A Trial of Fracture Fixation in the Operative Management of Hip Fractures

Fixation using Alternative Implants for the Treatment of Hip fractures (F.A.I.T.H) Investigators*

*The Writing Committee members are as follows:

Mohit Bhandari (Chair), PJ Devereaux, Gordon Guyatt, Lehana Thabane, Stephen Walter, Martin J. Heetveld, Kyle J. Jeray, Susan Liew, Emil H. Schemitsch, Paul Tornetta III, Gregory J. Della Rocca, Richard E. Buckley, Robert McCormack, Todd M. Oliver, Michiel J.M. Segers, Amar Rangan, Martin Richardson, Sheila Sprague, Taryn Scott, Julie Agel, Alisha Garibaldi, Qi Zhou, Diane Heels-Ansdell, Helena Viveiros, Stephanie M. Zielinski, Esther M.M. Van Lieshout, Herman Johal, Birgit C. Hanusch, and Marc Swiontkowski.

The author affiliations are as follows:

Division of Orthopaedic Surgery, Department of Surgery (M.B. MD, S.S. PhD, H.J. MD), Department of Clinical Epidemiology and Biostatistics (M.B. MD, P.J.D MD, A.G. MSc, G.G. MD, D.H.A. MSc, T.S. MSW, S.S PhD, L.T. PhD, H.V. BSc, S.W. PhD, Q.Z. PhD), Medicine (P.J.D. MD, G.G. MD), Population Health Research Institute (P.J.D. MD), McMaster University, Hamilton, ON, Department of Surgery (M.J.H. MD), Spaarne Gasthuis, Haarlem, The Netherlands, Department of Surgery (S.M.Z. MD, E.M.M.V.L. PhD), Erasmus MC, University Medical Center Rotterdam, Rotterdam, The Netherlands, Department of Orthopaedic Surgery (K.J.J. MD), Greenville Health System, Greenville, SC, Department of Orthopaedic Surgery (S.L. MBBS), The Alfred, Melbourne, VIC, Australia, Department of Surgery (E.H.S. MD), University of Western Ontario, London, ON, Department of Orthopaedic Surgery (P.T.III MD), Boston University School of Medicine, Boston, MA, Department of Orthopaedic Surgery (G.J.D.R. MD), Duke University, Durham, NC, Division of Orthopaedic Trauma Surgery (R.E.B. MD), Foothills Medical Centre, Calgary, AB, Department of Orthopaedic Surgery (R.M. MD), University of British Columbia, Vancouver, BC, Boone Hospital Center (T.M.O. MD), Columbia Orthopaedic Group, Columbia, MO, Department of Surgery (M.J.M.S. MD), St. Antonius Ziekenhuis, Utrecht, The Netherlands, Department of Orthopaedic Surgery (A.R. ChM, B.C.H. MRCS), The James Cook University Hospital, Middlesbrough, UK, Department of Surgery (M.R. FRACS), University of Melbourne, Melbourne, VIC, Australia, Department of Orthopaedic Surgery (J.A. MA, M.S. MD), University of Minnesota, Minneapolis, MN

Correspondence to:

Dr. Mohit Bhandari
Division of Orthopaedic Surgery, McMaster University
293 Wellington Street N. Suite 110,
Hamilton Ontario, Canada, L8L 8E7
bhandam@mcmaster.ca

ABSTRACT

Background

High rates of re-operations after initial hip fracture fixation, the associated morbidity, mortality, and costs motivated the Fixation using Alternative Implants for the Treatment of Hip fractures (FAITH) randomised controlled trial.

Methods

We randomised 1,079 patients with a low-energy femoral neck fracture fracture requiring fracture fixation in 81 centres to a single large diameter screw with a side-plate (sliding hip screw) or the current standard, multiple small diameter cancellous screws (Clinical Trials Identification Number: NCT01908751). The primary outcome was hip re-operation within 24 months. Health-related quality of life (HRQL) was measured by the SF-12, EQ-5D, and WOMAC score.

Findings

Re-operations did not convincingly differ by type of surgical fixation: 107 of 542 patients (19·7%) in the sliding hip screw group and 117 of 537 patients (21·8%) in the cancellous screws group (hazard ratio, 0·83; 95% CI, 0·63 to 1·09; p=0·18). Avascular necrosis was more common in the sliding hip screw group than in the cancellous screws group (50 patients [9·2%] vs. 28 patients [5·2%]; hazard ratio, 1·78; 95% CI, 1·09 to 2·91; p=0·02). The three HRQL instruments were consistent in showing no important difference by treatment group at 24 months. A priori subgroups suggested lower reoperation rates with sliding hip screws in patients with displaced fractures (interaction p=0·04), base of femoral neck fractures (interaction p=0·04), and current

smokers (interaction p=0·02); current smoking appeared the dominant effect modifier in an analysis that included all three variables.

Interpretation

Among patients with a femoral neck fracture fracture there was no convincing difference in hip re-operations or HRQL among patients allocated to sliding hip screw compared to cancellous screws. Avascular necrosis was higher with sliding hip screws.

Funding

National Institutes of Health, Canadian Institutes of Health Research, Stichting NutsOhra, Netherlands Organisation for Health Research and Development, and Physicians' Services Incorporated.

INTRODUCTION

Worldwide, 4·5 million persons are disabled from hip fractures yearly with an expected increase to 21 million persons living with disability in the next 40 years.[1,2] Despite surgical intervention, the need for hip re-operation remains high - from 10-48·8%, largely unchanged over the last 30 years[3,4] - and is associated with substantial morbidity, mortality, and costs.[5] The high rates of re-operation have generated controversy regarding the optimal approach for fixing femoral neck fractures.[6]

Biomechanical and laboratory studies suggest that although a fixed angle, single large screw and side-plate (sliding hip screw) provides greater biomechanical stability particularly in displaced and unstable fracture types, multiple cancellous screws are less invasive and could better preserve blood supply.[7] Prior small trials have failed to establish the relative impact of the two fixation approaches on outcomes important to patients, in particular re-operations, leaving uncertainty among surgeons regarding the optimal approach for fixing femoral neck fractures.[6]

We conducted the Fixation using Alternative Implants for the Treatment of Hip fractures (FAITH) trial to examine the effect of a sliding hip screw versus cancellous screws on the risk of re-operation and other key outcomes over 24 months.

METHODS

Study Design

FAITH was an international, multicentre, concealed randomised controlled trial evaluating the effects of sliding hip screw versus cancellous screws on re-operation rates over a 24-month follow-up in patients with a low-energy femoral neck fracture. A previous report details the trial objectives and methods.[8] All participating centres obtained ethics approval.

Participants

We enrolled patients with a low-energy fracture of the hip requiring fracture fixation across 81 clinical centres in the United States, Canada, Australia, the Netherlands, Norway, Germany, the United Kingdom and India between March 2008 and March 2014. Eligible patients included those 50 years or older with a low-energy femoral neck fracture requiring operative fixation. The Supplementary Appendix presents the complete eligibility criteria (Supplement Section 3·1). All patients provided informed consent.

Randomisation and Masking

Allocation by minimization, using a centralized computer system to ensure allocation concealment, balanced prognosis between intervention groups for fracture displacement, age, pre-fracture living status, pre-fracture function, American Society for Anesthesiologists (ASA) class, and centre.[9]

Procedures

Participants allocated to sliding hip screw received a single large (8·0 mm) diameter partially threaded screw affixed to the proximal femur with a side plate (with a minimum of two holes and a maximum of four holes) and no supplemental fixation. Those allocated to cancellous screws received multiple threaded screws, with a minimum of two screws and diameter of 6·5 mm. All participating surgeons had conducted a minimum of 25 hip fracture fixation procedures during their career, and at least five fracture fixation procedures in the year before participation.

Surgeons chose the manufacturer, reduction technique, whether to perform a capsulotomy or aspiration of intracapsular hematoma, and final screw position; injectable bone substitutes were not permitted. The protocol specified perioperative antibiotics, thromboprophylaxis, and weight-bearing regimens, but left patient positioning, fracture reduction, and surgical exposure in

the operating room to the surgeons' discretion. We provided surgeons with specific criteria for acceptability of post fixation radiographic fracture alignment.

Participants returned for follow-up at one and ten weeks, and six, nine, 12, 18, and 24 months after surgery. Supplement Sections 3·2, 3·3 and 3·4 provide additional details of the trial intervention and standardization of perioperative care, surgeon expertise, and follow-up processes.

Outcomes

The primary endpoint was re-operation, defined as surgery that occurred subsequent to the initial procedure and within 24 months to promote fracture healing, relieve pain, treat infection, or improve function. An independent Central Adjudication Committee, adjudicated all primary and key secondary outcomes (mortality, fracture healing, and fracture complications, including avascular necrosis, nonunion, implant failure, and infections). Health-related quality of life was measured by the Short Form-12 (SF-12), the EuroQol-5 Dimensions (EQ-5D), and the Western Ontario and McMaster Universities Arthritis Index (WOMAC). Supplement Sections 3·5 and 3·6 provide details of the primary outcomes, secondary outcomes, and adjudication processes.

Statistical Analysis

The sample size calculation was based on the primary outcome of hip re-operation and used the Cox proportional hazards model as described by Collett.[10] Originally we determined that enrollment of 1500 patients would give the trial 81·5% power to detect a hazard ratio of 0·75 in the sliding hip screw group, at a two-sided alpha level of 0·05, on the assumption that the rate of the primary outcome in the cancellous screws group would be 25%.[8] (Supplement, Section 3·7)

In January 2014 the Data and Safety Monitoring Board met after 589 patients completed follow-up. They provided the Steering Committee with overall event rates to inform a revised power analysis that balanced feasibility of completing recruitment within an acceptable time and supporting plausible hypotheses of relative treatment effect and baseline event rates. Based on the first 589 patients, we estimated a 24-month primary event rate of 27·2%; a 24-month mortality rate of 18·2%; a 24-month 5·9% incidence of loss to follow-up; and a combined 6·8% crossover rate. With these estimates, a sample size of 500 patients per group would provide 95·7% power to detect a relative risk reduction of 35%. Based on these data, we targeted a sample size of 1100 patients. A prior published methods paper presents details of the sample size calculations and rationale.[8]

Analyses followed the intention-to-treat principle and included all patients in the groups to which they were randomised. In patients who did not complete the 24-month follow-up, , for our binary outcomes, we censored the participant data at their last follow-up visit if they had not already achieved the outcome of interest. The data analyst, while conducting the analyses, remained blinded to treatment groups. Following assessment of its appropriateness, the primary analysis used a Cox proportional hazards model stratified by clinical site. We report the treatment effects as hazard ratios and 95% confidence intervals. An analysis adjusting for death as a competing risk provided a sensitivity analysis. The analyses of treatment effect on fracture-related adverse events and mortality also relied on a stratified Cox proportional hazards regression.

The health-related quality of life outcomes at 24 months were analyzed using a multiple linear regression model with treatment and pre-injury quality of life (collected at 1 week) included as independent variables. Results are reported as mean differences with corresponding 95% confidence intervals and p values.

At the trial onset we specified a single a priori subgroup analysis exploring fracture displacement as a possible effect modifier, anticipating that sliding hip screw relative to multiple cancellous screws would do better in displaced versus non-displaced fractures.[10] At the completion of the trial, but before unblinding and as described in our statistical analysis plan, we pre-specified an additional five subgroup analyses that explored a possible effect modification by location of fracture line, body mass index, verticality of the fracture line, smoking status, and quality of fracture reduction. We conducted an additional post-hoc subgroup analysis evaluating the possible effect modification of patient age. We undertook tests of interaction for individual subgroups and, when three provide significant results, an analysis that simultaneously considered all their possible interactions. We used multiple criteria to consider the credibility of any possible subgroup effects.[11,12] Section 3·8 in the Supplement provides details regarding hypothesized subgroup effects. All analyses were conducted with SAS version 9·4 (Cary, NC).

Study Oversight and Role of Funding Source

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

FINDINGS

Between March 2008 and March 2014 1108 patients were randomised, of whom 557 were assigned to receive a sliding hip screw and 551 to cancellous screws. The Adjudication Committee determined that 29 patients were ineligible, most as a result of an ineligible fracture type (15 patients), or delayed surgical treatment beyond four days in patients with displaced

fractures (6 patients), leaving 1079 patients in the final analyses. Supplement Section 3·9 provides the rationale for post-randomization exclusions. Of the 923 patients alive at 24 months, we achieved 24-month follow up for 844 (88·7%) patients (Figure 1, Supplement Table S1a, Table S1b). The mean length of follow-up was 633 +/- 208 standard deviation days.

Typical patients were females between 70 and 80 years of age who had fallen and sustained an isolated, non-displaced fracture of the femoral neck; group characteristics were similar (Table 1). Acceptable reduction (99·2%) was achieved in all patients (Table 1). In patients with displaced fractures, acceptable reduction was achieved in 99·3% of patients. Patients who underwent cancellous screw fixation typically received three parallel screws in a triangular configuration, while those patients in the sliding hip screw group received a single large compression screw in the center-center head position with a two hole side plate; peri-operative management was similar across groups. (Table 1, Supplement Tables S2, S3 and S4).

The overall crossover rate was 2·1%: compliance for the initial allocated surgical fixation approach was 99% for sliding hip screw group and 97% for cancellous screw group (Supplement, Tables S3 and S4) (p=0·06 for difference in likelihood of crossover).

The primary study endpoint, hip re-operation within 24 months, did not differ by type of surgical fixation: 107 of 542 patients (19·7%) in the sliding hip screw group and 117 of 537 patients (21·8%) in the cancellous screws group (hazard ratio, 0·83; 95% CI, 0·63 to 1·09; p=0·18) (Table 2 and Figure 2). A competing risk sensitivity analysis adjusting for death yielded similar results for our primary endpoint (hazard ratio, 0·89; 95% CI, 0·69 to 1·16).

Deaths occurred in 156 patients and did not differ between groups; 73 (13·5%) in the sliding hip screw group and 83 (15·5%) in the cancellous screws group (hazard ratio, 0·81; 95% CI, 0·58 to 1·12; p=0·20) (Table 2). Avascular necrosis occurred in 78 patients (7·2%) and

differed by fixation group; 50 patients (9·2%) in the sliding hip screw group and 28 patients (5·2%) in the cancellous screws group (hazard ratio, 1·78; 95% CI, 1·09 to 2·91; p=0·02). Of these, 54 patients (69·2%) required an operation; 38 patients (7%) in the sliding hip screw group and 16 patients (3%) in the cancellous screws group (p=0·002). Implant removal occurred less frequently in the sliding hip screw group than cancellous screws group (25 patients [4·6%] versus 49 patients [9·1%], respectively; hazard ratio, 0·42; 95% CI, 0·25 to 0·70; p=0·001). Implant exchange to revise to another internal fixation also occurred less frequently with sliding hip screws than cancellous screws (3 patients [0·6%] versus 14 patients [2·6%], respectively; hazard ratio, 0·21; 95% CI, 0·06 to 0·73; p=0·007). Alternatively, implant exchange to a total hip replacement, was more common in the sliding hip group (64 patients [11·8%] versus 40 patients [7·5%], respectively; hazard ratio, 1·51; 95% CI, 1·00 to 2·17; p=0·049).

Nonunions, implant failures, infections, fracture shortening, and fracture healing did not differ by surgical fixation approach (Table 2). Health-related quality of life did not differ between sliding hip screws and multiple cancellous screws at 12-month and 24-month follow-up (Table 3).

Medically related adverse events did not differ by treatment group (Supplement, Table S5).

Subgroup analyses favored sliding hip screw in patients with displaced fractures (hazard ratio for sliding hip screw group=0·57, 95% CI: 0·38-0·87; interaction p=0·04, Supplement, Tables S6-S9), fractures at the base of the femoral neck (hazard ratio for sliding hip screw=0·24, 95%CI: 0·06-0·93, interaction p=0·04), and in patients who were current smokers (hazard ratio for sliding hip screw=0·39, 95%CI: 0·19-0·77, interaction p=0·02) (Figure 3). Only smoking status remained significant when these three subgroups were entered into a single analysis

(Figure 3). Sliding hip screw was superior among current smokers, but not in former/non-smokers (hazard ratios: 0·39 and 0·99, respectively; interaction p=0·02, adjusted interaction p=0·01; Figure 3, Supplemental Table S10).

DISCUSSION

We found a similar risk of hip re-operation among patients with low energy femoral neck fractures randomised to sliding hip screw and cancellous screws at 24 months; avascular necrosis occurred more frequently in those patients allocated to sliding hip screw. Subgroup analyses of low to moderate credibility, suggested sliding hip screws reduced reoperations in patients with displaced fractures, fractures at the base of the femoral neck, and in current smokers.

Although the incidence of re-operations was similar between the two treatment groups, there were differences in the component outcomes of re-operations. Patients in the sliding hip screw group, compared to cancellous screws, had a lower frequency of a re-operation for an implant removal and an implant exchange based on an internal fixation approach, but experienced a higher frequency of re-operation for an implant exchange with total hip arthroplasty approach. Patients undergoing total hip arthroplasty following failed internal fixation compared to a primary total hip arthroplasty may be at higher risk of complications.[13] The lower rate of arthroplasties, thus, suggests a potential advantage of cancellous screws. Although, the decision to choose on approach to implant exchange over another was left to surgeon discretion it may also reflect surgeon preference.

Looking separately at possible effect modifiers, displaced versus non-displaced fractures, fracture site, and smoking status, interaction p values all reached conventional statistical significance, all suggesting benefits of sliding hip screws over cancellous screws in a

subpopulation of patients (Figure 3). All were a priori hypotheses with a biological rationale that led to a correct predicted direction of effect. In particular, the greater biomechanical stability of sliding hip screws may offer advantages in fracture with displacement and in smokers, who have greater risk of osteoporosis and diminished bone density compared to non-smokers.[7,14-17] Sliding hip screws remain the standard of care in patients with inter-trochanteric fractures, a region in close proximity to the base of the femoral neck,[18] providing a biological rationale for the finding that sliding hip screws reduced re-operations in the subgroup of patients with base of femoral neck fractures. Furthermore, the displacement hypothesis was originally our sole hypothesis and a minimization variable.[11,12] (Supplement Section 3·8)

On the other hand, when all three potential effect modifiers were considered together, only smoking retained a low – though not extremely low - p value (Figure 3). Further, we tested multiple hypotheses, and failed to find similar effects in health-related quality of life. Thus, considering all issues, the apparent subgroup effects have only modest credibility.

Strengths of FAITH include safeguards against risk of bias (concealed randomization, centralized and independent outcome adjudication, blinded analysis of data); high compliance with study procedures; broad inclusion criteria with a large number of centres in countries with diverse health care systems; focus on outcomes of importance to both patients and the health care system (i.e., re-operation, health-related quality of life); and rigorous exploration of subgroup effects, with due attention to their credibility.[11,12]

Our study has limitations. Surgeons and patients were not blinded. We did, however, minimize the associated risk of bias with central and independent, though unblinded, radiographic adjudication of the primary endpoint. Further, re-operation is an objective endpoint and a major procedure; surgeons will seldom decide to re-operate in the absence of a compelling

indication. Follow-up at 24 months was less than complete (88·7%) among patients who were alive; our success in following patients was consistent and in most cases superior to prior smaller trials.[3] There also existed unavoidable heterogeneity related to the variables that were not standardized: patient positioning, fracture reduction, surgical exposure, use of operative traction, surgical delay, type of anesthetic, and physiotherapy, and rehabilitation programs.

In relation to previous work, a prior meta-analysis of small trials suggested a non-significant difference in re-operations favoring sliding hip screw (relative risk, 0·86; 95% CI, 0·70 to 1·05; p=0·13).[13] An updated pooled analysis of re-operation including small trials with our FAITH results (n=8 trials, 1768 patients) shows a narrower confidence interval, but still consistent with no difference between fixation methods (relative risk, 0·89; 95% CI, 0·76 to 1·04; p=0·15, I^2=16%).[19-25]

With respect to avascular necrosis, our results differ importantly from a previous systematic review of small trials that suggested that sliding hip screw, in comparison to cancellous screws, may reduce the risk of avascular necrosis. Adding an additional small trial to a previous meta-analysis results in a significant reduction in risk of avascular with sliding hip screws (77 events, relative risk, 0·64; 95%CI, 0·43 to 0·97) p = 0·04, I^2 = 0%).[13,19]

Despite the prior results, increased risk of avascular necrosis from our results has a plausible biological rationale. Hip fractures can disrupt the retinacular vessels, crucial for vascular supply of the femoral head.[26] A randomised trial of 104 patients with femoral neck fractures using bone scintigraphy demonstrated reduced vascularity in patients treated with sliding hip screw compared to cancellous screws (35% versus 11%, p<0·01).[27] Further, suboptimal position of large implants such as sliding hip screws, risks damage to blood supply to the femoral head.[28] In terms of the importance of avascular necrosis, observational studies have

demonstrated that many patients remain asymptomatic, with only one in five requiring further surgery.[29,30]

Our results, in the context of prior results, leave the choice of internal fixation procedures a matter of discretion. Findings favoring cancellous screws include failure to establish a difference in re-operation rates between procedures, and our findings of a higher rate of avascular necrosis and subsequent total arthroplasties in patients receiving sliding hip screws. On the other hand, our finding of more avascular necrosis is inconsistent with other studies, and did not result in more operations or poorer quality of life in the total population. Moreover, findings across all trials remain consistent with overall decreased reoperations in those receiving sliding hip screws, and subgroup analyses of modest credibility suggest that patients with displaced fractures, smokers, and those with base of neck fractures may do better with sliding screws.

RESEARCH IN CONTEXT

Evidence Before this Trial

An international survey of orthopaedic surgeons identified that surgeons had a preference for multiple cancellous screws over sliding hip screw in fixation of femoral neck hip fractures. Despite the popularity of cancellous screws for hip fracture fixation, biological investigations suggested the sliding hip screw is a more biomechanically stable construct compared to cancellous screws. Moreover, a prior Cochrane meta-analysis of small trials demonstrated a non-significant reduction in re-operations with sliding hip screw compared to multiple cancellous screws (relative risk, 0·86; 95% CI, 0·70 to 1·05), and the risk of avascular necrosis with sliding hip screw was significantly reduced. In summary, prior evidence provided encouraging, but non-

definitive, evidence that sliding hip screw may reduce the risk of revision surgery and avascular necrosis compared to cancellous screws though small sample sizes and resultant imprecise estimates, and methodological limitations, left the issue in doubt.

Added Value of this Trial

Our trial enrolled over 1000 patients enrolled across multiple countries, providing both improved precision and greater generalizability to both developed and low-middle income countries. Our trial also addresses the paucity of health-related quality of life data following surgical fixation of femoral neck fractures.

Implications of All the Available Evidence

Although our findings, consistent with prior RCTs, failed to establish a difference in re-operation rates among patients randomised to sliding hip screw versus cancellous screws; health-related quality of life was similar across both interventions. We did, however, demonstrate a significant increase in rates of avascular necrosis with sliding hip screw. This finding, however, is not only inconsistent with prior results, but did not result in an overall increase in reoperations or a decrement in health-related quality of life. Moreover, our results raise the possibility that sliding hip screws relative to cancellous screws, may reduce reoperations in patients with displaced fractures, smokers, and those with base of neck fractures.

CONTRIBUTORS

The FAITH Trial full list of study investigators are available in the Supplement. The Clinical Advances through Research and Information Translation (CLARITY) Research Group at McMaster University coordinated the trial. The CLARITY Research Group was responsible for the trial randomization, maintenance of the database, data validation, data analyses, and study-centre coordination. The University of Minnesota (Minneapolis, USA), Erasmus MC, University Medical Centre (Rotterdam, NL), and James Cook University Hospital (North Yorkshire, UK) assisted in coordination of sites in the United States, the Netherlands, and United Kingdom, respectively. The Steering Committee designed the trial, pre-specified the statistical analysis plan, and vouch for the completeness and accuracy of the data and analyses. The first author (MB) and chair of the Writing Committee wrote the first draft of the manuscript; the Writing Committee (PJD, GG, LT, SW, MJH, KJJ, SL, EHS, PTIII, GJDR, REB, RM, TMO, MJMS, AR, MR, SS, TS, JA, AG, QZ, DHA, HV, SMZ, EMMVL, HJ, BCH, and MS) made revisions and decided to submit the manuscript for publication.

DECLARATION OF INTERESTS

MB reports grants from Canadian Institutes of Health Research, grants from National Institutes of Health, grants from Stichting NutsOhra, grants from Netherlands Organisation for Health Research and Development, grants from Physicians' Services Incorporated and Stryker GmBH, grants from Early Research Award Program during the conduct of the study, personal fees from Sanofi, Pendopharm, Ferring, DJO, Stryker, and grants from Pluristem, Amgen, outside the submitted work; MJH reports grants from Stichting NutsOhra and from The Netherlands Organization for Health Research and Development during the conduct of the study; PJD reports grants from Abbott Diagnostics, grants from Boehringer-Ingelheim, grants from

Covidien, grants from Octopharma, grants from Roche Diagnostics, grants from Stryker, outside the submitted work; KJJ reports grants from the National Institutes of Health and from Canadian Institutes of Health Research during the conduct of the study and personal fees from Zimmer, outside the submitted work; EHS reports personal fees from Stryker, personal fees from Smith & Nephew, personal fees from Zimmer, personal fees from Acumed, personal fees from Amgen, personal fees from Sanofi, personal fees from Bioventus, other from Elsevier, outside the submitted work; PTIII reports personal fees from Lippicott Williams & Wilkins, outside the submitted work, as well as having a patent US8888824 B2 with royalties paid by Smith & Nephew; GJDR reports grants from University of Minnesota during the conduct of the study, grants from DePuy-Synthes, personal fees from Bioventus, other from Amedica, other from The Orthopaedic Implant Company, other from LuminCare, other from Mergenet Medical, personal fees from DePuy-Synthes, and other from Intellectual ventures, outside the submitted work; RM reports personal fees from Sanofi, Pendopharm, outside the submitted work, AR reports grants from Canadian Institutes of Health Research, during the conduct of the study, grants from National Institute for Health Research (UK), grants from Orthopaedic Research UK, and grants from DePuy Ltd, outside the submitted work; SS reports other from McMaster University, other from Global Research Solutions, personal fees from University of Maryland, outside the submitted work; JA reports grants from National Institutes of Health during the conduct of the study; SMZ reports grants from Stichting NutsOhra (SNO-T-0602-43), grants from the Netherlands Organisation for Health Research and Development (80-82310-97-11032), during the conduct of the study; EMMVL reports grants from Stichting NutsOhra and from The Netherlands Organization for Health Research and Development during the conduct of the study; MS reports grants from National Institutes of Health/National Institute of Arthritis and

Musculoskeletal and Skin Diseases, during the conduct of the study, other from The Journal of Bone & Joint Surgery Editor, outside the submitted work; GG, LT, SW, SL, REB, TMO, MR, TS, AG, QZ, DHA, HV, HJ, BCH have nothing to disclose.

ACKNOWLEDGMENTS

Funding: Supported by research grants from the Canadian Institutes of Health Research (MOP-106630 and MCT-87771), National Institutes of Health (1R01AR055267-01A1), Stichting NutsOhra (SNO-T-0602-43), the Netherlands Organisation for Health Research and Development (80-82310-97-11032), Physicians' Services Incorporated and Stryker GmBH. MB was also funded, in part, through the Early Research Award Program which provided funding for the present study as well as by a Canada Research Chair in Musculoskeletal Trauma which is unrelated to the present study (McMaster University, Hamilton, ON, Canada).

Research reported in this publication was supported by the National Institute of Arthritis and Musculoskeletal and Skin Diseases of the National Institutes of Health under Award Number R01AR055267-01A1**.** The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. Research reported in this publication was also supported by The County Durham & Tees Valley Comprehensive Local Research Network which operates as part of the National Institute for Health Research Comprehensive Clinical Research Network in England. The funding sources had no role in design or conduct of the study; the collection, management, analysis, or interpretation of the data; or the preparation, review, or approval of the manuscript.

REFERENCES

1. Gullberg B, Johnell O, Kanis JA. World-wide projections for hip fracture. *Osteoporos Int* 1997;7:407–13.
2. Parker M, Johansen A. Hip fracture. *BMJ*. 2006;333:27-30.
3. Bhandari M, Devereaux PJ, Swiontkowski MF, Tornetta P 3rd, Obremskey W, Koval KJ, et al. Internal fixation compared with arthroplasty for displaced fractures of the femoral neck. A meta-analysis. *J Bone Joint Surg Am* 2003;85-A:1673–81.
4. Mundi S, Pindiprolu B, Simunovic N, Bhandari M. Similar mortality rates in hip fracture patients over the past 31 years. *Acta Orthop* 2014;85:54–9.
5. Zielinski SM, Bouwmans CA, Heetveld MJ, Bhandari M, Patka P, Van Lieshout EM, et al. The societal costs of femoral neck fracture patients treated with internal fixation. *Osteoporos Int* 2014;25:875–85.
6. Bhandari M, Devereaux PJ, Tornetta P 3rd, Swiontkowski MF, Berry DJ, Haidukewych G, et al. Operative management of displaced femoral neck fractures in elderly patients. An international survey. *J Bone Joint Surg Am* 2005;87:2122–30.
7. Hoshino CM, O'Toole RV. Fixed angle devices versus multiple cancellous screws: what does the evidence tell us? *Injury* 2015;46:474–7.
8. FAITH Investigators. Fixation using alternative implants for the treatment of hip fractures (FAITH): design and rationale for a multi-centre randomized trial comparing sliding hip screws and cancellous screws on revision surgery rates and quality of life in the treatment of femoral neck fractures. *BMC Musculoskelet Disord* 2014;15:219.
9. Scott NW, McPherson GC, Ramsay CR, Campbell MK. The method of minimization for allocation to clinical trials. a review. *Control Clin Trials* 2002;23:662–74.

10. Collett D. Modelling Survival Data in Medical Research. 1st ed. London, UK: Chapman and Hall, 1994.
11. Sun X, Briel M, Busse JW, You JJ, Akl EA, Mejza F, et al. Credibility of claims of subgroup effects in randomised controlled trials: systematic review. *BMJ* 2012;344:e1553.
12. Study to Prospectively Evaluate Reamed Intramedullary Nails in Tibial Fractures (SPRINT) Investigators, Sun X, Heels-Ansdell D, Walter SD, Guyatt G, Sprague S, et al. Is a subgroup claim believable? A user's guide to subgroup analyses in the surgical literature. *J Bone Joint Surg Am* 2011;93:e8.
13. Parker MJ, Gurusamy KS. Internal fixation implants for intracapsular proximal femoral fractures in adults. *Cochrane Database Syst Rev* 2001:i–73.
14. Deneka DA, Simonian PT, Stankewich CJ, Eckert D, Chapman JR, Tencer AF. Biomechanical comparison of internal fixation techniques for the treatment of unstable basicervical femoral neck fractures. *J Orthop Trauma* 1997;11:337–43.
15. Blair B, Koval KJ, Kummer F, Zuckerman JD. Basicervical fractures of the proximal femur. A biomechanical study of 3 internal fixation techniques. *Clin Orthop Relat Res* 1994;306:256–63.
16. Law MR, Hackshaw AK. A meta-analysis of cigarette smoking, bone mineral density and risk of hip fracture: recognition of a major effect. *BMJ* 1997;315:841–6.
17. Castillo RC, Bosse MJ, MacKenzie EJ, Patterson BM; LEAP Study Group. Impact of smoking on fracture healing and risk of complications in limb-threatening open tibia fractures. *J Orthop Trauma* 2005;19:151–7.
18. Parker MJ, Handoll HH. Gamma and other cephalocondylic intramedullary nails

versus extramedullary implants for extracapsular hip fractures in adults. *Cochrane Database Syst Rev*. 2010(9):CD000093.

19. Watson A, Zhang Y, Beattie S, Page RS. Prospective randomized controlled trial comparing dynamic hip screw and screw fixation for undisplaced subcapital hip fractures. *ANZ J Surg* 2013;83:679–83.
20. Benterud JG, Husby T, Nordsletten L, Alho A. Fixation of displaced femoral neck fractures with a sliding screw plate and a cancellous screw or two Olmed screws. A prospective, randomized study of 225 elderly patients with a 3-year follow-up. *Ann Chir Gynaecol* 1997;86:338–42.
21. Kuokkanen H, Korkala O, Antti-Poika I, Tolonen J, Lehtimäki MY, Silvennoinen T. Three cancellous bone screws versus a screw-angle plate in the treatment of Garden I and II fractures of the femoral neck. *Acta Orthop Belg* 1991;57:53–7.
22. Madsen F, Linde F, Andersen E, Birke H, Hvass I, Poulsen TD. Fixation of displaced femoral neck fractures. A comparison between sliding screw plate and four cancellous bone screws. *Acta Orthop Scand* 1987;58:212–6.
23. Harper WM. A prospective randomised trial comparing multiple parallel cannulated screws with a sliding hip screw and plate. In: Treatment of intracapsular proximal femoral fractures. Thesis. University of Leicester, 1994.
24. Sørensen JL, Varmarken JE, Bømler J. Internal fixation of femoral neck fractures. Dynamic Hip and Gouffon screws compared in 73 patients. *Acta Orthop Scand* 1992;63:288–92.

25. Paus A, Gjengedal E, Hareide A, Jørgensen JJ. Dislocated fractures of the femoral neck treated with von Bahr screws or hip compression screw. Results of a prospective, randomized study. *J Oslo City Hosp* 1986;36:55–61.
26. Swiontkowksi MF. Intracapsular fractures of the hip. *J Bone Joint Surg* 1994;76A:129–38.
27. Linde F, Andersen E, Hvass I, Madsen F, Pallesen R. Avascular femoral head necrosis following fracture fixation. *Injury* 1986;17:159–63.
28. Brodetti A. The blood supply of the femoral neck and head in relation to the damaging effects of nails and screws. *J Bone Joint Surg* 1960;42B:794–801.
29. Barnes R, Brown JT, Garden RS, Nicoll EA. Subcapital fractures of the femur. A prospective review. *J Bone Joint Surg Br*. 1976;58:2–24.
30. Nikolopoulos KE, Papadakis SA, Kateros KT, Themistocleous GS, Vlamis JA, Papagelopoulos PJ, Nikiforidis PA. Long-term outcome of patients with avascular necrosis, after internal fixation of femoral neck fractures. *Injury*. 2003;34:525–8.

FIGURES

Figure 1. Patient Flow Diagram

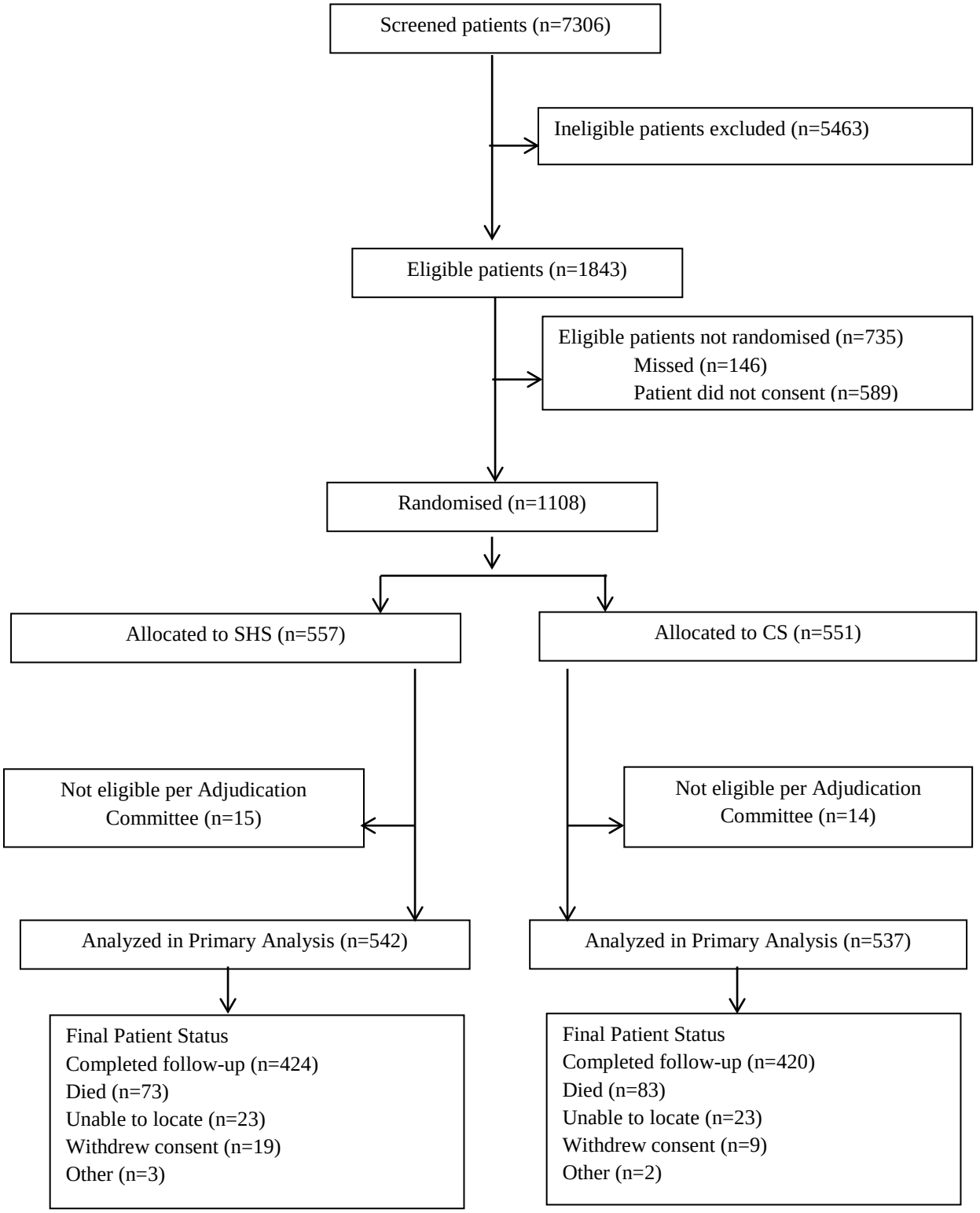
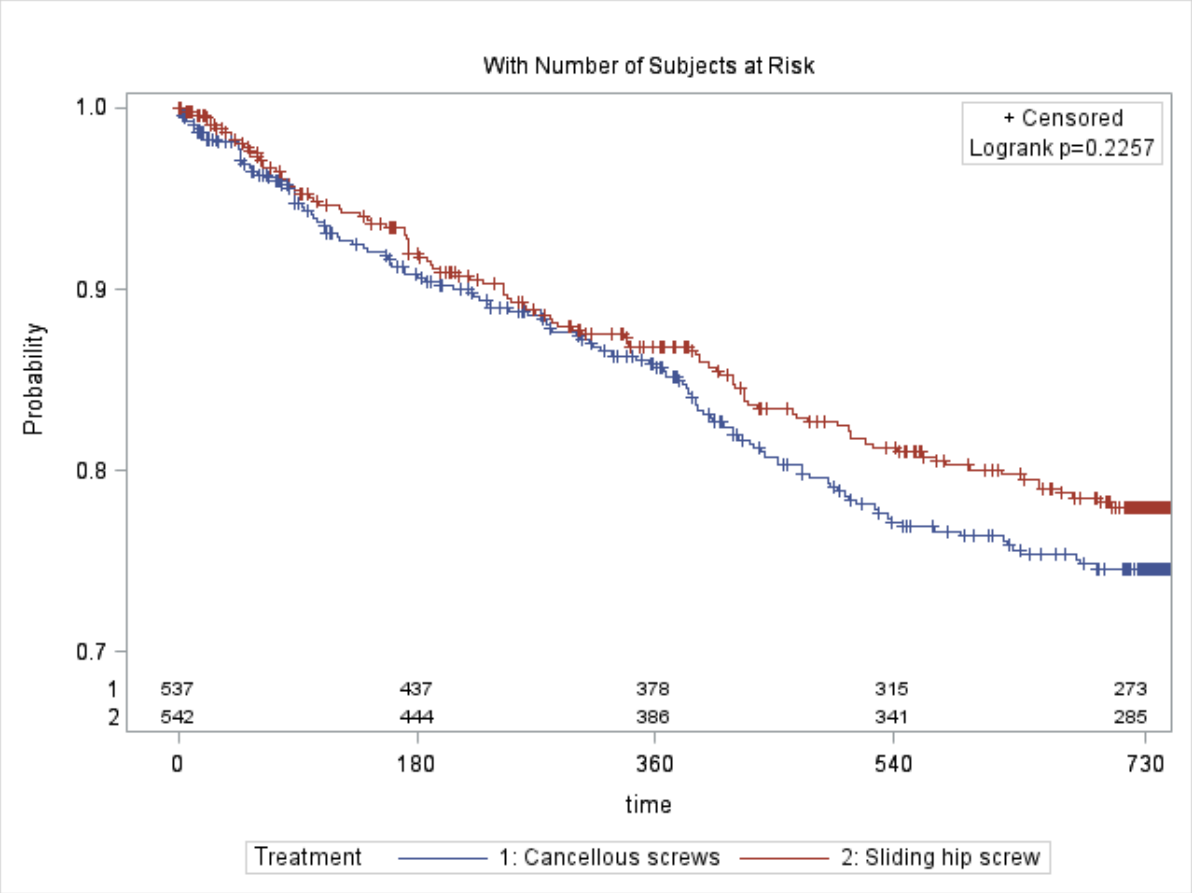


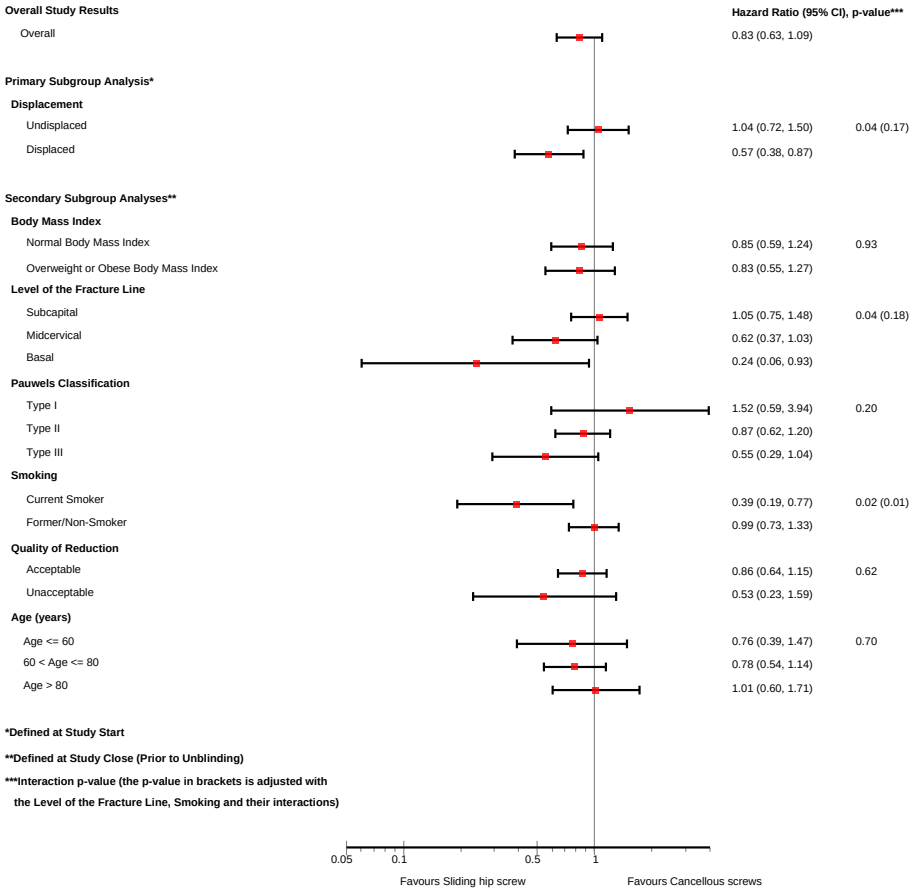
Figure 2. Kaplan-Meier Curves for the Surgical Fixation Primary Endpoint (Re-operation)



Legend:

- Multiple Cancellous Screws
- Sliding Hip Screw

Figure 3: Subgroup Analyses of Surgical Fixation Primary Endpoint (Re-operation)



TABLES

Table 1. Patient Demographics and Fracture Characteristics

	Sliding Hip Screw N=542	**Cancellous Screws N=537**	**Total N=1079**
Patient Characteristics			
Age, mean (SD) years	72·2 (12·0)	72·0 (12·3)	72·1 (12·2)
Gender, n (%)	N=535	N=535	N=1070
Males	212 (39·6%)	210 (39·3%)	422 (39·4%)
Females	323 (60·4%)	325 (60·7%)	648 (60·6%)
Ethnicity, n (%)	N=533	N=535	N=1068
Native	1 (0·2%)	3 (0·6%)	4 (0·3%)
South Asian	65 (12·2%)	65 (12·1%)	130 (12·1%)
East Asian	6 (1·1%)	4 (0·7%)	10 (0·9%)
Black	22 (4·1%)	18 (3·4%)	40 (3·8%)
Hispanic	3 (0·6%)	1 (0·2%)	4 (0·4%)
White/Caucasian	436 (81·8%)	444 (83·0%)	880 (82·4%)
Smoking History, n (%)	N=533	N=532	N=1065
Never Smoked	268 (50·3%)	276 (51·9%)	544 (51·1%)
Current Smoker	101 (19·0%)	100 (18·8%)	201 18·9%)

	Sliding Hip Screw N=542	**Cancellous Screws N=537**	**Total N=1079**
Former Smoker	164 (30·7%)	156 (29·3%)	320 (30·0%)
Current Medications, n (%)	N=535	N=534	N=1069
None	170 (31·8%)	179 (33·5%)	349 (32·7%)
NSAIDS	86 (16·1%)	64 (12·0%)	150 (14·0%)
General Cardiac Medications	167 (31·2%)	167 (31·2%)	334 (31·2%)
Analgesics: Opioid	43 (8·0%)	56 (10·5%)	99 (9·3%)
Pulmonary Medications	58 (10·8%)	69 (12·9%)	127 (11·9%)
Anti-hypertension Medications	244 (45·6%)	252 (47·1%)	496 (46·4%)
Osteoporosis Medications	67 (12·5%)	73 (13·6%)	140 (13·1%)
BMI, n (%)	N=530	N=528	N=1058
Underweight <18·5	37 (7·0%)	33 (6·3%)	70 (6·6%)
Normal Weight 18·5-24·9	276 (52·1%)	300 (56·8%)	576 (54·4%)
Overweight 25-29·9	159 (30·0%)	148 (28·0%)	307 (29·0%)
Obese 30-39·9	58 (10·9%)	47 (8·9%)	105 (9·9%)
Fractured Hip, n (%)	N=535	N=535	N=1070
Left	280 (52·3%)	281 (52·5%)	561 (52·4%)
Right	255 (47·7%)	254 (47·5%)	509 (47·6%)

	Sliding Hip Screw N=542	**Cancellous Screws N=537**	**Total N=1079**
Mechanism of Injury, n (%)	N=533	N=534	N=1067
Fall	515 (96·7%)	521 (97·6%)	1036 (97·1%)
Spontaneous	13 (2·4%)	6 (1·1%)	19 (1·8%)
Other Low Energy Trauma	5 (0·9%)	7 (1·3%)	12 (1·1%)
History of Surgery to Affected Hip, n (%)	N=535	N=535	N=1070
Yes	3 (0·6%)	0 (0%)	3 (0·3%)
No	532 (99·4%)	535 (100%)	1067 (99·7%)
Additional Injuries, n (%)	N=535	N=535	N=1070
Yes	67 (12·5%)	72 (13·5%)	139 (13·0%)
No	468 (87·5%)	463 (86·5%)	931 (87·0%)
Fracture Characteristics			
Level of the Fracture Line, n (%)	N=535	N=536	N=1071
Subcapital	331 (61·9%)	351 (65·5%)	682 (63·7%)
Midcervical	159 (29·7%)	154 (28·7%)	313 (29·2%)
Basal	45 (8·4%)	31 (5·8%)	76 (7·1%)

	Sliding Hip Screw N=542	**Cancellous Screws N=537**	**Total N=1079**
Garden Classification, n (%)	N=542	N=537	N=1079
Undisplaced	360 (66·4)	369 (68·7%)	729 (67·6%)
Garden I	257 (48·0%)	277 (51·7%)	534 (49·9%)
Garden II	99 (18·5%)	92 (17·2%)	191 (17·8%)
Displaced	182 (33·6%)	168 (31·3%)	350 (32·4%)
Garden III	121 (22·6%)	128 (23·9%)	249 (23·3%)
Garden IV	58 (10·8%)	39 (7·3%)	97 (9·1%)
Pauwel's Classification, n (%)	N=535	N=536	N=1071
Type I	59 (11·0%)	59 (11·0%)	118 (11·0%)
Type II	398 (74·4%)	394 (73·5%)	792 (74·0%)
Type III	78 (14·6%)	83 (15·5%)	161 (15·0%)
Pre-operative Traction, n (%)	N=535	N=535	N=1070
Skin Traction	75 (14·0%)	76 (14·2%)	151 (14·1%)
Skeletal Traction	7 (1·3%)	3 (0·6%)	10 (0·9%)
None	453 (84·7%)	456 (85·2%)	909 (85·0%)
Reduction Type of Reduction, n (%)	N=531	N=528	N=1059
None	210 (39·6%)	237 (44·9%)	447 (42·2%)

	Sliding Hip Screw N=542	**Cancellous Screws N=537**	**Total N=1079**
Closed	287 (53·9%)	277 (52·1%)	564 (53·0%)
Acceptable	286 (99·7%)	275 (99·3%)	561 (99·5%)
Unacceptable	1 (0·3%)	2 (0·7%)	3 (0·5%)
Open	34 (6·4%)	14 (2·6%)	48 (4·5%)
Acceptable	32 (94·1%)	14 (100%)	46 (95·8%)
Unacceptable	2 (5·9%)	0 (0%)	2 (4·2%)

SD = Standard deviation; NSAIDS = Nonsteroidal anti-inflammatory drugs; BMI = Body mass index

Table 2: Study Outcomes by Treatment Group

	Overall	Sliding Hip Screw	Cancellous Screws	Hazard Ratio	p value
	N=1079	N=542	N=537	(95% CI)	
Primary Endpoint (re-operation)	224 (20·8%)	107 (19·7%)	117(21·8%)	0·83 (0·63, 1·09)	0·18
Implant Removal	74 (6·9%)	25 (4·6%)	49 (9·1%)	0·42 (0·25, 0·70)	0·001
Implant Exchange – THA	104 (9·6)	64 (11·8%)	40 (7·5%)	1·51 (1·00, 2·27)	0·049
Implant Exchange – HA	55 (5·1%)	26 (4·8%)	29 (5·4%)	0·89 (0·52, 1·51)	0·66
Implant Exchange – Internal Fixation	16 (1·5%)	2 (0·4%)	14 (2·6%)	0·14 (0·03, 0·62)	0·002
Implant Exchange – Spacer	3 (0·3%)	1 (0·2%)	2 (0·4%)	0·50 (0·05, 5·45)	0·56
Soft Tissue Procedure	6 (0·6%)	4 (0·7%)	2 (0·4%)	1·98 (0·36, 10·77)	0·42
Proximal Femoral Osteotomy	1 (0·2%)	1 (0.2%)	1 (0·2%)	0·99 (0·06, 15.80)	0·99
Secondary Endpoints					
Avascular Necrosis	78 (7·2%)	50 (9·2%)	28 (5·2%)	1·91 (1·06 , 3.44)	0·03
Nonunion	66 (6·1%)	33(6·1%)	33 (6·2%)	0·92 (0·48, 1·75)	0·80
Implant Failure	87 (8·1%)	42 (7·8%)	45 (8·4%)	0·95 (0·61, 1·48)	0·81
Infection	19 (1·8%)	10 (1·9%)	9 (1·7%)	1·10 (0·45, 2·69)	0·83
Superficial	8 (0·7%)	4 (0·7%)	4 (0·7%)	0·99 (0.25, ·3·94)	0·99
Deep	11 (1·0%)	6 (1·1%)	5 (0·9%)	1·19 (0·37, 3·87)	0·77

	Overall	Sliding Hip Screw	Cancellous Screws	Hazard Ratio	p value
	N=1079	N=542	N=537	(95% CI)	
Fracture Healing (N=795)*					
Healed by Month 24	532 (66·9%)	262 (65·8%)	270 (68·0%)		0·71
Not Healed by Month 24	3 (0·4%)	2 (0·5%)	1 (0·3%)		
Not Healed at Time of Last Visit	260 (32·7%)	134 (33·7%)	126 (31·7%)		
Fracture Shortening >5mm (N=532)**	146 (27·4%)	69 (26·3%)	77 (28·5%)	0·92 (0·70, 1·22)	0·57
Mortality	156 (14·5%)	73 (13·5%)	83 (15·5%)	0·81 (0·58, 1·12)	0·20

THA=total hip arthroplasty; HA=hemiarthroplasty

Relative risk was calculated where the total number of events is less than 50

*795 patients were included in the fracture healing analysis. 284 patients did not have x-rays available for fracture healing adjudication, and therefore were not included in the denominator.

**532 patients were included in the shortening analysis based on the number of healed fractures with shortening data.

Table 3: Health-Related Quality of Life by Treatment Groups Without Interaction of Displacement

	Sliding Hip Screw Mean (SD), N	Cancellous Screws Mean (SD), N	Adjusted Mean Difference (95% CI)	p Value for Differences Between Groups/
12 Months				
SF-12 PCS	40·8 (11·1), 235	41·9 (10·7),224	-0·02 (-1·79, 1·74), N=435	0·98
WOMAC	44·69 (19·08), 240	41·32 (16·73), 226	1·98 (-1·13, 5·09), N=438	0·21
EQ-5D Index	0·77 (0·20), 249	0·80 (0·17), 238	-0·02 (-0·05, 0·02), N=460	0·33
24 Months				
SF-12 PCS	41·6 (10·9), 207	41·4 (11·8), 181	0·50 (-1·61, 2·61), N=358	0·64
WOMAC	40·97 (16·33), 205	39·75 (17·09), 183	0·35 (-3·03, 3·74), N=355	0·84
EQ-5D Index	0·79 (0·19), 232	0·80 (0·19), 207	-0·01 (-0·04, 0·02), N=406	0·51