

Clinical Study

Cost effectiveness of implanting a prosthesis after anterior cervical discectomy for radiculopathy: results of the NECK randomized controlled trial

Jan M. Heijdra Suasnabar, MSc^{a,*},
Carmen L.A. Vleggeert-Lankamp, MD, PhD, MSc^{b,c},
Caroline M.W. Goedmakers, BSc^a, Floor de Vries, BSc^a,
Mark P. Arts, MD, PhD^d, M. Elske van den Akker-van Marle, MSc, PhD^a

^a Department of Biomedical Data Science, Leiden University Medical Centre, Leiden, the Netherlands

^b Department of Neurosurgery, Leiden University Medical Centre, Leiden, the Netherlands

^c Spaarne Gasthuis, Haarlem/Hoofddorp, the Netherlands

^d Department of Neurosurgery, Haaglanden Medical Centre, Den Haag, the Netherlands

Received 27 October 2022; revised 13 January 2023; accepted 3 February 2023

Abstract

BACKGROUND CONTEXT: In the treatment of cervical radiculopathy due to a herniated disc, potential surgical treatments include: anterior cervical discectomy (ACD), ACD and fusion using a cage (ACDF), and anterior cervical disc arthroplasty (ACDA). Previous publications yielded comparable clinical and radiological outcome data for the various implants, but research on their comparative cost-utility has been inconclusive.

PURPOSE: To evaluate the cost utility of ACD, ACDF, and ACDA.

STUDY DESIGN: Cost-utility analysis.

PATIENT SAMPLE: About 109 patients with cervical radiculopathy randomized to undergo ACD, ACDF, or ACDA as part of the Netherlands Cervical Kinetics trial.

OUTCOME MEASURES: Quality-adjusted life-years (QALYs) estimated from patient-reported utilities using the EuroQol-5D questionnaire and EuroQol Visual Analogue Scale (EQ VAS), measured at baseline, 2, 4, 8, 12, 26, 52, and 104 weeks postprocedure. Societal costs including admissions to hospital (related and otherwise), GP visits, specialist visits, physical therapy, medications, home care, aids, informal care, productivity losses, and out of pocket condition-related expenses.

METHODS: The cost utility of the competing strategies over 1 and 2 years was assessed following a net benefit (NB) approach, whereby the intervention with the highest NB among competing strategies is preferred. Cost effectiveness acceptability curves were produced to reflect the probability of each strategy being the most cost effective across various willingness-to-pay (WTP) thresholds. Five sensitivity analyses were conducted to assess the robustness of results.

RESULTS: ACDF was more likely to be the most cost-effective strategy at WTP thresholds of €20,000 to 50,000/QALY in all but one of the analyses. The mean QALYs during the first year were 0.750, 0.817, and 0.807 for ACD, ACDF, and ACDA, respectively, with no significant differences between groups. Total healthcare costs over the first year were significantly higher for ACDA, largely due to the higher surgery and implant costs. The total societal costs of the three

FDA device/drug status: Not applicable.

Author disclosures: **JMHS:** Nothing to disclose. **CLAV-L:** Grants: CSRS Europe (A, paid directly to institution), Thromboembolic complications in Neurosurgery (Covidien), Fundamentals of radiculopathy (YM Fund/Achmea health Insurance and Eurospine), 5yr FU disc prosthesis in cervical spine surgery (CSRS E). Nuvasive congress speaker. Board of CSRS Europe and Netherlands Neurosurgical Society (NVvN) (F); Speaking and/or Teaching Arrangements: Stryker education (B); Scientific Advisory Board/Other Office: Rijndam Rehabilitation Centre Advisory board (C, paid directly to institution). **CMWG:** Nothing to disclose. **FdV:** Nothing to

disclose. **MPA:** Grants: Braun Aesculape (paid directly to institution), Zimmer-Biomet, Johnson and Johnson (paid directly to institution); Royalties: Johnson and Johnson; Consulting: Nuvasive, Johnson and Johnson (paid directly to institution). **MEvda-vM:** Nothing to disclose.

*Corresponding author. Jan M Heijdra Suasnabar, Department of Biomedical Data Science, Leiden University Medical Centre, Albinusdreef 2, 2333 ZB, Leiden, the Netherlands. Tel.: +31 715269111

E-mail address: j.m.heijdra_suasnabar@lumc.nl (J.M. Heijdra Suasnabar).

strategies were €12,173 for ACD, €11,195 for ACDF, and €13,746 for ACDA, with no significant differences between groups.

CONCLUSION: Our findings demonstrate that ACDF is likely to be more cost-effective than ACDA or ACD at most WTP thresholds, and this conclusion is robust to most sensitivity analyses conducted. It is demonstrated that the difference in costs is mainly caused by the initial surgical costs and that there are only minimal differences in other costs during follow-up. Since clinical data are comparable between the groups, it is to the judgment of the patient and surgeon which intervention is applied. © 2023 The Author(s). Published by Elsevier Inc. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>)

Keywords: Anterior cervical discectomy; Arthroplasty; Cage; Cervical disc herniation; Cost-utility

Background

In the treatment of a cervical radiculopathy due to a herniated disc, the anterior approach via a discectomy is a commonly performed treatment. The most commonly used method to bridge the gap created by the discectomy is to fill it with a cage, with or without securing it with a plate, which eventually will allow the two vertebra to fuse. Theoretically, this increases the load on the adjacent disc levels which is hypothesized to induce pain, decrease functionality in the short term, and induce new complaints at the adjacent levels in the long term. Therefore, to keep the target level mobile, the cervical disc prosthesis was introduced.

We previously reported on the 2-year clinical and radiological results of the NETHERlands Cervical Kinetics (NECK) trial, in which patients were (double-blindly) randomized to be subjected to anterior discectomy with a cage (ACDFusion), a prosthesis (ACDArthrodesis) or without an intervertebral device (ACD) in radiculopathy patients. It was demonstrated that neck disability, arm pain, neck pain, and quality of life were comparable in all three groups over a 2-year period [1]. Furthermore, no differences in reoperations, nor in radiological outcome, were reported and it was concluded that all three strategies yielded satisfactory results.

Additionally, it was stated that the prosthesis is far more costly than the two intervertebral alternatives (cage and none), and that this should not be the preferred surgical solution. However, a proper conclusion on cost-effectiveness should consider more factors than merely the costs of the implant. In the current study, we present a cost-effectiveness analysis considering the first 2 follow-up years from a societal perspective. We consider costs of reoperations, visits to health care workers, medication costs (direct costs), loss of productivity (indirect costs), and relate these to the gain in quality of life in the three groups of patients.

The vast majority of studies that have been published on the cost-effectiveness of ACDA versus ACDF are model-based studies or based on retrospective study designs [2]. Schuermans et al. [2] conducted an extensive review on cost effectiveness in cervical decompression surgery and identified only few studies that evaluated cost effectiveness based on data from blinded randomized trials. Furthermore, the risk of bias of the included studies was high to moderate, and numerous studies reported direct or indirect industry sponsorship [2].

The only included study which considered ACDF without plating concluded that it was cost effective, however, that evaluation did not adopt a societal perspective and had a small sample size (15 patients per group) [3]. In conclusion, there is currently inconclusive evidence on the most cost effective cervical decompression strategy (particularly when comparing ACDA vs. ACDF) that is based on a societal perspective and quality data from randomized clinical trials.

We conducted a cost effectiveness analysis alongside the three-arm NECK trial. One and 2-year costs and outcomes following ACD, ACDF, and ACDA were compared among patients with cervical radiculopathy.

Methods

Study design

A cost-utility analysis of the NECK trial was carried out. The NECK trial was a three-arm multicenter double-blind randomized controlled trial (RCT), which investigated the effectiveness and costs of ACDA compared to ACD and ACDF [1]. The trial (Dutch Trial Register Number: NTR1289) was approved by the Central Medical Ethics Committee of the Leiden University Medical Center, the Medical Ethics Committee Noord-Holland, and the board of directors of the participating hospitals trial [1]. All participants provided written informed consent before entry into the study.

Participants and interventions

The NECK trial design and its effectiveness findings are described elsewhere [1,4]. Briefly, included participants (N=109) suffered from cervical radiculopathy due to single-level disc herniation (diagnosed at one of the participating hospitals) and underwent either ACD, ACDF, or ADCA. To be eligible for participation, patients had to be 18 to 65 years old, have had radicular symptoms for at least 8 weeks, and had past unsuccessful treatment with conservative therapy. Key exclusion criteria included absence of motion, very narrow intervertebral space (<3 mm), severe segmental kyphosis, symptoms of myelopathy, past cervical surgery, metabolic and bone diseases, neoplasm or trauma of the cervical spine, and severe mental disorders [1]. Patients were randomly allocated to one of three treatment

arms after induction of anesthesia and allocation remained undisclosed to patients, the nursing department, and research nurses during the 2-year follow-up period.

For patients in the ACDA group, an activC flat artificial cervical disc (Aesculap AG, Tuttlingen, Germany) was implanted using slight distraction and fluoroscopic guidance. For the ACDF group, an interbody polyetheretherketone (PEEK) cage, either filled with synthetic bone substitute or autologous bone (chips locally harvested), was placed under fluoroscopic guidance. For the ACD group, no intervertebral device was placed [1].

As this was a three-arm trial, costs, outcomes, and cost-effectiveness probabilities were simultaneously compared between the three treatment groups (as opposed to choosing a single group as the reference).

Outcome measures

Quality-adjusted life-years

Data on participants' quality of life was gathered at baseline and seven other time-points (ie, 2, 4, 8, 12, 26, 52, and 104 weeks) over a 2-year period using the EuroQol 5-Dimension 3-Level questionnaire (EQ-5D-3L) and the EuroQol Visual Analogue Scale (EQ-VAS). The Dutch EQ-5D-3L tariff was used to calculate utility values for the health states described by the patients in the EQ-5D-3L questionnaire at each follow-up moment [5]. These utilities and the EQ-VAS scores (rescaled to range 0-1) were then used to calculate quality-adjusted life-years (QALYs) for 1- and 2-year follow-up by calculating the area under the utility curves for each patient. The proportions of missing data for health utilities (EQ-5D-3L and EQ-VAS scores) increased from 2% at 8 weeks to 6% and 10% at 1 year and 2 years, respectively. Of the participants with missing 1-year utilities (n=6), four belonged to the ACD group.

Costs

Our base case analysis was from a societal perspective and had a time horizon of 1 year. Due to the short time horizon, costs and outcomes were not discounted. We analyzed 2-year data as one of the sensitivity analyses.

Costs were calculated based on patient-reported questionnaires completed together with a research nurse at 8, 26, 52, and 104 weeks of follow-up. Data on patients' healthcare-related resource use included admissions to hospital (related and otherwise), visits (ie, to medical specialists, general practitioners, and physical therapy), medications, home care, and aids. Nonhealthcare resource use and expenses included paid domestic help, informal care, and out of pocket condition-related expenses. In addition, patients reported their absenteeism from work during the follow-up intervals. The proportions of missing patient cost questionnaires at 8 weeks, 26 weeks, 1 year, and 2 years were 1%, 5%, 6%, and 10%, respectively. Of the participants with missing 1-year cost questionnaires (n=6), four belonged to the ACD group.

We calculated costs in Euros based on patients' resource use and expenses using Dutch reference unit prices and corresponding sources outlined in the Dutch manual for costing research [6,7]. In line with a societal perspective, healthcare costs also included patient time and travel costs required to receive health care. Prices were converted to 2020 values using the national consumer price index [8]. For the surgical procedures (including reoperations, if any), the estimated cost was the product of the surgery duration in minutes times the approximate cost per minute of operating rooms according to hospital financial records. Operating room costs included all usual operation costs (eg, surgeon, disposables, anesthesia) and excluded operation-specific costs such as blood products and prostheses. Therefore, based on the prosthesis and cage costs at the time of the trial (updated to 2020 Euros), the amounts of €2107 and €421 were added to the operation costs for ADCA and ADCF, respectively. Finally, all reoperations were ACDFs regardless of initial group allocation and reoperation costs were calculated accordingly.

Productivity costs due to absenteeism or reductions in working hours were estimated using the friction cost method in the base case, with a friction period of 12 weeks and average productivity costs of €34.75 per hour, according to Dutch guidelines [9]. We calculated productivity costs based on the human capital method in one of the sensitivity analyses.

Statistical analysis

We assessed the cost effectiveness of interventions following an intention-to-treat principle on all analyses. To address potential biases due to missing data, we used multiple imputation by chained equations with predictive mean matching to produce 100 imputed datasets [10,11]. Besides the imputed variables, the covariates included in the imputation regressions were group allocation, sex, baseline EQ-5D-3L utility, duration of symptoms, smoking status, and pain severity (measured using a visual analogue scale). We then tested for between-group differences in mean costs and QALYs using linear regression and applying Rubin's rules [12,13]. All analyses were conducted using STATA version 17 (StataCorp, LLC).

The cost effectiveness of the competing strategies was assessed following a net benefit (NB) approach. From this perspective, an intervention is considered more cost effective when it has the highest NB among competing strategies for a given willingness to pay (WTP) threshold, where $NB = (WTP \times \text{intervention QALYs}) - \text{intervention costs}$. To address the statistical uncertainty surrounding these calculations and better accommodate the distributions of costs, NBs were calculated based on 1,000 nonparametric bootstrap replications per imputation dataset [14]. Additionally, as the NECK trial's effectiveness results reflected a between-group imbalance in baseline EQ5D utility (ie, baseline EQ-5D-3L utility was higher in the ACDF group),

we adjusted total mean costs and QALYs for this imbalance in each bootstrapped calculation by including the baseline EQ5D score in each regression [14,15]. We explored the effect of adjusting costs and outcomes for baseline EQ-5D-3L utility in the sensitivity analyses.

Based on the bootstrapped estimates of NBs, cost-effectiveness acceptability curves were produced to represent the probability of each intervention being cost effective over the other strategies at various willingness-to-pay thresholds. Specifically, these probabilities represent the proportion of times (across all bootstrapped replications) that each strategy had the highest NB for a given WTP threshold [16].

We carried out five sensitivity analyses to evaluate the robustness of our results. Specifically, analyses were repeated from a healthcare sector perspective, using a time horizon of 2 years, EQ-VAS utilities instead of EQ-5D-3L utilities, unadjusted costs and QALYs (for 1 and 2 years, separately), and using the human capital approach to estimate productivity losses.

Results

Utilities and QALYs

Overall, similar trends in QoL were observed for the three groups during the 2-year follow-up period (Fig. 1), regardless of the utility measurement method (ie, Dutch EQ-5D-3L index score or EQ-VAS utilities). However, mean utilities were consistently lower in the ACD group compared to other groups during the follow-up periods in the first year, although differences were not statistically significant. Based on the Dutch EQ-5D-3L, the mean QALYs during the first year were 0.750, 0.817, and 0.807 for the ACD, ACDF, and ACDA groups, respectively, with no significant differences between groups.

Costs

Healthcare costs

The mean costs per patient of initial treatment (ie, surgery, materials, and hospital stay) were significantly higher for ACDA (€5,624) compared to ACD and ACDF (€2,619 and €3,067, respectively). This difference was driven by both the additional prosthesis costs for ADCA and an approximately 30 minutes longer average surgery duration. Costs related to hospital admissions (approximately 2 days in all groups) and reoperations did not differ significantly between strategies (Table 1). Furthermore, besides costs for neurosurgeon visits which were significantly higher in the ACD arm, no other significant differences in healthcare costs were observed between groups during the first year.

Total healthcare costs over the first year were also significantly higher in the ACDA arm, largely due to the initially higher treatment costs which were not sufficiently compensated for across other cost categories (Table 1). That said,

the significantly higher costs for neurosurgeon visits in the ACD arm, as well as its (nonsignificantly) higher mean costs for physical therapy, specialist visits, and GP visits drove the total healthcare costs of ACD closer to the costs of ACDF (€5,193 and €5,197, respectively).

Societal costs

Total nonhealthcare costs (ie, mean productivity costs and other indirect expenses) were similar across strategies and differences were not significant (Table 1). Combining healthcare and nonhealthcare costs, the total societal costs in the first year were in favor of ACDF, although differences between groups were not significant (€12,173 for ADC, €11,195 for ACDF, and €13,746 for ACDA).

Cost-utility analysis

Given its higher QALYs and lower societal costs during the first year, ACDF was more likely to be cost effective than ACDA or ACD across all WTP thresholds considered (ie, up to €80,000/QALY), regardless of whether costs and outcomes were adjusted for baseline imbalances in utilities (Fig. 2). Based on adjusted estimates (Fig. 2), the probability of ADCF being the most cost-effective strategy is highest (62%) at a WTP of €22,000/QALY and then decreases slowly with higher WTP thresholds. Conversely, the probability of ACDA being the most cost-effective strategy increases with increasing WTP thresholds, although ACDA is never preferred over ACDF in the base case (this occurs only at unrealistically high WTPs above €120,000/QALY).

For comparison, Table 2 contains crude versus adjusted societal costs, health sector costs, and QALYs over 1 and 2 years. Additionally, Table A.1 contains detailed costs per category over 2 years.

Most sensitivity analyses yielded similar results to the base case (Figs. A.1–A.5). The probability of ACDF being the most cost-effective strategy increased further when QALY calculations were based on the EQ-VAS (Fig. A.1) and when the human capital approach was used to calculate productivity costs (Fig. A.2). On the other hand, in the sensitivity analysis adopting a healthcare perspective (ie, omitting nonhealthcare costs, Fig. A.3), ACD was initially more likely to be cost effective for WTP thresholds up to €10,000/QALY, after which ACDF again becomes the preferred strategy.

The only sensitivity analysis that resulted in ACDA being the most favorable intervention was the adjusted 2-year costs analysis (Fig. A.4). In this analysis, the probability of ACD being the preferred strategy is initially slightly greater compared to ADCF or ACDA at WTP thresholds less than €13,000/QALY. However, ADCA gains preference over the other strategies at WTP thresholds above €13,000/QALY. This is largely due to the slightly higher adjusted QALYs for ACDA at 2 years (Table 2). These trends are in contrast to the equivalent CEAC based on unadjusted 2-year costs and QALYs, where ACDF remains

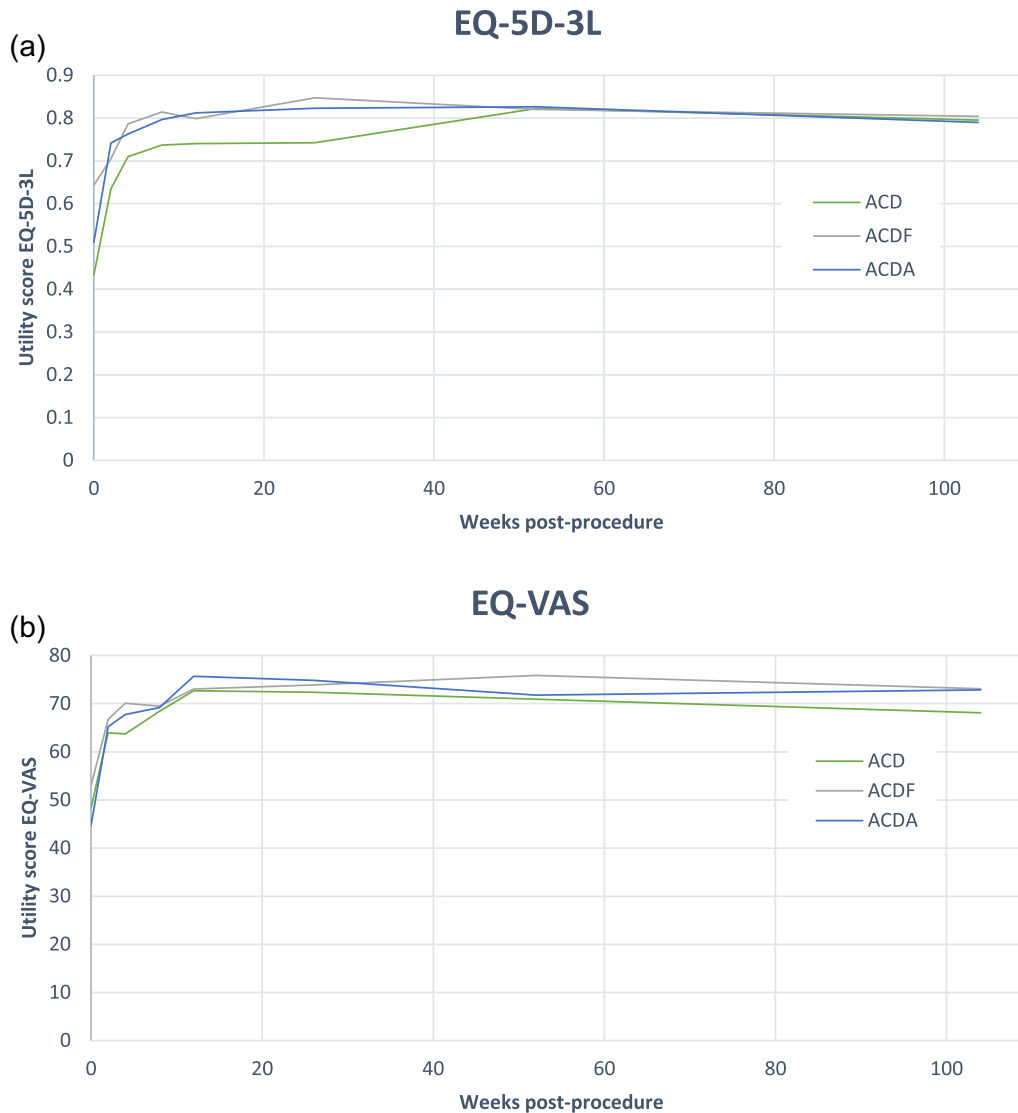


Fig. 1. (A) Utility curves based on the EQ-5D-3L and Dutch tariffs over 2 years of follow-up. (B) Utility curves based on the EQ-VAS over 2 years of follow-up. EQ-VAS, EuroQol Visual Analogue Scale measuring quality of life; EQ-5D-3L, EuroQol Five-Dimension Three-Level instrument measuring quality of life.

most likely to be cost effective across all WTP thresholds (Fig. A.5).

Discussion

In addition to the clinical and radiological outcome data that were published on the NECK trial [1], this cost-effectiveness analysis yields the conclusion that there is also no economic benefit from implanting a cervical disc prosthesis. There were no significant differences in total (societal) costs and QALYs across the three treatment arms over 1 and 2 years, although total healthcare costs were significantly higher in the ACDA arm. Overall, ACDF is likely to be more cost effective than ACDA or ACD at most WTP thresholds, and this conclusion is robust to nearly all the sensitivity analyses conducted. Importantly, the lack of statistically significant differences in societal costs and

outcomes does not necessarily translate into all strategies being equally cost-effective [17]. As the net benefit calculation explicitly incorporates the tradeoff between costs and outcomes (ie, with their corresponding confidence limits), the CEACs presented in this study reflect the probability that a given strategy, given its distributions of costs and outcomes, would produce the highest net benefit among competing alternatives for a given WTP threshold.

One key implication of our findings is that the excess costs associated with ACDA may not be justifiable given its similar clinical/radiological effectiveness compared to ACDF. Specifically, our findings and those from our effectiveness study [1] provide no strong evidence that the prosthesis (ACDA) performs better, yields better clinical or radiological outcome data, decreases the likelihood for a subsequent surgical intervention on the target or adjacent level, nor that it is more cost effective. These conclusions

Table 1
Resource use and mean costs* per patient during the first year after ACD, ACDF, and ACDA

| | ACD (n=38) | | ACDF (n=36) | | ACDA (n=35) | | p value |
|--|------------|----------------|-------------|----------------|-------------|----------------|---------|
| | Volume (%) | Cost (€) | Volume (%) | Cost (€) | Volume (%) | Cost (€) | |
| Initial treatment | | | | | | | |
| Treatment | 100 | 1,185 | 100 | 1,682 | 100 | 4,112 | <.001 |
| Hospital stay | 100 | 1,434 | 100 | 1,385 | 100 | 1,513 | .259 |
| Total (SE) | | 2,619 (106) | | 3,067 (110) | | 5,624 (109) | <.001 |
| Repeated surgery within 1 year | | | | | | | |
| Surgery + cage | 5 | 152 | 3 | 40 | 6 | 126 | .620 |
| Hospital stay | 5 | 103 | 3 | 36 | 6 | 38 | .608 |
| Total (SE) | | 255 (130) | | 76 (134) | | 164 (136) | .631 |
| Other healthcare costs | | | | | | | |
| Physical therapy | 65 | 977 | 60 | 793 | 54 | 669 | .628 |
| Other admissions to hospital | 7 | 135 | 17 | 169 | 4 | 28 | .421 |
| Neurologist | 24 | 55 | 28 | 94 | 20 | 32 | .175 |
| Neurosurgeon | 65 | 196 | 43 | 107 | 48 | 100 | .035 |
| Other specialists | 97 | 750 | 100 | 688 | 91 | 657 | .759 |
| General practitioner | 74 | 154 | 53 | 83 | 56 | 82 | .099 |
| Home care & aids | 4 | 5 | 14 | 55 | 6 | 304 | .319 |
| Drugs | 77 | 48 | 60 | 66 | 64 | 24 | .302 |
| Total health care costs (SE) | | 5,193 (396) | | 5,197 (402) | | 7,681 (405) | <.001 |
| Nonhealthcare costs | | | | | | | |
| Domestic help, informal care, and OOPs | 31 | 330 | 27 | 271 | 21 | 182 | .619 |
| Productivity costs (friction costs) | 82 | 6,650 | 77 | 5,727 | 69 | 5,883 | .724 |
| Total nonhealthcare costs (SE) | | 6,980 (880) | | 5,998 (908) | | 6,065 (912) | .685 |
| Total societal costs (SE) | | 12,173 (1,041) | | 11,195 (1,070) | | 13,746 (1,077) | .244 |

* Pooled estimates based on 100 multiply imputed datasets with covariates: group allocation, sex, baseline EQ-5D-3L utility, duration of symptoms, smoking status, and pain severity.

are consistent with those from Bhadra et al. [3] but in contrast to several other studies identified in Schuermans et al. recent review [2]. One explanation for these differences may be that few studies so far have been based on blinded RCTs that were not funded by industry and which adopted a societal perspective. Additionally, the detailed healthcare and nonhealthcare cost data collected through the NECK trial enabled a more exhaustive cost-utility assessment; the omission of certain cost categories likely influenced results of several existing studies [2]. Finally, the available

evidence on the cost effectiveness of ACDA in comparison to ACDF mainly comes from studies in which the ACDF procedure consisted of a cage with a plate. Only one of the available studies considered ACDF as cage without a plate [3]. Adding a plate to the ACDF procedure increases the costs of a cage implant (with plate and matching screws) to a more or less comparable level as the prosthesis.

Recently, clinical outcome data of the 5-year follow-up NECK were reported [18]. It was concluded that ACDA and ACDF perform equally well on the long term, but that

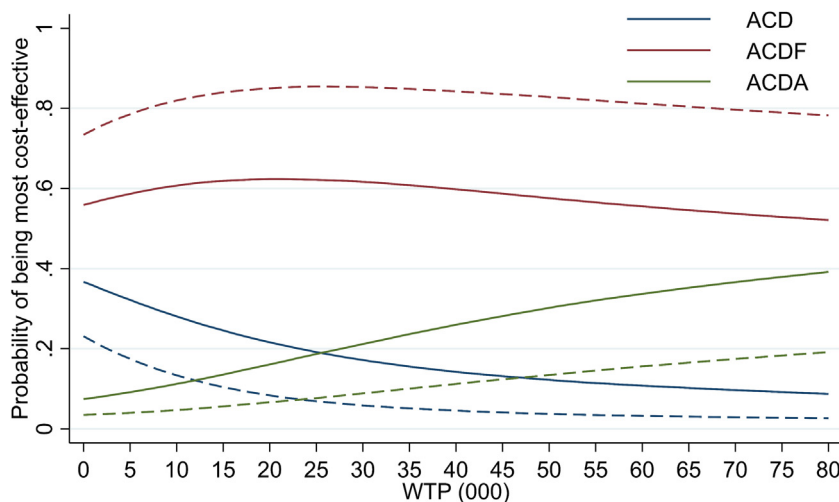


Fig. 2. Cost-effectiveness acceptability curves based on adjusted and unadjusted costs and QALYs over 1 year. Dashed lines correspond with probabilities calculated using unadjusted (for baseline EQ-5D-3L) costs and QALYs.

Table 2
Comparison of adjusted* versus unadjusted mean costs and outcomes of strategies

| | ACD | | ACDF | | ACDA | |
|------------------------------|----------------------|--------------------|----------------------|--------------------|----------------------|--------------------|
| | Unadjusted mean (SE) | Adjusted mean (SE) | Unadjusted mean (SE) | Adjusted mean (SE) | Unadjusted mean (SE) | Adjusted mean (SE) |
| Outcome[‡] | | | | | | |
| One-year QALYs [†] | 0.75 (0.03) | 0.67 (0.04) | 0.82 (0.03) | 0.70 (0.05) | 0.81 (0.03) | 0.72 (0.04) |
| Two-year QALYs [†] | 1.56 (0.06) | 1.39 (0.08) | 1.63 (0.06) | 1.38 (0.10) | 1.62 (0.06) | 1.42 (0.09) |
| Costs[‡] | | | | | | |
| One-year societal costs | 12,173 (1,041) | 13,594 (1,448) | 11,195 (1,070) | 13,306 (1,865) | 13,746 (1,077) | 15,419 (1,608) |
| One-year health sector costs | 5,193 (396) | 5,879 (545) | 5,197 (402) | 6,216 (698) | 7,681 (405) | 8,489 (600) |
| Two-year societal costs | 13,986 (1,180) | 16,152 (1,625) | 13,438 (1,204) | 16,657 (2,088) | 15,160 (1,217) | 17,711 (1,799) |
| Two-year health sector costs | 6,391 (571) | 7,739 (771) | 6,623 (565) | 8,626 (969) | 8,601 (579) | 10,189 (836) |

* Adjusted for baseline EQ-5D-3L score based on Dutch tariff.

† Based on Dutch EQ-5D-3L tariff.

‡ Pooled estimates based on 100 multiply imputed datasets with (additional) covariates: group allocation, sex, baseline EQ-5D-3L utility, duration of symptoms, smoking status, and pain severity.

the performance of ACD declines, mainly with regard to the patient perceived recovery. As no specific data on medication, paramedical treatment and productivity were gathered during the third to fifth year of follow-up, a detailed cost-effectiveness study on these years was not possible. However, based on available follow-up data (Table A.2), there were no significant differences in EQ5D scores after 5 years. Additionally, the number of reoperations was comparable across groups between 2 and 5 years of follow-up (1 in the ACDA group, 2 in the ACDF group, and 2 in the ACD group, Table A.3). Thus, considering that surgical costs represented the largest category of healthcare costs, it would be reasonable to expect the 5-year cost effectiveness estimates to yield broadly the same conclusions as this 2-year analysis.

Our findings should be interpreted in view of this study's limitations. Although this study is representative of the Dutch context, the generalizability of our findings to other settings may be limited. Naturally, the prosthesis and cage costs attainable in other settings may influence cost-effectiveness estimates. It is also worth noting that ACDF using allograft, which was not part of the NECK trial but saves the costs of a cage, may be preferred if it results in sufficiently comparable outcomes.

In line with the existing literature on statistical methods for trial-based economic evaluations, adjustment for baseline imbalances in EQ-5D-3L utility notably influenced results [14]. Although it is still uncommon to control for confounders and baseline QoL in economic evaluations, the importance of doing so is increasingly being recognized as such factors may strongly influence costeffectiveness estimates [14,19]. In this study, adjustment for baseline EQ5D utility only influenced overall conclusions in one of the sensitivity analyses (ie, looking at 2-year costs and QALYs). The relevance of the baseline imbalance in EQ-5D-3L utility in the NECK trial is debatable as it was likely due to chance (given the double-blind randomization) and because no such imbalance was present in baseline EQ-VAS

utilities. Moreover, we were conservative in our decision to adjust QALYs and costs for baseline utility, and there is no clear consensus on whether costs should also be adjusted for baseline utility. When only QALYs are adjusted for in the 2-year sensitivity analysis, ACDF remains the preferred strategy up to a WTP threshold of about €36,000/QALY, after which ACDA gains preference.

Conclusion

In this cost-utility analysis, ACDF was likely to be more cost-effective than ACDA or ACD over 2 years of follow-up. Sensitivity analyses demonstrated that this conclusion is robust to most alternative approaches/scenarios considered. The difference in costs is mainly caused by the initial surgery duration and prosthesis, and there are only minimal differences in the costs during follow up which likely extend beyond 2 years based on preliminary available data. Since clinical data are comparable between the groups, it is to the judgment of the patient and surgeon which intervention is applied, although ACDF is likely to be the most cost effective strategy.

Declarations of Competing Interests

One or more of the authors declare financial or professional relationships on ICMJE-TSJ disclosure forms.

Acknowledgments

No funding was received for this costeffectiveness study. The NECK trial was an investigator initiated study, partially funded by B. Braun Aesculap. The study was carried out by the Leiden - The Hague Spine Intervention Prognostic Study (SIPS) group without any interference of BBraun.

Supplementary materials

Supplementary material associated with this article can be found in the online version at <https://doi.org/10.1016/j.spinee.2023.02.003>.

References

- [1] Vleggeert-Lankamp CLA, Janssen TMH, van Zwet E, Goedmakers CMW, Bosscher L, Peul W, et al. The NECK trial: effectiveness of anterior cervical discectomy with or without interbody fusion and arthroplasty in the treatment of cervical disc herniation; a double-blinded randomized controlled trial. *Spine J* 2019;19:965–75. <https://doi.org/10.1016/j.spinee.2018.12.013>.
- [2] Schuermans VNE, Smeets AYJM, Boselie AFM, Zarrouk O, Hermans SMM, Droeghaag R, et al. Cost-effectiveness of anterior surgical decompression surgery for cervical degenerative disk disease: a systematic review of economic evaluations. *Eur Spine J* 2022;31(5):1206–18. <https://doi.org/10.1007/s00586-022-07137-7>.
- [3] Bhadra AK, Raman AS, Casey ATH, Crawford RJ. Single-level cervical radiculopathy: clinical outcome and cost-effectiveness of four techniques of anterior cervical discectomy and fusion and disc arthroplasty. *Eur Spine J* 2009;18:232–7. <https://doi.org/10.1007/s00586-008-0866-8>.
- [4] Arts MP, Brand R, van den Akker E, Koes BW, Peul WC. The Netherlands Cervical Kinematics (NECK) trial. Cost-effectiveness of anterior cervical discectomy with or without interbody fusion and arthroplasty in the treatment of cervical disc herniation; a double-blind randomised multicenter study. *BMC Musculoskelet Disord* 2010;11:122.
- [5] Lamers LM, McDonnell J, Stalmeier PFM, Krabbe PFM, Busschbach JJV. The Dutch Tariff: results and arguments for an effective design for national EQ-5D valuation studies. *Health Econ* 2006;15:1121–32. <https://doi.org/10.1002/hec.1124>.
- [6] Kanters TA, Bouwmans CAM, van der Linden N, Tan SS, Hakkaart-van Roijen L. Update of the Dutch manual for costing studies in health care. *PLoS One* 2017;12(11):e0187477. <https://doi.org/10.1371/journal.pone.0187477>.
- [7] Hakkaart-van Roijen L, van der Linden N, Bouwmans C, Kanters T, Tan S. Costing manual: methodology of costing research and reference prices for economic evaluations in healthcare [in Dutch: Kostenhandleiding: Methodologie van kostenonderzoek en referentieprijzen voor economische evaluaties in de gezondheidszorg]. Erasmus Universiteit Rotterdam; 2015. p. 2–65.
- [8] Central Bureau of Statistics [in Dutch: Centraal Bureau voor de Statistiek]. Dutch consumer price index 2019. <https://www.cbs.nl/nl-nl/cijfers/detail/83131ned#shortTableDescription>.
- [9] Versteegh M, Knies S, Brouwer W. From good to better: new Dutch guidelines for economic evaluations in healthcare. *Pharmacoeconomics* 2016;34:1071–4. <https://doi.org/10.1007/s40273-016-0431-y>.
- [10] Schafer J. Multiple imputation: a primer. *Stat Methods Med Res* 1999;8:3–15.
- [11] White IR, Royston P, Wood AM. Multiple imputation using chained equations: issues and guidance for practice. *Stat Med* 2011;30:377–99. <https://doi.org/10.1002/sim.4067>.
- [12] Li K-H, Meng X-L, Raghunathan T, Rubin D. Significance levels from repeated p-values with multiply-imputed data. *Stat Sin* 1991;1:65–92.
- [13] Rubin DB. Multiple imputation for nonresponse in surveys. New York: Wiley; 1987.
- [14] Mutubuki EN, el Alili M, Bosmans JE, Oosterhuis T, Snoek F J, Ostelo RWJG, et al. The statistical approach in trial-based economic evaluations matters: get your statistics together!. *BMC Health Serv Res* 2021;21:1–12. <https://doi.org/10.1186/s12913-021-06513-1>.
- [15] Hoch JS, Briggs AH, Willan AR. Something old, something new, something borrowed, something blue: a framework for the marriage of health econometrics and cost-effectiveness analysis. *Health Econ* 2002;11:415–30. <https://doi.org/10.1002/hec.678>.
- [16] Fenwick E, Claxton K, Sculpher M. Representing uncertainty: the role of cost-effectiveness acceptability curves. *Health Econ* 2001;10:779–87. <https://doi.org/10.1002/hec.635>.
- [17] Glick HA, Briggs AH, Polsky D. Quantifying stochastic uncertainty and presenting results of cost-effectiveness analyses. *Expert Rev Pharmacoecon Outcomes Res* 2001;1:25–36. <https://doi.org/10.1586/14737167.1.1.25>.
- [18] Goedmakers CMW, de Vries F, Bosscher L, Peul WC, Arts MP, Vleggeert-Lankamp CLA. Long-term results of the NECK trial: implanting a disc prosthesis after cervical anterior discectomy cannot prevent adjacent segment disease. 5-years clinical follow-up of a double-blinded randomised controlled trial. *Spine J* 2023;23:350–360. <https://doi.org/10.1016/j.spinee.2022.11.006>.
- [19] Manca A, Hawkins N, Sculpher MJ. Estimating mean QALYs in trial-based cost-effectiveness analysis: the importance of controlling for baseline utility. *Health Econ* 2005;14:487–96. <https://doi.org/10.1002/hec.944>.