The clinical and cost-effectiveness of total versus partial knee replacement in patients with medial compartment osteoarthritis (TOPKAT): 5-year outcomes of a randomised controlled trial

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Summary

Background  Late-stage isolated medial knee osteoarthritis can be treated with total knee replacement (TKR) or partial knee replacement (PKR). There is high variation in treatment choice and little robust evidence to guide selection. The Total or Partial Knee Arthroplasty Trial (TOPKAT) therefore aims to assess the clinical effectiveness and cost-effectiveness of TKR versus PKR in patients with medial compartment osteoarthritis of the knee, and this represents an analysis of the main endpoints at 5 years.

Methods  Our multicentre, pragmatic randomised controlled trial was done at 27 UK sites. We used a combined expertise-based and equipoise-based approach, in which patients with isolated osteoarthritis of the medial compartment of the knee and who satisfied general requirements for a medial PKR were randomly assigned (1:1) to receive PKR or TKR by surgeons who were either expert in and willing to perform both surgeries or by a surgeon with particular expertise in the allocated procedure. The primary endpoint was the Oxford Knee Score (OKS) 5 years after randomisation in all patients assigned to groups. Health-care costs (in UK 2017 prices) and cost-effectiveness were also assessed. This trial is registered with ISRCTN (ISRCTN03013488) and ClinicalTrials.gov (NCT01352247).

Findings  Between Jan 18, 2010, and Sept 30, 2013, we assessed 962 patients for their eligibility, of whom 431 (45%) patients were excluded (121 [13%] patients did not meet the inclusion criteria and 310 [32%] patients declined to participate) and 528 (55%) patients were randomly assigned to groups. 94% of participants responded to the follow-up survey 5 years after their operation. At the 5-year follow-up, we found no difference in OKS between groups (mean difference 1·04, 95% CI –0·42 to 2·50; p=0·159). In our within-trial cost-effectiveness analysis, we found that PKR was more effective (0·240 additional quality-adjusted life-years, 95% CI 0·046 to 0·434) and less expensive (–£910, 95% CI –1503 to –317) than TKR during the 5 years of follow-up. This finding was a result of slightly better outcomes, lower costs of surgery, and lower follow-up health-care costs with PKR than TKR.

Interpretation  Both TKR and PKR are effective, offer similar clinical outcomes, and result in a similar incidence of re-operations and complications. Based on our clinical findings, and results regarding the lower costs and better cost-effectiveness with PKR during the 5-year study period, we suggest that PKR should be considered the first choice for patients with late-stage isolated medial compartment osteoarthritis.

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Introduction  Knee replacement for osteoarthritis of the knee is an effective, common procedure,1,2 between 2015 and 2017, 303,960 knee replacements were performed in the UK.1 There are two main surgical options for late-stage medial compartment osteoarthritis of the knee: a partial knee replacement (PKR), otherwise known as a unicompartmental knee replacement, in which only the damaged compartment of the knee is replaced, or a total knee replacement (TKR).3 There is often disagreement between surgeons regarding the best choice of implant and the best decision for these patients, who often have identical pathology,1 which has led to variation in provision. Although fewer than 9% of knee replacements in the UK are partial,1 it is estimated that up to 47% of patients requiring knee replacements only have unicompartmental disease and are suitable for a PKR.1 The best treatment option remains uncertain because there is little level 1 evidence to inform the clinical effectiveness and cost-effectiveness of either management approach. The existing related medical literature comprises four small randomised studies,4–7 individual cohort studies,8,9 indirect comparisons,10,11 and retrospective...
Research in context

Evidence before this study

The evidence to guide choice in the type of arthroplasty used for late-stage isolated medial compartment knee arthritis is extremely poor. Our study began in 2009, and we searched all major databases (MEDLINE, Embase, and PubMed). We searched the medical literature for related studies between Jan 1, 1990, and Dec 31, 2008, with the search terms “total”, “partial”, “unicondylar”, “knee replacement”, “knee arthroplasty”, “trial”, and “outcome” and no language restrictions. Before 2009, only cohort studies, indirect comparisons, and retrospective studies had been undertaken, which aimed to address specific aspects of each operation, and no large, well-powered, multicentre randomised comparative controlled trials had been done. However, two small randomised trials had been done, both in the UK.

The Knee Arthroplasty Trial had a component comparing partial knee replacement (PKR) with total knee replacement (TKR) but this comparison had to be terminated early because of inadequate recruitment. Another small single-centre randomised controlled trial that was published in 1998 (5 years after starting) and followed up in 2009 (after 15 years) reported good long-term follow-up, and the trial showed benefits of PKR; however, the study was underpowered for both knee score and revision frequency. Since 2009, three new randomised controlled trials have been published, but these trials were also small single-centre studies (comprising 56–72 participants per trial). To our knowledge, there are five ongoing trials. Additionally, a propensity-matched cohort study from the National Joint Registry was published in The Lancet in 2014, but the focus was solely on adverse outcomes (namely, revision frequency—described in terms of implant survival—and death). In this time, two systematic reviews with meta-analyses have also been published, both of which confirmed that there are minimal randomised trial data on which to guide treatment, and there are no robust randomised trials reporting outcomes in the longer term (ie, beyond 5 years).

Added value of this study

Our addition of the first large multicentre randomised study provides the best quality evidence to date to guide knee replacement treatment globally, and these data show low concordance with well-established registry and cohort data. Our results after 5 years regarding the number of re-operations and revisions do not correspond to joint registry data, in which PKR has been shown to lead to more revisions than TKR. Also, our health economic data, which had previously not been assessed to this level of detail, adds an additional dimension and further weight to our overall interpretation and guidance for practice. Our trial reflects the breadth of current practice through the inclusion of all types of implants, which is a strength, and its funding source (namely, our dissociation from industry, in a context of commonplace industry-supported research on surgical devices) helps to ensure unbiased evidence.

Implications of all the available evidence

Knee replacement is increasing in frequency, and it has an associated substantial cost implication to any health-care provider. It is also essential that patients receive the most efficacious operation for this condition. Before our study, and despite several cohort-based reports, knowledge of whether one operation type is superior, remained uncertain. Our 5-year study has indicated that both TKR and PKR are beneficial interventions but, based on our combined clinical and cost-effectiveness data and providing the operation is performed by those with adequate experience, we recommend that PKR should be offered as the treatment of choice for late-stage isolated medial compartment osteoarthritis of the knee.

studies, often examining very specific aspects of each procedure. To our knowledge, no one has undertaken a large, adequately powered, multicentre randomised controlled trial with long-term follow-up of patient-reported outcomes, re-operation, or revision, to directly compare PKR with TKR. A revision procedure is a subsequent further operation to replace the original implant with a new device, usually because of device failure, infection, or persistent pain. Revision is often described in terms of implant survival, and it can be done at any time from initial implantation (in some cases up to 30 or 40 years after primary arthroplasty) but early revision (before 5 years) is considered an early failure of the original surgical intervention. It is therefore an important metric in arthroplasty outcome. Re-operations are any further or subsequent operation, which can be revision surgery or other kinds of surgery. Systematic reviews and unadjusted data from national registries show more frequent revision associated with PKR: the chance of revision with PKR is more than double that with a TKR. When comparing matched patients receiving PKRs and TKRs 8 years after the operations, higher frequencies of revision and re-operations with PKR were also identified in an observational, registry-based study. However, there are no comparable data on revisions from randomised trials to-date. Although registry and cohort data can provide useful information, to provide further robust and unbiased estimates to compare the procedures, a large randomised trial was required.

The primary objective for the Total or Partial Knee Arthroplasty Trial (TOPKAT) was, therefore, to assess the clinical effectiveness and cost-effectiveness of TKR versus PKR in patients with medial compartment osteoarthritis of the knee in a formal, randomised controlled comparison. Secondary objectives included investigation of complications (including re-operations and revisions), patient satisfaction, and the cost implications of the knee replacements for patients, employers, and health-care providers. This assessment represents the main
endpoint results after 5 years of a 10-year follow-up study.

Methods
Study design and participants
The detailed study design and protocol have previously been published. In summary, TOPKAT was a multicentre, pragmatic randomised controlled trial of patients with isolated medial compartmental osteoarthritis who were randomly assigned to receive either PKR or TKR. The trial had a combined expertise-based and equipoise-based approach. The expertise-based randomisation enabled surgeons who were not in the equipoise group to work in pairs, and each surgeon (as experts in a specific operation type) agreed to perform the operation type that they felt was appropriate (giving one surgeon in the pair who used TKR and one who used PKR); patients were then randomly assigned to a TKR or PKR surgeon in the pairs. The equipoise-based randomisation involved surgeons in the equipoise group who had sufficient experience of both operation types to perform either operation (PKR or TKR) without compromise. Minimum levels of expertise were ensured to participate in the trial. PKR-only and TKR-only surgeons were required to have had appropriate training, to have been practising their technique for at least 1 year, and to have performed their operation at least ten times in the previous year. Equipoise surgeons, who delivered both operations, were required to satisfy the criteria for both operations—ie, they had appropriate training in both operations and had performed a minimum of ten PKR and ten TKR procedures in the previous year.

We recruited patients from 27 sites across the UK (and 68 surgeons at these sites). Potential participants were identified in outpatient and pre-assessment clinics by participating surgeons. For study inclusion, participants had to have isolated osteoarthritis of the medial compartment of the knee and to satisfy general requirements for a medial PKR. Detailed inclusion and exclusion criteria are provided in the published protocol. Patients who required simultaneous bilateral knee replacement were excluded. Participants signed a consent form during their screening visit, and they were free to withdraw from the study at any time without affecting their routine perioperative care. The study obtained approval from the UK National Research Ethics Service (Research Ethics Committee South Central Oxford C) in September, 2009 (09/H0606/88).

Randomisation and masking
Participants were randomly assigned (1:1) to receive TKR or PKR. For the randomisation procedure (in which we also used minimisation), we used a web-based randomisation service at the Centre for Healthcare Randomised Trials (Health Services Research Unit, University of Aberdeen, UK). We also used a minimisation algorithm that incorporated sex, age band (<50, 50–70, or >70 years), baseline Oxford Knee Score (OKS) band (14 or less, 15–21, or 22 or more), and delivery unit. A delivery unit was either an equipoise surgeon or a pair of expertise surgeons with complementary expertise. Surgeons, patients, and follow-up assessors were not masked to allocation, but the implant type was not highlighted at any stage.

Procedures
Our trial compared the TKR procedure versus the PKR procedure rather than a specific brand of TKR implant versus a specific brand of PKR implant. As such, surgeons were free to use the implant of their own choice, or that of their institution. A TKR involves all surfaces of the knee being replaced. The procedure involves excising both diseased and normal femoral condyles, the tibial plateau—and often the patella—and removing or releasing some of the ligaments. The artificial implant can be cemented in position. A PKR or unicompartimental knee replacement involves only the diseased area of the joint being replaced by artificial implants, whereas healthy compartments of the knee and ligaments are retained.

The baseline assessment included a patient self-reported questionnaire to examine the frequency and intensity of knee pain and knee function (measured by the OKS), activity, health-care resource use, and the American Knee Society Score. Routine pre-operative X-rays were also used.

We recorded operative details in theatre, and we routinely took postoperative X-rays. Patients attended a clinic for an American Knee Society Score assessment and a complication review 2 months, 1 year, and 5 years after their operation. All other outcomes were collected with postal questionnaires at 2 months after the operation and 1 year after randomisation and, thereafter, annually (until 5 years after randomisation).

We collected data on complications and re-operation from various sources for cross-referencing and to ensure completeness. Complication data were collected from participants in their follow-up questionnaires and clinical assessment visits. Any reported re-admissions were followed up with the patient’s hospital to obtain further details. Local research teams did a final check of hospital records 5 years after the operations, to ensure that complications data were collected from all participants (ie, those who had not returned a questionnaire or attended a follow-up visit).

Outcomes
The primary outcome measure was the OKS 5 years after randomisation in all patients assigned to groups. The OKS is a patient self-reported outcome questionnaire that was specifically developed to assess function and pain after knee replacement surgery. This score is a validated and responsive measure of knee function and related pain.

The secondary outcome measures were assessed at 5 years after randomisation in all patients assigned to
receive an operation. These outcomes were the American Knee Society Score,\textsuperscript{22} the University of California, Los Angeles Activity Score,\textsuperscript{23} the High Activity Arthroplasty Score,\textsuperscript{24} the EuroQol EQ-5D-3L,\textsuperscript{25} the Lund Satisfaction Score,\textsuperscript{26} the frequency of complications (determining the number of patients who required re-admission and a re-operation), and three patient-reported anchor type questions regarding satisfaction, a comparison of problems with their knee before versus after the surgery, and whether they would have the operation again. The response categories are shown in the appendix (p 1).

We also assessed a composite outcome for failure (a combination of re-operation and poor outcomes, as determined by an improvement in OKS of less than four points). This composite outcome assessment has not been validated and it is therefore considered an exploratory outcome.

Length of hospital stay and data on use of health-care services were collected for an health economics analysis.

**Statistical analysis**

A necessary sample size was calculated for the OKS and the incidence of re-operations. Our trial was powered to detect a 2·0-point difference in OKS with 80% power (or, equivalently, 90% power to detect a 3·0-point change) at a 5% (two-sided) significance level with an SD of 10·0 points. For this power, a sample size of 500 patients was required.\textsuperscript{29,30} The sample size was adequate to detect a change in incidence of re-operations of 7% between groups (from 5% to 12%) at 80% power. Of note, a study\textsuperscript{31} done and published after the TOPKAT trial was planned suggested that a 5-point difference in OKS should become the appropriate minimally important difference in OKS.

Full details of the statistical analyses are contained in the statistical analysis plan (available on request).

In brief, the statistical analysis was primarily on an intention-to-treat basis and used all available participant data. The OKS scores at 5 years, which were compared with a linear regression analysis, were adjusted for minimisation factors and baseline OKS, and a cluster robust error was added for surgery delivery unit. A differential effect of expertise versus equipoise delivery of the intervention on treatment effect was explored with an interaction effect. The incidence of complications and re-operations, including revisions, and other binary variables were compared with Poisson regression, to estimate risk ratio, and they were adjusted for minimisation covariates and a cluster robust error for surgeon delivery unit. We used prespecified secondary analyses (unadjusted t test, a multilevel model to assess the marginal difference) and subgroup analyses (sex, OKS band, and age band, evaluated with treatment-by-subgroup interactions). To assess the effect of compliance (the operation being delivered as intended), an instrumental variable method was used to estimate the complier-average causal effect at 5 years after randomisation. We also performed a post-hoc analysis of OKS that used the area under the curve (AUC), generated for each participant with the trapezoidal rule, to describe the effects of TKR and PKR on OKS across all available timepoints.

Statistical significance was judged at the two-sided 5% level and treatment effect estimates are presented with corresponding 95% CIs. Low frequency event data, such as re-operations and revisions, were also analysed on an as-treated basis, to avoid misrepresentation from incompliance to the allocated intervention (ie, crossovers).

We also did a within-trial cost-effectiveness analysis. Total costs and quality-adjusted life-years (QALYs) for all 528 participants were estimated from the date of recruitment until the earliest of death, withdrawal from

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**Figure 1: Trial profile**

The 5-year intention-to-treat analysis includes only patients who provided results for the Oxford Knee Score assessment. PKR=partial knee replacement. TKR=total knee replacement.

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See Online for appendix
study, or the end of follow-up at 5 years. Both costs and QALYs were discounted at 3.5% per year. Missing data on EQ-5D score and health-care costs were imputed with multiple imputation by chained equations, assuming data was missing at random (since there was no evidence that the probability that data was missing depended on baseline participant characteristics or on lagged outcomes).32 Ten imputed datasets were created with predictive mean matching. Imputation was performed separately by treatment allocation. After imputation, the mean total health-care costs and QALYs were estimated with separate linear regression models controlling for treatment allocation, age band, sex, and baseline OKS band, following the main clinical analysis. For QALYs we additionally controlled for EQ-5D score at baseline. The incremental cost-effectiveness ratio was calculated by dividing the mean cost difference between PKR and TKR by the mean QALY difference. The joint

| PKR (n=264) | TKR (n=264) |
|-------------|-------------|
| Age, years  | 65·2 (8·8)  | 64·7 (8·5)  |
| Sex         |             |             |
| Male        | 153 (58%)   | 153 (58%)   |
| Female      | 111 (42%)   | 111 (42%)   |
| Study knee  |             |             |
| Left        | 140 (53%)   | 141 (53%)   |
| Right       | 124 (47%)   | 123 (47%)   |
| Duration of osteoarthritis |         |             |
| <3 years    | 75 (28%)    | 73 (28%)    |
| 3–5 years   | 82 (31%)    | 72 (27%)    |
| 6–10 years  | 59 (22%)    | 73 (28%)    |
| >10 years   | 36 (14%)    | 30 (11%)    |
| Missing data| 12 (5%)     | 16 (6%)     |
| Medical history of conditions |             |             |
| Other joint problems | 106 (40%) | 96 (36%) |
| Cardiovascular | 80 (30%) | 86 (33%) |
| Diabetes     | 27 (10%)    | 26 (10%)    |
| Gastrointestinal | 17 (6%) | 18 (7%) |
| Respiratory  | 19 (7%)     | 12 (5%)     |
| Cancer       | 6 (2%)      | 8 (3%)      |
| Renal or urological | 8 (3%) | 8 (3%) |
| Neurological | 7 (3%)      | 6 (2%)      |
| Mental health| 7 (3%)      | 6 (2%)      |
| Thyroid problems | 3 (1%) | 2 (1%) |
| Other*       | 5 (2%)      | 4 (2%)      |
| Employment status |         |             |
| Retired      | 159 (60%)   | 162 (61%)   |
| Unemployed   | 15 (6%)     | 21 (8%)     |
| Employed     | 82 (31%)    | 73 (28%)    |
| Missing data | 8 (3%)      | 8 (3%)      |
| Body-mass index (n=210 vs n=221) | 31·0 (4·6) | 31·1 (4·8) |
| Extent of knee arthritis affecting mobility (Charnley ABC) |             |             |
| Single       | 99 (38%)    | 119 (45%)   |
| Both         | 142 (54%)   | 121 (46%)   |
| Multiple arthritis or medical infirmity | 6 (2%) | 11 (4%) |
| Missing data | 17 (6%)     | 13 (5%)     |
| General health (n=259 vs n=260) | 2 6 (0·9) | 2 8 (0·9) |
| General health relative to 1 year ago (n=259 vs n=260) | 3 3 (0·8) | 3 3 (0·8) |

(Table 1 continues in next column)
uncertainty around incremental total costs and QALYs (ie, the difference between PKR and TKR), and in the cost-effectiveness, was also investigated. All statistical analyses were done with Stata version 15, and all health economic analyses were done with R version 3.4.3.

A summary of the results, masked for implant identifier, was sent to five separate independent reviewers (experts who were familiar with orthopaedics, or trial design or interpretation, or both) plus the trial steering committee chair, to obtain an unbiased interpretation and conclusion of the trial. Any TOPKAT team members with strong personal opinions or conflicts of interest, although helpful in the setting up of the study, had little or no part in the conduct of the study or interpretation of the results. This trial is registered with ISRCTN, (ISRCTN03013488) and ClinicalTrials.gov (NCT01352247).

Role of the funding source
The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results
Between Jan 18, 2010, and Sept 30, 2013, we recruited patients from 27 sites across the UK, and we included 68 surgeons from these sites. We assessed 962 patients for eligibility, of whom 431 (45%) patients were excluded (121 [13%] patients did not meet the inclusion criteria and 310 [32%] patients declined to participate) and 528 (55%) patients were randomly assigned to groups (figure 1). Three patients were randomly assigned to groups twice in error, and the second randomisation was treated as a post-randomisation exclusion. Of the 528 patients, 264 (50%) patients were assigned to the PKR group, of whom 233 (88%) patients provided results for assessment of the primary outcome, and 264 (50%) patients were assigned to the TKR group, of whom 231 (88%) patients provided results for assessment of the primary outcome.

44 participants had a knee replacement but did not receive their allocated device (crossovers). 31 (12%) patients allocated to PKR received TKR: in six (19%) patients, the crossover occurred before surgery (the osteoarthritis pattern was not suitable for PKR [n=2]; patient decision [n=1]; inflammatory arthropathy [not suitable for PKR; n=1]; after random allocation to groups, the patient was deemed not suitable for PKR because of a contraindication [n=1]; and because of an error in communication of group allocation at the site [n=1]); and in 25 (81%) patients, an intra-operative conversion was made (the osteoarthritis pattern was not suitable for PKR [n=20]; and the anterior cruciate ligament was found to be absent or deteriorated [n=5]). 13 (5%) patients who were allocated to TKR received PKR: in eight (62%) patients, the crossover occurred before surgery (patient decision [n=5]; and error in communication of randomisation allocation at site [n=3]); and in five (38%) patients, an intra-operative decision was made (independent surgeon decision—ie, all eligibility criteria met but decision made to use PKR). The groups were well balanced on all baseline characteristics (table 1). The types of implants used in the study reflected current practice (appendix p 2).

The operation time was similar in both groups, at around 70 min (PKR mean duration 69 min [SD 18]; TKR 70 min [22]; appendix p 15). The length of the hospital stay for the surgery differed significantly between

| Partial knee replacement | Total knee replacement | Effect size (95% CI) | p value |
|--------------------------|------------------------|----------------------|---------|
| Mean (SD) | n | Mean (SD) | n |
| Oxford Knee Score (primary outcome) | | | |
| Baseline | 18.8 (7.0) | 264 | 19.0 (7.2) | 264 | 1 (ref) | -- |
| 5 years | 38.0 (10.1) | 233 | 37.0 (10.6) | 231 | 1.04 (-0.42 to 2.50) | 0.159 |
| EQ-5D-3L score | | | |
| Baseline | 0.428 (0.30) | 257 | 0.381 (0.32) | 252 | 1 (ref) | -- |
| 5 years | 0.744 (0.29) | 224 | 0.717 (0.32) | 212 | 0.018 (-0.033 to 0.069) | 0.8 |
| EQ-SD visual analogue scale score | | | |
| Baseline | 62.8 (27.0) | 249 | 60.7 (28.7) | 257 | 1 (ref) | -- |
| 5 years | 75.4 (16.5) | 228 | 71.7 (19.7) | 217 | 4.02 (1.36 to 6.67) | 0.004 |
| High Activity Arthroplasty Score | | | |
| Baseline | 4.8 (2.3) | 258 | 4.6 (2.3) | 256 | 1 (ref) | -- |
| 5 years | 7.9 (3.5) | 218 | 7.6 (3.4) | 207 | 0.22 (-0.24 to 0.67) | 0.33 |
| University of California, Los Angeles Activity score | | | |
| Baseline | 3.6 (1.5) | 260 | 3.7 (1.5) | 260 | 1 (ref) | -- |
| 5 years | 5.0 (1.9) | 221 | 4.9 (2.0) | 215 | 0.17 (-0.09 to 0.43) | 0.19 |
| American Knee Society score (objective) | | | |
| Baseline | 42.0 (16.1) | 260 | 42.3 (16.0) | 259 | 1 (ref) | -- |
| 5 years | 85.8 (16.6) | 191 | 86.6 (16.4) | 185 | 0.89 (-5.18 to 3.41) | 0.68 |
| American Knee Society score (functional) | | | |
| Baseline | 59.3 (15.6) | 262 | 58.7 (15.5) | 259 | 1 (ref) | -- |
| 5 years | 82.6 (18.5) | 195 | 81.7 (19.0) | 192 | 0.37 (-3.81 to 4.55) | 0.86 |

Table 2: Estimated treatment effect on primary and secondary outcomes, at baseline and at 5 years

Figure 2: Oxford Knee Scores after randomisation

and error in communication of randomisation allocation at site [n=3]); and in five (38%) patients, an intra-operative decision was made (independent surgeon decision—ie, all eligibility criteria met but decision made to use PKR). The groups were well balanced on all baseline characteristics (table 1). The types of implants used in the study reflected current practice (appendix p 2).

The operation time was similar in both groups, at around 70 min (PKR mean duration 69 min [SD 18]; TKR 70 min [22]; appendix p 15). The length of the hospital stay for the surgery differed significantly between
groups: those receiving PKR stayed for a mean duration of 3-2 days (1-3), and those receiving TKR stayed for a mean duration of 4-3 days (3-6; risk ratio [RR] 0-74, 95% CI 0-63 to 0-87; p <0-0001). 5 years after randomisation, 94% of patients responded to the follow-up questionnaire (88% for the primary outcome; PKR n=233, TKR n=231). Patients in both groups had superior outcomes relative to their preoperative baseline status.

OKS had substantially changed in both groups: we found a mean change in OKS of more than 18 points for both procedures.

At the 5-year follow-up, we found no difference in OKS between groups (mean difference 1-04, 95% CI –0·42 to 2·50; p=0·159; table 2; figure 2). After 5 years, the EQ-5D visual analogue scale score was better in those who received PKR than those who received TKR (4·02, 1·36 to 6·67; p=0·004). However, we found no differences in the other secondary outcome scores at 5 years. Patient satisfaction after 5 years did not differ between the groups (190 [82%] of 233 patients receiving PKR vs 173 [77%] of 225 patients receiving TKR; RR 1·06, 95% CI 0·99 to 1·13; p=0·097; table 3). However, we found differences at 5 years in the results of the two questions asking about whether the patient’s knee was better to before their operation (219 [95%] of 230 PKR patients vs 200 [90%] of 222 TKR patients; 1·06, 1·01 to 1·11; p=0·016) and whether the patient would have the operation again (208 [91%] of 228 patients vs 183 [84%] of 217 patients; 1·08, 1·02 to 1·15; p=0·010).

At the 5-year analysis, OKS did not differ between the surgeon groupings (ie, expertise pair vs equipoise surgeons; interaction effect –1·31, 95% CI –5·34 to 2·73; p=0·518), nor between the age band, sex, or OKS band subgroups (appendix p 14). At 5 years, there was also no effect of surgeon experience, as defined by the number of procedures of each operation type performed by the surgeons before the study (appendix p 11).

Patients receiving TKR had more complications than those receiving PKR (73 [27%] of 269 patients vs 48 [20%] of 245 patients; RR 0·72, 95% CI 0·53–0·98; p=0·036; appendix pp 4–6). The most common complications were unexplained pain (nine patients receiving PKR vs eight patients receiving TKR), knee stiffness (0 patients vs ten patients) and both unexplained pain and knee stiffness together (one patient vs six patients). The number of re-operations and revisions were similar between groups (table 4). Of those who had surgery (ie, as treated), 15 (6%) of 245 patients receiving PKR had a re-operation and 21 (8%) of 269 patients receiving TKR had a re-operation (0·75, 0·37–1·53; p=0·432). After both surgeries, ten (4%) of 245 patients; RR 0·74, 0·51–1·08; p=0·118). During the 5-year follow-up, 17 deaths were reported: six (2%) deaths in the PKR group and 11 (4%) deaths in the TKR group (appendix p 12). These deaths were predominantly due to cancer (four deaths in the PKR group vs six deaths in the TKR group) and there were two deaths in each group for unknown reasons.

### Table 3: Estimated treatment effect on self-reported anchor questions at 5 years

| Treatment received | Treatment as allocated |
|---------------------|------------------------|
| PKR (n=245)         | TKR (n=269)            |
| PKR (n=263)         | TKR (n=251)            |
| Number of participants receiving a re-operation | 15 (6%) | 21 (8%) | 14 (5%) | 22 (9%) |
| Number of re-operations | 22 (9%) | 28 (10%) | 18 (7%) | 32 (13%) |
| Number of participants with revision | 10 (4%) | 10 (4%) | 8 (3%) | 12 (5%) |
| Unexplained pain | 2 | 5 | 1 | 6 |
| Bearing dislocation | 3 | 0 | 3 | 0 |
| Device loosening (tibia) | 2 | 0 | 1 | 1 |
| Bearing dislocation and unexplained pain | 1 | 0 | 1 | 0 |
| Ligamentous instability | 1 | 0 | 1 | 0 |
| Infection | 1 | 0 | 1 | 0 |
| Infection and mechanical failure | 0 | 1 | 0 | 1 |
| Knee stiffness and unexplained pain | 0 | 1 | 0 | 1 |
| Ligamentous instability and malalignment | 0 | 1 | 0 | 1 |
| Unknown | 0 | 2 | 0 | 2 |
| Number of other procedures | 12 | 18 | 10 | 20 |
| MUA | 0 | 12 | 1 | 11 |
| Aspiration | 3 | 2 | 3 | 2 |
| Arthroscopy | 3 | 0 | 3 | 0 |
| Arthroscopy and debridement or washout | 1 | 1 | 1 | 1 |
| Debridement, exploration, or washout | 2 | 0 | 0 | 2 |
| Open reduction and internal fixation | 1 | 0 | 1 | 0 |
| Marcene injection and MUA | 2 | 0 | 1 | 1 |
| Arthroscopy and MUA | 0 | 1 | 0 | 1 |
| Arthroscopy and biopsy | 0 | 1 | 0 | 1 |
| Arthroscopy and partial medial meniscectomy | 0 | 1 | 0 | 1 |

Data are n or n (%). PKR=partial knee replacement. TKR=total knee replacement. MUA=manipulation under anaesthetic.

### Table 4: Number of re-operations, including revisions, by treatment received and as allocated at 5 years

| Partial knee replacement | Total knee replacement | Risk ratio (95% CI) p value |
|--------------------------|------------------------|---------------------------|
| n (%) | Valid N | n (%) | Valid N | n (%) | Valid N |
| Satisfied with knee | 190 (82%) | 233 | 173 (77%) | 225 | 1·06 (0·99–1·13) | 0·097 |
| Knee better or worse, now versus before surgery | 219 (95%) | 230 | 200 (90%) | 222 | 1·06 (1·01–1·11) | 0·016 |
| Would choose to have knee operation again | 208 (91%) | 228 | 183 (84%) | 217 | 1·08 (1·02–1·15) | 0·010 |

Valid N data are the number who responded to the question.
In our within-trial cost-effectiveness analysis, we found that PKR was more effective (0.240 additional QALYs, 95% CI 0.046 to 0.434) and less expensive than TKR (–£910, 95% CI –1503 to –317) during the 5 years of follow-up (figure 3). The probability that PKR was the most cost-effective option was more than 99.9% for all reasonable threshold values. This finding was a result of better outcome, as measured by QALYs derived from EQ-5D scores (appendix p 7) and survival, lower costs of PKR surgery, and lower follow-up health-care costs with PKR than TKR. Even assuming equal costs of the implant device, PKR was less costly and more effective than TKR. The proportion of missing data imputed to inform the cost-effectiveness analysis was 12% per period, on average (appendix p 8). Index surgery costs and cost effectiveness comparisons are given in the appendix (pp 9–10).

The planned secondary analysis of the unadjusted OKS showed similar results to the primary outcome analysis, as did a marginal estimate over the whole 5-year follow-up (mean difference 1.39, 95% CI –0.12 to 2.90; p=0.071). The complier-average causal effect analysis at 5 years showed no difference (0.86, –0.62 to 2.34; p=0.254). The AUC of the OKS across the whole study period significantly favoured PKR versus TKR. The mean AUC was 36.6 (SD 8.3) for 233 participants in the PKR group and 35.1 (9.1) for the 231 participants in the TKR group (mean difference 1.54, 95% CI 0.07 to 3.01; p=0.040); notably, this difference is smaller than the revised estimated minimal important difference of 5 OKS points. A kernel density plot for OKS at baseline and 5 years is shown in the appendix (p 13).

Discussion

To our knowledge, our study is the largest multicentre randomised trial to compare TKR with PKR, and it provides the most robust evidence to date on the comparative effectiveness of the two approaches for the management of medial compartmental osteoarthritis. Our trial has high generalisability, since it involves many surgeons from several centres across the UK, and the hybrid design uniquely includes surgeons both in and out of equipoise, which allowed them to perform the surgery of their stated preference and expertise.

We found that both interventions (PKR and TKR) provided medium-term benefits for patients with medial compartment osteoarthritis by producing substantial changes in outcomes (more than 18 OKS points with both surgeries). Despite no differences in the primary outcome (on cross-sectional analysis), there was consistent evidence overall to suggest a modest clinical benefit of PKR over TKR. The analysis of the OKS AUC and patient-directed questions about patient satisfaction, perceived change in their knee problem, and willingness to choose to have the operation again all support this position. The duration of hospital stay was also lower with PKR.

Despite low power, we observed no differences between the number of re-operations and revisions between the trial groups. By contrast, nearly all global registries (which comprise non-randomised, observational data) report that PKR results in a substantially larger number of revisions than TKR (usually more than 6%). In TOPKAT, the frequency of complications was also observed to be increased in the TKR group. Although interpretation of these event findings in each study type is not straightforward, it is likely that non-randomised cohort data, despite matching, remain susceptible to selection bias (specific patients chosen for a particular implant). The difference might also reflect a lower threshold for revision of PKR outside of a controlled trial. However, Hawthorne-type effects and self-selection of the involved surgeons in the trial also cannot be excluded as reasoning for the lower frequency of revisions found with PKR in TOPKAT relative to other studies. It is important to emphasise that the revision and re-operation data are more susceptible to bias than some of the other variables. The sample size calculations were adequate to detect a change in the proportion of overall re-operations of 7% between groups (from 5% to 12%) with 80% power, and they might therefore be underpowered to provide concrete evidence on revisions. The anticipated differences for the power calculation were much larger than the differences in the revision frequencies found in our study. Furthermore, differences in the number of revisions between subgroups (eg, male vs female) would also remain undetected with the sample size that we used. Some of our most notable findings were in relation to the health economics data. During 5 years of follow-up in the TOPKAT trial, PKR was found...
to be more effective but also less costly than TKR. Lower costs with PKR were a result of lower costs of the index surgery (even when assuming equal device costs) and lower subsequent use of health-care services, especially due to fewer outpatient visits in the first 2 years after the index surgery. These data will have most relevance for the UK health-care system, but the findings are likely to be generalisable to settings with similar health-care systems.

There are many general strengths of this study. Globally, to our knowledge, our study is the largest, most complete, and longest randomised follow-up of any comparison of TKR versus PKR to date. Our study was well powered and any type 2 errors are highly unlikely. The external validity is high, and the pragmatic design lends itself to policy support or commissioning changes. The follow-up response to the questionnaires was very high (94% for all; 88% for the primary outcome). Our study included an expertise design, which accounted for surgeons who were not in the equipoise group. Our trial is unique in that it can provide strong empirical evidence to compare with large database studies evaluating TKR and PKR, and it could highlight the limitations of relying on cohort or non-randomised systematically collected data alone. An important strength is the unbiased and independent review of our interpretation.

The weaknesses of the study include the absence of masking, some missing data for the health-care resource and EQ-5D data (12% across all time periods), and some non-compliance. It was not feasible to keep patients masked from allocation for 5 years; expectancy bias (regarding a higher benefit of PKR) cannot therefore be entirely ruled out. The missing data was equal between groups, and it was found to have no effect on results; no imputation method was required for the clinical analysis but one was used for the health economics analysis. Some non-compliance with allocation (ie, conversion from PKR to TKR from operative findings) was anticipated and clinically understandable but a complier-average causal effects analysis that we used to assess the potential effects of non-compliance on outcomes did not find any issue. The number of participants who completed follow-up was just less than the power calculation of the target of 500 participants, and this disparity is therefore unlikely to affect the results, particularly since the main analyses benefited from greater precision (not accounted for in the original sample size) because of adjustment for minimisation variables and, where relevant, also the baseline score. It is also acknowledged that the 5-year timeframe prompts some limitations. First, the within-trial cost-effectiveness analysis was not designed to accommodate for the economic implications of potential future revisions; thus the longer term implications of any potential future changes in the revision profile have not been accounted for. Second, patients in both groups are expecting the effects of their knee surgery to last longer than 5 years, so major differences that occur later will also remain undetected. However, a 10-year follow-up has commenced and will provide a clearer picture on these data.

The magnitude of the difference observed in the primary outcome lies within the acknowledged minimally important difference in OKS at the time of study planning (a 2-point difference), although the 95% CI did not rule out the possibility that the effect of PKR could exceed 2 points. Irrespective, the observed difference is well within the more recently accepted minimally important difference in OKS (now set at 5 points). This scale of difference in OKS is unlikely to have any discernible impact on national or international practice by itself, but clinicians and patients themselves must decide whether these small magnitudes of difference, and the evidence from other variables, is sufficient to modify or support their own individual decision making. A kernel density analysis (appendix p 13) showed that there were more patients with OKS outcome scores of 40 and above in the PKR group than in the TKR group, but this finding was balanced by a greater number of TKR patients with mid-range scores. Hence, there is disagreement as to whether these data imply an important clinical signal for efficacy or a more contrived outcome to demonstrate differences. The re-operation and revision data are of note, suggesting that neither operation is associated with a high frequency of revision, a finding in contrast with previous reports that used cohort databases. The cost-effectiveness findings are undoubtedly the strongest marker, and they suggest that PKR is superior in a health-care provision context.

Both TKR and PKR remain treatment options for late-stage medial compartment arthritis of the knee. PKR should, however, be considered the first-choice procedure (based on 5-year outcomes). That said, the operation should only be done by those surgeons with sufficient experience and expertise.

Both TKR and PKR are effective, offer similar clinical outcomes, and result in similar frequencies of re-operations and complications. The number of revisions after PKR in our randomised trial were substantially lower than found in other, mainly non-randomised, cohort data. Assessments focusing on whether the patients’ knees felt better after the surgery and whether they would have the surgery again were better with PKR. And, of note, PKR was more cost-effective than TKR after 5 years. Although TKR provides good outcomes, based on the combined 5-year cost-effectiveness and clinical data, PKR should likely be considered the first choice for patients with late-stage isolated medial compartment osteoarthritis.

Contributors

DJB, LJD, JAC, AP, AC, HC, RF, NA, DM, and MKC designed and developed the trial protocol. LJD was the trial manager, GM oversaw the statistical analysis, JH conducted the statistical analysis, and SK conducted the health economics analysis. GM, SK, JH, and JL had access to all the data. DJB, JAC, GM, AC, JL, and MKC interpreted the data. DJB wrote the initial draft of the manuscript and subsequent revisions.
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Declaration of interests

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Data sharing

The data collected for the study, including individual participant data and a data dictionary defining each field in the set, will be made available to researchers on request to the study team and with appropriate reason when accompanied by a peer-reviewed protocol, with publication and on agreement of the Trial Steering Committee. The shared data will be deidentified participant data. Data will be shared with investigator support, after approval of a proposal, with a signed data access agreement. The study protocol, statistical analysis plan, and informed consent form are available online.

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For study documents see https://www.journalslibrary.nihr.ac.uk/programmes/hta/081408/
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