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Association of Perioperative Antibiotics with the Prevention of Postoperative Fistula after Cleft Palate Repair

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Background: There is debate amongst surgeons regarding the use of antibiotics to prevent fistulae after palatoplasty. Prescribing should be evidence based, as antibiotic stewardship is integral to reducing antibiotic resistance. Our aim was to determine whether differing perioperative regimens affect the prevalence of postoperative fistulae.

Methods: The sample comprised participants from the Cleft Collective who had undergone palatoplasty. Participants were recruited across all 16 UK cleft centers between 2013 and 2021. The exposure was perioperative antibiotic regimen prescribed at the time of palatoplasty. The primary outcome was the presence of palatal fistula.

Results: Fistula data were available for 167 participants when exploring antibiotic regimen and for 159 when exploring antibiotic agent. There was no evidence to suggest a difference in fistula rate between those receiving antibiotics on induction only versus as an inpatient or up to 7 days postoperatively ($\chi^2 = 4.57$; $P = 0.10$). There was no evidence to suggest a difference in fistula rate between those who received co-amoxiclav and those who had an alternative antibiotic ($\chi^2 = 0.16$; $P = 0.69$). Postoperative fistulae increased with the extent of the cleft ($\chi^2 = 20.39$; $P < 0.001$). When adjusting for cleft type, no evidence of an association between antibiotic regimen and fistulae was found (inpatient antibiotics: OR 1.36; 95% confidence interval, 0.53–3.51; antibiotics up to 7 days postoperatively: OR 0.68; 95% confidence interval, 0.26–1.80).

Conclusions: The choice of antibiotic and dosing regimen does not influence the formation of postoperative fistulae. These results should be supported by interventional trials. *(Plast Reconstr Surg Glob Open 2024; 12:e5589; doi: 10.1097/GOX.0000000000005589; Published online 6 February 2024.)*

INTRODUCTION

Infection after cleft palate repair can result in wound breakdown and subsequent oronasal fistula. The development of symptomatic fistulae has consequences for the development of speech, regurgitation of food, decreased oral health, and further scarring that can result in maxillary growth restriction.[1–5] Symptomatic fistulae require the child to undergo further procedures to close the defect. Multiple procedures during childhood may in turn affect the child's psychosocial development due to poor speech attainment,[6] missed schooling,[7] and increased exposure to anesthesia.[8]

Children with cleft lip and palate have a higher preoperative prevalence of *Staphylococcus aureus* in their saliva compared with the flora of those without a cleft.[9] It is thought that this is due to colonization from the nose and nasopharyngeal space, where most of *Staphylococcus aureus* are found. The same study noted no difference in bacterial prevalence between children with and without

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a cleft after repair, reflecting the separation of the oral and nasal spaces. These pathogens have been shown to cause postoperative wound infection in patients who have undergone palatoplasty[10]; the increased incidence in cleft patients is a concern.

To attempt to reduce the risk of postoperative infection and its consequences, some surgeons advocate administering antibiotics at the time of repair. Unfortunately, there is little published evidence to support its benefits in the prevention of postoperative infection and potential fistula formation. In one small study, the incidence of complications was reported to be independent of the preoperative oral flora and the use of prophylactic antibiotics; patients received a single dose of co-amoxiclav on induction of anesthesia (or a cephalosporin if penicillin allergic). Of those who developed postoperative complications, including fistula, none had positive preoperative swabs.[11]

With limited available evidence, practice within the United Kingdom is discordant, with a significant variability between the 16 cleft centers.[12] There may even be variance in practices between surgeons within a center. It remains unknown if antibiotics help prevent fistula formation, or indeed which regimen, if any, is clinically beneficial.

The injudicious use of antibiotics without proven benefit is not without issue, as there are health service costs, potential allergies and hypersensitivity reactions, and the emergence of antimicrobial resistant bacterial strains. In the era of evidence-based medicine, the benefits of targeted antibiotic usage should be tempered with limiting the negative effects of their widespread use. There is growing evidence to suggest that antibiotic exposure in childhood is associated with a changing microbiome and subsequent increased risk for a range of diseases.[13,14] The use of a prophylactic antibiotic at induction of anesthesia is justified to prevent the risk of surgical sepsis, given the high rate of bacteremia after palatal surgery[15]; however, further courses of antibiotics for the prevention of fistulae should be justified by evidence of an effect.

We sought to determine if data from the Cleft Collective, a national longitudinal cohort study within the UK, supported the use of a specific antibiotic regimen for the prevention of fistulae after palatoplasty. The use of multicenter data was paramount to avoid the influence of individual surgeon practice.

PATIENTS AND METHODS

Approval for the Cleft Collective cohort studies was obtained from the Southwest-Central Bristol NHS Research Ethics Service (REC13/SW/0064). Secondary data analysis for this study was approved by the University of Bristol Health Sciences Research Ethics Committee (ID 117297). To date, 3543 children have been recruited into the Cleft Collective. The analyses used surgical data collected through questionnaires completed at the time of palate repair. These forms document the use of perioperative antibiotics, including which antibiotic was used, and details of prescribing regimen (on induction of anesthesia; 24 hours postoperatively; 5–7 days postoperatively; other). Further data include, but are not limited to, the classification of cleft using LAHSHAL, where each letter sequentially denotes the lip, alveolus, hard palate, and soft palate[16] (converted to the Veau classification for ease of understanding); date of procedure; surgical technique; and cleft measurements.

Takeaways

Question: Do perioperative antibiotics influence the rate of fistula after cleft palate repair?

Findings: In this prospective multicenter cohort study, no significant difference was found in the rate of fistula between patients who received prophylactic antibiotics at the induction of anesthesia compared with those who received a postoperative antibiotic course.

Meaning: Additional postoperative antibiotic regimens do not reduce fistula rate after cleft palate repair.

At the point of analysis, the Cleft Collective had received 2136 surgical questionnaires on 1881 patients, of which 830 were primary palatoplasties. These included 100 soft palate clefts (Veau I), 270 involving the hard and soft palate (Veau II), and 246 involving the soft palate to the alveolus [179 unilaterally (Veau III) and 67 bilaterally (Veau IV)]. Note that Veau classification was available only for 616 of the cases. Data on antibiotic regimen and antibiotic agent used were available for 776 and 759 palatoplasty procedures, respectively.

Assessment forms from the nested speech and language substudy,[17] completed when the child was 18–24 months of age, were used to determine the presence of a fistula . The presence of a fistula was determined by the investigating team via direct visualization and was recorded as diagnosed, suspected, none, or unable to see. No measurements of the fistulae were taken. We included diagnosed and suspected fistulae of the hard and soft palate (Pittsburgh types I–V[18]) only, as lingual-alveolar and labial-alveolar fistulae (Pittsburgh types VI and VII) may have represented intentional fistulae left by the surgeon for closure at the time of alveolar bone grafting. Diagnosed and suspected fistulae were combined to create a binary outcome variable.

STATISTICAL ANALYSIS

Data used in our analyses were explored using descriptive statistics to describe the current practice of antibiotic use across the United Kingdom. Chi square tests of association were used to investigate associations between exposures (antibiotic regimen and antibiotic type) and outcome (formation of a fistula). Antibiotic regimen was categorized into three groups: (1) on induction only, (2) received as an inpatient, and (3) received up to 7 days postoperatively. The classifications were chosen based on reports of common prescribing practices in the United Kingdom.[12] Logistic regression was performed to further explore the association between antibiotic regimen and formation of a fistula while adjusting for the Veau cleft classification.

A sensitivity analysis was also conducted, excluding participants with a suspected fistula, from the logistic regression. (**See appendix, Supplemental Digital Content**

1, which displays the sensitivity analysis. **http://links.lww.com/PRSGO/D56**.) All analysis was conducted using STATA/MP, v16.0 (StataCorp, Texas, USA).

RESULTS

Data on whether antibiotics were prescribed were available for 803 children (97.8%). Almost all participants were prescribed perioperative or postoperative antibiotics (N = 780; 97.1%). Antibiotics were received on induction only by 233 participants (29.9%), 209 (26.8%) had received antibiotics as an inpatient, and 334 (42.8%) had received antibiotics up to 7 days postoperatively. Four participants (0.5%) received antibiotics at an unspecified perioperative or postoperative time point; we were, therefore, unable to categorize these participants.

Data on the antibiotic agent used were available for 759 participants (97.3%; 759/780). Co-amoxiclav was the most common antibiotic used, with 654 (86.2%) participants recording its use. Other antibiotics included benzylpenicillin, amoxicillin, metronidazole, and flucloxacillin. Numbers and proportions have not been reported due to small counts and the risk of disclosure of specific centers based on their general practice.

When combining datasets to include information on the presence of fistulae, our sample was reduced to 167 when exploring the antibiotic regimen and to 159 for the antibiotic agent (Fig. 1).

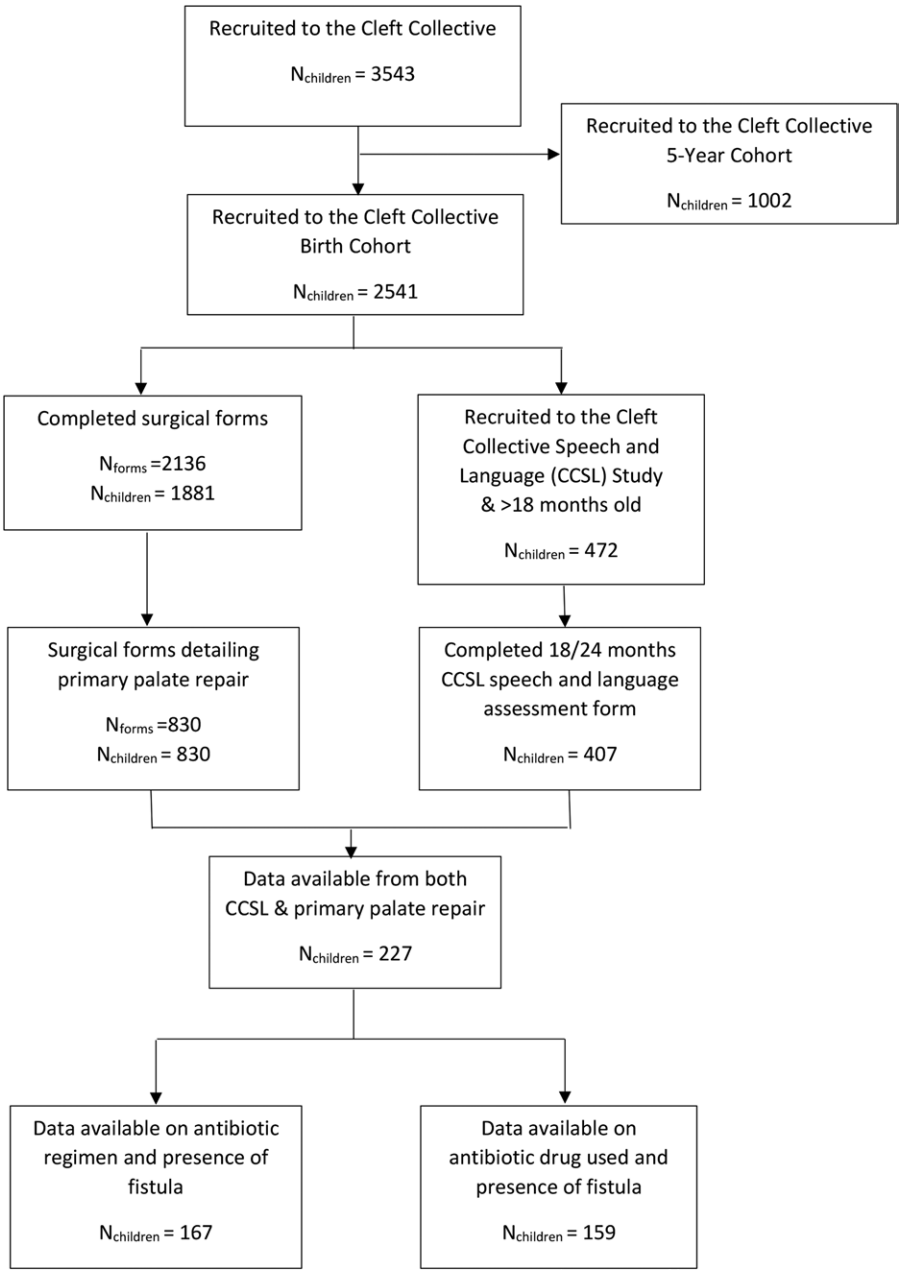

Fig. 1. Data flowchart of the sample sizes available for analysis.

Table 1. Characteristics of Patients by Antibiotic Regimen

	Antibiotic Regimen			
	Induction Only	**As an Inpatient**	**Up to 7 Days Postoperatively**	**n**
	Median [interquartile range; (min–max)]			
Age (mo) at the time of palatoplasty	7.6 (4.9–10.3; [3.1–23.2])	8.8 (6.8–11.0; [3.3–14.5])	10.0 (8.4–11.8; [3.2–14.3])	163
Kruskal Wallis test		*$\chi^2 = 13.285$ $P = 0.001$*		
Preoperaative soft edge width (mm) of the palatal cleft at the hard/soft palate junction	11 (8–15; [0–19])	8.5 (6–12; [0–20])	10 (7.5–12.8; [0–18])	130
Kruskal Wallis test		*$\chi^2 = 2.734$ $P = 0.255$*		
Veau classification	N (%)	N (%)	N (%)	167
Veau I/ II	16 (20.0%)	21 (26.3%)	43 (53.8%)	80 (47.9%)
Veau III	29 (47.5%)	16 (26.2%)	16 (26.2%)	61 (36.5%)
Veau IV	8 (30.8%)	8 (30.8%)	10 (38.5%)	26 (15.6%)
Chi Square test		*$\chi^2 = 14.853$ $P = 0.005$*		

Within this reduced sample, antibiotics were received on induction only by 53 participants (31.7%), 45 (26.9%) received antibiotics as an inpatient, and 69 (41.3%) received antibiotics up to 7 days postoperatively. Patient characteristics, for each of the regimen categories, are presented in Table 1. Co-amoxiclav was the most used antibiotic, with 128 participants (80.5%) reporting its use.

A fistula was reported in 38 participants (22.8%), who had data available on antibiotic regimen. There was no evidence to suggest a difference in fistula rate between the different timings of antibiotic regimen ($\chi^2 = 4.57$; $P = 0.102$). A fistula was reported in 35 participants (22.0%) who had data available on the antibiotic agent. When examining associations between the use of co-amoxiclav and fistula rate, there was no evidence to suggest a difference in fistula rate between those who received co-amoxiclav and those who did not ($\chi^2 = 0.16$; $P = 0.69$; Table 2).

There was strong evidence to suggest that the prevalence of postoperative fistulae increases with the extent of clefting per Veau classification ($\chi^2 = 20.39$; $P < 0.001$; Table 3). When adjusting for the Veau classification within logistic regression, there was no evidence of a difference in fistula rate between antibiotics on induction only and any of the other antibiotic regimens (inpatient antibiotics OR 1.36; 95% confidence interval, 0.53–3.51; $P = 0.528$; antibiotics up to 7 days postoperatively OR 0.68; 95% confidence interval, 0.26–1.80; $P = 0.437$).

DISCUSSION

National data from the UK suggest that the use of an antibiotic on induction and/or postoperatively, either while the patient remains in hospital or after discharge, does not have any association with the formation of postoperative fistulae. Combining doses of antibiotic at induction with postoperative regimens has no relationship to postoperative fistula formation. There is no evidence to suggest that the choice of antibiotic agent was accompanied by a reduction in the prevalence of postoperative fistulae. Therefore, advocating the use of antibiotics at any postoperative stage, in addition to a dose given on induction, with the sole purpose of preventing postoperative fistulae is not supported.

After palatoplasty, fistulae may be described as intentional or unintentional. Intentional fistulae are seen when the surgeon has elected to leave a portion of the cleft unrepaired: for example, the alveolus is left for closure at the time of bone grafting. Such patients were not included in this study, as antibiotic usage would not be associated with fistula formation. Unintentional fistulae occur secondary to wound breakdown and, unlike intentional fistulae, are thus surrounded by scar tissue. If left untreated, they may lead to nasal emissions, speech problems, hearing loss, or the regurgitation of food and fluids.[1] Fistulae are extremely difficult to repair and have a high recurrence rate, approaching 100%.[19–22] This is not surprising, given

Table 2. Associations between Antibiotic Regimen and Antibiotic Agent, and the Presence of Fistula

	Fistula Present?		Total
	No	**Yes**	
Antibiotic regimen			
On induction only	38 (71.7%)	15 (28.3%)	53
Received as an inpatient	32 (71.1%)	13 (28.9%)	45
Received up to 7 d postoperatively	59 (85.5%)	10 (14.5%)	69
$\chi^2 = 4.571$ $P = 0.102$			
Total	129	38	167
Antibiotic agent			
Co-amoxiclav			
No	25 (80.7%)	6 (19.4%)	31
Yes	99 (77.3%)	29 (22.7%)	128
$\chi^2 = 0.158$ $P = 0.691$			
Total	124	35	159

Table 3. Comparison of Fistula Rate by Veau Classification

	Fistula		
Veau Classification	No	Yes	Total
Veau I/II	74 (92.5%)	6 (7.5%)	80
Veau III	39 (63.9%)	22 (36.1%)	61
Veau IV	16 (61.5%)	10 (38.5%)	26
Total	129 (77.3%)	38 (22.8%)	167
Chi square test	$\chi^2 = 20.39\ P < 0.001$		

the presence of scarring from the primary palatoplasty, which may lead to poor tissue compliance and reduced vascularity.[23] Even small fistulae may be difficult to repair, given the decreased access required for complete removal of the tract.[24]

The causes of fistulae are multiple and broadly divided into intrinsic and extrinsic causes. Intrinsic are those related to the initial cleft phenotype and patient characteristics. They include extent of clefting (per Veau),[1,25] cleft width,[26] and patient age at the time of repair.[27] Several studies have, however, suggested that patient age does not affect fistula formation.[25,26,28] Extrinsic causes are related to surgical technique, which include repair under tension, single layer closure, and poor technique.[22,29] Some studies have suggested that the biggest factor influencing fistula formation is the surgeon[25,27]; this is refuted by others.[1,26,27] The choice of palatoplasty itself may influence fistula formation.[25] It has been suggested that the Wardill-Kilner repair has a high incidence of fistula formation attributed to the convergence of three suture lines.[28] The addition of intravelar veloplasty to the repair seems to have no influence on fistula formation.[25,28]

Given the implications of fistulae for speech, deglutition and, potentially, growth restriction from excess scarring, much attention has been given to their prevention. Postoperative infection may be amongst the main causes of fistulae.[30] It is suggested that the presence of certain bacteria is associated with an increased risk of dehiscence[10,31]; this has been disputed by others.[32] It, thus, follows that the use of prophylactic antibiotics may have a role in preventing fistulae.

The National Institute for Health and Care Excellence (NICE) in the United Kingdom defines an incision through which the respiratory or alimentary tract is entered under controlled conditions but with no contamination encountered, as clean-contaminated surgery. Palatoplasty, which takes place in the upper aerodigestive tract, therefore falls into this definition. For clean-contaminated surgery, NICE recommends that antibiotic prophylaxis be given on induction of anesthesia only. In reaching their conclusions, the Guideline Development Group reviewed the literature regarding antibiotic use in head and neck surgery. A systematic review[33] was identified that included three trials of patients undergoing cancer surgery. Meta-analysis demonstrated a significant reduction in wound infection rates in those who received antibiotics compared with those who received a placebo. Further evidence was provided by a systematic review of the use of prophylactic antibiotics in maxillofacial fractures,[34] which demonstrated statistically fewer wound infections in patients given antibiotics. Although the findings of these studies demonstrate statistical significance, the clinical significance of their findings to patients undergoing primary palatoplasty, with fistula formation, is unknown at the present time.

The widespread use of antibiotics is a major factor associated with high numbers of resistant pathogenic and commensal bacteria worldwide.[35] Antibiotic stewardship is integral to reducing antibiotic resistance and forms part of the national strategies for many countries.[36] The judicious use of antibiotics is reducing multidrug-resistant bacterial infections.[37] It would seem prudent to restrict antibiotic usage to evidence proven practices.

A 2008 survey of antibiotic usage amongst surgeons performing primary cleft repair in the United Kingdom demonstrated a lack of consensus and considerable disparity in antibiotic choice and prescribing regimen.[12] Similar findings were demonstrated in a survey of the American Cleft Palate-Craniofacial Association.[38] Our study demonstrates similar heterogeneity in prescribing practices amongst current cleft surgeons in the United Kingdom.

In an early study of antibiotic use at the time of palatal repair, it was suggested that penicillin significantly reduced the complication rate.[39] This study does not specify the regimen prescribed, nor specifically look at the postoperative fistula rate. No statistical analysis was presented, making it impossible to discern if the reported benefit is independent of covariates and confounding factors. Amland investigated the use of azithromycin as prophylaxis, across the spectrum of plastic surgical procedures.[40] This randomized-controlled trial did not demonstrate any benefit in cleft procedures. Cleft lip and palate procedures were grouped together, totaling 70 patients, and fistula formation was not a primary outcome. The American Society of Plastic Surgeons (ASPS) conducted a review of the literature and developed an evidence-based consensus on the use of antibiotic prophylaxis for preventing surgical-site infection.[41] Although advocating the use of prophylaxis for surgery of the head and neck, they did not specifically identify cleft palate procedures, nor did they look at fistula prevention.

In one of the few attempts to undertake a randomized controlled study of the effect of antibiotic usage for the prevention of complications after palatoplasty, Aznar et al noted a lower rate of fistula formation in patients who received a 5-day regimen of amoxicillin compared with a placebo. However, this did not demonstrate statistical significance.[42] Although the study was designed with sufficient

power to detect a difference, the authors accepted that the loss to follow-up in a remote setting made late postoperative evaluation difficult, with the maximum follow-up lasting little beyond an average of 2 months.

Data from our study and the current literature do not support the use of combining induction and postoperative antibiotics regimens to prevent infection that could result in fistula formation.

LIMITATIONS

Almost all the participants in our sample had received an antibiotic around the time of palatoplasty (97.1%). It was, therefore, not possible to explore if the use of no antibiotic at all made a difference to the fistula rate. If it were proven that no relationship existed, it is likely that the routine use of antibiotics would continue, as advocated by NICE and ASPS, given that the use of preoperative antibiotics at induction of anesthesia is justified to prevent other serious complications such as sepsis. The prevalence rate for asymptomatic bacteriemia after cleft surgery approaches 50%.[15] The use of prophylactic antibiotics may help protect at-risk patients, such as those with congenital heart disease, from the consequences of bacterial seeding at the time of surgery.

From Table 1, there was evidence to suggest differences in patient characteristics between the exposure categories on antibiotic regimen, namely age at the time of palatoplasty and extent of the cleft per the Veau classification. Surgical technique was not included, as where data were available, an intravelar veloplasty was mainly performed for soft palate repair (94.5%) and a vomer for hard palate repair (92.2%). It is possible that the small counts in some of these categories resulted in a type I error.

Nonetheless, certain preoperative characteristics that have a known relationship with postoperative fistula formation seem to influence surgeons' decision-making regarding antibiotic regimen choice. In keeping with other observational studies, our study is unable to control for all factors that may influence the outcome, including surgeons' decision-making. Further randomized-controlled studies are required to provide the most convincing evidence of any association between antibiotic exposure and fistula formation, as it is possible to control for the other variables by randomizing patients to each of the exposure groups. This would eliminate the confounding bias effect of surgeons' decision-making based on the other variables seen.

Although not a specific outcome of this study, we accept that there may be other metrics besides the formation of postoperative fistulae that antibiotics may influence. We are unable to comment if antibiotic usage reduces other consequences of infection such as postoperative bleeding and readmission rate. It is unknown if the prevention of infection is associated with improved speech or facial growth outcomes in children undergoing cleft repairs. Further investigation is required to understand the influence of antibiotics on these metrics.

CONCLUSIONS

Our national cohort study suggests that the choice of antibiotic and dosing regimen does not influence the formation of postoperative fistulae. Although no conclusive link can be demonstrated, the use of single-dose prophylactic antibiotic given on induction of anesthesia seems appropriate to reduce the risk of surgical sepsis, and this would be in keeping with the guidance from ASPS and NICE.

Ultimately, the conclusive answer as to whether the use of perioperative antibiotics, and what regimen, prevents the early formation of fistulae lies in a robust randomized-controlled trial. Centralization of cleft services in the United Kingdom has enabled standardization of operative procedures and timing for intervention, with closely audited follow-up of cleft patients. Such centralization makes the conduct of a nationalized trial feasible, and we therefore call for such a study to be conducted to answer this important research question.

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DISCLOSURE

The authors have no financial interest to declare in relation to the content of this article.

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