International Symposium Intra Articular Treatment

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WEBINARS

6:00-7:00 p.m. (CET)

"Recent NMA on IA treatment: several criticisms"

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Collegio Reumatologi Italiani CReI

International Symposium Intra Articular Treatment

ANTIAGE

Gemelli
Fondazione Policlinico Universitario Agostino Gemelli IRCCS
Università Cattolica del Sacro Cuore

DISCLOSURES

Alberto Migliore received grants as consultant from
ABIOGEN, KIOMED, FIDIA, CONTURA and IBSA for national and international studies and advisory boards.

Background

- HA is a linear polysaccharide which occurs naturally as a constituent of synovial fluid.
- The HA concentration in the joint decreases inexorably during the progression of knee OA and so, for nearly 30 years, HA has been used in the treatment of knee OA.
- International and domestic guidelines vary in the degree to which they recommend the use of IAHA with some supporting and others discouraging its usage.
- There are strong data from clinical trials, meta-analyses and umbrella reviews to support the use of IAHA in the treatment of knee OA
- The majority of the literature suggests that IAHA has a positive safety profile despite a few meta-analyses suggesting an increased risk of serious adverse effects.
- Further qualitative analysis is required in order to further explore these findings.

Osteoarthritis and Cartilage 33 (2025) 207–217

Osteoarthritis and Cartilage

Review

Effectiveness and safety of intra-articular interventions for knee and hip osteoarthritis based on large randomized trials: A systematic review and network meta-analysis

Tiago V. Pereira #, Pakeezah Saadat †, Pavlos Bobos ‡ §, Samir M. Iskander ¶, Nicolas S. Bodmer † ‖, Martina Rudnicki ##, Henry Dan Kiyomoto ††, Thais Montezuma ‡‡, Matheus O. Almeida ‡‡, Rishi Bansal #, Pai-Shan Cheng §§, Jason W. Busse ¶¶ ‖‖, Alex J. Sutton ###, Peter Tugwell ††† ‡‡‡, Gillian A. Hawker §§§, Peter Jüni # † §§§ [1], Bruno R. da Costa # † ¶¶¶ [1] *

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No rheumatologist
No orthopedic

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NMA design

- **Objective:** To quantify the effectiveness and safety of intra-articular interventions for knee and hip OA through a systematic review and Bayesian random-effects network meta-analysis.
- Design: We searched CENTRAL and regulatory agency websites (inception-2023) for large, English-language, RCTs (≥100 patients/group) examining any intra-articular intervention.
- Primary outcome: pain intensity.
- Secondary outcomes: physical function and safety outcomes.
- Pain and function outcomes were analyzed at 2, 6, 12, 24, and 52 weeks.
- The prespecified minimal clinically important between group difference (MID) was −0.37 SMD.
- Safety outcomes were presented as odds ratios (OR) (95% CrI).

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NMA results

- Findings: Among 57 RCTs (22,795 participants) examining 18 IA interventions, usual care or placebo, treatment effects were larger in 35 high-risk–of-bias trials than in 22 low/unclear-risk-of-bias trials.
- In the main analysis (excluding high-risk-of-bias trials), triamcinolone had the highest probabilities of reaching the MID at weeks 2 and 6 (75.3% and 90%, respectively) compared to placebo (1 trial).
- The complex homeopathic products Tr14/Ze14 showed therapeutic potential at week 6 compared to placebo (SMD:−0.42,95% CrI,−0.71 to −0.11, 63.5% probability of reaching the MID, 1 trial).
- Hyaluronic acid had no effect on pain

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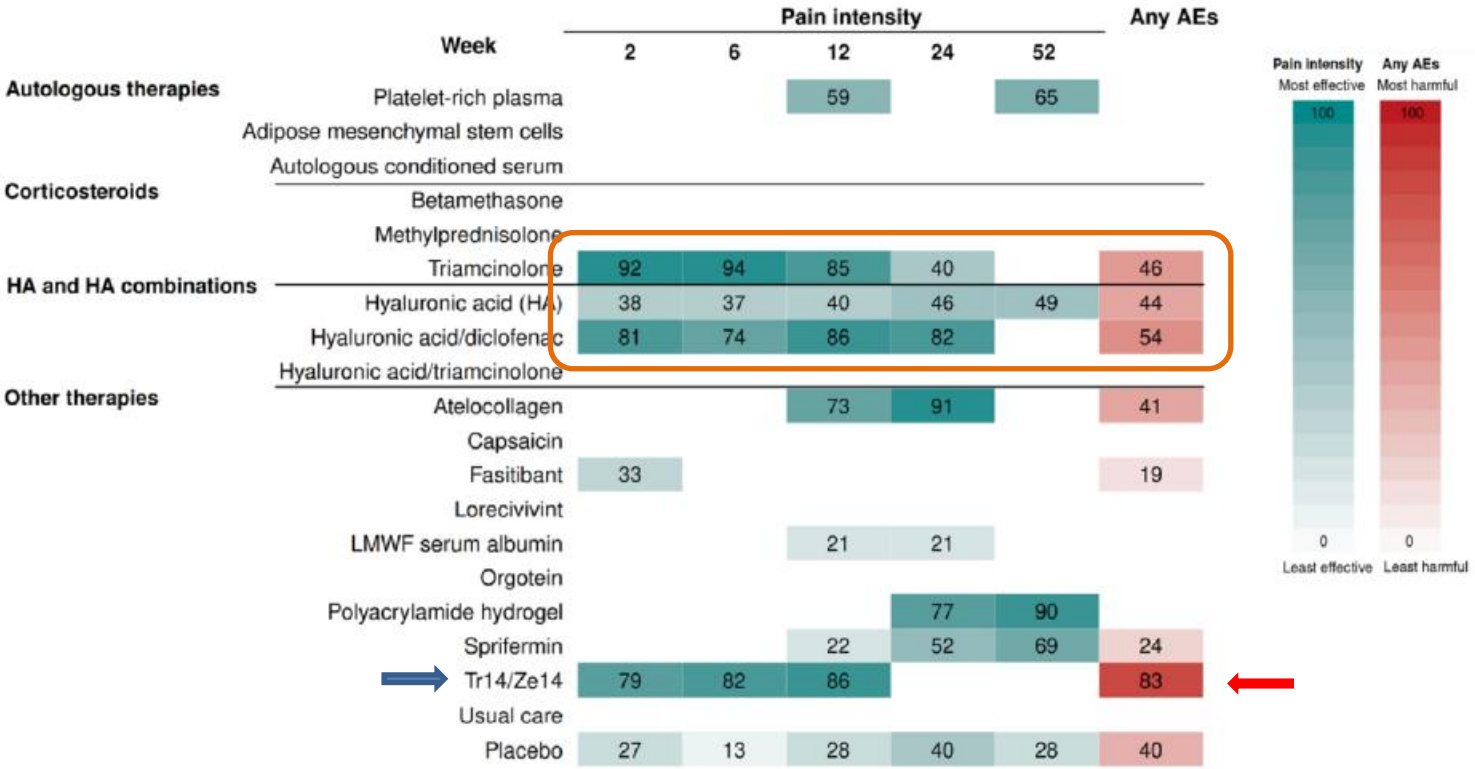
Values for different intra-articular treatments across time



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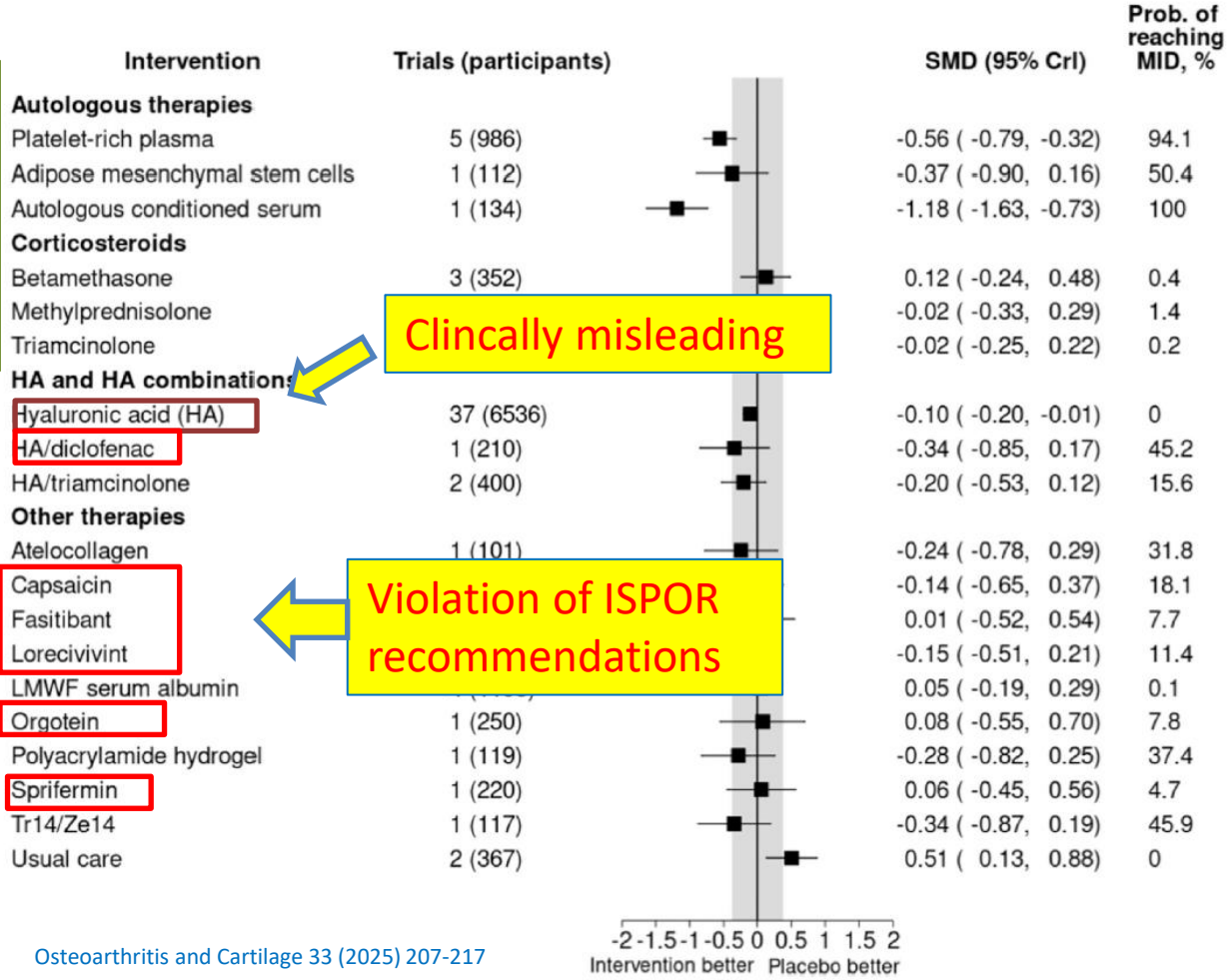
Summary treatment effects for pain intensity (12 weeks) comparing each active intervention to placebo



Clincally misleading

Violation of ISPOR recommendations

It is not a homogeneous group

these products are not registered nor on the market

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OAC15367R2 Letter to the Editor – Revised Version 2

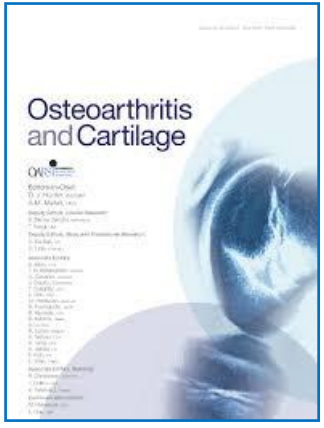
Comment on: Effectiveness and safety of intra-articular interventions for knee and hip osteoarthritis based on large randomized trials: A systematic review and network meta-analysis (Pereira et al., 2025)

Alberto Migliore [1], Ali Mobashe

behalf of the European Socie

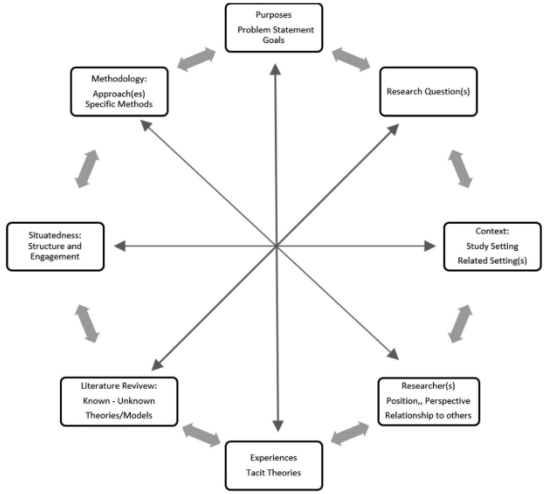
Osteoarthritis and Musculosk

we highlight key methodological concerns and multiple instances of non-compliance with these established standards



***The ESCEO Osteoart** ed Alokail, Patrick Ammann, Francis Berenbaum, Angie Botto-van Bemden, Maria Luisa Brandi, Olivier Bruyère, Nansa Burlet, Roland Chapurlat, Cyrus Cooper, Elaine Dennison, Nick Fuggle, Gun-il Im, Andreas Kurth, Emmanuel Maheu, Radmila Matijevic, Daniel Messina, Alberto Migliore, Ali Mobasheri, Jordi Monfort Faure, Régis Radermecker, François Rannou, Jean-Yves Reginster, René Rizzoli, Ralf Schmidmaier, Stuart Silverman, Julien Wegrzyn, Leith Zakraoui

Key methodological concerns



Key methodological concerns and multiple instances of non-compliance with NMA guidelines (1)

- The authors do not adhere to established NMA guidelines from the ISPOR (International Society for Pharmacoeconomics and Outcomes Research), Cochrane , PRISMA-NMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses for Network Meta-Analyses) , NICE (National Institute for Health and Care Excellence) , and GRADE

- This NMA inappropriately excludes high-risk-of-bias trials without conducting a proper sensitivity analysis, despite ISPOR guidelines recommending their assessment through sensitivity analyses or Bayesian weighting rather than outright exclusion.

Key methodological concerns and multiple instances of non-compliance with NMA guidelines (2)

- Exclusive focus on large RCTs (≥100 patients per group) introduces bias
- Assumption that large trials are inherently of higher quality is flawe
- Exclusion of small but well-conducted trials leads to an incomplete analysis.
- Arbitrary Exclusion of High-Risk-of-Bias Trials
- This exclusion may compromise result validity, particularly for PRP and IA CS, which rely on some of the excluded studies.

Key methodological concerns and multiple instances of non-compliance with NMA guidelines (3)

- Another major issue is the inclusion of investigational treatments (capsaicin, Lorecivivint, orgotein, Sprifermin, fasitibant) and non-standard dosages, contradicting ISPOR's recommendation to focus on regulatory-approved interventions for real-world applicability.

- Additionally, the study incorporates unapproved dosag **Bias of presentation** studies, which are not transparently reported, instead being relegated to Appendix 6, despite ISPOR strongly advising against this practice.

- These data do not reflect real-world prescribing patterns and may distort efficacy estimates.

Key methodological concerns and multiple instances of non-compliance with NMA guidelines (4)

- The choice of the MCID is not well justified. (−0.37 SMD : 9 mm on a 100-mm VAS) a the MCID without clear justification, disregarding ISPOR guidelines, which emphasize using validated sources for this threshold.
- NICE guidelines also recognize that even small pain reductions are meaningful, which makes this restrictive threshold potentially misleading.
- The authors do not satisfactorily address heterogeneity and inconsistency, despite ISPOR and PRISMA-NMA recommendations.
- High heterogeneity, especially concerning PRP and HA, is not adequately managed with subgroup analysis or Bayesian meta-regression.

Key methodological concerns and multiple instances of non-compliance with NMA guidelines (5)

- The study lacks a GRADE assessment, an essential component for evaluating evidence certainty.
- Without it, the reliability of conclusions is unclear, particularly for indirect comparisons, which limits their usefulness in clinical decision-making.
- The study does not assess industry sponsorship bias, despite explicit recommendations in methodological guidelines

Concerns from a clinical perspective

Concerns from a clinical perspective (1)

The efficacy evaluation of HA has some concerns.

- ✓ Combining hip and **knee** trials introduces bias, as **hip** injections require careful assessment of technique, including ultrasound guidance
- ✓ The study does not account for **differences in HA** MW, concentration, and dosing, despite HA products being highly variable in terms of molecular composition.
- ✓ Overlooking these factors contradicts previous meta-analyses and real-world data

Concerns from a clinical perspective (1)

The efficacy evaluation of HA: concerns

- ✓ Saline is not a true placebo for IA injections, as it alters various parameters including joint hydrostatic pressure and cytokine concentrations .
- ✓ A sham injection would have been the more appropriate comparator.
- ✓ Saline has been shown to reduce pain more than oral placebo or paracetamol (6), which means that concluding HA is ineffective based on this comparison is misleading.
- ✓ Overlooking these factors contradicts previous meta-analyses and real-world data

Concerns from a clinical perspective

Failure to Address Long-Term Risks of Triamcinolone

- The study highlights triamcinolone as the only effective treatment but ignores cartilage degradation risks
- Prior studies (e.g., McAlindon et al., JAMA 2017) report long-term joint deterioration
- Recommending triamcinolone without acknowledging risks is misleading.

Concerns from a clinical perspective: safety

- The reporting of safety outcomes appears to lack consistency and transparency
- While “dropouts due to adverse events (AEs)” are stated as the primary safety outcome, their prevalence is not presented clearly in the main text but displayed rather in Web-Appendix 15
- Also, key safety analyses are reported in Appendix 36
- The number of trials analysed varies widely across outcomes *(e.g., 12 trials for dropouts due to AEs, 10 for any AEs, 16 for severe AEs),* making interpretation difficult

Concerns from a clinical perspective: safety

- The authors do not assess their clinical **relevance or causality**, (fundamental in a robust safety evaluation). Instead, they refer to their previous meta-analyses, which did not classify AEs by treatment relationship, leading to potentially misleading conclusions

- In contrast, other reviews have found no major systemic risks with IAHA, reporting only a local AE rate of ~8% and rare post-injection arthritis (9).

Letter's Conclusion

- ✓ In conclusion, this study contains several methodological flaws that significantly undermine its validity and raise serious concerns about bias and reliability
- ✓ The unjustified exclusion of trials, inclusion of experimental treatments and dosages, an overly stringent MCID threshold, the lack of a GRADE assessment, and inconsistent safety data reporting all contribute to a distorted and misleading analysis
- ✓ Rather than providing meaningful insights, this NMA risks misinforming clinicians, decision-makers, and patients by offering a distorted portrayal of intra-articular treatments
- ✓ When used appropriately and in well-selected patient subgroups, IA HA have been shown to improve pain, function and quality of life significantly

Save the Date

8th ISIAT

International Symposium Intra Articular Treatment

Bucharest

2-4 October 2025

Thursday October 2nd

OPENING CEREMONY

Plenary Room

16.30-19.00 "Update from national and international consensus"

Moderators: *A. Migliore (Rome, Italy); R. Raghu (Chennai, India); X. Chevalier (Créteil, France);*

- **EUROVISCO GROUP update**
  T. Conrozier (Belfort, France)
- **GRIIP: indications, contraindications and misuses of PRP**
  F. Eymard (Créteil, France)
- **Latin American Consensus COLAVI**
  P. Hamdan, (Rio de Janeiro, Brazil)
- **ESSKA-ORBIT consensus on orthobiologics**
  R. Marinescu (Bucharest, Romania)
- **IA injections in the Multimodal Management of OA: the ESCEO** algorithm
  N. Veronese (Palermo, Italy)
- **SIOT: IA and non-surgical management of OA**
  R. Papalia (Palermo, Italy)
- **The role of IA injection in the OARSI guidelines for the non-surgical management of OA**
  R. Bannuru (Boston, USA)
- **Guidelines in comparison**
  Wojciech Glinkowski (Warsaw, Poland)
- **METAVISCO recommendations:**
  Rayan Hassoun

Thank you for your attention !

Key methodological concerns and multiple instances of non-compliance with NMA guidelines

- The authors do not adhere to established NMA guidelines from the ISPOR (International Society for Pharmacoeconomics and Outcomes Research) , Cochrane , PRISMA-NMA (*Preferred Reporting Items for Systematic Reviews and Meta-Analyses for Network Meta-Analyses*), NICE, anc GRADE.
- This NMA inappropriately excludes high-risk-of-bias trials without conducting a proper sensitivity analysis,.
- Exclusive focus on large RCTs (≥100 patients per group) introduces bias.
- Exclusion of small but well-conducted trials leads to an incomplete analysis.
- Inclusion of investigational treatments (**capsaicin, Lorecivivint, orgotein, Sprifermin, fasitibant**), contradicting ISPOR's recommendation to focus on regulatory-approved interventions for real-world applicability.
- The study incorporates unapproved dosages from dose-finding studies.
- These data do not reflect real-world prescribing patterns and may distort efficacy estimates.
- **The authors do not satisfactorily address heterogeneity and inconsistency**, despite ISPOR and PRISMA-NMA recommendations.

Concerns from a clinical perspective

The efficacy evaluation of HA has some concerns.

- ✓ **Combining hip and knee** trials introduces bias, as hip injections require careful assessment of technique, including ultrasound guidance.
- ✓ **Saline is not a true placebo** for IA injections, as it alters various parameters including joint hydrostatic pressure and cytokine concentrations .
- ✓ A sham injection would have been the more appropriate comparator.
- ✓ Saline has been shown to reduce pain more than oral placebo or paracetamol, which means that concluding HA is ineffective based on this comparison is misleading.
- ✓ The study does **not account for differences in HA MW, concentration, and dosing**, despite HA products being highly variable in terms of molecular composition.
- ✓ Overlooking these factors **contradicts previous meta-analyses and real-world data**

Key Criticisms of the Study 1

Selection Bias in Study Inclusion

- ✓ Exclusive focus on large RCTs (≥100 patients per group) introduces bias.
- ✓ Assumption that large trials are inherently of higher quality is flawed.
- ✓ Exclusion of small but well-conducted trials leads to an incomplete analysis.

Arbitrary Exclusion of High-Risk-of-Bias Trials

- ✓ Many interventions, such as PRP and ACS, rely on evidence from trials categorized as high risk.
- ✓ Excluding these trials entirely, rather than weighting them accordingly, skews the results.

Overly Stringent Minimal Clinically Important Difference (MCID) Threshold

- ✓ MCID set at −0.37 SMD (9 mm on a 100-mm VAS scale) is too high.
- ✓ Many widely accepted pain treatments have effect sizes below this threshold.
- ✓ Lack of justification for applying this strict cutoff to all interventions.

Key Criticisms of the Study 2

Misrepresentation of Hyaluronic Acid (HA) Efficacy and Safety

- ✓ Conclusion that HA is equivalent to placebo contradicts multiple meta-analyses and real-world data.
- ✓ Reported increase in serious adverse events (SAEs) lacks biological plausibility.
- ✓ No consideration of HA molecular weight variations, which impact efficacy.

Unfair Dismissal of Platelet-Rich Plasma (PRP) Evidence

- ✓ Only one PRP trial (Bennell et al., 2021) was included, while others were excluded as high risk.
- ✓ The retained trial differs in patient selection and injection technique from most PRP studies.
- ✓ Ignoring the broader body of PRP evidence presents an incomplete picture.

Key Criticisms of the Study 3

Failure to Address Long-Term Risks of Triamcinolone

- ✓ The study highlights triamcinolone as the only effective treatment but ignores cartilage degradation risks.
- ✓ Prior studies (e.g., McAlindon et al., JAMA 2017) report long-term joint deterioration.
- ✓ Recommending triamcinolone without acknowledging risks is misleading.

Lack of Clinical Context and Practical Guidance

- ✓ Study does not provide practical recommendations for clinicians.
- ✓ No consideration of how these findings apply to real-world OA management.
- ✓ Clinicians need guidance for patients unresponsive to oral treatments.

Methodological Issues and Non-Compliance with ISPOR/NICE/PRISMA-NMA/GRADE Guidelines

Arbitrary Exclusion of High-Risk-of-Bias Trials Without Adequate Sensitivity Analysis

- ISPOR guidelines recommend not excluding high-risk-of-bias studies outright but rather weighing their impact through sensitivity analysis or Bayesian weighting methods
- In this study, directly excluding these trials may have skewed the validity of the results, especially for interventions like PRP and ACS, which are mostly supported by the excluded studies

Arbitrary Selection of the Minimal Clinically Important Difference (MCID)

- The study defines −0.37 SMD (9 mm on a 100-mm VAS scale) as the MCID, but this threshold is unjustified.
- ISPOR recommends deriving the MCID from validation studies or previous meta-analyses, which was not done here
- ICE guidelines suggest that even small pain reductions can be clinically meaningful, meaning that using an overly strict cutoff may have led to misleading conclusions

Methodological Issues and Non-Compliance with ISPOR/NICE/PRISMA-NMA/GRADE Guidelines

Lack of GRADE Assessment for Certainty of Evidence

- The study fails to apply GRADE (Grading of Recommendations, Assessment, Development, and Evaluations) to assess the certainty of evidence, which is a crucial step in systematic reviews and NMAs
- Without a GRADE assessment, it is difficult to determine the strength and reliability of the conclusions, especially when handling multiple indirect comparisons.
- GRADE is widely used to classify evidence into high, moderate, low, or very low certainty, helping clinicians and policymakers make informed decisions

Methodological Issues and Non-Compliance with ISPOR/NICE/PRISMA-NMA/GRADE Guidelines

Failure to Fully Address Heterogeneity and Inconsistency

- ISPOR and PRISMA-NMA guidelines recommend exploring and explaining heterogeneity among studies, which was only partially done in this study
- The NMA exhibits high heterogeneity in results, especially for PRP and HA, yet the authors did not adequately apply techniques such as subgroup analysis or Bayesian meta-regression to control for publication bias

No Systematic Assessment of Industry Funding Bias

- Many included studies were industry-funded, yet there is no systematic analysis of sponsorship bias, as recommended by PRISMA-NMA and ISPOR

RECOMMENDATIONS LANDSCAPE

Journal of *Clinical Medicine*

MDPI

Review

Intra-Articular Hyaluronic Acid for Knee Osteoarthritis: A Systematic Umbrella Review

Wojciech Michał Glinkowski [1,2,*] and Wiesław Tomaszewski [3,4,*]

Report of 21 scientific associations

Conclusions:

- La VS rimane una modalità di trattamento per popolazioni selezionate di persone con OA, in particolare per la malattia precoce e moderata.
- Sono ancora necessari studi standardizzati di alta qualità per perfezionare il ruolo dell'IAHA e stabilire linee guida personalizzate per i singoli pazienti.
- Uno sforzo concertato per armonizzare le raccomandazioni globali e le strategie economiche, può aumentare l'accesso equo e ottimizzare l'integrazione dell'IAHA del trattamento multimodale per l'OA.

Total: 2 against; 5 uncertain; 15 in favour

J. Clin. Med. 2025, 14, 1272

A summary of the international and national guidelines on VS in KOA (2)

Guideline	Recommendation regarding Hyaluronic Acid in Knee OA
Société Française de Rhumatologie (SFR)	Recommends IAHA independent of molecular weight or number of injections
Società Italiana di Reumatologia (SIR)	"IA injection of HA of different MW may give symptomatic benefit with low toxicity and reduce the NSAID use"
Società Italiana di Ortopedia e Traumatologia (SIOT)	Recommends IAHA in chronic disease cases, not for acute, active disease
EULAR	EULAR provides general guidance on intra-articular therapies but does not explicitly endorse or reject IAHA for KOA.
ACR	The ACR and Arthritis Foundation (A.F.) conditionally recommend using IAHA for KOA, citing mixed evidence of its efficacy. Although IAHA may offer benefits, it is often modest and inconsistent, making it less favorable than CS injections. The ACR provides conditional recommendations for IAHA use in select patients, failing to respond to NSAIDs and physical therapy. The ACR emphasizes individualized decision making based on patient-specific factors
ISIAT	ISIAT recommends IAHA for mild-to-moderate KOA, highlighting innovative products that significantly and sustainably improve pain, joint function, and quality of life. The ISIAT emphasizes the need for further research on patient selection criteria and treatment protocols to tailor IAHA treatment to individual patients and to optimize outcomes
AOOS	strongly advises against using IAHA for KOA and HOA for routine use. However, VS may be appropriate for specific patients that do not respond to other treatments
AMSSM (American Medical Society for Sports Medicine)	AMSSM supports VS in KOA, particularly in athletes and physically active individuals. IAHA is,highlighted for managing OA symptoms and maintaining joint function
ESCEO	The ESCEO working group supports IAHA as a second-line treatment for KOA mainly when NSAIDs are ineffective or contraindicated and advocates for IAHA as a core part of OA management, particularly in early-to-moderate disease stages, because of its dual benefits of symptom relief and potential chondroprotection
OARSI	conditional recommendation for patients with comorbidities or after failure of core treatments
ICRS	Does not explicitly endorse IAHA for early and moderate osteoarthritis (OA) with specific claims of maintaining joint health, slowing cartilage degradation, and delaying surgical interventions

J. Clin. Med. 2025, 14, 1272

A summary of the international and national guidelines on VS in KOA (3)

Guideline	Recommendation regarding Hyaluronic Acid in Knee OA
Chinese Guidelines for Osteoarthritis	The Chinese Society recommend IAHA for KOA with persistent or moderate-to-severe pain, suggesting its use to **improve symptoms and delay joint replacement surgery**
Swiss Society of Rheumatology	The Swiss Society of Rheumatology **has expressed caution** regarding routine IAHA use, highlighting the need for individualized patient assessment and more comprehensive evidence regarding long-term efficacy and safety
The German Orthopaedic Society (DGOU) recommends cautious	The German Orthopaedic Society (DGOU) **recommends cautious** recommendations for IAHA, indicating potential benefits but emphasizing the need for more robust clinical trials to establish efficacy
NICE	**NICE does not recommend VS** as a routine treatment for OA due to a lack of apparent efficacy and **costeffectiveness data**.
EUROVISCO	This Group provides detailed recommendations for clinical trials to assess the disease-modifying effects and emphasizes the need for standardized study designs, including imaging and biological markers,
The South African Rheumatism and Arthritis Association (SARAA)	SARAA supports VS, particularly UHMW HA formulations, for KOA in patients requiring **sustained relief and aiming to delay surgical interventions**
The Brazilian Society of Orthopaedics and Traumatology (SBOT)	SBOT advocates using UHMW HAs for extended joint lubrication and pain relief in patients with OA
Korean recommendation	Korean guidelines support the conditional use of IAHA for joint symptom control when glucocorticoid injections or other interventions fail
Spanish Society of Rheumatology (SER)	The Spanish Society of Rheumatology recommends VS as an adjunct treatment for OA, favoring UHMW HAs for their potential to offer longer-lasting pain relief and improved quality of life
The Indian Rheumatology Association	Indian Association supports IAHA for OA management and recommends UHMW HA formulations for enhanced viscoelastic properties and sustained symptom relief

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Summary of other domestic guidelines on VS in KOA

Guideline	Year	Recommendation regarding Hyaluronic Acid in Knee OA
Arthroscopy Association of Canada	2019	"IA injections of HMW IAHA provide improved pain relief and the restoration of function compared with placebo and can be considered in patients with mild to moderate knee OA. Strength of recommendation: Good – A"
Royal Australian College of General Practitioners (RACGP)	2015–2018	Recommends against IAHA injections in this primary care context, primarily due to cost (not covered by Medicare)
Pan-American League of Associations for Rheumatology (PANLAR)	2016	"Intra-articular injection of HA of different molecular weights has proven to be beneficial in the treatment of knee OA"
Turkish League Against Rheumatism (TLAR)	2018	"Patients with moderate–severe symptoms, functional capacity of either normal or minimally limited and/or radiologic grade of 2–3 may be treated with NSAIDs in case of response to acetaminophen is absent or insufficient. These patients may be treated with IA HA even though its efficiency is uncertain."
Malaysian Delphi Consensus	2021	Recommends IAHA for advanced pharmacological therapy (following background treatment of SYSADOAs and topical NSAIDs with paracetamol if necessary) in "knee without effusion"

- There are a large number of guidelines for the treatment of knee OA emanating from international and domestic societies. Within this body of recommendations, there is variation in the extent to which IAHA is recommended for the treatment of knee OA and in some guidelines, there is a clear distinction between the primary and the secondary care settings.
- In terms of international guidelines, these mostly conditionally recommend the use of IAHA according to the patient's phenotype and according to the clinical context (primary care versus secondary care). The 2019 updated guidelines from ESCEO weakly recommend the use of IAHA in the context of the failure or contraindication of NSAIDs and in a second step after primary care 11.