HHS Public Access

Author manuscript

Anesthesiology. Author manuscript; available in PMC 2025 March 01.

Published in final edited form as:

Anesthesiology. 2024 March 01; 140(3): 375–386. doi:10.1097/ALN.0000000000004807.

Long-term outcomes with spinal versus general anesthesia for hip fracture surgery: A randomized trial

Emily A. Vail, MD MSc.[1], **Rui Feng, PhD**[2], **Frederick Sieber, MD**[3], **Jeffrey L. Carson, MD**[4], **Susan S. Ellenberg, PhD**[2], **Jay Magaziner, PhD MSHyg**[5], **Derek Dillane, MD**[6], **Edward R. Marcantonio, MD**[7], **Daniel I. Sessler, MD**[8], **Sabry Ayad, MD**[8], **Trevor Stone, MD**[9], **Steven Papp, MD**[10], **Derek Donegan**[11], **Samir Mehta**[11], **Eric S. Schwenk, MD**[12], **Mitchell Marshall, MD**[13], **J. Douglas Jaffe, DO**[14], **Charles Luke, MD**[15], **Balram Sharma, MD**[16], **Syed Azim, MD**[17], **Robert Hymes, MD**[18], **Ki-Jinn Chin, MD**[19], **Richard Sheppard, MD**[20], **Barry Perlman, PhD MD**[21], **Joshua Sappenfield**[22], **Ellen Hauck, DO PhD**[23], **Ann Tierney, MS**[24], **Annamarie D. Horan, PhD**[1], **Mark D. Neuman, MD MSc**[1] **REGAIN (Regional versus General Anesthesia for Promoting Independence after Hip Fracture) Investigators**

[1]Department of Anesthesiology and Critical Care, University of Pennsylvania, Philadelphia, Pennsylvania, United States.

[2]Department of Biostatistics, Epidemiology, and Informatics, University of Pennsylvania Perelman School of Medicine, Philadelphia, Pennsylvania, United States.

[3]Department of Anesthesiology and Critical Care Medicine, Johns Hopkins Medical Institutions, Baltimore, Maryland, United States.

[4]Division of General Internal Medicine, Rutgers Robert Wood Johnson Medical School, New Brunswick, New Jersey, United States.

[5]Department of Epidemiology and Public Health, University of Maryland School of Medicine, Baltimore, Maryland, United States.

[6]Department of Anesthesiology and Pain Medicine, University of Alberta Hospital, Edmonton, Alberta, Canada.

[7]Department of Medicine, Beth Israel Deaconess Medical Center, Boston, Massachusetts, United States.

Corresponding Author: Dr. Mark D. Neuman, Department of Anesthesiology and Critical Care, University of Pennsylvania Perelman School of Medicine, 308 Blockley Hall, 423 Guardian Drive, Philadelphia PA, 19106 United States, neumanm@pennmedicine.upenn.edu.

Conflicts of Interest: Emily Vail reports receipt of funding from the Agency for Healthcare Research and Quality and Transplant Foundation (Philadelphia, Pennsylvania) via competitive research grants. Susan Ellenberg reports funding from AbbVie outside the submitted work. Jay Magaziner reports consulting fees from Novartis, UCB, and Pluristem outside the submitted work, and service on Boards for the Own the Bone Program of the American Orthopedic Association and Fragility Fracture Network. Derek Dillane reports personal fees from the American Society of Regional Anesthesia and personal fees from Springer Nature, all outside the submitted work. Derek Donegan reports consulting fees from Depuy Synthes and stock options/intellectual property from ORTelligence outside the submitted work. Eric Schwenk reports receiving royalties from Up To Date. J. Douglas Jaffe has received payments from Konica Minolta Inc and Pacira life sciences. The other authors have no conflicts to disclose.

Trial registration:
Clinicaltrials.gov
URL: https://clinicaltrials.gov/ct2/show/NCT02507505
Principal Investigator: Mark D Neuman, MD, MSc
Registration date: July 24, 2015

[8]Department of Outcomes Research, Cleveland Clinic, Cleveland, Ohio, United States.

[9]Department of Orthopedics, University of British Columbia, Vancouver, British Columbia, Canada.

[10]Division of Orthopedics, Ottawa Hospital Civic Campus, Ottawa Ontario, Canada.

[11]Department of Orthopedic Surgery, University of Pennsylvania Perelman School of Medicine, Philadelphia, Pennsylvania, United States.

[12]Department of Anesthesiology, Sidney Kimmel Medical College at Thomas Jefferson University, Philadelphia, Pennsylvania, United States.

[13]Department of Anesthesiology, New York University Langone Medical Center, New York, New York, United States.

[14]Department of Anesthesiology, Wake Forest School of Medicine, Winston-Salem, North Carolina, United States.

[15]Department of Anesthesiology, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania, United States.

[16]Department of Anesthesiology, Lahey Hospital and Medical Center, Burlington, Massachusetts, United States.

[17]Department of Anesthesiology, Stony Brook University, Stony Brook, New York, New York, United States.

[18]Department of Orthopedic Surgery, Inova Fairfax Medical Campus, Falls Church, Virginia, United States.

[19]Department of Anesthesiology and Pain Medicine, University of Toronto, Toronto, Ontario, Canada.

[20]Department of Anesthesiology, Hartford Hospital, Hartford, Connecticut, United States.

[21]Peacehealth Medical Group, Springfield, Oregon, United States.

[22]Department of Anesthesiology, University of Florida College of Medicine, Gainesville, Florida, United States.

[23]Department of Anesthesiology, Lewis Katz School of Medicine at Temple University, Philadelphia, Pennsylvania, United States.

[24]Center for Clinical Epidemiology and Biostatistics, University of Pennsylvania Perelman School of Medicine, Philadelphia, Pennsylvania, United States.

Abstract

Background: The effects of spinal versus general anesthesia on long-term outcomes have not been well-studied. We tested the hypothesis that spinal anesthesia is associated with better long-term survival and functional recovery than general anesthesia.

Methods: We conducted a pre-specified analysis of long-term outcomes of a completed randomized superiority trial that compared spinal anesthesia versus general anesthesia for hip

fracture repair. Participants included previously ambulatory patients 50 years of age or older at 46 US and Canadian hospitals. Patients were randomized 1:1 to spinal or general anesthesia, stratified by sex, fracture type, and study site. Outcome assessors and investigators involved in the data analysis were masked to the treatment arm. Outcomes included survival at up to 365 days after randomization (primary); recovery of ambulation among 365-day survivors; and composite endpoints for death or new inability to ambulate and death or new nursing home residence at 365 days. Patients were included in the analysis as randomized.

Results: 1,600 patients were enrolled between February 12, 2016, and February 18, 2021; 795 were assigned to spinal anesthesia, and 805 were assigned to general anesthesia. Among 1,599 patients who underwent surgery, vital status information at or beyond the final study interview (conducted at approximately 365 days after randomization) was available for 1,427 (89.2%). Survival did not differ by treatment arm; at 365 days after randomization, there were 98 deaths in patients assigned to spinal anesthesia versus 92 deaths in patients assigned to general anesthesia (hazard ratio: 1.08; 95% confidence interval (CI): 0.81, 1.44, P=0.59). Recovery of ambulation among patients who survived a year did not differ by type of anesthesia (adjusted odds ratio, spinal vs. general: 0.87; 95% CI: 0.67, 1.14, P=0.31). Other outcomes did not differ by treatment arm.

Conclusions: Long-term outcomes were similar with spinal versus general anesthesia.

Summary Statement:

In a planned analysis of a randomized trial of general versus regional anesthesia for hip fracture surgery in older adults, there were no differences in mortality, recovery of ambulation, or other outcomes at one year.

INTRODUCTION

Spinal and general anesthesia are the most common options for individuals undergoing surgery on the lower extremities.[1] While spinal anesthesia has been theorized to improve survival after surgery through reductions in short-term complications, particularly among older adults, long-term differences in outcomes by anesthesia technique remain poorly characterized.[2,3]

Each year, 1.5 million older adults worldwide undergo surgery to repair a fractured hip,[4] and most patients receive either spinal or general anesthesia.[5] While one randomized trial found differences in 1-year mortality according to anesthesia technique,[6] others have found no differences in survival beyond the immediate perioperative period.[7,8] Hip fractures are associated with marked decreases in long-term survival and functional independence,[9-11] but past trials have not evaluated recovery of ambulation or the need for new nursing home care after spinal versus general anesthesia. Recently, the REGAIN multicenter trial found similar rates of recovery of ambulation, survival, and return to pre-fracture residence at 60 days with either spinal or general anesthesia.[12] Outcomes related to long-term survival, recovery of ambulation, and need for new nursing home placement have not yet been reported.

We conducted a pre-planned analysis of long-term outcomes of a multicenter pragmatic randomized trial comparing spinal versus general anesthesia for hip fracture surgery.[12,13] This study aimed to examine one-year survival, recovery of ambulation over the first year

after surgery, and new nursing home residence at one year among those living independently prior to fracture. Specifically, we tested the hypothesis that spinal anesthesia improves long-term outcomes compared to general anesthesia.

MATERIALS AND METHODS

Study design

The REGAIN Trial was a randomized superiority trial conducted in 46 hospitals in the United States and Canada (Clinicaltrials.gov identifier NCT02507505, Principal Investigator Mark D. Neuman, registered July 24, 2015). The study design and primary outcome analyses have been described previously.[12,13] We worked with patients and stakeholders to select outcomes of importance to patients.[14] The trial protocol was published in advance of patient enrollment.[13] The Institutional Review Board (IRB) of the University of Pennsylvania approved the protocol and was the IRB of record for 11 sites; approval at other sites was via local IRB review.[15]

Participants

At each study hospital, staff reviewed emergency department registration and hospital admission lists, and surgical case schedules to identify adults aged 50 years or older who were scheduled to undergo surgical repair of a clinically or radiographically diagnosed femoral neck, intertrochanteric, or subtrochanteric hip fracture.

Major exclusions were: the inability to walk approximately 10 feet (3m) or across a room without human assistance before fracture; the need for a concurrent procedure not amenable to spinal anesthesia; periprosthetic fracture; and contraindications to spinal anesthesia (coagulopathy; anticoagulant medications;[16,17] critical or severe aortic stenosis; infection at the injection site; or elevated intracranial pressure). Patients were also excluded if they had previously participated in the trial or were determined to be unsuitable for randomization by the surgeon or anesthesiologist. Written informed consent was obtained from the participant or, for individuals who could not provide consent, from their healthcare proxy.

Randomization and masking

Consenting patients were assigned to receive spinal anesthesia or general anesthesia in a 1:1 ratio using permuted block randomization with variable block sizes.[18,19] Randomization was stratified by hospital, sex, and fracture location (femoral neck versus intertrochanteric or subtrochanteric fracture) using a central online data management system. Site staff obtained the randomization assignment from the data management system web portal and communicated it to the treating anesthesia team immediately before the start of anesthesia care. When site personnel could not access the online system, the randomization assignment was communicated by telephone to site staff by the study principal investigator or a designated staff member. Participants, treating clinicians, and data and safety monitoring board (DSMB) members were not masked to treatment assignment. The principal investigator, co-investigators, clinical coordinating center staff, and statisticians remained masked to treatment assignment until the database was locked for analysis.

Procedures

Treatments were delivered by clinical anesthesia staff at each site. For patients assigned to spinal anesthesia, providers were instructed to perform single-injection spinal anesthetics with sedation as needed for patient comfort. Conversion to general anesthesia was permitted based on clinical circumstances or patient request. For patients assigned to general anesthesia, providers were instructed to use an inhaled anesthetic agent for maintenance and an endotracheal tube, supraglottic airway, or other device for airway management. All other aspects of care, including pre-, intra-, and post-operative analgesic medications and use of peripheral nerve blocks for pain management were determined by the clinical team. Follow-up was performed by phone interviews with participants or proxy informants at approximately 60, 180, and 365 days after randomization.

Outcomes

The primary outcome for this analysis was the number of days from randomization to death, censored at the time of the final study interview (conducted approximately 365 days after randomization) or post-randomization day 365, whichever came first. Survival status and date of death information were ascertained from site staff reports and via telephone interviews with participants or appropriate proxy informants conducted by central coordinating center staff who were masked to treatment assignment. Telephone interviews were recorded and randomly audited for quality control. For US patients whose vital status could not be otherwise ascertained, we searched the National Death Index through 2022 (the most recent year available). For subjects with partial date-of-death data (i.e., month and year only), the date of death was imputed as the 15th day of the month in which they died.

We evaluated three secondary outcomes: (1) recovery of ambulation as assessed at 60, 180, and 365 days among individuals surviving to day 365; (2) a composite of death or new inability to ambulate without human assistance at 1 year; and (3) a composite of death or residence in a nursing home or other institution at 1 year among individuals who were community-dwelling at the time of fracture. For composite endpoints, death was included to account for potential survivor bias. Ambulatory status and location of residence were ascertained via masked telephone interview as above. For the ambulatory status assessment, patients were queried regarding their ability to walk 10 feet (3m) or across a room independently or with a walker or cane but without the assistance of another person. As an exploratory outcome, we also report overall functional status at approximately 60, 180, and 365 days after randomization as collected via telephone interview using the 12-item World Health Organization Disability Schedule (WHODAS) 2.0, which assesses disability in six functional domains (cognition, mobility, self-care, social interaction, life activities, and community participation).[20] Adverse events were assessed at each follow-up interview.

Statistical analysis

Sample size planning for REGAIN was based on the overall study primary outcome, which was a composite of death or new inability to walk approximately 10 feet without human assistance at 60 days. We estimated that 1,600 participants would provide 80% power to detect a 0.78 relative risk for this outcome among patients assigned to spinal versus

general anesthesia at a two-sided significance level of 0.05, assuming a 34.2% rate of this outcome in the general anesthesia arm.[21] We did not conduct separate power analyses for the long-term outcomes presented here. Our main analysis included all patients in the modified intention-to-treat population with available outcome data. The modified intention-to-treat population included all patients who underwent randomization and did not die before receiving treatment. Patients were included in the analysis according to their original treatment assignment.

We compared survival time between treatment arms using Kaplan-Meier curves and a Cox proportional hazards regression model, adjusted for sex, fracture type, and country of enrollment. We assessed the proportional hazards assumption using failure-time graphs and statistical tests of zero slopes in the Schoenfeld residuals; additional models incorporating time-varying effects were considered when the proportional hazards assumption was not met. Recovery of ambulation over the first year after randomization was compared by group via logistic mixed effects regression model (generalized linear mixed model approach) using data from the 60-, 180-, and 365-day interviews. This model included all participants with at least one valid post-randomization ambulation assessment and was adjusted for sex, fracture type, country, and days since randomization at assessment. To account for within-subject correlation, we included a random intercept term per individual with an unstructured variance-covariance matrix. For binary outcomes (death or new inability to ambulate; death or new transition to a nursing home residence), we used the Mantel-Haenszel test for differences in proportions, stratified by sex, fracture type, and country.

For our primary survival outcome, we considered the possibility of heterogeneity of treatment effects by exploring treatment-covariate interactions for six pre-specified patient characteristics (age (≥85 years versus <85 years), sex, country of enrollment, location of residence before fracture (nursing home versus community residence), reliance on assistive devices to ambulate before fracture, and fracture type. We conducted exploratory subgroup analyses for interactions with P values of 0.20 or lower using Cox models adjusted as above. Our survival analysis included all patients in the modified intention-to-treat population; to assess whether our findings may have been influenced by patterns of censoring before the end of the study, we compared characteristics of patients in each study arm who were censored prior to the final study interview due to withdrawal or loss to follow up. Additionally, we carried out a supplementary analysis via a Cox model that imputed censored failure times.[22] For censored subjects, failure times were imputed based on a model including patient age, sex, fracture type, country of enrollment, assigned arm, and comorbidities. Finally, to assess the potential impact of non-adherence to the assigned treatment on the study outcomes, we used a structural Cox model to estimate the per-protocol effect of spinal anesthesia on survival time with the assigned treatment as an instrumental variable.[23]

Analyses were performed using SAS 9.4 (SAS Institute, Cary, North Carolina). All hypotheses were tested at a two-sided significance level of 0.05. Data were reviewed at pre-specified intervals by an independent DSMB. Analyses followed a pre-specified statistical analysis plan; this plan, plus all modifications made after initiation of analysis appear in a Supplement.

Role of the funding source

The funder had no role in the design or conduct of the study, the collection, management, analysis, or interpretation of data, the preparation, review, or approval of the manuscript, or the decision to submit the manuscript for publication.

RESULTS

Between Feb 12, 2016, and Feb 18, 2021, we screened 22,022 patients (Appendix Figure 1). 12,915 patients were excluded based on eligibility criteria; 3,565 declined consent; 2,660 were not enrolled because of staff unavailability, and 1,282 were excluded for other reasons. Of 1,600 patients who underwent randomization, 795 were assigned to spinal anesthesia, and 805 were assigned to general anesthesia. One patient in the general anesthesia group died before receiving either treatment; this patient was not included in any study analyses.

Pre-randomization characteristics were similar across treatment arms (Table 1). Among 1,599 patients randomized, 527 (33%) were male, with mean age 78 years (± standard deviation 10.7). 1,377 (91%) were admitted from home or a retirement home (versus a nursing home, rehabilitation facility, or another acute care hospital) and 497 (32%) used an assistive device when ambulating more than 10 feet (3m) two weeks before fracture. As reported previously, [12] 666 of 795 patients assigned to spinal anesthesia (84%) received spinal anesthesia only. Of the remaining patients in the spinal anesthesia arm, 119 (15%) received general anesthesia, with or without an initial attempt to place a spinal block. Eight patients (1%) withdrew before surgery and anesthesia type was not recorded. Of the 804 patients assigned to general anesthesia who were included in intention-to-treat analysis, 769 (96%) received general anesthesia and 28 (3%) received spinal anesthesia; 7 patients (0.9%) withdrew before surgery or did not have a recorded anesthesia type.

Among all patients, median follow up was 365 days (interquartile range 354, 365); there was no difference in the duration of follow-up between patients randomized to spinal versus general anesthesia. During the study period, 190 deaths occurred; 98 in the spinal anesthesia group and 92 in the general anesthesia group. Deaths were identified via US National Death Index search in 39 patients; for the remaining 151 patients, deaths were ascertained via telephone follow-up or site report. Vital status information at or beyond the final study interview (conducted at approximately 365 days) was available for 1,427 (89.2%) of the overall study population, including 714 of 795 (89.8%) and 713 of 804 (88.7%) patients allocated to spinal and general anesthesia, respectively (Appendix Table 1). Among these patients, 1-year mortality was 13.7% for patients in the spinal anesthesia arm and 12.9% for patients in the general anesthesia arm. Survival at up to 365 days after randomization did not differ by treatment arm (Figure 1; Table 2; hazard ratio (HR), spinal vs. general anesthesia: 1.08; 95% confidence interval (CI): 0.81, 1.44, P=0.59). Of 6 pre-specified interaction analyses, we observed a P-value for interaction of 0.2 or less for two patient characteristics: age less than 85 years versus 85 years or older and country of randomization. Adjusted hazards of death were not significantly different among these subgroups. In the model including patients 85 years or older, failure-time graphs and diagnostic tests did not verify the proportional hazards assumption; we subsequently confirmed the findings from this model by estimating the hazard ratio for death at 365 days in a Cox model that

incorporated a time-varying effect (Appendix Table 2). Diagnostic testing of other Cox models did not indicate violations of the proportional hazards assumption.

Recovery of independence in ambulation over the first year after surgery did not differ among patients assigned to spinal anesthesia versus general anesthesia (adjusted odds ratio (OR), spinal vs. general: 0.87; 95% CI: 0.67, 1.14, P=0.31, Appendix Table 3). At the 60-day, 180-day, and 365-day interviews, death or new inability to walk occurred in 18.5% (132 of 712), 19.6% (136 of 694), and 24.1% (165 of 684) of patients assigned to receive spinal anesthesia and 18.0% (132 of 732), 18.7% (132 of 707), and 21.6% (146 of 676) of patients assigned to receive general anesthesia (Figure 2). The incidence of death or new inability to walk across study visits did not vary between treatment arms by visual inspection. The adjusted odds of dying or being newly unable to ambulate at 365 days did not differ by treatment arm (Table 3). Among patients not living in a nursing home before fracture, death or new transition to nursing home residence occurred in 119 of 584 patients assigned to spinal anesthesia (20.4%) versus 116 of 572 patients assigned to general anesthesia (20.3%; adjusted OR, spinal vs. general: 1.01, 95% CI 0.76, 1.35). Median WHODAS 2.0 scores were similar by treatment assignment across study visits (Appendix Table 4). Adverse events reported at up to 365 days were similar across treatment arms (Appendix Table 5).

Appendix Table 6 shows characteristics of patients without available vital status information at or beyond the 365-day interview due to loss to follow-up or study withdrawal. Sensitivity analyses imputing survival status for these patients returned results comparable to those from our main models (HR for spinal vs. general anesthesia: 1.08; 95% CI: 0.81, 1.44; P=0.59). Analyses that accounted for treatment non-adherence did not differ from our main results (HR for spinal vs. general anesthesia 1.10; 95% CI: 0.78, 1.56; P=0.59).

DISCUSSION

In this pre-specified secondary analysis of a pragmatic randomized trial of 1,600 adults aged 50 years and older, assignment to spinal anesthesia versus general anesthesia did not impact survival at up to 1 year after hip fracture surgery. Secondary outcomes, including recovery of ambulation over the first year after surgery, death or inability to walk without human assistance at 365 days, and death or new transition to nursing home residence at 365 days did not differ by anesthesia type.

Among older adults undergoing surgical procedures for which spinal or general anesthesia may be suitable, information on how anesthesia choices may influence survival and functional recovery over the first year after surgery can inform treatment choices by patients and clinicians. Most recent randomized trial data have not suggested major differences in short-term outcomes by anesthesia type.[12, 24] However, some differences have been noted that could plausibly affect longer-term outcomes. A recent meta-analysis found lower rates of acute kidney injury among patients randomized to spinal versus general anesthesia,[3] which could potentially impact long-term survival. A prior analysis of data from REGAIN suggested potential differences in pain and opioid use in the early postoperative period among patients who received spinal anesthesia,[25] which could possibly influence rehabilitation and recovery of ambulation.

To date, few studies have compared 1-year outcomes with spinal versus general anesthesia. A 2017 meta-analysis by Guay and colleagues[2] identified two single-center trials from the 1980s that evaluated survival at 1 year among patients assigned to spinal versus general anesthesia for hip fracture surgery and found no difference in survival by anesthesia type among a total of 726 patients enrolled across both studies.[7,8] More recently, Parker and Griffiths reported mortality at 1 year to be 20.2% with spinal anesthesia versus 12.1% with general anesthesia in a single-center randomized trial enrolling 322 hip fracture patients.[6]

The current study provides important new insights that add to and extend beyond past work in this area. Studies conducted in the 1980s predated the introduction of modern anesthesia medications and monitoring standards; the present study employed pragmatic treatment protocols to represent current standards of practice across the diverse US and Canadian hospitals in our network. We did not confirm findings from Parker and Griffith's prior trial of differences in survival at 1 year by anesthesia type;[6] this may have been due to differences in the characteristics of the patients enrolled in each study, in anesthesia techniques employed, or in postoperative care delivery across studies. In contrast to prior studies of long-term anesthesia outcomes, we evaluated outcomes of major importance to patients and families beyond survival alone, including recovery of ambulation and the need for new nursing home care 1 year after surgery. The large sample recruited for the present study also permitted additional analyses to examine for heterogeneity of treatment effects on survival outcome according to patient age and country of enrollment. These subgroup analyses did not identify significant differences in these groups according to anesthesia type.

Our study has limitations. Some patients were censored before completing the final study visit due to withdrawal or loss to follow-up. Sensitivity analyses conducted to address missing data produced results similar to those of primary analyses; however, since these analyses rely on assumptions we cannot fully verify, we cannot rule out bias due to missing data. As previously reported, some patients in each group failed to receive the assigned treatment.[12] Nonetheless, our findings regarding survival remained unchanged in supplemental analyses that accounted for crossover between spinal and general anesthesia using instrumental variable analyses. As we did not obtain cause-of-death information for most decedents in our analysis, we are unable to compare differences in the cause of death between groups. One-year mortality in our sample was lower than has been reported in unselected populations of hip fracture patients,[11] which may have been due to study eligibility criteria or differences in enrollment rates between sicker versus healthier patients. While the confidence intervals reported here argue against large effects of anesthesia type on long-term outcomes, the available sample does not permit us to fully exclude the potential for more subtle effects. Finally, based on resources available for the present study, we chose to conduct ambulation and location of residence assessments by telephone at three time points over the first year after surgery; it is possible that more frequent assessments or in-person evaluations may have produced different results.

Use of spinal anesthesia has increased over time,[5] potentially reflecting beliefs regarding potential outcome benefits.[26] Our finding of similar outcomes at 365 days with either technique in hip fracture patients suggests that, for older surgical patients who may be candidates for either spinal or general anesthesia, treatment choices can be based on

operative planning and patient preference rather than on anticipated differences in clinical outcomes.

Conclusions

In a large multicenter randomized trial of spinal versus general anesthesia for hip fracture surgery in older adults, mortality, ambulation, or other patient-centered outcomes at one year after surgery did not vary by anesthesia type.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements:

We thank the 1,600 older adults who volunteered to participate in the REGAIN trial, their families, and the many anesthesiologists, nurse anesthetists, orthopedic surgeons, and research staff members who helped to make this trial a success.

Funding Statement:

Patient-Centered Outcomes Research Institute, Washington, DC, United States (Award 1406-18876). Sponsors had no role in the design or conduct of the study, the collection, management, analysis, or interpretation of data, the preparation, review, or approval of the manuscript, or the decision to submit the manuscript for publication. The views presented in this work are solely the responsibility of the authors and do not necessarily represent the views of the Patient-Centered Outcomes Research Institute, its board of governors, or its methodology committee.

Appendix

Collaborating investigators by role: REGAIN Investigators Group

Writing Committee: Emily Vail, Susan Ellenberg, Annamarie Horan, Ann Tierney, Rui Feng, Mark Neuman.

Collaborators: Thomas Looke, Sandra Bent, Ariana Franco-Mora, Pamela Hedrick, Matthew Newbern (Advent Health); Rafik Tadros, Karen Pealer (Allegheny and Forbes Hospital); Kamen Vlassakov, Carolyn Buckley, Lauren Gavin, Svetlana Gorbatov, James Gosnell, Talora Steen, Avery Vafai, Jose Zeballos (Brigham & Women's Hospital); Jennifer Hruslinski (Center for Advocacy for the Rights and Interests of the Elderly); Louis Cardenas, Ashley Berry, John Getchell, Nicholas Quercetti (Christiana Hospital); Manal Hassan, Gauasan Bajracharya, Damien Billow, Michael Bloomfield, Evis Cuko, Mehrun K. Elyaderani, Robert Hampton, Hooman Honar, Dilara Khoshknabi, Daniel Kim, David Krahe, Michael M. Lew, Conjeevram B. Maheshwer, Azfar Niazi, Partha Saha, Ahmed Salih, Robert J. de Swart, Andrew Volio (Cleveland Clinic); Kelly Bolkus, Matthew DeAngelis, Gregory Dodson, Jeffrey Gerritsen, Brian McEniry, Ludmil Mitrev (Cooper University Hospital); M. Kwesi Kwofie, Anne Belliveau, Flynn Bonazza, Vera Lloyd, Izabela Panek (Dalhousie University); Jared Dabiri, Chris Chavez, Jason Craig, Todd Davidson, Chad Dietrichs, Cheryl Fleetwood, Mike Foley, Chris Getto, Susie Hailes, Sarah Hermes, Andy Hooper, Greg Koener, Kate Kohls, Leslie Law, Adam Lipp, Allison Losey, William Nelson, Mario Nieto, Pam Rogers, Steve Rutman, Garrett Scales, Barbara Sebastian, Tom Stanciu (Dell Seton Medical Center at the University of Texas); Gregg

Lobel, Michelle Giampiccolo, Dara Herman, Margit Kaufman, Bryan Murphy, Clara Pau, Thomas Puzio, Marlene Veselsky (Englewood Hospital and Medical Center); Kelly Apostle, Dory Boyer, Brenda Chen Fan, Susan Lee, Mike Lemke, Richard Merchant, Farhad Moola, Kyrsten Payne, Bertrand Perey, Darius Viskontas (Fraser Health); Mark Poler (Geisinger Medical Center); Patricia D'Antonio, Greg O'Neill (Gerontological Society of America); Amer Abdullah, Jamie Fish-Fuhrmann (Hartford Hospital); Mark Giska, Christina Fidkowski, Stuart Trent Guthrie, William Hakeos, Lillian Hayes, Joseph Hoegler, Katherine Nowak (Henry Ford Hospital); Jeffery Beck, Jaslynn Cuff, Greg Gaski, Sharon Haaser, Michael Holzman, A. Stephen Malekzadeh, Lolita Ramsey, Jeff Schulman, Cary Schwartzbach (Inova Fairfax Medical Center); Tangwan Azefor, Arman Davani, Mahmood Jaberi, Courtney Masear (Johns Hopkins Bayview Medical Center); Syed Basit Haider, Carolyn Chungu, Ali Ebrahimi, Karim Fikry, Andrew Marcantonio, Anitha Shelvan (Lahey Hospital and Medical Center); David Sanders, Collin Clarke, Abdel Lawendy (London Health Sciences Center); Gary Schwartz, Mohit Garg, Joseph Kim (Maimonides Medical Center); Juan Caruci, Ekow Commeh, Randy Cuevas, Germaine Cuff, Lola Franco, David Furgiuele (New York University Langone Medical Center); Matthew Giuca, Melissa Allman, Omid Barzideh, James Cossaro, Armando D'Arduini, Anita Farhi, Jason Gould, John Kafel, Anuj Patel, Abraham Peller, Hadas Reshef, Mohammed Safur, Fiore Toscano (New York University-Winthrop Hospital); Tiffany Tedore, Michael Akerman, Eric Brumberger, Sunday Clark, Rachel Friedlander, Anita Jegarl, Joseph Lane, John P. Lyden, Nili Mehta, Matthew T. Murrell, Nathan Painter, William Ricci, Kaitlyn Sbrollini, Rahul Sharma, Peter A.D. Steel, Michele Steinkamp, Roniel Weinberg, David Stephenson Wellman (NewYork-Presbyterian Hospital – Weill Cornell Medicine); Antoun Nader, Paul Fitzgerald, Michaela Ritz (Northwestern Memorial Hospital); Greg Bryson, Alexandra Craig, Cassandra Farhat, Braden Gammon, Wade Gofton, Nicole Harris, Karl Lalonde, Allan Liew, Bradley Meulenkamp, Kendra Sonnenburg, Eugene Wai, Geoffrey Wilkin (Ottawa Hospital); Karen Troxell, Mary Ellen Alderfer, Jason Brannen, Christopher Cupitt, Stacy Gerhart, Renee McLin, Julie Sheidy, Katherine Yurick (Reading Hospital); Fei Chen, Karen Dragert, Geza Kiss, Halina Malveaux, Deborah McCloskey, Scott Mellender, Sagar S. Mungekar, Helaine Noveck, Carlos Sagebien (Rutgers-Robert Wood Johnson University Hospital); Luat Biby, Gail McKelvy, Anna Richards (Peace Health Sacred Heart Medical Center at Riverbend); Ramon Abola, Brittney Ayala, Darcy Halper, Ana Mavarez, Sabeen Rizwan (Stony Brook Medicine); Stephen Choi, Imad Awad, Brendan Flynn, Patrick Henry, Richard Jenkinson, Lilia Kaustov, Elizabeth Lappin, Paul McHardy, Amara Singh (Sunnybrook Health Sciences Center); Joanne Donnelly, Meera Gonzalez, Christopher Haydel, Jon Livelsberger, Theresa Pazionis, Bridget Slattery, Maritza Vazquez-Trejo (Temple University Hospital); Jaime Baratta, Michael Cirullo, Brittany Deiling, Laura Deschamps, Michael Glick, Daniel Katz, James Krieg, Jennifer Lessin, Jeffrey Mojica, Marc Torjman (Thomas Jefferson University Hospitals); Rongyu Jin, Mary Jane Salpeter (Toronto Western Hospital); Mark Powell, Jeffrey Simmons, Prentiss Lawson, Promil Kukreja, Shanna Graves, Adam Sturdivant, Ayesha Bryant, Sandra Joyce Crump (University of Alabama Birmingham Medical Center); Michelle Verrier, James Green, Matthew Menon (University of Alberta); Richard Applegate, Ana Arias, Natasha Pineiro, Jeffrey Uppington, Phillip Wolinsky (University of California Davis Medical Center); Amy Gunnett, Jennifer Hagen, Sara Harris, Kevin Hollen, Brian Holloway, Mary Beth Horodyski,

Trevor Pogue, Ramachandran Ramani, Cameron Smith, Anna Woods (University of Florida College of Medicine); Matthew Warrick, Kelly Flynn, Paul Mongan (University of Florida Jacksonville); Yatish Ranganath, Sean Fernholz, Esperanza Ingersoll-Weng, Anil Marian, Melinda Seering, Zita Sibenaller, Lori Stout, Allison Wagner, Alicia Walter, Cynthia Wong (University of Iowa Hospitals & Clinics); Denise Orwig (University of Maryland); Maithri Goud, Chris Helker, Lydia Mezenghie, Brittany Montgomery, Peter Preston, J. Sanford Schwartz, Ramona Weber, Lee A. Fleisher, Samir Mehta, Alisa J. Stephens-Shields, Cassandra Dinh, Aron Schwartz (University of Pennsylvania/Penn Presbyterian Medical Center); Jacques E. Chelly, Shiv Goel, Wende Goncz, Touichi Kawabe, Sharad Khetarpal, Amy Monroe, Vladislav Shick (University of Pittsburgh Medical Center); Max Breidenstein, Timothy Dominick, Alexander Friend, Donald Mathews (University of Vermont Medical Center); Richard Lennertz, Robert Sanders, Helen Akere, Tyler Balweg, Amber Bo, Christopher Doro, David Goodspeed, Gerald Lang, Maggie Parker, Amy Rettammel, Mary Roth, Marissa White, Paul Whiting (University of Wisconsin-Madison); Brian F.S. Allen, Tracie Baker, Debra Craven, Matt McEvoy, Teresa Turnbo (Vanderbilt University Medical Center); Stephen Kates, Melanie Morgan, Teresa Willoughby (Virginia Commonwealth University Medical Center); Wade Weigel, David Auyong, Ellie Fox, Tina Welsh (Virginia Mason Medical Center); Bruce Cusson, Sean Dobson, Christopher Edwards, Lynette Harris, Daryl Henshaw, Kathleen Johnson, Glen McKinney, Scott Miller, Jon Reynolds, B. Scott Segal, Jimmy Turner, David VanEenenaam, Robert Weller (Wake Forest Baptist Medical Center); Jineli Lei, Miriam Treggiari, Shamsuddin Akhtar, Marcelle Blessing, Chanel Johnson, Michael Kampp, Kimberly Kunze, Mary O'Connor (Yale-New Haven Hospital).

Executive Committee: Mark D. Neuman (Chair), Jeffrey Carson, Susan Ellenberg, Lakisha J. Gaskins, Jay Magaziner, Frederick Sieber

Recruiting Site Leads : Thomas Looke (Advent Health); Rafik Tadros (Allegheny and Forbes Hospital); Kamen Vlassakov (Brigham & Women’s Hospital); Louis Cardenas (Christiana Hospital); Daniel I. Sessler (Cleveland Clinic Main Campus); Sabry Ayad (Cleveland Clinic Fairview); Manal Hassan (Cleveland Clinic Hillcrest); Kelly Bolkus; Ludmil Mitrev (Cooper University Hospital); M. Kwesi Kwofie (Dalhousie University); Jared Dabiri (Dell Seton Medical Center at the University of Texas); Gregg Lobel (Englewood Hospital and Medical Center); Trevor Stone (Fraser Health); Mark Poler (Geisinger Medical Center); Richard Sheppard (Hartford Hospital); Mark Giska (Henry Ford Hospital); Robert Hymes (Inova Fairfax Medical Center); Frederick Sieber (Johns Hopkins Bayview Medical Center); Balram Sharma (Lahey Hospital and Medical Center); David Sanders (London Health Sciences Center); Gary Schwartz (Maimonides Medical Center); Mitchell Marshall (New York University Langone Medical Center); Matthew Giuca (New York University-Winthrop Hospital); Tiffany Tedore (NewYork-Presbyterian Hospital – Weill Cornell Medicine); Antoun Nader (Northwestern Memorial Hospital); Stephen Papp, Greg Bryson (Ottawa Hospital); Karen Troxell (Reading Hospital); Jeffrey Carson, Geza Kiss (Rutgers-Robert Wood Johnson University Hospital); Barry Perlman (Peace Health Sacred Heart Medical Center at Riverbend); Syed Azim (Stony Brook Medicine); Stephen Choi (Sunnybrook Health Sciences Center); Ellen Hauck (Temple University Hospital); Eric Schwenk (Thomas Jefferson University Hospitals); Ki Jinn Chin

(Toronto Western Hospital); Mark Powell (University of Alabama Birmingham Medical Center); Derek Dillane (University of Alberta); Richard Applegate (University of California Davis Medical Center); Joshua Sappenfield (University of Florida College of Medicine); Matthew Warrick (University of Florida Jacksonville); Yatish Ranganath (University of Iowa Hospitals & Clinics); Derek Donegan, Nabil Elkassabany, Mark Neuman (Penn Presbyterian Medical Center); Jacques E. Chelly, Charles Luke (University of Pittsburgh Medical Center); Mark A. Hoeft (University of Vermont Medical Center); Richard Lennertz, Robert Sanders (University of Wisconsin-Madison); Brian F.S. Allen (Vanderbilt University Medical Center); Stephen Kates (Virginia Commonwealth University Medical Center); Wade Weigel (Virginia Mason Medical Center); J. Douglas Jaffe (Wake Forest Baptist Medical Center); Jinlei Li (Yale-New Haven Hospital)

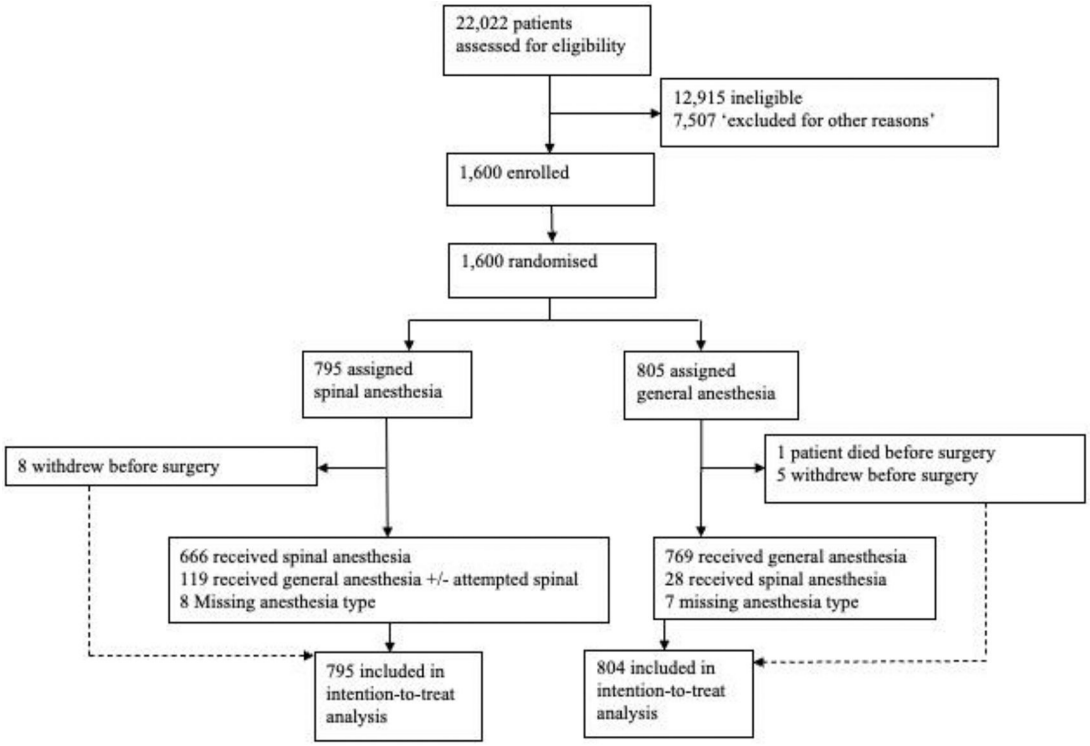
Data and Safety Monitoring Board: Duminda N. Wijeysundera (Chair), Sachin Kheterpal, Reneé H. Moore, Alexander K. Smith, Laura L. Tosi

Publications and Ancillary Studies Committee: Mark D. Neuman (Chair), Jeffrey Carson, Derek Dillane, Susan Ellenberg, Nabil Elkassabany, Rui Feng, Robert A. Hymes, Thomas Looke, Jay Magaziner, Diane Menio, Daniel Sessler, Frederick Sieber

Adverse Event Monitoring Committee: Samir Mehta (Chair), Jeffrey Carson, Annamarie Horan, Lee Fleisher

Patient Engagement Committee: Mark D. Neuman (Co-Chair), Diane Menio (Co-Chair), Jennifer Hruslinski, Robert A. Hymes, J. Douglas Jaffe, Lolita Ramsey, Lakisha J. Gaskins, Christine Langlois

Site Monitoring Team: Lakisha J. Gaskins (Lead), Lydia Mezenghie, Brittany Montgomery, Samuel Oduwole, Thomas Rose



Appendix Figure 1.
CONSORT diagram

Appendix Table 1.

Recorded patient outcomes by follow-up period

	All participants (N=1,599)		
	60 Day (31-90 day window)	**180 Day (135-225 day window)**	**365 Day (305-425 day window)**
Status	**No. (%)**	**No. (%)**	**No. (%)**
Died by mid-window	63 (3.9)	132 (8.3)	190 (11.9)
Interview completed	1,381 (86.4)	1,269 (79.4)	1,170 (73.2)
Known alive at start of window (walking status unknown)	112 (7.0)	111 (6.9)	67 (4.2)
Withdrawn prior to window (vital status unknown)	23 (1.4)	39 (2.4)	62 (3.9)
Unknown	20 (1.3)	48 (3.0)	110 (6.9)

Appendix Table 2.

Sensitivity analysis. Hazard ratio for death at day 365 between spinal versus general anesthesia among patients 85 years of age or older, adjusted for time-treatment interaction

Hazard ratio for death at day 365, spinal versus general anesthesia	95% CI
2.59[a]	0.25 - 27.1

[a] Cox proportional hazards model adjusted for sex, fracture type, country, and a time-treatment interaction.

Appendix Table 3.

Recovery of independence in ambulation over time within the overall study sample

	Day after trial enrollment	Randomized to spinal anesthesia		Randomized to general anesthesia	
		Number of patients	No. (%)	Number of patients	No. (%)
Able to walk without human assistance	Day 60	628	551 (87.7)	649	574 (88.4)
	Day 180	600	542 (90.3)	621	561 (90.3)
	Day 365	586	519 (88.6)	584	530 (90.8)

Appendix Table 4.

Median 12-item WHODAS 2.0 scores between groups at 60, 180, and 365 days

	Randomized to spinal anesthesia		Randomized to general anesthesia	
Days after trial enrollment	No.	Median WHODAS 2.0 score (IQR)	No.	Median WHODAS 2.0 score (IQR)
60	225	22.7 (8.3, 43.2)	241	18.2 (6.3, 31.8)
180	249	10.4 (2.3, 27.1)	274	10.4 (2.1, 27.3)
365	280	10.4 (2.1, 29.2)	276	8.3 (0.0, 22.9)

IQR: interquartile range, WHODAS: 12-item World Health Organization Disability Schedule 2.0 scale; scores range from 0 to 100, with lower scores indicating lower degrees of disability.

Appendix Table 5.

Site-reported adverse events, by treatment arm, grouped by Medical Dictionary for Regulatory Activities System Organ Class

	Spinal N=795							General N=805					
	Severity grade[a]							Severity grade[a]					
System organ class	1	2	3	4	5	All grades		1	2	3	4	5	All grades
Blood and lymphatic system disorders	33	26	79	1	0	139		35	30	79	0	0	144
Cardiac disorders	13	29	18	5	5	70		7	15	7	10	7	46
Gastrointestinal disorders	35	24	17	3	4	83		51	27	16	3	0	97

	Spinal N=795							General N=805					
	Severity grade[a]							Severity grade[a]					
System organ class	**1**	**2**	**3**	**4**	**5**	**All grades**		**1**	**2**	**3**	**4**	**5**	**All grades**
General disorders and administration site conditions	36	33	14	0	63	146		39	22	6	1	68	136
Infections and infestations	23	30	35	5	5	98		14	38	24	4	1	81
Injury, poisoning and procedural complications	20	26	28	2	2	78		29	24	40	4	2	99
Metabolism and nutrition disorders	31	15	17	3	1	67		27	12	16	5	1	61
Nervous system disorders	28	24	19	2	5	78		22	18	13	1	2	56
Psychiatric disorders	22	21	7	1	0	51		24	23	23	1	0	71
Renal and urinary disorders	16	20	3	3	1	43		16	25	4	1	1	47
Respiratory, thoracic and mediastinal disorders	17	19	16	5	2	59		27	18	24	6	7	82
Surgical and medical procedures	27	35	16	1	0	79		24	38	23	1	0	86
Vascular disorders	15	25	24	1	2	67		14	15	15	2	2	48
Other organ systems[b]	23	27	15	2	0	67		26	19	16	1	1	63
Totals	339	354	308	34	90	1125		355	324	306	40	92	1117

[a] Severity grades range from 1 (mild) to 5 (death).

[b] Includes congenital, familial, and genetic disorders; eye disorders; hepatobiliary disorders; investigations; musculoskeletal and connective tissue disorders; neoplasms, benign, malignant, and unspecified; reproductive system and breast disorders. All events with a listed start date through post randomization day 365 are shown. Where subjects had more than one event reported within a given grade, all reported events are included.

Appendix Table 6.

Comparison of trial participant characteristics with- and without- missing vital status data at 365 days after randomization

	Vital status at or beyond 365 day interview after randomization	
	Known No. = 1427	**Unknown No. = 172**
Randomized to general anesthesia	713/1427 (50.0)	91/172 (52.9)
Randomized to spinal anesthesia	714/1427 (50.0)	81/172 (47.1)
Age at randomization, years		
<65	187/1427 (13.1)	25/171 (14.6)
65-74	329/1427 (23.1)	55/171 (32.2)
75-84	476/1427 (33.4)	52/171 (30.4)
85 and older	435/1427 (30.5)	39/171 (22.8)
Male sex	475/1426 (33.3)	51/172 (29.7)
Race		
White	1230/1376 (89.4)	143/159 (89.9)

	Vital status at or beyond 365 day interview after randomization	
	Known No. = 1427	**Unknown No. = 172**
Black	111/1376 (8.1)	11/159 (6.9)
Other or more than one race	35/1376 (2.5)	5/159 (3.1)
Hispanic	23/1352 (1.7)	4/160 (2.5)
Enrolled at a Canadian site	371/1427 (26.0)	50/172 (29.1)
Number of coexisting conditions[a]	1 (0 - 1)	1 (0 - 1)
American Society of Anesthesiologists Physical Status Classification		
I or II, no or mild systemic disease	478/1421 (33.6)	61/154 (39.6)
III or IV, moderate or severe systemic disease	943/1421 (66.4)	93/154 (60.4)
Do Not Resuscitate status documented	220/1427 (15.4)	26/171 (15.2)
Use of assistive walking device when ambulating 10 feet or across a room 2 weeks prior to fracture	450/1402 (32.1)	47/169 (27.8)
3D-CAM assessment positive for delirium prior to randomization[b]	176/1337 (13.2)	24/161 (14.9)
Pre-admission residence		
Home or retirement home	1228/1349 (91.0)	149/161 (92.5)
Nursing home or other location	121/1349 (9.0)	12/161 (7.5)

Data are No. / total No. (%) or median (IQR).

[a]Included coexisting conditions are chronic pulmonary disease, disseminated cancer, diabetes mellitus, coronary artery disease, congestive heart failure, cerebrovascular disease, dementia, and creatinine > 2mg/dL or current dialysis.

[b]3D-CAM: 3-minute Diagnostic Interview for Confusion Assessment Method.

Abbreviations

CI	confidence interval
DSMB	data and safety monitoring board
HR	hazard ratio
IRB	institutional review board
OR	odds ratio
REGAIN	Regional versus General Anesthesia for Promoting Independence after Hip Fracture
US	United States
WHODAS	World Health Organization Disability Schedule

References

1. Guay J, Choi P, Suresh S, Albert N, Kopp S, Pace NL. Neuraxial blockade for the prevention of postoperative mortality and major morbidity: an overview of Cochrane systematic reviews. Cochrane Database Syst Rev 2014; 1: CD010108.

2. Guay J, Parker MJ, Gajendragadkar PR, Kopp S. Anaesthesia for hip fracture surgery in adults. Cochrane Database Syst Rev 2016; 2: CD000521. [PubMed: 26899415]

3. Kunutsor SK, Hamal PB, Tomassini S, Yeung J, Whitehouse MR, Matharu GS. Clinical effectiveness and safety of spinal anesthesia compared with general anesthesia in patients undergoing hip fracture surgery using a consensus-based core outcome set and patient-and public-informed outcomes: a systematic review and meta-analysis of randomized controlled trials. Br J Anaesth 2022; 129(5): 788–800. [PubMed: 36270701]

4. Johnell O, Kanis JA. An estimate of the worldwide prevalence and disability associated with osteoporotic fractures. Osteoporos Int 2006; 17(12): 1726–33. [PubMed: 16983459]

5. Maxwell BG, Spitz W, Porter J. Association of Increasing Use of Spinal Anesthesia in Hip Fracture Repair With Treating an Aging Patient Population. JAMA Surg 2020; 155(2): 167–8. [PubMed: 31746959]

6. Parker MJ, Griffiths R. General versus regional anesthesia for hip fractures. A pilot randomized controlled trial of 322 patients. Injury 2015; 46(8): 1562–6. [PubMed: 26049662]

7. McKenzie PJ, Wishart HY, Smith G. Long-term outcome after repair of fractured neck of femur. Comparison of subarachnoid and general anaesthesia. Br J Anaesth 1984; 56(6): 581–5. [PubMed: 6721969]

8. Valentin N, Lomholt B, Jensen JS, Hejgaard N, Kreiner S. Spinal or general anaesthesia for surgery of the fractured hip? A prospective study of mortality in 578 patients. Br J Anaesth 1986; 58(3): 284–91. [PubMed: 3947489]

9. Hannan EL, Magaziner J, Wang JJ, Eastwood EA, Silberzweig SB, Gilbert M, Morrison RS, McLaughlin MA, Orosz GM, Siu AL. Mortality and locomotion 6 months after hospitalization for hip fracture: risk factors and risk-adjusted hospital outcomes. JAMA 2001; 285(21): 2736–42. [PubMed: 11386929]

10. Haentjens P, Magaziner J, Colon-Emeric CS, Vanderschueren D, Milisen K, Velkeniers B, Boonen S. Meta-analysis: excess mortality after hip fracture among older women and men. Ann Intern Med 2010; 152(6): 380–90. [PubMed: 20231569]

11. Tajeu GS, Delzell E, Smith W, Arora T, Curtis JR, Saag KG, Morrisey MA, Yun H, Kilgore ML. Death, debility, and destitution following hip fracture. J Gerontol A Biol Sci Med Sci 2014; 69(3): 346–53. [PubMed: 23873945]

12. Neuman MD, Feng R, Carson JL, Gaskins LJ, Dilane D, Sessler DI, Sieber F, Magaziner J, Marcantonio ER, Mehta S, Menio D, Ayad S, Stone T, Papp S, Schwenk ES, Elkassabany N, Marshall M, Jaffe JD, Luke C, Sharma B, Azim S, Hymes R, Chin KJ, Sheppard R, Perlman B, Sappenfield J, Hauck E, Hoeft MA, Giska M, Ranganath Y, Tedore T, Choi S, Li J, Kwofie MK, Nader A, Sanders RD, Allen BFS, Vlassakov K, Kates S, Fleisher LA, Dattilo J, Tierney A, Stephens-Shields AJ, Ellenberg S, REGAIN Investigators. Spinal Anesthesia or General Anesthesia for Hip Surgery in Older Adults. N Engl J Med 2021; 385(22): 2025–35. [PubMed: 34623788]

13. Neuman MD, Ellenberg SS, Sieber FE, Magaziner JS, Feng R, Carson JL, REGAIN Investigators. Regional versus General Anesthesia for Promoting Independence after Hip Fracture (REGAIN): protocol for a pragmatic, international multicenter trial. BMJ Open 2016; 6(11): e013473.

14. Hruslinski J, Menio DA, Hymes RA, Jaffe JD, Langlois C, Ramsey L, Gaskins LJ, Neuman MD, REGAIN Investigators. Engaging patients as partners in a multicenter trial of spinal versus general anaesthesia for older adults. Br J Anaesth 2021; 126(2): 395–403. [PubMed: 33279102]

15. Neuman MD, Gaskins LJ, Ziolek T, REGAIN Investigators. Time to institutional review board approval with local versus central review in a multicenter pragmatic trial. Clin Trials 2018; 15(1): 107–11. [PubMed: 28982261]

16. Horlocker TT, Vandermeuelen E, Kopp SL, Gogarten W, Leffert LR, Benzon HT. Regional Anesthesia in the Patient Receiving Antithrombotic or Thrombolytic Therapy: American Society of Regional Anesthesia and Pain Medicine Evidence-Based Guidelines (Fourth Edition). Reg Anesth Pain Med 2018; 43(3): 263–309. [PubMed: 29561531]

17. Horlocker TT, Wedel DJ, Rowlingson JC, Enneking FK, Kopp SL, Benzon HT, Brown DL, Heit JA, Mulroy MF, Rosenquist RW, Tryba M, Yuan C-S. Regional anesthesia in the patient receiving antithrombotic or thrombolytic therapy: American Society of Regional Anesthesia and

Pain Medicine Evidence-Based Guidelines (Third Edition). Reg Anesth Pain Med 2010; 35(1): 64–101. [PubMed: 20052816]

18. Matts JP, Lachin JM. Properties of Permuted-Block Randomization in Clinical-Trials. Control Clin Trials 1988; 9(4): 327–44. [PubMed: 3203524]
19. Lachin JM, Matts JP, Wei LJ. Randomization in clinical trials: conclusions and recommendations. Control Clin Trials 1988; 9(4): 365–74. [PubMed: 3203526]
20. World Health Organization. Measuring Health and Disability: Manual for WHO Disability Assessment Schedule (WHODAS 2.0). Geneva, Switzerland: WHO Press; 2010.
21. Carson JL, Terrin ML, Noveck H, Sanders DW, Chaitman BR, Rhoads GG, Nemo G, Dragert K, Beaupre L, Hildebrand K, Macaulay W, Lewis C, Cook DR, Dobbin G, Zakriya KJ, Apple FS, Horney RA, Magaziner J, FOCUS Investigators. Liberal or restrictive transfusion in high-risk patients after hip surgery. N Engl J Med 2011; 365(26): 2453–62. [PubMed: 22168590]
22. Jackson D, White IR, Seaman S, Evans H, Baisley K, Carpenter J. Relaxing the independent censoring assumption in the Cox proportional hazards model using multiple imputation. Stat Med 2014; 33(27): 4681–94. [PubMed: 25060703]
23. Martinussen T, Nørbo Sørensen D, Vansteelandt S. Instrumental variables estimation under a structural Cox model. Biostatistics 2019; 20(1): 65–79. [PubMed: 29165631]
24. Li T, Li J, Yuan L, Wu J, Jiang C, Daniels J, Mehta RL, Wang M, Yeung J, Jackson T, Melody T, Jin S, Yao Y, Wu J, Chen J, Smith FG, Lian Q, RAGA Study Investigators. Effect of regional vs general anesthesia on incidence of postoperative delirium in older patients undergoing hip fracture surgery: The RAGA randomized trial. JAMA 2022; 327(1): 50–58. [PubMed: 34928310]
25. Neuman MD, Feng R, Ellenberg SS, Sieber F, Sessler DI, Magaziner J, Elkassabany N, Schwenck ES, Dillane D, Marcantonio ER, Menio D, Ayad S, Hassan M, Stone T, Papp S, Donegan D, Marshall M, Jaffe JD, Luke C, Sharma B, Azim S, Hymes R, Chin K-J, Sheppard R, Perlman B, Sappenfield J, Hauck E, Hoeft MA, Tierney A, Gaskins LJ, Horan AD, Brown T, Dattilo J, Carson JL, REGAIN Investigators.. Pain, Analgesic Use, and Patient Satisfaction With Spinal Versus General Anesthesia for Hip Fracture Surgery : A Randomized Clinical Trial. Ann Intern Med 2022; 175(7): 952–60. [PubMed: 35696684]
26. White SM, Altermatt F, Barry J, Ben-David B, Coburn M, Coluzzi F, Degoli M, Dillane D, Foss NB, Gelmanas A, Griffiths R, Karpetas G, Jim J-H, Kluger M, Lau P-W, Matot I, McBrien M, McManus S, Montoya-Pelaez LF, Moppett IK, Parker M, Porrill O, Sanders RD, Shelton C, Sieber F, Trikha A, Xueging X. International Fragility Fracture Network Delphi consensus statement on the principles of anesthesia for patients with hip fracture. Anaesthesia 2018; 73(7): 863–874. [PubMed: 29508382]

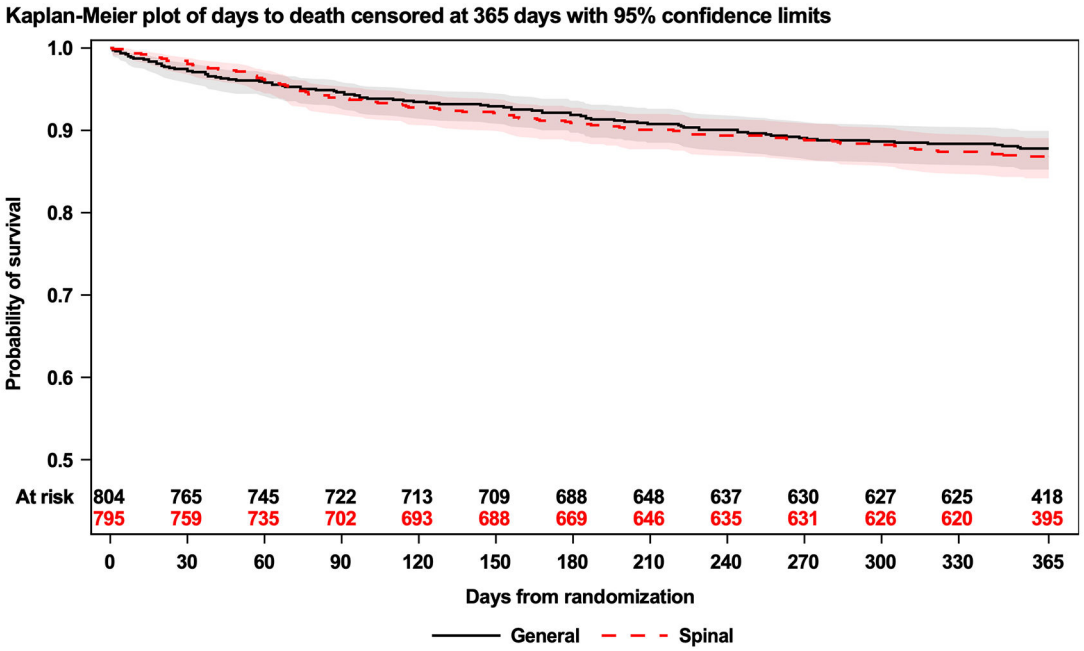


Figure 1. Kaplan-Meier plot of days to death censored at 365 days

Shading represents 95% confidence limits (CI). Log-rank P=0.59. Hazard ratio from the Cox model adjusting for age group, fracture type, and country of randomization: 1.08 (95% CI 0.81, 1.44), P=0.59.

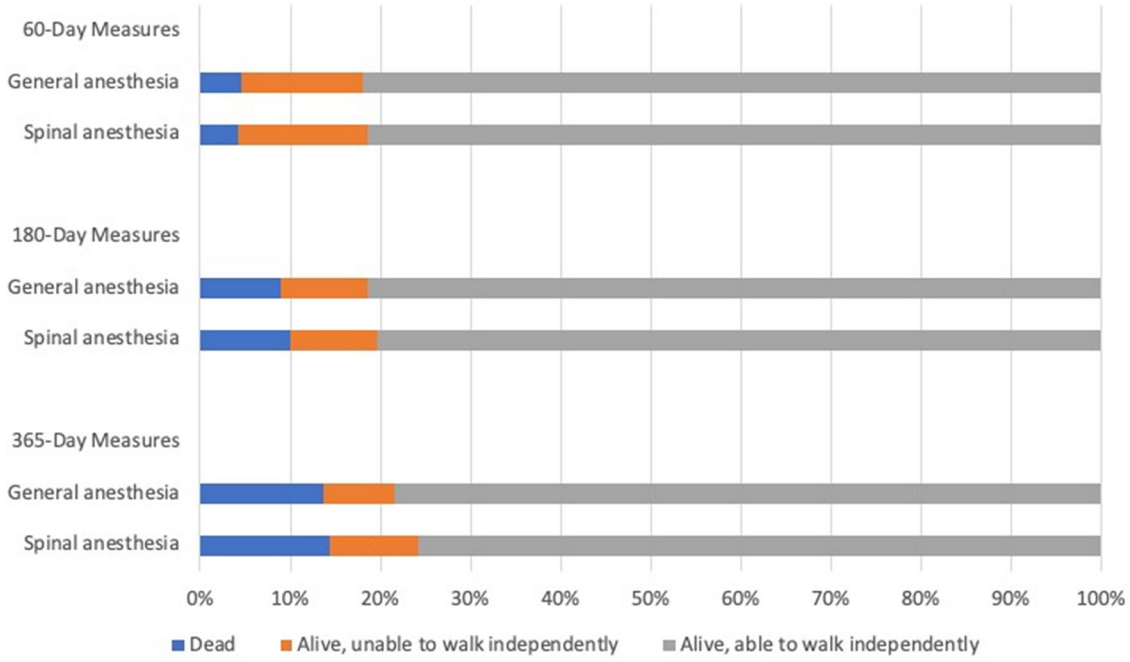


Figure 2. Unadjusted ambulation and survival outcomes at approximately 60, 180, and 365 days after randomization, stratified by treatment group

60-day interview data were available for 712 patients in the spinal anesthesia group and 732 patients in the general anesthesia group; 180-day interview data were available for 694 patients in the spinal anesthesia group and 707 in the general anesthesia group. 365-day interview data were available for 684 patients in the spinal anesthesia group and 676 in the general anesthesia group.

Table 1.

Patient characteristics by treatment assignment

	Randomized to spinal anesthesia N = 795	Randomized to general anesthesia N = 804
Age at randomization, yr — no. / total no. (%)		
<65	116/795 (14.6%)	96/803 (12.0%)
65-74	191/795 (24.0%)	193/803 (24.0%)
75-84	262/795 (33.0%)	266/803 (33.1%)
85 and older	226/795 (28.4%)	248/803 (30.9%)
Male sex — no. / total no. (%)	258/795 (32.5%)	269/804 (33.5%)
Race — no. / total no. (%)		
White	683/762 (89.6%)	690/773 (89.3%)
Black	55/762 (7.2%)	67/773 (8.7%)
Other or more than one race	24/762 (3.1%)	16/773 (2.1%)
Hispanic ethnic group — no. / total no. (%)	15/750 (2.0%)	12/762 (1.6%)
Enrolled at a Canadian site — no. / total no. (%)	210/795 (26.4%)	211/804 (26.2%)
Number of coexisting medical conditions[a] — median (IQR)	1 (0 - 2)	1 (0 - 1)
American Society of Anesthesiologists' Physical Status Classification — no. / total no. (%)		
I or II, no or mild systemic disease	251/782 (32.1%)	288/793 (36.3%)
III or IV, moderate or severe systemic disease	531/782 (67.9%)	505/793 (63.7%)
Do Not Resuscitate status documented	125/795 (15.7%)	121/803 (15.1%)
Use of assistive walking device when ambulating 10 feet (3m) or across a room 2 weeks before fracture — no. / total no. (%)	249/779 (32.0%)	248/792 (31.3%)
3D-CAM assessment positive for delirium before randomization[b] — no. / total no. (%)	96/746 (12.9%)	104/752 (13.8%)
Preadmission residence — no. / total no. (%)		
Home or retirement home	688/748 (92.0%)	689/762 (90.4%)
Nursing home or other location	60/748 (8.0%)	73/762 (9.6%)
WHODAS 2.0 summary score[c] — median (IQR)	9.1 (2.1 - 22.9)	8.3 (2.1 - 25.0)

[a] Coexisting conditions included chronic pulmonary disease, diabetes mellitus, disseminated cancer, coronary artery disease, congestive heart failure, cerebrovascular disease, dementia, and serum creatinine >2mg/dL or current dialysis.

[b] 3D-CAM: 3-minute Diagnostic Interview for Confusion Assessment Method.

[c] WHODAS 2.0: World Health Organization Disability Schedule 2.0. Scores range from 0 to 100, with lower scores indicating lower degrees of disability.

Table 2.

Effect of spinal anesthesia versus general anesthesia on survival at up to 365 days after randomization

	Hazard ratio, spinal versus general anesthesia (95% CI)	P
Overall study sample		
	1.08 (0.81 - 1.44)[a]	0.59
Subgroup analyses [b]		
Age: <85	0.91 (0.61 - 1.36)[a]	
Age: ≥85	1.35 (0.90 - 2.01)[c]	
Country of enrollment: United States	0.98 (0.71 - 1.34)[d]	
Country of enrollment: Canada	1.63 (0.85 - 3.12)[d]	

[a] Cox proportional hazards model for death over the study period adjusted for sex, fracture type, and country. Proportional hazards assumption confirmed via examination of failure time graph and P>0.05 in test for zero slope in Schoenfeld residuals.

[b] We tested for interactions between treatment assignment and the following pre-specified patient characteristics on the primary outcome: age 85 years or older versus younger than 85 years; sex; country of enrollment; the need for assistive devices to ambulate prior to fracture; location of residence prior to fracture; and fracture type. Subgroup analyses were carried out only when the p-value for the interaction term was 0.20 or less.

[c] Cox proportional hazards model for death at 365 days after enrollment adjusted for sex, fracture type, and country. Failure time graphs and test for zero slope in Schoenfeld residuals did not confirm proportional hazards assumption (P=0.02); additional analyses shown in Appendix Table 1.

[d] Cox proportional hazards model adjusted for sex and fracture type. Proportional hazards assumption confirmed via examination of failure time graph and P>0.05 in test for zero slope in Schoenfeld residuals.

Table 3.

Effect of spinal anesthesia versus general anesthesia on composite secondary outcomes

	Spinal anesthesia		General anesthesia		
	No. of patients	**No. (%)**	**No. of patients**	**No. (%)**	**Odds ratio (95% CI)**
Death or inability to walk without human assistance at 365 days	684	165 (24.1)	676	146 (21.6)	1.16 (0.90 - 1.50)[a]
Death or new nursing home admission at 365 days[b]	584	119 (20.4)	572	116 (20.3)	1.01 (0.76 - 1.35)[a]

[a.] Mantel-Haenszel test adjusted for sex and fracture type.

[b.] Among community-dwelling patients at randomization.