**Outcome of Kinematic versus Mechanical Alignment in TKA using Patient-Specific Instrumentation: A Meta-analysis and Subgroup Analysis of Randomised Trials**

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**Abstract**

Aims: A meta-analysis of patient reported outcome measures between patients treated with total knee arthroplasty (TKA) using kinematic (KA) versus mechanical (MA) alignment.

Materials and Methods: A literature search in PubMed, EMBASE and Cochrane databases identified four randomized controlled trials comparing patients undergoing TKA using KA and MA. Authors of three trials provided raw and unpublished data on Western Ontario McMaster Universities Arthritis Index (WOMAC), Knee Society Score (KSS) and radiogical outcomes to allow subgroup analysis. Meta-analysis comparing MA to KA change scores was performed. Subgroup analysis was done on the KA group to identify subsets of patients more likely to benefit from KA technique, and whether accuracy of the patient-specific instrumentation affected outcomes.

Results: Meta-analysis showed no significant difference in WOMAC (mean difference, 3.4; 95% confidence interval, -0.5-7.3), KSS function (1.3, -3.9-6.4) or KSS combined (7.2, -0.8-15.2) change scores between MA and KA technique. A small advantage was seen for KSS pain in the KA group (3.6, 0.2-7.1). Subgroup analysis showed no difference in outcomes between preoperative varus, valgus and neutral alignment groups, nor those that achieved ShapeMatch (SM) plans, however patients who were pain-free at 1 year were more likely to have achieved their SM plans.

Conclusions: Pain and functional outcome scores following TKA performed using KA technique are at least as good as traditional MA technique, however any clinical advantage is likely to be small. We were unable to identify patient subgroups more likely to benefit from KA technique, and the long-term results of KA remain unknown.

## Introduction

The concept of mechanical alignment (MA) in total knee arthroplasty (TKA) is to position both the tibial and femoral components perpendicular to the mechanical axis of each bone, aligning the overall hip-knee-ankle angle of the limb to neutral. This is a longstanding principle of TKA, in the belief that MA optimises load distribution and will minimise implant failure though polyethylene wear or component loosening (1-5).

In contrast, kinematic alignment (KA) aims to position TKA implants to match the pre-arthritic anatomy of each individual patient. In the native knee, on average the articular surface of the tibia will be in slight varus and that of the femur in slight valgus. However, there is also significant variation, with over 30% of male non-arthritic patients reported to have a hip-knee-ankle angle of >3 varus (6). The KA technique aims to reproduce the individual patient anatomy and alignment, and KA advocates suggest this will improve soft tissue balancing, reduce the need for ligament releases, and enhance functional outcome following TKA (7-9).

Recently, several randomised controlled trials (RCTs) have been published comparing KA TKAs performed with patient-specific instrumentation (ShapeMatch, OtisMed Inc, Alameda, CA, USA) to standard MA technique, with conflicting results (7, 10-12). This KA patient-specific is no longer commercially available, and this collaborative study between authors of these RCTs aims to combine data from the trials, to analyse functional and radiological outcomes of kinematic alignment performed using patient-specific guides versus mechanically aligned TKA. In addition, by combining raw data we hoped to identify whether subgroups of patients may be more likely to benefit from KA technique. Specifically, we sought to answer the following questions:

1. Using meta-analysis, do **patient reported outcome measures** differ between patients treated with TKA using kinematic alignment (KA) versus mechanical alignment (MA) techniques?

2. Are there differences in outcomes for KA for patient **subgroups,** such as whether the KA plan was achieved?

3. What are the differences between KA patients with good versus poor patient-reported outcome scores?

**Materials and methods**

A primary search was done using the electronic databases of PubMed (1950 to May 2016), EMBASE (1950 to May 2016) and Cochrane databases (1980 to May 2016), using the key words: total knee replacement or arthroplasty AND kinematic* AND alignment*. A secondary search was done examining the reference list of relevant papers. Unpublished studies were searched using the meta-register of clinical trials (13). The search strategy was in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (14)(Appendix 1). Eligibility criteria for study selection included: randomised controlled trial examining KA TKA technique versus MA, reported functional and radiological outcomes, at least one year follow-up period, English language and published data.

Data was extracted and analysed and outcomes that were common across the studies were extracted independently onto a spreadsheet for statistical analyses (Table 1). This included: 1) patient demographics – sample size, sex, age, and body mass index (BMI); 2) patient reported outcome measures (PROMs) – Knee Society Score (KSS,

0-100 worst to best), Western Ontario McMaster Universities Arthritis Index (WOMAC, converted to a scale of 0-100 worst to best) and the Oxford Knee Score (OKS, 0-48 worst to best); and 3) radiological outcomes – hip-knee-ankle (HKA) angle, lateral distal femoral angle (LDFA), medial proximal tibial angle (MPTA) and tibial component slope (TCL). Data on post-surgical complications was recorded qualitatively. Unpublished data was obtained from the authors of three studies (10-12), including radiological data on individual study patients and unpublished outcome measures such as WOMAC score (derived from KOOS, (11)) and KSS pain and function components (10). Despite numerous attempts, authors of a fourth study did not respond to requests for additional data therefore only published results were included in the analysis (7, 8).

Methodological quality and risk of bias was assessed using three different modalities to incorporate different measured constructs and improve reliability (15, 16)( Appendix 2): 1) The Quality Assessment Tool for Quantitative Studies (Effective Public Health Practice Project, EPHPP, McMaster University, Ontario, Canada); 2) The Cochrane Collaboration's tool for assessing risk of bias in randomised trials (CCRBT)(17); and 3) the Jadad scale(18). Two reviewers conducted the appraisal for each study independently and any discrepancy was resolved by consensus.

Statistical analysis

Meta analyses were conducted on pre- and post- operative change scores for WOMAC and KSS (pain, function and combined) between KA and MA groups. The change scores were pooled using the standardized mean differences, accounting for heteroscedastic variances for each population between the two groups (19, 20). P

values <0.05 were considered significant. Post-surgical radiological outcomes were also compared between KA and MA groups.

Subgroup analyses were conducted on three parameters in the KA group: 1) pre-operative alignment subdivided into varus, valgus and neutral (defined as a pre-operative HKA angle <-3°, >3° or between -3 and 3, respectively), 2) if post-operative alignment (HKA, LDFA, and MPTA) was within 3° of the ShapeMatch plan, and 3) patients who were relatively 'pain-free' at one-year post-operation (defined as a WOMAC ≥80).

**Source of funding**

No external source of funding was used for this study.

**Results**

Literature search

Four studies were selected for analysis in this review (Fig. 1). The primary and secondary searches resulted in 373 records. Examination of title/abstract excluded 355 records, and a further 14 were excluded after the studies were examined closely. Eight studies on kinematic alignment lacked a comparative group (21-28). One was excluded as it was a retrospective cohort analysis that did not examine functional scores (29). Two studies were excluded based on an inappropriate patient cohort: one consisted of revision TKAs following unicompartmental knee arthroplasty (30) and another was a repeat cohort of a selected study (8). One record was an incomplete

study (31) and one used a different method to establish kinematic alignment (32). The meta-register of clinical trials yielded three studies that would meet the criteria for inclusion, but all were either abandoned or incomplete.

Study characteristics and Quality

Two authors conducted quality assessment on the four studies using three different methods (Table 1). Two of four studies scored a strong rating while the other two scored a moderate and weak rating. When combining outcome scores for analysis, two studies used full WOMAC version (7, 10), one used a reduced version (12) and the other derived the reduced version from a Knee and Osteoarthritis Outcome Score (KOOS)(11). Comparisons of full and reduced WOMAC scales are highly valid, with a correlation coefficient of 0.96 (33). Three of the four studies had follow-up data at one year (10-12), and two had follow-up data at two years (8, 12). Recent studies showed that post-operative function scores are largely predictive of long-term scores (34, 35). The KSS pain component for one study was derived from a VAS scale (11). The standard deviation (of change scores) from one study was not included as this was not available in published data (7).

Pooled outcomes

The pooled mean difference in change scores (post- minus pre- operative scores) between KA and MA were 3.4 (95% confidence interval [CI], -0.5, 7.3; Fig 2A), 3.6 (0.2, 7.1; Fig 2B), 1.3 (-3.9, 6.4; Fig 2C) and 7.2 (-0.8, 15.2; Fig 2D) for WOMAC, KSS pain, function and combined, respectively. There was no significant difference in function between KA and MA groups as zero was included in the 95% CI. The 95% CI for WOMAC and combined KSS had a lower boundary close to zero and an upper boundary far from zero, suggesting a trend to a higher score in the KA group. Mean

difference in KSS pain was 3.6 higher in the KA than the MA group, although the 95% CI was close to 0. There was no significant heterogeneity in treatment effect in all four studies regarding KSS (pain, function and combined) and WOMAC scores (p-values were between 0.18 and 0.41, Fig 2).

The pooled mean difference in post-surgical radiological angles were 0.4 (95% CI, -0.9, 1.7), 1.4 (0.9, 1.9) and -1.7 (-2.4, 1.0) for HKA, LDFA and MPTA angles, respectively (Table 2). Heterogeneity exists between radiological outcomes (p = <0.01, Table 2).

Subgroup-analysis

*Pre-operative alignment*

Analysis of variance indicates that in the pooled data of three studies (10-12), there was no significant difference in 1 year change scores of KSS combined and WOMAC across the three pre-operative alignment groups of varus, neutral, or valgus (Table 3). Change scores at 1 year for WOMAC and KSS combined were negatively associated with pre-operative scores (estimates respectively -1.0 and -0.8, p values <0.01).

*ShapeMatch (SM) plan achieved*

There was no significant difference in function scores (WOMAC and KSS function) between those that achieved their SM plans (within 3°) and those that did not (Table 4). There was no significant difference in KSS pain between those that achieved HKA and LDFA SM plans versus those that did not, but KSS pain was different between those that achieved MPTA SM plans and those that did not (p = 0.01).

*Characteristics of 'pain-free' group (WOMAC score* ≥80)

Multiple logistic regression analysis showed that in the pain-free group (Table 5), the difference between SM planned and post-operative measured MPTA was significantly lower (P<0.001) when controlling for other confounders (pre-operative WOMAC and pre-operative alignment groups). Analysis was not done on age and sex as data was not available for one study (10). There were no significant differences with pre-operative alignment (varus, valgus and neutral). HKA and MPTA angles were positively correlated (Pearson's correlation coefficient = 0.4, p<0.001).

## Discussion

A significant percentage of patients report dissatisfaction with the outcome of TKA performed using traditional MA technique (36, 37). Advocates of KA technique argue that more closely reproducing individual patient anatomy will enhance the functional outcome of TKA. Others point out the original rationale for MA technique was to enhance implant durability, and argue the alterations in alignment of KA may compromise survivorship (38). While currently the long-term results of kinematically aligned TKA are unknown, this meta-analysis found that early patient reported outcome measures with KA are at least as good as those of MA, however any clinical advantage, if present, is likely to be small.

There are several limitations to this study. Firstly, all included randomised trials used patient-specific instrumentation (PSI) manufactured by a single company (OtisMed Inc, Alameda, CA, USA) for the KA group, using proprietary software analysis of the pre-operative MRI scan to determine the target 'kinematic' alignment. The current results therefore may not be generalizable to other "KA" methods such as those using

manual instrumentation (23, 39). However, the consistent technique across the four randomised trials is also a strength of the meta-analysis, and the PSI guides used account for most KA cases reported in the literature. (9, 21, 26, 40) Their accuracy has also been validated in a clinical study (41). Furthermore, as these guides are no longer commercially available no further RCTs using this method of KA are expected, and this study represents an important opportunity to examine combined data. Secondly, the follow up period in all four studies was too short to assess long term complications such as component loosening, and the long-term effect of KA remains unknown (42, 43). Finally, while we obtained raw data from three studies, we were unable to obtain data from authors of the fourth study. Clinical and radiographic findings of this study were however published in detail across two manuscripts (7, 8), and these results were included in our main meta-analysis.

Several recent systematic reviews have attempted to combine published data comparing KA versus MA, generally reporting functional results in favour of KA (44-46). However, the published results of the RCTs included in these reviews do not include all details of the WOMAC or KSS scores, therefore this is the first analysis to combine these outcome scores across all four RCTs. In addition, by sharing raw data among the authors we were also able to analyse change scores (post- minus pre-operative scores). Pre-operative scores are strongly related to post-operative scores in an individual patient, and there were inter-study differences in absolute pre-operative scores and the pattern between MA and KA groups. In contrast to previous reviews, we found no difference in improvement between KA and MA for WOMAC, KSS combined or KSS function scores, and a small advantage to KA in KSS pain scores. In addition to the above methodological differences, previous reviews reporting findings more favourable to KA have included non-comparative case series from a

development centre for PSI guides (44, 45), and included duplicated results from the two published papers on the RCT performed by Dossett et al, which strongly favoured KA (46). These reasons may explain the less positive findings in our study compared to previous reviews.

A further advantage of sharing raw data was the ability to perform more detailed subgroup analysis, to identify whether KA may be of more benefit in certain patients. With the numbers available, we were unable to identify pre-operative alignment parameters which might be more suitable to KA technique. This is important as each trial included in this study differed slightly in their inclusion criteria regarding alignment parameters, with variable boundaries/inclusion criteria as to what was acceptable deformity. This reflects the fact that several questions regarding KA technique remain unanswered, such as whether patients with higher degrees (eg >3°) of pre-operative varus should be placed in their natural 'kinematic' alignment, or corrected closer to neutral. There is evidence that excessive varus increases load at the implant-bone interface and may compromise survivorship (42, 47), however clinical data is mixed (43) and reported mid-term results of KA are encouraging (22). Factors such as the degree of post-operative component varus or valgus alignment, (47) and patient age and BMI (48) are likely to be important, but currently there is conflicting data with which to define 'acceptable' alignment parameters, and how these will affect the functional outcome of KA technique.

In conclusion, this analysis of level 1 studies found KA technique using PSI resulted in pain and functional improvements at least as good as MA technique. Pooled data for function scores showed a trend towards a greater benefit in the KA group, but any advantage as measured by these instruments appears. Subgroup-analysis suggests that differences in pre-operative alignment did not alter outcomes with the KA

technique. Future research should focus on safe alignment boundaries and whether the alterations in alignment using KA technique alter long term durability.

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## Legends

**Figure 1. PRISMA search strategy**

**Figure 2. Meta-analysis of pain and function change scores**

**Table 1. Study evaluation**

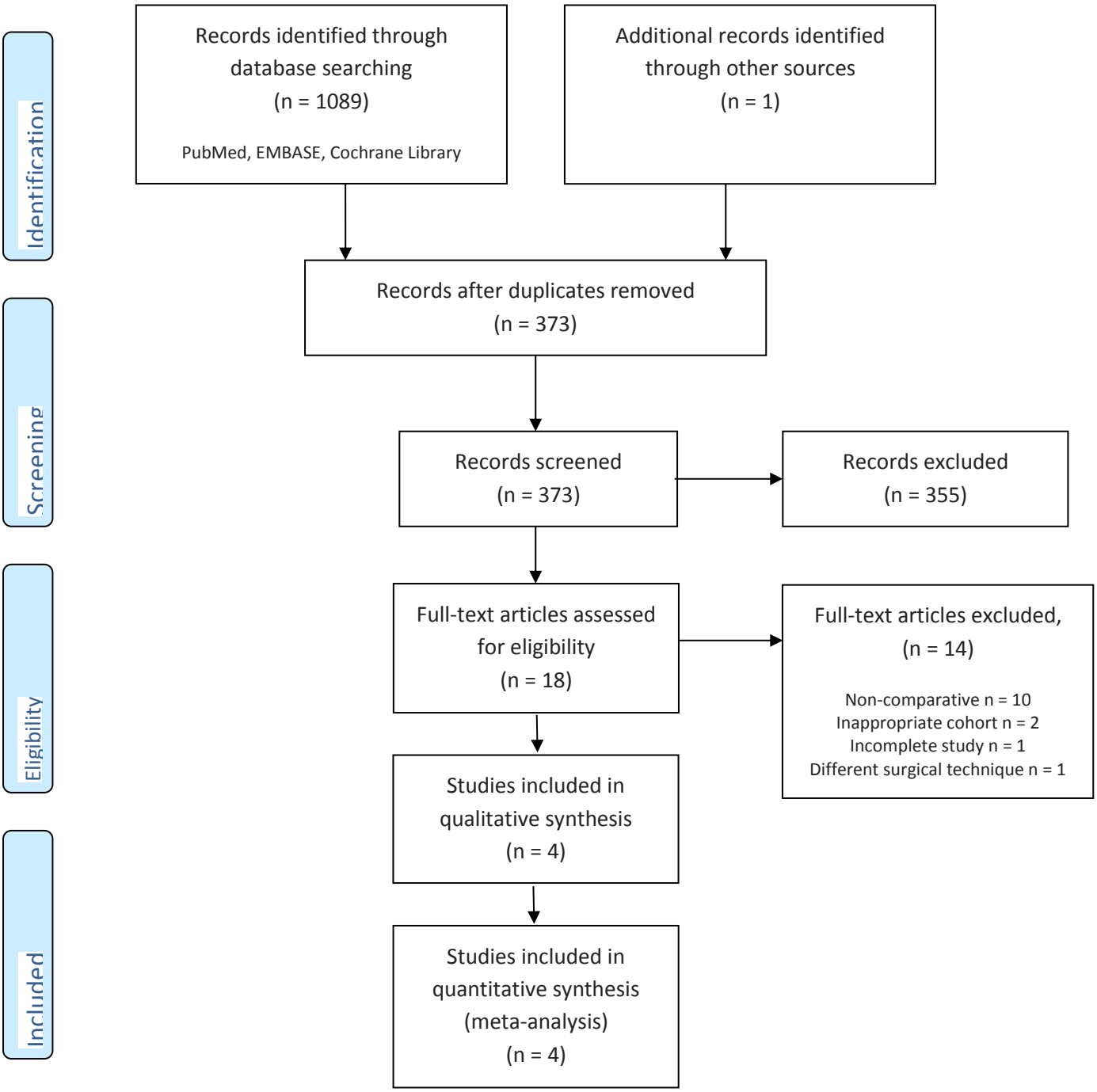
**Table 2. Summary of radiological outcomes**

**Table 3. Subgroup analysis of pre-operative alignment in the kinematic group**

**Table 4. Subgroup analysis of patients that achieved ShapeMatch plans in the kinematic group**

**Table 5. Subgroup analysis of patients that were ‘pain-free’ at 1 year in the kinematic group**

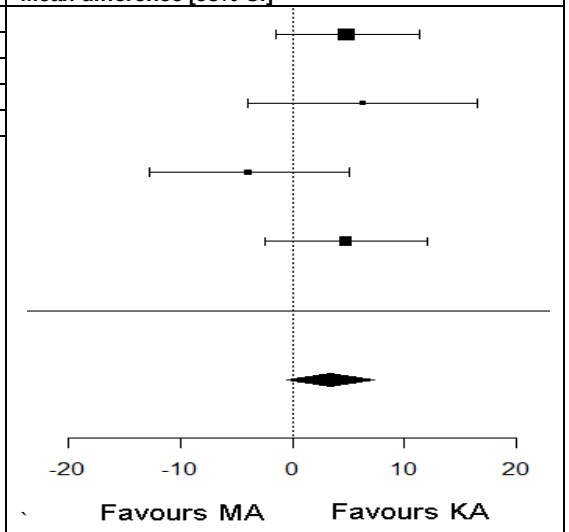
**Figure 1. PRISMA search strategy**



## Figure 2 – Meta-analysis of pain and function scores

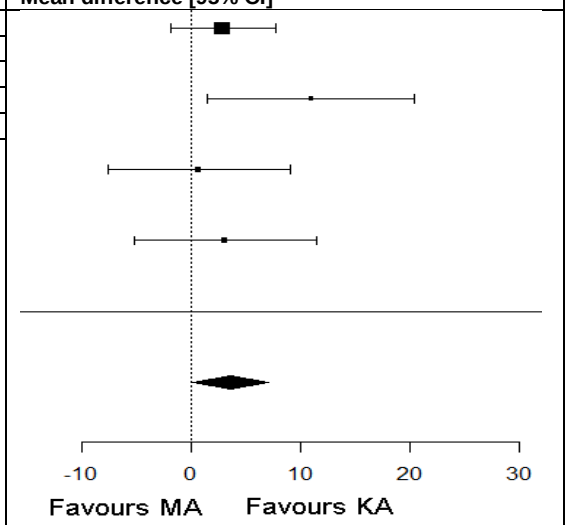
| A. WOMAC | KA | | | MA | | | | |
|---|---|---|---|---|---|---|---|---|
| **Study** | **Mean** | **SD** | **Total** | **Mean** | **SD** | **Total** | **Weight %** | **Mean difference [95% CI]** |
| Calliess et al., 2016 | 50** | 29** | 100 | 45** | 15** | 100 | 64.9 | 4.90 [-1.55, 11.35] |
| Dossett et al., 2016 | 40** | | 44 | 33** | | 44 | 7.5 | 6.30 [-3.99, 16.59] |
| Waterson et al., 2016 | 29*** | 15*** | 36 | 31*** | 21*** | 35 | 19.9 | -3.90 [-12.86, 5.06] |
| Young et al., 2016 | 38 | 18 | 49 | 35 | 19 | 50 | 7.7 | 4.80 [-2.44, 12.04] |
| **Results from meta-analysis** | | | **229** | | | **229** | **100** | **3.39 [-0.53, 7.31]** |

Heterogeneity: $Tau^2 = 0$; Q (df = 3) = 3.2 (p = 0.36); $I^2 = 0\%$

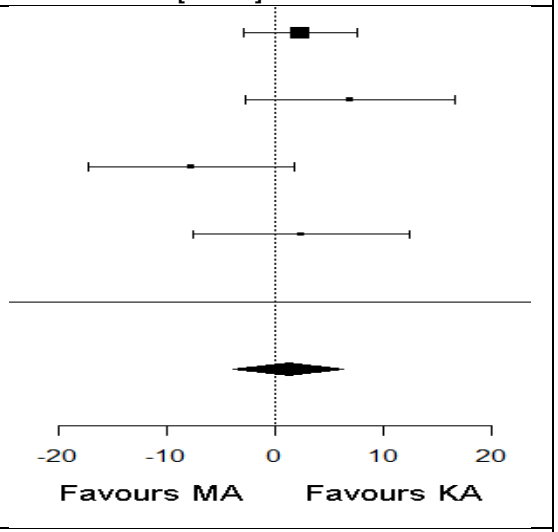


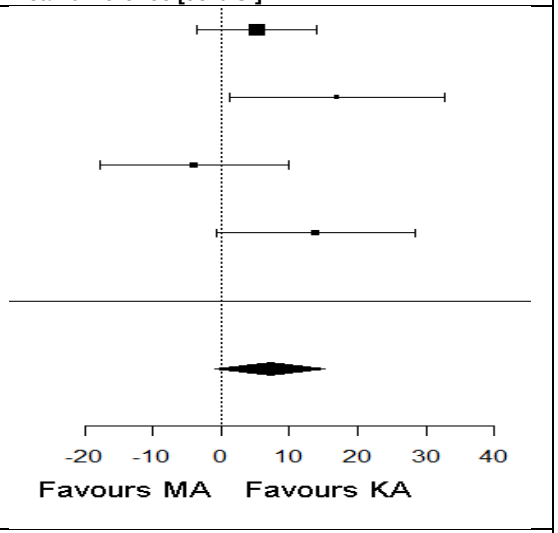

| B. KSS pain | KA | | | MA | | | | |
|---|---|---|---|---|---|---|---|---|
| **Study** | **Mean** | **SD** | **Total** | **Mean** | **SD** | **Total** | **Weight %** | **Mean difference [95% CI]** |
| Calliess et al., 2016 | 39 | 19 | 100 | 36 | 15 | 100 | 64.9 | 2.90 [-1.88, 7.68] |
| Dossett et al., 2016 | 38 | | 44 | 27 | | 44 | 7.5 | 11.00 [1.54, 20.46] |
| Waterson et al., 2016 | 41* | 17* | 36 | 41* | 18* | 35 | 19.9 | 0.70 [-7.63, 9.03] |
| Young et al., 2016 | 54 | 19 | 49 | 50 | 17 | 50 | 7.7 | 3.10 [-5.21, 11.41] |
| **Results from meta-analysis** | | | **229** | | | **229** | **100** | **3.64 [0.18, 7.09]** |

Heterogeneity: $Tau^2 = 0$; Q (df = 3) = 2.9 (p = 0.41); $I^2 = 0\%$



| C. KSS function | KA | | | MA | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Study** | **Mean** | **SD** | **Total** | **Mean** | **SD** | **Total** | **Weight %** | **Mean difference [95% CI]** | **Mean difference [95% CI]** |
| Calliess et al., 2016 | 34 | 22 | 100 | 32 | 16 | 100 | 64.9 | 2.40 [-2.86, 7.66] | |
| Dossett et al., 2016 | 26 | | 44 | 19 | | 44 | 7.5 | 7.00 [-2.75, 16.75] | |
| Waterson et al., 2016 | 28 | 25 | 36 | 36 | 15 | 35 | 19.9 | -7.70 [-17.28, 1.88] | |
| Young et al., 2016 | 30 | 21 | 49 | 23 | 24 | 50 | 7.7 | 2.50 [-7.55, 12.55] | |
| **Results from meta-analysis** | | | **229** | | | **229** | **100** | **1.27 [-3.86, 6.41]** | |
| Heterogeneity: $Tau^2$ = 9.7; Q (df = 3) = 4.9 (p = 0.18); $I^2$ = 34.9% | | | | | | | | | |
| **D. KSS combined** | **KA** | | | **MA** | | | | | |
| **Study** | **Mean** | **SD** | **Total** | **Mean** | **SD** | **Total** | **Weight %** | **Mean difference [95% CI]** | **Mean difference [95% CI]** |
| Calliess et al., 2016 | 73 | 36 | 100 | 68 | 27 | 100 | 64.9 | 5.30 [-3.47, 14.07] | |
| Dossett et al., 2016 | 63 | | 44 | 46 | | 44 | 7.5 | 17.00 [1.15, 32.85] | |
| Waterson et al., 2016 | 70 | 33 | 36 | 74 | 27 | 35 | 19.9 | -4.00 [-17.87, 9.87] | |
| Young et al., 2016 | 77 | 34 | 49 | 74 | 34 | 50 | 7.7 | 13.90 [-0.67, 28.47] | |
| **Results from meta-analysis** | | | **229** | | | **229** | **100** | **7.20 [-0.83, 15.24]** | |
| Heterogeneity: $Tau^2$ = 24.5; Q (df = 3) = 4.9 (p = 0.18); $I^2$ = 36.3% | | | | | | | | | |




KA = kinematic alignment, MA = mechanical alignment

*KSS Pain derived from VAS

**WOMAC conversion to 0 to 100 (worst to best)

***WOMAC derived from KOOS

**Table 1. Overview of studies.**

| **Study** | | **Calliess et al 2016** | **Dossett et al 2014** | **Waterson et al 2016** | **Young et al 2016** |
|---|---|---|---|---|---|
| **Sample size** | | 88 | 200 | 71 | 98 |
| **Follow-up period** | | 1 year | 2 years | 1 year | 1 and 2 years |
| **Surgical technique** | | Triathlon, fixed cemented, CR | Vanguard, fixed cemented, CR | Triathlon, fixed cemented, CR | Triathlon, fixed cemented, CR |
| **PROMs of interest (published and unpublished)** | | KSS pain and function, WOMAC | KSS pain and function, WOMAC, OKS | KOOS, KSS function | KSS pain and function, WOMAC, OKS |
| **Radiology** | | HKA, LDFA, MPTA, tibial slope | HKA, LDFA, MPTA | HKA, LDFA, MPTA | HKA, LDFA, MPTA, tibial slope |
| **Quality assessment** | **EPHPP** | 3 | 2 | 1 | 1 |
| | **CCRBT** | High risk | Low risk | Low risk | Low risk |
| | **Jadad** | 1 | 5 | 4 | 5 |

**Table 2 – Summary of radiological outcomes**

| Study | Calliess et al 2016 | | Dossett et al 2014 | | Waterson et al 2016 | | Young et al 2016 | | Pooled mean difference [95% CI] | Heterogeneity Q testing (p value) |
|---|---|---|---|---|---|---|---|---|---|---|
| **Treatment group** | **KA** | **MA** | **KA** | **MA** | **KA** | **MA** | **KA** | **MA** | | |
| **n** | 100 | 100 | 44 | 44 | 36 | 35 | 49 | 50 | 229 | |
| **HKA (SD)** | 1 (3) | -1 (1) | -0.1 (2.8) | 0.1 (2.5) | -0.7 (4.4) | -0.5 (3.9) | -0.4 (3.5) | -0.7 (2.0) | 0.39 (-0.94,1.71) | 83.1% (0.00) |
| **LDFA (SD)** | 2 (2) | 1 (0) | 1.3 (2) | -0.8 (2.7) | 1.4 (2.2) | 0.1 (2.4) | 2.1 (2.5) | 0.5 (1.6) | 1.38 (0.88, 1.89) | 91.0% (<0.00) |
| **MPTA (SD)** | -2 (1) | -1 (0) | -2.2 (2.6) | 0 (2.1) | -3.1 (2.8) | -0.9 (2.0) | -2.6 (3.1) | -0.7 (1.8) | -1.68 (-2.38, -0.99) | 68.3% (<0.00) |
| **Tibial slope (SD)** | 5 (3) | 5 (3) | 5 (5.4)* | 3 (4.7)* | NA | NA | 4 (2.5) | 1.3 (2) | 0.84(0.67,1.01) | 80.7% (0.00) |

HKA = hip-knee-ankle, LDFA = lateral distal femoral angle, MPTA = medial proximal tibial angle, KA = kinematic alignment, MA = mechanical alignment

Positive values are in valgus (converted for Calliess and Dossett)

*from Dossett et al., 2012

Waterson values obtained from raw data

**Table 3. Subgroup analysis of pre-operative alignment in the kinematic group from three studies**

| Study | Alignment | Sample Size | WOMAC (SD) | | | KSS pain (SD) | | | KSS function (SD) | | | KSS combined (SD) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Pre | 1y | Δ | Pre | 1y | Δ | Pre | 1y | Δ | Pre | 1y | Δ |
| **Calliess et al, 2016** | **Varus** | 45 | 39 (22) | 88 (18) | 45 (35) | 50 (11) | 95 (6) | 45 (14) | 60 (12) | 96 (11) | 36 (15) | 110 (16) | 190 (12) | 81 (20) |
| | **Valgus** | 10 | 41 (19) | 97 (5) | 56 (18) | 59 (8) | 91 (9) | 32 (8) | 56 (14) | 99 (3) | 43 (14) | 115 (19) | 189 (8) | 74 (16) |
| | **Neutral** | 44 | 36 (18) | 91 (14) | 55 (21) | 56 (13) | 94 (11) | 38 (14) | 60 (12) | 95 (10) | 36 (18) | 115 (21) | 190 (14) | 74 (26) |
| | | | | | | | | | | | | | | |
| **Waterson et al, 2016** | **Varus** | 21 | 57 (12) | 89 (12) | 32 (13) | 48 (13) | 93 (8) | 41 (20) | 55 (20) | 90 (14) | 29 (34) | 99 (3) | 169 (51) | 70 (48) |
| | **Valgus** | 3 | 52 (8) | 65 (24) | 13 (19) | 52 (15) | 81 (8) | 29 (20) | 37 (28) | 70 (44) | 33 (16) | 89 (39) | 151 (48) | 62 (17) |
| | **Neutral** | 3 | 71 (19) | 96 (1) | 25 (20) | 61 (18) | 91 (13) | 30 (32) | 80 (14) | 78 (32) | -3 (18) | 141 (4) | 168 (45) | 27 (50) |
| | | | | | | | | | | | | | | |
| **Young et al, 2016** | **Varus** | 40 | 52 (13) | 91 (11) | 37 (22) | 34 (15) | 78 (13) | 45 (23) | 53 (16) | 84 (18) | 30 (27) | 87 (26) | 156 (38) | 74 (42) |
| | **Valgus** | 7 | 41 (13) | 83 (31) | 42 (31) | 50 (14) | 86 (14) | 37 (21) | 61 (12) | 90 (15) | 29 (16) | 110 (20) | 176 (29) | 66 (34) |
| | **Neutral** | 3 | 85 (14) | 93 (9) | 45 (11) | 48 (4) | 70 (19) | 23 (15) | 57 (12) | 70 (10) | 13 (6) | 104 (14) | 140 (27) | 36 (19) |
| | | | | | | | | | | | | | | |
| **Combined data** | **Varus** | 106 | 46 (19) | 89 (15) | 40 (28) | 43 (15) | 89 (12) | 44 (18) | 56 (15) | 90 (15) | 32 (24) | 99 (25) | 175 (35) | 77 (34) |
| | **Valgus** | 20 | 43 (16) | 87 (23) | 45 (27) | 55 (12) | 88 (11) | 33 (15) | 55 (17) | 91 (20) | 37 (16) | 110 (23) | 179 (27) | 69 (23) |
| | **Neutral** | 50 | 38 (19) | 90 (14) | 53 (22) | 55 (13) | 92 (12) | 37 (15) | 60 (13) | 93 (13) | 33 (20) | 116 (21) | 185 (20) | 70 (29) |

P-value: analysis of variance showed no difference in WOMAC or KSS combined scores between varus, valgus or neutral pre-operative alignment groups in the combined data.

**Table 4. Subgroup analysis of patients that achieved HKA ShapeMatch plans in the kinematic group**

| Angle | SM plan achieved | Sample size | WOMAC – Mean (SD) | | | | KSS pain – Mean (SD) | | | | KSS function – Mean (SD) | | | | KSS combined – Mean (SD) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Pre | 1y | Δ | p | Pre | 1y | Δ | p | Pre | 1y | Δ | p | Pre | 1y | Δ | p |
| **HKA** | **Yes** | 126 | 45 (19) | 90 (16) | 44 (23) | | 48 (14) | 89 (12) | 41 (16) | | 58 (15) | 91 (15) | 33 (19) | | 105 (24) | 180 (22) | 75 (27) | |
| | **No** | 40 | 37 (19) | 88 (16) | 51 (23) | 0.54 | 52 (14) | 92 (11) | 39 (16) | 0.43 | 56 (15) | 93 (13) | 37 (19) | 0.58 | 108 (25) | 185 (20) | 75 (28) | 0.78 |
| **LDFA** | **Yes** | 148 | 43 (19) | 89 (16) | 47 (24) | | 49 (15) | 90 (12) | 41 (17) | | 57 (15) | 91 (16) | 35 (20) | | 105 (25) | 181 (23) | 76 (29) | |
| | **No** | 18 | 48 (17) | 88 (16) | 40 (20) | 0.17 | 49 (14) | 89 (12) | 40 (17) | 0.73 | 63 (11) | 94 (8) | 31 (13) | 0.07 | 113 (20) | 183 (17) | 70 (22) | 0.29 |
| **MPTA** | **Yes** | 151 | 43 (19) | 89 (16) | 46 (24) | | 48 (15) | 90 (13) | 42 (17) | | 57 (15) | 91 (15) | 34 (19) | | 105 (25) | 181 (23) | 76 (28) | |
| | **No** | 15 | 42 (22) | 89 (18) | 48 (24) | 0.75 | 60 (6) | 90 (10) | 30 (11) | 0.01 | 59 (16) | 91 (16) | 33 (23) | 0.82 | 118 (20) | 181 (20) | 64 (25) | 0.12 |

**Table 5. Subgroup analysis of patients that were 'pain-free' at 1 year in the kinematic group**

| First author | Young | | Waterson | | Calliess | | Combined | |
|---|---|---|---|---|---|---|---|---|
| **1y WOMAC ≥ 80** | **No** | **Yes** | **No** | **Yes** | **No** | **Yes** | **No** | **Yes** |
| **Sample size (n)** | 8 | 40 | 5 | 12 | 13 | 85 | 26 | 137 |
| **Age (SD)** | 64 (9) | 70 (6) | 74 (8) | 78 (7) | NA | NA | 68 (10) | 72 (7) |
| **Sex (%M)** | 50 | 58 | 50 | 67 | NA | NA | 50 | 61 |
| **Pre-op WOMAC** | 49 (14) | 50 (13) | 50 (7) | 60 (12) | 36 (22) | 37 (19) | 43 (19) | 44 (18) |
| **Varus (%)** | 75 | 83 | 60 | 75 | 54 | 42 | 62 | 58 |
| **Valgus (%)** | 13 | 13 | 40 | 8 | 8 | 12 | 15 | 12 |
| **Neutral (%)** | 13 | 5 | 0 | 16 | 38 | 46 | 23 | 31 |
| **Pre-operative HKA (SD)** | -6 (6) | -6 (6) | 0 (10) | -7 (6) | -3 (5) | -3 (5) | -4 (7) | -4 (6) |
| **ShapeMatch plan HKA (SD)** | 0 (3) | 0 (3) | 0 (4) | -2 (3) | -1 (2) | 1 (2) | -1 (3) | -1 (2) |
| **ShapeMatch plan MPTA (SD)** | -1 (3) | -2 (2) | -1 (2) | -4 (2) | -3 (1) | -3 (1) | -3 (2) | -3 (2) |
| **Post-operative HKA (SD)** | -3 (2) | 0 (3) | 1 (8) | - 1 (3) | 2 (4) | 1 (3) | -1 (5) | 0 (3) |
| **Post-operative MPTA (SD)** | -1 (4) | -3 (3) | -4 (4) | -3 (3) | -2 (2) | -1 (2) | -1 (4) | -2 (3) |

Multiple logistic regression analysis: the difference between SM planned and post-operative measured MPTA was significantly lower in the pain-free group ($P<0.001$) when controlling for other confounders (pre-operative WOMAC and pre-operative alignment groups). There were no significant differences with pre-operative alignment (varus, valgus and neutral). HKA and MPTA angles were positively correlated (Pearson's correlation coefficient = 0.4, $p<0.001$).

**Appendix 1. PRISMA checklist**

| Section/topic | # | Checklist item | Reported on page # |
|---|---|---|---|
| **TITLE** | | | |
| Title | 1 | Identify the report as a systematic review, meta-analysis, or both. | 1 |
| **ABSTRACT** | | | |
| Structured summary | 2 | Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number. | 2 |
| **INTRODUCTION** | | | |
| Rationale | 3 | Describe the rationale for the review in the context of what is already known. | 3 |
| Objectives | 4 | Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS). | 4 |
| **METHODS** | | | |
| Protocol and registration | 5 | Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number. | NA |
| Eligibility criteria | 6 | Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. | 4 |
| Information sources | 7 | Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched. | 4 |
| Search | 8 | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated. | 4 |
| Study selection | 9 | State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis). | 4 |
| Data collection process | 10 | Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators. | 4 |
| Data items | 11 | List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made. | 4 |

| | | | |
|---|---|---|---|
| Risk of bias in individual studies | 12 | Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis. | 5 |
| Summary measures | 13 | State the principal summary measures (e.g., risk ratio, difference in means). | 6 |
| Synthesis of results | 14 | Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., $I^2$) for each meta-analysis. | 6, 21, 22 |
| Section/topic | # | Checklist item | Reported on page # |
| Risk of bias across studies | 15 | Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies). | 10 |
| Additional analyses | 16 | Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified. | 6 |
| **RESULTS** | | | |
| Study selection | 17 | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram. | 6, 19 |
| Study characteristics | 18 | For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations. | 7 |
| Risk of bias within studies | 19 | Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12). | 20 |
| Results of individual studies | 20 | For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot. | 21, 22 |
| Synthesis of results | 21 | Present results of each meta-analysis done, including confidence intervals and measures of consistency. | 21, 22 |
| Risk of bias across studies | 22 | Present results of any assessment of risk of bias across studies (see Item 15). | |
| Additional analysis | 23 | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]). | 24, 25, 26 |
| **DISCUSSION** | | | |
| Summary of evidence | 24 | Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers). | 9 |

| | | | |
|---|---|---|---|
| Limitations | 25 | Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias). | 10 |
| Conclusions | 26 | Provide a general interpretation of the results in the context of other evidence, and implications for future research. | 11 |
| **FUNDING** | | | |
| Funding | 27 | Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. | 6 |

**Appendix 2. Quality Assessment Tool**

| Study | Selection bias | Study design | Confounders | Blinding | Data collection methods | Withdrawals | Intervention integrity | Appropriateness of analysis | Overall |
|---|---|---|---|---|---|---|---|---|---|
| **Calliess et al, 2016** | 3 | 1 | 1 | 1 | 1 | 2 | 1 | 1 | 2 |
| **Dossett et al, 2014** | 2 | 1 | 1 | 2 | 1 | 3 | 3 | 1 | 3 |
| **Waterson et al 2016** | 1 | 1 | 1 | 2 | 1 | 1 | 1 | 1 | 1 |
| **Young et al 2016** | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |

**Appendix 3 – Summary of complications**

| First author | Group | Major | Minor |
|---|---|---|---|
| **Calliess et al, 2016** | KA | 2 | NA |
| | MA | 1 | NA |
| **Dossett et al, 2014** | KA | 1 | 3 |
| | MA | 1 | 3 |
| ***Waterson et al, 2016** | KA | 1 | NA |
| | MA | NA | NA |
| **Young et al, 2016** | KA | 1 | 3 |
| | MA | 3 | 2 |

Major = revision for instability, deep infection, periprosthetic fracture, or extensor mechanism dysfunction
Minor = haematoma evacuation, patella revision/instability, stiffness/manipulation under anaesthesia
*Patient with complication not included in final analysis