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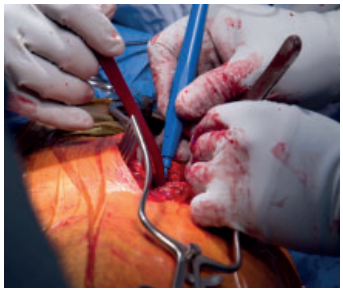
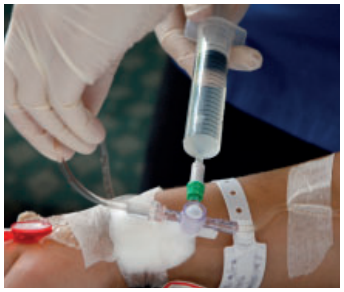


Outcomes after single and two stage revision for hip prosthetic joint infection p 227



Effect of oral antibiotic prophylaxis before colorectal surgery p 228

Antihyperglycaemic drugs and risk of COPD exacerbations p 230

ORIGINAL RESEARCH Pragmatic, parallel group, open label, RCT

Clinical and cost effectiveness of single stage compared with two stage revision for hip prosthetic joint infection (INFORM)

Blom AW, Lenguerrand E, Strange S, et al

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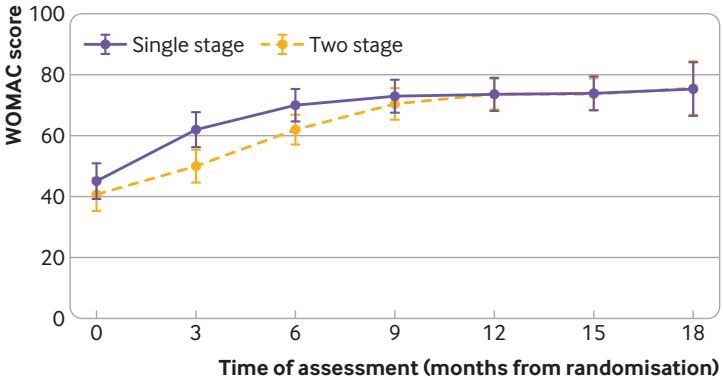
Find this at doi: 10.1136/bmj-2022-071281

Study question Does revision in one operation (single stage) give better patient outcomes than the widely used revision in two operations (two stage) for a prosthetic joint infection of the hip?

Methods 140 adults (≥18 years) who had prosthetic joint infections of the hip requiring revision, at high volume tertiary referral centres or orthopaedic units in the UK and Sweden, were randomly assigned to single stage (n=65) or two stage revision (n=75). The primary intention-to-treat outcome was the Western Ontario and McMasters Universities Osteoarthritis Index (WOMAC) score combining pain, stiffness, and functional limitations 18 months after randomisation. Secondary outcomes included surgical complications and joint infection. The economic evaluation undertaken on UK participants compared quality adjusted life years and costs between randomised groups.

Study answer and limitations
Single stage revision is not superior to two stage revision for treatment of prosthetic joint infection of the hip, as assessed by the WOMAC measure at 18 months (mean difference 0.13 (95% CI −8.20 to 8.46), P=0.98). Single stage revision gave quicker restoration of function and relief of pain (11.53 (3.89 to 19.17) at three months, P=0.003), was associated with fewer surgical complications (5 (8%) *v* 20 (27%)), and was cost effective (an incremental net monetary benefit of £11 167 (95% CI £638 to £21 696) at a £20 000 per quality adjusted life years threshold). The primary outcome was not infection eradication and the INFORM trial would have needed to have been unfeasibly large to be of sufficient size to use this as the main outcome. However, a validated core patient reported outcome measure was used.

What this study adds Single stage revision had a better outcome at three months, fewer surgical complications, and was cost effective.



Mean (95% CI) total WOMAC score after single stage and two stage revision for prosthetic joint infection of the hip during 18 months of follow-up

Funding, competing interests, and data sharing Funded by the National Institute for Health and Care Research. No competing interests declared. Anonymised data will be available to researchers for ethically approved research projects.

Trial registration ISRCTN10956306.

Oral antibiotics before colorectal surgery?

ORIGINAL RESEARCH Multicentre, double blind, randomised placebo controlled trial

Effect of oral antimicrobial prophylaxis on surgical site infection after elective colorectal surgery

Futier E, Jaber S, Garot M, et al; on behalf of the COMBINE study group

Cite this as: *BMJ* 2022;379:e071476
Find this at doi: 10.1136/2022-071476

Study question Does the use of adjunct oral antimicrobial prophylaxis to intravenous antibiotic prophylaxis before skin incision reduce surgical site infections in patients undergoing colorectal surgery?

Methods Multicentre, randomised, double blind, placebo controlled trial in adults scheduled for elective colorectal surgery. Patients were randomised to receive either a single 1 g dose of ornidazole or placebo orally 12 hours before surgery, in addition to intravenous antimicrobial prophylaxis (cefoxitin 2 g) before surgical incision. The primary outcome was the proportion of patients with surgical site infection within 30 days after surgery.

Primary and infection related secondary outcomes of participants in modified intention-to-treat population

Outcomes	Oral prophylaxis group (n=463)	Placebo group (n=463)
Primary outcome		
Any surgical site infection within 30 postoperative days	60 (13.0)	100 (21.6)
Secondary outcomes		
Superficial incisional infection	15 (3.2)	24 (5.2)
Deep incisional infection	22 (4.8)	37 (8.0)
Organ space infection	23 (5.0)	39 (8.4)

Study answer and limitations Of the 960 patients who were enrolled, 926 (96%) were included in the analysis. Surgical site infection occurred in 60 of 463 patients (13%) in the oral prophylaxis group and 100 of 463 (22%) in the placebo group (absolute difference −8.6%, 95% confidence interval −13.5% to −3.8%; relative risk 0.60, 95% confidence interval 0.45 to 0.80). This difference was statistically significant. Given that current French national guidelines for preoperative prophylaxis suggest enhanced anaerobic coverage, the use of cefoxitin, a second generation cephalosporin, for intravenous antimicrobial prophylaxis in this trial may limit external validity. Moreover, whether the effect of oral antimicrobial prophylaxis results from improved anaerobic coverage or from a decrease in the bioburden of oral antibiotics deserves further evaluation.

What this study adds Compared with placebo, oral antimicrobial prophylaxis using a single dose of 1 g ornidazole 12 hours before surgery as an adjunct to intravenous antibiotic prophylaxis resulted in significantly fewer surgical site infections within 30 days in adults undergoing elective colorectal surgery.

Funding, competing interests, and data sharing Funded by a grant from the French Ministry of Health and Clermont-Ferrand University Hospital. See full paper on bmj.com for competing interests. Data about the study will be shared with researchers of further studies on reasonable request upon sharing policy of Clermont-Ferrand University Hospital.

Study registration ClinicalTrials.gov NCT02618720.

COMMENTARY Adding an oral agent may reduce surgical site infections, says new trial

The perioperative use of prophylactic oral antibiotics for patients undergoing colorectal surgery has been studied for over 60 years,[3 4] following the dogma of maximising the reduction of bacterial bioburden in the gut lumen.[5] The same principle guides mechanical bowel preparation and enemas. Despite this dogma, the effects of either intervention on the gut microbiome and the effects of the gut microbiome on risk of surgical site infection are only recently being investigated.[5 6]

In their paper, Futier and colleagues report a multicentre placebo controlled trial on the efficacy of adding a preoperative oral antibiotic, ornidazole, to the usual perioperative intravenous antibiotic for preventing surgical site infection after colorectal surgery.[7] This pragmatic and well conducted clinical trial reports impressive

Researchers designing further studies should compare different oral antibiotic agents head to head

reductions in risk of surgical site infection with a single antibiotic dose administered 12 hours before surgery.

The authors also report statistically and clinically significant reductions in the risk of anastomotic leak (a secondary outcome of the study) associated with receipt of ornidazole.

Implementing Futier and colleagues' findings in real life will be challenging, however. Firstly, microbiologists and infectious disease doctors may argue that the effect of the intervention was mediated mainly by ornidazole's improved antimicrobial activity against anaerobic bacteria, and not the effect of an additional oral antibiotic in itself. The intravenous antibiotic used, cefoxitin, has suboptimal coverage of anaerobes, as evidenced by an update of French national guidelines that occurred during the trial.[8] This calls into question the relevance of the findings where complete intraoperative anaerobic coverage by metronidazole is the rule.

Secondly, the authors' choice of the study drug, ornidazole, is also arguable. Previous clinical trials used non-absorbable antibiotics such as neomycin, whereas others used antibiotics with systemic absorption and activity against aerobic bacteria, such as ciprofloxacin.[9] The heterogeneity of antibiotic regimens evaluated in the existing literature could hamper widespread adoption.

Thirdly, patients with a body mass index of more than 35 were excluded from the trial, which is regrettable because obesity is an increasingly prevalent risk factor for surgical site infection after colorectal surgery,[10] and these patients are likely to benefit the most from additional preventive measures.

Finally, the overall risk of surgical site infection in the placebo group (22%) was

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DRAGOS CONDREA/ALAMY

unexpectedly high for elective colorectal surgery.[11] Experienced surgeons could argue that this high rate is unlikely to reflect usual practice and that other preventive measures should be optimised before introducing an additional prophylactic antibiotic regimen with potential adverse effects.

Bowel preparation

Futier and colleagues' trial does not provide a definitive answer to the most pressing question of whether mechanical bowel preparation is a useful adjunct to oral antibiotics.[12] Use of mechanical bowel preparation was left to the surgeons' discretion, and it was given to a third of all participants. A prespecified subgroup analysis suggested that the reduction in risk of surgical site infection associated with ornidazole was greater for patients treated with mechanical bowel preparation (compared with those treated without). Bowel preparation without oral antibiotics is, however, associated with higher risk of surgical site infection, which is why the World Health Organization recommends strongly against this practice.[13] This was confirmed in the current trial: among participants given a placebo, the authors found a significantly increased risk of surgical site infection associated with mechanical bowel preparation compared with no mechanical bowel preparation.

Use of bowel preparation (and oral antibiotics) before colon surgery still varies widely—from 30% in Europe (mostly without oral antibiotics)[14] to 55% in Australia (mostly with oral antibiotics)[15] to around 80-95% in the United States (mostly with oral antibiotics).[16] Although a recent network meta-analysis[17] suggests that oral antibiotics alone are superior to oral antibiotics plus mechanical bowel preparation for reducing surgical site infections, additional evidence is still required to convince clinicians to change practice.

For this reason, the results of the ORALEV2 study[18] comparing oral antibiotics with placebo in patients not receiving bowel preparation is eagerly awaited. Until then, researchers designing further studies should compare different oral antibiotic agents head to head, avoid trial arms where mechanical bowel preparation is administered without oral antibiotics, and plan studies of the gut microbiome in patients having colorectal surgery (with an additional focus on development of antibiotic resistance).[20]

Adding a preoperative oral antibiotic is one of several interventions, across different indications, which opposes conventional wisdom to limit antibiotic use to reduce antimicrobial resistance. The findings of this study and others suggest that there may be occasions when using more antibiotics provides additional benefits that outweigh the risks.[21 22]

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Find the full version with references at http://dx.doi.org/10.1136/bmj.o2547

Novel antihyperglycaemic drugs and prevention of chronic obstructive pulmonary disease exacerbations among patients with type 2 diabetes

Pradhan R, Lu S, Yin H, et al

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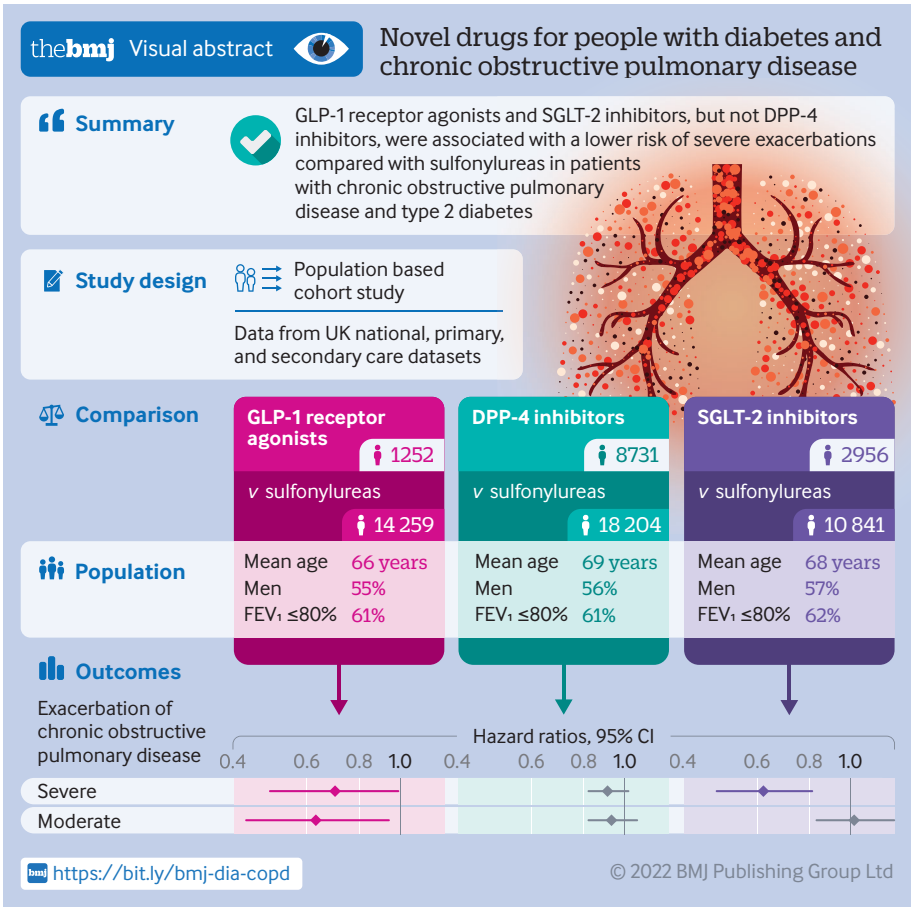
Find this at doi: 10.1136/bmj-2022-071380

Study question Is the use of glucagon-like peptide 1 (GLP-1) receptor agonists, dipeptidyl peptidase 4 (DPP-4) inhibitors, and sodium-glucose co-transporter-2 (SGLT-2) inhibitors, associated with a decreased risk of exacerbations of chronic obstructive pulmonary disease among patients with chronic obstructive pulmonary disease and type 2 diabetes?

Methods This population based cohort study used data from the UK Clinical Practice Research Datalink to compare patients with chronic obstructive pulmonary disease and type 2 diabetes starting treatment with GLP-1 receptor agonists (n=1252), DPP-4 inhibitors (n=8731), and SGLT-2 inhibitors (n=2956) with those starting sulfonylureas (n=14 259, n=18 204, and n=10 841, respectively) with respect to the incidence of severe and moderate exacerbations of chronic obstructive pulmonary disease.

Study answer and limitations GLP-1 receptor agonists were associated with a 30% decreased risk of severe exacerbation (3.5 *v* 5.0 events per 100 person years; hazard ratio 0.70, 95% confidence interval 0.49 to 0.99) and moderate exacerbation (0.63, 0.43 to 0.94). DPP-4 inhibitors were associated with a modestly decreased incidence of severe exacerbation (4.6 *v* 5.1 events per 100 person years; hazard ratio 0.91, 0.82 to 1.02) and moderate exacerbation (0.93, 0.82 to 1.07), with confidence intervals including the null value. SGLT-2 inhibitors were associated with a 38% decreased risk of severe exacerbation (2.4 *v* 3.9 events per 100 person years; hazard ratio 0.62, 0.48 to 0.81) but not moderate exacerbation (1.02, 0.83 to 1.27). Given the observational nature of the study, these findings will need to be investigated in future randomised controlled trials.



Relative risks for severe exacerbation of chronic obstructive pulmonary disease comparing novel antihyperglycaemic drugs with sulfonylureas

Drug	Patients	Events	Person years	Incidence rate (95% CI)*†	Weighted HR (95% CI)†
Sulfonylureas	14 259	1261	24 126	5.0 (4.7 to 5.3)	1.00 (reference)
Glucagon-like peptide 1 receptor agonists	1252	64	1853	3.5 (2.7 to 4.4)	0.70 (0.49 to 0.99)
Sulfonylureas	18 204	1827	30 537	5.1 (4.9 to 5.4)	1.00 (reference)
Dipeptidyl peptidase 4 inhibitors	8731	611	13 219	4.6 (4.3 to 5.0)	0.91 (0.82 to 1.02)
Sulfonylureas	10 841	1006	15 740	3.9 (3.6 to 4.2)	1.00 (reference)
Sodium-glucose co-transporter-2 inhibitors	2956	92	3803	2.4 (2.0 to 3.0)	0.62 (0.48 to 0.81)

CI=confidence interval; HR=hazard ratio.
*Per 100 person years.
†Weighted using propensity score fine stratification.

What this study adds

Novel antihyperglycaemic drugs, such as GLP-1 receptor agonists and SGLT-2 inhibitors, may have benefits in preventing exacerbations of chronic obstructive pulmonary disease.

Funding, competing interests, and data sharing
This study was funded by a foundation scheme grant from the Canadian Institutes of Health Research.

See full paper on bmj.com for competing interests.
As the Clinical Practice Research Datalink database is not publicly available, no source data can be shared.