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ORIGINAL ARTICLE

Cemented or Uncemented Hemiarthroplasty for Intracapsular Hip Fracture

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ABSTRACT

BACKGROUND

Controversy exists over the use of bone cement in hip fractures treated with hemiarthroplasty. Only limited data on quality of life after cemented as compared with modern uncemented hemiarthroplasties are available.

METHODS

We conducted a multicenter, randomized, controlled trial comparing cemented with uncemented hemiarthroplasty in patients 60 years of age or older with an intracapsular hip fracture. The primary outcome was health-related quality of life measured with the use of utility scores on the EuroQol Group 5-Dimension (EQ-5D) questionnaire at 4 months after randomization (range of scores, -0.594 to 1 , with higher scores indicating better quality of life; range for minimal clinically important difference, 0.050 to 0.075).

RESULTS

A total of 610 patients were assigned to undergo cemented hemiarthroplasty and 615 to undergo modern uncemented hemiarthroplasty; follow-up data were available for 71.6% of the patients at 4 months. The mean EQ-5D utility score was 0.371 in patients assigned to the cemented group and 0.315 in those assigned to the uncemented group (adjusted difference, 0.055; 95% confidence interval [CI], 0.009 to 0.101; $P=0.02$). The between-group difference at 1 month was similar to that at 4 months, but the difference at 12 months was smaller than that at 4 months. Mortality at 12 months was 23.9% in the cemented group and 27.8% in the uncemented group (odds ratio for death, 0.80; 95% CI, 0.62 to 1.05). Periprosthetic fractures occurred in 0.5% and 2.1% of the patients in the respective groups (odds ratio [uncemented vs. cemented], 4.37; 95% CI, 1.19 to 24.00). The incidences of other complications were similar in the two groups.

CONCLUSIONS

Among patients 60 years of age or older with an intracapsular hip fracture, cemented hemiarthroplasty resulted in a modestly but significantly better quality of life and a lower risk of periprosthetic fracture than uncemented hemiarthroplasty. (Funded by the National Institute for Health Research; WHiTE 5 ISRCTN number, ISRCTN18393176.)

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 A Quick Take
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HIP FRACTURE IN OLDER PEOPLE IS A global problem that impairs health-related quality of life¹ and places a substantial socioeconomic burden on health care systems.² Globally, the incidence of hip fractures is projected to reach 6.26 million per year by 2050.³

Approximately half of hip fractures occur at the neck of the femur, and the majority of these fractures are treated with a partial hip replacement in which the head of the femur is replaced with a metal implant (hemiarthroplasty).⁴ There is controversy about how best to fix the hemiarthroplasty implant to the bone of the femur. If the implant is not securely bonded to the patient's bone, it can loosen, causing pain and restricting activities of daily living. A meta-analysis of randomized, controlled trials showed that implants fixed with bone cement were associated with less postoperative pain and better mobility than the first generation of "press-fit" uncemented implants (e.g., Austin Moore prosthesis).⁵ However, injection of bone cement during surgery has been associated with a drop in patients' blood pressure and, in rare cases, cardiovascular collapse and death.⁶

More recent uncemented implants have been designed to provide better integration with the bone.⁷ Proponents of these newer hydroxyapatite-coated uncemented implants suggest that they provide reliable fixation, which promotes early return to normal activities, while avoiding the potential risks of using bone cement. We conducted the World Hip Trauma Evaluation (WHiTE) 5 trial to compare health-related quality of life in adults 60 years of age or older with a displaced intracapsular hip fracture who were randomly assigned to undergo either cemented hemiarthroplasty or modern uncemented hemiarthroplasty.

METHODS

TRIAL DESIGN AND OVERSIGHT

WHiTE 5 was a multicenter, randomized, controlled superiority trial. The protocol has been published previously⁸ and is available with the full text of this article at NEJM.org. The trial was conducted as an initial feasibility phase in 4 centers followed by a main phase in 14 centers. Recruiting centers took part in the WHiTE cohort study,⁹ which involves patients with a hip fracture admitted to participating centers and

provides a framework for identifying participants for embedded randomized trials.

The trial was coordinated by the University of Oxford, United Kingdom. A steering committee and independent data and safety monitoring committee oversaw trial conduct and patient safety. The Wales Research Ethics Committee 5 approved the trial.

PATIENTS

Patients 60 years of age or older with a displaced intracapsular hip fracture whose planned treatment was a hemiarthroplasty were eligible to enter the trial. Patients who were unable to provide consent owing to a lack of capacity were included under a process of consultee agreement in accordance with the Mental Capacity Act in England and Wales.¹⁰

TRIAL PROCEDURES

After consent had been obtained, Web-based randomization software managed by the University of Oxford was used to assign patients in a 1:1 ratio to undergo either cemented hemiarthroplasty (cemented group) or modern hydroxyapatite-coated uncemented hemiarthroplasty (uncemented group). The randomization sequence was generated with the use of variable block sizes, stratified according to center. Patients were unaware of the trial-group assignments. Operating surgeons had to be aware of the trial-group assignments but were not involved in patient follow-up or assessment.

Preoperative investigations, perioperative antibiotic treatment, the choice between regional and general anesthetic technique, analgesia, and venous thromboembolic prophylaxis were guided by local policy. The surgical steps of canal preparation, implant trialing, cementation (where applicable), and insertion of the definitive implant were inherent to the trial-group assignments, but the surgical approach and method of wound closure were left to the discretion of the operating surgeon. In the postoperative period, patients in both groups underwent assessments for physiotherapy or occupational therapy aimed at mobilization on the day of or day after surgery.

OUTCOMES

Outcome data were obtained through telephone interviews with the patient (or, for those lacking capacity, the main caregiver) and from routine

medical records. The primary outcome was death-adjusted health-related quality of life (with death imputed as a score of 0 on the EuroQol Group 5-Dimension [EQ-5D] questionnaire) measured with the use of the EQ-5D utility score¹¹ at 4 months after randomization (range of scores, -0.594 to 1, with higher scores indicating better quality of life).

The EQ-5D questionnaire is a validated, patient-rated instrument comprising a visual analogue scale (VAS) that measures health from 0 (worst imaginable state of health) to 100 (best imaginable state of health) and a health-status instrument that consists of a five-level response from “no problems” to “unable” for five domains related to daily activities: mobility, self-care, usual activities, pain or discomfort, and anxiety or depression.¹¹ The EQ-5D score has been shown to be responsive to changes in health-related quality of life, including when reported by proxy for persons with cognitive impairment.^{12,13} The minimal clinically important difference (MCID) in the EQ-5D utility score is estimated to be between 0.050 and 0.075.¹⁴ The responses on the EuroQol 5-Dimension 5-Level (EQ-5D-5L) instrument for each of the five domains of health were converted into a single utility score with the use of the Crosswalk Index Value Calculator of the 3-Level (3L) instrument and its established time trade-off utility algorithm for the U.K. population.¹⁵

Secondary outcomes were health-related quality of life (EQ-5D utility score) at 1 month and 12 months; mortality at 12 months; complications; mobility status at 1 month, 4 months, and 12 months on an ordinal scale from “freely mobile without aids” to “no functional mobility (using lower limbs)”; and residential status at hospital discharge on an ordinal scale from “own home or sheltered housing” to “acute care hospital.” We also performed a prespecified analysis of the EQ-5D-5L domain scores, EQ-5D VAS scores, and EQ-5D scores without adjustment for death (i.e., with EQ-5D scores excluded rather than set to 0 for those who died). Cost effectiveness is being analyzed separately.

STATISTICAL ANALYSIS

A minimum sample of 1128 patients was selected to detect a between-group difference in the EQ-5D utility score (primary outcome measure) of 0.075 at 4 months with 90% power, a type I error rate

of 5% (significance level), and the assumption of 40% loss to follow-up.⁸ High loss to follow-up was anticipated owing to the fact that the patients represent a frail, older population with multiple coexisting conditions and care needs who may have difficulty completing patient-reported questionnaires. Patients' baseline characteristics and outcome data were summarized with the use of means and standard deviations for symmetrically distributed continuous (i.e., approximately normally distributed) variables, as medians and interquartile ranges for nonsymmetrically distributed continuous variables, and as frequencies and percentages for binary and categorical variables.

We performed an initial analysis testing for differences between the trial groups using linear regression analysis. In addition to this unadjusted analysis, we performed regression analyses to adjust for age and sex without inclusion of the baseline EQ-5D utility score. Inclusion of the baseline EQ-5D utility score in the model was found to reduce the data available for analysis, owing to missingness of the baseline EQ-5D utility score; therefore, as prespecified in the statistical analysis plan, it was not included in the model.⁸ (The statistical analysis plan is available with the protocol at NEJM.org.) The primary analysis was therefore a mixed-effects model of the death-adjusted EQ-5D utility score at 4 months (i.e., with death imputed as a score of 0),¹⁶ with adjustment for age and sex, with recruiting center as a random effect and treatment included in the model on an intention-to-treat (as randomly assigned) basis. In addition, a per-protocol analysis was undertaken, in which patients who did not receive their assigned intervention were excluded to assess the effect of the actual treatment (cemented or uncemented) that was received. Analysis of EQ-5D utility scores at 1 month and 12 months was performed with the use of the strategy defined above for the primary analysis.

A longitudinal mixed-effects model was also fitted to the totality of EQ-5D data (from 1 month, 4 months, and 12 months), with the same fixed-effects structure as the primary model (i.e., with adjustment for age and sex) but with a three-level random-effects structure in which observations (time points) were nested within patients and patients were nested within recruitment centers. In the protocol, we refer to this model

as the area-under-the-curve analysis,⁸ which provides an estimate of the average treatment effect throughout the follow-up period. To test the sensitivity of the main analysis to missing data, data were imputed in the R package mice (Multivariate Imputation by Chained Equations)¹⁷ with the use of predictive mean matching (using 100 imputations with age, sex, recruitment center, baseline EQ-5D utility score and EQ-5D VAS score, alcohol consumption, status with respect to diabetes, smoking status, status with respect to chronic renal failure, residential status, and treatment as predictors), to provide pooled estimates (using Rubin's rules) of treatment effects.

Dichotomous secondary outcome variables (e.g., complications) were analyzed with the use of a mixed-effects logistic-regression analysis. Time-to-event analysis (Kaplan–Meier) was used to assess the risk of death, and Cox proportional-hazards regression was used to test for differences in mortality between the trial groups after adjustment for age and sex. Odds ratios for mobility outcomes were estimated with the use of proportional-odds (cumulative) logistic-regression models.

Treatment effects were summarized with the use of 95% confidence intervals. A two-sided P value of less than 0.05 for the primary outcome was considered to indicate statistical significance. The statistical analysis plan did not include a provision for correcting for multiplicity when tests were conducted for secondary outcomes. Because the widths of the confidence intervals have not been adjusted for multiplicity, these intervals should not be used to infer definitive treatment effects for secondary outcomes. Analyses were conducted with the use of the R software packages lme4 and lmerTest.^{18–20}

RESULTS

PATIENTS

From March 2017 through December 2019, a total of 1225 patients were randomly assigned to undergo either cemented hemiarthroplasty (610 patients) or modern uncemented hemiarthroplasty (615 patients). Final follow-up was completed in January 2021 (Fig. 1). Baseline demographic data were similar in the two trial groups (Table 1). The number of patients who enrolled at each trial center and details regarding the use of bone-protection medication, venous thromboprophylaxis, physiotherapy, and discharge destination are provided in Tables S1 through S4 in the Supplementary Appendix, available at NEJM.org.

ADHERENCE TO ASSIGNED INTERVENTION

A total of 91.1% of the patients received their assigned intervention (Fig. 1); 50 patients (8.2%) assigned to the cemented group underwent uncemented hemiarthroplasty, and 43 patients (7.0%) assigned to the uncemented group underwent cemented hemiarthroplasty. Seven patients received treatments not described in the protocol, and 9 patients did not undergo surgery because they died.

PRIMARY OUTCOME

Primary outcome data (EQ-5D utility score at 4 months) were available for 877 of 1225 patients (71.6%). The primary adjusted intention-to-treat analysis of health-related quality of life showed higher utility scores in the cemented group than in the uncemented group at 4 months after randomization, with a mean difference of 0.055 (95% confidence interval [CI], 0.009 to 0.101; P=0.02) (Table 2). Results of a per-protocol analysis were similar (Table S5).

There was no evidence that the patients who did not provide EQ-5D data at 4 months (348 patients [28.4%]) differed materially in their baseline characteristics (e.g., age, sex, and EQ-5D utility score) from those who did provide such data (Table S6). An analysis that used multiple imputation for missing data yielded results similar to those of the primary analysis (mean difference in the EQ-5D utility score at 4 months, 0.041 [95% CI, 0.003 to 0.079], favoring cemented hemiarthroplasty).

SECONDARY OUTCOMES

EQ-5D data were available for 927 of 1225 patients (75.7%) at 1 month and 876 of 1225 patients (71.5%) at 12 months after randomization. The between-group difference in mean scores from the mixed-effects regression analysis was 0.049 (95% CI, 0.009 to 0.089; favoring cemented hemiarthroplasty) at 1 month and 0.034 (95% CI, -0.012 to 0.079) at 12 months. Estimated differences for the per-protocol analysis are shown in Table S5. The unadjusted analysis yielded similar results (Table S7). A breakdown of the EQ-5D-5L domain scores, EQ-5D VAS scores, and EQ-5D scores without adjustment for

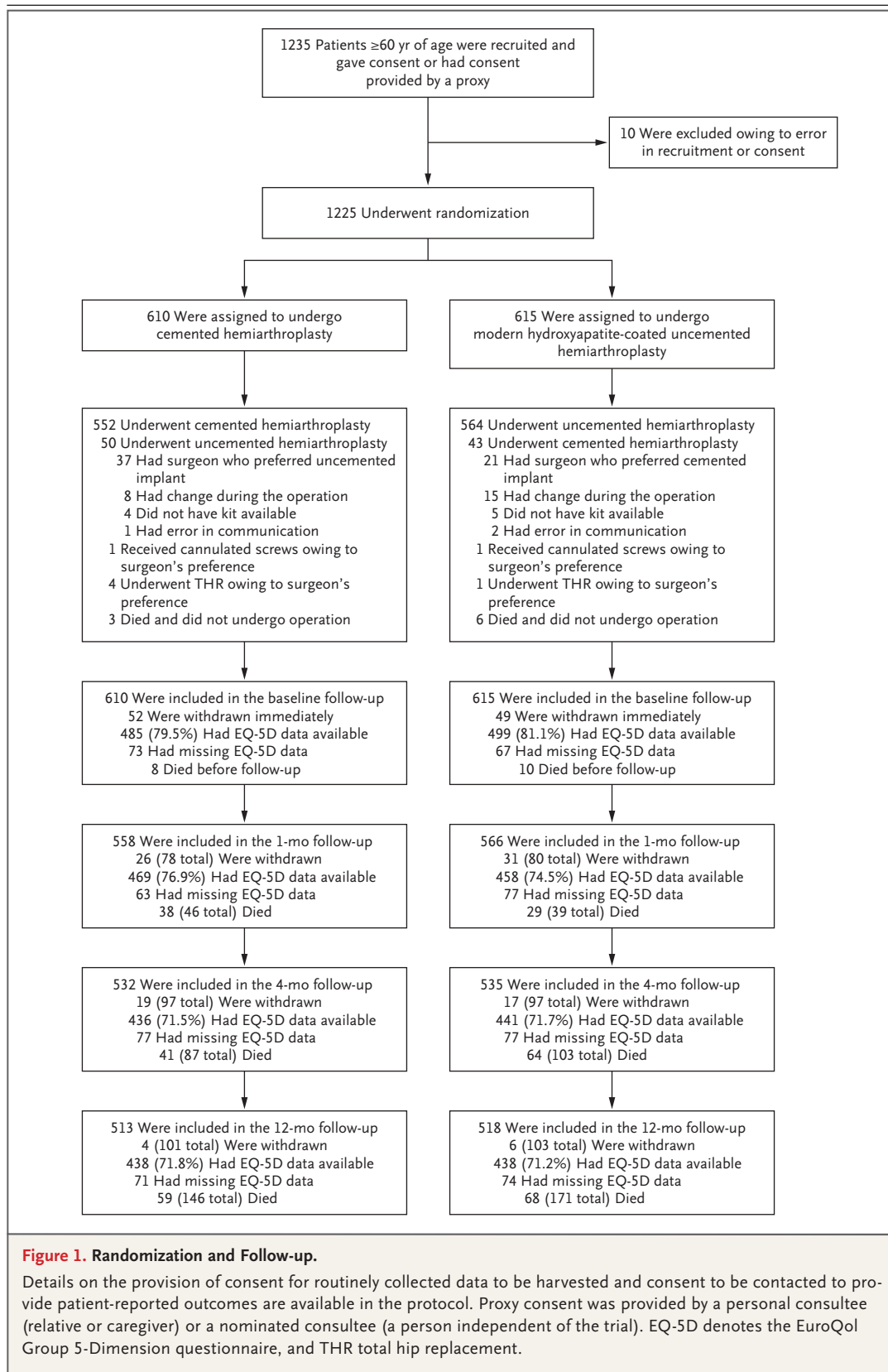


Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Cemented Hemiarthroplasty (N=610)	Uncemented Hemiarthroplasty (N=615)
Age — yr	84.5±7.6	84.3±7.4
EQ-5D utility score†	0.58±0.29	0.56±0.30
EQ-5D VAS score‡	61.6±21.0	62.5±21.4
Proxy consent — no. (%)§	324 (53.1)	337 (54.8)
Female sex — no. (%)	421 (69.0)	411 (66.8)
Current smoker — no. (%)	50 (8.2)	38 (6.2)
Chronic renal failure — no. (%)	52 (8.5)	53 (8.6)
Diabetes — no. (%)	100 (16.4)	95 (15.4)
Alcohol consumption — no. (%)¶		
0–7 units/wk	494 (81.0)	515 (83.7)
8–14 units/wk	28 (4.6)	22 (3.6)
15–21 units/wk	10 (1.6)	9 (1.5)
>21 units/wk	13 (2.1)	9 (1.5)
Missing data	65 (10.7)	60 (9.8)
Residential status before injury — no. (%)		
Own home or sheltered housing	425 (69.7)	400 (65.0)
Residential care	67 (11.0)	79 (12.8)
Nursing care	58 (9.5)	62 (10.1)
Acute care hospital	12 (2.0)	16 (2.6)
Rehabilitation unit	1 (0.2)	8 (1.3)
Other	3 (0.5)	4 (0.7)
Missing data	44 (7.2)	46 (7.5)

* Plus-minus values are means ±SD. Percentages may not total 100 because of rounding.

† Utility scores on the EuroQol Group 5-Dimension (EQ-5D) questionnaire range from -0.594 to 1, with higher scores indicating better quality of life. Data were available for 485 patients in the cemented group and 499 patients in the uncemented group. Scores were reported by a proxy for 286 of 485 patients (59.0%) in the cemented group and 311 of 499 patients (62.3%) in the uncemented group.

‡ Scores on the visual analogue scale (VAS) of the EQ-5D questionnaire range from 0 to 100, with higher scores indicating better quality of life. Data were available for 466 patients in the cemented group and 484 patients in the uncemented group.

§ Proxy consent was provided by a personal consultee (relative or caregiver) or a nominated consultee (a person independent of the trial).

¶ One unit equals 10 ml or 8 g of pure alcohol.

death is also provided in Tables S7 and S8 and Figure S1.

Death occurred in 146 of 610 patients (23.9%) in the cemented group and in 171 of 615 patients (27.8%) in the uncemented group at 12 months (odds ratio, 0.80; 95% CI, 0.62 to 1.05). The survival analysis yielded a hazard ratio of

0.83 (95% CI, 0.67 to 1.04) (Fig. 2). Results of the per-protocol analysis are shown in Table S9.

Periprosthetic fractures occurred more commonly in the uncemented group (2.1%) than in the cemented group (0.5%) (odds ratio [uncemented vs. cemented], 4.37; 95% CI, 1.19 to 24.00). Other complications and revision surgery were uncommon and balanced between the trial groups (Table 3 and the Results section in the Supplementary Appendix).

Mobility assessments are shown in Table S10. There was no material between-group difference in the percentage of patients returning to their own home after hospital discharge. Of those patients admitted from their own home, 298 of 425 (70.1%) in the cemented group and 279 of 400 (69.8%) in the uncemented group were discharged back to their own home (Tables S2 and S11).

DISCUSSION

In adults 60 years of age or older with an intra-capsular hip fracture, cemented hemiarthroplasty resulted in a modestly but significantly better health-related quality of life at 4 months after randomization than uncemented hemiarthroplasty. The mean between-group difference in the EQ-5D utility score (0.055) is within the range reported for the MCID (0.050 to 0.075) and is similar to the loss of utility that has been associated with asthma (0.05) and acute myocardial infarction (0.06).²¹ These observations suggest that the difference may be clinically important for patients, although a slightly smaller estimate was suggested in an analysis that used multiple imputation to account for missing data. The results of mobility assessments at 1 month, but not later, were consistent with the results for health-related quality of life, favoring cemented hemiarthroplasty.

Periprosthetic fractures were more common in the uncemented group than in the cemented group (2.1% vs. 0.5%). However, the overall incidence was lower than that reported in other randomized, controlled trials of modern uncemented implants, which have shown incidences of 5.5 to 15%.²²⁻²⁶ The reason for this lower incidence is unclear and could represent increasing experience with modern uncemented techniques among surgeons.

This trial is larger than previous studies that

Table 2. Results from Mixed-Effects Regression Analysis of EQ-5D Utility Scores (Intention-to-Treat Population).*

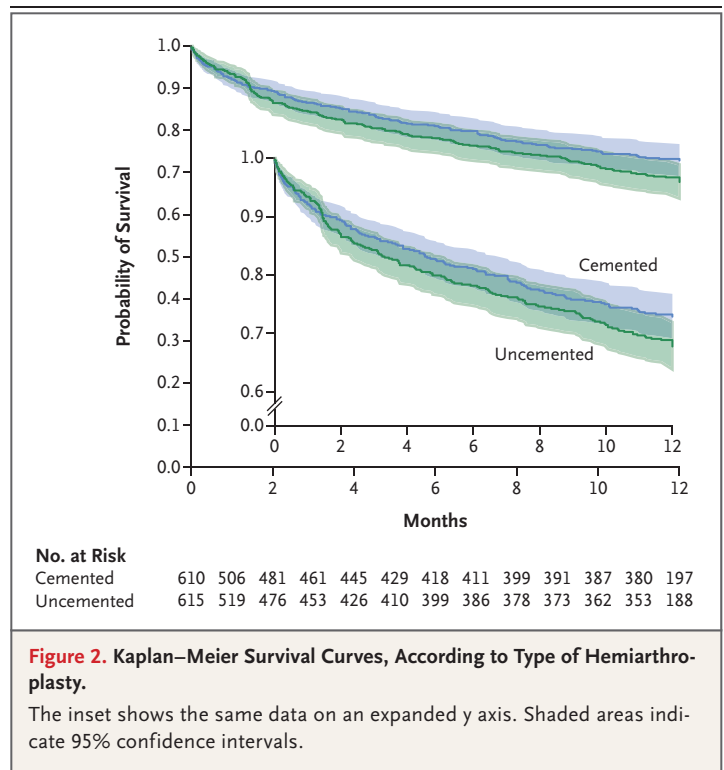
Outcome	Cemented Hemiarthroplasty		Uncemented Hemiarthroplasty		Difference (95% CI)†	P Value
	No. of Patients	Mean Score	No. of Patients	Mean Score		
Primary analysis: EQ-5D utility score at 4 mo	436	0.371±0.356	441	0.315±0.342	0.055 (0.009 to 0.101)	0.02
Baseline-adjusted analysis: EQ-5D utility score at 4 mo	397	0.395±0.354	403	0.332±0.343	0.047 (0.006 to 0.089)	—
EQ-5D utility score at 1 mo	469	0.344±0.324	458	0.293±0.305	0.049 (0.009 to 0.089)	—
EQ-5D utility score at 12 mo	438	0.329±0.349	438	0.293±0.343	0.034 (−0.012 to 0.079)	—
Area-under-the-curve analysis: EQ-5D utility score‡	495	0.348±0.305	500	0.300±0.292	0.045 (0.020 to 0.071)	—

* Plus-minus values are means ±SD. The EQ-5D utility score at 4 months was reported by a proxy for 167 of 436 patients (38.3%) in the cemented group and 175 of 441 patients (39.7%) in the uncemented group.

† Between-group differences were obtained from a mixed-effects model, with recruiting center as a random effect and with adjustment for age and sex and where explicitly stated also adjusted for the baseline EQ-5D utility score. The widths of the confidence intervals for secondary outcomes have not been adjusted for multiplicity and cannot be used to infer treatment effects.

‡ Shown are the results of a longitudinal mixed-effects model of the average treatment effect across assessments at 1 month, 4 months, and 12 months, with adjustment for age and sex. Patients included in the analysis provided one or more EQ-5D utility scores during follow-up, with means and standard deviations estimated from weighted measures based on the number of EQ-5D utility scores available for each patient.

have addressed this research question and provides more information on quality-of-life outcomes, which are considered important to patients and caregivers.^{27,28} Three smaller randomized, controlled trials^{22,24,25} and one registry study²⁹ that compared these procedures have yielded inconsistent findings with respect to quality of life. One trial that involved 220 patients 70 years of age or older showed little difference between groups in EQ-5D scores at 3 months and 12 months,²⁴ whereas two other trials showed significantly better quality-of-life scores with cemented hemiarthroplasty than with uncemented hemiarthroplasty. One of these trials, involving 141 ambulatory and cognitively intact patients, showed higher EQ-5D index scores at 4 months and 12 months in favor of cemented hemiarthroplasty²²; the other trial (201 patients)²⁵ showed higher 12-Item Short-Form Health Survey physical component scores (indicating better function) at 6 and 12 weeks after surgery in the cemented group than in the uncemented group. Data from the Norwegian Hip Fracture Register (30,178 patients) showed no significant difference in EQ-5D-3L scores at 1 year after surgery between patients who underwent cemented hemiarthroplasty and those who underwent uncemented hemiarthroplasty.²⁹ The inclusion of patients with cognitive impairment in the current trial is an important strength because this large



subgroup is often excluded from research.³⁰ The cohort in which this trial was nested has been shown to be representative of the national population of adults with hip fracture (Table S12),³¹

Table 3. Complications Reported during 12 Months of Follow-up.

Complication	Cemented Hemiarthroplasty (N=610)	Uncemented Hemiarthroplasty (N=615)	Odds Ratio, Uncemented vs. Cemented (95% CI)*
	number (percent)		
Routinely reported complications			
Dislocation	5 (0.8)	5 (0.8)	—
Neurologic injury	3 (0.5)	1 (0.2)	—
Vascular injury	1 (0.2)	0	—
Tendon injury	0	2 (0.3)	—
Deep-vein thrombosis	8 (1.3)	6 (1.0)	0.74 (0.21–2.45)
Erythema	30 (4.9)	20 (3.3)	0.65 (0.35–1.20)
Dehiscence	6 (1.0)	4 (0.7)	0.66 (0.14–2.80)
Other	92 (15.1)	102 (16.6)	1.12 (0.81–1.54)
Any	129 (21.1)	130 (21.1)	1.00 (0.75–1.33)
Additional complications			
Wound infection	13 (2.1)	8 (1.3)	0.61 (0.22–1.59)
Venous thromboembolism	1 (0.2)	2 (0.3)	—
Pneumonia	2 (0.3)	1 (0.2)	—
Urinary tract infection	39 (6.4)	52 (8.5)	1.35 (0.86–2.14)
Stroke	6 (1.0)	5 (0.8)	0.83 (0.20–3.26)
Myocardial infarction	4 (0.7)	4 (0.7)	0.99 (0.18–5.35)
Blood transfusion	31 (5.1)	31 (5.0)	0.99 (0.58–1.71)
Chest infection	41 (6.7)	40 (6.5)	0.97 (0.60–1.56)
Acute kidney injury	28 (4.6)	22 (3.6)	0.77 (0.42–1.42)
Pulmonary embolism	5 (0.8)	2 (0.3)	—
Periprosthetic fracture	3 (0.5)	13 (2.1)	4.37 (1.19–24.00)
Failure of fixation	1 (0.2)	1 (0.2)	—
Additional hip surgery	10 (1.6)	12 (2.0)	1.19 (0.47–3.11)
Other	4 (0.7)	7 (1.1)	1.74 (0.44–8.16)

* Odds ratios were calculated with Fisher's exact test. The widths of the confidence intervals have not been adjusted for multiplicity and cannot be used to infer treatment effects.

although no data were available on race or ethnic group. The outcomes measured are part of the core outcome set for hip fracture,³² a consensus-derived set of outcomes that are important to patients, caregivers, and health care professionals.¹²

This trial has some limitations. The rate of attrition and missing baseline data in this older and often frail patient group was high (28.5% in the cemented group and 28.3% in the uncemented group at 4 months), although it was lower than the 40% loss to follow-up used in the sample-size calculation.⁸ The high frequency of missing data probably reflects the realities of

accessing data from the frailest subgroup of patients with hip fracture and cognitive impairment and without consultees, such as next of kin or main caregivers, and may introduce an attrition bias toward a slightly fitter sample. The inclusion of patients with cognitive impairment means that more data within the trial were reported by proxy rather than being obtained directly from the patients. However, including information to inform the care of this subgroup of patients is important, because approximately 40% of all patients with hip fracture have some degree of cognitive impairment on admission to

a hospital. Crossovers occurred in both trial groups, with similar frequency; these were predominantly explained by surgeon preference or surgical factors identified during the operation (8.2% in the cemented group and 7.0% in the uncemented group). Per-protocol analyses generally supported the intention-to-treat analyses but are subject to bias because they do not reflect the randomized patient groups.

Meta-analyses of studies of the first generation of uncemented implants showed outcomes that were inferior to those obtained with cemented implants, in particular with respect to postoperative pain (attributed to the lack of surface coating of early uncemented designs).⁵ Modern hydroxyapatite-coated uncemented hemiarthroplasty provides better integration with the patients' bone, and meta-analyses have shown similar rates of death (although higher rates of periprosthetic fracture) as compared with contemporary cemented hemiarthroplasty.^{7,33} How-

ever, these meta-analyses focused on mortality and surgical complications and not on quality of life.

We found that cemented hemiarthroplasty resulted in modestly but significantly better quality of life and a lower risk of periprosthetic fracture than uncemented hemiarthroplasty among patients 60 years of age or older with a displaced intracapsular hip fracture.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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REFERENCES

- Griffin XL, Parsons N, Achten J, Fernandez M, Costa ML. Recovery of health-related quality of life in a United Kingdom hip fracture population: the Warwick Hip Trauma Evaluation — a prospective cohort study. *Bone Joint J* 2015;97-B:372-82.
- Johnell O, Kanis JA. An estimate of the worldwide prevalence, mortality and disability associated with hip fracture. *Osteoporos Int* 2004;15:897-902.
- Cooper C, Campion G, Melton LJ III. Hip fractures in the elderly: a world-wide projection. *Osteoporos Int* 1992;2:285-9.
- The HEALTH Investigators. Total hip arthroplasty or hemiarthroplasty for hip fracture. *N Engl J Med* 2019;381:2199-208.
- Parker MJ, Gurusamy KS, Azegami S. Arthroplasties (with and without bone cement) for proximal femoral fractures in adults. *Cochrane Database Syst Rev* 2010;6:CD001706.
- Donaldson AJ, Thomson HE, Harper NJ, Kenny NW. Bone cement implantation syndrome. *Br J Anaesth* 2009;102:12-22.
- Nantha Kumar N, Kunutsor SK, Fernandez MA, et al. Effectiveness and safety of cemented and uncemented hemiarthroplasty in the treatment of intracapsular hip fractures. *Bone Joint J* 2020;102-B:1113-21.
- Fernandez MA, Achten J, Lerner RG, et al. Randomised controlled trial comparing hydroxyapatite coated uncemented hemiarthroplasty with cemented hemiarthroplasty for the treatment of displaced intracapsular hip fractures: a protocol for the WHITE 5 study. *BMJ Open* 2019;9(12):e033957.
- Costa ML, Griffin XL, Achten J, et al. World Hip Trauma Evaluation (WHiTE): framework for embedded comprehensive cohort studies. *BMJ Open* 2016;6(10):e011679.
- Mental Capacity Act. 2005 (<http://www.legislation.gov.uk/ukpga/2005/9/contents>).
- Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Qual Life Res* 2011;20:1727-36.
- Parsons N, Griffin XL, Achten J, Costa ML. Outcome assessment after hip fracture: is EQ-5D the answer? *Bone Joint Res* 2014;3:69-75.
- Bryan S, Hardyman W, Bentham P, Buckley A, Laight A. Proxy completion of EQ-5D in patients with dementia. *Qual Life Res* 2005;14:107-18.
- Walters SJ, Brazier JE. Comparison of the minimally important difference for two health state utility measures: EQ-5D and SF-6D. *Qual Life Res* 2005;14:1523-32.
- van Hout B, Janssen MF, Feng Y-S, et al. Interim scoring for the EQ-5D-5L: mapping the EQ-5D-5L to EQ-5D-3L value sets. *Value Health* 2012;15:708-15.
- Parsons N, Griffin XL, Achten J, Chesser TJ, Lamb SE, Costa ML. Modelling and estimation of health-related quality of life after hip fracture: a re-analysis of data from a prospective cohort study. *Bone Joint Res* 2018;7:1-5.
- van Buuren S, Groothuis-Oudshoorn K. mice: Multivariate Imputation by Chained Equations in R. *J Stat Software* 2011;45(3):1-67 (<https://www.jstatsoft.org/article/view/v045i03>).
- The R Project for Statistical Computing (<https://www.R-project.org/>).
- Bates D, Mächler M, Bolker B, Walker S. Fitting linear mixed-effects models using lme4. *J Stat Software* 2015;67(1):1-48 (<https://www.jstatsoft.org/article/view/v067i01>).
- Kuznetsova A, Brockhoff PB, Christensen RHB. lmerTest package: tests in linear mixed effects models. *J Stat Software* 2017;82(13):1-26 (<https://www.jstatsoft.org/article/view/v082i13>).
- Sullivan PW, Slejko JF, Sculpher MJ, Ghushchyan V. Catalogue of EQ-5D scores for the United Kingdom. *Med Decis Making* 2011;31:800-4.
- Inngul C, Blomfeldt R, Ponzer S, Enocson A. Cemented versus uncemented arthroplasty in patients with a displaced fracture of the femoral neck: a randomised controlled trial. *Bone Joint J* 2015;97-B:1475-80.
- Taylor F, Wright M, Zhu M. Hemiarthroplasty of the hip with and without cement: a randomized clinical trial. *J Bone Joint Surg Am* 2012;94:577-83.
- Figved W, Opland V, Erihagen F, Jervidalo T, Madsen JE, Nordsetten L. Cemented versus uncemented hemiarthroplasty for displaced femoral neck fractures. *Clin Orthop Relat Res* 2009;467:2426-35.
- Moerman S, Mathijssen NMC, Niesten DD, et al. More complications in uncemented compared to cemented hemiarthroplasty for displaced femoral neck

fractures: a randomized controlled trial of 201 patients, with one year follow-up. *BMC Musculoskelet Disord* 2017;18:169.

26. Parker MJ, Cawley S. Cemented or uncemented hemiarthroplasty for displaced intracapsular fractures of the hip: a randomized trial of 400 patients. *Bone Joint J* 2020;102-B:11-6.

27. Griffiths F, Mason V, Boardman F, et al. Evaluating recovery following hip fracture: a qualitative interview study of what is important to patients. *BMJ Open* 2015;5(1):e005406.

28. Tutton E, Saletti-Cuesta L, Langstaff D, Wright J, Grant R, Willett K. Patient

and informal carer experience of hip fracture: a qualitative study using interviews and observation in acute orthopaedic trauma. *BMJ Open* 2021;11(2):e042040.

29. Kristensen TB, Dybvik E, Kristoffersen M, et al. Cemented or uncemented hemiarthroplasty for femoral neck fracture? Data from the Norwegian Hip Fracture Register. *Clin Orthop Relat Res* 2020; 478:90-100.

30. Hebert-Davies J, Laflamme G-Y, Rouleau D, HEALTH and FAITH investigators. Bias towards dementia: are hip fracture trials excluding too many patients? A systematic review. *Injury* 2012;43:1978-84.

31. Metcalfe D, Costa ML, Parsons NR, et al. Validation of a prospective cohort study of older adults with hip fractures. *Bone Joint J* 2019;101-B:708-14.

32. Haywood KL, Griffin XL, Achten J, Costa ML. Developing a core outcome set for hip fracture trials. *Bone Joint J* 2014; 96-B:1016-23.

33. Veldman HD, Heyligers IC, Grimm B, Boymans TAEJ. Cemented versus cementless hemiarthroplasty for a displaced fracture of the femoral neck: a systematic review and meta-analysis of current generation hip stems. *Bone Joint J* 2017;99-B:421-31.

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