

# Proton Pump Inhibitor Use Affects Pseudarthrosis Rates and Influences Patient-Reported Outcomes

Global Spine Journal  
2020, Vol. 10(1) 55-62  
© The Author(s) 2019  
Article reuse guidelines:  
sagepub.com/journals-permissions  
DOI: 10.1177/2192568219853222  
journals.sagepub.com/home/gsj



John J. Mangan III, MD, MHA<sup>1</sup>, Srikanth N. Divi, MD<sup>2</sup>, James C. McKenzie, MD<sup>1</sup>, Justin D. Stull, MD<sup>1</sup>, William Conaway, MD<sup>1</sup>, David S. Casper, MD<sup>1</sup>, Dhruv K. C. Goyal, BA<sup>2</sup>, Kristen J. Nicholson, PhD<sup>2</sup>, Matthew S. Galetta, BA<sup>2</sup>, Scott C. Wagner, MD<sup>3</sup>, I. David Kaye, MD<sup>2</sup>, Mark F. Kurd, MD<sup>2</sup>, Barrett I. Woods, MD<sup>2</sup>, Kristen E. Radcliff, MD<sup>2</sup>, Jeffery A. Rihn, MD<sup>2</sup>, D. Greg Anderson, MD<sup>2</sup>, Alan S. Hilibrand, MD<sup>2</sup>, Alexander R. Vaccaro, MD, PhD, MBA<sup>2</sup>, Gregory D. Schroeder, MD<sup>2</sup>, and Christopher K. Kepler, MD, MBA<sup>2</sup>

## Abstract

**Study Design:** Retrospective cohort review

**Objectives:** Cervical pseudarthrosis is a frequent cause of need for revision anterior cervical discectomy and fusion (ACDF) and may lead to worse patient-reported outcomes. The effect of proton pump inhibitors on cervical fusion rates are unknown. The purpose of this study was to determine if patients taking PPIs have higher rates of nonunion after ACDF.

**Methods:** A retrospective cohort review was performed to compare patients who were taking PPIs preoperatively with those not taking PPIs prior to ACDF. Patients younger than 18 years of age, those with less than 1-year follow-up, and those undergoing surgery for trauma, tumor, infection, or revision were excluded. The rates of clinically diagnosed pseudarthrosis and radiographic pseudarthrosis were compared between PPI groups. Patient outcomes, pseudarthrosis rates, and revision rates were compared between PPI groups using either multiple linear or logistic regression analysis, controlling for demographic and operative variables.

**Results:** Out of 264 patients, 58 patients were in the PPI group and 206 were in the non-PPI group. A total of 23 (8.71%) patients were clinically diagnosed with pseudarthrosis with a significant difference between PPI and non-PPI groups ( $P = .009$ ). Using multiple linear regression, PPI use was not found to significantly affect any patient-reported outcome measure. However, based on logistic regression, PPI use was found to increase the odds of clinically diagnosed pseudarthrosis (odds ratio 3.552,  $P = .014$ ). Additionally, clinically diagnosed pseudarthrosis negatively influenced improvement in PCS-12 scores ( $P = .022$ ).

**Conclusions:** PPI use was found to be a significant predictor of clinically diagnosed pseudarthrosis following ACDF surgery. Furthermore, clinically diagnosed pseudarthrosis negatively influenced improvement in PCS-12 scores.

## Keywords

anterior cervical discectomy and fusion, cervical spine surgery, degenerative cervical spine disorders, proton pump inhibitor, patient-reported outcome measures, Short Form Survey-12, Neck Disability Index, Visual Analogue Scale, cervical revision surgery, nonunion, pseudarthrosis

<sup>1</sup> Thomas Jefferson University, Philadelphia, PA, USA

<sup>2</sup> Rothman Orthopaedics, Philadelphia, PA, USA

<sup>3</sup> Walter Reed National Military Medical Center, Bethesda, MD, USA

## Corresponding Author:

John J. Mangan, Rothman Institute, 925 Chestnut Street, Philadelphia, PA 19107, USA.

Email: [John.mangan@jefferson.edu](mailto:John.mangan@jefferson.edu)



Creative Commons Non Commercial No Derivs CC BY-NC-ND: This article is distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs 4.0 License (<https://creativecommons.org/licenses/by-nc-nd/4.0/>) which permits non-commercial use, reproduction and distribution of the work as published without adaptation or alteration, without further permission provided the original work is attributed as specified on the SAGE and Open Access pages (<https://us.sagepub.com/en-us/nam/open-access-at-sage>).

## Introduction

Anterior cervical discectomy and fusion (ACDF) has been established as a reliable treatment for cervical spine radiculopathy and myelopathy. In the United States, there are approximately 70 cervical spine surgeries performed annually for every 100 000 people, and ACDF procedures account for 68% of all cervical surgeries.<sup>1</sup> Despite its reliability, known complications following ACDF include pseudarthrosis, graft subsidence, and adjacent segment disease.<sup>2</sup> Pseudarthrosis is the leading cause of revision ACDF procedures, accounting for an estimated 45% and 56% of all revision procedures.<sup>3</sup> The risk of pseudarthrosis has been estimated to be as high as 20% of patients with a single-level fusion and as high as 60% in patients with a multilevel fusion.<sup>2</sup> Pseudarthrosis can result in abnormal segmental motion that can lead to persistent neck pain and radicular symptoms as well as increase the risk of hardware failure.<sup>2</sup>

Known patient risk factors that increase the risk of pseudarthrosis include smoking, diabetes, obesity, age, osteoporosis, and poor nutritional status.<sup>4-6</sup> Proton pump inhibitors (PPIs) are a widely prescribed class of medications used to treat gastroesophageal reflux disease (GERD), whose side effects include malnutrition, alterations in the immune system's effectiveness, as well as changes in bone metabolism.<sup>7,8</sup> PPIs were the third most commonly prescribed medication in the United States in 2008 and first-generation PPIs have been available over-the-counter since 2003; thus, many patients may be using the drug without self-reporting use.<sup>9,10</sup> Basic science studies have demonstrated that PPIs alter bone healing and metabolism through decreasing the effectiveness of bone resorption by osteoclasts.<sup>7</sup> Despite their widespread use and their effects on the musculoskeletal system, there has been relatively little published regarding the effects of PPIs in orthopedic surgery and specifically spinal fusion. The purpose of this study was to determine if there was an association between PPI use and the development of a pseudarthrosis after ACDF.

## Methods

After institutional review board approval was obtained, a retrospective cohort review was performed via analysis of patient records obtained from a single institution's electronic medical record (EMR) system. All the patients included underwent ACDF performed by one of several fellowship-trained orthopedic spine surgeons between January 1, 2015, and December 31, 2016. Patients over the age of 18 who underwent surgery to address radiculopathy, myelopathy, or myeloradiculopathy symptoms were included. Patients were grouped based on their documented preoperative use of PPIs in the EMR. Patients under the age of 18 years, those with less than a year of follow-up, or patients that received surgery for trauma, infection, metastatic disease, or revision were excluded from this study.

Basic demographic data for the patients in the cohort including age, sex, body mass index (BMI), months followed-up,

preoperative symptom duration, smoking status, number of levels fused, graft type utilized, preoperative cervical diagnosis, and presence of adjacent level spondylolisthesis was collected and recorded. Patient-reported outcome measurements (PROMs) from at least 1-year follow-up, including the Neck Disability Index (NDI), Short Form-12 Physical Component Score (PCS-12), Short Form-12 Mental Component Score (MCS-12), and both Visual Analogue Scale Neck (VAS Neck) and Arm (VAS Arm) pain scores were collected and compared between the PPI groups.

The primary endpoint of this study was the rate of clinical diagnosis of pseudarthrosis based on persistent neck pain or radicular symptoms at follow-up. Based on surgeon preference, all patients with clinically diagnosed pseudarthrosis subsequently had radiographic confirmation using either a computed tomography (CT) scan, static anteroposterior (AP) and lateral cervical radiographs, or dynamic lateral flexion and extension radiographs. However, since this institution does not routinely obtain CT scans at follow-up and only a small subset of patients underwent CT, the rate of radiographic pseudarthrosis on dynamic radiographs was chosen as a secondary endpoint. Some patients received dynamic radiographs at routine follow-up due to surgeon-specific post-operative protocol, even if they had no cervical symptoms. The criteria used for determining radiographic pseudarthrosis on flexion and extension radiographs was previously defined by Song et al, where an interspinous motion of 1 mm between flexion and extension films at the surgically fused levels combined with 4 mm of interspinous motion at the superjacent unfused levels.<sup>11</sup> All images were obtained from the institution's Picture Archiving and Communication System (PACS; Siemens Magic Software, Munich Germany; precision of 0.1 mm). Both PPI groups were also compared for differences in cervical revision surgery rates.

## Statistical Analysis

Standard descriptive statistics including mean and 95% confidence interval were used for univariate analysis of basic demographic data and patient reported outcomes. The recovery ratio (RR) was calculated using the following equation:  $(\Delta \text{ outcome score}) / (\text{optimal score} - \text{baseline score})$ . The optimal scores for NDI, VAS Neck, and VAS Arm pain were defined as 0, while the those for PCS-12 and MCS-12 were defined as 100.<sup>12</sup> The percentage of patients reaching a minimal clinically important difference (MCID) after surgery was calculated and compared between groups using Pearson  $\chi^2$  analysis. The following MCID cutoff scores were used: NDI, 15 points; PCS-12, 8.1 points; MCS-12, 4.7 points; VAS Neck, 2.5 points; and VAS Arm, 2.5 points.<sup>13,14</sup> Multiple linear regression analysis was used to determine if PPI use was a significant predictor of patient outcomes, controlling for demographic and operative variables. Multiple logistic regression was used to determine if PPI use increased odds of nonunion rates or cervical revision rates. Continuous variables were compared using

**Table 1.** Descriptive Characteristics of the Cohort by PPI Use.

	Overall (N = 264)	On PPI (N = 58)	Not on PPI (N = 206)	P
Age, mean [95% CI]	53 [52, 54]	55 [52, 58]	53 [51, 54]	<i>P</i> = .974
Sex, n (%)				<i>P</i> = .036*
Male	123 (47%)	20 (34.5%)	103 (50%)	
Female	141 (53%)	38 (64.6%)	103 (50%)	
BMI, mean [95% CI]	29.6 [28.8, 30.3]	30.5 [28.9, 32.0]	29.3 [28.5, 30.1]	<i>P</i> = .697
Months follow-up, mean [95% CI]	19.8 [19.0, 20.6]	19.1 [17.4, 20.8]	20.0 [19.1, 20.9]	<i>P</i> = .784
Symptom duration, n (%)				<i>P</i> = .434
<1 Month	18 (6.8%)	3 (5.2%)	15 (7.3%)	
1-3 Months	41 (15.5%)	9 (15.5%)	32 (15.5%)	
3-6 Months	46 (17.4%)	13 (22.4%)	33 (16.0%)	
6 Months to 2 years	72 (27.3%)	11 (19.0%)	61 (29.6%)	
2 Years+	87 (33.0%)	22 (37.9%)	65 (31.6%)	
Smoking status, n (%)				<i>P</i> = .126
Never	152 (57.6%)	30 (51.7%)	122 (59.2%)	
Current	43 (16.3%)	7 (12.1%)	36 (17.5%)	
Former	69 (26.1%)	21 (36.2%)	48 (23.3%)	
# Levels fused, n (%)				<i>P</i> = .158
1	61 (23%)	12 (20.7%)	49 (23.8%)	
2	125 (47%)	27 (46.6%)	98 (47.6%)	
3	65 (25%)	13 (22.4%)	52 (25.2%)	
4	12 (5%)	5 (8.6%)	7 (3.4%)	
5	1 (<1%)	1 (1.7%)	0 (0%)	
Graft type, n (%)				<i>P</i> = .493
Allograft	243 (92.0%)	54 (93.1%)	189 (83.6%)	
Iliac crest bone graft	21 (8.0%)	4 (6.9%)	17 (16.4%)	
Diagnosis, n (%)				<i>P</i> = .357
Radiculopathy	122 (46.2%)	22 (37.9%)	100 (48.5%)	
Myelopathy	64 (24.2%)	16 (27.6%)	48 (23.3%)	
Myeloradiculopathy	78 (29.6%)	20 (44.5%)	58 (28.2%)	

Abbreviations: PPI, proton pump inhibitor; CI, confidence interval; BMI, body mass index.

\*Indicates statistical significance (*P* < .05).

independent *t* tests or Mann-Whitney *U* test, depending on normality of the data. Categorical variables were compared using Fisher's exact or Pearson's  $\chi^2$  test. A *P* value < .05 was considered statistically significant.

## Results

### Demographic Data

A total of 264 patients were included in our analysis based on inclusion criteria. Overall, there were a total of 206 patients who were not taking a PPI versus 58 patients that were taking a PPI prior to surgery. There were no baseline differences in demographics except for sex, with the PPI group having a higher proportion of females (64.6% vs 50%, *P* = .036). The average age for all patients was 53 years, and the mean BMI was 29.6. The mean follow-up was 19.8 months. With regard to duration of symptoms preoperatively, 18 (6.8%) experienced less than 1 month of symptoms, 41 (15.5%) experienced 1 to 3 months, 46 (17.4%) experienced 3 to 6 months, 72 (27.3%) experienced 6 months to 2 years, and 87 (33.0%) experienced 2+ years (*P* = .434). Descriptive statistics for the entire cohort can be found in Table 1.

### Patient-Reported Outcome Measurements

Overall, there were no significant differences in outcome scores, recovery ratios, or % of patients reaching MCID in terms (Table 2). Based on multiple linear regression analysis, PPI use was not found to be a significant predictor for change in any outcome score: NDI (*P* = .578), PCS-12 (*P* = .841), MCS-12 (*P* = .909), VAS Neck (*P* = .654), and VAS Arm (*P* = .762; Table 2). Additional regression analysis revealed that a higher BMI was found to negatively influence NDI score ( $\beta$  = 0.498 [0.103, 0.893], *P* = .014). Length of follow-up was also found to be a significant predictor of changes in NDI ( $\beta$  = 0.521 [0.142, 0.900], *P* = .007) and VAS Neck ( $\beta$  = 0.081 [0.019, 0.142], *P* = .010). Longer duration of preoperative symptoms was found to negatively affect NDI ( $\beta$  = 2.373 [0.503, 4.243], *P* = .013) and MCS-12 ( $\beta$  = -1.795 [-3.137, -0.453], *P* = .009) scores. In addition, the preoperative diagnosis was a significant predictor of MCS-12 score ( $\beta$  = 2.294 [0.207, 4.380], *P* = .031), with the presence of myelopathy and myeloradiculopathy predicting improved outcomes. Smoking status was a significant predictor of VAS Neck scores ( $\beta$  = -0.497 [-0.949, -0.045], *P* = .031) and iliac crest bone graft use influenced VAS Arm scores ( $\beta$  = 2.579 [0.806, 4.352], *P* = .005).

**Table 2.** Preoperative and Postoperative Patient-Reported Outcome Measurements Comparisons Between PPI Groups<sup>a</sup>.

	On PPI (N = 58)	Not on PPI (N = 206)	<i>p</i> <sup>b</sup>	<i>p</i> <sup>c</sup>
NDI				.578
Pre	42.9 [37.9, 47.9]	42.3 [39.6, 45.0]	.766	
Post	24.1 [18.7, 29.6]	26.0 [22.9, 29.2]	.103	
Δ	-18.9 [-24.2, -13.5]	-16.2 [-19.0, -13.5]	.373	
RR	0.32 [0.12, 0.52]	0.38 [0.31, 0.44]	.507	—
% MCID	58.6%	46.1%	.092	—
PCS-12				.841
Pre	32.5 [30.5, 34.5]	33.4 [32.3, 34.5]	.524	
Post	39.6 [36.8, 42.5]	40.8 [39.3, 42.3]	.514	
Δ	7.2 [5.0, 9.9]	7.2 [5.9, 8.5]	.994	
RR	0.10 [0.06, 0.14]	0.10 [0.08, 0.12]	.918	—
% MCID	43.1%	45.1%	.782	—
MCS-12				.909
Pre	44.3 [41.3, 47.3]	45.6 [43.9, 47.3]	.359	
Post	48.2 [45.2, 51.2]	49.4 [47.8, 51.0]	.688	
Δ	3.8 [0.1, 7.6]	3.6 [1.7, 5.6]	.934	
RR	0.04 [-0.03, 0.11]	0.03 [0.00, 0.07]	.933	—
% MCID	48.3%	42.7%	.451	—
VAS Neck				.654
Pre	5.7 [4.8, 6.5]	5.7 [5.3, 6.1]	.618	
Post	3.2 [2.4, 4.0]	3.1 [2.7, 3.5]	.810	
Δ	-2.5 [-3.4, -1.6]	-2.5 [-2.9, -2.1]	.991	
RR	0.46 [0.33, 0.60]	0.41 [0.32, 0.50]	.583	—
% MCID	50.0%	44.2%	.431	—
VAS Arm				.762
Pre	5.7 [4.9, 6.5]	5.0 [4.5, 5.4]	.112	
Post	3.1 [2.3, 3.8]	2.7 [2.3, 3.1]	.269	
Δ	-2.7 [-3.6, -1.8]	-2.3 [-2.8, -1.8]	.512	
RR	0.47 [0.33, 0.62]	0.51 [0.41, 0.61]	.705	—
% MCID	50.0%	44.7%	.471	—

Abbreviations: PPI, proton pump inhibitor; RR, recovery ratio; MCID, minimal clinically important difference; NDI, Neck Disability Index; SF-12, Short Form-12; PCS-12, Physical Component Score of SF-12; MCS-12, Mental Component Score of SF-12; VAS, Visual Analogue Score; VAS Neck, VAS neck pain; VAS Arm, VAS arm pain.

<sup>a</sup>Values are reported as mean [95% CI].

<sup>b</sup>Independent samples *t* tests (preoperative, postoperative, and Δ scores, and recovery ratios, between groups), or Pearson  $\chi^2$  analysis (% MCID).

<sup>c</sup>Multiple linear regression analysis.

### Pseudarthrosis and Cervical Revision Rates

Twenty-three patients (8.71%) were clinically diagnosed with symptomatic pseudarthrosis out of the entire cohort of 264 patients (Table 3). There was a significant difference between groups, with 10 patients in the PPI group (17.2% of all patients taking a PPI) and the remaining 13 (6.3% of all patients not taking a PPI) in the non-PPI ( $P = .009$ ). Philips iSite (Philips Health, USA) was used which has a measurement error rate of  $\pm 0.5$  mm per measurement. Of the 264 patients, 150 had dynamic radiographs performed at follow-up, all patients had AP and lateral radiographs taken. Using the previously mentioned dynamic radiographic criteria for pseudarthrosis developed by Song et al, 21 of 150 (14.0%) patients were found to have pseudarthrosis (Table 3) with 7 (33.3%) in the PPI group and the other 14 (66.7%) in the non-PPI group

( $P = .100$ ). There were a total of 22 patients that underwent cervical revision surgery to address pseudarthrosis, with 5 (22.7%) patients belonging to the PPI group and 17 (77.3%) belonging to the non-PPI group ( $P = .929$ ; Table 4).

Using multiple logistic regression, PPI use was found to increase odds of clinically diagnosed pseudarthrosis by 3.5 fold ( $\beta = 1.268$ , odds ratio [OR] = 3.552,  $P = .014$ ), but not for rates of pseudarthrosis on dynamic radiographs ( $P = .381$ ) or rates of cervical revision surgery ( $P = .685$ ). In addition, patients with a 3 or more level fusion had a 13-fold and 10-fold increased odds of radiographic pseudarthrosis compared to a 1-level and 2-level fusion, respectively ( $[\beta = 2.564$ , OR = 13.0,  $P = .044$ ] for 1-level;  $[\beta = 2.313$ , OR = 10.1,  $P = .027$ ] for 2-level). None of the other factors included in logistic regression were found to be significant predictors of cervical revision surgery or pseudarthrosis.

When comparing outcome scores in patients with a clinically diagnosed pseudarthrosis, postoperative VAS Neck and Arm scores were found to be significantly different ( $P = .002$  and  $P = .001$ , respectively; Table 5) with the pseudarthrosis group exhibiting worse disability in each of these domains. In addition, these patients exhibited diminished recovery in PCS-12 ( $P = .035$ ) and VAS Neck scores ( $P = .035$ ). On linear regression analysis, clinically diagnosed pseudarthrosis negatively influenced improvement in PCS-12 ( $\beta = -4.865$  [-9.025, -0.706],  $P = .022$ ). When comparing outcomes between patients with pseudarthrosis diagnosed on dynamic radiographs, patients with pseudarthrosis showed diminished recovery in PCS-12 scores ( $P = .019$ ; Table 6), but none of the other PROMs.

### Discussion

ACDF is a common and reliable surgery for the treatment of cervical radiculopathy and myelopathy. However, pseudarthrosis is a well-known complication following ACDF and is one of the leading causes for revision surgery.<sup>3</sup> While there are several well-established risk factors for cervical pseudarthrosis including age, diabetes, obesity, smoking, osteoporosis, and malnutrition, there are no studies assessing the preoperative use of PPIs as a risk factor. Currently, PPIs are the leading class of medications prescribed for the treatment of GERD.<sup>15</sup> Recent studies have shown that many PPIs are inappropriately prescribed, raising questions regarding safety with long-term use.<sup>15</sup> In addition, many patients may be taking PPIs without reporting its use since they are readily available over-the-counter. PPIs achieve their effect by decreasing the production of stomach acid; however, they are known to affect osteoclasts and thus influence bone metabolism and delay spinal fusion rates in animal studies.<sup>7,8</sup> Some studies have found a modest association with PPI use and spine fractures, but no studies thus far have assessed the effect of preoperative PPI use on patient outcomes or pseudarthrosis following cervical spine surgery.<sup>16,17</sup>

The results of this study demonstrate that patients with preoperative PPI use had a higher rate of clinically

**Table 3.** Pseudarthrosis Rates and PPI Use<sup>a</sup>.

	Overall	On PPI	Not on PPI	<i>p</i> <sup>b</sup>	<i>p</i> <sup>c</sup>
Clinical diagnosis of pseudarthrosis	(N = 264)	(N = 58)	(N = 206)		
Yes, n (%)	23 (8.7%)	10 (17.2%)	13 (6.3%)	.009*	.014*
No, n (%)	241 (91.3%)	48 (82.8%)	193 (93.7%)		
Pseudarthrosis on dynamic radiographs	(N = 150)	(N = 30)	(N = 120)		
Yes, n (%)	21 (14.0%)	7 (23.3%)	14 (11.7%)	.100	.381
No, n (%)	129 (86.0%)	23 (76.7%)	106 (88.3%)		

Abbreviation: PPI, proton pump inhibitor.

<sup>a</sup>Revision surgery, and clinical and radiographic pseudarthrosis, between PPI groups.

<sup>b</sup>Pearson  $\chi^2$  analysis or Fisher's exact test.

<sup>c</sup>Binary logistic regression.

\*Indicates statistical significance ( $P < .05$ ).

**Table 4.** Revision Rates and PPI Use<sup>a</sup>.

	Overall (N = 264)	On PPI (N = 58)	Not on PPI (N = 206)	<i>p</i> <sup>b</sup>	<i>p</i> <sup>c</sup>
Total, n (%)	22 (8.3%)	5 (8.6%)	17 (8.3%)	.929	.685
Pseudarthrosis	15	2 (3.5%)	13 (6.3%)	.531	.413
Adjacent segment disease	7	3 (5.2%)	2 (91.7%)		
New onset myelopathy	1	—	1 (0.5%)		
Seroma	1	—	1 (0.5%)		

Abbreviation: PPI, proton pump inhibitor.

<sup>a</sup>Reasons for revision between PPI groups.

<sup>b</sup>Pearson  $\chi^2$  analysis or Fisher's exact test.

<sup>c</sup>Binary logistic regression.

diagnosed pseudarthrosis compared with patients that were not taking preoperative PPIs ( $P = .009$ ). Additionally, preoperative PPI use was demonstrated to be an independent risk factor of a pseudarthrosis on logistic regression analysis (OR = 3.552,  $P = .014$ ). However, PPIs were not associated with a significantly higher revision rate in this cohort and PPI use did not influence patient reported outcomes after ACDF at the 1-year time point.

PPIs are a common class of medication that is seen frequently in patients presenting to the orthopedic and spine clinic. They are the mainstay of treatment for GERD, which has been estimated to affect 20% of the US population.<sup>18</sup> Additionally, PPIs are the standard of care for stress ulcer prophylaxis in hospitalized and critical care patients.<sup>19</sup> They exert their effect by blocking hydrogen-potassium ATPase pumps to decrease acid production of gastric parietal cells. However, this blockade is not specific for the gastric mucosa and affects similar ion pumps of osteoclasts, macrophages, and other immune system cell types.<sup>20</sup> These alterations in osteoclast function in turn affect bone metabolism by decreasing trabecular bone density and may also affect bone healing, potentiating the risk of fractures.<sup>8</sup> Histing et al found that administration of daily PPIs in a mouse femur fracture model resulted in significantly degraded biomechanics with higher amounts of cartilaginous and fibrous tissue and decreased bone formation.<sup>7</sup> In addition, these mice also showed reduced amounts of the bone formation markers bone morphogenic protein (BMP)-2, BMP-4, and cysteine-rich protein (CYR61).<sup>7</sup> Currently, the

biology of endochondral bone formation in fracture healing is well understood, and while the biology of spinal fusion may not be fully delineated, it shares significant similarities.<sup>21</sup> The full interactions of PPIs with critical steps involved in spinal fusion are currently not known.

Population-wide studies have also been done evaluating fracture risk and PPI use. Vestergaard et al, in a case-control study of the Danish population, demonstrated that PPI use resulted in an increased risk of hip, wrist, and spine fractures.<sup>22</sup> This has been acknowledged by Federal Drug Administration, which has labeled PPIs as being known to increase the likelihood of a fracture.<sup>10</sup> There is also growing evidence of an association between prolonged PPI use and increased risk of spine fractures.<sup>16,17</sup> This growing body of evidence relating PPIs and fractures suggest that these medications have an adverse effect on bone quality and may affect stability with instrumentation in elective spine fusion. The present study did not assess the incidence of fractures or hardware complications postoperatively, but it did find a significantly higher clinical pseudarthrosis rate (OR = 3.552,  $P = .014$ ) in patients taking PPI, suggesting a significant interaction. The effects of PPI use on fusion rates after elective spine surgery are not fully understood and deserve further attention.

Pseudarthrosis after ACDF is a relatively common postoperative complication and is clinically apparent when patients present with recurrent or worsening radicular symptoms or neck pain.<sup>2,23</sup> However, patients with pseudarthrosis do not

**Table 5.** Preoperative and Postoperative Patient-Reported Outcome Measurements Comparisons Between Pseudarthrosis Groups<sup>a</sup>.

	Clinical Pseudarthrosis Diagnosis (N = 264)			
	No Pseudarthrosis (N = 241)	Pseudarthrosis (N = 23)	<i>p</i> <sup>b</sup>	<i>p</i> <sup>c</sup>
<b>NDI</b>				
Pre	41.9 [39.4, 44.3]	48.3 [39.0, 57.6]	.766	.407
Post	24.7 [21.9, 27.5]	35.1 [24.3, 45.9]	.103	
Δ	-17.2 [-19.6, -14.6]	-13.0 [-21.9, -4.1]	.317	
RR	0.39 [0.33, 0.45]	0.11 [-0.32, 0.54]	.184	—
% MCID	49.4%	43.5%	.589	—
<b>PCS-12</b>				
Pre	33.5 [32.4, 34.5]	30.2 [27.3, 33.1]	.454	.022*
Post	41.2 [39.8, 42.6]	33.2 [29.1, 37.3]	.288	
Δ	7.6 [6.4, 8.8]	3.0 [-1.5, 7.5]	.067	
RR	0.11 [0.09, 0.13]	0.04 [-0.03, 0.10]	.035*	—
% MCID	45.6%	34.8%	.317	—
<b>MCS-12</b>				
Pre	45.3 [43.8, 46.9]	45.3 [39.7, 50.8]	.419	.661
Post	49.2 [47.7, 50.7]	48.5 [43.6, 53.4]	.288	
Δ	3.7 [2.0, 5.5]	3.0 [-4.4, 10.4]	.842	
RR	0.04 [0.01, 0.07]	0.01 [-0.12, 0.14]	.818	—
% MCID	43.6%	47.8%	.694	—
<b>VAS Neck</b>				
Pre	5.6 [5.3, 6.0]	6.2 [4.8, 7.6]	.999	.113
Post	3.0 [2.6, 3.4]	4.7 [3.4, 6.1]	.002*	
Δ	-2.6 [-3.0, -2.2]	-1.5 [-2.8, -0.2]	.096	
RR	0.44 [0.36, 0.52]	0.26 [0.06, 0.45]	.035*	—
% MCID	46.9%	30.4%	.130	—
<b>VAS Arm</b>				
Pre	5.0 [4.6, 5.4]	6.5 [5.4, 7.7]	.815	.997
Post	2.7 [2.3, 3.0]	3.8 [2.5, 5.2]	.001*	
Δ	-2.3 [-2.8, -1.9]	-2.8 [-4.0, -1.5]	.769	
RR	0.51 [0.42, 0.60]	0.43 [0.25, 0.62]	.174	—
% MCID	46.1%	43.5%	.812	—

Abbreviations: NDI, Neck Disability Index; RR, recovery ratio; MCID, minimal clinically important difference; SF-12, Short Form-12; PCS-12, Physical Component Score of SF-12; MCS-12, Mental Component Score of SF-12; VAS, Visual Analogue Score; VAS Neck, VAS neck pain; VAS Arm, VAS arm pain.

<sup>a</sup>Preoperative and postoperative values are reported as mean [95% CI].

<sup>b</sup>Mann-Whitney *U* test (preoperative, postoperative, and Δ scores, and recovery ratios, between groups), or Pearson  $\chi^2$  analysis (% MCID).

<sup>c</sup>Multiple linear regression analysis.

\*Indicates statistical significance ( $P < .05$ ).

always present with symptoms and the management of asymptomatic pseudarthrosis remains controversial.<sup>2</sup> Lee et al recently evaluated the results of patients that had a pseudarthrosis after ACDF at 1 year after surgery. In their study, they identified 32.6% (29/89) of patients had a pseudarthrosis at 1-year point, and out of these 29 patients, 21 went on to achieve bony union by the 2-year point.<sup>2</sup> Persistent nonunion in their cohort was associated with worse functional outcomes at 2 years in terms of VAS Neck and NDI scores; however, it is unclear whether these patients had radiographic or clinically diagnosed pseudarthrosis.<sup>2</sup> Delamarter et al, on the other hand, evaluated the reoperation rates of patients undergoing ACDF and identified that 13.1% (8/61) underwent a revision

**Table 6.** Preoperative and Postoperative Patient-Reported Outcome Measurements Comparisons Between Radiographic Pseudarthrosis Groups<sup>a</sup>.

	Pseudarthrosis on Dynamic Radiographs (N = 150)			
	No Pseudarthrosis (N = 129)	Pseudarthrosis (N = 21)	<i>p</i> <sup>b</sup>	<i>p</i> <sup>c</sup>
<b>NDI</b>				
Pre	42.7 [39.6, 45.8]	44.6 [35.4, 53.8]	.355	.935
Post	25.2 [21.5, 29.0]	27.6 [17.1, 38.1]	.762	
Δ	-17.3 [-20.8, -13.9]	-18.1 [-26.8, -9.5]	.717	
RR	0.39 [0.31, 0.47]	0.34 [0.15, 0.54]	.535	—
% MCID	51.9%	47.6%	.713	—
<b>PCS-12</b>				
Pre	32.7 [31.4, 33.9]	30.8 [26.9, 34.7]	.462	.064
Post	41.8 [39.8, 43.7]	35.3 [30.2, 40.4]	.211	
Δ	8.9 [7.2, 10.6]	4.2 [-2.2, 10.5]	.146	
RR	0.13 [0.10, 0.15]	0.04 [-0.03, 0.12]	.019*	—
% MCID	49.6%	33.3%	.166	—
<b>MCS-12</b>				
Pre	45.9 [43.8, 48.0]	47.9 [43.3, 52.5]	.439	.541
Post	49.4 [47.4, 51.4]	49.2 [43.8, 54.6]	.211	
Δ	3.3 [0.9, 5.7]	0.3 [-6.2, 6.8]	.505	
RR	0.03 [-0.01, 0.07]	-0.01 [-0.11, 0.09]	.521	—
% MCID	40.3%	33.3%	.544	—
<b>VAS Neck</b>				
Pre	5.7 [5.2, 6.2]	6.2 [4.9, 7.5]	.954	.879
Post	3.2 [2.7, 3.7]	3.8 [2.3, 5.2]	.225	
Δ	-2.4 [-3.0, -1.9]	-2.2 [-3.4, -1.1]	.736	
RR	0.46 [0.38, 0.54]	0.33 [0.16, 0.51]	.182	—
% MCID	45.7%	33.3%	.288	—
<b>VAS Arm</b>				
Pre	4.6 [4.0, 5.1]	5.0 [3.5, 6.5]	.566	.609
Post	2.6 [2.1, 3.0]	3.4 [1.8, 5.1]	.125	
Δ	-1.9 [-2.6, -1.2]	-1.9 [-4.1, 0.3]	.886	
RR	0.54 [0.44, 0.64]	0.40 [0.10, 0.69]	.280	—
% MCID	45.0%	33.3%	.319	—

Abbreviations: NDI, Neck Disability Index; RR, recovery ratio; MCID, minimal clinically important difference; SF-12, Short Form-12; PCS-12, Physical Component Score of SF-12; MCS-12, Mental Component Score of SF-12; VAS, Visual Analogue Score; VAS Neck, VAS neck pain; VAS Arm, VAS arm pain.

<sup>a</sup>Preoperative and postoperative values are reported as mean [95% CI].

<sup>b</sup>Mann-Whitney *U* test (preoperative, postoperative, and Δ scores, and recovery ratios, between groups), or Pearson  $\chi^2$  analysis (% MCID).

<sup>c</sup>Multiple linear regression analysis.

\*Indicates statistical significance ( $P < .05$ ).

procedure at their index surgical level and 75% (6/8) of those patients underwent revision for a symptomatic pseudarthrosis.<sup>20</sup> Similarly, Kaiser et al suggest that revision of a symptomatic pseudarthrosis should be considered as this is associated with an improved clinical outcome.<sup>23</sup> Despite a difference in clinical pseudarthrosis rates, this study did not find a significant difference in reoperation rates ( $P = .929$ ) between groups and PPI use was not a significant predictor of revision ( $P = .685$ ) on regression analysis. In addition, while the present study did not identify any significant differences in PROMs postoperatively between PPI groups, patients with clinical pseudarthrosis reported worse postoperative VAS Neck and VAS Arm scores ( $P = .002$  and  $P = .001$ ) and the presence

of pseudarthrosis negatively influenced improvement in PCS-12 scores ( $P = .022$ ).

This analysis is the first to look at the association between PPIs and the development of a pseudarthrosis after ACDF. In this cohort, preoperative PPI use was identified as an independent predictor of developing a pseudarthrosis after ACDF ( $P = .014$ ). While this study did not identify a difference in revision rates or pseudarthrosis on dynamic radiographs, the difference in clinically diagnosed pseudarthrosis is a pertinent one. Spine surgeons should be aware of patients taking PPIs preoperatively as this may increase the risk of the development of a clinically symptomatic pseudarthrosis after ACDF necessitating possible revision. In their analysis, Vestergaard et al identified that patients on histamine (H2) blockers had a decreased fracture risk compared with patients on PPIs as well as the rest of the general population. This may represent a perioperative alternative for patients on PPIs presenting for elective ACDF.<sup>22</sup> The risks and benefits of PPI use in the perioperative period or the alteration of therapy should be tailored to each individual patient's situation. Future studies to understand the effect of PPIs on patients undergoing spinal fusion is necessary.

There are several limitations to this retrospective study. Preoperative PPI use was identified based on patient-reported medications as well as preoperative medical clearance forms. Due to the fact that PPIs are available over-the-counter some patients may have failed to reported usage of this medication. Also due to the retrospective nature of this study, we are unable to identify the full duration of PPI use prior to surgery. Since further investigation for pseudarthrosis after ACDF is generally determined by the presence of symptoms, our study was designed to determine the rates of clinical pseudarthrosis as would be detected in clinical follow-up. We acknowledge that this study design has some limitations, among which include a decreased ability to determine clinically silent nonunions. In addition, the mean follow-up was around 19 months, which may not be long enough to determine whether a clinically symptomatic pseudarthrosis may resolve or require further intervention. Similarly, no differences in revision rates were found, which may be significant at a longer follow-up. Finally, radiographs and not CT was used to determine pseudarthrosis, which may have underestimated radiographic nonunion rates.

## Conclusion

In conclusion, this is the first study to associate PPI use with a risk of developing a symptomatic pseudarthrosis after ACDF. Patients on preoperative PPIs did not have a difference identified in their pre- and postoperative outcomes measures; however, patients with pseudarthrosis has significantly worse VAS Neck and VAS Arm scores. Further investigation into the relationship of PPIs and the development of pseudarthrosis of the cervical spine is needed.

## Ethical Approval

This study was approved by the Institutional Review Board at the Thomas Jefferson University Hospital. Each author certifies that his or her institution approved the human protocol for this investigation and that all investigations were conducted in conformity with ethical principles of research.


## Declaration of Conflicting Interests


The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.


## Funding


The author(s) received no financial support for the research, authorship, and/or publication of this article.


## ORCID iD

Srikanth N. Divi  <https://orcid.org/0000-0002-5776-2044>

William Conaway  <https://orcid.org/0000-0003-4073-5784>

Dhruv K. C. Goyal  <https://orcid.org/0000-0002-5789-5410>

Alan S. Hilibrand  <https://orcid.org/0000-0001-8811-9687>

Alexander R. Vaccaro  <https://orcid.org/0000-0002-8073-0796>

## References

1. Baird EO, Egorova NN, McAnany SJ, Qureshi SA, Hecht AC, Cho SK. National trends in outpatient surgical treatment of degenerative cervical spine disease. *Global Spine J*. 2014;4:143-150.
2. Lee DH, Cho JH, Hwang CJ, et al. What is the fate of pseudarthrosis detected 1 year after anterior cervical discectomy and fusion? *Spine (Phila Pa 1976)*. 2018;43:E23-E28. doi:10.1097/brs.0000000000002077
3. Leven D, Cho SK. Pseudarthrosis of the cervical spine: risk factors, diagnosis and management. *Asian Spine J*. 2016;10:776-786.
4. Hilibrand AS, Fye MA, Emery SE, Palumbo MA, Bohlman HH. Impact of smoking on the outcome of anterior cervical arthrodesis with interbody or strut-grafting. *J Bone Joint Surg Am*. 2001;83-A:668-673.
5. Bolesta MJ, Rechtine GR 2nd, Chrin AM. One- and two-level anterior cervical discectomy and fusion: the effect of plate fixation. *Spine J*. 2002;2:197-203.
6. Phillips FM, Carlson G, Emery SE, Bohlman HH. Anterior cervical pseudarthrosis. Natural history and treatment. *Spine (Phila Pa 1976)*. 1997;22:1585-1589.
7. Histing T, Stenger D, Scheuer C, et al. Pantoprazole, a proton pump inhibitor, delays bone remodeling during fracture healing in mice. *Calcif Tissue Int*. 2012;90:507-514.
8. Al Subaie A, Emami E, Tamimi I, et al. Systemic administration of omeprazole interferes with bone healing and implant osseointegration: an in vivo study on rat tibiae. *J Clin Periodontol*. 2016; 43:193-203.
9. Harris G. FDA approves over-counter sales of top ulcer drug. *The New York Times*. [www.nytimes.com/2003/06/21/business/fda-approves-over-counter-sales-of-top-ulcer-drug.html](http://www.nytimes.com/2003/06/21/business/fda-approves-over-counter-sales-of-top-ulcer-drug.html). Published June 21, 2003. Accessed May 22, 2019.
10. Wang L, Li M, Cao Y, et al. Proton pump inhibitors and the risk for fracture at specific sites: data mining of the FDA Adverse

- Event Reporting System. *Sci Rep.* 2017;7:5527. doi:10.1038/s41598-017-05552-1
11. Song KS, Piyaskulkaew C, Chuntarapas T, et al. Dynamic radiographic criteria for detecting pseudarthrosis following anterior cervical arthrodesis. *J Bone Joint Surg Am.* 2014;96:557-563. doi:10.2106/JBJS.M.00167
  12. Radcliff K, Davis R, Hisey M, et al. Long-term evaluation of cervical disc arthroplasty with the Mobi-C<sup>®</sup> cervical disc: a randomized, prospective, multicenter clinical trial with seven-year follow-up. *Int J Spine Surg.* 2017;11:31. doi:10.14444/4031
  13. Carreon LY, Glassman SD, Campbell MJ, Anderson PA. Neck Disability Index, Short Form-36 Physical Component Summary, and pain scales for neck and arm pain: the minimum clinically important difference and substantial clinical benefit after cervical spine fusion. *Spine J.* 2010;10:469-474.
  14. Parker SL, Godil SS, Shau DN, Mendenhall SK, McGirt MJ. Assessment of the minimum clinically important difference in pain, disability, and quality of life after anterior cervical discectomy and fusion: clinical article. *J Neurosurg Spine.* 2013;18:154-160.
  15. Freedberg DE, Kim LS, Yang YX. The risks and benefits of long-term use of proton pump inhibitors: expert review and best practice advice from the American Gastroenterological Association. *Gastroenterology.* 2017;152:706-715. doi:10.1053/j.gastro.2017.01.031
  16. Yang SD, Chen Q, Wei HK, et al. Bone fracture and the interaction between bisphosphonates and proton pump inhibitors: a meta-analysis. *Int J Clin Exp Med.* 2015;8:4899-4910.
  17. Kwok CS, Yeong JK, Loke YK. Meta-analysis: risk of fractures with acid-suppressing medication. *Bone.* 2011;48:768-776. doi:10.1016/j.bone.2010.12.015
  18. National Institute of Diabetes and Digestive and Kidney Diseases. Treatment for GER & GERD. <https://www.niddk.nih.gov/health-information/digestive-diseases/acid-reflux-ger-gerd-adults/treatment>. Published November 2014. Accessed May 22, 2019.
  19. Alshamsi F, Belley-Cote E, Cook D, et al. Efficacy and safety of proton pump inhibitors for stress ulcer prophylaxis in critically ill patients: a systematic review and meta-analysis of randomized trials. *Crit Care.* 2016;20:120. doi:10.1186/s13054-016-1305-6
  20. Sarges R, Gallagher A, Chambers TJ, Yeh LA. Inhibition of bone resorption by H<sup>+</sup>/K<sup>+</sup>-ATPase inhibitors. *J Med Chem.* 1993;36:2828-2830. doi:10.1021/jm00071a014
  21. Ludwig SC, Boden SD. Osteoinductive bone graft substitutes for spinal fusion: a basic science summary. *Orthop Clin North Am.* 1999;30:635-645.
  22. Vestergaard P, Rejnmark L, Mosekilde L, et al. Proton pump inhibitors, histamine H<sub>2</sub> receptor antagonists, and other antacid medications and the risk of fracture. *Calcif Tissue Int.* 2006;79:76-83. doi:10.1007/s00223-006-0021-7
  23. Kaiser MG, Mummaneni PV, Matz PG, et al. Management of anterior cervical pseudarthrosis. *J Neurosurg Spine.* 2009;11:228-237. doi:10.3171/2009.2.SPINE08729