synvisc
Shemesh et al., 2011[108]	Septic arthritis	3	64, 70, 75	1 M, 2 F	Hypertension and or hyperlipidemia	NR
Other						
Iizuka et al., 2005[109]	Saphenous nerve injury	1	68	F	Hypertension, gout	NR
Martens, 2001[110]	Systematic inflammatory reaction	1	70	F	NR	Synvisc
Rees et al., 2001[111]	Systemic reaction	1	79	F	Hypertension	Synvisc
Banerjee, 2002[112]	Eosinophiluria	1	68	M	Ischemic heart disease, mild renal impairment	Hyalgan
Semih et al., 2009[113]	Herpes zoster	1	71	M	NR	Sodium hyaluronate
Calvo et al.,	Erythema	1	70	F	Hypertension,	Go-On

Author, Year	AE	N	Age	Sex	Co-morbidities	Brand
2007[114]					pyrazolone allergy	
Michou et al., 2004[115]	Granulomatous synovitis	2	71, 72	F	NR	Synvisc

Table 10. McHarm Table

Author, Year	Were the harms pre-defined using standardized or precise definitions?	Was the mode of harms collection specified as active?	Was the potential occurrence of harmful events collected at pre-specified intervals; for example, the occurrence of post-operative complications were evaluated on a daily basis within 30 days of the surgery?	Did the author(s) specify the number for each type of harmful event for each study group?	Was the total number of participants affected by harms specified for each study arm?	If the study reported that there were no serious AEs reported did they define serious AEs?
Altman et al., 1998[69]	No	No	Yes	Yes	Yes	Not applicable
Berenbaum et al., 2012[70]	Yes	No	No	Yes	Yes	Not applicable
Blanco et al., 2008[51]	No	Yes	Yes	No	Yes	Not applicable
Brandt et al., 2001[71]	Yes	Yes	Yes	No	Yes	Not applicable
DeCaria et al., 2012[72]	Unclear	Unclear	No	No	No	No
Dixon et al., 1988[68]	No	Yes	Yes	Yes	Yes	Not applicable
Dougados et al., 1993[49]	Unclear	Unclear	No	Yes	Yes	No
Grecomoro et el., 1987[83]	No	Unclear	Yes	Yes	Yes	No
Henderson et al., 1994[84]	Unclear	No	Yes	No	Unclear	Not applicable
Huang et al., 2011[73]	Unclear	Unclear	Yes	No	Yes	Not applicable
Huskisson et al., 1999[74]	Unclear	Unclear	Yes	Yes	Yes	Not applicable
Kahan et al., 2003[75]	Unclear	Unclear	Unclear	No	Yes	Not applicable
Karlsson et al., 2002[76]	Yes	Unclear	Unclear	Unclear	Yes	Not applicable

Author, Year	Were the harms pre-defined using standardized or precise definitions?	Was the mode of harms collection specified as active?	Was the potential occurrence of harmful events collected at pre-specified intervals; for example, the occurrence of post-operative complications were evaluated on a daily basis within 30 days of the surgery?	Did the author(s) specify the number for each type of harmful event for each study group?	Was the total number of participants affected by harms specified for each study arm?	If the study reported that there were no serious AEs reported did they define serious AEs?
Khanasuk et al., 2012[77]	No	No	No	No	Yes	Not applicable
Leopold et al., 2003[87]	Unclear	Unclear	Yes	No	Yes	Not applicable
Lundsgaard et al., 2008[81]	No	No	Yes	Yes	Yes	No
Pavelka et al., 2011[78]	No	No	Yes	No	Yes	Not applicable
Petrella et al., 2002[79]	No	No	No	No	No	No
Petrella et al., 2008[79]	No	Unclear	Yes	N/A	Unclear	No
Petrella et al., 2011[89]	No	No	No	No	No	No
Pham et al., 2004[82]	No	Yes	Yes	Yes	Yes	Not applicable
Raman et al., 2008[80]	No	No	Yes	No	Yes	No
Roman et al., 2000[85]	No	Unclear	Unclear	Unclear	No	Not applicable
Tamir et al., 2001[86]	Yes	No	Unclear	Yes	Yes	Not applicable

Discussion

Key Findings and Strength of Evidence

Intra-articular HA and TKR

Three randomized trials and 13 observational studies reported on total knee replacement (TKR).

Of the three trials, two did not regard receipt of TKR as an outcome (and therefore were not designed specifically to test the hypothesis), the participants in one study had a mean age under 65, and the trials were not powered to compare the rates of TKR between HA and comparison groups.

A number of observational studies reported rates of TKR among HA recipients as approximately 20%. One large observational study that assessed the rates of TKR by age group, pain at baseline, and various other factors among stage IV patients considered TKR candidates reported that age was the only factor associated with the likelihood of undergoing TKR: OA patients in the 60-69 year old age group were significantly more likely than patients under 50, patients 70-79, and those over 80 to undergo TKR.[56] This study also assessed the time interval between entering care in their practice and undergoing TKR in 1,342 patients over a 12-year follow-up period. Mean time to TKR for HA recipients was 2.8 years (patients who did not undergo TKR were followed for a mean of 8.7 years); the overall incidence of TKR in this group was 25%. The authors stated that for patients not treated with HA, the average interval between entering care in their practice and undergoing TKR was 3 months. Survival analysis demonstrated that HA treatment delayed the need for TKR in 75% of patients by 7.3 years. As in the original analysis, age was the only factor associated with tendency to undergo TKR. **Given the designs of the studies, the strength of evidence is insufficient to draw conclusions regarding the effect of TKR treatment on delay or avoidance of TKR (see Table 2).**

Intra-articular HA and Function

Eighteen randomized trials reported on the effects of HA compared to sham-injected placebo control, another HA, or some other active treatment on function, as measured by the WOMAC, Lequesne index, KOOS, or ADLs, among patients whose average age was 65 or older. Pooling of ten placebo-controlled studies that reported outcomes for the WOMAC or Lequesne, all assessor blinded, revealed a small increase in function in favor of HA (-0.23, 95%CI -0.34, -0.02); this difference did not achieve the MCID of -0.37 applied by Rutjes and colleagues but did exceed the MCID of -0.15 recommended by the OMERACT-OARSI guidelines and the MCII of -0.12 derived by Tubach and colleagues (based on the pooled effect size, about 11 percent would have exceeded the MCID of 0.37 in improvement); eight of the ten studies measured outcomes at 6 months. One study reported placebo to be more effective and one found no difference.

One trial reported on the effects of HA on ADLs. This study found no change from baseline in the HA or placebo group.

One head-to-head study reported the proportion of patients who experienced improvement in function alone that exceeded the MCII: This study, which compared the intermediate molecular weight Go-On with the lower molecular weight Hyalgan, found that 69% of patients who received Go-On and 56% of patients given Hyalgan experienced improvement that met or exceeded the MCII. Four double-blind placebo-controlled trials that reported on function

reported the proportion of patients who achieved a prespecified level of overall improvement; of these four, three reported a higher proportion of HA-treated patients than placebo-treated patients who achieved either patient- or investigator-reported improvement.

The duration of effect on function could not be ascertained: few studies followed patients long enough to truly measure durability of effect.

Too few head-to-head trials were identified to be able to draw any conclusions about the superiority of any one product over another.

None of the identified studies stratified findings by age, sex, or any other outcome of interest.

The strength of evidence for the conclusion that HA, on average, modestly improves function in patients with knee OA based on placebo-controlled trials is low (trials were not all well designed and two found no effect). The strength of evidence for the conclusion that one HA is better than another, head-to-head comparisons, is insufficient(Table 2).

Intra-articular HA and QoL

Three trials reported on the effects of HA treatment on quality of life. One trial, which compared Hyalgan to treatment with two different volumes of saline, found no change in quality of life from baseline using the KOOS quality-of-life component.[81] Two head-to-head trials that compared Synvisc with Hyalgan assessed quality of life, one using the SF-36 mental component summary to assess QoL[77] and one using the EuroQol-5D index to assess HRQoL.[80] The trial that used the SF-36 reported no increase in quality of life for either group, but the trial that used the EuroQol-5D reported a slight increase in QoL for Synvisc from 3 through 12 months but only an increase in HRQoL for patients on Hyalgan at 3 months.

As only three trials reported both QoL and functional outcomes, no conclusions can be drawn about the relationship between these two parameters.

The strength of evidence for any conclusions regarding an effect of HA on quality of life is insufficient.

Intra-articular HA and Pain

Two large, comprehensive, recent good to high quality systematic reviews compared the effects of HA with sham or non- intervention controls or with placebo and all pharmacologic agents on pain reduction.

A 2012 systematic review reported that HA injections significantly reduced pain, both statistically and clinically (that is, reaching the MCID) when measured at 3 months; however, this effect was lessened to non-significance when only studies with blinded outcome assessment and at least 100 participants per study arm were included in the analysis. Stratified analysis that compared 54 studies with sham controls with 18 studies with non-blinded controls showed a statistically significant effect of HA on pain in the studies with sham controls that nearly met the MCID. They did not conduct a stratified analysis to assess the effect of age of participants. The authors reported evidence for publication bias, which we did not identify in our pooled analysis for effects on function.

A 2015 network meta-analysis compared the effects of oral and intraarticular pharmacologic agents, oral and intraarticular placebo, and HA on pain at 3 months among 129 RCTs (52 studies compared HA with intraarticular placebo).[42] This study reported a significant effect size of HA compared with placebo (-0.34; 95% CI -0.42, -0.26), (similar to that of the Rutjes review) and exceeding the prespecified absolute MCID of -0.20, based on the OARSI-OMERACT responder criteria; sensitivity analysis showed that limiting study size to 50 or more did not change the

effect size but limiting the analysis to studies of 100 or more did reduce the effect size to less than the MCID. This network meta-analysis found minimal evidence for reporting bias among the placebo-controlled HA studies.

Two new trials compared the effects of two different HAs on pain and were not included in prior SRs. One found that single injections of a high- and low-molecular weight were equally effective in reducing pain at 6 months, whereas another found that three injections of an intermediate molecular weight might be superior to low molecular weight HA over 6 months.

Based on the findings of the two prior systematic reviews, we believe that the strength of evidence is moderate that HA reduces pain, on average, by an amount about equivalent to the minimum clinically important difference.

Intra-articular HA and AEs

We identified twenty four trials, three large cohort and case series studies, and 18 case reports that reported on the incidence of adverse events among individuals 65 years of age and over who were given HA to treat OA of the knee.

In placebo-controlled trials of HA, serious adverse events were small in number, and their precise frequency cannot be estimated from current data. The rate of non-serious AEs was higher but did not differ between the HA-treated and sham-control groups.

Among three large cohort studies and case series, representing nearly 6,000 recipients of HA (some more than one series), one serious adverse event was reported: severe swelling and synovial fluid accumulation.

Eighteen case reports provided reports of adverse events among 30 individuals 65 years of age or older, including five cases of sepsis (one case of staphylococcus scalded skin syndrome), and one case each of saphenous nerve injury, eosinophiluria, erythema, and new-onset herpes zoster.

These findings suggest that the adverse events associated with intra-articular injections of HA are nearly all at the site of injection or within the joint, largely confined to pain or swelling, and not different from those of patients who received sham injections. The FDA PMA database revealed no post-marketing reports of unexpected adverse events. Information provided by manufacturers about five products was limited to already published data.

The strength of evidence for the conclusion that serious adverse events are rare is moderate. The strength of evidence for a statistically significant difference in SAEs and non SAEs between intervention and placebo groups is low.

Findings in Relation to What is Already Known

To our knowledge, this report represents the first systematic review to attempt to assess the effects of intra-articular HA injections on the combination of delay or avoidance of TKR, pain, function, quality of life, and adverse events.

No other systematic reviews have attempted to synthesize the effects of HA on TKR, and the present review found insufficient evidence to draw a conclusion about the effects of HA on those outcomes, identifying only three RCTs (two of which did not regard TKR as a study outcome) and a number of observational studies.

Regarding the effect of HA on function, we calculated an effect size of -0.23 (95% CI -0.45, -0.01) , which was smaller than the MCID specified in the review by Rutjes but larger than the MCID used in the network meta-analysis by Bannuru (the Rutjes review reported an effect size

of-0.33, [95% CI -0.43, -0.22]; the Bannuru review reported an effect size of -0.30 [95% CI -0.40, -0.20] for function. Also similar to the Bannuru network meta-analysis, our analysis of the effects of HA on function compared with intraarticular placebo showed no evidence of publication bias.

The moderate effect of HA on function that was identified in the review by Rutjes was no longer considered clinically significant when only large trials (100 or more participants per study arm, or at least 200 per trial) with assessor blinding were considered (-0.09, 95% CI -0.17, 0.00, based on 15 trials).[17] The review by Bannuru, which included only double-blind placebo-controlled trials, found no significant difference in effect size when they included only studies enrolling 50 or more participants but did see a decrease in the effect size when they included only studies of 100 or more participants. However, study size is not typically a criterion in assessing study quality/risk of bias. Our meta-analysis on the outcome of function included only intraarticular placebo-controlled trials that incorporated assessor blinding; we did not find any studies that met our inclusion criteria that enrolled more than 100 participants per study arm.

The 2013 American Academy of Orthopedic Surgeons guidelines for the treatment of osteoarthritis of the knee also conducted a systematic review of the literature on the effects of HA on WOMAC-assessed pain, function, and stiffness. These guidelines recommend against the use of hyaluronic acid to treat patients with symptomatic conditions based on the finding that although statistically significant improvement was seen in pain and function with HA compared to placebo, the improvements did not meet the standard of exceeding the MCII (the issue of considering MCID and MCII is discussed further below) (in contrast, the 2008 AAOS guidelines had found insufficient evidence to recommend for or against HA, based on an AHRQ review that found evidence of publication bias).[19] The 2012 American College of Rheumatology Guidelines for the treatment of osteoarthritis of the knee also conducted a systematic review of the literature on the effects of HA and other modalities and issued a conditional recommendation for the use of HA for the initial management of patients with knee OA.[9]

The current review is the first to consider only studies of individuals of average age 65 or older. Approximately half of the trials included in the 2012 review by Rutjes and colleagues that assessed the outcome of pain enrolled populations of average age less than 65; and of the 52 trials they included in their analysis of the effects of HA on function, nearly all included participants of average age less than 65.[17] Although patient age might affect the ability to experience (or realize) improved function from a treatment, no evidence exists that would suggest age would affect the ability to experience pain relief. Therefore, we believe the analyses in the reviews by Rutjes and Bannuru, given the much larger number of studies they included, were more adequately powered to assess the effects of HA on pain than would be an analysis limited to studies of individuals of average age 65 and over.

The current review found only a small number of serious AEs and in pooling placebo-controlled RCTs, found no statistical differences between serious AEs in treatment and placebo conditions. The 2012 review pooled data on serious AEs from14 trials that reported on AEs and found an increased risk for serious AEs in the HA-treated groups,[17] whereas a 2013 review of 29 studies,[90] as well as the 2015 network meta-analysis by Bannuru and colleagues found no difference between HA and placebo for any AE, in agreement with the present study. To derive a potential explanation for the disparity in the apparent risk for serious AEs between the review by Rutjes and colleagues and ours, we re-abstracted the data on serious AEs (both those reported by original study authors as being serious, those deemed serious by the criteria of the present study, and those deemed serious by the criteria of the 2012 review). We included only studies that

would have met our inclusion criteria (making an exception for mean age); therefore we excluded studies in the Rutjes analysis that were not assessor blinded, studies in which patients served as their own controls, and conference abstracts. The reported increase in risk for serious AEs among patients who received HA compared with placebo in the 2012 review appears to be attributable to several factors. The methods use for the statistical analyses differed slightly between the two reviews. In addition, the criteria used to define serious AEs, the criteria for accepting original authors' definitions of serious AEs, and the criteria for plausible associations differed between the two reviews; fewer than half of the trials included in the serious AE analysis of the review by Rutjes and colleagues[17] actually described specific AEs, and a number of studies that did describe the specific AEs they observed had methodological limitations. The network meta-analysis by Bannuru and colleagues, as well as another recent (2014) meta-analysis by this group compared the efficacy and safety of intraarticular HA with NSAIDs for the treatment of knee OA: Although the small number of studies they were able to pool showed no differences in efficacy between HA and NSAIDs, NSAIDs were associated with a significantly increased risk for gastrointestinal AEs compared with HA We address the issue of adverse event reporting further below in our discussion of limitations.

Regarding non-serious AEs, the 2012 review limited its assessment to flare-ups (a joint reaction), finding no statistically significant difference between treated and placebo groups.[14] This finding agrees with that of the present review, which found no statistically significant differences between actively treated and sham/placebo-treated groups for non-serious local, joint, and "other" AEs. It is not possible to assess whether the potentially high numbers of these non-serious AEs indicate that a large proportion of study participants experience these AEs because most studies do not report the total numbers of participants who experience at least one AE (so one participant could report many AEs). In addition, the observation that the number of "other" (not joint related and not local, e.g., "headache") non-serious AEs is far higher than the numbers of local and joint-related non-serious AEs, supports a lack of association between these occurrences and the intervention and suggests knowledge of such events may not have much of an impact on the decision-making of an individual seeking the chance for relief.

Applicability

To increase potential applicability, we limited studies included in the current review with functional outcomes to those with an average age of 65 or older. Nevertheless, no studies excluded patients younger than 65. Given that the only study that assessed factors that might influence the likelihood of undergoing TKR found that age was the only influential factor, age of study participants is likely to be an important consideration for this outcome.

The larger trials included in the assessment of functional outcomes were mostly conducted in academic settings; this typical characteristic of randomized trials tends to limit their applicability to community settings. However a number of the observational studies that addressed the outcome of TKR were conducted in private medical practices.

Implications for Clinical and Policy Decision Making

The evidence identified for the current study is insufficient to support a decision either way about the efficacy of intra-articular HA injection based on the delay or avoidance of TKR. In addition, the strength of evidence is insufficient regarding the efficacy of HA for improving quality of life or function in a population 65 years of age or older.

Limitations of the Comparative Effectiveness Review Process

Given the key questions specified by the partner and specified in our study protocol, we did not attempt to review studies of populations of average age less than 65 years to determine whether they found improvements in function or quality of life. However, removing the exclusion criterion of age for studies that assessed the outcome of TKR, we still identified only three randomized trials that reported TKR, and it was considered a primary outcome in only one study. We also did not contact authors of original research studies to request raw data by patient age and did not attempt to do new pooling of the data on pain in the studies included in the review by Rutjes and colleagues, to include only studies of older populations for reasons explained above.

In addition, as we discuss in the next paragraph (Limitations of the Evidence Base), in choosing the 6-month time point for pooling of effects on function, rather than a shorter follow-up time, we may have underestimated the effect of HA.

Limitations of the Evidence Base

The majority of trials identified for the current report were of relatively mediocre quality, with poor reporting. Few trials described their recruitment strategy or method for allocation concealment. A number of studies had dropout rates higher than 20% (no studies addressed differences between dropouts and completers), and although most excluded individuals who had recently received corticosteroids or other courses of an HA, most also did not bar participants from using other modes of pain relief, such as NSAIDs. Further, few or no studies attempted to determine whether response to HA differed between groups of patients stratified by characteristics such as baseline age, disease severity (stage) or type; or duration of treatment, few studies followed patients long enough to truly measure durability of effect, and adverse events were not measured using any standardized method.

Specific to the outcome of function, no trials measured the duration of effect. A 2011 meta-analysis by Bannuru and colleagues assessed the therapeutic trajectory of intraarticular HA in placebo-controlled trials among patients with knee OA.[116] The review identified 54 studies and computed effect sizes for changes from baseline in pain from 4 to 24 weeks. A significant effect size was seen for HA by 4 weeks and this effect peaked at 8 weeks, decreasing thereafter so that only a small effect remained by 6 months. The studies we identified that reported on function at multiple time points were insufficient in number to estimate a trajectory of effect for function.

Also specific to function, only one trial reported the percentage of participants whose function improved (seven studies reported on the percent who achieved a prespecified level of global improvement, of which four were double-blind placebo-controlled trials).

Specific to the outcome of TKR, only one small RCT measured knee replacement as a primary outcome. A number of observational studies, including several large retrospective data analyses, reported delays in TKR among patients who received IA HA, compared with patients who did not receive HA. However observational studies cannot control for the selection effect whereby patients who are more or less inclined to TKR are selected by their physicians for getting—or not getting—IA HR. Therefore without randomized trials designed and adequately powered to assess the effect of HA on TKR, it is not possible to draw conclusions at this time regarding the effect of HA treatment on delay or avoidance of TKR

Another challenging issue for studies of HA is that of the potential placebo effect inherent in the kinds of studies we reviewed. Although we limited our assessment to double-blind placebo-controlled trials (using only intraarticular placebos), the main analysis in the systematic review by Rutjes and colleagues included studies with various types of control groups, including both intraarticular and oral placebo. A 2012 meta-analysis by Colen and colleagues that included 74 studies specifically noted the large effect size for placebo alone (approximately 30%).[16] The network meta-analysis by Bannuru and colleagues found that the effect size for intraarticular placebo exceeded that of all active oral treatments for pain[42], prompting a commentary on the role of placebo controls in studies of the treatment of knee OA.[117] Identifying the proper control for studies of interventions such as the injection of hyaluronic acid can be challenging, but at the same time, the existing trials, with intraarticular saline controls, are capable of assessing whether HA has any specific active effect over and above the injection of inexpensive saline.

A related but slightly different issue is that a number of studies allowed the use of rescue medications (acetaminophen, NSAIDs, and less often, CS or opioids) between treatments, which could have eliminated any observable difference between active treatment and placebo.

The use of statistical significance vs. clinical significance in studies such as the ones included in this review (as well as the review itself) also needs to be mentioned. The attainment of both statistical significance and MCID or MCII is critical for demonstrating effectiveness of any clinical treatment. However the threshold chosen for the MCID and how it is applied is controversial.[118] The evidence is limited as to what the MCID should be for an effect of HA on function, whether it should be the same as for pain, and whether it should be limited to the use of only certain outcome measures. In trying to interpret our results regarding HA and function, we used three levels of MCID/MCII that have been proposed and used by others: our observed effect size exceeded the lower MCIIs of 0.12 and 0.20 but did not meet the MCID used in the review by Rutjes, 0.37 (an effect size of 0.2-0.4 is normally considered small to moderate according to Cohen's classification). But we acknowledge as a limitation that additional research could improve estimates of the MCID/MCII. Perhaps more importantly, we identified almost no studies that reported the proportion of patients who achieved either a statistical or clinical improvement.

Finally an issue of possible concern is that many studies of HA show potential financial conflict of interest (FCOI), either direct industry funding of the research or employment of authors by manufacturers of the agents being tested.[90, 91] A 2013 systematic review examined 48 trials of intraarticular HA for the treatment of knee OA to determine whether industry sponsorship was associated with the likelihood of a positive finding. Of 33 trials that identified a sponsor, 30 were industry sponsored; therefore, determining whether industry sponsorship affected outcomes was impossible. However the study also assessed the association between industry authorship (compared with academic authorship) and outcomes. Of the 17 studies with industry authors, none reported unfavorable conclusions (all reported favorable or neutral conclusions); 11 of the 31 academic authored studies reported unfavorable conclusions and 9 reported neutral conclusions. Another 2013 systematic review assessed only studies of HA that employed US-approved HA products; this review, which identified 29 studies and was funded by a trade group representing the pharm industry, reported statistically and clinically significant pooled effects sizes for the outcomes of pain and function compared with saline controls and no difference in serious AEs.[90] However, the 2015 network meta-analysis by Bannuru and colleagues reported comparable effect sizes and was funded by the Agency for Healthcare Research and Quality.

Research Gaps

Many of the research gaps we identified were discussed in the previous section on the limitations of the evidence base. This section presents several specific research needs based on the outcomes of greatest interest.

Clear research gaps exist regarding studies of the effectiveness of HA among individuals 65 years of age and older and the effect of HA, if any, on delay or avoidance of TKR. Two searches for ongoing studies of HA and OA of the knee on Clinicaltrials.gov and review of entries provided by manufacturers revealed no completed, ongoing, or recruiting studies on older individuals with knee OA or with outcomes of TKR. The observational studies identified for this review could not definitively answer the question of whether HA delays or prevents the need for TKR. However, data from any of the large administrative databases maintained by commercial payers offer an alternate possibility. Preliminary findings of three such studies have been presented at two recent meetings. An abstract presented at the 2013 meeting of the American College of Rheumatology reported using the Truven Marketscan database to match 7,000 HA recipients (66% female) with 19,627 non-recipients with OA of the knee (propensity score matching with the non-HA cohort was 98%).[119] With one episode of HA treatment, the median times from the initial specialist visit to TKR were 199 and 443 days for the non-HA cohort and HA cohort, respectively. Additional treatment episodes increased the median gap by an average 202 days, suggesting true dose-response.

Dasa and colleagues presented the findings of a similar audit of IMS Health's PharMetrics Plus Health Plan Claims at the 2014 annual meeting of the Academy of Managed Care Pharmacy.[120] In an industry-sponsored study, they identified 18,217 patients who initiated treatment with Supartz/Hyalgan between 2007 and 2010 and were followed for 3 years: 13,561 patients received a single course of treatment, 2,999 received 2 courses, 1,012 received 3 courses, 404 received 4 courses, and 241 received 5 or more courses. Successive courses of HA led to greater proportions of patients without TKR at 3 years: 96.3% of those who received 5 or more courses avoided TKR compared with 72.7% who received 1 course (HR 0.113, $p<0.0001$). In a study funded by Horizon Blue Cross Blue Shield of New Jersey, Khan and colleagues conducted a retrospective analysis of claims from beneficiaries who had been plan participants for 5 or more years and had a confirmed diagnosis of IA: of 2,728 patients who received a first dose of HA, 35% underwent knee surgery within the first year and another 34.2% underwent surgery the second year. However the study did not specify the type of surgery and included patients who had undergone prior knee surgery; thus the authors concluded that although 69% of patients underwent surgery (of some type) within two years of treatment, further research is needed that enrolls patients with appropriate eligibility criteria.[121]

The decision to undergo TKR is difficult to predict, as it is affected by a number of factors beside severity of osteoarthritis, such as age, comorbidities, pain tolerance, activity level, aversion to surgical intervention, and expectations about one's life expectancy; OMERACT has considered this issue and has suggested considering two alternative outcomes for assessing the effect of treatments for knee OA: "time to physician's decision to recommend surgery" and "time to fulfilling criterial for total joint replacement."[122] However, if the primary question of interest is whether or not intraarticular HA can delay joint replacement, a double-blind placebo controlled trial could be conducted that enrolls a group of people who have already been deemed "appropriate for surgery" and randomizes them to receive intraarticular HA or an intra-articular placebo. Comparison of the time to TKR could then be appropriately compared. We did identify one small pilot study that employed this design, the study conducted by Blanco and colleagues,

which reported a delay in time to TKR in the HA group that did not achieve statistical significance.[51]

Research is also needed to confirm the suggestion that higher molecular weight, more cross-linked HA products are more effective than lower molecular weight products: a subgroup analysis in the review by Rutjes suggested a trend toward greater pain relief for very high molecular weight products but studies are needed to assess whether this observation generalizes to function and also to compare the newer, larger products with the smaller ones.

Another issue of concern is the effectiveness (and safety) of HA over time and with repeated treatment cycles. Given that most studies of HA have been 6 months or less in duration and that OA of the knee is a chronic condition, studies are needed to assess both the safety and effectiveness of repeated cycles of HA over time and whether HA decreases the need for pharmacotherapy (NSAIDS, corticosteroids, and opioids), which has its own safety concerns.

Finally, as discussed above, the way that AEs are recorded and reported merits concern. Although issues such as potential underreporting affect active interventions as well as placebo-treated controls within the same study, the disparity in that of Bannuru) reinforces the need for standardization in the way that adverse events are documented. Based on a systematic review conducted in 2013, a group of researchers has developed an ACTTION (Analgesic, Anesthetic, and Addiction Clinical Trial Translations, Innovations, Opportunities, and Networks) AE checklist to improve the accuracy and completeness of AE data abstracted from reports of trials.[123]

Conclusions

Trials enrolling older participants show a small, statistically significant effect of HA on function. Whether this effect is clinically meaningful is less clear: The research literature varies on its definition of minimum clinically important improvement. Based on our analyses, HA demonstrated clinically important improvements using two out of three of these definitions for this assessment. HA shows relatively few serious adverse events; however no studies limited participation to those 65 years or older. No conclusions can be drawn from the available literature on delay or avoidance of TKR through the use of HA. Studies that can compare large numbers of treated and untreated individuals, preferably with a randomized design, are needed to answer this question.

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Abbreviations / Acronyms

ADL	Activities of Daily Living
AEs	Adverse Events
AHRQ	Agency for Healthcare Research and Quality
CMS	Centers for Medicare and Medicaid Services
DJD	Degenerative Joint Disease
FDA	Food and Drug Administration
HA	Hyaluronic acid
HRQoL	Health-Related Quality of life
IADLs	Instrumental Activities of Daily Living
KOOS	Knee Injury and Osteoarthritis Outcomes Score
TKR	Knee Replacement
MCID	Minimum clinically important difference
MCII	Minimum Clinically Important Improvement
OA	Osteoarthritis
OARSI	Osteoarthritis Research Society International
OMERACT	Outcome Measures in Rheumatology
OR	Odds-Ratio
PICOTs	Participants, Interventions, Comparators, Outcomes, and Timeframes
PMA	Post-Marketing Assessment
QoL	Quality of Life
RCTs	Randomized Controlled Trials
ROB	Risk of Bias
SCEPC	Southern California Evidence-based Practice Center
SD	Standard Deviation
SF-36	Short form-36
SIPS	Scientific Information Packets
SMD	Standardized Mean Difference
SOE	Strength of Evidence
SRC	Scientific Resource Center
TAP	Technology Assessment Program
TKR	Total Knee Replacement
VAS	Visual analog scale
WOMAC	Western Ontario and McMaster Universities Osteoarthritis Index