

Patterns and predictive factors of complications after endoscopic retrograde cholangiopancreatography

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Background: With an increased use of magnetic resonance imaging, the indications for endoscopic retrograde cholangiopancreatography (ERCP) have changed. Consequently, the patterns and factors predictive of complications after ERCP performed during current routine clinical practice are not well known.

Methods: A prospective multicentre cohort study was undertaken in 11 Norwegian hospitals. Complications and mortality within 30 days after ERCP were analysed by univariable and multivariable regression analysis.

Results: There were 2808 ERCP procedures, of which 2573 (91.6 per cent) were therapeutic. More than half of the patients were aged 70 years or more. Common bile duct cannulation was achieved in 2557 procedures (91.1 per cent). Complications occurred in 327 (11.6 per cent) of the procedures, including cholangitis in 100 (3.6 per cent), pancreatitis in 88 (3.1 per cent), bleeding in 66 (2.4 per cent), perforation in 25 (0.9 per cent) and cardiovascular-respiratory events in 32 (1.1 per cent). In the multivariable regression analysis, older age, increasing American Society of Anesthesiologists fitness score, centre ERCP volumes of more than 150 procedures annually and precut sphincterotomy were predictive factors for severe complications. The overall 30-day mortality rate was 2.2 per cent (63 patients), with a procedure-related mortality rate of 1.4 per cent (39 patients). Malignancy was diagnosed in 46 (73 per cent) of the patients who died.

Conclusion: ERCP is a procedure with considerable risk for complications. Morbidity and mortality are related to patient age and co-morbidity, as well as hospital volume of ERCP procedures and the type of intervention.

Paper accepted 27 September 2012

Published online 6 December 2012 in Wiley Online Library (www.bjs.co.uk). DOI: 10.1002/bjs.8992

Introduction

In recent years various clinical features of endoscopic retrograde cholangiopancreatography (ERCP), including technical performance and complications^{1–4}, quality assessment^{5–8} and aspects of education⁹, have been addressed. However, outcomes reported from highly dedicated centres do not necessarily mirror general ERCP practice². To evaluate complications and possible risk factors for these complications in unselected populations, several multicentre studies have been performed^{3,4,10–17}. Nevertheless, a number of concerns, including study design

and differences in study populations, definitions and their interpretations, as well as the quality and completeness of the registrations, make it difficult to evaluate and compare reported figures in the various studies¹⁸. A meta-analysis of patient-, procedure- or operator-dependent factors associated with ERCP complications has supported these concerns¹⁹.

The evaluation of general ERCP practice remains important because of possible changes over time, such as the implementation of other imaging modalities, and different clinical traditions across continents, as well as

changes in demographics or the disease spectrum. Quality indicators in ERCP, as described⁶, illustrate the need for a consecutive and consistent documentation of daily practice including outcome measures to assess quality.

The true incidence and pattern of ERCP complications in a general hospital or clinical practice remain unclear. The main objective of this study was to evaluate complication patterns and rates in routine ERCP practice over a time interval in a representative selection of Norwegian hospitals. A secondary aim was to identify possible risk factors for these complications.

Methods

As part of a national quality assurance programme for endoscopic activity in Norway, a system for voluntary reporting of consecutive ERCP procedures performed at Norwegian hospitals was designed, elaborating on the existing Gastronet quality network²⁰. Gastronet is a national quality assurance network for gastrointestinal endoscopy and the official quality assurance platform for the Norwegian Gastroenterological Association. In 2006, 35 Norwegian hospitals had an ERCP service²¹; these hospitals were invited to report consecutive data to a clinical database designed for prospective multicentre registration.

Study population and selection

All patients aged 18 years or more scheduled for ERCP were included in the study. Information on the total number of ERCP procedures performed at each hospital during the study interval was available²¹. Updated activity numbers were supplemented and confirmed by each participating endoscopy unit. During the 36-month study period, hospitals started to report prospectively at different time points. Consequently, several hospitals reported ERCP activity for a shorter time interval. To ensure valid data from each hospital, for inclusion in the study at least 75 per cent of the consecutive procedures performed for the duration of participation were required to be reported.

The study was approved by the Norwegian Social Science Data Service and the National Data Inspectorate, with no request for individual informed consent, but anonymization of the data. The study is part of the Gastronet quality assurance programme. Further evaluation and approval by the Regional Ethics Committee for Medical and Health research was not required.

Data collection

Primary data, which consisted of ERCP procedural details, complications and undesirable events during the procedure

or within the 30-day follow-up period, were recorded prospectively and reported consecutively to the registry. Hospital records and notes from the outpatient clinic were reviewed for completeness of data by a designated endoscopist.

Interpretation, evaluation of reports and definitions

Patients were categorized according to the American Society of Anesthesiologists (ASA) physical status classification system²². When several complications occurred in the same patient, the most severe complication was used for grading. Procedure-related mortality was evaluated and categorized as follows: death within 48 h after a procedure with complications or incomplete endoscopic treatment (for example, relief of bile duct obstruction was not achieved by the intervention) was regarded as a procedure-related death. Death between the second and seventh day after a procedure was classified as probably linked to the procedure. If death occurred more than 1 week after ERCP, the association to the procedure was recorded as uncertain unless there was obvious evidence for this. In patients who had more than one ERCP procedure, the time to death was calculated from the date of the last ERCP.

Endoscopic retrograde cholangiopancreatography

ERCP was defined as an endoscopic procedure with intention to cannulate the bile duct and/or pancreatic duct, and to visualize the ducts with a contrast medium. Intended ERCP with failure to cannulate was reported as an ERCP procedure.

Precut sphincterotomy

Any precannulation diathermy cut to the sphincter to gain ductal access, regardless of the method employed, was considered a precut sphincterotomy.

Complications and grading

A complication was defined as a condition or event unfavourable to the patient's health, causing irreversible damage, or requiring a change in therapeutic policy that occurred in relation to the procedure and during the first 30 days after ERCP²³. Complications were categorized and graded according to Cotton *et al.*²⁴. In addition, all complications were reclassified retrospectively according to the Dindo–Clavien classification²⁵.

Statistical analysis

Median values are given with the interquartile range (i.q.r.). χ^2 test or Fisher's exact test was applied

when appropriate to compare categorical variables, and the Mann–Whitney U test was used for continuous variables. Risk factors were analysed by univariable logistic regression analysis. Variables with $P < 0.250$ in univariable analyses were included in the multivariable logistic regression modelling. Both stepwise forward and backward selection procedures were performed to identify variables included in the final model. Case-wise deletion of cases with missing values was used. Goodness-of-fit was verified by the Hosmer–Lemeshow test. Independent analyses were performed for: cholangitis, pancreatitis, bleeding, perforation, cardiovascular–respiratory events, complications with severity grade 3 according to the Cotton classification²⁴ and complications graded 3–5 according to the Dindo–Clavien classification²⁵. Risk is presented as odds ratios (ORs) with 95 per cent confidence intervals (c.i.). All test results were two-tailed, and statistical significance was defined as $P < 0.050$. PASW Statistics version 18.0 for Mac (IBM, Armonk, New York, USA) was used for statistical analysis.

Results

Completeness of data

Among the 35 hospitals with an ERCP service at that time, 14 hospitals eventually reported to the Gastronet registry between January 2007 and December 2009. Eleven hospitals met the inclusion criteria with respect to completeness of reporting data: two university hospitals, five central hospitals and four general district hospitals. A total of 2808 ERCP procedures were available for evaluation – 94.6 per cent of the 2968 ERCPs performed in the 11 hospitals included in the study.

Demographics and procedural characteristics

Some 1546 (55.1 per cent) of the 2808 ERCP procedures were done in women. Some 478 procedures (17.0 per cent) were performed in patients younger than 50 years, and in 1509 (53.9 per cent) the patient was aged 70 years or more. Increased co-morbidity, indicated by an ASA fitness score of III or higher, was found in 846 patients (30.1 per cent). Most patients received either intravenous midazolam or diazepam as single drugs or in combination with pethidine. Deep sedation was reported with propofol in 28 procedures (1.0 per cent) and with general anaesthesia in 43 (1.5 per cent). The procedures were performed by a total of 48 endoscopists. Median procedure time was 25 (i.q.r. 18–40) min, and 56 (2.0 per cent) of the ERCPs were completed as emergency procedures outside normal working hours.

Indications, findings, procedures and success rates

The main indications were various therapeutic interventions to the bile ducts in 2573 (91.6 per cent) of the procedures. Specific treatment of pancreatic disease was reported for 38 procedures (1.4 per cent), and therapeutic interventions on the papilla of Vater, including relief of suggested sphincter of Oddi dysfunction, for 32 (1.1 per cent) of the ERCP procedures.

Bile duct obstruction, including common bile duct (CBD) stones in 1359 procedures (48.4 per cent) and bile duct strictures in 892 (31.8 per cent), were the most common findings. Normal bile ducts were reported for 287 ERCPs (10.2 per cent). However, an endoscopic sphincterotomy (EST) was performed in 170 of these ‘normal’ ERCPs, and brush cytology in 16. Thus, the number of ERCP procedures with ‘true’ normal bile ducts, 101 (3.6 per cent), was low.

Sphincterotomy of the bile duct was performed in 1525 (54.3 per cent) of the ERCPs. Placement or exchange of a CBD endoprosthesis was done in 790 (28.1 per cent) and 303 (10.8 per cent) of the ERCPs respectively. Biopsy/cytology was reported for 237 procedures (8.4 per cent), and evaluation or treatment of postoperative complications prompted ERCP in 15 (0.5 per cent). Various treatments for pancreatic diseases or conditions related to the papilla of Vater were employed in 38 (1.4 per cent) and 32 (1.1 per cent) of the procedures respectively. Successful cannulation of the CBD was achieved in 2557 procedures (91.1 per cent). The papilla was pre-cut in 144 ERCPs (5.1 per cent), with subsequent successful CBD cannulation in 103 (71.5 per cent). A guidewire was used for cannulation in 1912 (68.1 per cent) of the procedures, and in 634 (22.6 per cent) carbon dioxide was used. Cannulation of the pancreatic duct was intended in 103 ERCPs (3.7 per cent), and unintended cannulation (contrast injection or catheter/wire insertion) was reported in 522 (18.6 per cent).

Complications

Complications were reported in 327 (11.6 per cent) of the 2808 procedures. More than one complication occurred in 13 ERCPs. The most common complications are summarized in *Table 1*. Sixty-three patients died during the 30-day follow-up, giving a mortality rate of 2.2 per cent (*Fig. 1*). A diagnosis of malignancy was confirmed in 46 (73 per cent) of these patients. Based on available information, 39 patients (1.4 per cent) died from ERCP-related causes (probable relationship with ERCP, 35; possible association, 4). The remaining 24 patients died from unrelated causes.

Table 1 Frequency and grading* of common complications after endoscopic retrograde cholangiopancreatography

	No. of complications				
	Total†	Mild	Moderate	Severe	Fatal
Cholangitis	100 (32.2)	66 (66.0)	15 (15.0)	8 (8.0)	11 (11.0)
Pancreatitis	88 (28.3)	69 (78)	12 (14)	7 (8)	0 (0)
Bleeding	66 (21.2)	44 (67)‡	14 (21)	6 (9)	2 (3)
Cardiovascular–respiratory complications	32 (10.3)	10 (31)	6 (19)	5 (16)	11 (34)
Perforation	25 (8.0)	6 (24)	9 (36)	7 (28)	3 (12)

Values in parentheses are percentages. *Complications were graded according to Cotton *et al.*²⁴. †A total of 311 of the most common complications were recorded; the frequency of each complication is calculated from the total number of these five common complications. ‡Includes 33 cases of bleeding during the procedure with no clinical consequences; bleeding during and after the procedure was observed in six patients.

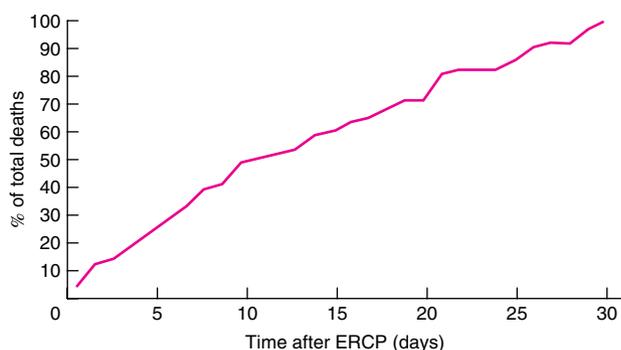


Fig. 1 Cumulative deaths during the first 30 days after 2808 endoscopic retrograde cholangiopancreatography (ERCP) procedures. Half of the deaths occurred within the first 10 days

Unsuccessful ERCP as a result of duct cannulation failure was reported for 12 (19 per cent) of the 63 procedures with a fatal outcome, and one (1.6 per cent) therapeutic procedure failed despite successful cannulation.

A precut sphincterotomy (EST) was done in 144 procedures, of which ten (6.9 per cent) involved severe or fatal complications.

Factors predictive of severe complications and death

Increasing age, ASA score of III or IV, precut EST and an ERCP centre volume of more than 150 procedures annually were predictive factors for an increased risk of severe complications according to the Cotton classification²⁴ (Table 2). Endoscopic treatment of CBD stones was associated with low risk. According to the Dindo–Clavien classification²⁵, 101 (30.9 per cent) of the complications were classified as severe (Dindo–Clavien grade 3–5) (Table 3).

Pancreatitis

Post-ERCP pancreatitis (PEP) was reported after 88 procedures (3.1 per cent), with severe pancreatitis in seven

Table 2 Multivariable regression analysis of independent risk factors for severe or fatal complications after endoscopic retrograde cholangiopancreatography according to the classification of cotton *et al.*²⁴

	Severe or fatal complications (n = 67)*	All procedures (n = 2808)†	Odds ratio	P
Age group (years)				< 0.001
70–89	39	1379	1.00 (reference)	
< 30	0	104	0.00	0.997
30–49	2	374	0.13 (0.08, 1.01)	0.051
50–69	12	812	0.46 (0.23, 0.91)	0.026
≥ 90	14	130	4.36 (2.18, 8.73)	0.001
ASA fitness score				< 0.001
I	4	650	1.00 (reference)	
II	21	1270	2.09 (0.61, 7.17)	0.243
III	26	756	3.26 (0.95, 11.16)	0.060
IV/V	16	90	25.27 (6.90, 92.56)	< 0.001
Precut EST	10	144	3.01 (1.42, 6.38)	0.004
> 150 ERCPs annually	42	1393	1.74 (1.02, 2.98)	0.043
Treatment of CBD stones	13	1215	0.46 (0.23, 0.87)	0.018

Values in parentheses are 95 per cent confidence intervals. *Corresponds to grade 3 according to the classification of Cotton *et al.*²⁴. †A total of 2675 procedures were included in the multivariable regression analysis. ASA, American Society of Anesthesiologists; EST, endoscopic sphincterotomy; ERCP, endoscopic retrograde cholangiopancreatography; CBD, common bile duct.

Table 3 Multivariable regression analysis of risk factors for severe or fatal complications after endoscopic retrograde cholangiopancreatography according to the Dindo–Clavien classification²⁵

	Severe or fatal complications (n = 101)*	All procedures (n = 2808)†	Odds ratio	P
Age group (years)				< 0.001
70–89	57	1379	1.00 (reference)	
< 30	3	104	0.91 (0.27, 3.07)	0.873
30–49	4	374	0.23 (0.07, 0.75)	0.015
50–69	22	812	0.60 (0.36, 1.01)	0.056
≥ 90	15	130	3.04 (1.61, 5.75)	0.001
ASA fitness score				< 0.001
I	15	650	1.00 (reference)	
II	37	1270	1.04 (0.54, 2.00)	0.897
III	33	756	1.35 (0.68, 2.66)	0.387
IV/V	16	90	8.67 (3.87, 19.41)	< 0.001
Precut EST	12	144	2.50 (1.30, 4.80)	0.006
> 150 ERCPs annually	70	1393	2.45 (1.56, 3.84)	0.043
Use of guidewire	60	1912	0.59 (0.39, 0.91)	0.016

Values in parentheses are 95 per cent confidence intervals. *Grade 3–5 according to the Dindo–Clavien classification²⁵. †A total of 2675 procedures were included in the multivariable regression analysis. ASA, American Society of Anesthesiologists; EST, endoscopic sphincterotomy; ERCP, endoscopic retrograde cholangiopancreatography.

Table 4 Multivariable regression analysis of risk factors for pancreatitis after endoscopic retrograde cholangiopancreatography

	Patients with pancreatitis (n = 88)	All procedures (n = 2808)	Odds ratio	P
Significant only in univariable analysis				
Use of guidewire	70	1912	1.74 (1.03, 2.94)	0.038
Total procedure time	88	2732	1.01 (1.00, 1.02)	0.044
Significant in multivariable analysis*				
ASA fitness score				0.036
I	29	650	1.00 (reference)	
II	42	1270	0.71 (0.43, 1.17)	0.181
III	13	756	0.39 (0.20, 0.77)	0.006
IV/V	4	90	1.26 (0.43, 3.74)	0.676
Precut EST	12	144	2.82 (1.47, 5.38)	0.002
> 150 ERCPs annually	54	1393	1.70 (1.08, 2.69)	0.023
Pancreatic duct stent placement	3	27	1.88 (1.01, 3.51)	0.047
Biliary stent exchange	2	303	0.23 (0.06, 0.93)	0.039

Values in parentheses are 95 per cent confidence intervals. *A total of 2612 procedures were included in the multivariable regression analysis. ASA, American Society of Anesthesiologists; EST, endoscopic sphincterotomy; ERCP, endoscopic retrograde cholangiopancreatography.

(8 per cent) of these patients (Table 1). No deaths were reported.

In the multivariable regression analysis, precut EST, pancreatic duct stent placement and an annual ERCP centre volume of more than 150 procedures were independent predictors of PEP (Table 4). In addition, comorbidity as assessed by the ASA fitness score predicted a risk of developing PEP. Biliary stent exchange procedures had a low risk for PEP.

Perforation

Perforation was reported in 25 (0.9 per cent) of the procedures; three patients died during follow-up (Table 1).

In the multivariable regression analysis, removal of a CBD stent was the only predictive factor for an increased risk of perforation (OR 4.80, 95 per cent c.i. 1.72 to 13.41; $P = 0.003$). Although not statistically significant, precut EST (OR 3.47, 0.99 to 12.15; $P = 0.052$) could also be of clinical importance.

Predictors of other complications

Independent predictors of cholangitis were CBD stent removal (OR 3.67, 2.11 to 6.39; $P < 0.001$), more than 150 ERCPs annually per centre (OR 3.27, 2.00 to 5.43; $P < 0.001$), CBD stent placement (OR 2.32, 1.51 to 3.57; $P < 0.001$) and CBD stent exchange (OR 1.93, 1.07 to 3.47;

$P = 0.028$). Women had a decreased risk of developing cholangitis (OR 0.61, 0.40 to 0.94; $P = 0.023$). Bleeding was independently predicted by EST (OR 4.09, 2.12 to 7.91; $P < 0.001$), as was age 50 years or above, especially pronounced in patients aged 90 years or more. In addition, prolonged procedure time predicted bleeding ($P = 0.022$), particularly for procedures of 41–60 min.

Cardiovascular–respiratory events were predicted in centres with an annual volume of more than 150 procedures (OR 4.02, 1.69 to 9.54; $P = 0.002$), and when a CBD stent was placed (OR 2.86, 1.36 to 6.01; $P = 0.005$). The risk increased with age, especially in patients aged 90 years or more. Thirty of the 32 patients for whom a cardiorespiratory event was recorded were aged 70 years or above. Use of a guidewire predicted a decreased risk of cardiorespiratory events (OR 0.39, 0.19 to 0.80; $P = 0.011$).

Discussion

This study showed an increased risk of complications after ERCP in patients with greater age and higher ASA fitness score, and when a precut sphincterotomy was performed. An increased risk of severe complications was observed in centres with an annual ERCP volume of more than 150 procedures. Death occurred in approximately one in ten patients who developed complications or had failed cannulation of the bile duct. The majority of patients who died had a malignant disease. The risk of developing PEP was increased in patients without co-morbidity, and the risk of bleeding following EST increased with age.

The observed age and sex distributions, and indications for ERCP, were comparable with those in other European studies^{3,8,13,15}. In contrast to reports from North America^{2,10,26}, a low prevalence of young female patients with suspected sphincter of Oddi dysfunction was encountered. The observed technical success rate of 91.1 per cent in this study is in agreement with recent reports and suggested guidelines^{5,6,9}.

The observed overall morbidity rate was 11.6 per cent and 30-day mortality 2.2 per cent; half of the deaths were related directly to the ERCP procedure. Although these results are similar to others^{1,3,8,10,13–15,26–29}, reported complication rates range from 4.0 to 12.6 per cent in prospective multicentre studies^{3,4,10–15}. A recent population-based Swedish study with follow-up data provided from governmental databases reported a 30-day mortality rate of 5.9 per cent¹⁵, which corresponds well with the 5.8 per cent rate reported from a single-centre Danish study²⁸.

The likelihood of complications after ERCP has been linked to a number of risk factors. Unfortunately, recent studies have only in part analysed the same variables^{2–4,10,13,14,28,30}. In the present study, treatment of CBD stones decreased the risk of complications, in contrast to the findings of Cotton and colleagues², who reported a significantly increased risk of fatal complications in patients with suspected or known CBD stones. Precut EST seems to be a common risk factor across studies^{3,4,10,14}. In the present study, 12 (19 per cent) of the 63 deaths within 30 days of ERCP occurred in patients with failed cannulation. As shown in a recent paper³¹, the success rate of cannulation following precut EST is only 71.5 per cent. Patients with cannulation failure and damage of the papilla from a precut are at increased risk of worse outcome. Severe or fatal complications were observed in 6.9 per cent of the procedures after a precut EST, which was a significant predictor of severe complications. According to a recent meta-analysis, precutting does not increase the cannulation rate, but may reduce the incidence of PEP³².

In contrast to other studies^{3,12}, complication rates in the present study were not related to lower annual ERCP procedure volumes. A possible association between the annual procedure volume of a centre and complications should be interpreted with caution. Observations may be biased by a number of factors, including case mix and referral patterns, differences in endoscopists' experience and treatment traditions, safety culture³³ and, finally, whether the ERCP service offers an educational programme for specialist training.

The incidence of PEP varies between 1.3 and 5.1 per cent, as reported in nine prospective multicentre studies^{3,4,10,12,14,15,26,30,34}, with an incidence of 2.6 per cent reported from a large single-centre study² and 3.5 per cent in a recent systematic review¹. These results are similar to the 3.1 per cent incidence of PEP found in the present study. The observation of an increased risk of PEP in healthy patients (ASA grade I) has not been reported previously. Precut EST was found to be an independent risk factor for PEP in this study, in agreement with other studies^{11,14,26,34}. However, in a recent meta-analysis, early precutting was found to reduce the risk of pancreatitis, whereas the total number of complications remained the same³⁵.

A large proportion of the patients referred for ERCP are elderly, with significant co-morbidity, often in need of palliative endoscopic treatment for known malignant disease. For various reasons, a short hospital stay is necessary. Therefore, the definitions and grading of ERCP complications suggested by Cotton and co-workers²⁴ two decades ago are not well suited to the current clinical

practice in many European countries. Approximately 40 per cent of ERCP procedures in Norway are performed by surgeons²¹, and it is suggested that the Dindo–Clavien classification of surgical complications may be used for other invasive procedures, such as ERCP. However, based on the retrospective reclassification of complications, the pattern of severe complications according to the Dindo–Clavien grading was similar to that observed with the Cotton classification.

With almost 3000 procedures included in this study, there is a high statistical power in many of the analyses. However, rare complications were also considered in the logistic regression modelling and this limits the statistical power. Main analyses provided complication rates of around 3 per cent, which implies a power of at least 80 per cent for detecting an OR of 1.75 or more for binary explanatory variables. The significant effects found in the logistic regression models in this study are likely to be of clinical relevance. Owing to the large number of tests performed, it is acknowledged that some statistically significant results may have been obtained by chance.

A strength of this multicentre study is that all types of hospital were represented, and the distribution of hospitals with an ERCP service is in line with the overall national hospital pattern²¹. Only factors of clear clinical importance were included in the study. A careful 30-day follow-up enabled the collection of high-quality data for patients discharged from hospital, which was not always the case in other studies.

Acknowledgements

This study was organized and coordinated by Gastronet, and the contributions made by staff and nurses at each participating ERCP unit and by Gastronet secretaries are much appreciated.

The Regional Health Trust of Southeastern Norway and Regional Health Trust of Western Norway provided financial support to Gastronet. In addition, support and partial funding was offered by the Norwegian Gastroenterological Association and Folke Hermansens Cancer Research Fund (grant no. 424501), Stavanger, Norway.

Disclosure: The authors declare no conflict of interest.

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