Journal Club Pre-Session Handout

Date: September 9, 2025, 3-4 pm
Topic: Spinal vs General Anesthesia in Hip Arthroplasty (Hip Fracture vs Elective THA)
Resident Leads: Derron Yu, MD and David Lester, MD
Faculty Leads: Brian Pitts, MD,MS,MEHP and Ken Furukawa, MD

Purpose

This journal club session focuses on evidence from the REGAIN trials comparing *spinal vs general anesthesia* in elderly patients undergoing hip fracture surgery. It contrasts these findings with best practice recommendations for elective total hip arthroplasty (THA).

Topic

Spinal vs General Anesthesia in Hip Arthroplasty (Hip Fracture vs Elective THA)

Objectives:

1. Practice **critical appraisal skills** using a structured checklist (validity, results, applicability).
2. Interpret **effect sizes and confidence intervals**, moving beyond p-values.
3. Apply findings to **clinical vignettes** relevant to anesthesia practice.
4. Recognize limits of generalizing fracture trial data to elective THA, where **ERAS pathways and regional techniques** remain standard of care.

Note: The session emphasizes **active resident-led discussion** rather than lecture, linking appraisal skills directly to **PBLI milestones (1)** and clinical decision-making.

Articles for Review

1. **Vail et al., Anesthesiology 2024** — REGAIN Long-Term Outcomes (1-year survival & ambulation)
2. **Ritz et al., Ann Intern Med 2022** — REGAIN Pain, Analgesic Use, and Satisfaction
3. **Haslam et al., BJA Education 2024** — Perioperative Best Practice for Primary Elective THA

Pre-Work Instructions

1. Before the session:

- Read all three articles.
- Complete the **Critical Appraisal Checklist** (1–2 bullet points per question).
- Prepare a **BLUF statement** (Bottom Line Up Front: one-sentence summary) for your assigned article.
- Bring notes to guide group discussion.

2. Pre-Work Deliverable

- Completed checklist (per primary article).
- BLUF statement (1 sentence per article).
- Be ready to discuss these articles and how you will apply them to your daily practice

Critical Appraisal Checklist (complete before session) [3]

1. Are the results valid? (Internal Validity)

- ☐ Was randomization adequate?
- ☐ Was allocation concealed?
- ☐ Who was blinded (if anyone)?
- ☐ Were baseline characteristics similar?
- ☐ Was ITT analysis performed?
- ☐ Were crossovers or missing data important?

2. What were the results? (Magnitude & Precision)

- ☐ Effect sizes: HR, OR, CI, ARR, NNT/NNH?
- ☐ Were results clinically meaningful or only statistically significant?
- ☐ Were harms/adverse effects reported?
- ☐ Any time-course patterns (early vs late outcomes)?

3. Will these results help my patients? (Applicability)

- ☐ Does the study population match our patients?
- ☐ Are the outcomes patient-centered (survival, ambulation, pain, satisfaction)?
- ☐ Any barriers in our practice (anticoagulation, resources, PACU staffing)?
- ☐ How might local ERAS/THA pathways differ?

PICO at a Glance

Study	Population (P)	Intervention (I)	Comparison (C)	Outcomes (O)	Time (T)
Vail 2024	Hip fracture, ≥50, ambulatory pre-fracture	Spinal	GA	1-yr survival, ambulation, disability, nursing-home residence	60, 180, 365 d
Ritz 2022	Same cohort (hip fracture)	Spinal	GA	Pain (POD1–3, 60/180/365 d), Rx analgesic use (day 60), satisfaction	POD1–3, 60, 180, 365 d
Haslam 2024	Elective primary THA	Neuraxial or RA/LIA + ERAS	GA alone	Complications, mobilization, LOS, pain control	Periop–discharge

Key Reminders

- Hip fracture ≠ elective THA.
- **REGAIN findings:**
  - No difference in 1-yr survival or ambulation (spinal vs GA).
  - Spinal = ↑ pain POD1, ↑ prescription analgesic use at day 60, similar satisfaction.
- **Haslam best practice (THA):**
  - ERAS pathways.
  - Neuraxial or motor-sparing RA/LIA.
  - Multimodal analgesia.
  - GA-only is not considered best practice.

NOTES

1. PBLI Milestones

Demonstrate PBLI 2 by critiquing trial validity, PBLI 3 by questioning how this applies to our hip fracture patients, and PBLI 4 by teaching each other critical appraisal.

Milestone	Description	How This Session Links
PBLI 2	Incorporates Evidence into Practice	Residents critique validity, interpret results, and apply findings to cases
PBLI 3	Analyzes Practice to Improve	Residents question how REGAIN findings fit hip fracture care vs elective THA
PBLI 4	Scholarship and Teaching	Residents practice BLUFs, facilitate discussion, and teach each other critical appraisal

2. References

1. Vail EA, Feng R, Sieber F, Carson JL, Ellenberg SS, Magaziner J, Dillane D, Marcantonio ER, Sessler DI, Ayad S, Stone T, Papp S, Donegan D, Mehta S, Schwenk ES, Marshall M, Jaffe JD, Luke C, Sharma B, Azim S, Hymes R, Chin KJ, Sheppard R, Perlman B, Sappenfield J, Hauck E, Tierney A, Horan AD, Neuman MD; for the REGAIN Investigators. Long-term outcomes with spinal versus general anesthesia for hip fracture surgery: a randomized trial. *Anesthesiology.* 2024;140(3):375–386. doi:10.1097/ALN.0000000000004807

2. Ritz J, Memtsoudis SG, Sieber F, Carson JL, Ellenberg SS, Magaziner J, Dillane D, Marcantonio ER, Sessler DI, Ayad S, Stone T, Papp S, Donegan D, Mehta S, Schwenk ES, Marshall M, Jaffe JD, Luke C, Sharma B, Azim S, Hymes R, Chin KJ, Sheppard R, Perlman B, Sappenfield J, Hauck E, Tierney A, Horan AD, Neuman MD; for the 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):952–960. doi:10.7326/M22-0320

3. Haslam N, Halvey E, Scott C. Perioperative care of patients undergoing total hip arthroplasty. *BJA Education.* 2024;24(6):183–190. doi:10.1016/j.bjae.2024.03.002

3. Critical Appraisal Checklist

1. Are the results valid? (Internal Validity)

These questions determine whether the trial was designed and conducted in a way that minimizes bias. If randomization, blinding, or handling of missing data were weak, the results may not be trustworthy no matter what the numbers show.

2. What were the results? (Magnitude & Precision)

Here we move beyond "$p < 0.05$" to quantify the actual effect size and the certainty around it. Knowing the magnitude (HR, OR, ARR, NNT/NNH) and precision (confidence intervals) tells us whether the difference is clinically meaningful and relevant to patient care.

3. Will these results help my patients? (Applicability)

Even valid, statistically significant results may not apply if the study population or setting doesn't resemble ours. Applicability questions ensure we translate research responsibly, considering patient mix, resources, and current best-practice pathways like ERAS.

ANESTHESIOLOGY

Long-term Outcomes with Spinal *versus* General Anesthesia for Hip Fracture Surgery: A Randomized Trial

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ANESTHESIOLOGY 2024; 140:375–86

ABSTRACT

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

Methods: A prespecified analysis was conducted 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 yr of age or older at 46 U.S. 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: A total of 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% CI, 0.81 to 1.44, $P = 0.59$). Recovery of ambulation among patients who survived a year did not differ by type of anesthesia (adjusted odds ratio for spinal *vs.* general, 0.87; 95% CI, 0.67 to 1.14; $P = 0.31$). Other outcomes did not differ by treatment arm.

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

(ANESTHESIOLOGY 2024; 140:375–86)

EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Hip fractures are associated with substantial mortality and disability
- The Regional versus General Anesthesia for Promoting Independence after Hip Fracture (REGAIN) trial showed that spinal and general anesthesia for hip fracture surgery resulted in similar rates of recovery of ambulation, survival, and return to prefracture residence at 60 days of follow-up
- Few data are available comparing spinal and general anesthesia with respect to long-term mortality and other patient outcomes

What This Article Tells Us That Is New

- In this prespecified secondary analysis of this large, pragmatic, rigorously conducted, multicenter randomized controlled clinical trial, there was no meaningful difference in rates of survival at 1 yr with spinal anesthesia *versus* general anesthesia for hip fracture repair
- Other outcomes assessed, including recovery of ambulation over the first year after surgery and death or new transition to nursing home residence at 365 days, were also similar with spinal *versus* general anesthesia

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]

This article is featured in "This Month in ANESTHESIOLOGY," page A1. This article is accompanied by an editorial on p. 352. This article has a related Infographic on p. A17. Supplemental Digital Content is available for this article. Direct URL citations appear in the printed text and are available in both the HTML and PDF versions of this article. Links to the digital files are provided in the HTML text of this article on the Journal's Web site (www.anesthesiology.org). This article has an audio podcast. This article has a visual abstract available in the online version.

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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-yr 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 Regional versus General Anesthesia for Promoting Independence after Hip Fracture (REGAIN) multicenter trial found similar rates of recovery of ambulation, survival, and return to prefracture 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 preplanned 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 1-yr survival, recovery of ambulation over the first year after surgery, and new nursing home residence at 1 yr among those living independently before 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 (Philadelphia, 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 yr 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 (3 m) or across a room without human assistance before fracture; the need for a concurrent procedure

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*Members of the REGAIN Investigators are listed in the appendix.

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 *vs.* 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 members were not masked to treatment assignment. The principal investigator, coinvestigators, 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 postoperative 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 postrandomization 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 U.S. 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 yr; and (3) a composite of death or residence in a nursing home or other institution at 1 yr 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 (3 m) 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 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 postrandomization 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 prespecified patient characteristics: age (85 yr or older *vs.* less than 85 yr), sex, country of enrollment, location of residence before fracture (nursing home *vs.* 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 before 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 nonadherence 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, USA). All hypotheses were tested at a two-sided significance level of 0.05. The data were reviewed at prespecified intervals by an independent data and safety monitoring board. Analyses followed a prespecified statistical analysis plan; this plan plus all modifications made after initiation of analysis appear in the supplemental digital content (https://links.lww.com/ALN/D351).

Table 1. Patient Characteristics by Treatment Assignment

Characteristic	Randomized to Spinal Anesthesia (N = 795)	Randomized to General Anesthesia (N = 804)
Age at randomization, n/N (%)		
Less than 65 yr	116/795 (14.6%)	96/803 (12.0%)
65 to 74 yr	191/795 (24.0%)	193/803 (24.0%)
75 to 84 yr	262/795 (33.0%)	266/803 (33.1%)
85 yr or older	226/795 (28.4%)	248/803 (30.9%)
Male sex, n/N (%)	258/795 (32.5%)	269/804 (33.5%)
Race, n/N (%)		
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, n/N (%)	15/750 (2.0%)	12/762 (1.6%)
Enrolled at a Canadian site, n/N (%)	210/795 (26.4%)	211/804 (26.2%)
Number of coexisting medical conditions,* median (interquartile range)	1 (0 – 2)	1 (0 – 1)
American Society of Anesthesiologists Physical Status classification, n/N (%)		
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, n/N (%)	125/795 (15.7%)	121/803 (15.1%)
Use of assistive walking device when ambulating 10 feet (3 m) or across a room 2 weeks before fracture, n/N (%)	249/779 (32.0%)	248/792 (31.3%)
3D-CAM assessment positive for delirium before randomization, n/N (%)	96/746 (12.9%)	104/752 (13.8%)
Preadmission residence, n/N (%)		
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,† median (interquartile range)	9.1 (2.1 – 22.9)	8.3 (2.1 – 25.0)

*Coexisting conditions included chronic pulmonary disease, diabetes mellitus, disseminated cancer, coronary artery disease, congestive heart failure, cerebrovascular disease, dementia, and serum creatinine greater than 2 mg/dl or current dialysis. †WHODAS scores range from 0 to 100, with lower scores indicating lower degrees of disability.

3D-CAM, 3-minute Diagnostic Interview for Confusion Assessment Method; WHODAS 2.0, World Health Organization Disability Schedule 2.0.

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 February 12, 2016, and February 18, 2021, we screened 22,022 patients (supplemental fig. 1, https://links.lww.com/ALN/D349). A total of 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.

Prerandomization characteristics were similar across treatment arms (table 1). Among 1,599 patients randomized, 527 (33%) were male, with mean age of 78 yr (± SD 10.7). A total of 1,377 (91%) were admitted from home or a retirement home (*vs.* a nursing home, rehabilitation facility, or another acute care hospital), and 497 (32%) used an assistive device when ambulating more than 10 feet (3 m) 2 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 to 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* U.S. 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%) patients allocated to spinal anesthesia and 713 of 804 (88.7%) patients allocated to general anesthesia (supplemental table

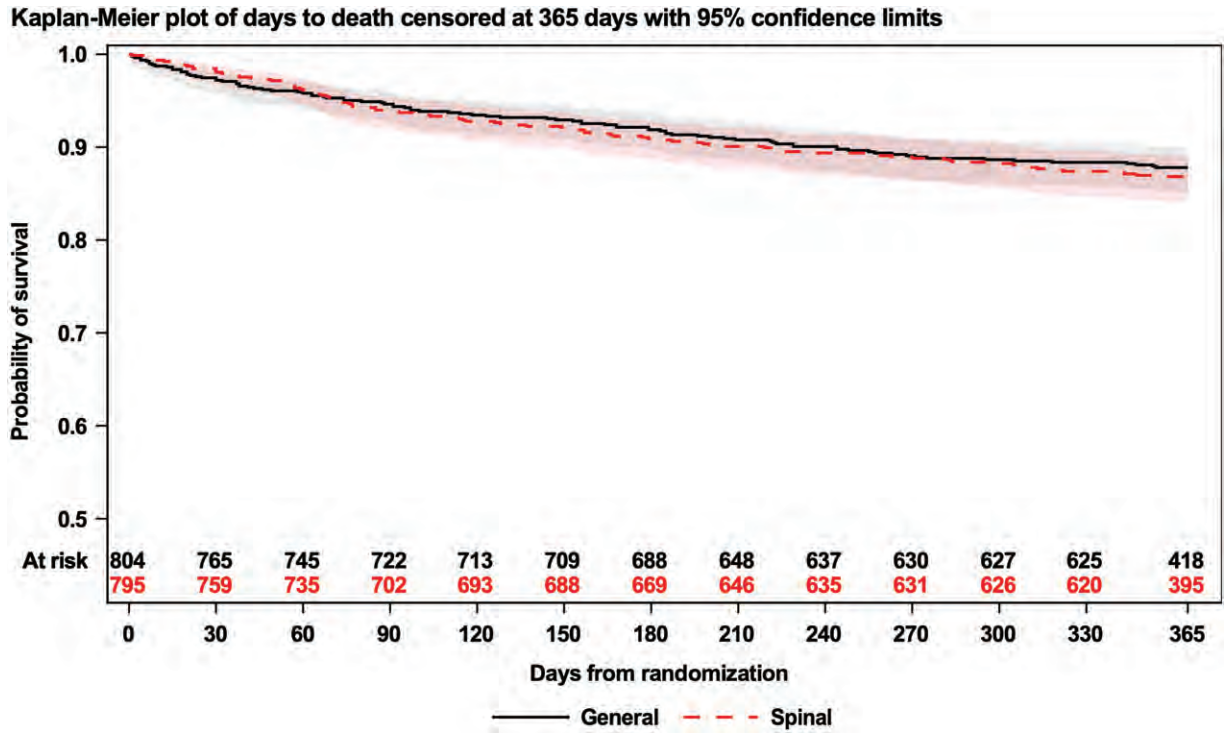

Fig. 1. Kaplan–Meier plot of days to death censored at 365 days. *Shading* represents 95% confidence limit (log-rank $P = 0.59$). The hazard ratio from the Cox model adjusting for age group, fracture type, and country of randomization is 1.08 (95% CI, 0.81 to 1.44; $P = 0.59$).

1, https://links.lww.com/ALN/D349). Among these patients, 1-yr 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 (fig. 1; table 2; hazard ratio, spinal *vs*. general anesthesia: 1.08; 95% CI, 0.81 to 1.44; $P = 0.59$). Of six prespecified interaction analyses, we observed a *P* value for interaction of 0.2 or less for two patient characteristics: age less than 85 yr *versus* 85 yr or older and country of randomization. Adjusted hazards of death were not significantly different among these subgroups. In the model including patients 85 yr 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 (supplemental table 2, https://links.lww.com/ALN/D349). 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 for spinal *vs*. general, 0.87; 95% CI, 0.67 to 1.14; $P = 0.31$; supplemental table 3, https://links.lww.com/ALN/D349). At the 60-, 180-, 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, respectively (fig. 2).

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* Value
Overall study sample	1.08 (0.81 – 1.44)*	0.59
Subgroup analyses†		
Age		
Less than 85 yr	0.91 (0.61 – 1.36)*	
85 yr or older	1.35 (0.90 – 2.01)‡	
Country of enrollment		
United States	0.98 (0.71 – 1.34)§	
Canada	1.63 (0.85 – 3.12)§	

*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. †We tested for interactions between treatment assignment and the following prespecified patient characteristics on the primary outcome: age 85 yr or older *versus* younger than 85 yr; sex; country of enrollment; the need for assistive devices to ambulate before fracture; location of residence before fracture; and fracture type. Subgroup analyses were carried out only when the *P* value for the interaction term was 0.20 or less. ‡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 are shown in supplemental table 1 (https://links.lww.com/ALN/D349). §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.

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 odds ratio for spinal *vs*. general, 1.01; 95% CI, 0.76 to 1.35). Median World Health Organization Disability Schedule 2.0 scores were similar by treatment assignment across study visits (supplemental table 4, https://links.lww.com/ALN/D349). Adverse events reported at up to 365 days were similar across treatment arms (supplemental table 5, https://links.lww.com/ALN/D349).

Supplemental table 6 (https://links.lww.com/ALN/D349) 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 (hazard ratio for spinal *vs*. general anesthesia, 1.08; 95% CI, 0.81 to 1.44; $P = 0.59$). Analyses that accounted for treatment nonadherence did not differ from our main results (hazard ratio for spinal *vs*. general anesthesia 1.10; 95% CI, 0.78 to 1.56; $P = 0.59$).

Discussion

In this prespecified secondary analysis of a pragmatic randomized trial of 1,600 adults aged 50 yr and older, assignment to spinal anesthesia *versus* general anesthesia did not affect survival at up to 1 yr 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 affect long-term survival. A previous 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.

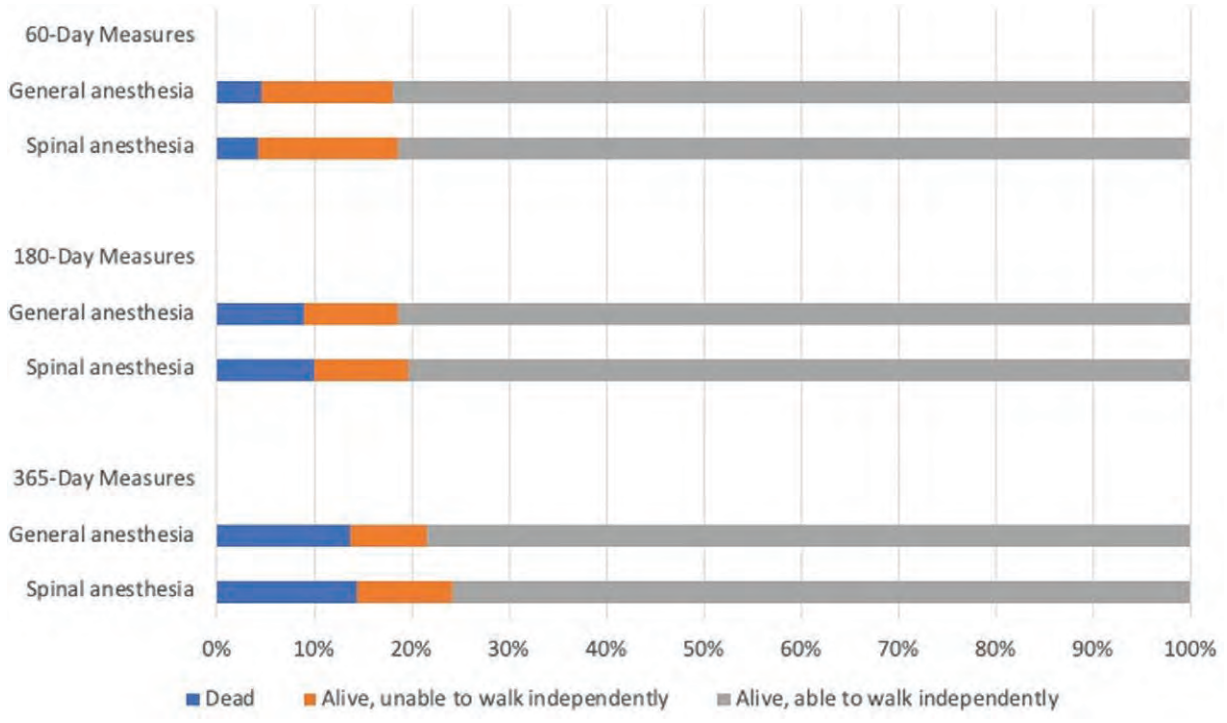

Fig. 2. Unadjusted ambulation and survival outcomes at approximately 60, 180, and 365 days after randomization, stratified by treatment group. Data from 60-day interviews were available for 712 patients in the spinal anesthesia group and 732 patients in the general anesthesia group; data from 180-day interviews were available for 694 patients in the spinal anesthesia group and 707 patients in the general anesthesia group; and data from 365-day interviews were available for 684 patients in the spinal anesthesia group and 676 patients in the general anesthesia group.

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)*
Death or new nursing home admission at 365 days†	584	119 (20.4)	572	116 (20.3)	1.01 (0.76 – 1.35)*

*Mantel–Haenszel test adjusted for sex and fracture type. †Among community-dwelling patients at randomization.

To date, few studies have compared 1-yr outcomes with spinal *versus* general anesthesia. A 2017 meta-analysis by Guay *et al.*[2] identified two single-center trials from the 1980s that evaluated survival at 1 yr 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[6] reported mortality at 1 yr to be 20.2% with spinal anesthesia *versus* 12.1% with general anesthesia in a single-center randomized trial enrolling 322 hip fracture patients.

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 current study employed pragmatic treatment protocols to represent current standards of practice across the diverse U.S. and Canadian hospitals in our network. We did not confirm findings from Parker and Griffith's previous trial of differences in survival at 1 yr 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 previous 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 yr after surgery. The large sample recruited for the current 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-yr 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 CI 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 current 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 1 yr after surgery did not vary by anesthesia type.

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Competing Interests

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Reproducible Science

Full protocol available at: neumanm@pennmedicine.upenn.edu. Raw data available at: neumanm@pennmedicine.upenn.edu. IRB approval and a completed data use agreement are required for data sharing.

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Supplemental Digital Content

Supplemental appendix, https://links.lww.com/ALN/D349

Study protocol, https://links.lww.com/ALN/D350
Statistical analysis plan, https://links.lww.com/ALN/D351

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ORIGINAL RESEARCH

Annals of Internal Medicine

Pain, Analgesic Use, and Patient Satisfaction With Spinal Versus General Anesthesia for Hip Fracture Surgery

A Randomized Clinical Trial

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Background: The REGAIN (Regional versus General Anesthesia for Promoting Independence after Hip Fracture) trial found similar ambulation and survival at 60 days with spinal versus general anesthesia for hip fracture surgery. Trial outcomes evaluating pain, prescription analgesic use, and patient satisfaction have not yet been reported.

Objective: To compare pain, analgesic use, and satisfaction after hip fracture surgery with spinal versus general anesthesia.

Design: Preplanned secondary analysis of a pragmatic randomized trial. (ClinicalTrials.gov: NCT02507505)

Setting: 46 U.S. and Canadian hospitals.

Participants: Patients aged 50 years or older undergoing hip fracture surgery.

Intervention: Spinal or general anesthesia.

Measurements: Pain on postoperative days 1 through 3; 60-, 180-, and 365-day pain and prescription analgesic use; and satisfaction with care.

Results: A total of 1600 patients were enrolled. The average age was 78 years, and 77% were women. A total of 73.5% (1050 of 1428) of patients reported severe pain during the first 24 hours after surgery. Worst pain over the first 24 hours after surgery was greater with spinal anesthesia (rated from 0 [no pain] to 10 [worst pain imaginable]; mean difference, 0.40 [95% CI, 0.12 to 0.68]). Pain did not differ across groups at other time points. Prescription analgesic use at 60 days occurred in 25% (141 of 563) and 18.8% (108 of 574) of patients assigned to spinal and general anesthesia, respectively (relative risk, 1.33 [CI, 1.06 to 1.65]). Satisfaction was similar across groups.

Limitation: Missing outcome data and multiple outcomes assessed.

Conclusion: Severe pain is common after hip fracture. Spinal anesthesia was associated with more pain in the first 24 hours after surgery and more prescription analgesic use at 60 days compared with general anesthesia.

Primary Funding Source: Patient-Centered Outcomes Research Institute.

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* For members of the REGAIN Investigators, see the **Appendix** (available at Annals.org).

More than 250 000 older U.S. adults each year experience a hip fracture (1). Nearly all patients with hip fracture undergo surgery (2), most often with spinal anesthesia or general anesthesia (3). Outcomes after hip fracture surgery are similar with regard to recovery of ambulation and survival at 60 days, delirium, and hospital length of stay with either spinal or general anesthesia (4). As a result, measures of patient experience, such as pain and satisfaction with care, may be important for guiding patients' choices about anesthesia.

See also:

Editorial comment. 1039
Summary for Patients I-34

Web-Only
Supplement

Little is known about the effects of spinal versus general anesthesia on pain, analgesic use, and satisfaction with care after hip fracture surgery. Prior randomized studies have suggested that patients may have less pain in the first few hours after hip fracture surgery with spinal anesthesia (5–8). However, few data exist to characterize differences in pain by anesthesia type at later time points or to describe satisfaction with care for patients receiving spinal versus general anesthesia (7, 9).

We conducted a preplanned secondary analysis of a multicenter pragmatic randomized trial comparing spinal versus general anesthesia for hip fracture surgery for which the primary outcome analysis has been previously published (4). We report end points related to postoperative pain during hospitalization and at up to 1 year after surgery, analgesic use, and satisfaction with care. We tested the hypothesis that spinal anesthesia is associated with less pain after hip fracture surgery, less analgesic

use, and greater satisfaction with care compared with general anesthesia.

METHODS

Trial Design and Oversight

The REGAIN (Regional versus General Anesthesia for Promoting Independence after Hip Fracture) trial was funded by the Patient-Centered Outcomes Research Institute. The study design and primary outcome analyses have been described previously (4, 10). We worked with patients and stakeholders to select outcomes of importance to patients (11). The institutional review board of the University of Pennsylvania approved the protocol and was the institutional review board of record for 11 sites; approval at other sites was via local institutional review board review (12). Written informed consent was obtained from the participant or, for persons who could not provide consent, from their health care proxy.

Trial Population

Staff at 46 hospitals in the United States and Canada reviewed emergency department registration lists, 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 inability to walk approximately 10 feet or across a room without human assistance before fracture, need for a concurrent procedure not amenable to spinal anesthesia, periprosthetic fracture, and contraindications to spinal anesthesia (coagulopathy, anticoagulant medications [13, 14], critical or severe aortic stenosis, infection at the injection site, and elevated intracranial pressure). Patients were excluded if they had previously participated or were determined to be unsuitable for randomization by the surgeon or anesthesiologist on the basis of clinical assessment. Consenting patients were assigned to receive spinal anesthesia or general anesthesia in a 1:1 ratio using permuted block randomization with variable block sizes (15, 16). Randomization was stratified by hospital, sex, and fracture location (femoral neck vs. intertrochanteric or subtrochanteric fracture) and was done centrally through an 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 principal investigator (M.D.N.) or lead project manager (L.J.G.).

Treatments

Treatments were delivered by clinical anesthesia staff at each site. For patients assigned to spinal anesthesia, providers were instructed to do a single-shot spinal anesthetic with sedation as needed for patient comfort. Conversion to general anesthesia was permitted on the basis of 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 preoperative, intraoperative, and postoperative analgesic medications and use of peripheral nerve blocks for pain management, were determined by the clinical team. Participants and treating clinicians were not masked to treatment assignment.

Outcomes

Patients were interviewed in person by trained site study staff once daily from postoperative day 1 through postoperative day 3 or until discharge (whichever came first) to assess worst pain over the past 24 hours, average pain over the past 24 hours, and pain at the time of interview. Pain data were also collected at approximately 60, 180, and 365 days after randomization via telephone interviews by clinical coordinating center staff who were masked to treatment assignment. Telephone interviews assessed the worst pain over the 2 weeks before the interview, average pain over the 2 weeks before the interview, and pain at the time of interview. All pain assessments used a numerical rating scale ranging from 0 (no pain) to 10 (worst pain imaginable) (17, 18); we considered a response of 7 or greater to correspond to severe pain (19–21). Intravenous and oral opioid administrations were recorded over the 24 hours before surgery and through postoperative day 3 or discharge. Opioid dosages were converted to oral morphine milligram equivalents using standard conversion tables (22, 23). Patients were queried before randomization and at the 60-, 180-, and 365-day interviews about whether they had taken prescription analgesics in the 2 weeks preceding the interview.

The Bauer anesthesia satisfaction questionnaire (24) was administered by site study staff on postoperative day 3 or at discharge, whichever came first. This instrument includes 10 items assessing anesthesia-related discomfort (drowsiness, pain at the site of surgery, thirst, hoarseness, sore throat, postoperative nausea and vomiting, feeling cold, cognitive deficits, pain at the anesthesia injection site, and shivering) and 5 items assessing satisfaction with aspects of anesthesia care (information provision before anesthesia, emergence from anesthesia, pain therapy, treatment of nausea and vomiting, and overall anesthesia care). Discomfort items were scored on a 3-point scale (none, moderate, and severe). Satisfaction items are scored on a 4-point scale ranging from "very satisfied" to "very dissatisfied." As an additional measure of satisfaction, we administered an assessment modeled on the United Kingdom National Health Service's 2013 Friends and Family Test (25, 26) that asked patients whether they would recommend the same type of anesthesia to a friend or family member.

We did exploratory analyses of cognitive status at 60, 180, and 365 days among study patients in each group. Cognitive status was assessed at these time points via telephone interview using the Short Blessed Test, a 6-item test of orientation, memory, and concentration (27) that has been validated for telephone administration (28).

Table 1. Baseline Demographic and Clinical Characteristics of Patients Included in the Analysis for ≥1 Study Outcomes

Characteristic	Spinal Anesthesia Group	General Anesthesia Group
Mean age (SD), *y**	78 (11)	78 (11)
Male, *n/N* (%)	255/785 (32.5)	267/796 (33.5)
Race, *n/N* (%)		
White	675/752 (89.8)	682/765 (89.2)
Black	54/752 (7.2)	67/765 (8.8)
Asian	21/752 (2.8)	15/765 (2.0)
Other (including others and multiple)	2/752 (0.3)	1/765 (0.1)
Hispanic, *n/N* (%)	15/740 (2.0)	12/754 (1.6)
Enrolled at a non-U.S. site, *n/N* (%)	206/785 (26.2)	207/796 (26.0)
Coexisting conditions, *n/N* (%)		
Chronic pulmonary disease	123/785 (15.7)	99/796 (12.4)
Disseminated cancer	58/785 (7.4)	49/796 (6.2)
Diabetes mellitus	154/785 (19.6)	142/796 (17.8)
Coronary artery disease	115/785 (14.6)	118/796 (14.8)
Congestive heart failure	45/708 (6.4)	33/717 (4.6)
Cerebrovascular disease	76/785 (9.7)	66/796 (8.3)
Dementia	109/785 (13.9)	93/796 (11.7)
Creatinine >2 mg/dL or current dialysis	47/780 (6.0)	41/789 (5.2)
Final confirmed fracture type, *n/N* (%)		
Femoral neck	401/785 (51.1)	404/796 (50.8)
Intertrochanteric	350/785 (44.6)	347/796 (43.6)
Subtrochanteric	32/785 (4.1)	32/796 (4.0)
Multiple locations	2/785 (0.3)	13/796 (1.6)
Preadmission residence, *n/N* (%)		
Home or retirement home	679/739 (91.9)	682/755 (90.3)
Nursing home	38/739 (5.1)	36/755 (4.8)
Rehabilitation or acute care hospital	22/739 (3.0)	37/755 (4.9)
Median average pain in the 2 wk before fracture (IQR)†‡	0 (0–5)	0 (0–5)
Median worst pain in the 2 weeks before fracture (IQR)†§	2 (0–8)	2 (0–8)
Median pain at the time of interview (IQR)†‖	5 (2–7)	5 (2–8)
Used prescription analgesics in the 2 wk before fracture, *n/N* (%)	136/714 (19.0)	121/733 (16.5)

IQR = interquartile range.
* Data available for 785 patients in the spinal anesthesia group and 796 patients in the general anesthesia group.
† Pain assessments used a numerical rating scale ranging from 0 (no pain) to 10 (worst pain imaginable).
‡ Data available for 703 patients in the spinal anesthesia group and 724 patients in the general anesthesia group.
§ Data available for 703 patients in the spinal anesthesia group and 728 patients in the general anesthesia group.
‖ Data available for 716 patients in the spinal anesthesia group and 735 patients in the general anesthesia group.

Data were reviewed at prespecified intervals by an independent data and safety monitoring board. Members of the data and safety monitoring board were aware of treatment assignment. The principal investigator, statisticians, clinical coordinating center staff, and coinvestigators remained masked to treatment assignment until the database was locked for analysis.

Statistical Analysis

Sample size planning for REGAIN was based on the overall primary outcome of the study, which was a composite of death or new inability to walk approximately 10 feet without human assistance at 60 days. We estimated that 1600 participants would provide 80% power to detect a 0.78 relative risk (RR) for this outcome among patients assigned to spinal versus general anesthesia at a 2-sided significance level of 0.05, assuming a 34.2% rate of the primary outcome in the general anesthesia group (29). We did not do separate power analyses for secondary outcomes.

Our main analysis included all randomized patients with available outcome data. Patients were included in the analysis according to their original treatment assignment (that is, intention to treat). Pain response data for patients assigned to spinal versus general anesthesia were compared using a linear mixed-effects model, adjusted for sex, fracture type, country, baseline pain score, and postoperative day. Differences in pain data by day across groups were estimated by including treatment-day interactions. Separate models were fit for each pain assessment domain (worst pain, average pain, and current pain) for data collected over postoperative days 1 to 3 and separately for data collected at the 60-, 180-, and 365-day interviews. A random effect with unstructured covariance for each individual patient was included to account for within-subject correlation. Opioid receipt over postoperative days 1 to 3 were compared using mixed-effects logistic regression adjusted for sex, fracture location, country of enrollment, and preoperative opioid use; separate models were fit for each postoperative day.

Prescription analgesic use at 60, 180, and 365 days was assessed as a binary outcome using the Mantel–Haenszel test, stratified by sex, fracture type, and country; this outcome was assessed among all randomized patients and within a subgroup restricted to patients who reported no prescription analgesic use over the 2 weeks before fracture. Mantel–Haenszel tests, stratified as noted earlier, were also used to compare the percentage in each group reporting severe discomfort across each of the 10 domains noted earlier, the percentage indicating a response of

"dissatisfied" or "very dissatisfied" to any of the 5 Bauer satisfaction items, and the fraction indicating that they would not recommend the same anesthesia type to a friend or family member. For rare outcomes that had zero counts within 1 or more strata, we reduced the number of stratification factors for the Mantel–Haenszel tests in the order of country, fracture type, and sex until all stratified counts became positive. We used the Breslow–Day test to assess heterogeneity of RRs across strata. We did not adjust the width of CIs for multiplicity in outcome analyses.

For each outcome, the main analysis included patients who had complete data for that outcome; to assess the effect of missing data, we also did an inverse probability–weighted analysis (30) for all comparisons. This analysis weighted each patient by the inverse probability of having complete data, as estimated on the basis of 10 prerandomization factors (age, sex, enrollment country, fracture location, pulmonary disease, cancer, diabetes, coronary artery disease, cerebrovascular disease, and dementia) and postoperative day, as appropriate; extreme weights were not trimmed. Analyses were done using SAS, version 9.4 (SAS Institute). All hypotheses were tested at a 2-sided significance level of 0.05.

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 12 February 2016 and 18 February 2021, we screened 22 022 patients (**Appendix Figure**, available at Annals.org). Of these patients, 12 915 were excluded on the basis of eligibility criteria, including 1328 patients for whom a physician declined enrollment. A total of 3565 patients declined consent. Other reasons accounted for 3942 exclusions. Of 1600 patients enrolled, 795 were assigned to spinal anesthesia and 805 were assigned to general anesthesia.

Prerandomization characteristics were similar across treatment groups (**Table 1**). Among patients with available outcome data, the average age was approximately 78 years; 33% were men, and 8% were Black. Pain in the 2 weeks before fracture and at the time of the baseline interview were similar across groups. We have previously reported information on intraoperative anesthetic care received by each group (4). Of 795 patients who were assigned to the spinal anesthesia group, 666 (83.8%) received spinal anesthesia only, and 86.6% of these patients (577 of 666) received propofol for sedation; of the remaining patients in the spinal anesthesia group, 64 (8%) had a spinal block attempted or placed before converting to general anesthesia, 55 (6.9%) received general anesthesia without having a spinal block attempted, and 10 (1.3%) withdrew before surgery or had missing data on anesthesia type. Among 805 patients assigned to receive general anesthesia, 769 (95.5%) received general anesthesia, with an inhaled agent used for maintenance in 93.6% of cases (720 of 769); of the remaining patients, 28 (3.5%)

Table 2. Pain During Hospitalization by Treatment Group

Outcome	Mean (SD)		Adjusted Mean Difference (95% CI)*
	Spinal Anesthesia Group	General Anesthesia Group	
Worst pain during the past 24 h before interview†			
Postoperative day 1	7.9 (2.6)	7.6 (2.8)	0.40 (0.12 to 0.68)
Postoperative day 2	7.1 (2.7)	7.1 (2.8)	0.08 (−0.22 to 0.38)
Postoperative day 3	6.8 (2.9)	6.6 (3.0)	0.17 (−0.17 to 0.51)
Average pain during the 24 h before interview‡			
Postoperative day 1	5.5 (2.6)	5.2 (2.8)	0.43 (0.15 to 0.72)
Postoperative day 2	4.9 (2.5)	4.7 (2.6)	0.19 (−0.08 to 0.47)
Postoperative day 3	4.6 (2.5)	4.5 (2.6)	0.05 (−0.24 to 0.34)
Pain at the time of the interview§			
Postoperative day 1	3.9 (3.0)	3.8 (3.1)	0.13 (−0.17 to 0.42)
Postoperative day 2	3.4 (2.8)	3.4 (3.0)	−0.04 (−0.33 to 0.26)
Postoperative day 3	3.3 (2.9)	3.1 (2.9)	0.19 (−0.12 to 0.51)

* Mean difference (spinal anesthesia vs. general anesthesia) obtained from linear mixed-effects model, adjusted for sex, fracture type, country, baseline pain score, and postoperative day; separate models were fit for each pain assessment domain (average pain, worst pain, and current pain). Pain assessments used a numerical rating scale ranging from 0 (no pain) to 10 (worst pain imaginable).
† Of 795 patients randomly assigned to spinal anesthesia, data were available for 706, 667, and 539 patients on postoperative days 1, 2, and 3, respectively. Of 805 patients randomly assigned to general anesthesia, data were available for 722, 676, and 576 patients on postoperative days 1, 2, and 3, respectively.
‡ Of 795 patients randomly assigned to spinal anesthesia, data were available for 696, 656, and 535 patients on postoperative days 1, 2, and 3, respectively. Of 805 patients randomly assigned to general anesthesia, data were available for 719, 665, and 565 patients on postoperative days 1, 2, and 3, respectively.
§ Of 795 patients randomly assigned to spinal anesthesia, data were available for 716, 681, and 549 patients on postoperative days 1, 2, and 3, respectively. Of 805 patients randomly assigned to general anesthesia, data were available for 738, 688, and 585 patients on postoperative days 1, 2, and 3, respectively.

Table 3. Pain by Treatment Group at 60, 180, and 365 Days

Outcome	Mean (SD)		Adjusted Mean Difference (95% CI)*
	Spinal Anesthesia Group	General Anesthesia Group	
60-d outcomes†			
Worst pain in the 2 wk before interview	4.5 (3.2)	4.2 (3.2)	0.29 (−0.20 to 0.77)
Average pain in the 2 wk before interview	3.0 (2.6)	2.8 (2.5)	0.12 (−0.27 to 0.51)
Pain at the time of interview	2.0 (2.6)	1.9 (2.4)	0.20 (−0.17 to 0.57)
180-d outcomes‡			
Worst pain in the 2 wk before interview	3.5 (3.3)	3.4 (3.3)	0.14 (−0.39 to 0.67)
Average pain in the 2 wk before interview	2.4 (2.5)	2.3 (2.5)	0.12 (−0.28 to 0.52)
Pain at the time of interview	1.6 (2.5)	1.6 (2.5)	0.03 (−0.36 to 0.42)
365-d outcomes§			
Worst pain in the 2 wk before interview	3.1 (3.2)	3.2 (3.3)	−0.12 (−0.66 to 0.43)
Average pain in the 2 wk before interview	2.2 (2.6)	2.2 (2.5)	−0.02 (−0.44 to 0.41)
Pain at the time of interview	1.4 (2.3)	1.3 (2.4)	0.02 (−0.38 to 0.41)

* Mean difference (spinal anesthesia vs. general anesthesia) obtained from linear regression model, adjusted for sex, fracture type, country, and baseline pain score; separate models were fit for each pain assessment domain (average pain, worst pain, and current pain). Pain assessments used a numerical rating scale ranging from 0 (no pain) to 10 (worst pain imaginable).
† Of 795 patients randomly assigned to spinal anesthesia, data were available for 315, 313, and 320 patients on worst, average, and current pain, respectively. Of 805 patients randomly assigned to general anesthesia, data were available for 320, 325, and 332 patients on worst, average, and current pain, respectively.
‡ Of 795 patients randomly assigned to spinal anesthesia, data were available for 284, 283, and 290 patients on worst, average, and current pain, respectively. Of 805 patients randomly assigned to general anesthesia, data were available for 302, 303, and 306 patients on worst, average, and current pain, respectively.
§ Of 795 patients randomly assigned to spinal anesthesia, data were available for 266, 268, and 270 patients on worst, average, and current pain, respectively. Of 805 patients randomly assigned to general anesthesia, data were available for 275, 271, and 279 patients on worst, average, and current pain, respectively.

received spinal anesthesia, and 8 (1%) died, withdrew before surgery, or had missing data on anesthesia type.

Intravenous hydromorphone and fentanyl were administered intraoperatively to 5.7% (45 of 784) and 64% (502 of 784) of patients assigned to spinal anesthesia and to 34% (270 of 795) and 90.4% (719 of 795) of patients assigned to general anesthesia, respectively. Of patients assigned to spinal anesthesia, 32% (251 of 784) received a peripheral nerve block for pain treatment compared with 35.1% (279 of 795) of patients assigned to general anesthesia (**Supplement Table 1**, available at Annals.org).

Among patients with available data, 73.5% (1050 of 1428), 64.9% (872 of 1343), and 60.8% (678 of 1115) rated their worst pain over the preceding 24 hours as severe (that is, a score of 7 or greater on a numerical rating scale from 0 [no pain] to 10 [worst pain imaginable]) at the postoperative day 1, 2, and 3 interviews, respectively. Average pain over the preceding 24 hours was rated as severe by 35.4% (501 of 1415), 26.3% (348 of 1312), and 23.3% (256 of 1100) of patients on postoperative days 1, 2, and 3, respectively. Patients assigned to receive spinal anesthesia reported more pain over the preceding 24 hours on postoperative day 1 (worst pain: spinal anesthesia: mean, 7.9 [SD, 2.6]; general anesthesia: mean, 7.6 [SD, 2.8]; mean difference, 0.40 [95% CI, 0.12 to 0.68]; average pain: spinal anesthesia: mean, 5.5 [SD, 2.6]; general anesthesia: mean, 5.2 [SD, 2.8]; mean difference, 0.43 [CI, 0.15 to 0.72]). Other measures of pain over postoperative days 1 to 3 were similar across groups (**Table 2**; **Supplement Figure 1**, available at Annals.org), as was postoperative day 1 to 3 opioid administration (**Supplement Table 2**, available at Annals.org); the number of patients with available postoperative pain data decreased from postoperative day 1 through postoperative day 3 because of discharge timing. Pain did not differ by treatment assignment at the 60-, 180-, and 365-day interviews (**Table 3**; **Supplement Figure 2**, available at Annals.org). Use of prescription analgesics over the 2 weeks before the 60-day interview was higher with spinal anesthesia among all randomized patients (spinal anesthesia: 141 of 563 [25%]; general anesthesia: 108 of 574 [18.8%]; RR, 1.33 [CI, 1.06 to 1.65]) and among patients reporting no prescription analgesic before fracture (spinal anesthesia: 86 of 421 [20.4%]; general anesthesia: 67 of 450 [14.9%]; RR, 1.35 [CI, 1.02 to 1.82]). Use of prescription analgesics reported at the 180- or 365-day interview did not differ by treatment group (**Table 4**).

Severe sore throat occurred in 15 of 650 (2.3%) patients assigned to spinal anesthesia versus 36 of 669 (5.4%) patients assigned to general anesthesia (RR, 0.42 [CI, 0.23 to 0.76]), whereas severe shivering occurred in 40 of 650 (6.2%) patients assigned to spinal anesthesia versus 21 of 667 (3.1%) patients assigned to general anesthesia (RR, 1.94 [CI, 1.16 to 3.25]). Dissatisfaction with an aspect of anesthesia care and unwillingness to recommend the same care to a friend or family member were similar across groups (**Table 5**). Responses to individual anesthesia satisfaction items did not differ by anesthesia type (**Supplement Table 3**, available at Annals.org). Short Blessed Test scores were similar across treatment groups at all time points (**Supplement Table 4**, available at Annals.org). Stratification factors used in the statistical analysis remained balanced by group throughout study follow-up (**Supplement Table 5**, available at Annals.org).

In the inverse probability–weighted analysis, the risk for prescription analgesic use at 365 days among patients reporting no prescription analgesic use before fracture was higher in the spinal anesthesia group (RR, 1.50 [CI, 1.06 to 2.14]). Findings from inverse probability–weighted analyses were otherwise consistent with our main results (**Supplement Tables 6** to **10**, available at Annals.org).

Discussion

In this pragmatic randomized trial of 1600 older adults, more than 70% of enrolled patients had severe pain after hip fracture surgery. Spinal anesthesia was associated with worse pain during the first 24 hours after surgery compared with general anesthesia. Pain scores were similar across groups at other time points during hospitalization and at up to 365 days after randomization. Patients assigned to spinal anesthesia more often reported prescription analgesic use at 60 days compared with patients assigned to general anesthesia. Rates of severe sore throat and severe shivering differed by anesthesia type, but satisfaction with anesthesia care was similar across groups.

Our findings add to available data on patient experiences after spinal versus general anesthesia for hip fracture surgery (7). Small trials have found lower pain scores in the postanesthesia care unit with spinal anesthesia versus general anesthesia for hip fracture surgery (6, 8); however, available data conflict as to whether these differences persist beyond the first few hours after surgery. A small trial done at 1 center in Italy found similar pain scores at 12 hours after spinal versus general anesthesia for hip fracture surgery (6). In contrast, a trial involving 387 patients done at 2 hospitals in Iran found lower pain scores with spinal versus general anesthesia on postoperative day 2 (5). Our study, which enrolled a large and representative sample of patients with hip fracture from a diverse sample of hospitals, did not identify differences in postoperative pain by anesthesia type beyond the first 24 hours after the surgical procedure. We found spinal anesthesia to be associated with higher levels of pain versus general anesthesia on postoperative day 1. It is possible that these differences may have been due to relative undertreatment of pain for patients in the spinal anesthesia group at the time of spinal block resolution during the first 24 hours after surgery. We did not find differences in pain by anesthesia type at other time points during hospitalization or after discharge.

We found a higher rate of prescription analgesic use at 60 days among patients assigned to receive spinal versus general anesthesia. We believe that this unexpected finding should be interpreted cautiously and considered hypothesis generating, especially given the number of comparisons presented here. Pain in the acute setting may contribute to increased long-term pain and prolonged opioid use after discharge (31); however, the differences in pain we found across groups were small and did not persist beyond the first postoperative day. Future research, potentially also considering factors not examined here, such as opioid prescribing at discharge and delivery of physical therapy (32), may explore the relationship between anesthesia technique, postoperative pain management, and patterns of analgesic use after hip fracture surgery.

In terms of anesthesia-related discomfort and patient satisfaction, we did find some differences in severe discomfort by anesthesia type. Whereas severe sore throat occurred more commonly among patients assigned to general anesthesia, those assigned to spinal anesthesia more frequently reported discomfort due to severe shivering after surgery. However, similar proportions of patients assigned to spinal anesthesia and general anesthesia indicated being dissatisfied with 1 or more aspects of anesthesia care, and similar proportions stated that they would be willing to recommend the same type of anesthesia to a friend or family member. Exploratory analyses showed similar cognitive status measures at 60, 180, and 365 days by anesthesia type.

Table 4. Prescription Analgesic Use at 60, 180, and 365 Days*

Outcome	Spinal Anesthesia Group, *n/N* (%)	General Anesthesia Group, *n/N* (%)	Mantel-Haenszel Relative Risk (95% CI)†
60-d outcomes			
Any reported prescription analgesic use in the 2 wk before interview	141/563 (25)	108/574 (18.8)	1.33 (1.06–1.65)
New prescription analgesic use in the 2 wk before interview‡	86/421 (20.4)	67/450 (14.9)	1.35 (1.02–1.82)
180-d outcomes			
Any reported prescription analgesic use in the 2 wk before interview	69/522 (13.2)	65/540 (12.0)	1.10 (0.80–1.51)
New prescription analgesic use in the 2 wk before interview‡	32/394 (8.1)	36/425 (8.5)	0.97 (0.61–1.53)
365-d outcomes			
Any reported prescription analgesic use in the 2 wk before interview	65/497 (13.1)	52/494 (10.5)	1.25 (0.88–1.76)
New prescription analgesic use in the 2 wk before interview‡§	37/387 (9.6)	24/385 (6.2)	1.55 (0.95–2.57)

* Denominators vary across items and assessment time points because of missing data. Total number randomly assigned to spinal anesthesia: 795; total number randomly assigned to general anesthesia: 805. Number of patients in the spinal anesthesia group reporting no prior opioid use: 575; number of patients in the general anesthesia group reporting no prior opioid use: 606.
† Mantel–Haenszel adjusted for sex, fracture location, and country of enrollment except where noted. *P* value for homogeneity of relative risks across strata >0.2 by Breslow–Day test for all comparisons.
‡ Defined as reported use of prescription pain medicine at the 60-d interview among patients indicating no prescription analgesic use in the 2 wk before fracture.
§ Mantel–Haenszel adjusted for sex and fracture location.

Table 5. Severe Anesthesia-Related Discomfort and Satisfaction With Anesthesia Care*

Outcome	Spinal Anesthesia Group, *n/N* (%)	General Anesthesia Group, *n/N* (%)	Mantel–Haenszel Relative Risk (95% CI)†
Severe anesthesia-related discomfort			
Drowsiness‡	70/650 (10.8)	69/666 (10.4)	1.04 (0.76–1.43)
Pain at the site of surgery	161/652 (24.7)	172/669 (25.7)	0.96 (0.80–1.16)
Thirst	122/650 (18.8)	145/669 (21.7)	0.86 (0.70–1.07)
Hoarseness	23/645 (3.6)	37/668 (5.5)	0.64 (0.39–1.07)
Sore throat	15/650 (2.3)	36/669 (5.4)	0.43 (0.24–0.77)
Nausea	26/652 (4.0)	32/670 (4.8)	0.84 (0.51–1.39)
Feeling cold	46/649 (7.1)	39/667 (5.8)	1.22 (0.80–1.84)
Confusion or disorientation	35/653 (5.4)	28/666 (4.2)	1.27 (0.78–2.06)
Pain at the site of the anesthetic injection	6/641 (0.9)	8/622 (1.3)	0.73 (0.25–2.09)
Shivering	40/650 (6.2)	21/667 (3.1)	1.95 (1.16–3.26)
Satisfaction with anesthesia care			
Dissatisfaction with ≥1 aspects of anesthesia care§	85/647 (13.1)	97/661 (14.7)	0.89 (0.68–1.17)
Unwilling to recommend the same type of anesthesia to a friend or family member‡	22/554 (4.0)	15/559 (2.7)	1.51 (0.79–2.86)

* Denominators vary across items because of missing data. Total number randomly assigned to spinal anesthesia: 795; total number randomly assigned to general anesthesia: 805.
† Mantel–Haenszel adjusted for sex, fracture location, and country of enrollment (drowsiness, pain at the site of surgery, thirst, feeling cold, and dissatisfaction with ≥1 aspects of anesthesia care); sex and fracture location (hoarseness, sore throat, nausea, confusion or disorientation, pain at the site of anesthetic injection, and shivering); and sex (not willing to recommend the same type of anesthesia to a friend or family member). *P* value for homogeneity of relative risks across strata was >0.2 by Breslow–Day test except where noted.
‡ Breslow–Day *P* value for homogeneity of relative risks across strata <0.2.
§ Corresponds to a response of "dissatisfied" or "very dissatisfied" to ≥1of 5 Bauer questionnaire items assessing the following domains: information given by anesthesiologist before surgery, waking up from anesthesia, pain therapy after surgery, treatment of nausea and vomiting after surgery, and care provided by department of anesthesia in general. Please refer to Supplement Table 6 (available at Annals.org) for detailed item response information.

Our study has limitations. Some data were missing for each of the study outcomes. Sensitivity analyses that assessed the potential effect of missing data were consistent with analyses of complete data for selected end points. However, such analyses rely on assumptions that all factors associated both with missingness and outcome have been accounted for, which cannot be verified. In addition, our results may still not represent the experiences of certain groups of patients within our sample, such as those who may have been unable to answer study questionnaires because of dementia or other cognitive impairment. Because of the pragmatic nature of our study, we did not collect data on nonopioid analgesic medications or nonpharmacologic pain treatments administered during hospitalization, analgesic prescribing at discharge, or the types or doses of prescription analgesic medications patients reported using before fracture or at the day 60 interview. As reported previously (4), approximately 10% of all randomized patients did not receive the assigned anesthetic. This may have reduced the power of our study to detect differences between groups. Finally, we did not adjust the width of our CIs to account for multiple comparisons. Our results should thus be considered exploratory and hypothesis generating.

Prior analyses of data from REGAIN found that spinal anesthesia was not associated with a lower risk for death or new inability to walk at 60 days and that new-onset delirium and hospital length of stay did not differ by anesthesia type (4). In this context, information about patients' experiences after hip fracture surgery can help to inform choices about care. Our findings do not suggest that spinal anesthesia is associated with less postoperative pain or analgesic use or with greater patient satisfaction compared with general anesthesia. Rather, they suggest that patients receiving spinal anesthesia may have more pain during the first 24 hours after surgery and more prescription analgesic use at 60 days. As a large proportion of patients in each group reported high levels of pain over the first 3 days after surgery, our results also highlight the need for additional efforts to better manage postoperative pain regardless of whether patients receive general or spinal anesthesia.

In this multicenter pragmatic trial of 1600 older adults undergoing hip fracture surgery, severe postoperative pain occurred commonly with both spinal and general anesthesia. Pain after surgery did not differ by anesthesia type beyond the first 24 hours after surgery or at up to 365 days after discharge. However, spinal anesthesia was associated with higher rates of prescription analgesic use at 60 days. Satisfaction with care was similar across groups. Clinicians and policymakers should prioritize efforts to improve pain care after hip fracture surgery.

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Data Sharing Statement: The following data will be made available (anticipated date: 22 April 2023): deidentified participant data and data dictionary (www.icpsr.umich.edu/). The following supporting documents will be made available with publication: informed consent form (contact Dr. Neuman; e-mail, neumanm@pennmedicine.upenn.edu). These data will be made available to researchers whose proposed use of the data has been approved. Data requests for nonscientific uses, such as in support of litigation, general educational purposes, quality improvement projects, and for promotional/marketing purposes will not be accepted. Data will be made available after approval of a proposal and completion of a data use agreement. (Restrictions: full details on data sharing for this project can be found in the Patient-Centered Outcomes Research Institute data sharing policy at www.pcori.org/sites/default/files/PCORI-Policy-for-Data-Management-and-Data-Sharing.pdf).

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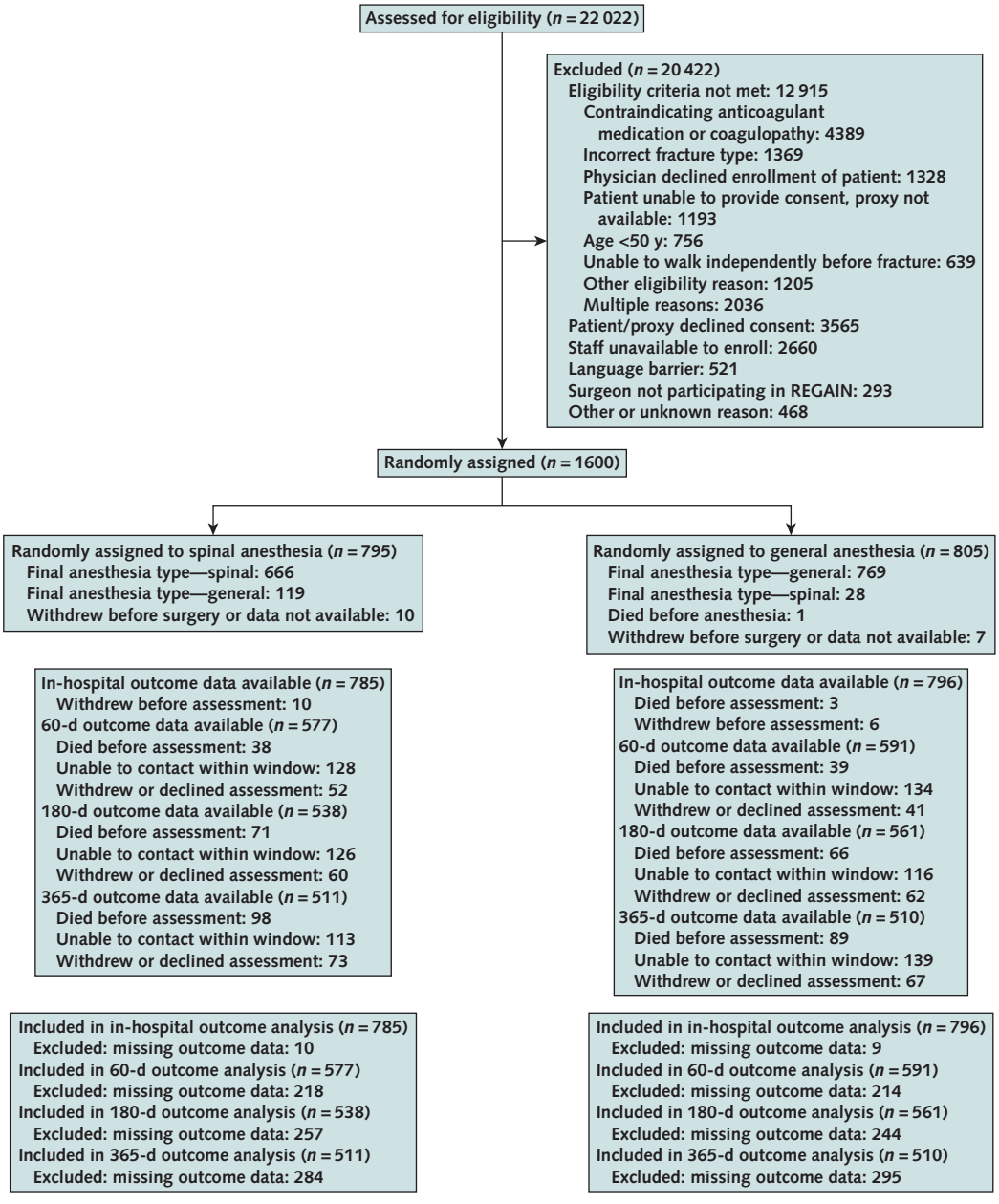
Appendix Figure. Screening, enrollment, randomization, and follow-up.



"Other eligibility reasons" include no surgery planned, malignant hyperthermia, prior REGAIN participation, elevated intracranial pressure, skin infection, concurrent surgery, severe aortic stenosis, and prisoner status. Among 3565 patients declining consent, 950 (27%) had concerns about spinal anesthesia; 480 (13%) had concerns about general anesthesia; 1024 (29%) had concerns about participating in research; and 334 (9%), 88 (8%), and 480 (13%) offered no reason, multiple reasons, or other reasons, respectively. REGAIN = Regional versus General Anesthesia for Promoting Independence after Hip Fracture.

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Review Article

CLINICAL PRACTICE

Anaesthetic care of patients undergoing primary hip and knee arthroplasty: consensus recommendations from the International Consensus on Anaesthesia-Related Outcomes after Surgery group (ICAROS) based on a systematic review and meta-analysis

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Abstract

Background: Evidence-based international expert consensus regarding anaesthetic practice in hip/knee arthroplasty surgery is needed for improved healthcare outcomes.
Methods: The International Consensus on Anaesthesia-Related Outcomes after Surgery group (ICAROS) systematic review, including randomised controlled and observational studies comparing neuraxial to general anaesthesia regarding major complications, including mortality, cardiac, pulmonary, gastrointestinal, renal, genitourinary, thromboembolic, neurological, infectious, and bleeding complications. Medline, PubMed, Embase, and Cochrane Library including Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, NHS Economic Evaluation Database, from 1946 to May 17, 2018 were queried. Meta-analysis and Grading of Recommendations Assessment, Development and Evaluation approach was utilised to assess evidence quality and to develop recommendations.
Results: The analysis of 94 studies revealed that neuraxial anaesthesia was associated with lower odds or no difference in virtually all reported complications, except for urinary retention. Excerpt of complications for neuraxial *vs* general anaesthesia in hip/knee arthroplasty, respectively: mortality odds ratio (OR): 0.67, 95% confidence interval (CI): 0.57–0.80/OR: 0.83, 95% CI: 0.60–1.15; pulmonary OR: 0.65, 95% CI: 0.52–0.80/OR: 0.69, 95% CI: 0.58–0.81; acute renal failure OR: 0.69, 95% CI: 0.59–0.81/OR: 0.73, 95% CI: 0.65–0.82; deep venous thrombosis OR: 0.52, 95% CI: 0.42–0.65/OR: 0.77, 95% CI: 0.64–0.93; infections OR: 0.73, 95% CI: 0.67–0.79/OR: 0.80, 95% CI: 0.76–0.85; and blood transfusion OR: 0.85, 95% CI: 0.82–0.89/OR: 0.84, 95% CI: 0.82–0.87.
Conclusions: Recommendation: primary neuraxial anaesthesia is preferred for knee arthroplasty, given several positive postoperative outcome benefits; evidence level: low, weak recommendation. Recommendation: neuraxial anaesthesia is recommended for hip arthroplasty given associated outcome benefits; evidence level: moderate-low, strong recommendation. Based on current evidence, the consensus group recommends neuraxial over general anaesthesia for hip/knee arthroplasty.
Trial registry number: PROSPERO CRD42018099935.

Keywords: anaesthesia, epidural; anaesthesia, general; anaesthesia, spinal; arthroplasty, replacement, hip; arthroplasty, replacement, knee; assessment, outcomes

Editor's key points

- In this state-of-the-art systematic review and analysis of the literature, a multinational expert group reached a consensus on the optimal anaesthetic approach for patients undergoing lower-limb arthroplasty.
- Considering multiple perioperative outcomes, the consensus was that neuraxial anaesthesia is the preferred anaesthetic technique (when no contraindications exist), and that this reduces the risk of most (but not all) complications.
- Neuraxial anaesthesia, which remains underutilised in many countries, may be used to improve perioperative outcomes, although limitations of the current literature may mandate the revision of these recommendations when new data become available.

Total joint arthroplasty (TJA) is amongst the most commonly performed surgical procedures in the developed world.[1] Globally, millions of patients receive total hip and knee arthroplasties every year with large projected increases as the population ages.[2] Despite the fact that TJA represents a value-based solution to end-stage arthritis of the hip and knee,[3] the procedure is associated with a moderate risk for complications. Complications affecting major organ systems have been reported to occur in approximately 8% of patients undergoing either hip or knee arthroplasty.[4] The identification of risk-modifying perioperative interventions represents an attractive target, given the large burden of resources required for the management of complications on a population-health level.

In this context, a number of recently published population-based studies have supported findings of earlier clinical trials, indicating that the type of anaesthetic technique may influence perioperative outcomes.[5,6] Whilst earlier RCTs suggested a potential benefit of neuraxial anaesthesia (NA) for outcomes, such as blood loss and thromboembolic events, these investigations were not sufficiently powered to study low-incidence outcomes, such as mortality, infectious, or cardiovascular complications.[7] Furthermore, earlier clinical trials were primarily conducted before the widespread use of chemical thromboembolic prophylaxis and contemporary blood-loss prevention practices.[8] The advent of population-based scientific approaches utilising large data sets that encompass healthcare information from hundreds of thousands of patients in actual practice environments has allowed researchers to add to the available knowledge in this field. Guided by a series of publications suggesting better outcomes with NA, a number of healthcare entities have developed policies encouraging the use of this anaesthetic type for TJA.[9]

Despite this development, definitive evidence in the form of large RCTs or pragmatic, multicentre trials is lacking. Moreover, it is questionable whether such studies will ever exist, given the challenges of feasibility and cost. As population-level data suggesting cost and outcome benefits of neuraxial approaches across a wide range of patient characteristics continue to emerge,[10–12] it is also unclear if the necessary pre-RCT condition of equipoise can exist to support an experimental trial design.

In light of these factors and given that the utilisation of NA remains low in many countries,[13] this international group of perioperative clinicians, researchers, quality experts, librarians, educators, and administrators assembled to (i) systematically investigate current published evidence to determine whether the type of anaesthesia technique can influence perioperative outcomes in patients undergoing total hip and knee arthroplasty; (ii) grade the level of evidence quality; and (iii) develop and formulate clinical practice recommendations, each with its own rating of strength.

The aim of the present consensus project was to systematically analyse and interpret current research evidence with regard to the impact of regional, and specifically neuraxial, anaesthesia in comparison to general anaesthesia (GA) on major perioperative outcomes for patients undergoing total hip or knee arthroplasties.

Methods

Consensus group

The International Consensus on Anaesthesia-Related Outcomes after Surgery (ICAROS) consensus group included 50 individuals with extensive expertise in the perioperative care of orthopaedic surgery patients. Included in this multidisciplinary group were anaesthesiologists, orthopaedic surgeons, healthcare outcomes and quality researchers, administrators, librarians, and methodologists from North America, Europe, and Oceania representing 19 nationalities, working in 10 countries. A 10-member steering committee was formed and tasked with overseeing day-to-day aspects of the project.

Study plan and healthcare question

A study plan was specified in advance, defining the healthcare questions and basic parameters, including intervention (NA) and alternative management strategy (GA), population, outcomes of interest, and inclusion and exclusion criteria. The detailed respective protocol, including analyses conducted for this project was registered on the International Prospective Register of Systematic Reviews (protocol number: CRD42018099935).[14] An institutional review board approval was not required because of the analysis of previously published data.

The healthcare questions posed to the group were:

(i) Does NA *vs* GA influence perioperative outcomes in patients undergoing total hip arthroplasty (THA)?
(ii) Does NA *vs* GA influence perioperative outcomes in patients undergoing total knee arthroplasty (TKA)?

The predefined outcomes of interest included the following major perioperative complications: mortality, cardiac (with and without myocardial infarction), pulmonary (including pneumonia), gastrointestinal, renal (including acute renal failure), genitourinary (including urinary retention and urinary tract infection), thromboembolic (DVT and pulmonary embolism [PE]), neurological (including CNS complications and stroke), infectious, and wound complications, as well as blood loss (in ml), transfusion requirements (both binary and in ml), and inpatient falls. To account for resource utilisation, the study plan also included outcomes, such as cost of care, length of hospitalisation, and admission to critical care settings. However, because of the lack of studies on cost of care, the outcome could *de facto* not be included in the quantitative meta-analysis.[15,16]

As specified in the study protocol, the consensus group will also address the impact of peripheral nerve block utilisation in patients undergoing total hip and knee arthroplasty. This healthcare question is currently being investigated and will be the focus of a subsequent analysis.

Selection criteria

Eligible studies included RCTs and observational prospective or retrospective studies in adult patients primarily undergoing elective total hip or knee arthroplasties. We included only studies directly comparing perioperative outcomes amongst patients who received NA *vs* those under GA. GA was defined as total intravenous, inhalational, or combination thereof, or when termed specifically as 'general anaesthesia' by the study authors. NA was defined as spinal, extradural, combined spinal and extradural, and caudal anaesthesia. Exclusion criteria encompassed patients under 18 yr, studies not reporting on postoperative outcomes of interest, case reports, and case series, and also studies without control groups.

Search strategy

A systematic literature search was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

The search strategy, including Medical Subject Headings (MeSH), keywords, and controlled vocabulary terms, was crafted and validated by the expert group in collaboration with two institutional librarians. Medline, PubMed, Embase, and Cochrane Library, including Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Cochrane Central Register of Controlled Trials, Cochrane Methodology Register, Health Technology Assessment Database, and NHS Economic Evaluation Database, were queried from database inception (1946) to May 17, 2018. The search cross-referenced MeSH terms, keywords, and controlled vocabulary terms for the predefined areas of interest according to the healthcare question.

The following is the excerpt of respective search terms: arthroplasty, replacement, hip, total hip arthroplasty, total hip arthroplasties, hip prosthesis, total joint replacement, knee, knee replacement arthroplasty, knee replacement arthroplasties, total knee arthroplasty, knee prosthesis, total knee replacements, lower extremity, lower joints, anaesthesia, neuraxial, spinal, epidural, conduction, regional anaesthesia, intrathecal, peridural, and combined spinal epidural.

The full search strategy is reported in Supplementary materials and can be found in Supplementary Appendix A1. The search yielded 8985 studies. In addition to the electronic search, a manual search of previously published corresponding systematic reviews was performed for the purpose of completeness.

Study identification and data extraction

After deduplication, abstracts of 5553 studies were extracted and imported into the Covidence platform. Covidence is a web tool that provides a comprehensive framework for the complete process of a systematic literature review, including the steps of title and abstract screening, full-text review, data extraction, and quality assessment (risk of bias).[17] As required, each step was performed independently by two reviewers. In case of a disagreement, a third reviewer was consulted for resolution.

After the title and abstract screening, full-text articles of 956 studies were imported into Covidence for a detailed review and data extraction. Extracted data were categorised according to the predefined outcomes. Furthermore, within the Covidence platform, the risk of bias for each individual study was assessed and established as high, low, or unknown, according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) criteria for RCTs and observational studies.[18]

A flow chart describing the complete literature search process is depicted in Figure 1.

Quantitative analysis

To provide estimates of intervention effects for each outcome of interest,[19] RCT and observational data were pooled by meta-analysis. Review Manager software (Review Manager (RevMan) [Computer program]. Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) was utilised to facilitate data analysis and graphic presentation as is commonly used for preparing Cochrane reviews.[20] Summary estimates were calculated separately for each outcome (odds ratios [ORs] and 95% confidence intervals [CIs]), whilst heterogeneity utilising (I^2 statistic) was also determined in quantitative analysis. For binary outcomes, group-specific risk was presented in events per 1000, whilst the relative effect was presented in ORs. For continuous variables, risk was presented as mean difference.

The primary analysis was performed including all eligible studies for both types of surgery, respectively (n=27 for TKA; n=49 for THA). A separate analysis was performed amongst studies that reported on THA/TKA mixed populations (n=21).

Secondary analyses were performed to test the influence of combined NA+GA compared with GA on perioperative outcomes in THA and TKA separately (n=12 and n=4, respectively), and also in the mixed THA/TKA surgical cohort (n=8).

The following are the additional sensitivity analyses:

(i) Sensitivity analysis to investigate outcomes when only including evidence from RCTs (n=25 for THA; n=12 for TKA; n=2 for THA/TKA)
(ii) Sensitivity analysis to investigate outcomes when removing studies that did not explicitly exclude all revision/trauma-related surgery or bilateral arthroplasties

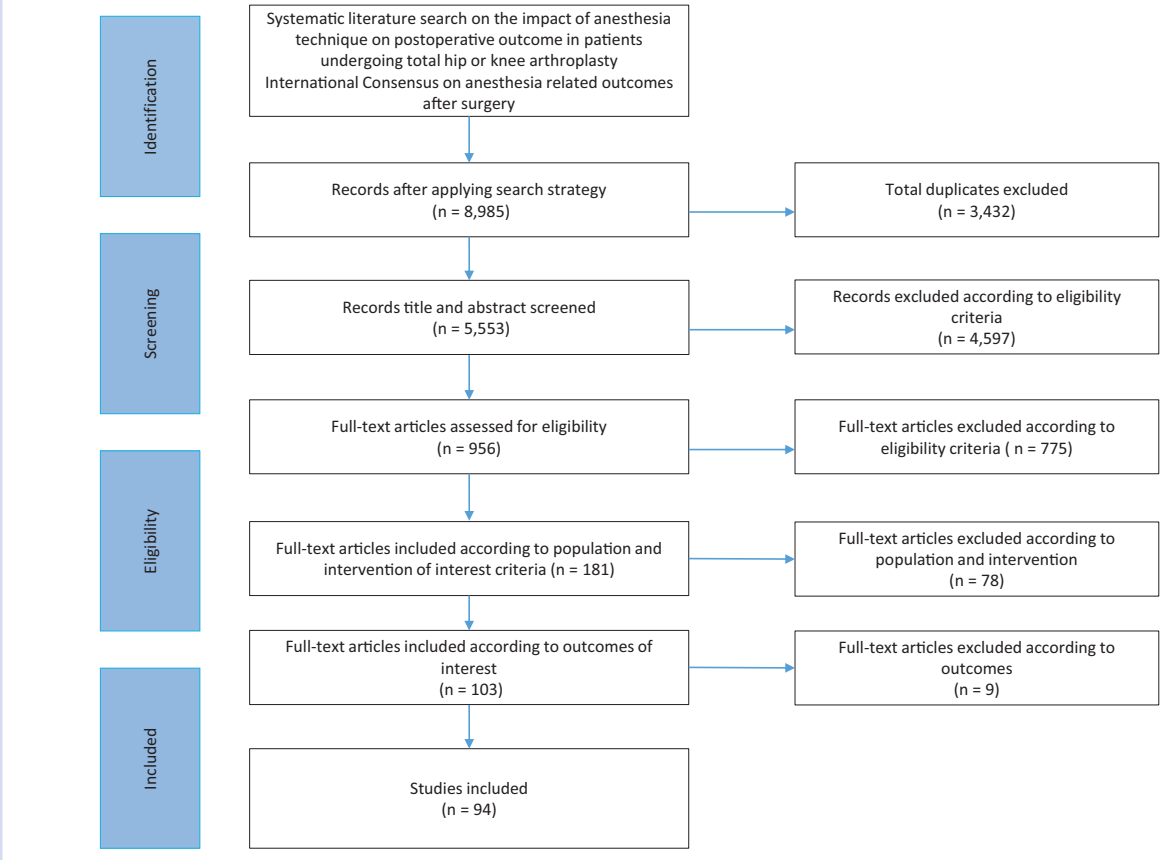

Fig 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.

in their cohorts (n=46 for THA; n=25 for TKA; n=17 for THA/TKA)

(iii) Sensitivity analysis to investigate the potential impact of recent changes in utilisation of perioperative thromboembolic prophylaxis protocols on the outcome of thromboembolic complications (DVT+PE).

Qualitative analysis

To provide useful recommendations for the practice of evidence-based treatment at the point of care, we utilised the GRADE system.[15,16] This methodology for rating the quality of evidence and grading the strength of recommendations has been widely adopted for the purpose of providing high-quality summaries of research evidence in systematic reviews and for standardised guideline development. Subsequent to data collection and quantitative analysis, GRADE offers a comprehensive framework for assessing the quality of the body of evidence and for carrying out steps required for developing recommendations.[21] The concept of the certainty or quality of evidence represents the confidence in effect estimates and the extent to which they are sufficiently credible to support a particular recommendation. GRADE specifies four levels of certainty: high, moderate, low, and very low. This rating is determined for each relevant outcome by the systematic and transparent assessment of study design, limitations of the body of evidence, and special circumstances that increase the quality of evidence. Explicit criteria according to GRADE that were utilised for downgrading the quality of evidence included risk of bias according to study design and study conduct, inconsistency or heterogeneity (lack of similarity of point estimates and overlap of CIs; determination of I^2 statistic), imprecision (optimal information size for adequate power), indirectness (strength of association to the healthcare question), and publication bias (utilising funnel plots).[15] These criteria were assessed for each reported outcome of interest across informing studies. However, risk of bias was also assessed previously for each individual study, whilst in qualitative analysis the impact of risk of bias on cumulative evidence for each outcome was determined. The rationale for upgrading the quality of evidence, particularly for methodologically rigorous observational studies, includes large effect size, presence of a dose–response relationship, or when all plausible confounders or biases would decrease an apparent treatment effect.[22] Utilising the GRADEpro software (McMaster University and Evidence Prime Inc.),[23] final results, including the pooled estimates of effect and the quality of evidence, are presented in summary of findings (Tables 1 and 2 for THA and TKA, respectively).

Recommendations

The assessment of the quality of evidence, the formulation of recommendations, and the determination of their strength are separate processes. When moving from evidence to recommendations, the GRADE strategy focuses on integrating factors that are basic for the formulation of guidelines or recommendations.[19,24] Thus, critical factors beyond the quality of evidence include the balance between benefits and harms; patient values and preferences; resource considerations; and issues pertaining to feasibility, equity, and acceptability of recommendations.[19] GRADE distinguishes between strong and weak recommendations.

The balance between desirable and undesirable outcomes and the application of patients' values determine the direction of the recommendation. Moreover, these factors, along with the quality of evidence, resource implications, and clinical feasibility considerations, determine the strength or grade of recommendations.

Strong recommendations reflect a clear preference for one alternative and should apply to almost all eligible patients. Weak recommendations are appropriate when there is a close balance between desirable and undesirable consequences or alternative management strategies, uncertainty regarding the effects of the alternatives, uncertainty or variability in patient's values and preferences, or questionable cost-effectiveness. Weak recommendations usually require accessing the underlying evidence and a shared decision-making approach.[15,19,21] In certain circumstances, a strong recommendation is based on low-quality evidence.[16]

Modified Delphi process and consensus meeting

Subsequent to analyses completion, two pairs of participants were tasked with summarising the evidence, formulating conclusions, and suggesting recommendations. This work was distributed in the form of white papers for the THA and TKA cohorts separately. The white papers, together with detailed files and summary tables of analysis results, were distributed to the entire group with the request for anonymous edits and comments according to the modified Delphi process,[25] and repeated after revisions.[26]

Finally, the group met in person on December 8, 2018, in New York, NY, USA, to review the process; discuss results; and reach a consensus on conclusions, recommendations, and their strength. Approval was assessed in an anonymous vote after statements were finalised as facilitated by a group discussion.

Results

A summary of findings for patients undergoing THA and TKA, including the estimates of effect and the quality of evidence by outcomes, is found in Tables 1 and 2, respectively.

Additional in-depth quantitative and qualitative analysis data and figures are provided as Supplementary material.

Impact of the type of anaesthesia in total hip arthroplasties

Primary analyses (NA vs GA)

Amongst all hip arthroplasty patients, NA without GA was associated with fewer complications in most categories, except for urinary retention, when compared with patients who received GA (Table 3).

NA was associated with decreased odds for all-cause mortality (OR: 0.67, 95% CI: 0.57, 0.80; absolute effect: 2 per 1000 with GA *vs* 1 per 1000 with NA, 95% CI: 1, 2), pulmonary complications (OR: 0.65; 95% CI: 0.52, 0.80), pneumonia (OR: 0.69; 95% CI; 0.56, 0.84), and acute renal failure (OR: 0.69; 95% CI: 0.59, 0.81). NA was also associated with fewer thromboembolic events compared with GA, including DVT (OR: 0.52; 95% CI: 0.42, 0.65) and PE (OR: 0.63; 95% CI: 0.50–0.81). Furthermore, CNS complications (OR: 0.39; 95% CI: 0.23, 0.65), stroke (OR: 0.37; 95% CI: 0.22, 0.64), all-cause infections (OR:

Table 1 Grading of Recommendations Assessment, Development and Evaluation (GRADE) summary of findings for total hip arthroplasty (THA). CI, confidence interval; GA, general anaesthesia; MI, myocardial infarction; NA, neuraxial anaesthesia; OR, odds ratio. GRADE Working Group grades of evidence: high certainty (we are very confident that the true effect lies close to that of the estimate of the effect), moderate certainty (we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different), low certainty (our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect), and very low certainty (we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect). *The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). †Publication bias: funnel plot not symmetric. ‡Heterogeneity: widely differing estimates of effect.

Summary of findings

NA compared with GA for THA

Patient or population: THA
Setting: perioperative care
Intervention: NA
Comparison: GA

Outcomes/complications	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with GA	Risk with NA				
Mortality	2 per 1000	1 per 1000 (1–2)	OR: 0.67 (0.57–0.80)	(3 RCTs, 4 observational studies)	⊕⊕◯◯ Low	
Cardiac including MI	57 per 1000	53 per 1000 (50–58)	OR: 0.94 (0.88–1.02)	(3 RCTs, 3 observational studies)	⊕⊕◯◯ Low	
Cardiac excluding MI	48 per 1000	47 per 1000 (43–50)	OR: 0.96 (0.88–1.03)	(2 RCTs, 3 observational studies)	⊕◯◯◯ Very low†	
MI	3 per 1000	3 per 1000 (2–4)	OR: 0.94 (0.71–1.24)	(2 RCTs, 2 observational studies)	⊕⊕◯◯ Low	
Pulmonary	7 per 1000	4 per 1000 (3–5)	OR: 0.65 (0.52–0.80)	(3 observational studies)	⊕⊕⊕◯ Moderate	
Pneumonia	10 per 1000	7 per 1000 (5–8)	OR: 0.69 (0.56–0.84)	(2 RCTs, 2 observational studies)	⊕⊕⊕◯ Moderate	
Gastrointestinal	10 per 1000	8 per 1000 (7–10)	OR: 0.83 (0.67–1.02)	109 732 (1 observational study)	⊕⊕◯◯ Low	
Acute renal failure	15 per 1000	10 per 1000 (9–12)	OR: 0.69 (0.59–0.81)	(1 RCT, 5 observational studies)	⊕⊕◯◯ Low‡	
Urinary retention	111 per 1000	277 per 1000 (199–370)	OR: 3.05 (1.98–4.69)	(3 RCTs, 3 observational studies)	⊕⊕⊕◯ Moderate	
Urinary tract infection	15 per 1000	13 per 1000 (10–15)	OR: 0.86 (0.70–1.06)	(2 observational studies)	⊕⊕◯◯ Low	
DVT	15 per 1000	8 per 1000 (6–10)	OR: 0.52 (0.42–0.65)	(5 RCTs, 8 observational studies)	⊕⊕⊕◯ Moderate	
Pulmonary embolism (PE)	3 per 1000	2 per 1000 (2–2)	OR: 0.63 (0.50–0.81)	(7 RCTs, 6 observational studies)	⊕⊕◯◯ Low	
Thromboembolism (DVT+PE)	5 per 1000	3 per 1000 (3–4)	OR: 0.61 (0.53–0.71)	(15 RCTs, 16 observational studies)	⊕⊕⊕◯ Moderate	
CNS	2 per 1000	1 per 1000 (0–1)	OR: 0.39 (0.23–0.65)	(3 observational studies)	⊕⊕⊕◯ Moderate	
Stroke	2 per 1000	1 per 1000 (0–1)	OR: 0.37 (0.22–0.64)	(2 observational studies)	⊕⊕⊕◯ Moderate	
	25 per 1000	19 per 1000 (17–20)	OR: 0.73 (0.67–0.79)	(2 RCTs, 7 observational studies)		

Continued

Table 1 Continued

Summary of findings

NA compared with GA for THA

Patient or population: THA
Setting: perioperative care
Intervention: NA
Comparison: GA

Outcomes/complications	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with GA	Risk with NA				
All infections (including pneumonia and sepsis)					⊕⊕◯◯ Low	
Wound superficial infection	8 per 1000	9 per 1000 (7–12)	OR: 1.21 (0.93–1.56)	(1 RCT, 2 observational studies)	⊕⊕◯◯ Low	
Wound deep infection	7 per 1000	6 per 1000 (5–7)	OR: 0.86 (0.70–1.06)	(3 observational studies)	⊕⊕◯◯ Low	
Blood transfusion	224 per 1000	197 per 1000 (192–205)	OR: 0.85 (0.82–0.89)	(8 RCTs, 9 observational studies)	⊕◯◯◯ Very low†	
Critical care admission	2 per 1000	1 per 1000 (1–2)	OR: 0.80 (0.49–1.32)	(2 observational studies)	⊕⊕◯◯ Low	
Readmission	38 per 1000	34 per 1000 (30–39)	OR: 0.91 (0.80–1.04)	28 857 (1 observational study)	⊕⊕◯◯ Low	
Nerve injury	2 per 1000	2 per 1000 (1–3)	OR: 0.81 (0.56–1.18)	(1 RCT, 4 observational studies)	⊕⊕◯◯ Low	
Falls	16 per 1000	13 per 1000 (12–15)	OR: 0.81 (0.72–0.92)	166 871 (1 observational study)	⊕⊕◯◯ Low	
Blood loss (ml)	The mean blood loss was 0.	The mean blood loss in the intervention group was 146.12 lower (173.73 lower to 118.51 lower).	—	1546 (12 RCTs, 4 observational studies)	⊕⊕⊕◯ Moderate‡	
Length of stay (days)	The mean length of hospital stay (LOS) was 0.	The mean LOS in the intervention group was 0.16 lower (0.22 lower to 0.1 lower).	—	(1 RCT, 1 observational study)	⊕⊕◯◯ Low	
Blood transfusion (ml)	The mean blood transfusion was 0.	The mean blood transfusion in the intervention group was 187.83 lower (272.29 lower to 103.38 lower).	—	(2 RCTs, 3 observational studies)	⊕⊕◯◯ Low	

Table 2 GRADE summary of findings for total knee arthroplasty (TKA). CI, confidence interval; GA, general anaesthesia; GRADE, Grading of Recommendations Assessment, Development and Evaluation; MI, myocardial infarction; NA, neuraxial anaesthesia; OR, odds ratio. GRADE Working Group grades of evidence: high certainty (we are very confident that the true effect lies close to that of the estimate of the effect), moderate certainty (we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different), low certainty (our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect), and very low certainty (we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect). *The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). †Imprecision. ‡Risk of bias: random sequence generation.

Summary of findings:

NA compared with GA for TKA

Patient or population: TKA
Setting: perioperative care
Intervention: NA
Comparison: GA

Outcomes/complications	Absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with GA	Risk with NA				
Mortality	1 per 1000	1 per 1000 (1–1)	OR: 0.83 (0.60–1.15)	259 847 (2 RCTs, 4 observational studies)	⊕⊕◯◯ Low	
Cardiac including MI	59 per 1000	60 per 1000 (58–63)	OR: 1.03 (0.98–1.08)	261 695 (1 RCT, 6 observational studies)	⊕⊕◯◯ Low	
Cardiac excluding MI	57 per 1000	58 per 1000 (55–61)	OR: 1.02 (0.97–1.08)	259 332 (4 observational studies)	⊕⊕◯◯ Low	
MI	2 per 1000	2 per 1000 (2–3)	OR: 0.99 (0.80–1.22)	261 695 (1 RCT, 6 observational studies)	⊕⊕◯◯ Low	
Pulmonary	6 per 1000	4 per 1000 (4–5)	OR: 0.69 (0.58–0.81)	259 392 (1 RCT, 4 observational studies)	⊕⊕⊕◯ Moderate	
Pneumonia	8 per 1000	6 per 1000 (6–7)	OR: 0.82 (0.72–0.94)	275 947 (1 RCT, 5 observational studies)	⊕⊕◯◯ Low	
Gastrointestinal	7 per 1000	7 per 1000 (6–8)	OR: 0.99 (0.85–1.15)	223 108 (1 observational study)	⊕⊕◯◯ Low	
Acute renal failure	14 per 1000	10 per 1000 (9–11)	OR: 0.73 (0.65–0.82)	273 384 (5 observational studies)	⊕⊕◯◯ Low	
Urinary retention	235 per 1000	203 per 1000 (121–317)	OR: 0.83 (0.45–1.51)	277 (2 RCTs, 1 observational study)	⊕⊕⊕◯ Moderate†	
Urinary tract infection	15 per 1000	12 per 1000 (11–14)	OR: 0.82 (0.71–0.96)	52 779 (4 observational studies)	⊕⊕◯◯ Low	
DVT	36 per 1000	27 per 1000 (22–32)	OR: 0.77 (0.64–0.93)	19 756 (6 RCTs, 6 observational studies)	⊕⊕◯◯ Low	
Pulmonary embolism (PE)	6 per 1000	4 per 1000 (4–5)	OR: 0.79 (0.67–0.94)	238 066 (3 RCTs, 4 observational studies)	⊕⊕◯◯ Low	
Thromboembolism (DVT+PE)	7 per 1000	5 per 1000 (5–6)	OR: 0.77 (0.68–0.88)	257 793 (8 RCTs, 10 observational studies)	⊕⊕◯◯ Low	
CNS	1 per 1000	1 per 1000 (1–1)	OR: 0.77 (0.55–1.08)	259 594 (1 RCT, 3 observational studies)	⊕⊕◯◯ Low	
Stroke	1 per 1000	1 per 1000 (1–1)	OR: 0.70 (0.49–1.01)	259 585 (1 RCT, 4 observational studies)	⊕⊕◯◯ Low	
All infections	22 per 1000	17 per 1000 (16–18)	OR: 0.80 (0.76–0.85)			

Continued

Table 2 Continued

Summary of findings:

NA compared with GA for TKA

Patient or population: TKA
Setting: perioperative care
Intervention: NA
Comparison: GA

Outcomes/complications	Absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with GA	Risk with NA				
				571 503 (1 RCT, 12 observational studies)	⊕⊕◯◯ Low	
Wound superficial infection	6 per 1000	4 per 1000 (3–6)	OR: 0.77 (0.60–0.98)	52 839 (1 RCT, 4 observational studies)	⊕⊕◯◯ Low	
Wound deep infection	2 per 1000	2 per 1000 (1–3)	OR: 1.01 (0.60–1.69)	31 843 (3 observational studies)	⊕⊕◯◯ Low	
Blood transfusion	165 per 1000	142 per 1000 (139–146)	OR: 0.84 (0.82–0.87)	259 332 (4 observational studies)	⊕⊕◯◯ Low	
Critical care admission	1 per 1000	0 per 1000 (0–1)	OR: 0.17 (0.04–0.75)	20 936 (1 observational study)	⊕⊕⊕◯ Moderate†	
Readmission	76 per 1000	38 per 1000 (23–59)	OR: 0.48 (0.29–0.77)	1629 (1 observational study)	⊕⊕⊕◯ Moderate	
Nerve injury	4 per 1000	5 per 1000 (2–10)	OR: 1.16 (0.58–2.32)	25 243 (4 observational studies)	⊕⊕◯◯ Low	
Falls	0 per 1000	0 per 1000 (0–0)	OR: 0.00 (–0.03 to 0.03)	118 (1 observational study)	⊕⊕◯◯ Low	Not estimable
Blood loss (ml)	The mean blood loss was 0.	The mean blood loss in the intervention group was 13.54 higher (25.75 lower to 52.83 higher).	—	130 (1 RCT)	⊕⊕⊕◯ Moderate‡	
Length of stay (days)	The mean length of hospital stay (LOS) was 0.	The mean LOS in the intervention group was 0.09 lower (0.15 lower to 0.02 lower).	—	36 956 (3 RCTs, 5 observational studies)	⊕⊕◯◯ Low	

Table 3 Influence of anaesthesia type on perioperative outcomes in total hip arthroplasty. CI, confidence interval; GA, general anaesthesia; MI, myocardial infarction; NA, neuraxial anaesthesia; OR, odds ratio; PE, pulmonary embolism. All infections, including pneumonia and sepsis; pulmonary complications, excluding pneumonia; *n* (NA/GA): total number of patients with NA/GA.

Complication	NA *vs* GA					NA+GA *vs* GA				
	Studies	OR (95% CI)	*n* (NA)	*n* (GA)	*P*-value	Studies	OR (95% CI)	*n* (NA)	*n* (GA)	*P*-value
Mortality	Various authors[5,27–36]	0.67 (0.57–0.80)	60 499	148 583	<0.0001	Various authors[5,30]	0.58 (0.38–0.89)	15 331	98 230	0.014
Cardiac including MI	Various authors[5,28,32–34,37]	0.94 (0.88–1.02)	28 182	121 215	0.135	Various authors[5,38]	0.76 (0.54–1.07)	15 281	98 139	0.113
Cardiac excluding MI	Various authors[5,27,32–34]	0.96 (0.88–1.03)	32 639	133 832	0.255	Memtsoudis and colleagues[5]	1.01 (0.95–1.09)	15 261	98 122	0.689
MI	Various authors[5,33,34,37]	0.94 (0.71–1.24)	23 022	115 759	0.647	Various authors[5,38]	0.76 (0.54–1.07)	15 281	98 139	0.113
Pulmonary	Various authors[5,28,33]	0.65 (0.52–0.80)	28 029	121 058	<0.0001	Memtsoudis and colleagues[5]	0.66 (0.52–0.84)	15 261	98 122	0.001
Pneumonia	Various authors[5,33,34,37]	0.69 (0.56–0.84)	23 022	115 759	<0.0001	Memtsoudis and colleagues[5]	0.88 (0.74–1.05)	15 261	98 122	0.165
Gastrointestinal	Memtsoudis and colleagues[5]	0.83 (0.67–1.02)	11 610	98 122	0.078	Memtsoudis and colleagues[5]	0.79 (0.65–0.95)	15 261	98 122	0.013
Acute renal failure	Various authors[5,33,37,39,40]	0.69 (0.59–0.81)	34 366	133 687	<0.0001	Memtsoudis and colleagues[5]	0.75 (0.65–0.86)	15 261	98 122	<0.0001
Urinary retention	Various authors[34,39–43]	3.05 (1.98–4.69)	252	628	<0.0001	Various authors[44,45]	1.91 (1.05–3.48)	123	163	0.035
Urinary tract infection	Various authors[30,33]	0.86 (0.70–1.06)	11 334	17 648	0.164	Brinker and colleagues[30]	1.14 (0.43–2.99)	70	108	0.793
DVT	Various authors[30,33,36,41,43,46–53]	0.52 (0.42–0.65)	15 688	20 477	<0.0001	Various authors[30,38]	0.81 (0.17–3.89)	90	125	0.795
PE	Various authors[5,33–37,41,48–53]	0.63 (0.50–0.81)	34 875	123 934	<0.0001	Memtsoudis and colleagues[5]	0.68 (0.46–1.03)	15 261	98 122	0.066
DVT+PE	Various authors[5,30,33–37,41,43,46–57]	0.61 (0.53–0.71)	59 573	157 731	<0.0001	Various authors[5,30,38]	0.69 (0.47–1.02)	15 351	98 247	0.065
CNS	Various authors[5,33,58]	0.39 (0.23–0.65)	22 977	115 712	<0.0001	Various authors[5,34,59]	0.68 (0.42–1.09)	15 306	98 162	0.112
Stroke	Various authors[5,33]	0.37 (0.22–0.64)	22 927	115 662	<0.0001	Memtsoudis and colleagues[5]	0.71 (0.44–1.16)	15 261	98 122	0.176
All infections	Various authors[5,28,30,33,34,37]	0.73 (0.67–0.79)	62 385	254 465	<0.0001	Various authors[5,30]	0.86 (0.79–0.92)	30 592	196 352	<0.0001
Wound (superficial)	Various authors[30,33,34]	1.21 (0.93–1.56)	11 363	17 679	0.152	Brinker and colleagues[30]	1.56 (0.21–11.33)	70	108	0.661
Wound (deep)	Various authors[28,33,54]	0.86 (0.70–1.06)	24 603	35 688	0.159					
Blood transfusion	Various authors[5,30,33,34,37,41,43,60–69]	0.85 (0.82–0.89)	25 033	117 443	<0.0001	Various authors[5,30,38,61]	0.78 (0.75–0.82)	15 421	98 317	<0.0001
Critical care	Various authors[27,33]	0.80 (0.49–1.32)	20 690	33 125	0.387					
Readmission	Haughom and colleagues[33]	0.91 (0.80–1.04)	11 317	17 540	0.161					
Nerve injury	Various authors[30,33,34,69]	0.81 (0.56–1.18)	19 842	27 106	0.278	Brinker and colleagues[30]	0.30 (0.01–6.39)	70	108	0.442
Falls	Kendrišić and colleagues[71]	0.81 (0.72–0.92)	20 985	145 886	0.001					
Blood loss (ml)	Various authors[36,43,50–52,60–62,66,68,72–77]	−146.12 (−173.73 to −118.51)	902	644	<0.0001	Various authors[38,59,61,74,77–79]	−20.13 (−50.10 to 9.83)	226	216	0.188
Length of stay (days)	Various authors[28,80]	−0.16 (−0.22 to −0.10)	5146	5442	<0.0001	Benson and colleagues[59]	−6.00 (−14.77 to 2.77)	16	9	0.18
Blood transfusion (ml)	Various authors[43,50,51,60,66]	−187.83 (−272.29 to −103.38)	310	195	<0.0001					

0.73; 95% CI: 0.67, 0.79), blood transfusion requirements (OR: 0.85; 95% CI: 0.82, 0.89), and postoperative falls (OR: 0.81; 95% CI: 0.72, 0.92) were reduced with NA *vs* GA.

We did not identify any differences in cardiac, gastrointestinal, or wound complications; critical care admissions; readmissions; and nerve injuries between NA and GA amongst hip arthroplasty patients.

Impact of the type of anaesthesia in total knee arthroplasties

Primary analyses (NA vs GA)

Amongst patients undergoing total knee arthroplasties, the utilisation of NA in comparison to GA was associated with improved outcomes with regard to multiple complications (Table 4). Amongst patients who received NA, reduced odds were observed for pulmonary complications (OR: 0.69; 95% CI: 0.58–0.81), pneumonia (OR: 0.82; 95% CI: 0.72, 0.94), acute renal failure (OR: 0.73; 95% CI: 0.65, 0.82), urinary tract infection (OR: 0.82; 95% CI: 0.71, 0.96), DVT (OR: 0.77; 95% CI: 0.64, 0.93), PE (OR: 0.79; 95% CI: 0.67, 0.94), all-cause infections (OR: 0.80; 95% CI: 0.76, 0.85), superficial wound infections (OR: 0.77; 95% CI: 0.60, 0.98), blood transfusions (OR: 0.84; 95% CI: 0.82, 0.87), critical care admissions (OR: 0.17; 95% CI: 0.04, 0.75), and readmissions (OR: 0.48; 95% CI: 0.29, 0.77).

Impact of the type of anaesthesia in studies reporting outcomes in mixed total knee/hip arthroplasties

Primary analyses (NA vs GA)

The results are presented in Supplementary Table A5. Overall, improved outcomes were seen in association with the use of NA *vs* GA in this cohort of studies.

Secondary analyses (NA+GA vs GA)

In a secondary analysis, we compared the utilisation of combined NA+GA *vs* GA only to assess the impact on studied outcomes in patients undergoing THA and TKA (Tables 3 and 4, and Supplementary Table A5). The output indicated a similar trend as observed in the NA *vs* GA analysis. The outcomes with significantly reduced odds for combined NA+GA *vs* GA included mortality, pulmonary complications, gastrointestinal complications, acute renal failure, all-cause infections, and blood transfusions, whilst the odds for urinary retention were increased as seen in the NA *vs* GA comparison.

Sensitivity analyses

Randomised clinical trials only

The first sensitivity analysis focused on RCTs only and verified that NA was associated with fewer thromboembolic events than GA (Tables 5 and 6, and Supplementary Table A6). NA patients also had less blood loss and received lower blood transfusion volumes (Table 5). This analysis did not present statistically significant differences in other complications, which may be attributable to the much smaller sample size in RCTs compared with population-based analyses.

Exclusion of studies likely containing a minority of revision/trauma surgery or bilateral arthroplasty cases

Our primary analysis included all patients from all candidate studies, which encompassed RCTs and observational studies. In some of these investigations, revision/trauma-related arthroplasty patients could not be excluded with certainty. To test the potential effect that this patient population may have on outcomes, we excluded them in a sensitivity analysis. The relationship between anaesthetic type and outcomes when excluding revision/trauma arthroplasty was nearly identical compared with the primary inclusive analysis (Supplementary Tables A2–A4).

Sensitivity analysis: thromboembolic complications (DVT+PE)

To account for potential prognostic imbalance as a result of recent emerging differences in perioperative care with regard to the implementation of thrombosis prophylaxis in recent years, we performed a further sensitivity analysis. Estimates of intervention effects were established for the outcome of thromboembolic complications (DVT+PE) when including all eligible studies, when excluding studies without thrombosis prophylaxis, and when excluding studies published before 1995.

NA was associated with a 24% reduction in thromboembolic events when including all studies (n=37; OR: 0.76; 95% CI: 0.71, 0.83), a 14% reduction when excluding studies lacking thromboembolic prophylaxis (n=9; OR: 0.86; 95% CI: 0.79, 0.92), and a 16% reduction when excluding studies before 1995 (n=14; OR: 0.84; 95% CI: 0.78, 0.90).

Discussion

Recommendations and comments

Does type of anaesthesia influence perioperative outcomes in THA?

The utilisation of NA over GA for THA was associated with lower complication odds for most studied outcomes. The utilisation of combined NA and GA was also associated with better perioperative outcomes compared with GA alone, although the magnitude and diversity of benefits were decreased compared with using NA alone (Tables 1 and 3).

(i) Level of evidence: low to moderate
(ii) Recommendation: NA is recommended for primary unilateral THA when there is no significant contraindication or special circumstance to preclude its use.
(iii) Strength of recommendation: strong
(iv) Rationale: Based on the findings of our analysis and the grading of evidence, the group reached a unanimous decision on the aforementioned recommendation. The results of all analyses showed improvement in outcomes with NA compared with GA in most cases, or no impact, with the sole exception of urinary retention, albeit the latter is a known, expected side-effect of NA.[101]

The level of evidence underlying the individual analyses by outcome was low to moderate. When considering the factors integrated by the GRADE approach for the development of recommendations,[19] the majority of the group (n=33 out of 43 votes) determined it to be overall strong.

The latter conclusion was based on the observations that: (i) the evidence was largely in favour of the intervention, (ii)

Table 4 Influence of anaesthesia type on perioperative outcomes in total knee arthroplasty. CI, confidence interval; GA, general anaesthesia; MI, myocardial infarction; NA, neuraxial anaesthesia; OR, odds ratio; PE, pulmonary embolism. All infections, including pneumonia and sepsis; pulmonary complications, excluding pneumonia; *n* (NA/GA): total number of patients with NA/GA.

Complication	NA *vs* GA					NA+GA *vs* GA				
	Studies	OR (95% CI)	*n* (NA)	*n* (GA)	*P*-value	Studies	OR (95% CI)	*n* (NA)	*n* (GA)	*P*-value
Mortality	Various authors[5,6,54,57,81,82]	0.83 (0.60–1.15)	43 653	216 194	0.261	Memtsoudis and colleagues[5]	0.73 (0.51–1.05)	34 135	194 682	0.094
Cardiac including MI	Various authors[5,6,54,57,81,83,84]	1.03 (0.98–1.08)	44 831	216 864	0.324	Various authors[5,85]	1.07 (0.85–1.34)	34 165	194 715	0.553
Cardiac excluding MI	Various authors[5,6,54,57]	1.02 (0.97–1.08)	43 386	215 946	0.349	Memtsoudis and colleagues[5]	1.07 (1.02–1.12)	34 135	194 682	0.007
MI	Various authors[5,6,54,57,81,83,84]	0.99 (0.80–1.22)	44 831	216 864	0.896	Various authors[5,85]	1.07 (0.85–1.34)	34 165	194 715	0.553
Pulmonary	Various authors[5,6,54,57,86]	0.69 (0.58–0.81)	43 416	215 976	<0.0001	Various authors[5,85]	0.89 (0.77–1.03)	34 165	194 715	0.132
Pneumonia	Various authors[5,6,54,57,86,87]	0.82 (0.72–0.94)	50 804	225 143	0.003	Memtsoudis and colleagues[5]	1.02 (0.90–1.16)	34 135	194 682	0.727
Gastrointestinal	Memtsoudis and colleagues[5]	0.99 (0.85–1.15)	28 426	194 682	0.855	Various authors[5,85]	1.07 (0.93–1.22)	34 165	194 715	0.344
Acute renal failure	Various authors[5,6,54,57]	0.73 (0.65–0.82)	49 416	223 968	<0.0001	Memtsoudis and colleagues[5]	0.96 (0.87–1.05)	34 135	194 682	0.377
Urinary retention	Various authors[32,86,88]	0.83 (0.45–1.51)	111	166	0.537					
Urinary tract infection	Various authors[6,54,57,87]	0.82 (0.71–0.96)	22 348	30 431	0.011					
DVT	Various authors[6,47,56,82,83,89–95]	0.77 (0.64–0.93)	9466	10 222	0.005	[85]	0.53 (0.05–6.21)	30	33	0.617
PE	Various authors[5,6,42,82,90,92,94]	0.79 (0.67–0.94)	34 890	203 176	0.007	Memtsoudis and colleagues[5]	0.78 (0.66–0.93)	34 135	194 682	0.006
DVT+PE	Various authors[5,6,42,47,56,82,83,89,90,92–95]	0.77 (0.68–0.88)	44 373	213 420	<0.0001	Various authors[5,85]	0.78 (0.66–0.93)	34 165	194 715	0.005
CNS	Various authors[5,6,54,57,81]	0.77 (0.55–1.08)	43 520	216 074	0.133	Various authors[5,85,96]	1.03 (0.75–1.43)	34 270	194 823	0.84
Stroke	Various authors[5,6,54,57,82]	0.70 (0.49–1.01)	43 519	216 066	0.059	Various authors[5,85]	1.06 (0.76–1.49)	34 165	194 715	0.72
All infections	Various authors[5,6,54,57,86,87]	0.80 (0.76–0.85)	109 150	462 353	<0.0001	Memtsoudis and colleagues[5]	0.98 (0.93–1.03)	68 270	389 364	0.464
Wound (superficial)	Various authors[6,54,57,86,87]	0.77 (0.60–0.98)	22 378	30 461	0.034					
Wound (deep)	Various authors[6,57,87]	1.01 (0.60–1.69)	14 164	17 679	0.982					
Blood transfusion	Various authors[5,6,54,57]	0.84 (0.82–0.87)	43 386	215 946	<0.0001	Memtsoudis and colleagues[5]	1.02 (0.99–1.05)	34 135	194 682	0.197
Critical care	Basques and colleagues[54]	0.17 (0.04–0.75)	8184	12 752	0.019					
Readmission	Belmont and colleagues[97]	0.48 (0.29–0.77)	586	1043	0.003					
Nerve injury	Various authors[6,57,70]	1.16 (0.58–2.32)	7304	17 939	0.665					
Falls	Harsten and colleagues[32]	0.00 (0.00–0.00)	58	60	<0.0001	Kendrišić and colleagues[71]	0.91 (0.81–1.02)	24 699	145 886	0.092
Blood loss (ml)	Zhou and colleagues[95]	13.54 (−25.75 to 52.83)	63	67	0.499	Kudoh and colleagues[96]	13.10 (−18.99 to 45.19)	75	75	0.424
Length of stay (days)	Various authors[6,54,57,81,82,98–100]	−0.09 (−0.15 to −0.02)	15 326	21 630	0.009					

Table 5 Subgroup RCTs: influence of anaesthesia type on perioperative outcomes in total hip arthroplasty. CI, confidence interval; GA, general anaesthesia; MI, myocardial infarction; NA, neuraxial anaesthesia; OR, odds ratio; PE, pulmonary embolism. All infections, including pneumonia and sepsis; pulmonary complications, excluding pneumonia; *n* (NA/GA): total number of patients with NA/GA.

Complication	NA *vs* GA					NA+GA *vs* GA				
	Studies	OR (95% CI)	*n* (NA)	*n* (GA)	*P*-value	Studies	OR (95% CI)	*n* (NA)	*n* (GA)	*P*-value
Mortality	Various authors[32,34,36]	0.34 (0.01–8.80)	135	137	0.519					
Cardiac including MI	Various authors[32,34,37]	0.82 (0.19–3.48)	153	157	0.783	Dauphin and colleagues[38]	1.78 (0.15–21.51)	20	17	0.651
Cardiac excluding MI	Various authors[32,34]	0.65 (0.08–5.38)	87	91	0.687					
MI	Various authors[34,37]	0.75 (0.14–4.07)	95	97	0.736	Dauphin and colleagues[38]	1.78 (0.15–21.51)	20	17	0.651
Pneumonia	Various authors[34,37]	1.03 (0.14–7.53)	95	97	0.973					
Acute renal failure	Liang and colleagues[37]	0.33 (0.01–8.21)	66	66	0.498					
Urinary retention	Various authors[34,41,42]	1.65 (0.89–3.05)	158	162	0.113					
DVT	Various authors[36,41,50,51]	0.33 (0.20–0.55)	177	174	<0.0001	Dauphin and colleagues[38]	0.81 (0.17–3.89)	20	17	0.795
PE	Various authors[34,36,37,41,50,51]	0.40 (0.20–0.79)	255	257	0.008					
DVT+PE	Various authors[34,36,37,41,50,51,55,56]	0.43 (0.30–0.63)	482	479	<0.0001	Dauphin and colleagues[38]	0.81 (0.17–3.89)	20	17	0.795
CNS						Various authors[34,59]	0.26 (0.03–2.28)	45	40	0.222
All infections	Various authors[34,37]	1.03 (0.14–7.53)	95	97	0.973					
Wound (superficial)	34	0.33 (0.03–3.40)	29	31	0.354					
Blood transfusion	Various authors[34,37,41,61–63,67,68]	0.43 (0.28–0.65)	357	364	<0.0001	Various authors[38,61]	0.50 (0.24–1.05)	90	87	0.067
Nerve injury	Hole and colleagues[34]	0.34 (0.01–8.80)	29	31	0.519					
Blood loss (ml)	Various authors[36,50,51,61,62,68,72–75,77]	−121.82 (−152.22 to −91.42)	334	335	<0.0001	Various authors[38,59,61,74,77–79]	−20.13 (−50.10 to 9.83)	226	216	0.188
Length of stay (days)	Williams-Russo and colleagues[80]	−3.00 (−6.25 to 0.25)	44	46	0.07	Benson and colleagues[59]	−6.00 (−14.77 to 2.77)	16	9	0.18
Blood transfusion (ml)	Various authors[50,51]	−542.64 (−771.95 to −313.32)	45	45	<0.0001					

Table 6 Subgroup RCTs: influence of anaesthesia type on perioperative outcomes in total knee arthroplasty. CI, confidence interval; GA, general anaesthesia; MI, myocardial infarction; NA, neuraxial anaesthesia; OR, odds ratio; PE, pulmonary embolism. All infections, including pneumonia and sepsis; pulmonary complications, excluding pneumonia; *n* (NA/GA): total number of patients with NA/GA.

Complication	NA *vs* GA					NA+GA *vs* GA				
	Studies	OR (95% CI)	*n* (NA)	*n* (GA)	*P*-value	Studies	OR (95% CI)	*n* (NA)	*n* (GA)	*P*-value
Mortality	Various authors[81,82]	0.93 (0.13–6.64)	267	248	0.941					
Cardiac including MI	Williams-Russo and colleagues[81]	1.28 (0.28–5.84)	134	128	0.748					
MI	Williams-Russo and colleagues[81]	0.95 (0.19–4.82)	134	128	0.955					
Pulmonary	Chu and colleagues[86]	0.48 (0.04–5.63)	30	30	0.561					
Pneumonia	Chu and colleagues[86]	0.19 (0.01–4.06)	30	30	0.286					
Urinary retention	Various authors[32,86]	0.86 (0.47–1.59)	88	90	0.628					
DVT	Various authors[56,82,89–91,95]	0.82 (0.56–1.18)	256	327	0.283					
PE	Various authors[42,82,90]	1.17 (0.45–3.03)	163	149	0.748					
DVT+PE	Various authors[42,56,82,89,90,95]	0.78 (0.56–1.10)	436	498	0.157					
CNS	Williams-Russo and colleagues[81]	1.31 (0.59–2.89)	134	128	0.503	Kudoh and colleagues[96]	0.74 (0.16–3.42)	75	75	0.7
Stroke	Williams-Russo and colleagues[82]	2.73 (0.11–67.61)	133	120	0.54					
All infections	Chu and colleagues[86]	0.19 (0.01–4.06)	30	30	0.286					
Wound (superficial)	Chu and colleagues[86]	0.48 (0.04–5.63)	30	30	0.561					
Falls	Harsten and colleagues[32]	0.00 (0.00–0.00)	58	60	<0.0001					
Blood loss (ml)	Zhou and colleagues[95]	13.54 (−25.75 to 52.83)	63	67	0.499	Kudoh and colleagues[96]	13.10 (−18.99 to 45.19)	75	75	0.424
Length of stay (days)	Various authors[81,82,98]	−0.14 (−0.56 to 0.28)	308	295	0.512					

the desirable effects of the intervention outweigh the undesirable ones, (iii) the intervention was associated with neutral to beneficial resource utilisation, (iv) the intervention is acceptable to stakeholders, and (v) the intervention is feasible.

Does type of anaesthesia influence perioperative outcomes in TKA?

Compared with GA, NA was associated with fewer complications or no difference in complications in all reported outcomes after TKA (Tables 2 and 4).

NA was associated with lower odds of thromboembolic events and blood transfusion, and also infectious complications, including pneumonia and all-cause infections. Furthermore, lower odds for acute renal failure and respiratory complications were found amongst patients receiving NA for TKA. With regard to outcomes of resource utilisation, NA was associated with fewer admissions to critical care units, lower rates of hospital readmissions, and a shorter length of hospital stay (mean difference: −0.08; 95% CI: −0.15 to 0.01 days).

Our analysis failed to find any significant differences in the odds for mortality, composite CNS complications, or stroke. There was also no effect of anaesthetic type on cardiac or gastrointestinal complications.

(i) Level of evidence: low
(ii) Recommendation: Provided no contraindication, a primary neuraxial anaesthetic technique is preferred for TKA, given several positive benefits of NA on important post-TKA outcomes, together with no evidence of worse outcomes.
(iii) Strength of recommendation: weak
(iv) Rationale: Based on the findings of our analysis and the grading of the level of evidence, the group reached a majority (n=42 out of 43 votes) decision on the aforementioned recommendation. The results of all analyses showed improvement with NA for outcomes compared with GA for some but not all outcomes. The effect was smaller than that seen in the larger THA cohort.

The level of evidence underlying the individual analyses by outcome was low.

When considering the factors integrated by the GRADE approach for the development of recommendations, the majority of the group (n=31 out of 43 votes) determined it to be overall weak.

The latter conclusion was based on the observations that the evidence was in favour of the intervention, but to a lesser extent than that observed in the THA cohort. However, the group believed that the desirable effects of the intervention outweigh the undesirable effects, and that the intervention was associated with beneficial resource utilisation. Further, the intervention is acceptable to stakeholders and is clinically feasible.

Comments

Several limitations to our consensus approach have to be considered. Perioperative care has evolved significantly over years and decades, including surgical techniques. This may be a source of unmeasured or unknown confounding that is not adequately balanced by randomisation.

Further, the group discussed extensively the lack of detailed information regarding the potentially wide variability in the conduct of GA and the potential influence of GA technique on outcomes. Whilst NA as a technique may vary to certain degrees (type of local anaesthetic used, use of spinal *vs* extradural *vs* combined spinal/extradural, and level of neuraxial block), the group agreed that the conduct of the technique and its major characteristics are standardised and have been in place for many decades. In contrast, the conduct of GA has evolved significantly over time with changes in pharmacological agents (both intravenous and inhalational), assistive technology (target-controlled infusion), airway devices, monitoring, and ventilation equipment, and also care strategies.

Therefore, it seems appropriate to re-evaluate the differential impact of modern general anaesthetic techniques in this context once such granular information becomes reliably available in the future.

Additional factors that may influence outcomes include the use of procedural sedation and its depth, which may, in practice, approach levels seen with GA.[102] However, at this time, such an analysis is not feasible because of the lack of adequate data. In addition, the inherent anaesthetic-related risks of each technique (GA or NA) were not considered in this analysis, but are rare for either approach.

In the last decade, advances in regional anaesthesia, such as the utilisation of ultrasound-guided peripheral nerve block techniques, have gained significant popularity in the clinical setting. Thus, our research group is currently reviewing evidence regarding the perioperative impact of peripheral nerve blocks. However, given the numerous options and combinations of various anaesthesia-related procedures, further studies are needed to address specifically the impact of peripheral nerve blocks as adjuncts to GA when compared with NA.

Further, the group discussed what future research would be needed to derive definitive data on the questions addressed in this consensus article. Whilst large, multicentre RCTs or pragmatic trials may provide definitive evidence, they are not and may never be available. Future studies are indicated to better evaluate the mechanisms by which the observed beneficial effects associated with NA are realised. The group acknowledged that, whilst a plausible mechanism for improved outcomes is likely related to NA-associated reductions in stress response, the body of evidence establishing this link is scarce.[103] Further, it was determined that future research is needed to elucidate the relationship between anaesthetic type and outcomes in the ever-increasing commonality of high-risk patient populations presenting for joint arthroplasty. Moreover, comparative literature for some complications, such as postoperative cognitive dysfunction, is rare, and these topics require more scientific investigations to allow robust analysis and conclusions in the context of anaesthesia practice.[58,81] Finally, the group commented that, given the potential benefits and relative underutilisation of NA, research with focus on identification and amelioration of barriers to the widespread implementation of NA techniques is needed.

Executive summary

Does type of anaesthesia influence perioperative outcomes in THA?

The utilisation of NA over GA for THA was associated with lower complication risk for most studied outcomes. Furthermore, the utilisation of combined NA and GA was also associated with better perioperative outcomes compared with GA alone, although the magnitude and diversity of benefits were decreased compared with using NA alone (Tables 1 and 3).

(i) Level of evidence: low to moderate
(ii) Recommendation: NA is recommended for primary unilateral THA when there is no significant contraindication or special circumstance to preclude its use.
(iii) Strength of recommendation: strong

Does type of anaesthesia influence perioperative outcomes in TKA?

(i) Level of evidence: low
(ii) Recommendation: Provided no contraindication, a primary neuraxial anaesthetic technique is preferred for TKA, given several positive benefits of NA on important post-TKA outcomes, together with no evidence of worse outcomes.
(iii) Strength of recommendation: weak

Authors' contributions

Study conception: SGM
Study design/planning/execution: SGM, NES, CC, JB, JL, EMS, ERM, RLJ, MJH, GG
Reviewing/expanding study plan: EA, MJB, AB, JDA, NE, PEG, PG, AGDV, EG, PK, SLK, PL'H, CHML, CBM, DM, AM, JMN, MP, JPa, LP, JPo, LAP, BDS, OS, ECS, ERV, EGV-V, CW, JTYD
Literature search: CC, RG, BJ, LP, BHL, PW, MB, GG, SJK, LB, DW, GH
Data extraction: JB, DB, CC, BHL, PW, MB, GG, SJK, LB, DW, GH, JL, SGM
Data analysis: CC, SGM, NES, JPo, JB, JL, ES, ERM, RLJ, MJH, GG
Reviewing results of data analysis: EA, MJB, AB, JDA, NE, PEG, PG, AGDV, EG, PK, SLK, PL'H, CHML, CBM, DM, AM, JMN, MP, JPa, LP, JPo, LAP, BDS, OS, ECS, ERV, EGV-V, CLW, JTYD
Interpreting results: CC, SGM, NES, JPo, JB, JL, ES, ERM, RLJ, MJH, GG
Reviewing/editing white papers: EA, MJB, AB, JDA, NE, PEG, PG, AGDV, EG, PK, SLK, PL'H, CHML, CBM, DM, AM, JMN, MP, JPa, LP, JPo, LAP, BDS, OS, ECS, ERV, EGV-V, CLW, JTYD
Writing paper: SGM, CC, NES, JB, JL, EMS, ERM, RLJ, MJH, GG
All authors reviewed, commented on, and approved the study plan; reviewed the data and the analysis results; commented on and gave feedback to the interpretation of results, including quantitative and qualitative analyses; and convened in person or were given the opportunity to join remotely in an all-day consensus conference held on December 8, 2018 at the Hospital for Special Surgery, New York, NY, USA, where the entire analysis steps and results were presented, and the GRADE approach was utilised for the interpretation of the body of evidence and the formation of recommendations.
SGM had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declarations of interest

SGM is a director of the boards of the American Society of Regional Anesthesia and Pain Medicine and the president of the Society of Anesthesia and Sleep Medicine. He is a one-time consultant for Teikoku, Sandoz Inc. and a consultant/investor for HATH. Furthermore, SGM has a US Patent application pending for a Multicatheter Infusion System (US-2017-0361063). He is the owner of SGM Consulting, LLC, and co-owner of FC Monmouth, LLC. None of these relations influenced the conduct of the present project. ERM is a director of the board of the American Society of Regional Anesthesia and Pain Medicine and an officer of the California Society of Anesthesiologists. ERM is also an employee of the United States government, and his contribution to this project is supported with resources based at the Veterans Affairs (VA) Palo Alto Health Care System (Palo Alto, CA, USA). The contents do not represent the views of VA or the United States Government. NE is a board member of the American Society of Regional Anesthesia and Pain Medicine. NE is also a consultant for Foundry Therapeutics, but declared no conflict of interest. ECS reports consulting fees from Egalet, Inc. and the Mission Lisa foundation and acknowledges funding from the National Institute on Drug Abuse (K08DA042314). which are unrelated to this work. The other authors declare that they have no conflicts of interest.

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Disclaimer

The conclusions and recommendations resulting from this project are not intended to establish practice guidelines or standards, nor can they—if followed—guarantee successful outcomes. Many adequate reasons exist why a clinician or patient may deviate from the recommendations in this article, including, but not limited to, medical circumstances, individual patient and clinician preferences, and the availability of resources. The present conclusions and recommendations are based on the currently available literature, established in a systematic review process; thus, reassessment and revisions are required as new or different evidence emerges.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bja.2019.05.042.

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