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Hand and Foot Surgery Rates in Rheumatoid Arthritis Have Declined From 1986 to 2011, but Large-Joint Replacement Rates Remain Unchanged

Results From Two UK Inception Cohorts

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Objective. **To assess whether there have been any secular changes in orthopedic interventions in patients with rheumatoid arthritis (RA) since 1986, as examined in 2 early rheumatoid arthritis (RA) inception cohorts with up to 25 years of followup.**

Methods. **The study examined orthopedic data from the UK Early RA Study (1986–1999, 9 centers; n = 1,465) and the UK Early RA Network (2002–2012, 23 centers; n = 1,236) with linkage to national data sets (Hospital Episode Statistics, National Joint Registry, and Office of National Statistics). Clinical and laboratory measures and hand and foot radiographs were standardized and obtained yearly in both cohorts. The use of disease-modifying antirheumatic drugs (DMARDs), corticosteroids, and biologic therapies reflected the contemporary conventional practices and guidelines of the time frames examined. Recruitment years were grouped into 6 periods, and interventions were classified into major, intermediate, and minor categories.**

Results. **A total of 1,602 orthopedic surgical procedures were performed in 770 patients (29%) over a maximum of 25 years of followup. The 25-year cumulative incidence rate of major interventions was 21.7% (range 19.4–24.0%), and that of intermediate interventions was 21.5% (range 17.8–25.5%). There was a decline in the 10-year cumulative incidence of intermediate surgeries over time ($P < 0.001$), but not of major/minor surgery. This decline coincided with a gradual shift from sequential monotherapy to combination DMARD therapies and biologic agents in recent recruitment periods.**

Conclusion. **Orthopedic surgery is an important and common outcome in RA. Only the rates of hand/foot surgery showed a consistent decline from 1986 to 2011. Possible explanations include differences in the pathophysiologic processes affecting the joints, variations in the responses to therapy between large-joint and small-joint destructive processes, and changes in service provision and thresholds for surgery over time.**

Structural damage in the joints of patients with rheumatoid arthritis (RA) and the consequent failure of the joints can vary considerably, depending on the duration and degree of inflammation. Although not often reported, orthopedic surgery in RA, especially in the larger joints, is an important outcome and one of the most costly interventions for patients with RA. It is

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considered to be one of the markers of disease severity (1) and reflects failure of medical treatment (2). There have been important changes in the approaches to treatment in RA, with great emphasis in recent years on earlier initiation of treatment and use of more intensive therapies, including biologic agents, aiming to suppress disease activity (3–5). Therefore, it is of interest to examine whether changes in clinical practice have had an impact on the rates of orthopedic surgery.

Long-term structural damage in RA has been measured traditionally by radiographic assessment of changes in the joints of the hands and feet. Since the large joints are not routinely imaged in RA, orthopedic intervention is considered a surrogate marker for large-joint damage, and yet results are rarely reported, with the published findings being mainly from cross-sectional and population studies. The few reports that have described the results of cohort studies are mainly from Europe (6–9) and the US (2). One cohort study from the UK described orthopedic outcomes in RA, but the study period covered only the first 5 years of disease (10).

The absence of contemporary studies in the UK that have examined structural damage and orthopedic surgical rates over the long term in patients with RA, covering the period prior to and during the era of biologic agents, prompted the undertaking of the present analysis. The primary aim of the study was to examine whether there have been any secular changes in the rates of orthopedic surgery for RA in the UK over time, utilizing data from the Early RA Study (ERAS) and the Early RA Network (ERAN) cohorts. A secondary aim was to examine whether any changes were related to the gradual shift in treatment strategies reflected in the years of recruitment to these 2 studies.

PATIENTS AND METHODS

Patient databases. The ERAS involves a multicenter inception cohort of patients with early RA (<2 years disease duration, no prior disease-modifying antirheumatic drug [DMARD] therapy) recruited between 1986 and 1999 from district general hospitals of 9 regions (rural, urban, and inner city) in England. A total of 1,465 patients were recruited and followed up yearly for up to 25 years (median followup 10 years). Treatments included conventional therapies such as traditional DMARDs, which were used according to local guidelines.

The ERAN involves a similarly designed multicenter inception cohort of patients with early RA (<3 years disease duration, no prior DMARD therapy) formed from collaborations between 23 centers in England, Wales, and Ireland from 2002 to 2012. A total of 1,236 patients were recruited and followed up yearly for up to 10 years (median followup 6 years).

The principal aims of both cohort studies were to evaluate long-term outcomes in patients receiving conventional RA therapies in normal clinical settings, and to develop prognostic factors for clinical, radiologic, and functional outcomes. Entry to both cohorts was based on the clinician's diagnosis. Among all patients included, 70% fulfilled the minimum American College of Rheumatology (ACR) 1987 revised classification criteria for RA (11) at baseline, and 96% fulfilled the ACR criteria by the last visit. Patients who were subsequently reclassified as non-RA were excluded from the study.

Both the ERAS and the ERAN recorded information on clinical, laboratory, and functional features at baseline and at 3, 6, and 12 months for the first year of inclusion in the cohort, and then once yearly, on standardized forms. These measures included the swollen and tender joint counts, the Health Assessment Questionnaire (HAQ) score, the erythrocyte sedimentation rate (ESR), and the hemoglobin (Hgb) level, as previously described (12). Baseline measures included duration of RA symptoms and positivity for rheumatoid factor (RF).

Details of all orthopedic interventions undertaken included the date and type of surgery (e.g., dynamic hip screw or excision arthroplasty). The median time from symptom onset to first rheumatology outpatient visit was 6 months in both cohorts, and the time to initiation of the first DMARD was 2 months in the ERAS and 1 month in the ERAN. Disease activity was calculated according to the original 3-variable algorithm of the Disease Activity Score (DAS) (13,14) in the ERAS, and the more recent 4-variable DAS in 28 joints (DAS28) (15–17) in the ERAN. A transformation formula was used to make the DAS and DAS28 comparable (18). Outcomes included function, work disability, comorbidity, and mortality (19).

Treatment profiles. All centers followed the framework of the published UK guidelines for management of RA, which includes the provision of therapy services, appropriate orthopedic interventions, and appropriate symptom-relieving and disease-suppressing drugs. In the ERAS, this included mainly the sequential use of DMARDs, with steroids and other symptom-relieving measures utilized. Step-up and combination therapies were initially reserved for more severe RA only, but gradually became more common (20). In the ERAN, the use of combination DMARD therapies and biologic agents was more frequent and occurred earlier in the disease process, consistent with contemporary UK guidelines (21). The choice of DMARD was based on the clinician's preference, with dosing schedules utilizing regimens graduated to maximum doses, according to the standard practice for each drug. Biologic drugs were available from 2002 onward, in accordance with the UK National Institute for Health and Clinical Excellence (NICE) guidelines. The main biologic drugs used were tumor necrosis factor α (TNFα) inhibitors, namely adalimumab, etanercept, and infliximab.

Orthopedic data. *Clinical data sets.* Data from the ERAS and ERAN were collected yearly by interview and from case notes on all in-patient and day-case episodes, which included dates of and reason for admission as text descriptions. The ERAS also included the reason for orthopedic surgery (RA, osteoarthritis [OA], or fracture), orthopedic wait times, whether the surgery occurred in the National Health Service (NHS) or in an independent hospital, duration of hospital

stay, and any postoperative complications, as previously described (10).

Hospital Episode Statistics (HES). The HES data set provided information on all NHS inpatient and outpatient orthopedic interventions in all NHS hospitals in England. This also included information on private patients treated in NHS hospitals. Each HES record represents 1 complete hospital episode and contains information on the type of orthopedic intervention, the start and end date for each episode, and site. The site and nature of the interventions were coded according to the Office of Population Censuses and Surveys. A total of 2,048 patients (83%) from the cohorts were matched to the HES data set from 1997 onward, using NHS identification numbers.

National Joint Registry (NJR). Established in 2002, the NJR contains information on hip, knee, and ankle joint replacement surgery across both the NHS and the independent healthcare sector. Since the HES does not include the latter, ERAS and ERAN participants were matched to the NJR using NHS identification numbers, which provided dates and types of joint replacement surgery from 2003 onward (coded from text descriptions) and details of primary diagnosis (RA, OA, or fracture).

Analysis of clinical and national data sets and surgical categories. One complete data set containing information from all 4 databases was created. Two rheumatologists (EN and AY) and two trained research assistants performed highly detailed cross-checking to remove all duplicate episodes from the 4 data sources.

Validation of the ERAS data was sought by comparing episodes with the HES where these overlapped, i.e., after 1997. There was an 89% match in coding in these patients (n = 198). Differences were minor, and in the presence of mismatches, details were cross-checked with paper records. Combining the clinical data with the national data sets allowed for the creation of more accurate and complete followup, as even patients lost to followup in the ERAS and ERAN were tracked from the Office of National Statistics linked to the HES.

Orthopedic interventions were categorized based on joint type and procedure, as previously described (10). The categories were as follows: 1) major intervention, representing mainly primary or secondary large-joint replacement surgery; 2) intermediate intervention, representing mainly wrist, hand, and hindfoot/forefoot joint reconstructive procedures (excision arthroplasty, synovectomy, arthrodesis); and 3) minor intervention, representing mainly soft-tissue procedures (e.g., carpal tunnel decompression and tendon surgery), but not including joint injections.

The ERAS/ERAN databases hold the dates of the first rheumatology consultation, the dates of start and cessation of DMARDs, and the reasons for DMARD discontinuation, but not details on the dosage (initial or any changes) of DMARDs or steroids. The regimens used are known to vary between centers and with time, but the data do not allow us to define "intensive" therapies based on escalation of actual drug dosages, with or without steroids, and over what period of time, but only the cumulative number of drugs.

For these reasons, the two cohorts were split into 6 recruitment periods (1986–1989, 1990–1991, 1992–1994, 1995–2001, 2002–2005, and 2006–2011), based on the numbers of patients adequate for analysis. The time span of 1995–2001 includes the period of limited recruitment, during the time when the ERAS wound down and before the ERAN commenced in 2002. The changing treatment strategies during the study period reflected a gradual shift from monotherapy to sequential monotherapy to step-up (or add-on) to combination DMARD therapy (20). The principal aim of splitting the data into recruitment periods was to allow comparisons to be made between the gradually evolving phases of changing trends in therapies over the study years, and to investigate the possible impact of this on the nature and incidence of orthopedic intervention.

Statistical analysis. Summary statistics were used to outline differences in demographic and baseline clinical and laboratory data. Significant differences between recruitment periods were investigated using linear regression and chi-square analyses, where appropriate. The 5-year and 10-year cumulative incidence rates were then calculated using the methods described by Gooley et al (22). Uninformative censoring has been shown to overestimate the incidence rates. Death was included as a competing risk in order to increase the accuracy of surgery incidence rates. Time at risk for all patients was defined as the time from study entry to time to first orthopedic event or death. Patients who did not experience any event were censored after 10 years from study entry or at the end of 2011. To investigate whether different recruitment periods had an effect on the rates of minor, intermediate, and major surgery (including total hip replacement and total knee replacement individually), a competing-risk proportional hazards model was constructed. The 5-year and 10-year cumulative incidence rates were calculated for each recruitment period, with the earliest recruitment period (1986–1989) used as the referent category. The model was adjusted for age, sex, and DAS at baseline.

RESULTS

Baseline demographic and clinical features of the study subjects by recruitment period. From a total of 2,701 patients recruited into the clinical cohorts, 67% were female, the mean ± SD age was 56 ± 14 years, and 62% were RF positive. The median length of followup was 9 years (interquartile range 13 years). The age at diagnosis increased significantly from first to last recruitment period, with older patients recruited in the last 10 years. The DAS and ESR decreased, the Hgb level increased, and the HAQ score remained similar from baseline to followup across the treatment periods (Table 1). The proportion of patients initially treated with monotherapy and sequential monotherapy significantly decreased over the recruitment periods ($P < 0.001$), whereas the proportion of patients receiving DMARD add-on therapy significantly increased ($P = 0.019$), as did the proportion of patients receiving triple DMARD combination or DMARD with anti-TNF therapy ($P < 0.001$). Methotrexate was increasingly used as the first-line DMARD (1% of patients in 1986–1989 versus 70% of patients in 2006–2011).

Table 1. Demographic features and baseline disease characteristics of the study subjects across recruitment periods*

	1986–1989 (n = 293)	1990–1991 (n = 389)	1992–1994 (n = 578)	1995–2001 (n = 207)	2002–2005 (n = 569)	2006–2011 (n = 665)	*P*
Age, mean ± SD years	54.5 ± 14.7	54.9 ± 14.3	55.2 ± 14.4	57.3 ± 15.5	55.8 ± 14.1	58.1 ± 14.3	<0.001
Female, no. (%)	209 (71.3)	253 (65)	372 (64.4)	140 (67.6)	390 (68.5)	448 (67.4)	0.339
Followup, median (IQR) years	23 (11)	21 (9)	18 (7)	15 (6)	8 (1)	5 (3)	<0.001
RF positive, no. (%)	199 (68.2)	221 (57.1)	344 (60.1)	150 (72.5)	302 (60.5)	334 (60.6)	0.001
DAS, mean ± SD	4.9 ± 1.4	5.2 ± 1.2	5.0 ± 1.8	4.8 ± 1.4	4.6 ± 1.5	4.5 ± 1.6	<0.001
HAQ score >1, no. (%)	127 (43.6)	204 (52.7)	303 (52.5)	92 (44.4)	292 (52.3)	289 (46.2)	0.014
Low Hgb, no. (%)	131 (44.9)	141 (38)	221 (38.4)	66 (32.2)	122 (21.4)	172 (26.2)	<0.001
Treatment, no. (%)							
Monotherapy	158 (58.7)	155 (45.3)	235 (46.3)	89 (49.4)	186 (44.1)	104 (38.8)	<0.001
Sequential DMARD	35 (13)	53 (15.5)	95 (18.7)	24 (13.3)	61 (14.5)	22 (8.2)	<0.001
DMARD add-on	27 (10)	48 (14)	75 (14.8)	29 (16.1)	95 (22.5)	48 (17.9)	0.019
2-combination DMARDs†	7 (2.6)	10 (2.9)	12 (2.4)	7 (3.9)	22 (5.2)	13 (4.9)	0.444
3-combination DMARDs‡	0 (0)	0 (0)	0 (0)	0 (0)	6 (1.4)	22 (8.2)	<0.001
DMARDs + anti-TNF	0 (0)	0 (0)	0 (0)	0 (0)	33 (7.8)	52 (9.4)	<0.001

* Data were obtained from the Early Rheumatoid Arthritis (RA) Study and the Early RA Network data sets; missing data were excluded. Treatments refer to those drugs that were being administered by 3 years of followup. The Disease Activity Score (DAS) was assessed as follows: score <2.6 = remission, 2.6–3.2 = mild, 3.21–5.1 = moderate, and >5.1 = severe disease. The Health Assessment Questionnaire (HAQ) score ranged from 0 to 3, where 0–1 = mild-to-moderate disability, 1–2 = moderate-to-severe disability, and 2–3 = severe-to–very severe disability. The normal ranges for the hemoglobin (Hgb) level are 13–17 gm/dl in men and 12–16 gm/dl in women; low Hgb levels were defined as <13 gm/dl in men and <12 gm/dl in women. IQR = interquartile range; RF = rheumatoid factor; anti-TNF = anti–tumor necrosis factor α.
† The 2-combination regimen of disease-modifying antirheumatic drugs (DMARDs) comprised 2 DMARDs at the outset.
‡ The 3-combination regimen of DMARDs comprised standard triple-DMARD therapy with methotrexate, sulfasalazine, and hydroxychloroquine.

Figure 1 shows the cumulative rates of the therapies used during the first 3 years of followup, in comparison with the more recent treatment periods. This illustrates the gradual shift to more intensive treatment approaches in more recent recruitment periods, with an increasing use of DMARD add-on therapy, combination therapy with 2 or 3 DMARDs at the start of treatment, and anti-TNF drugs in the 2 most recent recruitment periods. A trend toward less use of monotherapy is also demonstrated.

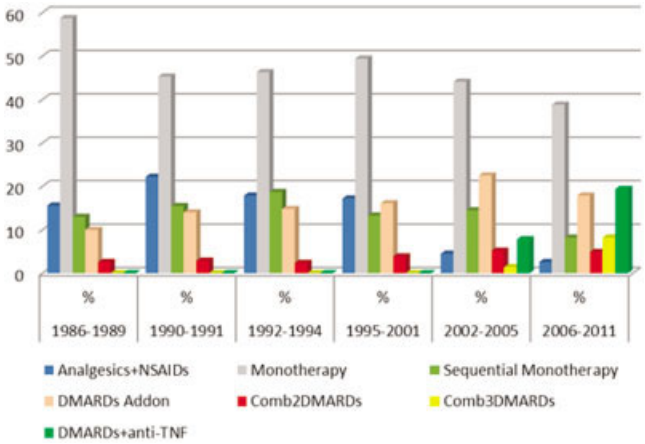

Figure 1. Cumulative rates of therapy over the first 3 years of followup in each of the 6 recruitment periods. NSAIDs = nonsteroidal antiinflammatory drugs; Comb2DMARDs = combination of 2 disease-modifying antirhematic drugs (DMARDs) at outset; Comb3DMARDs = standard triple-DMARD therapy with methotrexate, sulfasalazine, and hydroxychloroquine; anti-TNF = anti–tumor necrosis factor α.

Orthopedic surgery episodes. A total of 1,602 procedures were undertaken in 770 patients (29% of all patients) over 25 years. The 25-year cumulative incidence rate of major interventions was 21.7% (95% CI 19.4–24.0%) and that of intermediate interventions was 21.5% (95% CI 17.8–25.5%). The 10-year cumulative incidence rate was 11.7% (95% CI 10.4–13.4%) for major interventions and 8.3% (95% CI 7.1–9.7%) for intermediate interventions (Table 2).

Table 3 shows the different types of orthopedic interventions undertaken over the 25-year study period. Thirty-five percent of all procedures were total joint replacements (46% of all patients underwent total knee replacement and 36% underwent total hip replacement), 24% were intermediate procedures (43% of all patients underwent hand/wrist surgery and 46% underwent foot/ankle surgery), and 33% were minor surgeries. Large-joint surgery for fracture, e.g., the dynamic hip screw procedure, accounted for 4% of all procedures, and cervical spine surgery accounted for 0.6% of all procedures. For the purposes of the current analysis, all large-joint replacement surgeries, internal fixation of fracture of the femoral neck, and atlantoaxial or subaxial arthrodesis were included as major interventions.

Cumulative incidence. The results from the competing-risk proportional hazards model indicated that there was a significant decline in the 10-year

Table 2. Cumulative incidence of different types of orthopedic interventions across the recruitment periods*

Type of intervention	1986–1989	1990–1991	1992–1994	1995–2001	2002–2005	2006–2011
5-year cumulative incidence						
Minor intervention	6.3	4.6	7.0	7.8	7.0	4.8
Intermediate intervention	6.3	4.8	2.4†	3.4	2.2†	3.3†
Major intervention	6.4	4.0	5.7	5.3	5.3	4.6
10-year cumulative incidence						
Minor intervention	12.1	12.0	13.7	10.0	10.4	–
Intermediate intervention	14.4	10.0	7.5†	6.7†	4.1†	–
Major intervention	11.9	14.4	11.5	10.7	11.9	–

* The cumulative incidence rates are expressed as percentages.
† $P < 0.05$ versus 1986–1989.

cumulative incidence of intermediate interventions. The 10-year cumulative incidence rate was significantly higher among patients recruited in the earliest period, 1986–1989, whose cumulative incidence rate of intermediate orthopedic surgery was 14.4%, when compared to those recruited in 1992–1994 (cumulative incidence rate 7.5%), 1995–2001 (cumulative incidence rate 6.7%), and 2002–2005 (cumulative incidence rate 4.1%) ($P < 0.05$ for all comparisons), as shown in Table 2. A similar decline in intermediate interventions was observed over 5 years, with a significant difference in the 5-year cumulative incidence rate between the 1986–1989 recruitment period (cumulative incidence rate 6.3%) and the recruitment periods of 1992–1994 (cumulative incidence rate 2.4%), 2002–2005 (cumulative incidence rate 2.2%), and 2006–2011 (cumulative incidence rate 3.3%) ($P < 0.05$ for all comparisons). No significant difference between recruitment periods was identified for the cumulative incidence of minor or major orthopedic surgeries. Figure 2 demonstrates the trends in cumula-

Table 3. Type and number of orthopedic interventions

Procedure category, intervention	No. of procedures	% within category
Major intervention (n = 642 procedures)		
Total joint replacement		
Shoulder/elbow	57	10.1
Hip	221	39.3
Knee	277	49.4
Unknown site	7	1.2
Total joint replacement for fracture		
Hip, total	13	18.3
Hip, dynamic screw procedure	57	80.3
Knee	1	1.4
Cervical spine		
Atlantoaxial/subaxial fusion	9	100
Intermediate intervention (n = 383 procedures)		
Medium/small joint		
Shoulder/elbow	22	5.7
Hip/knee	21	5.5
Wrist/hand	158	41.3
Wrist, for fracture	5	1.3
Hind/forefoot	169	44.1
Hind/forefoot, for fracture	8	2.1
Minor intervention (n = 527 procedures)		
Soft-tissue surgery	527	100

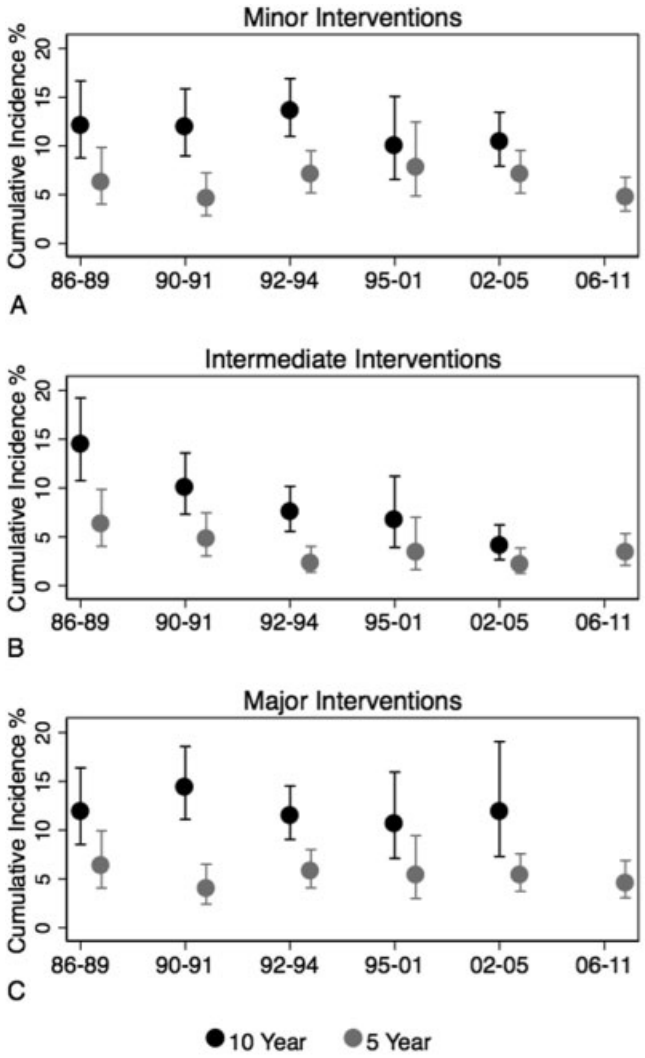

Figure 2. The 5- and 10-year cumulative incidence of minor **(A)**, intermediate **(B)**, and major **(C)** interventions by recruitment period. Bars show the cumulative incidence as a percentage and the 95% confidence intervals.

tive incidence rates (along with 95% confidence intervals) across the treatment periods.

DISCUSSION

This is the first UK study to describe the types and incidence of orthopedic interventions in RA patients over a 25-year followup period, covering major changes in treatment practices in the UK, including mainly sequential monotherapy initially, through to early and more intensive combination DMARDs and the biologics era. The baseline demographic features and disease characteristics of the 2 cohorts are typical of early RA cohorts, representative of the "classic" early RA population. There were 2 main findings from this study. First, a high proportion of patients required either major orthopedic surgery (large-joint replacements in 35%) or intermediate-type procedures (hand/wrist/forefoot surgery in 24%). Second, there was a significant decline in the cumulative incidence of the intermediate surgery over time ($P < 0.001$), but not in the cumulative incidence of major surgery.

Results of this study are supported by the findings from previous studies (23–26). A study by Boonen et al (24) showed no significant difference in the proportion of patients undergoing major joint surgery ("joint-sacrificing" surgery) in 2 cohorts (pre- and post-1997). In a retrospective, incidence case review study in Finland, the age-standardized incidence rate ratio of total joint replacement increased almost 10-fold for the knee and 2-fold for the hip in patients without RA, but was virtually unchanged in patients with RA. A recent retrospective study involving medical record review (23) did not reveal any significant decline in the cumulative incidence of primary joint arthroplasty from an early cohort (1988–1994) to a later cohort (1995–2007) (15.2% versus 10.3%; $P = 0.36$). Most studies have shown that total joint replacement is more commonly performed than intermediate-type surgery (2,27).

There are a number of possible explanations for the differences in intervention rates seen for the large and small joints, including reduced thresholds for large-joint surgery, different pathophysiologic processes affecting the large and small joints, and variations in therapeutic responses. Orthopedic procedures are thought to be influenced by both small and large regional variations, differences in demographics, and the supply of "health professionals" (2). Published rates of orthopedic surgery for RA vary greatly between countries, regardless of whether the healthcare system is different or similar (28). However, the cumulative incidence rates of large-joint orthopedic surgery that were sustained throughout our study suggest that surgery will continue to be a major outcome of the disease and a marker of treatment failure for the foreseeable future (29). Population aging and the consequent increased prevalence of OA could be one of the main reasons for the substantial increase overall in knee and hip total joint replacements that has occurred since the early 1980s (30,31). However, the rate of total joint replacement among patients with RA has either decreased in recent years (29,32–35) or, as in our study, remained stable (23,26).

NHS reforms in the UK and government targets that were introduced in 2007 to improve patient waiting times and treatments have provided British patients greater and faster access to hospital services, including orthopedic surgery (Department of Health Report, 2011–2012; available at http://www.official-documents.gov.uk). Furthermore, the attitudes of both doctors and patients toward surgery have been enhanced by major advances in orthopedic surgical and anesthetic techniques, implants, and postoperative care, as well as the increased availability of orthopedic surgeons, which lowers the thresholds for surgery.

It has been postulated that 2 separate pathophysiologic processes result in joint failure in RA, one being mainly joint space reduction, the other being bony erosions and destruction (36), which may explain the weak link between clinical synovitis and erosions in individual joints (37,38). These variations could be extended to explain the differences between large- and small-joint pathology, and the different responses to drug therapies. The unchanged incidence of major interventions with time could be explained, at least in part, by the preexistence of unrelated OA, which is further supported by the increase in age at disease presentation with time.

Although it is possible that the declines in hand/foot surgery rates could be attributed to the presentation of a milder form of RA in hospitals in more recent years, it is more likely attributable to the more intensive treatments used. These are reflected in the recruitment periods shown in this study, and include biologic agents, which became available from 2002 onward and, therefore, were available to patients in the early years of disease in the more recent recruitment periods.

Therapeutic decisions have become increasingly more target-driven, and achievement of a low DAS is now a realistic outcome. Radiologic progression of RA in the hands/feet is a commonly used clinical outcome measure in the UK, and is used to support clinical findings and to guide treatment decisions. However, detecting synovitis in the shoulder/hip is less easy than in

the hands/feet and, therefore, the shoulders and hips are not as routinely imaged, raising the possibility of suboptimal therapy if the disease process mainly affects the large joints and if there is earlier joint destruction. The concept that intermediate intervention reflects more precisely the RA disease process and/or its treatment is an attractive one, and lack of change in the rate of major interventions in comparison with the rate of intermediate interventions serves to highlight this point. It is important to note that as the designs of these cohorts did not include randomized treatments, it is not possible to imply causal effects. Nonetheless, the secular decline seen in the rate of intermediate surgery coincided with the introduction of more effective first-line DMARD therapies and drug combinations.

The observation of a better clinical status in more recent years is similar to that noted in a European study in which the investigators examined two cross-sectional cohorts of consecutive patients receiving standard care for RA (125 patients between 1984 and 1986 [the 1985 cohort] and 150 patients between 1999 and 2001 [the 2000 cohort]) (39), with improvement in the clinical status seen in the 2000 cohort compared to the 1985 cohort. This was based both on measures of disease activity (the ESR, Hgb levels, DAS in 28 joints, and HAQ score) and on measures of damage (Larsen radiographic score). Differences were associated with aggressive second-line therapy and appeared to antedate the introduction of biologic agents, similar to what was observed in our study.

The results of this study are not directly comparable to the UK national data, because population rates are provided as annual incidence by year of surgery, whereas data from inception cohorts, including this one, provide cumulative incidence rates. In addition, national reports focus on the 2 major types of large-joint replacements, total hip replacements and total knee replacements, and the data on primary diagnosis are not reliable. In an examination of UK HES data, Dixon and colleagues (31) found that the incidence of total hip replacements and total knee replacements (primary and revisions) increased between 1991 and 2000. These findings are supported in a study by Culliford et al (40), in which they examined the General Practice Research Database and demonstrated that the rates of total hip replacements and total knee replacements had increased significantly ($P < 0.0001$ for both) during a 16-year period (1991–2006) and was greater for total knee replacements, especially in the last 5 years. It is important to note that UK national data on the rates of orthopedic surgery primarily are a reflection of the degenerative pathology of RA necessitating orthopedic surgery. The unchanged rates of total hip replacement and total knee replacement surgery in RA patients shown in the present study as well as the increasing rates of total joint replacements observed in the general population are consistent with the findings of other European investigators (27), and these findings could indirectly be a reflection of the impact of improved RA treatments, although this remains speculative.

Direct comparisons between this study and other longitudinal studies are made difficult by differences both in the methods used (few are genuine inception cohorts) and in the clinical practices, which may vary by geography, as described above. Moreover, the case definition with regard to what is considered to be "RA-related" joint surgery may vary. Secondary pathophysiologic processes, including degenerative changes as seen in OA or other diseases, may be the main factor leading to orthopedic intervention (9). However, distinguishing between the separate pathophysiologic processes that affect the joints and the predominance of one over another can be challenging. An attempt was made by the ERAS clinicians to distinguish between degenerative and inflammatory processes leading to joint surgery, and a separate analysis by this group, in which OA was excluded, made no difference to the overall results. For this reason, the general approach utilized in other studies has been adopted in the present study, whereby any surgery performed post–RA diagnosis has been treated as being related to RA.

Selection bias is unlikely to have been a factor in either the ERAS or the ERAN, as recruitment was directly originated from primary care physicians, who refer most RA patients to secondary care, and these patients represent a typical mix of rural and urban populations. All patients were seen at the early stages of RA and prior to use of second-line treatments.

The "real life" setting of the ERAS and the ERAN, the high followup rates provided by the HES, and the long followup period covering major changes in both medical and surgical treatment practices in the UK are among the strongest advantages of this study. Furthermore, the matching with the national data sets allowed the capturing of information from both the NHS and the private healthcare sector. Estimates from national data show that 1 of 5 total hip replacements and total knee replacements in England are undertaken in the private sector (41). No other studies on surgery for RA in the UK have included both sectors.

Thus, the results of the present study suggest that the observed reduction in the rates of intermediate surgery of the hands and feet could either be the result of the earlier and more intensive treatments used,

consistent with changes in the standard practices of the time, or could be attributable to the fact that the RA patients presenting to the hospital had a milder form of the disease, or both. Failure to see the same trend in major joint surgery could be explained by differences in the pathophysiologic processes affecting the large and small joints, uncontrolled synovitis in the large joints (not easily detected clinically), variations in the responses to therapy between the large-joint and small-joint destructive processes, and finally, changes in service provision and thresholds for different types of orthopedic surgery over time. Early control of disease has been shown to improve RA outcomes, and we have performed a separate detailed analysis of the baseline and first-year variables in this cohort as predictors of orthopedic outcomes, to be submitted for publication this year. The results of the current study highlight the fact that orthopedic surgery remains a common end point in patients with RA. Further followup in these cohorts could provide important information on the value of biologic agents in relation to orthopedic surgery rates. Improving treatments that can reduce the risk of subsequent surgery continues to have substantial potential to reduce both the personal and economic burden of chronic RA.

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All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Young had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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