



## Risk factors for failure of ileal pouch-anal anastomosis in patients with refractory ulcerative colitis

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### ABSTRACT

**Background:** Proctocolectomy with ileal pouch-anal anastomosis is the standard surgical procedure for ulcerative colitis refractory to medical treatment. In a few cases, ileal pouch-anal anastomosis cannot be completed due to intraoperative technical problems. The aim of this single-center study was to identify risk factors for a technically failed ileal pouch-anal anastomosis.

**Methods:** In total, 391 patients with ulcerative colitis who received ileal pouch-anal anastomosis were identified. Clinical and perioperative data from patients with successful ileal pouch-anal anastomosis (IPAA+) were compared to data from failed ileal pouch-anal anastomosis (IPAA-). Definition of failed ileal pouch-anal anastomosis was intraoperative failure to perform ileal pouch-anal anastomosis. Risk factors for failed ileal pouch-anal anastomosis were assessed by logistic regression. Cut-off values were calculated on the basis of receiver operating characteristic curves and the Youden Index.

**Results:** The rate of failed ileal pouch-anal anastomosis was 26 of 391 (6.6%). In 22 of 26 cases (84.6%), there was an insufficient length of the small intestinal mesentery. Patients with failed ileal pouch-anal anastomosis were more often male (80.8% vs 54.5%,  $P = .009$ ), older ( $47.1 \pm 14.1$  vs  $39.2 \pm 12.8$  years,  $P = .007$ ), had a higher body mass index  $27.2 \pm 4.5$  vs  $23.7 \pm 4.3$  kg/m<sup>2</sup>,  $P < .001$ ), and had extraintestinal manifestations more frequently (65.4% vs 26.3%,  $P < .001$ ). Further risk factors for failed ileal pouch-anal anastomosis were hypertension and Cushing's syndrome.

**Conclusion:** Technical failure of ileal pouch-anal anastomosis is elevated in patients with higher body mass index, with refractory ulcerative colitis, and/or extended immunosuppressive medication. Three-staged ileal pouch-anal anastomosis and optimizing preoperative conditions may help to elevate the rate of successful ileoanal pouch construction in these patients.

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### Introduction

Since its initial description more than 40 years ago,<sup>1</sup> proctocolectomy with ileal-pouch anal anastomosis (IPAA) has evolved into the gold standard for the surgical treatment of ulcerative colitis and colitis-associated intraepithelial neoplasia.<sup>2,3</sup> By use of pouch construction and IPAA, stool passage can be reconstructed with

good quality of life, and in many cases lifelong use of an ileostomy can be avoided.<sup>4–6</sup> The procedure has undergone continuous technical evolution, with the J-pouch being today's standard.<sup>7</sup> Furthermore, the operation is often performed laparoscopically or with laparoscopic assistance.<sup>8</sup> According to the current guidelines of the European Crohn and Colitis Organisation,<sup>9</sup> IPAA is performed with a diverting loop ileostomy as a 2-stage procedure, or as a 3-stage procedure in severe cases and long-term pharmacological immunosuppression, with metachronous colectomy, later resection of rectal remnant with IPAA, and diverting loop ileostomy. Regardless of the anastomotic technique, constitutional or technical problems may arise that may render a successful IPAA operation more difficult or even impossible.<sup>10,11</sup> In these cases, the

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procedure ends with terminal ileostomy. The aim of this study was to identify risk factors for a failed IPAA among patients with ulcerative colitis.

## Methods

### Patients

The case-control study included 391 patients who underwent restorative proctocolectomy for histologically confirmed ulcerative colitis from 2000 to 2020 at our tertiary referral center Charité—Universitätsmedizin Berlin, Campus Benjamin Franklin. Indication for surgery was based on the failure of pharmacological therapy, dysplasia, or malignancy, or on acute events (perforation, toxic megacolon, bleeding). If surgery was performed during a high activity of UC or in an emergency setting, a 3-step approach was chosen with colectomy and end ileostomy as the first step. Data were prospectively collected and maintained, whereas we retrospectively analyzed clinical data (age, sex, comorbidities, duration of illness, American Society of Anesthesiologists Physical Status Classification System [ASA], body mass index [BMI], medication).

### Surgical procedures

For planned multistage procedures, a colectomy preserving the ileocolic vessels with end ileostomy and air fistula or blind closure of rectal remnant took place months before the pouch anastomosis. The pouch configuration we used was the ileo-ileal J-Pouch.

The anastomosis was created after complete proctocolectomy preserving the ileocolic vessels by means of transanal access and hand sutures or stapler as a single, double, or triple stage procedure. If anastomosis seemed to be not possible, no IPAA was performed and a terminal ileostomy was created. In cases of multistage procedures, the index operation was defined as the operation that was begun with the intention to perform the IPAA. To achieve a greater length in the mesentery for the IPAA, various options are generally used: (1) complete mobilization of the terminal ileum and the mesenteric root to the superior mesenteric vein and complete mobilization from the ligament of Treitz; (2) incision of the peritoneum of the mesenteric root; (3) mobilization of the liver by dissecting the falciform ligament; and (4) clamping of peripheral vessels to the terminal ileum. If perfusion of the terminal ileum remained intact: ligation of these vessels and severing of the peripheral branches of the superior mesenteric artery, thereby protecting the vascular arcade and the ileocolic artery. Incision of the peritoneal coating of the small intestinal mesentery can create additional length. All these techniques were undertaken in a standardized manner in every case to create additional length. If these techniques failed in creating adequate length, IPAA was not attempted and a terminal ileostomy was created. The ileocolic vessels and the superior mesenteric artery were preserved for the IPAA.

Procedures that were successful on the first attempt were defined as successful IPAA (IPAA+) (control). Operations in which the anastomosis was intraoperatively not technically possible were defined as failed IPAA (IPAA-) (case). The reason for failure of the operation was analyzed using the assessment of the operating surgeon in the operative report. All procedures were performed by 6 colorectal attending surgeons.

### Statistics

Statistical analysis was performed with IBM SPSS, v. 27 (IBM, Armonk, NY). Normality was tested with the Shapiro-Wilk test and showed that most variables were not normally distributed. Unless otherwise indicated, metric data are reported as mean and

**Table 1**

Frequency (n) of the reasons provided by the operating surgeon for ending the attempted IPAA operation

Mesentery too short: due to mesenterial adiposity	15
Mesentery too short: due to inflammatory shortening	12
Narrow pelvis	3
High fragility of tissues	3
Bleeding by portal vein thrombosis	1
Poor blood perfusion	1
Backwash ileitis	1
Mesenterial venous thrombosis	1
Total	35

There were 26 patients with failed IPAA, but for several of them, more than one reason for ending the operation was given.

IPAA, ileal pouch-anal anastomosis.

standard deviation. Categorical variables were compared by means of  $\chi^2$  tests or Fisher exact test. The comparison of the 2 independent samples (IPAA+ versus IPAA-) for continuous variables was performed with Mann-Whitney *U* tests. Risk analysis was performed by means of logistic regression. In a first step, we selected potential covariates by clinical evaluation of a plausible connection to the intraoperative features given in Table 1. To exclude multicollinearity, we used a correlation table and variation inflation factor analysis. The covariates finally included in the model were selected using stepwise forward inclusion based on the likelihood ratio and the Akaike information criterion. The maximum of sensitivity and specificity was determined by means of receiver operating characteristic (ROC) curves (Youden Index: sensitivity + specificity – 1).

### Ethics

The study protocol was approved by the Medical Ethical Committee of Charité—Universitätsmedizin Berlin (EA4/195/20).

## Results

### Patients

The study included a total of 391 patients whose operation was begun primarily with the intention to perform IPAA for UC. Of those, 365 (93.4%) were successful (“IPAA+”) and 26 (6.6%) could not initially be completed with an IPAA as planned (“IPAA-”). If IPAA seemed futile during the index operation, a terminal ileostomy was created. No significant difference in indications for restorative proctocolectomy of the groups IPAA+ versus IPAA- was found ( $P = .789$ ): failure of pharmacological therapy (70.7% vs 73.1%), high-grade dysplasia or neoplasia (20.3% vs 15.4%), and emergency procedures for toxic megacolon, perforation, or ileus (9.0% vs 11.5%). All emergency interventions were performed as 3-stage procedures. In the early years of the study period, there were a total of 7 (1.8%) single-stage operations without diverting loop ileostomy. The portion of 2-stage operations in the groups IPAA+ versus IPAA- was 34.0% vs 65.4%, and the portion of 3-stage operations was 64.1% vs 34.6% ( $P = .005$ ). There were 253 (64.7%) procedures that were performed laparoscopically. Handsewn anastomoses were created in 234 cases (59.8%); however, no stapled anastomosis was used before 2010. The rate of stapled anastomoses between 2010 and 2020 was 157 of 232 (67.7%).

### Risk factors for failed IPAA

In 22 (84.6%) of the 26 unsuccessful operations, it was technically impossible to produce the IPAA free of tension due to a relative

**Table II**

Univariate group comparisons of epidemiological data, procedural details, accompanying illnesses, and medications of the study sample (n = 391) at the time of the restorative proctocolectomy, with success (IPAA+) or failure (IPAA-)

		Prevalence	(%)	Success (IPAA+)	(%)	Failure (IPAA-)	(%)	P value
Total		391	(100)	365	(93.4)	26	(6.6)	
Sex	Male	220	(56)	199	(55)	21	(81)	
	Female	171	(44)	166	(45)	5	(19)	.009
Age	[years]	39.7	±13.0	39.2	±12.8	47.1	±14.1	.007
Time since initial diagnosis	[years]	10.4	±8.8	10.1	±8.5	15.3	±11.2	.026
Indication for IPAA								
Failure of pharm. therapy		277	(71)	258	(71)	19	(73)	
Malignancy		78	(20)	74	(20)	4	(15)	
Emergency		36	(9)	33	(9)	3	(12)	.789
Single-stage		7	(2)	7	(2)	0	(0)	
Two-stage		141	(36)	124	(34)	17	(65)	
Three-stage		243	(62)	234	(64)	9	(35)	.005
Body mass index	[kg/m <sup>2</sup> ]	23.9	±4.4	23.7	±4.3	27.2	±4.5	<.001
Number of comorbidities	[n]	1.0	±1.2	1.0	±1.2	1.5	±1.5	.069
Hypertension		57	(15)	48	(13)	9	(35)	.003
Diabetes		34	(9)	29	(8)	5	(19)	.048
Atrial fibrillation		5	(1)	3	(1)	2	(8)	.003
Extraintestinal Manifestation		113	(29)	96	(26)	17	(65)	<.001
Cushing syndrome		24	(6)	19	(5)	5	(19)	.004
CMV assoc. colitis		22	(6)	18	(5)	4	(15)	.025
Medications currently taken	[n]	0.5	±0.8	0.4	±0.7	1.1	±1.2	.001
Prednisolone		82	(21)	69	(19)	13	(50)	<.001
Azathioprine		21	(5)	16	(4)	5	(19)	.003
5ASA		53	(14)	45	(12)	8	(31)	.015
Prednisolone daily dose		3.4	±10.6	2.7	±9.3	13.1	±19.6	<.001
ASA category	1	15	(4)	15	(4)	0	(0)	
	2	321	(82)	307	(84)	14	(54)	
	3	55	(14)	43	(12)	12	(46)	<.001

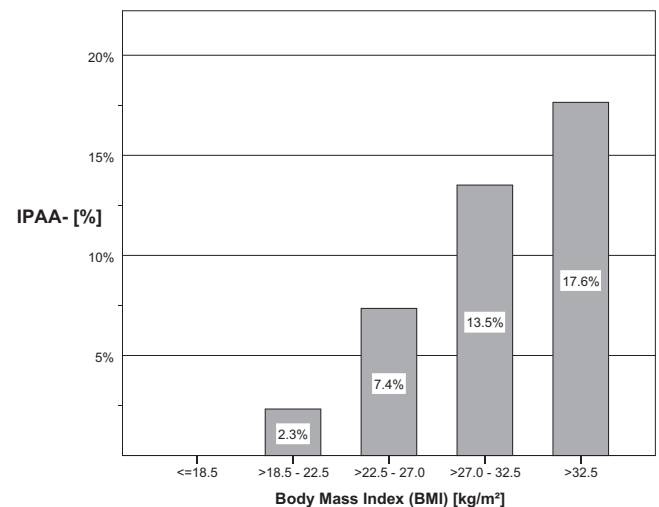
ASA, American Society of Anesthesiologists Physical Status Classification System; CMV, cytomegalovirus-associated colitis; IPAA, ileal pouch-anal anastomosis; IQR, interquartile range.

shortening of the small intestinal mesentery. In 11 cases, more than one reason for the unsuccessful course of the operation was given (Table I).

In univariate group comparisons, sex, age, duration of UC, and BMI were identified as statistically significant risk factors for IPAA- (Table II). There was a rising portion of IPAA- among increasing categories of BMI (P = .004) (Fig 1). IPAA+ and IPAA- differed in terms of the prevalence of arterial hypertension, diabetes, cytomegalovirus-associated colitis, and extraintestinal manifestations of UC (joint involvement, erythema nodosum) and Cushing's syndrome (Fig 2). Patients with failed IPAA were taking more immunosuppressants in general (1.1 ± 1.2 vs 0.4 ± 0.7, P = .001) and had a higher preoperative daily dose of prednisolone than patients with successful IPAA (13.1 ± 19.6 mg/d vs 2.7 ± 9.3 mg/d, P < .001).

In the multivariable logistic regression model, these independent risk factors for an IPAA- were identified: male sex, extraintestinal manifestations of ulcerative colitis, ASA 3, higher BMI, higher prednisolone dose, and higher age. The model fit showed a medium amount of explained variance as shown by Nagelkerke's R-square = 0.379. Goodness of fit was assessed using the Hosmer-Lemeshow test, indicating a good model fit (χ<sup>2</sup> = 6.46, P = .596). The overall percentage of accuracy in classification was 94.1%, with a sensitivity of 26.9% and a specificity of 98.9%. All 6 variables entered into the regression model contributed significantly in predicting IPAA-. All model coefficients and odds can be found in Table III. The area under the curve (AUC) from the receiver operating characteristics (ROC) for the model was 0.886 (95% CI 0.806–0.952).

On the ROC curves for BMI, age, and prednisolone dose, the point with the best relation of sensitivity and specificity was determined (Youden Index) (Fig 3). These values were applied as cut-off values to discriminate between 2 groups of higher and lower risk for operative failure. The maximal discriminatory power

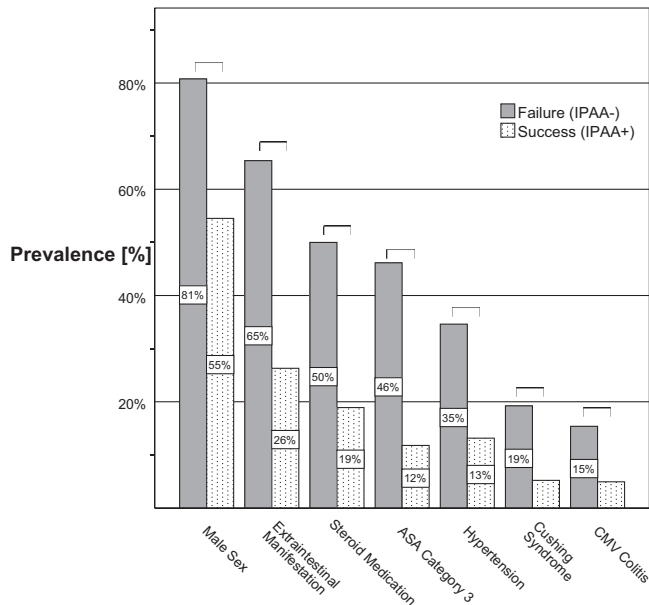


**Fig 1.** The portion of failed operations (% IPAA-) among various ranges of body mass index (BMI). Patients were distributed into 5 BMI categories. IPAA-, failed ileal pouch-anal anastomosis.

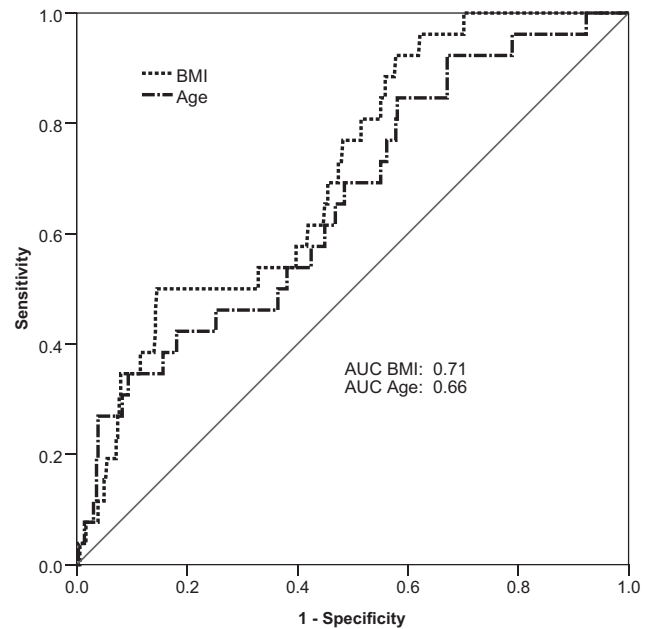
was 27.5 kg/m<sup>2</sup> for BMI, 35 years for age, and 5 mg daily for prednisolone. The risk for a failed IPAA was significantly elevated above these defined cut-off values (Table IV). The AUC was: AUC<sub>BMI</sub> 0.71, AUC<sub>Age</sub> 0.66, AUC<sub>Predni</sub> 0.67.

**Discussion**

Restorative proctocolectomy is the gold standard in the curative treatment of severe UC. In a few cases, the procedure could not be completed successfully because it was impossible to perform IPAA.



**Fig 2.** Comparison of epidemiology, comorbidity, and medication in patients with successful (IPAA+) versus failed (IPAA-) operations. CMV, cytomegalovirus associated colitis; IPAA+, successful ileal pouch-anal anastomosis; IPAA-, failed ileal pouch-anal anastomosis.



**Fig 3.** Receiver operating characteristic (ROC) curves for body mass index (BMI) and age. AUC, area under the curve.

**Table III**  
Multivariable logistic regression analysis of risk factors for a failed IPAA

	B	SE	Wald	Odds ratio	95% CI	P value
Sex (m)	1.403	0.597	5.525	4.066	(1.262–13.096)	.019
Extraintestinal manifestation	1.954	0.522	14.011	7.056	(2.537–19.629)	<.001
ASA category 3	1.422	0.505	7.919	4.147	(1.540–11.166)	.005
Body mass index (BMI)	0.157	0.055	8.122	1.170	(1.050–1.304)	.004
Prednisolone daily dose	0.037	0.012	9.245	1.037	(1.013–1.062)	.002
Age	0.047	0.020	5.459	1.048	(1.008–1.091)	.019

The model coefficients and odds for the continuous variables (BMI [kg/m<sup>2</sup>], age [years], and prednisolone daily dose [mg/d]) refer to a change of 1 unit. Degrees of freedom were 1 for all Wald statistics.

B, regression coefficient B; BMI, body mass index; CI, confidence interval; SE, standard error.

This study aimed to analyze reasons and risk factors for intraoperative failure of IPAA.

In this retrospective, single-center study, we showed that planned IPAA could not be completed in 6.6% of the patients with ulcerative colitis. Male sex, arterial hypertension, extraintestinal manifestations of the disease, ASA class III, elevated BMI, and elevated prednisolone daily dose were identified as independent risk factors. Cut-off scores of 27.5 kg/m<sup>2</sup> for BMI, 35 years for age, and 5 mg/day for prednisolone dose were calculated. Above these cut-off scores, the risk for a failed IPAA was significantly increased. This distinction can be helpful in advising and making responsible shared decisions with patients and should not be regarded as sharp discrimination between 2 groups of high risk and low risk.

Performing an IPAA free of tension is a critical step in the procedure.<sup>12</sup> Technical difficulties can be caused by a shortened or thickened mesentery,<sup>13</sup> which also was the leading issue in this study, either by adiposity or inflammation. Scoring the peritoneum and selective arterial ligation under preservation of the mesenteric arterial arcade is essential for elongation of the mesentery; branches of the superior mesenteric artery and ileocolic artery may be divided if necessary and in case of sufficient vascular collateralization.<sup>14</sup> In our study cohort, the intended IPAA could not be performed in 6.6% mainly because the mesentery of the small

intestine was too short. In other studies, a lower failure rate of 4% is reported.<sup>15</sup> One reason for this difference could be the higher age of our patients, and thus also a longer duration of illness and more comorbidity. Previous reports showed an increasing risk of failed IPAA procedures rising from ages 40 upward.<sup>11</sup> Advantages in regard to the complication rate and long-term outcomes have been shown for the 3-stage procedure, particularly in cases of acute operations among high-dose pharmacological immunosuppression.<sup>16–18</sup> In addition, we were able to show that a successful IPAA benefits from a 3-stage procedure. A possible explanation could be that in a 3-staged concept, the IPAA is performed under less disease activity and more often under freedom from immunosuppressive medication, thus leading to less mesenteric edema.

Patients with failed IPAA were predominantly male. It is known that operations in the male pelvis are more demanding due to the tight anatomical conditions.<sup>19</sup> In addition to the inflammatory shortening of the mesentery, the fat distribution in the mesentery, which is typical for men with a thickened mesenteric root, may lead to problems when performing the IPAA.

A higher BMI represents another independent risk factor for technical problems and postoperative morbidity in visceral surgery. A higher rate of complications after pouch operations was reported

**Table IV**

Determination of the Youden index (sensitivity + specificity – 1) and the cut-off value

	Sensitivity	Specificity	Youden Index	Cut-off value	P value
BMI	0.500	0.855	0.355	27.5 kg/m <sup>2</sup>	<.001
Age	0.846	0.419	0.265	35 years	.023
Prednisolone Daily dose	0.500	0.825	0.325	5 mg	.001

The risk for a failed IPAA was significantly increased above this cut-off value.

BMI, body mass index; IPAA, ileal pouch-anal anastomosis.

in patients with high BMI.<sup>20,21</sup> Furthermore, the conversion rate during laparoscopically assisted IPAA is elevated among patients with a high BMI.<sup>8</sup> In our patients, we were able to show that an elevated BMI raises the risk for a failed IPAA.

The effect of immunosuppressives and steroids on the rate of complications and the success of IPAA is debated in the literature. TNF-alpha blockers appear to have only a small influence on postoperative morbidity.<sup>22,23</sup> Use of these immunosuppressives was not associated with a negative influence on the success rate of IPAA in our study. By contrast, long-term therapy with steroids at high doses is associated with an elevation of septic complications and a worse long-term function.<sup>24,25</sup> Concerning the perioperative medication with corticosteroids, a cut-off value was identified in our study at 5 mg/day, as the point of optimal sensitivity and specificity to discriminate between 2 groups of higher and lower risk for a failure of the IPAA. The perioperative steroid dose thus represents a potential risk factor, not only for the postoperative period but also for the success of the IPAA procedure.

One limitation of the present study is the retrospective design. Furthermore, we note that the number of IPAA- ( $n = 26$ ) is low compared with the overall size. Thus, estimation issues due to the rather strong imbalance might be apparent and the regression model might be unstable in means of its predictive quality. Since the number of events is low, we performed Firth's bias corrected logistic regression analysis. The results are almost identical. However, the results of this study should be validated in larger subsequent trials, thereby avoiding overfitting. A strength of the study is the homogenous way of diagnosing and treating UC, owing to the single-center setting in a tertiary referral center for inflammatory bowel disease.

Future studies are necessary to investigate whether the risk for failure may be predicted preoperatively in more detail, for example, by measuring the length of the mesentery preoperatively via CT scan.<sup>26</sup> Furthermore, prospective studies are needed to further evaluate the suggested cut-off scores.

In summary, we identified several independent risk factors that are associated with failed IPAA in patients with refractory ulcerative colitis. These risk factors have a plausible connection to mesenteric shortening, which was the main technical reason for failed IPAA. Optimizing preoperative conditions, such as obesity, inflammation, and immunosuppressive medication, may help to elevate the rate of patients with successful ileoanal pouch construction.

### Funding/Support

None declared.

### Conflict of interest/Disclosure

The authors declare that they have no competing interests.

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The data collection was done by reviewing the electronic health records at the Charité Universitätsmedizin Berlin. Relevant data

were collected in Microsoft Excel and analyzed descriptively. The data are stored on the Charité server and, to avoid a violation of access rights, the data are encrypted using a password only known to the study physicians. The data that support the findings of this study are available, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are, however, available from the authors upon reasonable request.

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