45-day mortality after 467 779 knee replacements for osteoarthritis from the National Joint Registry for England and Wales: an observational study

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Summary

Background **Understanding the risk factors for early death after knee replacement could help to reduce the risk of mortality after this procedure. We assessed secular trends in death within 45 days of knee replacement for osteoarthritis in England and Wales, with the aim of investigating whether any change that we recorded could be explained by alterations in modifiable perioperative factors.**

Methods **We took data for knee replacements done for osteoarthritis in England and Wales between April 1, 2003, and Dec 31, 2011, from the National Joint Registry for England and Wales. Patient identifiers were used to link these data to the national mortality database and the Hospital Episode Statistics database to obtain details of death, sociodemographics, and comorbidity. We assessed mortality within 45 days by Kaplan-Meier analysis and assessed the role of patient and treatment factors by Cox proportional hazards models.**

Findings **467 779 primary knee replacements were done to treat osteoarthritis during 9 years. 1183 patients died within 45 days of surgery, with a substantial secular decrease in mortality from 0·37% in 2003 to 0·20% in 2011, even after adjustment for age, sex, and comorbidity. The use of unicompartmental knee replacement was associated with substantially lower mortality than was total knee replacement (hazard ratio [HR] 0·32, 95% CI 0·19–0·54, p<0·0005). Several comorbidities were associated with increased mortality: myocardial infarction (HR 3·46, 95% CI 2·81–4·14, p<0·0005), cerebrovascular disease (3·35, 2·7–4·14, p<0·0005), moderate/severe liver disease (7·2, 3·93–13·21, p<0·0005), and renal disease (2·18, 1·76–2·69, p<0·0005). Modifiable perioperative risk factors, including surgical approach and thromboprophylaxis were not associated with mortality.**

Interpretation **Postoperative mortality after knee replacement has fallen substantially between 2003 and 2011. Efforts to further reduce mortality should concentrate more on older patients, those who are male and those with specific comorbidities, such as myocardial infarction, cerebrovascular disease, liver disease, and renal disease.**

Funding **National Joint Registry for England and Wales.**

Introduction

Knee joint replacement is one of the most common surgical procedures, with numbers now exceeding those for hip replacement.[1] Both operations are associated with a short-term increase in mortality.[2,3] Early mortality after hip replacement has decreased in recent years, and several modifiable determinants are associated with mortality, such as surgical approach and type of anaesthesia.[2]

Both knee and hip joint replacement are largely done to relieve pain and disability resulting from advanced osteoarthritis. Research into both osteoarthritis and joint replacement often assumes that knee and hip problems, and their surgical treatments, are very similar, although abundant evidence to the contrary exists. For example, the epidemiological associations of hip and knee osteoarthritis differ, as do the rate of progression and outcomes.[1] Furthermore, advances in knee surgery have led to two quite distinct operative options for the most common form of knee osteoarthritis—anteromedial compartment disease—a unicondylar replacement (UKR) of the medial compartment of the knee or total knee replacement (TKR).

Many surgeons and patients favour TKR over UKR because this option seems to be a more definitive answer to knee osteoarthritis and because of the evidence that UKRs are revised more often than are TKRs.[1] Other researchers have argued that implant survival should not only be looked at in isolation,[4] but also alongside clinical outcomes. If early mortality favoured UKR, opinions and practice might change.

Decision making around knee replacement needs to consider perioperative mortality and patient related outcomes (such as pain, function, and satisfaction) and longevity of implants.[5] We have therefore examined early mortality after knee joint replacement, exploring time trends in early mortality during the past 10 years, and to what extent these trends are determined by patient, surgical, and anaesthetic factors. We postulated that age, sex, year of surgery, surgical approach, thromboprophylaxis, implant type, health status, and serious medical comorbidity would be associated with mortality.

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Methods

Data sources

In this observational study, we linked data from three large UK datasets to examine these questions: the National Joint Registry for England and Wales (NJR), the Office of National Statistics (ONS), and the Hospital Episode Statistics for England (HES). The NJR was established in April, 2003, and records all knee replacements done in England and Wales. The ONS accurately records all deaths in England and Wales, and HES records all inpatient episodes for National Health Service (NHS) funded care in England.

For the **ASA Physical Status Classification System** see http://www.asahq.org/For-Members/Clinical-Information/ASA-Physical-Status-Classification-System.aspx

Patient details from the NJR were passed to the NHS Personal Demographics Service who provided death dates from the ONS, for which the NHS number was traceable. NJR was further linked to inpatient and day case episodes in HES. We produce part 3 of the annual report of the NJR and, in that capacity, receive the appropriate dataset each year in April. Our HES dataset was received concurrently with the annual report dataset in April, 2012, but contained no entries beyond Sept 30, 2011.

See Online for appendix

Our base series was 499 695 primary knee operations done between April 1, 2003, and Dec 31, 2011, with valid anonymised person-level identifiers. Of these operations, we included 480 796 for which the only reason for surgery was osteoarthritis. We further excluded simultaneous bilateral operations (done on the same day: 12 866 operations, 6433 patients), and 151 for which the patient's NHS number was not traceable (hence whose deaths could not be ascertained) or for which consent had been withdrawn. Our results are based on the remaining 467 779 operations.

We obtained the HES extract by first searching for records with procedure (OPCS 4) codes relating to primary knee replacements within the NJR. For the patients identified, we extracted HES episodes for hospital admissions for any reason. We then merged the NJR and HES datasets. We restricted our HES records, and therefore the associated comorbidity, to a 5-year period before the relevant knee replacement to give all the knee replacements in NJR the same potential time coverage. Our HES entries went back to April, 1997, which was 5 years before the start of the NJR on April 1, 2003. Every patient, therefore, would have had a potential 5 years of episodes in HES, but those in early years could not have had more than 5 years.

86 841 (19%) of 450 268 primary operations done before Sept 30, 2011 (the last date of our HES extract), had no HES records. Of 86 841, 21 535 (5% of total 450 268) had been done in Wales, 42 587 (9%) were privately funded, and funding was uncertain in 4576 (1%). The remaining 18 143 (4%) operations were NHS funded, but no HES entries. We do not know why these entries were missing; 15 827 of 18 143 operations were NHS funded in independent hospitals or treatment centres, but the remaining 2316 were in English NHS hospitals. HES might not be as complete as it should be.

Procedures

We assessed factors related to time of death from any cause, censoring at 45 days or Dec 31, 2011. We investigated several variables—surgical approach, implant type and fixation, day of the week when surgery was done, anaesthetic type, thromboprophylaxis, age, sex, and body-mass index (BMI), which were all available in the NJR. We used several measures of comorbidity as potential confounders for death. The NJR provided the American Society of Anesthesiologists (ASA) six point scale of surgical fitness. We also used the International Classification of Diseases 10 codes reported in all HES inpatient episodes up to, and including, the primary operation, to define 16 so-called high risk subgroups with increased expected mortality, as originally proposed by Charlson and colleagues.[6,7] To mitigate potential bias due to data incompleteness, calculation of comorbidity was restricted to operations on or before Sept 30, 2011, the last date of our HES extract; the appendix shows further details. We extracted data for ethnic origin and area deprivation score from HES. If the coding of a person's ethnic origin was inconsistent, we used the ethnic group stated most frequently. We used the Lower Super Output Area Level (SOAL)—as defined by the Office for National Statistics—closest in time to the date of the primary operation as our geographical unit of analysis. SOAL was then linked to the English Indices of Multiple Deprivation for 2007[8] and patients were characterised according to the area quintile in which they resided (1=most deprived area, 5=least deprived).

Statistical analysis

We used Kaplan-Meier estimates to describe the 45-day mortality of different sex and age groups. We chose 45 days rather than 90 days because most of the short-term deaths seem to have occurred within this time, although modelling results for 45 days and 90 days proved very similar. During periods longer than 90 days, disengagement of mortality associated with the knee operation from that which would normally be expected because of the patient's age becomes difficult—as shown by a hazard rate that increased at later times, which was similar to that we observed in our previous hip study.[2]

We used Cox proportional hazards models to investigate the effects of patient and treatment factors and secular period, on the risk of death within 45 days. Age (grouped as <55, 55–59, 60–64, 65–69, 70–74, 75–79, and ≥80 years) and sex were included in all models. We first separately examined the effects of year of operation, ASA, surgical approach, mechanical and chemical thromboprophylaxis, anaesthetic used, and implant type, each adjusted for age and sex. We tested for interactions between age and sex, mechanical and chemical thromboprophylaxis, and year of operation and implant type. Proportionality of hazards was checked graphically with a series of plots of –ln(-ln(survivor function) *vs* ln(time), initially for age group and sex together (one adjusting for the other) and then for

each of the other variables in turn with adjustment for both sex and age group. We then constructed a series of multivariable models with all the above factors and with further adjustment for comorbidity, BMI, ethnic origin, and social area deprivation.

A high proportion of BMIs was missing, especially in the early phase of NJR, possibly leading to bias in a complete case analysis. We did a series of multiple imputations, assuming that data were missing at random, with the imputation by chained equations procedure (appendix). The imputation models included all predictor variables for the Cox model, together with the outcome variable (Nelson-Aalen estimate and whether or not the patient died) because they had information about missing values of the predictors. We also added other covariates that could help with the imputation model (appendix).

To compare actual mortality with expected mortality, we calculated mortality by age group and sex for every calendar year using national data. For every patient, we calculated the total time at risk within every calendar year (up to a maximum total of 45 days from the primary operation), and calculated expected mortality by multiplying these times at risk by the appropriate rates. These were then summed by year of primary operation (figure 1). Analysis used Stata software (version 11.2, StataCorp LP, TX, USA, 1985–2009).

Role of the funding source

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

Results

During 8 years of follow-up available for the whole cohort, the hazard rate for mortality increased with time from operation (data not shown), with steeper slopes for men and in older age groups. The hazard rate within the first 90 days after the operation (figure 1) suggests a short-term peak risk of death in the perioperative period that subsided by 45 days, which is why we focused on this first period, in which there were 1183 deaths.

45-day mortality increased with age and was higher in men than in women for all age groups (table 1). With adjustment for age and sex, mortality decreased with calendar year of procedure (from 0·37% to 0·20%) with the relative risk reduced by 40% during 8 years (table 2). If we account for the expected population mortality, one can see that the mortality in this cohort is less than expected (healthy selection effect) at all times, but has also shown a progressive reduction in the observed to expected ratio (table 2).

Table 3 shows results of a series of multivariable analyses with the Cox model. First, every variable was assessed in turn, adjusting only for age and sex. No significant interaction was noted between age and sex ($p_{interaction}$=0·47)

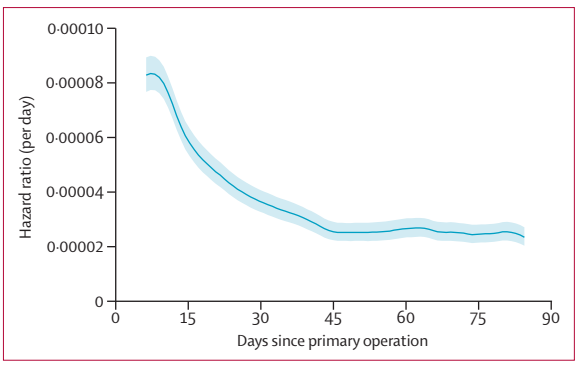

Figure 1: **Smoothed hazard ratio showing change in risk of death changed during first 90 days**
Smoothing calculated from changes in the Nelson-Aalen cumulative hazard estimates and smoothed with band half-width 5; shaded area shows point-wise 95% CI.

	Patients (n)	Deaths (n)	Kaplan-Meier estimate of cumulative % deaths at 45 days (95% CI)
Men			
<55 years	12 575	7	0·06% (0·03–0·12)
55–59 years	17 612	13	0·07% (0·04–0·13)
60–64 years	33 740	34	0·10% (0·07–0·14)
65–69 years	39 028	58	0·15% (0·12–0·19)
70–74 years	40 963	97	0·23% (0·19–0·28)
75–79 years	33 971	148	0·43% (0·37–0·51)
≥80 years	25 045	291	1·15% (1·03–1·29)
Women			
<55 years	17 154	6	0·04% (0·02–0·08)
55–59 years	22 670	10	0·04% (0·02–0·08)
60–64 years	37 557	25	0·07% (0·05–0·10)
65–69 years	45 404	53	0·11% (0·09–0·15)
70–74 years	51 991	78	0·15% (0·12–0·18)
75–79 years	48 645	119	0·24% (0·20–0·28)
≥80 years	41 424	244	0·59% (0·52–0·67)

Table 1: **45-day mortality by age and sex**

For the **mortality risk data from the Office of National Statistics** see http://www.ons.gov.uk/ons/publications/re-reference-tables.html?edition=tcm%3A77-276237

	Operations (n)	Kaplan-Meier estimate of cumulative % deaths at 45 days	Hazard ratio* (95% CI), adjusted for sex and age	Deaths within 45 days (n)	Expected number of deaths†	Actual/expected number of deaths
2003	12 283	0·37%	1 (reference)	46	53·6	0·84
2004	25 141	0·34%	0·96 (0·67–1·37)	88	100·2	0·88
2005	38 309	0·28%	0·78 (0·56–1·11)	108	147·3	0·73
2006	45 503	0·32%	0·89 (0·64–1·24)	146	168·2	0·87
2007	61 563	0·31%	0·89 (0·65–1·23)	194	218·9	0·89
2008	68 899	0·23%	0·67 (0·48–0·93)	161	238·6	0·67
2009	70 789	0·23%	0·65 (0·47–0·90)	160	231·6	0·69
2010	73 109	0·18%	0·53 (0·38–0·73)	134	236·2	0·57
2011	72 183	0·20%	0·60 (0·43–0·83)	146	216·1	0·68

*Cox proportional hazards model. †Calculated from data for mortality risk by age, sex, and year risk from the Office of National Statistics.

Table 2: **Changes in mortality by year of primary operation**

	Separate multivariable analyses (adjusted for sex and age group)*			Multivariable analysis (adjusted for sex and age group)†		Multivariable analysis (adjusted for sex, age group, and comorbidity)‡	
	n	Hazard ratio (95% CI)	p value	Hazard ratio (95% CI)	p value	Hazard ratio (95% CI)	p value
Year of primary operation							
2003–05	75 733	1 (reference)	..	1 (reference)	..	1 (reference)	..
2006–08	175 965	0·92 (0·79–1·07)	0·27	0·91 (0·78–1·07)	0·26	0·89 (0·74–1·07)	0·21
2009–11	216 081	0·67 (0·57–0·79)	<0·0005	0·67 (0·56–0·79)	<0·0005	0·61 (0·50–0·74)	<0·0005
ASA physical status							
P1	68 173	1 (reference)	..	1 (reference)	..	1 (reference)	..
P2	331 888	1·23 (0·99–1·54)	0·068	1·35 (1·07–1·71)	0·012	1·15 (0·88–1·50)	0·31
P3	65 984	2·34 (1·85–2·97)	<0·0005	2·59 (2·02–3·33)	<0·0005	1·40 (1·05–1·87)	0·020
P4/P5	1734	6·93 (4·55–10·56)	<0·0005	7·09 (4·57–11·00)	<0·0005	2·19 (1·31–3·68)	0·003
Approach§							
Lateral parapatella	5567	1·25 (0·77–2·02)	0·36	1·25 (0·77–2·06)	0·37	1·31 (0·76–2·28)	0·33
Medial parapatella	432 666	1 (reference)	..	1 (reference)	..	1 (reference)	..
Midvastus	8242	0·99 (0·64–1·54)	0·96	1·12 (0·72–1·75)	0·61	1·04 (0·62–1·74)	0·88
Subvastus	6590	0·65 (0·36–1·18)	0·16	0·59 (0·32–1·11)	0·10	0·57 (0·28–1·15)	0·12
Other	14 570	0·97 (0·70–1·36)	0·88	0·95 (0·67–1·34)	0·77	1·01 (0·70–1·46)	0·96
Mechanical prophylaxis¶							
No	61 396	1 (reference)	..	1 (reference)	..	1 (reference)	..
Yes	405 072	0·82 (0·70–0·96)	0·014	0·95 (0·80–1·13)	0·57	0·98 (0·81–1·18)	0·80
Chemical prophylaxis¶							
None	61 403	1 (reference)	..	1 (reference)	..	1 (reference)	..
Aspirin(only)	62 355	0·84 (0·67–1·04)	0·11	0·86 (0·68–1·07)	0·18	0·82 (0·63–1·06)	0·14
Heparin (+/–aspirin) only	293 808	0·90 (0·76–1·06)	0·21	0·91 (0·77–1·09)	0·31	0·93 (0·76–1·14)	0·47
Others/other combs	48 902	0·81 (0·64–1·03)	0·091	0·93 (0·72–1·20)	0·58	0·86 (0·64–1·17)	0·34
Anaesthesia type‖							
Spinal only	180 669	1 (reference)	..	1 (reference)	..	1 (reference)	..
General only	100 560	0·98 (0·83–1·15)	0·79	1·02 (0·87–1·20)	0·82	1·01 (0·84–1·22)	0·89
Epidural only	19 319	1·22 (0·93–1·60)	0·14	1·17 (0·90–1·54)	0·24	1·03 (0·76–1·40)	0·84
Nerve block only	6255	1·08 (0·65–1·77)	0·77	1·04 (0·63–1·71)	0·87	1·06 (0·62–1·81)	0·83
Spinal and general	30 999	1·14 (0·90–1·43)	0·28	1·21 (0·96–1·53)	0·11	1·36 (1·05–1·75)	0·019
Spinal and epidural	9446	1·57 (1·14–2·17)	0·006	1·32 (0·95–1·83)	0·096	1·20 (0·85–1·70)	0·31
Spinal and nerve block	29 032	0·94 (0·73–1·21)	0·63	0·96 (0·75–1·24)	0·78	0·95 (0·72–1·26)	0·75
General and epidural	11 105	1·01 (0·69–1·49)	0·96	0·96 (0·65–1·42)	0·83	1·00 (0·65–1·53)	>0·995
General and nerve block	60 854	1·04 (0·86–1·25)	0·68	1·03 (0·85–1·24)	0·75	1·06 (0·86–1·30)	0·61
Other combinations	5275	1·09 (0·64–1·85)	0·76	1·07 (0·63–1·82)	0·81	1·19 (0·69–2·08)	0·53
Knee type**							
Cemented	388 608	1 (reference)	..	1 (reference)	..	1 (reference)	..
Uncemented	26 503	1·11 (0·87–1·40)	0·40	1·03 (0·80–1·33)	0·81	1·14 (0·85–1·53)	0·38
Hybrid	6546	1·02 (0·63–1·65)	0·94	1·03 (0·64–1·66)	0·91	0·84 (0·47–1·53)	0·58
Patello-femoral	5655	0·85 (0·38–1·90)	0·69	0·91 (0·40–2·03)	0·81	1·10 (0·45–2·67)	0·83
Unicondylar	40 428	0·37 (0·25–0·54)	<0·0005	0·37 (0·25–0·56)	<0·0005	0·32 (0·19–0·54)	<0·0005
Myocardial infarction††							
No	353 106	..	..	..	..	1 (reference)	
Yes	10 321	..	..	..	..	3·46 (2·89–4·14)	<0·0005
Congestive heart failure							
No	356 178	..	..	..	..	1 (reference)	
Yes	7249	..	..	..	..	3·41 (2·81–4·14)	<0·0005
Peripheral vascular disease							
No	356 903	..	..	..	..	1 (reference)	
Yes	6524	..	..	..	..	1·19 (0·89–1·58)	0·23

(Table 3 continues on next page)

	Separate multivariable analyses (adjusted for sex and age group)*			Multivariable analysis (adjusted for sex and age group)†		Multivariable analysis (adjusted for sex, age group, and comorbidity)‡	
	n	Hazard ratio (95% CI)	p value	Hazard ratio (95% CI)	p value	Hazard ratio (95% CI)	p value
(Continued from previous page)							
Cerebrovascular disease							
No	356 101	..	..	..	..	1 (reference)	
Yes	7326	..	..	..	..	3·35 (2·70–4·14)	<0·0005
Dementia							
No	362 485	..	..	..	..	1 (reference)	
Yes	942	..	..	..	..	1·39 (0·72–2·69)	0·33
Chronic pulmonary disease							
No	315 710	..	..	..	..	1 (reference)	..
Yes	47 717	..	..	..	..	1·15 (0·96–1·37)	0·12
Connective tissue disease or rheumatic disease							
No	349 008	..	..	..	..	1 (reference)	..
Yes	14 419	..	..	..	..	1·27 (0·95–1·68)	0·11
Peptic ulcer disease							
No	357 732	..	..	..	..	1 (reference)	..
Yes	5695	..	..	..	..	1·17 (0·81–1·69)	0·41
Liver disease							
No	361 230	..	..	..	..	1 (reference)	..
Mild	1834	..	..	..	..	1·49 (0·74–3·00)	0·27
Moderate/severe	363	..	..	..	..	7·20 (3·93–13·21)	<0·0005
Diabetes							
No	321 595	..	..	..	..	1 (reference)	..
Without complications	39 759	..	..	..	..	1·32 (1·10–1·57)	0·002
With complications	2073		..		..	1·46 (0·87–2·46)	0·15
Paraplegia or hemiplegia							
No	361 960	..	..	..	..	1 (reference)	
Yes	1467	..	..	..	..	0·46 (0·23–0·95)	0·037
Renal disease							
No	354 968	..	..	..	..	1 (reference)	
Yes	845	..	..	..	..	2·18 (1·76–2·69)	<0·0005
Cancer							
No	348 657	..	..	..	..	1 (reference)	
Cancer	13 192	..	..	..	..	1·01 (0·76–1·34)	0·97
Metastatic cancer	1578	..	..	..	..	3·01 (1·70–5·33)	<0·0005

ASA=American Society of Anesthesiologists. *Separate multivariable analyses for each of the listed variables in turn, namely year, ASA, approach, mechanical and chemical prophylaxis, anaesthetic and knee type, in each case adjusting only for age and sex (subgroup sizes in left hand column). †Fully-adjusted multivariable analyses for year, ASA, approach, prophylaxis (mechanical and chemical), anaesthetic and knee type, with further adjustment for sex and age group (452 490 cases with complete information; 1127 deaths within 45 days). ‡Multivariable analysis as for † but with further adjustment for 16 comorbidity subgroups (349 905 cases with complete information; 903 deaths within 45 days). §Approach 144 (0·03%) missing; ¶1311 (0·28%) missing; ||14 265 (3·05%) missing. **Unsure for 39 (0·01%). ††No comorbidity for 104 352 either with no Hospital Episode Statistics records or with the primary operation done after Sept 30, 2011.

Table 3: **Cox proportional hazards models of 45-day mortality by variables**

and, after adjustment for age and sex, no significant interaction was noted between mechanic and chemical prophylaxis ($p_{interaction}$=0·43). Compared with cemented TKRs, mortality was lower in unicondylar (p<0·001), but not in uncemented, hybrid, and patellofemoral types. The effect of implant type did not change significantly across the three groups by year ($p_{interaction}$=0·92) and persisted in our fully adjusted multivariate analysis, which adjusted for all the other variables as well as age and sex, and also with further adjustment for the Charlson comorbidities. Both of these sets of analysis are shown in table 3. Of note, HIV was excluded because there were only six cases and none died. Further adjustment for BMI, ethnic origin, and area deprivation did not change the results much (appendix).

Graphical checking did not suggest that hazard rates were substantially non-proportional (curves non-parallel) during this fairly short interval of 45 days. A global test based on Schoenfeld residuals, as

implemented in Stata software (Stata version 11.2, StataCorp LP, Texas, 1985–2009), for the model with age, sex, year, ASA, and implant type was not significant (p=0·38)

Surgical approach, mechanical and chemical thromboprophylaxis, and type of anaesthesia did not affect mortality, except that spinal and general anaesthetic combined was associated with increased mortality compared with spinal alone (table 3). Day of the week when surgery was done was not related to mortality (appendix).

Worse general health measured by the ASA grade and some comorbidities were associated with increased risk of mortality (table 3). Cerebrovascular disease, congestive cardiac failure, and myocardial infarction were associated with a three-fold and severe liver disease with a seven-fold increase in relative risk of death within 45 days of surgery (table 3).

When our model included BMI, we recorded that being overweight at the time of surgery (BMI 26–30 kg/m²) was associated with reduced 45-day mortality (HR 0·69, 95% CI 0·54–0·88, p=0·003) referenced to a normal BMI of 19–25 kg/m² (appendix). The hazard ratio of individuals with a BMI greater than 30 kg/m² was 0·79 (95% CI 0·61–1·01, p=0·06) and for those with BMI less than 19 kg/m² was 1·31 (0·41–4·11, p=0·65). However, data for BMI were either missing from the NJR or the values were deemed out of range (<10 kg/m² or >60 kg/m²) for 266 514 of (57%) 467779 of operations, therefore these results should be interpreted with caution. Our reanalysis with several multiple imputation strategies produced almost identical results to the complete case analysis (appendix). As explained in some detail in our previous publication[2] about mortality after hip replacement, the number of cases recorded in the NJR has risen greatly during the studied period because of increased compliance with uploading data, rather than increased activity (figure 2).

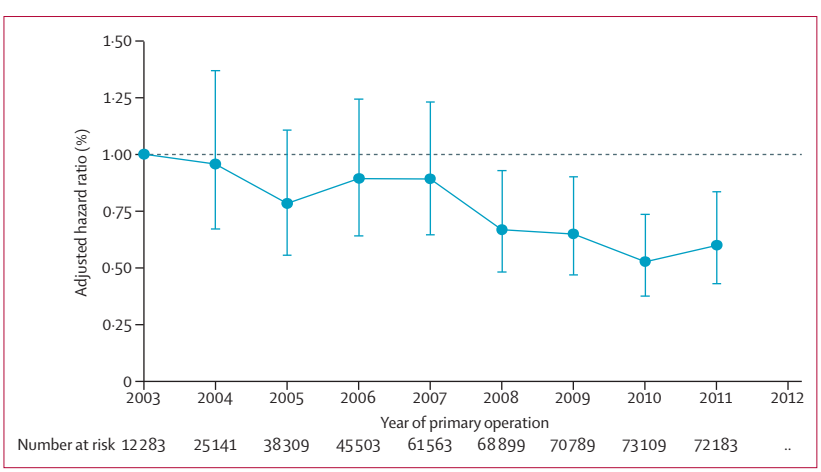

Figure 2: **Changes in 45-day mortality with time**
Hazard ratios with 95% CI for every year of primary after adjustment for sex and age. *Numbers shown underneath the plotted values are the number of primary operations done that year.

Discussion

We have shown a fall in early mortality after total knee replacement undertaken for osteoarthritis in England and Wales between 2003 and 2011 (panel). This result is similar to our findings for hip replacements for osteoarthritis.[2] One possible explanation in the case of hip replacement is the shift to surgical and anaesthetic techniques with reduced risk,[2] but this shift is not the case for knee replacement. We believe that the most likely explanation is that patients coming to surgery are generally fitter and less frail, because evidence shows worldwide trends to increased longevity. However, this evidence does not fully explain the magnitude of the decrease during a fairly short period, because the trends we recorded persisted after adjustment for comorbidity. Patients undergoing knee replacement have lower observed than expected mortality for their age and sex. This difference is most probably due to a so-called healthy-surgery effect whereby high risk patients are excluded from elective surgery.

As would be expected, older people and men are the most likely to die. The increased risk associated with cardiovascular, hepatic, and renal comorbidities argues strongly for routine screening for and careful counselling of patients who have these problems.

Our findings for BMI are much the same for the knee as for the hip—being overweight, but not obese, is associated with a reduced risk of mortality, a finding recorded in other arthroplasty cohorts[26] and in patients with cardiovascular disease.[27] These findings challenge the accepted definition of what constitutes an ideal BMI for these patients. We have recorded a U-shaped relation between mortality and BMI. WHO has defined normal BMI between 19 kg/m² and 25 kg/m². However, we noted that BMI 25–30 kg/m² is associated with the lowest mortality, suggesting that the ideal BMI for our study population, who are old (median age 70 years), European, and have advanced osteoarthritis, might differ from the ideal BMI of the world population as a whole. Some evidence suggests that the apparent so-called protective effect of obesity on mortality is seen in the general population, but has only emerged recently and is seen in a subgroup of older people with comorbidity, as noted in the NHANES-III dataset.[28] This result might show a healthy survivor effect such that obese individuals who survive to older age are less susceptible to the usual causes of premature mortality (cardiometabolic disease). In these cases, increased bodyweight might also be associated with greater muscle mass and perhaps reduced frailty, thereby being more resistant to the acute stresses that follow an operative procedure. However, they might also be because of residual confounding and thus need to be investigated further in other cohorts.

Using the NJR to explore 90-day mortality after hip replacement, we showed that surgical approach, anaesthetic technique, and thromboprophylaxis had important associations with postoperative mortality.

However, we found little evidence that the equivalent variables were associated with mortality after knee replacement once the data were adjusted for age and sex, although we did record an increased hazard ratio for combined spinal and general anaesthetic, which might be a type I error since no increased risk was associated with general anaesthetic. These findings were surprising and presumably relate partly to the fact that knee and hip osteoarthritis are quite different disorders, and that hip and knee replacement are very different operations. This argues for the disease in the two joints to be considered separately, and not, as so often happens in research studies, linked together. Surgical techniques to replace these joints are also quite different—for example, a tourniquet is used during knee replacement, but not during hip replacement, effectively isolating the operative site from the rest of the body. These operative differences could relate to the absence of any apparent effect of thromboprophylaxis on mortality and might account for low frequency of pulmonary embolism and death from pulmonary embolism after knee replacement compared with hip replacement.[27] Despite the fact that NICE[29] concluded that there was "no significant evidence on the effects of thromboprophylaxis on fatal and non fatal PE [pulmonary embolism] in TKR", and that there is no evidence that the use of thromboprophylaxis is of benefit in reducing all cause mortality, the use of thromboprophylaxis is recommended in NICE guidelines. Our data support the view that if there is a substantial risk of TKR causing bleeding, thromboprophylaxis should not be used. Indeed, new anticoagulants are associated with increased risks of bleeding.[29,30]

Lower mortality after UKR than after TKR was perhaps to be expected because UKR is a less invasive operative procedure than is TKR; most of the native knee is preserved and postoperative adverse events are uncommon.[31] Despite the fact that UKR was associated with a substantially reduced mortality, this association is unlikely to have contributed much to the overall decline in early mortality after knee replacement that we recorded; UKR accounted for only 8·6% of knee replacements, and no discernible increase in use of UKR was recorded during the 8 year follow-up.

Many, but not all, patients with osteoarthritis of the knee are suitable for either TKR or UKR. Both the patient and the surgeon need to consider several factors when choosing between them, including the risk of perioperative death, the risk of major complications, the chances of good relief of pain and disability, and survival of the implants. Decreased mortality and complications will obviously be regarded as a major advantage by patients, but they have to weigh up this advantage against the higher rates of revision that are consistently reported for UKR than for TKR.[1] Whether UKR results in better clinical outcomes than does TKR is unclear, with researchers reporting opposing findings.[24,25] The TOPKAT study,[22] which is a continuing multicentre trial comparing UKR with TKR, should elucidate comparative patient-based outcomes.

Aylin and colleagues[23] suggested that operations done at the end of the week increased the risk of mortality. Their analysis combined several procedures, including TKR. Our findings show that day of the week did not affect mortality after TKR for osteoarthritis in the first 45 days.

Panel: Research in context

Systematic review

We searched the Cochrane Library, Medline, and Embase from Jan 1, 1995, to Nov 30, 2013, for studies of total knee arthroplasty and mortality. Our search terms were total knee replacement, unicompartmental arthroplasty, prosthesis, and mortality. We found two systematic reviews,[9,10] eight national registry studies,[11–18] one large regional registry study (>10 000 patients),[19] and two large institutional registry studies (>10 000 patients).[20,21] Five national registry studies[9–11,22,23] were based on the same registry (the Nationwide Inpatient Sample, an all-payer inpatient discharge database from the USA) and so were considered together as Nationwide Inpatient Sample (NIS). One systematic review[24] analysed 80 studies that investigated mortality after hip or knee arthroplasty, and identified only non-significant trends of lower 90-day mortality in women. The NIS studies reported decreasing in-hospital mortality with time, although one[10] showed a slight increase between 2000 and 2004 compared with the earlier time periods, 1990–94, and 1995–99, based on 3 830 420 arthroplasties. Only one national registry study used longer-term mortality, based on the Swedish Knee Arthroplasty Register with up to 28 years' follow-up.[12] This study showed initial reduced mortality in the first 12 postoperative years for patients aged younger than 55 years at the time of their primary knee arthroplasty compared with the general population, but from 12 years onwards, increased mortality compared with the general population. One systematic review[25] analysed 64 studies that investigated outcomes after total joint arthroplasty for osteoarthritis, and identified older age and male sex as predictors of mortality. The remaining registry studies identified older age,[9–11,13,16,17,22,23] male sex,[9–11,13,15,22,23] higher numbers of comorbidities,[9–11,13,16,17,22,23] (with specific comorbidities of cardiovascular disease[9–11,22,23] dementia,[9–11,22,23] renal disease,[9–11,22,23] cerebrovascular disease,[9–11,22,23] and cardiopulmonary disease[17]), and high ASA grade[16] as patient related predictors of mortality. One institutional registry study[17] of 22 540 consecutive total knee arthroplasties identified higher mortality in cemented than in uncemented prostheses. One national registry study[14] of 35 878 total knee arthroplasties showed no difference in mortality with or without the use of epidural anaesthesia. Although all national registry studies were linked to national databases for identification of mortality, only two[9–11,15,22,23] were linked to national databases that allowed accurate study of comorbidities, suggesting potential underlying confounding for any associations seen.

Interpretation

The National Joint Registry of England and Wales has the biggest joint replacement database in the world, allowing us to analyse more than 450 000 primary knee operations between April, 2003, and September, 2011, reducing problems that can arise from selection bias. Linkage to Hospital Episode Statistics (a data warehouse containing details of all admissions to National Health Service hospitals in England with records of clinical information about diagnoses) allowed us to accurately assess comorbidities, and thereby control for confounding. Our findings show that all-cause mortality at 45 days has decreased between 2003 and 2011, echoing the previous findings of a reduction in in-hospital mortality. Similar to other registry studies, we have identified increasing age, male sex, and comorbidities, particularly cardiovascular and liver disease, as predictors of mortality. Furthermore, we identified that unicompartmental knee replacement is associated with decreased mortality. Efforts to further reduce mortality should concentrate more on older patients, those who are male and those with specific comorbidities, such as myocardial infarction, cerebrovascular disease, liver disease, and renal disease.

The strengths of this study include the large size and comprehensive coverage of the NJR, enhancing confidence in the validity and generalisability of the findings. Weaknesses are the facts that observational data cannot prove causality and that all potential confounders could not be accounted for. Confounding by indication remains a possibility, especially for the data on implant type.

Thus, we have shown that 45-day mortality after knee replacement is declining. Male sex, age, and specific comorbidities are strongly associated with increased mortality and efforts to reduce mortality should concentrate on these patients.

Contributors

LPH, YB-S, EMC, PD, AJ, AJM, JHT, and AWB designed the study. LH and KV managed and analysed the data. EMC and AWB reviewed the literature. All authors contributed to data interpretation and preparation of the report.

Declaration of interests

AJ has received consultancy fees from Anthera Pharmaceuticals, Servier, the UK Renal Registry, and Oxford Craniofacial Unit, and received a research grant from Roche. The University of Bristol has a research grant from Stryker. All other authors declare no competing interests.

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