

Posterolateral or direct lateral approach for cemented hemiarthroplasty after femoral neck fracture (APOLLO): protocol for a multicenter randomized controlled trial with economic evaluation and natural experiment alongside



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Background and purpose — The posterolateral and direct lateral surgical approach are the 2 most common surgical approaches for performing a hemiarthroplasty in patients with a hip fracture. It is unknown which surgical approach is preferable in terms of (cost-)effectiveness and quality of life.

Methods and analysis — We designed a multicenter randomized controlled trial (RCT) with an economic evaluation and a natural experiment (NE) alongside. We will include 555 patients ≥ 18 years with an acute femoral neck fracture. The primary outcome is patient-reported health-related quality of life assessed with the EQ-5D-5L. Secondary outcomes include healthcare costs, complications, mortality, and balance (including fear of falling, actual falls, and injuries due to falling). An economic evaluation will be performed for quality adjusted life years (QALYs). We will use variable

block randomization stratified for hospital. For continuous outcomes, we will use linear mixed-model analysis. Dichotomous secondary outcome measures will be analyzed using chi-square statistics and logistic regression models. Primary analyses are based on the intention-to-treat principle. Additional as-treated analyses will be performed to evaluate the effect of protocol deviations.

Study summary — (i) Largest RCT addressing the health-related patient outcome of the main surgical approaches of hemiarthroplasty. (ii) Focus on outcomes that are important for the patient. (iii) Pragmatic and inclusive RCT with few exclusion criteria, e.g., patients with dementia can participate. (iv) Natural experiment alongside to amplify the generalizability. (v) The first study conducting a cost-utility analysis comparing both surgical approaches.

Table 1. Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
≥ 18 years at the time of trauma Acute fracture of the femoral neck (< 7 days old) Cemented hemiarthroplasty as recommended treatment according to national guidelines Dutch or English fluency and literacy Written informed consent (by proxy in patients with mental impairment)	Multi trauma (defined as an injury severity score > 15) Secondary surgery after failed internal fixation Known metastatic disease and a confirmed pathological fracture of the hip High risk of non-compliance/adherence to study procedures ^a
^a For example, no Dutch residency—such as tourists—during follow-up period, or other factors that impair follow-up data collection such as patients who have a life expectancy of less than 6 months.	

The worldwide incidence of hip fractures is expected to rise by fourfold to 6.26 million in 2050, making it a globally important healthcare problem (1). Hemiarthroplasty is a common treatment for hip fractures. Preferences for surgical approach vary between surgeons, hospitals, and countries (2). A systematic review (2) comparing the posterolateral approach (PLA) and direct lateral approach (DLA) reported only 1 randomized study, which was ended prematurely (3).

The PLA is assumed to be beneficial regarding HRQoL and is thought to produce fewer walking problems postoperatively (4). However, these results may be based on a relatively healthy and cognitively fit group of patients, as another registry study did not report this superior HRQoL (5). Another Scandinavian observational study showed less need for walking aids with PLA 1 year after the hip fracture (6).

The presumably faster rehabilitation and better balance due to the scatheless gluteus musculature in patients treated using the PLA may be counterbalanced by the increased risk of dislocation (5-8). Recurrent dislocations can be devastating and cause a persistent decline in HRQoL (9). To the contrary, the loss of abductor muscle strength after hemiarthroplasty through the DLA can lead to limping and reduced mobility (4,6,10). Hypothetically, this loss of abductor strength influences the balance, which might increase the risk of falling. Conclusive evidence on which of these 2 approaches results in better patient outcomes is lacking.

Therefore, we will assess the (cost-)effectiveness of the PLA compared with DLA in patients treated with a cemented hemiarthroplasty for a hip fracture. The primary outcome is health-related quality of life and secondary outcomes include physical performance, independence, complications, costs, and tendency to fall.

Methods and analysis

Overview of study design

We will perform a randomized controlled multicenter superiority trial in the Netherlands with a natural experiment (NE) and economic evaluation alongside. Randomization takes place in hospitals where orthopedic surgeons can perform

both the DLA and PLA. The NE takes place in hospitals where surgeons solely perform the PLA or the DLA, according to their preference. In the NE, the topographical location where the trauma takes place determines the hospital to which the patient is admitted and thereby determines allocation to the PLA or DLA. This is assumed to resemble random assignment.

Surgeon expertise

Surgeons participating in the RCT have to be competent in both surgical approaches, and they have to meet 1 of the following criteria of expertise for the PLA and DLA: (i) performed at least 20 hemiarthroplasties with the PLA and DLA in their career (including residency experience in which they were the primary surgeon during the procedure), (ii) performed at least 5 hemiarthroplasties with the PLA and DLA in the last year. Residents may perform the procedure if the attending supervising surgeon meets the above criteria.

Patient selection

Eligibility criteria

To be eligible for this study, a subject must meet all of the criteria listed in Table 1. Cognitive impairment, such as dementia, is not an exclusion criterion. We will recruit incapacitated patients for study entry with involvement of their proxy in the informed consent procedure and data collection.

Patient recruitment and screening

We will screen all patients admitted to hospital with a hip fracture for eligibility. Eligible patients admitted to the hospitals where both surgical techniques are performed are invited to participate in our RCT prior to the surgery. Patients in the NE are invited to participate prior to or at the latest 1 day after surgery. To obtain informed consent, we inform the patients verbally and the patient information letter will be handed out to eligible patients or to their healthcare proxy. The first patient was included on February 6, 2018 and the last patient on January 7, 2022.

Randomization and blinding

After obtaining informed consent at the emergency depart-

ment or patient ward, patients will be randomly assigned in a 1:1 allocation ratio to either the PLA or the DLA. Randomization will be done in CASTOR EDC (www.castoredc.com), an online secured study and data management system with built-in randomization (variable block method, stratified per center). Surgeons, patients, or outcome assessors will not be blinded as the different surgical approaches are easily distinguishable (i.e., based on the location of the scar). Data analysts and the Steering Committee will remain blinded throughout the trial. We will first interpret the blinded results of the primary analysis before breaking the randomization code.

Study interventions

Posterolateral approach

In the PLA group, the skin incision starts posterior to the lateral side of the greater trochanter and runs slightly curved towards the femoral axis. Dissection of the insertions of the external rotators and piriformis follows, and the surgeon performs a posterior capsulotomy. The gluteus medius and vastus lateralis are preserved. When closing the hip joint the capsule is sutured and the piriformis is reattached. Whether the piriformis was spared or reattached was left to the surgeon's preference.

Direct lateral approach

In the DLA group a longitudinal incision starts 3–5 cm proximally, crossing the greater trochanter, and runs over the femoral axis. Release of the anterior insertion of the gluteus medius proximally and splitting fibers of the vastus lateralis distally follows. The surgeon performs an anterior capsulotomy. The stronger posterior capsule is preserved. When closing the hip joint the capsule is sutured as well as the fibers of the vastus lateralis and gluteus medius.

Peri- and postoperative care

All operations will be performed by experienced surgeons or residents under the direct supervision of an experienced surgeon. All implants are inserted with cement. The type and brand of the prosthesis are at the surgeons' discretion. Antibiotic and thromboembolic prophylaxis, suture materials and techniques, and wound dressing are done according to the surgeons' judgment and local guidelines. Physical therapy and rehabilitation will be administered following the standard protocols and local guidelines. According to the Dutch guideline patients are advised to undertake early weightbearing as tolerated. There are no movement restrictions or mandatory use of ADL aids after a hemiarthroplasty. Patients will use the assistive devices when they need to. To improve generalizability to regular clinical practice, we designed a pragmatic trial without substantial restrictions on other clinical care processes, which are known to vary between hospitals.

Study outcomes

Table 2 provides an overview of the outcomes at the different measurement moments.

Primary study outcome

The primary outcome is the health-related quality of life (EQ-5D-5L) as reported by the patient or proxy at 6 months after surgery (11). Patients' EQ-5D-5L health states will be converted to utility values using the Dutch tariff (12).

Secondary study outcomes

Secondary outcomes are listed in Table 2.

Study follow-up

The primary outcome EQ-5D-5L and the secondary outcomes will be assessed through questionnaires online, by hardcopy, or by phone at baseline, 3 and 6 months postoperatively. The cost questionnaires will be administered at 4 weeks, and 3 and 6 months' follow-up. One additional measurement moment (SPPB) at 4 months' follow-up is introduced for a subgroup who participate in the RCT. These patients will be asked to perform the SPPB test during a home visit by a researcher. We shall check the patient's medical record 6 months postoperatively if they had any complications or readmissions during the study period.

Sample size

We calculated the sample size for superiority using a 2-sided significance level (α) of 0.05 and a power (β) of 80%. With a standard deviation (SD) of 0.3 on the EQ-5D and a minimal clinically important difference (MCID) of 0.08, retrieved from the study of Walter and Brazier (13), a minimum of 222 subjects are needed in each treatment arm. Taking into account a 20% loss to follow-up after 6 months, a total of 555 participants will be included in the RCT. A subgroup of 70 randomized patients will perform an additional physical test to assess balance and physical performance. During the inclusion period of the RCT, additional patients will be included in the NE in hospitals that are only comfortable with 1 of both surgical approaches.

Data analysis

Effectiveness analysis

To investigate the difference in the clinical effectiveness of both surgical approaches, we will use linear mixed-model analysis for continuous outcomes. Primary analyses will be based on the intention-to-treat principle. Additional "as treated" analyses will provide insight into the influence of protocol deviations. Analyses will be done using the Statistical Package for the Social Sciences (SPSS, Version 27.0; IBM Corp, Armonk, NY, USA). For all analyses, a 2-tailed value of $\alpha < 0.05$ is considered to be significant. In the absence of statistical significance, the potential relevance of any differences between groups will be discussed with respect to the study sample size and reported thresholds for clinical relevance. The primary database is the RCT database. For the NE data, a crude analysis will be performed similar to the RCT. Because selection bias may be present in the NE, we will assess bal-

Table 2. Outcomes and measurement moments

Variable	Description	Baseline	4 weeks	3 months	4 months	6 months
Baseline characteristics		RCT/NE				
	Including age, gender, BMI, comorbidities, living status, ASA, prescribed medication					
Peri-/ postoperative outcomes		RCT/NE				
	Including length of stay, surgery time, blood loss, discharge destination					
EQ-5D-5L		RCT/NE		RCT/NE		RCT/NE
	Health-related quality of life states consisting of 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) that are scored on 5 levels (no problems, slight problems, moderate problems, severe problems, and extreme problems)					
Katz ADL		RCT/NE		RCT/NE		RCT/NE
	Activities of daily living (ADL) functionality as introduced by Katz, resulting in a score ranging from 0 (ADL independent) to 6 (ADL dependent),					
Mobility score		RCT/NE		RCT/NE		RCT/NE
	5 item mobility score (27), ranging from 0, indicating no walking aids, to 5, indicating no functionality of lower extremity					
Health-related and societal costs			RCT	RCT		RCT
	Cost questionnaires to assess the use of healthcare resources and informal care as well as productivity losses from unpaid and paid work (i.e., absenteeism and presenteeism). All resource use will be valued in accordance with the "Dutch Manual of Costing" (29).					
Pain				RCT/NE		RCT/NE
	Numerical rating scale (NRS) ranging from 0 (no pain) to 10 (worst imaginable pain) for mean and maximum pain over the week					
Fear of falling				RCT/NE		RCT/NE
	Falls Efficacy Scale International (FES-I), resulting in a score of 16 (no concern about falling) to 64 (severe concern about falling)					
Tendency to fall				RCT/NE		RCT/NE
	Number of falls, additional injuries as a result of falling, as reported by patients and/or retrieved from hospital charts					
Complications				RCT/NE		RCT/NE
	Re-interventions and (surgical) complications as reported by patients, and/or retrieved from hospital charts					
Mortality						RCT/NE
	As reported by patient's contact person and/or retrieved from hospital charts					
Short Physical Performance Battery test (SPPB)					RCT ^a	
	SPPB is a group of measures that combines the results of the gait speed, chair stand, and balance tests. Each segment has a maximum of 4 points and the total score has a maximum of 12 points; high scores suggest better physical performance (28)					

^a A subgroup of 70 patients will perform the SPPB test.

ance on the covariates. We will consider the covariates balanced if the absolute standardized mean difference for each covariate is at most 0.1. If the covariates are unbalanced, different matching methods will be used until balance is obtained (14,15). The matched data will then be analyzed in a similar way to the RCT.

The goal of combining the randomized controlled trial and NE data is to improve the precision of the estimators for the primary and secondary outcome. Lu et al. developed a method specifically for this type of study (16). They show that the estimators can be improved if there are no confounders besides the measured baseline covariates and they propose a test for this assumption. If the assumption is satisfied, the data will be combined according to their method. If the proposed test fails, a sensitivity analysis will provide insight into the effect of an unmeasured confounder on the study outcomes. The sensitivity method developed by Dorie et al. will be used, which

models the response surface with a linear model and machine learning methods (17). Dorie et al. show empirical validation of the latter method, even in the presence of non-linearities in the true response surface (18).

Primary study parameter

In the primary linear mixed model, EQ-5D-5L utility scores will be analyzed as dependent variable. Treatment allocation (DLA vs. PLA) and baseline EQ5D score will be included as fixed factors. Repeated measures within-subjects and groups of patients within hospitals will be clustered using random effects. Differences between groups over time will be evaluated by incorporating the interaction term of group and time. The primary endpoint is 6 months after trauma.

Secondary parameters

Continuous secondary outcome variables (functionality on

the KATZ, physical performance on the SPPB, tendency to fall, fear of falling on the FES-I, number of falls, and pain on the NRS) will be analyzed using similar linear mixed models. Dichotomous secondary outcome measures (additional injuries as a result of falling, re-interventions, discharge destination, and (surgical) complications) will be analyzed using chi-square statistics and logistic regression models.

Heterogeneity of treatment effect/exploratory analyses

Treatment effects can vary across the patients in both intervention groups. Besides the crude analysis of the primary and secondary outcomes, we will also adjust for potential confounders, by adding their baseline values as covariates in a multivariable mixed model (e.g., age, gender, living status, dementia, ASA, BMI, Katz ADL, mobility) in an adjusted regression analysis.

Treatment effects can vary across the patients in both intervention groups. We will therefore assess effect modification, by exploring interactions between the treatment group and each of the potential confounders listed above.

Cost-effectiveness analysis

An economic evaluation will be performed for QALYs, from both the societal and healthcare perspective, and in accordance with the intention-to-treat principle. QALYs will be estimated by multiplying the patients' utility values by the duration for which they experienced a certain health state (19). Missing data will be imputed using multivariate imputation by chained equations (20). Cost and effect differences will be estimated using linear mixed models. It is very important to use such mixed-model analyses and account for the possible clustering of cost and effect data (e.g., at the hospital level), as most economic evaluations fail to do so, whereas ignoring the possible clustering of data might lead to inaccurate levels of uncertainty and inaccurate point estimates (21). Incremental cost effectiveness ratios (ICERs) will be calculated by dividing the difference in costs by that in effects. Bootstrapping techniques will be used to estimate the uncertainty surrounding the cost-effectiveness estimates. Uncertainty will be shown in cost-effectiveness planes and cost-effectiveness acceptability curves. Sensitivity analyses will be performed to test the robustness of the study results (22-24).

Registration, ethics, data sharing plan, funding, and potential conflicts of interests

This trial was registered at clinicaltrials.gov (NCT04438226) prior to the start of inclusion.

The study has been approved by the local and the Medical Ethics Committee (METC) (number NL63378.100.17) and will be conducted according to the principles of the Declaration of Helsinki, as amended in Seoul and Fortaleza (64th WMA General Assembly, October 2013) (25) and in accordance with the Medical Research Involving Human Subjects Act (WMO) and other guidelines, regulations, and Acts. In

all participating hospitals the study protocol will be submitted for review and approval by the local research ethics board. Any substantial amendments will be notified to the accredited Medical Ethical Committee. The investigator will report all SAEs related to the treatment to the sponsor and report the SAEs through the web portal ToetsingOnline to the accredited METC that approved the protocol, within 7 days of first knowledge for SAEs that result in death or are life threatening. All other SAEs will be reported within a maximum period of 15 days after the sponsor has first knowledge of the serious adverse events.

Data will be managed and archived for 15 years at the initiating hospital (OLVG). We intend to facilitate data sharing in line with the FAIR (Findability, Accessibility, Interoperability, and Reuse) principles, taking into account European laws and guidelines for privacy, and upon reasonable request. All included patients receive a trial code, which pseudonymizes their personal data. The link between the trial code and the patient's personal data is saved in a separate secured file with access only by the coordinating investigator (MCJMT) and research assistant (AR). The outcome data is only accessible for the coordinating investigator (MCJMT), principal investigator (RWP), research assistant (AR), supervisor (NWW), and authorized research personnel of the Joint Research team in OLVG Amsterdam. The handling of personal data will comply with the Dutch Personal Data Protection Act. The results from the study will be submitted for publication in peer-reviewed journals and presented at international conferences. This trial is supported by the Dutch Organisation for Health Research and Development (ZonMw grant number: 8430041 12). There are no conflicts of interests for all authors.

Steering and data monitoring committee

The steering committee for this study consists of 2 independent orthopedic surgeons (RGHHN, DJFM) and 1 independent trauma surgeon (IBS). The interim analyses will be performed by the research assistant (AR) and blinded for treatment groups. The steering committee will evaluate the interim results to decide whether the study can be continued without compromising patient safety. Data monitoring is conducted by an independent study monitor at the initiating hospital (OLVG).

Discussion

We designed a randomized controlled trial with a natural experiment and economic evaluation alongside, to compare the PLA and DLA for a hemiarthroplasty after a hip fracture. Currently, the choice of surgical approach is mostly based on surgical preference because there is a lack of evidence. This study will be the largest RCT worldwide addressing this subject and may improve the quality of life and healthcare for patients with hip fractures treated with a hemiarthroplasty. Furthermore, this RCT will be the first to conduct an economic

evaluation and provide detailed insight into the healthcare and societal costs of both approaches. Our study outcomes, including quality of life, fear of falling, level of independence, physical performance, and complications are important for patients.

We aimed to design a study with a good reflection of the elderly population. Therefore, we shall not exclude patients with dementia. As older adults with dementia are well represented in the population of patients with a hip fracture, including them will increase the generalizability of the study results. The primary outcome can be completed by proxy, which is a validated questionnaire in the elderly patient (26).

In the Netherlands the majority of trauma surgeries are conducted by trauma surgeons, general surgeons specialized in trauma. Approximately 1/3 of all hip hemiarthroplasties in 2020 are placed by general trauma surgeons. Trauma surgeons are mostly competent in one surgical approach.

There are some limitations to our study. First, we did not exclude patients with fractures or contusion of the lower/upper limbs with an ISS score of less than 16. Such additional injuries are likely to affect patient outcomes. Given the large sample size and the randomized design, we expect the incidence of additional injuries to be similar between the 2 groups and therefore not to affect the intervention effect. Another limitation is that we did not document whether the piriformis was spared or reattached, which was at the surgeon's discretion. There is no high-level evidence of the effect of piriformis-sparing approaches of hemiarthroplasty. Currently, the HemiSpaire study is comparing the direct lateral approach with a piriformis-sparing posterior approach. This will give additional insights to the results of our study.

In addition to the traditional RCT design, we will conduct an NE in hospitals where only one of the surgical approaches is performed. Although we are aware this is not formal randomization on participant level, the NE design has several advantages: (i) prevents surgical expertise bias; (ii) facilitates better generalizability of our trial results as more centers are able to participate; (iii) helps implement our trials results; (iv) reduces selection bias, by including patients and hospitals that may not have agreed to randomization.

Currently there is substantial practice variation due to the absence of high-quality evidence reporting which approach is most valuable for the patient. With this study we aim to close the existing knowledge gap concerning which surgical approach is preferable for patient outcome.

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