Silver Nitrate–coated versus Standard Indwelling Pleural Catheter for Malignant Effusions
The SWIFT Randomized Trial

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Abstract

Rationale: Tunneled, indwelling pleural catheters (IPCs) have been demonstrated to be an effective method of managing malignant pleural effusions. However, they allow pleurodesis and can therefore be removed in only a subset of patients. A novel, silver nitrate–coated IPC was developed with the intention of creating a rapid, effective chemical pleurodesis to allow more frequent and earlier catheter removal. This study represents the pivotal clinical trial evaluating that catheter versus the standard IPC.

Objectives: To compare the efficacy of a novel silver nitrate–eluting indwelling pleural catheter (SNCIPC) with that of a standard, uncoated catheter.

Methods: The SWIFT [A Pivotal Multi-Center, Randomized, Controlled, Single-Blinded Study Comparing the Silver Nitrate-Coated Indwelling Pleural Catheter (SNCIPC) to the Uncoated PleurX® Pleural Catheter for the Management of Symptomatic, Recurrent, Malignant Pleural Effusions] trial was a multicenter, parallel-group, randomized, controlled, patient-blind trial. Central randomization occurred according to a computer-generated schedule, stratified by site. Recruitment was from 17 secondary or tertiary care hospitals in the United States and 3 in the United Kingdom and included adult patients with malignant pleural effusion needing drainage, without evidence of lung entrapment or significant loculation. The intervention group underwent insertion of an

SNCIPC with maximal fluid drainage, followed by a tapering drainage schedule. The control group received a standard, uncoated catheter. Follow-up was conducted until 90 days. The primary outcome measure was pleurodesis efficacy, measured by fluid drainage, at 30 days.

Results: A total of 119 patients were randomized. Five withdrew before receiving treatment, leaving 114 (77 SNCIPC, 37 standard IPC) for analysis. The mean age was 66 years (standard deviation, 11). More patients in the SNCIPC group were inpatients (39% vs. 14%; $P = 0.009$). For the primary outcome, pleurodesis rates were 12 (32%) of 37 in the control group and 17 (22%) of 77 in the SNCIPC group (rate difference, -0.10; 95% confidence interval, -0.30 to 0.09). Median time to pleurodesis was 11 days (interquartile range, 9 to 23) in the control group and 4 days (interquartile range, 2 to 15) in the SNCIPC group. No significant difference in treatment-related adverse event rates was noted between groups.

Conclusions: The SNCIPC did not improve pleurodesis efficacy compared with a standard IPC. This study does not support the wider use of the SNCIPC device.

Clinical trial registered with www.clinicaltrials.gov (NCT02649894).

Keywords: pleurodesis; ambulatory; outpatient; malignant pleural effusion; drainage

Malignant pleural effusion (MPE) is estimated to affect in excess of 750,000 people each year across Europe and the United States (1, 2). MPE commonly leads to significant dyspnea and recurs without definitive therapy. The use of pleurodesis agents (such as graded talc or silver nitrate) effectively reduces the chances of recurrence and further intervention after a single treatment but requires an inpatient stay of several days and requires there to be sufficient pleural apposition present (3). Rarely, they may also be associated with systemic inflammatory reactions (4–6).

By contrast, an indwelling pleural catheter (IPC) is typically placed on an outpatient basis using local analgesia, allowing repeated drainage of pleural effusions at home using vacuum bottles. IPCs are now commonplace and provide excellent effusion and symptom control (5). However, they do not reliably lead to pleurodesis, meaning they may have to remain in place for the remainder of a person's life. When spontaneous "autopleurodesis" does occur, it may take many weeks to develop (7, 8).

Recently, a novel silver nitrate–coated indwelling pleural catheter (SNCIPC) was developed to address some of the shortcomings of an uncoated IPC (9). The silver nitrate coating was designed to gradually elute from the catheter surface, with the hope that it would lead to an effective, rapid pleurodesis but with fewer acute inflammatory complications. For those

who do not achieve pleurodesis once the drug has eluted, the device functions as a normal IPC and can be drained as required. After successful animal studies (10), a small-scale, outpatient, phase I trial of the SNCIPC suggested an acceptable safety profile in humans and a pleurodesis profile comparable to that of inpatient methods (11).

Here, we describe a randomized phase II trial designed to determine whether pleurodesis efficacy with the SNCIPC was superior to that of a standard, uncoated IPC for the treatment of MPE.

Methods

Trial Design

The SWIFT [A Pivotal Multi-Center, Randomized, Controlled, Single-Blinded Study Comparing the Silver Nitrate-Coated Indwelling Pleural Catheter (SNCIPC) to the Uncoated PleurX® Pleural Catheter for the Management of Symptomatic, Recurrent, Malignant Pleural Effusions] study was an international, multicenter, randomized, placebo-controlled, patient-blind, parallel group superiority trial. Ethical approval for recruitment was obtained from local institutional review boards for U.S. sites and the Central Research Ethics Committee for UK National Health Service sites. Appropriate national regulatory approvals were gained (IDE G150146 and EudraCT CIV-GB-16-07-

016364 for the United States and the United Kingdom, respectively) before study initiation. The study was registered with www.clinicaltrials.gov (NCT02649894), with the full protocol made available (12).

Setting and Participants

The trial recruited from 17 hospitals in the United States and 3 in the United Kingdom. Potential participants were identified from local centers' pulmonary and thoracic surgical inpatient and outpatient services. Patients were eligible if *1*) they had a proven (or suspected) free-flowing MPE to be managed with an IPC and *2*) had undergone at least one thoracentesis after which there was no evidence of trapped lung on a chest radiograph (defined as hydropneumothorax, ≥20% air space, or ≥20% residual fluid plus chest pain or cough during the thoracentesis). Exclusion criteria included age younger than 18, extensive fluid loculation, prior ipsilateral attempt at pleurodesis, and any contraindication to trial procedures. Informed consent was gained in all cases.

Randomization and Blinding

On the day of insertion, participants were randomized in a 2:1 ratio to receive either the SNCIPC (investigational group) or a standard IPC (PleurX, Becton, Dickinson and Company [BD]) (control group). Randomization was stratified solely by site, in blocks of 3, preserving the 2:1 ratio,

according to a computer-generated schedule prepared by an independent statistician. Participants and the individual assessing the third-party radiological component of the primary endpoint, but not study investigators, were kept blind to treatment allocation. Data were unblinded for analysis after the study database was locked.

Insertion, Drainage, and Follow-Up

After catheter insertion, the pleural cavity was maximally drained, and postinsertion radiography was performed to once more assess for trapped lung. All participants were seen in follow-up for up to 90 days after insertion. Catheters were maximally drained (as tolerated) daily for 14 days, then no less than three times per week to Day 30, then as often as deemed necessary by the clinician thereafter. Volumes were recorded by those performing drainage.

Subjects were evaluated at follow-up visits on Days 14, 30, 60, and 90, with further telephone assessments at Days 7, 45, and 75, with outcome measures assessed at these points. In addition, subjects were asked to inform investigators if catheter drainage values reduced sufficiently to suspect pleurodesis (criteria below), in which case further visits for assessment with or without catheter removal could be scheduled.

Primary Outcome Measure

The primary outcome was defined as the proportion (percentage) of patients achieving pleurodesis (without fluid recurrence) at 30 days. Pleurodesis criteria were met if *1*) pleural fluid output via the catheter measured ≤50 ml on three consecutive drainages over a minimum of 5 days and *2*) chest radiographic assessment demonstrated opacification (due to fluid) of <25% of the hemithorax.

Additional Outcome Measures

Secondary outcomes were time to pleurodesis, time to fluid recurrence, thoracic pain (measured on a 100-mm visual analogue scale), patient-reported dyspnea (measured using the modified Borg scale), and quality of life (measured using the EuroQol five-level health status questionnaire [EQ-5D-5L]).

Device-related adverse events were recorded for all patients. For those in the intervention group, serum and pleural fluid silver levels were measured at a central, independent analytical laboratory (Intertek Pharmaceutical Services).

Trial Oversight

An independent data safety monitoring board oversaw the trial and reviewed data at regular intervals, including conducting a preplanned interim analysis (details below). BD acted as sponsor.

Sample Size and Interim Analysis

Based on previous trial and pilot data, unadjusted rates of pleurodesis were expected to be 75% in the SNCIPC group and 35% in the control group. However, on the basis of experiences from studies in similar populations, it was assumed that 20% of subjects would be randomized with unidentified trapped lung and that 20% of the remaining subjects would be unable to provide primary outcome data at Day 30 (and therefore would be considered pleurodesis failure). Adjusted pleurodesis rates were therefore assumed to be 48% and 22% for SNCIPC and IPC, respectively.

The necessary sample size to demonstrate superiority of the SNCIPC over a standard IPC was estimated on the basis of the following assumptions: one-sided test, $\alpha = 0.025$, 80% power, adjusted Day 30 pleurodesis rates of 48% (SNCIPC) and 22% (IPC), and randomization ratio of 2:1. Accordingly, a sample size of 79 SNCIPC subjects and 40 control (IPC) subjects was planned. A sample size evaluation at interim analysis, after 80 participants had been randomized, was stipulated in the statistical analysis plan to ensure sufficient power at the final analysis.

Outcome Analyses

The full trial statistical analysis plan was made publicly available (12). Analyses were performed using SAS version 9.4. The main analysis for each outcome was performed using a modified intention-to-treat principle; all patients with an observed outcome were analyzed according to their allocated treatment group. Patients who did not provide primary outcome data at 30 days were defined to have pleurodesis failure.

The proportion of subjects meeting the primary outcome was summarized for each treatment group, with 95% confidence intervals (CIs) by exact binomial method. The exact unconditional CI for risk difference was used to calculate rate difference and 95% CI. Superiority was demonstrated if the one-sided *P* value was <0.025. All chest radiographs were assessed by an independent central radiology review service.

To meet standards for regulatory clearance, key secondary outcomes (time to pleurodesis and time to recurrence) were initially assessed as noninferiority, with further superiority assessment to be undertaken when noninferiority was established.

Time to confirmed pleurodesis was defined as the duration between the study device insertion and the date of confirmed pleurodesis, and time to recurrence was defined as the duration between confirmed pleurodesis and the date of recurrence. Both outcomes were analyzed using a proportional hazards model (to estimate hazard ratio [HR]) and Kaplan-Meier time-to-event analysis. For time to pleurodesis, noninferiority was established if the HR was >0.7, and for time to recurrence, noninferiority was established if the HR was <1.3. For both outcomes, summaries were provided for 25th percentile, median, and 75th percentile when estimable from the Kaplan-Meier estimates for each treatment group. Kaplan-Meier curves for each treatment group were provided (12).

For quality of life, dyspnea, and pain outcomes, comparisons were made between treatment groups at each time point using a two-sample *t* test. In addition, change from baseline between the two treatment groups was analyzed using a two-sample *t* test. Superiority was demonstrated if the one-sided *P* value was <0.025 using a proportional hazards model.

Results

Recruitment and Baseline Characteristics

A total of 153 patients were assessed for eligibility between March 2016 and January 2018. During recruitment, the findings of the interim analysis were reviewed by the data safety monitoring board, which recommended continuing the study to completion. In total, 119 patients underwent randomization (38 IPC, 81 SNCIPC); however, 5 patients withdrew from the study before catheter insertion (3 withdrew consent, 2 had insufficient fluid for insertion) meaning 37 (97%) of 38 and 77 (95%) of 81 received their allocated treatment. Thirty-five (95%) of 37 and 57 (74%) of 77 in the IPC and SNCIPC groups, respectively, completed follow-up to the Day 30 primary endpoint. *See* Figure 1 for the full trial Consolidated Standards of Reporting Trials diagram.
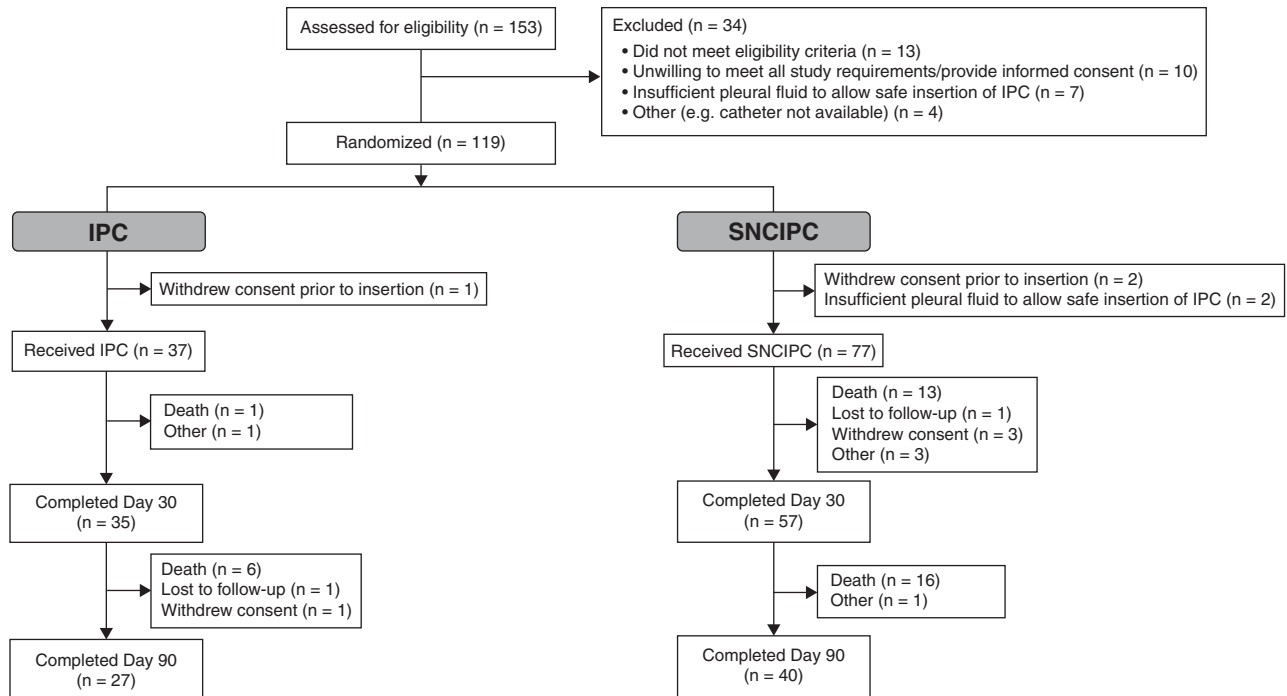
Figure 1. Consolidated Standards of Reporting Trials diagram for the SWIFT trial. IPC = indwelling pleural catheter; SNCIPC = silver nitrate-eluting indwelling pleural catheter.

The clinical and demographic characteristics of the two treatment groups were generally well matched at baseline (Table 1). Mean age across both groups was 66 years (standard deviation [SD], 11 yr), and 66 (58%) of 114 were female. Lung cancer was the most frequent cause of MPE, affecting 20 (26%) of 77 and 14 (38%) of 37 in the IPC and SNCIPC groups, respectively.

Five (14%) of 37 IPC patients had hematological malignancy, but none in the SNCIPC group did. In addition, an unexpected imbalance between the groups was noted in hospital status at enrollment, with 5 (14%) of 37 IPC participants having their treatment as an inpatient compared with 30 (39%) of 77 of those allocated to SNCIPC ($P = 0.009$).

In total, 35 (95%) of 37 subjects in the IPC group and 57 (74%) of 77 in the SNCIPC groups, respectively, remained in the trial until the primary endpoint. Mortality was the largest contributor to study discontinuation (IPC group, 1 [2.7%] of 37 at 30 d and 7 [18.9%] of 37 at 90 d; SNCIPC group, 13 [16.9%] of 77 at 30 d and 29 [37.7%] of 77 at 90 d).

Table 1. Baseline subject characteristics

Characteristics	SNCIPC (n = 77)	IPC (n = 37)	Total (N = 114)
Age, yr, mean ± SD	64.8 ± 11.0	67.0 ± 10.3	65.5 ± 10.8
Male sex, n (%)	33 (42.9)	15 (40.5)	48 (42.1)
Inpatient placement status, n (%)	30 (39)	5 (14)	35 (31)
Cancer type, n (%)			
Lung	20 (26)	14 (38)	34 (30)
Breast	17 (22)	7 (19)	24 (21)
Ovaries	10 (13)	4 (11)	14 (12)
Kidney	6 (8)	2 (5)	8 (7)
Pancreas	5 (6)	1 (3)	6 (5)
Pleura	4 (5)	1 (3)	5 (4)
Blood	0 (0)	5 (14)	5 (4)
Prostate	2 (3)	2 (5)	4 (4)
Esophageal	4 (5)	0 (0)	4 (4)
Other	9 (12)	1 (3)	10 (9)
Baseline chest pain, VAS score, mean ± SD	24.9 ± 27.3	20.9 ± 28.0	23.5 ± 27.4
Baseline modified Borg dyspnea score, mean ± SD	3.01 ± 2.47	2.54 ± 1.61	2.86 ± 2.22
Baseline EQ-5D-5L index score, mean ± SD	0.70 ± 0.20	0.74 ± 0.16	0.71 ± 0.19
Baseline EQ-5D-5L mobility score, mean ± SD	1.96 ± 1.03	1.70 ± 0.91	1.88 ± 0.99

Definition of abbreviations: EQ-5D-5L = EuroQol five-level health status questionnaire; IPC = indwelling pleural catheter; SD = standard deviation; SNCIPC = silver nitrate-eluting indwelling pleural catheter; VAS = visual analog scale.

Table 2. Subjects achieving pleurodesis without recurrence by 30 days (intent-to-treat)

	SNCIPC (*n* = 77)	IPC (*n* = 37)
Subjects achieving pleurodesis without recurrence by Day 30, *n* (%)	17 (22.1%)	12 (32.4%)
Rate difference (95% confidence interval, lower, upper)	−0.10 (−0.30 to −0.09)	
Superiority criteria		Fail

Definition of abbreviations: IPC = indwelling pleural catheter; SNCIPC = silver nitrate-eluting indwelling pleural catheter.

Primary Outcome

For the primary endpoint in the intent-to-treat population, 12 (32%) of 37 patients in the IPC group achieved pleurodesis without recurrence by Day 30, compared with 17 (22%) of 77 in the SNCIPC group. The rate difference was −0.10 (95% CI, −0.30 to 0.09), indicating a failure to meet the predefined superiority criteria for the SNCIPC (*see* Table 2).

Secondary Outcomes

The median time to pleurodesis during the 90-day follow-up period was 11 days (interquartile range, 9–23) in the IPC group and 4 days (interquartile range, 2–15) in the SNCIPC group. Overall, no significant difference in time to pleurodesis was observed (Figure 2). No patients in the IPC group experienced fluid recurrence, having stopped draining. A single patient (1 [1.3%] of 77) in the SNCIPC group had fluid recur after 60 days.

No significant between-group differences were identified at any follow-up time point in change from baseline in thoracic pain, patient-reported dyspnea, or quality of life as measured using the EQ-5D-5L index score. Patients in the IPC group had a greater improvement in EQ-5D visual analog scale score from baseline at Day 14 (+8.4; SD, 17) and Day 30 (+8.0; SD, 21) than those treated with the SNCIPC (Day 14, −0.1; SD, 17; *P* = 0.02; Day 30, −2.0; SD, 22; *P* = 0.04). *See* Figures E1–E4 in the data supplement.

Adverse Events

There were 443 treatment-emergent adverse events (TEAEs) reported during the study, affecting 30 (81.1%) of 37 subjects treated with the IPC and 70 (90.9%) of 77 subjects treated with the SNCIPC (*P* = 0.22) overall. One hundred fifty-one TEAEs were noted in the IPC group, and 292 were noted in the SNCIPC group, with 1 of 151 (0.7%; affecting 1 [2.7%] of 37 patients) and 13 of 292 (4.5%; affecting 9 [11.7%] of 77 patients), respectively, meeting the criteria for a serious adverse event and being categorized as probably or possibly related to the study device (*P* = 0.16).

The most frequently reported TEAEs were pleural effusion, anemia, dyspnea, pneumonia, and catheter site pain. Other than pleural effusion (total 22 of 114 patients; IPC group, 3 [8.1%] of 37; SNCIPC group, 19 [24.7%] of 77), the proportion of patients affected by these was similar. Pleural infection/empyema affected five patients (4.4%) overall. Four patients (3.5%) developed respiratory failure, but none was categorized as related to a study device. A full summary of TEAEs is provided in Table 3.

Thirty-seven subjects who received catheters died during the study: 30 (39.0%) of 77 treated with the SNCIPC and 7 (18.9%) of 37 treated with the IPC (*P* = 0.036; HR, 2.42; 95% CI, 1.06–5.52). Most deaths (34 [91.9%] of 37) were due to progressive disease. No deaths were attributable to study devices or procedures.

Silver Levels

See the data supplement and Figures E5 and E6 for details of silver analyses.

Post hoc Analyses

Effect of randomization. An analysis was performed to establish whether the randomization process had, by chance, created a group with potentially elevated risk of death. Univariate analysis demonstrated significant associations between mortality and serum neutrophil-to-lymphocyte ratio >9, male sex, inpatient status, lower EQ-5D-5L index score at baseline, and randomization to the SNCIPC group. However, upon subsequent Cox multivariate regression analysis, randomization to SNCIPC no longer predicted mortality, with only low baseline EQ-5D-5L index score being significantly associated (HR, 0.14; 95% CI, 0.03–0.74; *P* = 0.02).

Fluid loculation. An analysis was performed to determine whether those in the SNCIPC group were more likely to develop radiographic fluid loculation (and hence undrainable collections), a possible surrogate

Kaplan-Meier Graph - Time to Confirmed Pleurodesis (ITT-P)

Number of Patients at Risk:

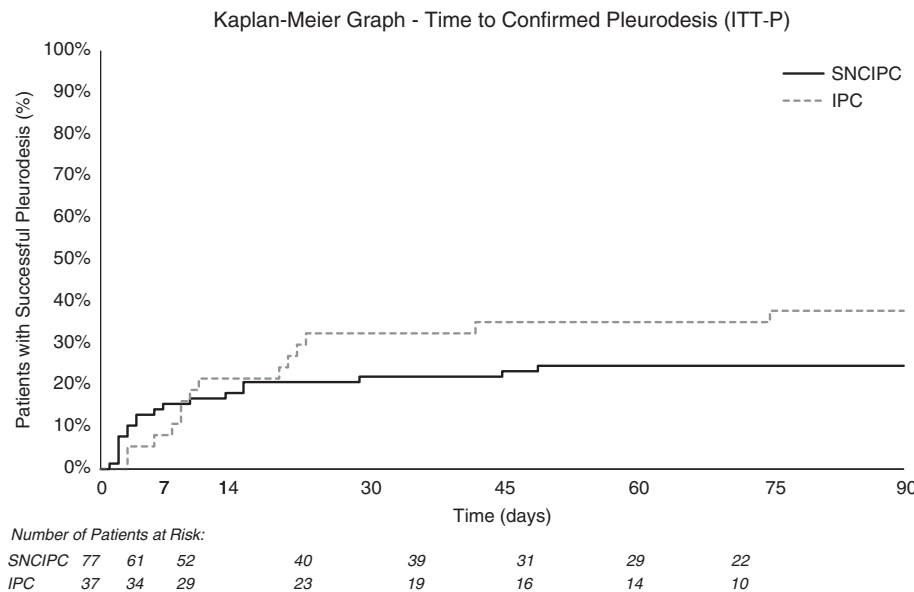|	0	7	14	30	39	45	60	75	90
SNCIPC	77	61	52	40	39	31	29	22	
IPC	37	34	29	23	19	16	14	10	

Figure 2. Time to confirmed pleurodesis in the treatment groups (intent-to-treat population [ITT-P]). IPC = indwelling pleural catheter; SNCIPC = silver nitrate-eluting indwelling pleural catheter.
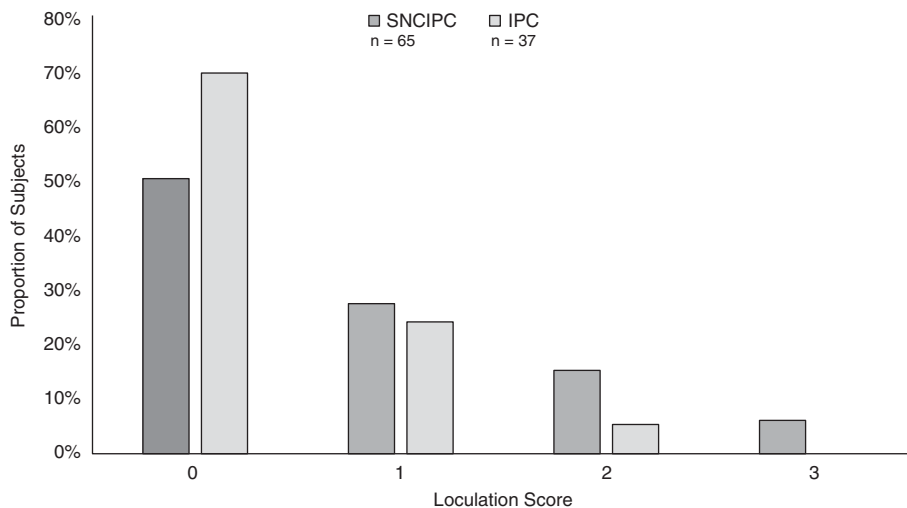
Figure 3. *Post hoc* assessment of the development of loculations to determine whether more complex pleural spaces developed in the silver nitrate-eluting indwelling pleural catheter arm. Loculation scores were assigned on a scale of 0 (no loculation) to 3 (extensive loculation) based on chest radiograph review by authors J.B.S. and N.A.M. IPC = indwelling pleural catheter; SNCIPC = silver nitrate-eluting indwelling pleural catheter.

for pleural inflammation. Authors J.B.S. and N.A.M. independently reviewed postinsertion chest radiographs of all subjects to assign a loculation score (0 = no loculation; 1 = mild; 2 = moderate; 3 = severe) (Figure 3). Both assessors were blind to study group but were aware of other clinical information, and any scoring disagreements were resolved through joint re-review. The analysis identified a significantly higher incidence of loculations in the SNCIPC group, with a 19% lower rate of a 0 loculation score (IPC group, 26 [70%] of 37; vs. SNCIPC group, 33 [51%] of 77; $P = 0.03$).

Discussion

The results of this randomized trial comparing the novel drug-eluting SNCIPC with a standard IPC for MPE did not demonstrate superiority in pleurodesis efficacy, with 32.4% of the IPC group and only 22.1% of the SNCIPC group achieving pleurodesis without subsequent recurrence. Furthermore, on the basis of several patient-reported outcomes, the SNCIPC appeared to perform less well than the standard IPC. On the basis of these findings, the SWIFT trial does not support routine use of the SNCIPC.

IPCs are now a routine treatment for MPE in many countries. Since their introduction 20 years ago, they have been shown to provide improvements in

breathlessness similar to the historic gold standard, chemical pleurodesis, while allowing management to occur in an outpatient setting (5, 7, 13–15). However, for many, the main perceived disadvantage of an IPC (in patients without trapped lung) has been the lower likelihood of achieving "spontaneous" pleurodesis, and thus IPC removal, as well as the longer time needed for pleurodesis to occur (16). These issues are important for both patient comfort and convenience and because pleural infection is theoretically more likely to develop the longer an IPC remains *in situ* (17). Although previously reported as higher in retrospective studies, recent prospective, pragmatic trials have consistently shown pleurodesis rates with IPC alone to be approximately 20% (8, 18), compared with approximately 75% for treatment with talc via chest tube as an inpatient. In addition, reported mean delay to achieving pleurodesis with an IPC is 52 days (16), whereas inpatient treatment with talc typically requires approximately 4 days (3). Administering talc via an IPC as an outpatient or increasing the frequency of drainages can improve pleurodesis efficacy over IPC alone to approximately 45% (8, 18), but these approaches carry extra burden for patients and may be logistically challenging.

The SNCIPC evaluated in this study incorporates a layer of the pleurodesis agent silver nitrate onto the surface of a normal IPC, which is designed to elute into the

pleural space gradually over 3–5 days. The SNCIPC was developed by BD to address the limitations of using an IPC alone while being as flexible and convenient a solution to MPE management as possible. The SNCIPC was approved for investigational use after the encouraging results of a small-scale phase I trial, which demonstrated an acceptable side effect profile in conjunction with a pleurodesis success rate of 89%, occurring at a median of 4 days (11). Given this, the findings of our study were surprising.

There were, however, a number of unanticipated difficulties encountered with the execution of the SWIFT trial, which may have impacted the results. Issues with trial execution included missing subject diaries (which included the drainage volume logs) in 17 subjects (16 of them in the SNCIPC group), incomplete subject diaries in 5 subjects (4 in the SNCIPC group), a high number of protocol deviations relating to drainage, and inconsistencies in chest radiograph interpretation between study sites and the independent assessor. Incomplete drainage data impacted the assessment of pleurodesis, and the discordance in imaging assessments casts doubt on the robustness of the decision algorithm for the primary endpoint. An additional 14 subjects were ineligible for primary endpoint analysis as a result of death before 30 days, and, combined, these occurrences are likely to have had a major impact on results. The failure to reject the null hypothesis also may have been impacted by the trial's strict definition for pleurodesis, to which some sites struggled to adhere.

The results were also likely impacted by a statistically improbable baseline imbalance between the groups, burdening the SNCIPC group. Although the study stratified by center, it did not adjust for baseline performance status, inpatient versus outpatient status, or cancer type, likely allowing the occurrence of this imbalance between groups and rendering interpretation of the study results challenging. The results of our *post hoc* multivariate analysis would support this, demonstrating that being randomized to the SNCIPC did not predict mortality. We therefore believe that the higher death rate in the SNCIPC group may have resulted from this group having an overall higher risk for death at baseline.

A prior possible concern with the use of the SNCIPC was the development of excess pleural fluid loculation and that this might

Table 3. Treatment-emergent adverse events

Preferred Term	SNCIPC (n = 77) Subjects Who Had Event, n (%)	No. of Events	IPC (n = 37) Subjects Who Had Event, n (%)	No. of Events	Total (N = 114) Subjects Who Had Event, n (%)	No. of Events
Pleural effusion	19 (24.7)	22	3 (8.1)	3	22 (19.3)	25
Anemia	11 (14.3)	15	4 (10.8)	5	15 (13.2)	20
Dyspnea	12 (15.6)	15	4 (10.8)	4	16 (14.0)	19
Pneumonia	11 (14.3)	11	4 (10.8)	5	15 (13.2)	16
Catheter site pain	9 (11.7)	10	4 (10.8)	4	13 (11.4)	14
Urinary tract infection	4 (5.2)	4	4 (10.8)	5	8 (7.0)	9
Pyrexia	8 (10.4)	8	0	0	8 (7.0)	8
Pulmonary embolism	4 (5.2)	4	3 (8.1)	3	7 (6.1)	7
Constipation	2 (2.6)	2	4 (10.8)	4	6 (5.3)	6
Cough	4 (5.2)	4	2 (5.4)	2	6 (5.3)	6
Diarrhea	5 (6.5)	6	0	0	5 (4.4)	6
Lower respiratory tract infection	4 (5.2)	4	2 (5.4)	2	6 (5.3)	6
Noncardiac chest pain	2 (2.6)	2	4 (10.8)	4	6 (5.3)	6
Catheter site infection	3 (3.9)	5	0	0	3 (2.6)	5
Post-procedural infection	1 (1.3)	1	0	0	1 (0.9)	1
Pleural infection	2 (2.6)	3	1 (2.7)	1	3 (2.6)	4
Procedural pain	1 (1.3)	1	3 (8.1)	3	4 (3.5)	4
Cellulitis	1 (1.3)	1	1 (2.7)	1	2 (1.8)	2
Empyema	1 (1.3)	1	1 (2.7)	1	2 (1.8)	2
Acute respiratory failure	2 (2.6)	2	0	0	2 (1.8)	2
Respiratory failure	2 (2.6)	2	0	0	2 (1.8)	2
Device breakage	1 (1.3)	1	0	0	1 (0.9)	1
Device dislocation	1 (1.3)	1	0	0	1 (0.9)	1
Device occlusion	1 (1.3)	1	0	0	1 (0.9)	1
Skin infection	1 (1.3)	1	0	0	1 (0.9)	1

Definition of abbreviations: IPC = indwelling pleural catheter; SNCIPC = silver nitrate-eluting indwelling pleural catheter.

result in worse outcomes. Our *post hoc* analysis addressing this question does show significantly greater loculation formation with the SNCIPC, a problem that, based on previous reports, does not appear to be substantial when talc is injected via an IPC (18, 19). It is possible that this relates to the gradual release of the pleurodesis agent as opposed to the single instance of pleural inflammation caused by talc. However, it seems unlikely that the modest increase in the development of loculations with the SNCIPC wholly accounts for the poorer outcomes seen in this treatment group.

The study protocol stipulated drainage was to take place every day for the first 2 weeks after catheter placement, with no prescribed drainage regimen thereafter. The findings of this study, with a 30-day

pleurodesis rate of 32.4% in the IPC group, further corroborate recent evidence that daily IPC drainage is more likely than more commonly used intermittent regimens to lead to pleurodesis (8, 20).

Last, in the entire SWIFT study cohort, 31% of patients died before 90 days. This emphasizes importance of considering the appropriateness of hospitalization for MPE treatments, with alternatives to IPC usually requiring an inpatient stay, the length of which may represent a significant proportion of a patient's remaining life.

Conclusions
This international, multicenter, randomized study did not demonstrate superiority of a drug-eluting, silver nitrate–coated IPC over the standard IPC in pleurodesis rate in

patients with MPE. This outcome may have resulted from baseline imbalances between the randomized groups and/or the development of more pleural fluid loculation in the treatment group. This study does not support the wider use of the SNCIPC device. ∎

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