Appendicectomy plus standard medical therapy versus standard medical therapy alone for maintenance of remission in ulcerative colitis (ACCURE): a pragmatic, open-label, international, randomised trial

*The ACCURE Study Group**

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See Online for appendix

Summary

Background The appendix might have an immunomodulatory role in ulcerative colitis. Appendicectomy has been suggested as a potentially therapeutic intervention to maintain remission in ulcerative colitis. We aimed to evaluate the clinical effectiveness of laparoscopic appendicectomy in maintaining remission in patients with ulcerative colitis.

Methods We did a pragmatic, open-label, international, randomised controlled superiority trial in 22 centres across the Netherlands, Ireland, and the UK. Patients with established ulcerative colitis who were in remission but had been treated for disease relapse within the preceding 12 months were randomly assigned (1:1) to undergo appendicectomy plus continued maintenance medical therapy (intervention group) or to continue maintenance medical therapy alone (control group). Randomisation was done with a central, computer-generated allocation concealment, stratified by disease extent. Patients and treating physicians were unmasked to group allocation. The prespecified primary outcome was the proportion of patients with a disease relapse within 1 year, predefined as a total Mayo score of 5 or higher with an endoscopic subscore of 2 or 3, or, in absence of endoscopy, based on a centrally independent masked review by a critical event committee as an exacerbation of abdominal symptoms (eg, elevated stool frequency subscore of ≥1 point from baseline) with a rectal bleeding subscore of ≥1 or faecal calprotectin level above 150 µg/g or necessitating treatment intensification other than mesalazine. Analyses were done on an intention-to-treat principle. This trial is complete and was registered with the Netherlands Trial Register (NTR2883) and ISRCTN (ISRCTN60945764).

Findings Between Sept 20, 2012, and Sept 21, 2022, 1386 patients were screened. 201 patients were randomly assigned to the appendicectomy group (n=101) or the control group (n=100). After exclusion of four patients due to eligibility violations (three had active disease and one received biological agents at time of randomisation), 99 patients in the appendicectomy group and 98 patients in the control group were included in the intention-to-treat analyses. The 1-year relapse rate was significantly lower in the appendicectomy group than in the control group (36 [36%] of 99 patients *vs* 55 [56%] of 98 patients; relative risk 0·65 [95% CI 0·47–0·89]; p=0·005; adjusted p=0·002). Adverse events occurred in 11 (11%) of 96 patients in the appendicectomy group and 10 (10%) of 101 patients in the control group. The most frequently reported adverse events were postoperative temporary self-limiting abdominal pain in the appendicectomy group (three [3%] patients) and skin rash in the control group (three [3%] patients). Two cases (2%) of low-grade appendiceal mucinous neoplasm were incidentally found in resected appendix specimens in the appendicectomy group. Serious adverse events occurred in two (2%) of 96 patients who underwent appendicectomy and none in the control group. There were no deaths.

Interpretation Appendicectomy is superior to standard medical therapy alone in maintaining remission in patients with ulcerative colitis.

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Introduction

Ulcerative colitis is a chronic inflammatory bowel disease affecting an estimated 5 million individuals globally as of 2023, with a rising incidence worldwide.[1–3] This disease affects the mucosal layer of the colon and rectum, and is characterised by a relapsing-remitting course. The inflammation typically starts in the rectum (proctitis) and with subsequent relapses it might extend proximally, involving the entire colon (pancolitis). Clinical symptoms of active colitis include frequent and urgent bowel movements, rectal bleeding, abdominal pain, and fatigue, and the condition is associated with an impaired health-related quality of life.[4–6]

The therapeutic goal in ulcerative colitis is to maintain health and related quality of life and avoid disability by adequately inducing and maintaining clinical and

Research in context

Evidence before this study

An inverse association between appendicectomy and the development of ulcerative colitis was first reported in 1987, with subsequent case-control studies confirming this observation, and suggesting a possible role of the appendix in ulcerative colitis. In 2016, our research group did a systematic review and meta-analysis of available (case-control) studies. This analysis showed that previous appendicectomy was associated with a significantly reduced risk of developing ulcerative colitis, with an overall odds ratio of 0·39 (95% CI 0·29–0·52). Additionally, in 2012, our group published a systematic review assessing the effect of appendicectomy on the clinical course of ulcerative colitis. This review included six observational studies (five case-control studies and one cohort study) comprising 2532 patients. Although the heterogeneity among these studies precluded a formal meta-analysis, and data were scarce and conflicting, most studies suggested a beneficial effect of appendicectomy on the disease course in ulcerative colitis. We searched PubMed for literature published between Jan 1, 1998, and Oct 31, 2024, using the terms ("appendectomy"[MeSH Terms] OR "append*"[Title/Abstract]) AND ("colitis, ulcerative"[MeSH Terms] OR "ulcerative colitis"[Title/Abstract] OR "ulcerous colitis"[Title/Abstract] OR "colitis ulcerativa"[Title/Abstract] OR "colitis ulcerosa"[Title/Abstract] OR "ulcerative proctocolitis"[Title/Abstract]) AND ("Randomized Controlled Trial"[Publication Type] OR "Controlled Clinical Trial"[Publication Type] OR "random*"[Title/Abstract] OR "crossover*"[Title/Abstract] OR "cross over*"[Title/Abstract] OR ("doubl*"[Title/Abstract] AND "blind*"[Title/Abstract]) OR ("singl*"[Title/Abstract] AND "blind*"[Title/Abstract]) OR "trial*"[Title/Abstract] OR "intervention stud*"[Title/Abstract]). This searched confirmed that no randomised controlled trial of appendicectomy as an intervention in ulcerative colitis has been done to date.

Added value of this study

The ACCURE trial is the first randomised controlled trial evaluating the clinical effectiveness of appendicectomy in maintaining remission in patients with ulcerative colitis without advanced medical therapy (ie, biologicals or small molecules). This trial shows that laparoscopic appendicectomy, in addition to standard medical therapy, significantly reduces the relapse rates within 1 year.

Implications of all the available evidence

Appendicectomy might be an effective and safe option for reducing the relapse rate within 1 year in patients with ulcerative colitis in addition to standard medical therapy, offering a potential addition to standard medical therapies.

endoscopic remission.[7] Therefore, current medical therapy follows a step-up strategy to reduce inflammation until remission is reached, thereby preventing disease-related complications, such as colectomy, and development of colorectal neoplasia.[8]

The cause of ulcerative colitis is multifactorial, encompassing genetic predispositions, environmental triggers, microbial composition, and dysregulated immune responses. Recent studies[9,10] have highlighted the potential immunomodulatory role of the appendix in ulcerative colitis. The appendix is thought to have an important role by producing inflammatory cytokines, triggering cascade responses and thereby contributing to disease progression.[9,10] Preliminary case-control and small-scale cohort studies have indicated the potential beneficial effects of appendicectomy and suggested it as a therapeutic strategy supplementing medical treatments, which form the mainstay of modern ulcerative colitis management.[11,12] No randomised controlled trial of this intervention has been done to date. We aimed to evaluate the clinical effectiveness of laparoscopic appendicectomy in maintaining remission in patients with ulcerative colitis.

Methods

Study design

We did this investigator-initiated, two-arm, pragmatic, open-label, international, randomised controlled superiority trial at 22 sites across the Netherlands, Ireland, and the UK. The central ethics committee and institutional review board at each participating Dutch and Irish site, and the Research Ethical Committee in the UK approved the trial protocol and any amendments. The final versions of the protocol and statistical analysis plan were completed on May 18, 2021, and Aug 28, 2023, respectively.[13,14] Patient enrolment was completed on Sept 29, 2022, with database closure on Jan 26, 2024. The trial adhered to Good Clinical Practice guidelines and the Declaration of Helsinki.[15] Written informed consent was obtained from all patients before trial-related procedures. This trial is registered with the Netherlands Trial Register (NTR2883) and ISRCTN (ISRCTN60945764).

Patients

Eligible patients were aged 18 years or older, had established ulcerative colitis and were in remission, but had required treatment for an episode of active disease within the preceding 12 months. Remission was defined as a Mayo score of 2 or lower, with stool frequency, rectal bleeding, and physician's global assessment subscores of 0 or 1, confirmed by a Mayo endoscopic score of 0 or 1 within 3 months before randomisation.[16] In cases in which endoscopy could not be done due to restrictions during the COVID-19 pandemic, a protocol amendment in 2020 allowed remission to be confirmed by a faecal calprotectin level of below 150 µg/g in patients with a previously documented history of raised faecal calprotectin levels (>500 µg/g) during a previous disease

flare. Patients were excluded if they had previous appendicectomy or major abdominal surgery that would preclude a safe procedure; suspicion of Crohn's disease; received any biological agents within 3 months before randomisation; a partial Mayo score of 3 or more; an endoscopic Mayo score of more than 1; or medical comorbidities that increase perioperative morbidity. All endoscopy and faecal calprotectin assessments were done locally, with calprotectin used only when endoscopy could not be done, such as during COVID-19 restrictions. Complete enrolment criteria are detailed in the appendix (p 5).

Randomisation and masking

Eligible patients were randomly assigned in a 1:1 ratio to either undergo laparoscopic appendicectomy and continue standard medical therapy (appendicectomy group) or to continue standard medical treatment alone (control group). Randomisation was done by the research team using the computer-generated randomisation software ALEA and was stratified according to disease extent based on the Montreal classification (proctitis, left-sided colitis, pancolitis).[17] Patients and treating physicians were not masked to allocation during the trial. Group allocation was concealed from the critical event committee, which remained masked to ensure unbiased assessment of clinical relapses.

Procedures

Patients in the appendicectomy group underwent laparoscopic appendicectomy within 9 weeks of randomisation. The appendix, including the cuff of caecal pole surrounding the appendiceal orifice, was removed using a laparoscopic endostapler by or under direct supervision of a senior colorectal surgeon; a detailed standard operating procedure is listed in the appendix (p 6). Standard day-care procedures were followed across sites, similar to those used for typical day-case laparoscopic colorectal operations. Patients were typically discharged on the same day, provided they met standard discharge criteria: being afebrile and clinically stable, tolerating oral intake, mobilising independently, having adequate pain control with oral analgesia, and showing no signs of complications. No standard additional postoperative antibiotics were prescribed. Both groups continued their medical therapy at the discretion of the treating gastroenterologist.

Follow-up included outpatient clinic visits or telephone consultations at 3, 6, 9, and 12 months after appendicectomy or after randomisation for the control group. Postoperative complications and surgical morbidity were assessed at 6 weeks after appendicectomy. Relapse data, disease activity, outpatient clinic visits, hospital admission, and medication use were assessed quarterly. Disease activity was measured using the total Mayo score at baseline and 12 months, and the non-invasive partial Mayo score at 3, 6, and 9 months.[16] An endoscopy was done at the time of clinical suspicion of a relapse or at the end of the 12-month trial period to objectively assess mucosal appearance and determine the total Mayo score. Health-related quality of life was measured with the EQ-5D 3-level utility score (EQ-5D-3L; range –0·33 to 1·00, with higher scores indicating better health status),[18] the European Organisation for Research and Treatment of Cancer quality of life core score (EORTC QLQ-C30; range 0 to 100, with higher scores indicating better global quality of life),[19] and Inflammatory Bowel Disease Questionnaire (IBDQ; range 32 to 224, with higher scores indicating better quality of life),[20] and questionnaires were completed at baseline and quarterly throughout the 12-month follow-up period. The protocol was amended after 79 patients had been enrolled to remove concomitant immunomodulators as an exclusion criterion (to increase the trial's generalisability and external validity, and to enhance recruitment rates) and to include a dichotomous patient-reported global change assessment at 12 months follow-up, to assess the clinical relevance of IBDQ changes. The trial design and procedures are detailed in the appendix (p 11).

Outcomes

The primary outcome was the proportion of patients with a disease relapse within 1 year. Relapse was predefined as a total Mayo score of 5 or higher with an endoscopic subscore of 2 or 3. During the COVID-19 pandemic, the protocol was amended to overcome logistical challenges related to the restricted availability of endoscopic procedures. To ensure the study's continuity and maintain data integrity, the relapse definition was expanded to include, in cases of no endoscopy, an exacerbation of abdominal symptoms (elevated stool frequency subscore of ≥1 point from baseline) with a rectal bleeding subscore of 1 or more, or faecal calprotectin level above 150 µg/g, or necessitating treatment intensification other than mesalazine. This clinical definition was assessed in a centrally independent review by a critical event committee, comprising an inflammatory bowel disease gastroenterologist and surgeon, who were masked to group allocation. The comprehensive relapse definition is available in the appendix (p 7).

Secondary outcomes included number of relapses per patient at 12 months; time to first relapse (defined as the time from the date of randomisation to the first day of clinical symptoms of an endoscopically or clinically confirmed relapse; patients who did not relapse during follow-up were censored at the time of their last available follow up assessment); disease activity (as measured using the partial Mayo score at 3, 6, and 9 months, and the total Mayo score at 12 months); total number of colectomies at 1 year; medication use (none, topical therapy, oral mesalazine, systemic steroid, immunomodulators, and biologic agents; for each category, use was documented as a binary outcome [yes or no] at each time point) at 3, 6, 9, and 12 months; and health-related

quality of life (EQ-5D-3L, EORTC-QLQ-C30, IBDQ at 3, 6, 9, and 12 months, and the global change assessment at 12 months).

Safety assessments were based on adverse events or serious adverse events that occurred between appendicectomy or randomisation and the 3-month follow-up (appendix pp 78–79). Intraoperative and postoperative complications were reported using the Clavien–Dindo grade.[21] Major complications were defined as Clavien–Dindo grade of III or more.

Data on sex were reported based on medical records, which were documented according to the individual's national identification documents. No planned interim efficacy analysis was scheduled. However, an interim safety analysis was conducted by the data monitoring and safety committee in March, 2021, following published research suggesting a relation between appendicectomy and development of colorectal neoplasia in ulcerative colitis.[22] The trial continued without recommendation for early termination.

Statistical analysis

We assumed that the relapse rate at 12 months would be reduced by 50%, from 40% in the control group to 20% in the appendicectomy group. To detect this clinically relevant difference in relapse, with 80% power at a 5% two-sided significant level, we calculated that 82 participants per group were needed to evaluate whether appendicectomy plus medical therapy was superior to medical therapy alone. Accounting for a 10% dropout rate, we aimed to enrol 92 patients per group. In Sept 4, 2019, the trial started in the UK as the ACCURE-UK 2 trial with an identical protocol to improve recruitment and increase the statistical power to 90%. The recruitment target was revised to 244 patients, with the aim of analysing 218 patients (109 per study group). However, owing to the COVID-19 pandemic pressures, the trial required a prolonged recruitment period and enrolment was closed in Sept 29, 2022.

Prespecified outcomes[14] and analyses are provided in the appendix (pp 72–80). The demographic and clinical characteristics of the patients at baseline were summarised descriptively. All primary analyses (primary and secondary outcomes) were done on an intention-to-treat principle. χ^2 test of two proportions was used to compare relapse rates between the appendicectomy and control group, reported with relative risk (RR) and corresponding 95% CIs. Logistic regression on the 1-year relapse rate was used to adjust for disease extent as the stratification factor during randomisation to obtain correct variance estimates and explore the interaction between treatment and disease extent, and to adjust for age at time of randomisation, sex, current smoker, disease extent, time between start of most recent disease exacerbation and randomisation. In addition, the interaction between treatment and country (the Netherlands *vs* the UK) was exploratively addressed.

A pragmatic intention-to-treat analysis was done for the primary endpoint only and included relapses during the appendicectomy waiting period. Poisson regression was done to compare the number of relapses per patient reported with RR and 95% CIs, and Kaplan–Meier survival analysis with log-rank testing to compare the time to first relapse between the groups. Medication use over time was descriptively reported by number and percentages, and generalised estimating equation was used to analyse the effect of appendicectomy on medication use over time within treatment, time and the interaction between treatment, and time as model parameters, reported with odds ratios (ORs) and 95% CIs.

Additional generalised linear mixed models were applied to investigate whether a different pattern of change over time existed between the groups in the Mayo score and health-related quality of life, and were reported with mean differences (MD) and 95% CIs. The optimal covariance structure for the repeated measures data were determined based on visual

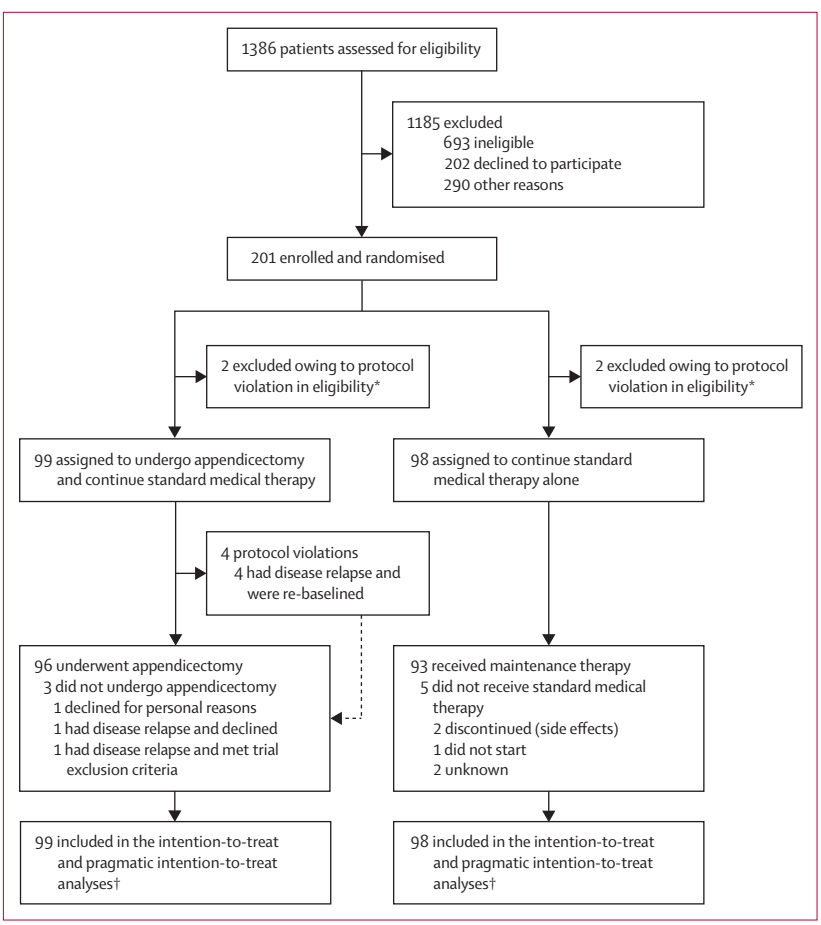

Figure 1: **Trial profile**

*Three patients were excluded because of active disease (two in appendicectomy group and one in the control group) and one patient in the control group was excluded due to receiving biological agents at the time of randomisation. †In the pragmatic intention-to-treat analysis, the same patients and allocation groups were used as in the intention-to-treat analysis, with the distinction in the relapse outcome of the re-baselined patients during the waiting period for appendicectomy.

assessment and Akaike's information criterion values. Covariance structures evaluated included unstructured, autoregressive 1, Toeplitz matrix, and compound symmetry. The cohort-specific minimum clinically important difference in the IBDQ was determined to assess the clinical relevance of differences in the IBDQ, by using a clinical anchor-based method calculating the difference in IBDQ change scores from baseline between patients responding yes or no to the global change question. The correlation coefficient between the IBDQ change score and the global change question was calculated by Pearson's correlation method, with a minimum correlation of at least 0·30 regarded as acceptable.[23–25]

Safety data were reported by treatment group and analysed based on the treatment actually received (as-treated analysis), with absolute risk differences (ARD) and corresponding 95% CIs.

No adjustments were made for multiplicity in secondary outcome analyses, and these should be considered exploratory. Missing outcome data were not imputed (appendix p 16). All statistical tests were two-sided and p values less than 0·05 were considered statistically significant. Additional details of the statistical methods were published and listed in the appendix (pp 8–9).[14] Data were analysed with SPSS (version 28.0.1.1) and Stata (version 17.0). All outcomes and statistical methods presented in this Article were prespecified in the study protocol and corresponding statistical analysis plan. Additionally, a post-hoc sensitivity analysis of the primary outcome was done, limited to patients with available endoscopic follow-up data.

The patient safety and trial evaluation were monitored by an independent data monitoring and safety committee (appendix p 5).

	Appendicectomy group (n=99)	Control group (n=98)
Age, years	42·2 (12·5)	43·2 (13·0)
Age at diagnosis, years	33·7 (11·0)	35·5 (12·6)
Sex		
Female	56 (57%)	55 (56%)
Male	43 (43%)	43 (44%)
Disease duration, years*	5·1 (1·8–11·6)	5·3 (1·8–11.3)
Smoking status		
Current smoker	14 (14%)	12 (12%)
Former smoker	39 (39%)	47 (48%)
BMI, kg/m²†	24·3 (3·4)	24·8 (3·7)
Classification of physical status‡ of more than category ASAII	0	1 (1%)
Primary sclerosing cholangitis†	1 (1%)	0
Family history of inflammatory bowel disease†	24 (24%)	30 (31%)
Medication at baseline		
No medication	9 (9%)	4 (4%)
Topical therapy	23 (23%)	22 (22%)
Oral mesalazine	76 (77%)	81 (83%)
Systemic steroids	1 (1%)	1 (1%)
Immunomodulators	6 (6%)	12 (12%)
Extent of disease§		
Proctitis, E1	38 (38%)	39 (40%)
Left-sided colitis, E2	34 (34%)	36 (37%)
Pancolitis, E3	27 (27%)	23 (23%)
Time from start of most recent exacerbation ulcerative colitis before randomisation, weeks†	30·7 (17·9)	32·0 (19·4)
Partial Mayo score		
0	73 (74%)	77 (79%)
1	24 (24%)	17 (17%)
2	4 (4%)	2 (2%)
Total Mayo score		
0	32 (41%), n=79	44 (51%), n=86
1	38 (48%), n=79	31 (36%), n=86
2	9 (11%), n=79	11 (13%), n=86
Endoscopic subscore=1	33 (42%), n=79	31 (36%), n=86

Data are mean (SD), n (%), or median (IQR). *Disease duration is the time since diagnosis of ulcerative colitis to randomisation. †Data were missing for one patient in the control group for BMI; for 27 patients in the appendicectomy group and 32 in the control group for primary sclerosing cholangitis; for one patient in the appendicectomy group for family history of inflammatory bowel disease; and for five patients in the appendicectomy group and two in the control group for most recent exacerbation of ulcerative colitis. ‡Classification of physical status according to the American Society of Anesthesiologists. §According to Montreal classification.

Table: **Baseline demographic and disease characteristics (intention-to-treat population)**

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, writing of the report.

Results

Between Sept 20, 2012, and Sept 21, 2022, 1386 patients were assessed for eligibility, of whom 201 were randomly assigned to the appendicectomy group (n=101) or the control group (n=100). After exclusion of four patients due to protocol violation in eligibility (three had active disease and one received biological agents at time of randomisation), 99 patients in the appendicectomy group and 98 patients in the control group were included in the intention-to-treat and pragmatic intention-to-treat analyses (figure 1). Of the total participants, 168 were enrolled in the Dutch trial arm (which also included two participants from the Irish site) and 29 in the ACCURE-UK trial 2 arm. The demographics and clinical characteristics of the patients were similar across the groups at baseline (table). Mean age was 42·2 years (SD 12·5) in the appendicectomy group and 43·2 years (SD 13·0) in the control group. 56 (57%) of 99 participants in the in the appendicectomy group and 55 (56%) of 98 in the control group were women. Most patients (76 [77%] of 99 in the appendicectomy group and 81 [83%] of 98 in the control group) were using oral mesalazine as maintenance therapy. Seven (7%) patients in the appendicectomy group and two (2%) patients in the control group had previously used biological therapy for their most recent exacerbation, but only more than 3 months before randomisation; median time to appendicectomy was 2·0 months (IQR 1·0–3·0).

Six (6%) patients in the appendicectomy group had a relapse during the waiting period for appendicectomy. Among these, four patients were treated to complete remission (ie, re-baselined) and subsequently underwent appendicectomy, one patient achieved remission but opted to not have an appendicectomy, and one patient started a biological agent and therefore met the trial's exclusion criteria and became ineligible for appendicectomy. Additionally, one patient declined appendicectomy after randomisation. Thus, three patients in the appendicectomy group ultimately did not undergo appendicectomy.

At 1 year, the relapse rate was significantly lower in the appendicectomy group than in the control group (36 [36%] of 99 patients *vs* 55 [56%] of 98 patients; RR 0·65 [95% CI 0·47–0·89]; p=0·005; adjusted p=0·002; figure 2). Two of the 63 patients who remained in remission after appendicectomy had a relapse during the waiting period and were re-baselined. When considering these two patients as relapses in the pragmatic intention-to-treat analysis, the results were similar (38 [38%] of 99 patients *vs* 55 [56%] of 98 patients; RR 0·68 [95% CI 0·50–0·93]; p=0·01). For details of other prespecified analysis for the primary outcome and for the post-hoc sensitivity analysis see the appendix (pp 12, 17).

In the appendicectomy group, 29 (81%) of 36 relapsed patients had one relapse each and seven (19%) had two relapses each, whereas in the control group, 38 (69%) of 55 relapsed patients had one relapse each, 12 (22%) patients had two relapses each, and five (9%) patients had three relapses each (RR 0·85 [95% CI 0·59–1·24]; p=0·40). Median time-to-first relapse was not reached in the appendicectomy group and was 50·57 weeks (95% CI 37·59–63·56) in the control group (hazard ratio for relapse 0·54 [95% CI 0·36–0·82]; p=0·003; figure 3A). Disease activity over the trial period showed increases in the total and partial Mayo scored in both groups, with the appendicectomy group showing a lower total mayo score at 12 months (mean 1·2 points [SD 1·8]) compared with the control group (1·8 points [SD 2·3]; MD 0·70 [95% CI 0·11–1·29]; p=0·02). There were no colectomies done during the 12-month follow-up period.

Medication use during the trial period is shown in figure 4. Biological agents were initiated less frequently in the appendicectomy group than in the control group over the trial follow-up period (OR 0·003 [95% CI 0·00–0·27]; p=0·01). Both groups showed significantly decreasing use of oral mesalazine (OR 0·82 [95% CI 0·69–0·97]; p=0·02) over the trial period. At 12 months, for those with available data, 58 (62%) of 94 patients in the appendicectomy group and 73 (80%) of 91 patients in the control group used mesalazine that there were no other significant changes in medication use in the study.

The EQ-5D-3L utility score and the EORTC QLQ-C30 scores showed no significant between-group differences

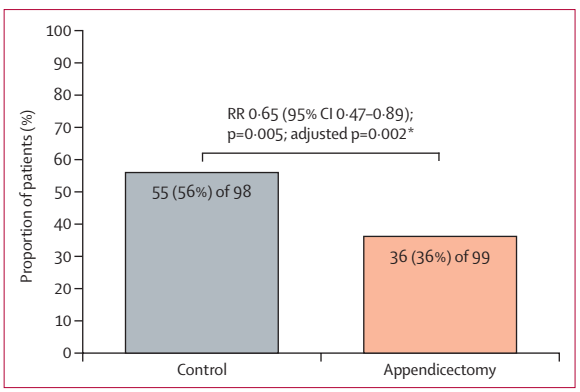

Figure 2: **Primary outcome result**
*Adjusted for age, sex, current smoking, disease extent, and weeks since most recent exacerbation.

over time. The total IBDQ score and IBDQ bowel symptoms domain score significantly differed over time between the groups in favour of the appendicectomy group (total IBDQ score: MD 3·80 [95% CI 1·20–6·40], p=0·005; IBDQ bowel symptoms domain score: MD 0·16 [95% CI 0·06–0·25], p=0·002), with, at 12 months, a mean total IBDQ score difference between the groups of 6·4 points (95% CI 2·3–15·0). The mean total IBDQ score change between the groups was in favour of the appendicectomy group, with a mean difference between the groups of 11 points (95% CI 2·6–19·6; p=0·01). There were no significant differences in the other IBDQ subdomains. The minimum clinically important difference was calculated as 17·8 point change in IBDQ score (95% CI 5·8–29·9). Comprehensive analyses of secondary outcomes and missing secondary endpoint data are summarised in the appendix (pp 13–16).

Postoperative complications occurred in five (5%) of 96 patients who underwent appendicectomy, of which two (2%) were classified as major and reported as serious adverse event. One patient had an internal herniation requiring laparotomy and another had an intra-abdominal haematoma that was successfully drained. Both patients remained in remission during follow-up. No serious adverse events were reported in the control group (ARD 2·1% [95% CI –0·77 to 4·9]; p=0·24). Adverse events were reported in 11 (11%) of 96 patients in the appendicectomy group and in 10 (10%) of 101 patients in the control group (ARD 1·6% [95% CI –7·1 to 10·2]; p=0·72). The most frequently reported adverse events were postoperative temporary self-limiting abdominal pain, which occurred in three (3%) patients in the appendicectomy group, and skin rash, reported in three (3%) patients in the control group. Two cases (2%) of low-grade appendiceal mucinous neoplasm were incidentally found in resected appendix specimens in the appendicectomy group and did not require further treatment. Safety and postoperative complication outcomes are listed in the appendix (p 17). There were no deaths reported in either group.

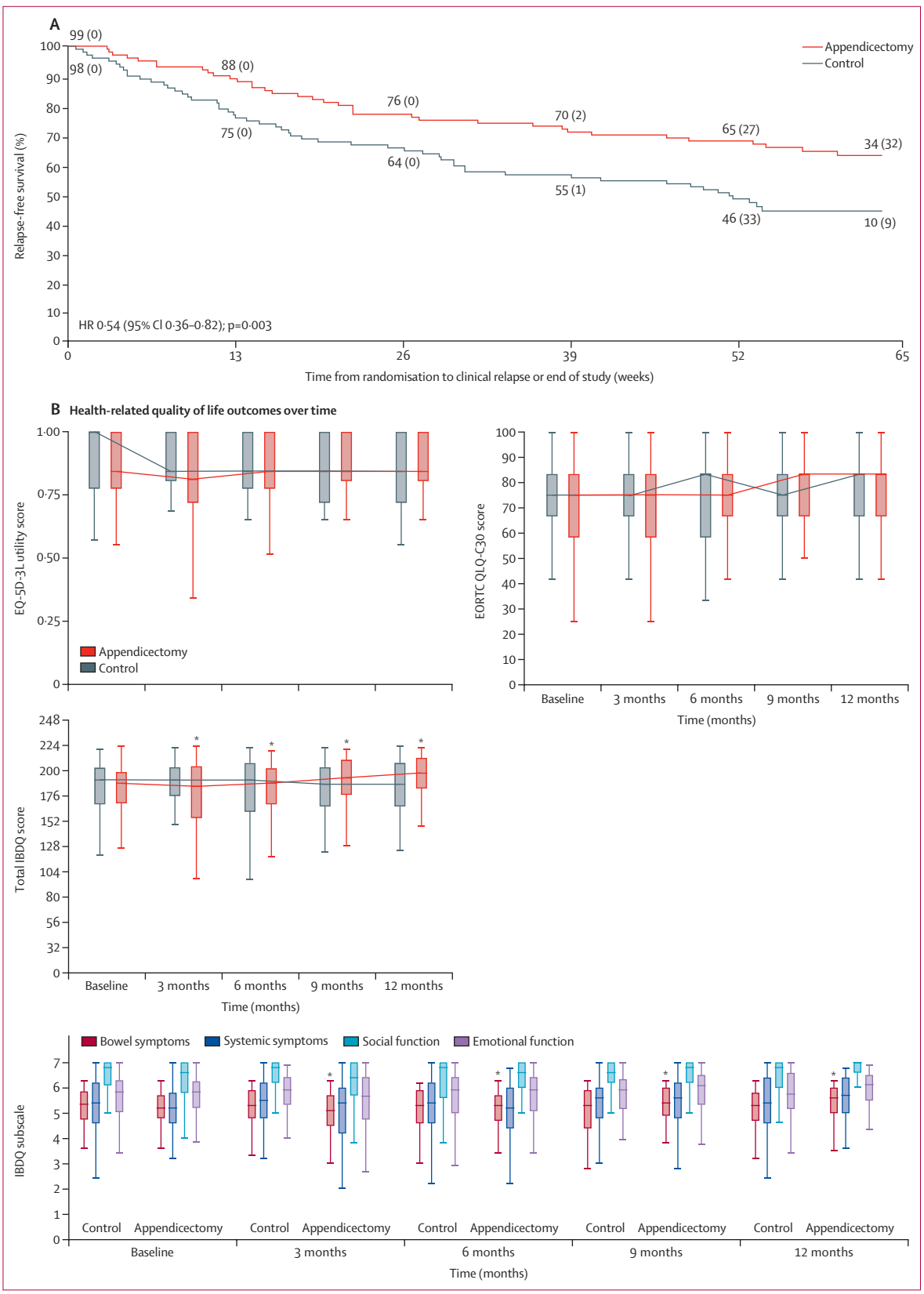

Figure 3: **Secondary outcome results**

(A) Kaplan–Meier survival analysis with log-rank testing. Kaplan–Meier plot with log-rank testing comparing the time-to-first-relapse following randomisation between the appendicectomy and control groups. Hazard rate is unadjusted for age, sex, current smoking, disease extent, and weeks since most recent exacerbation. Data at each timepoint are number at risk (number censored). (B) Health-related quality-of-life outcomes over time. EQ-5D-3L=EQ-5D 3-level. IBDQ=Inflammatory Bowel Disease Questionnaire. *p<0·05 in generalised linear mixed models.

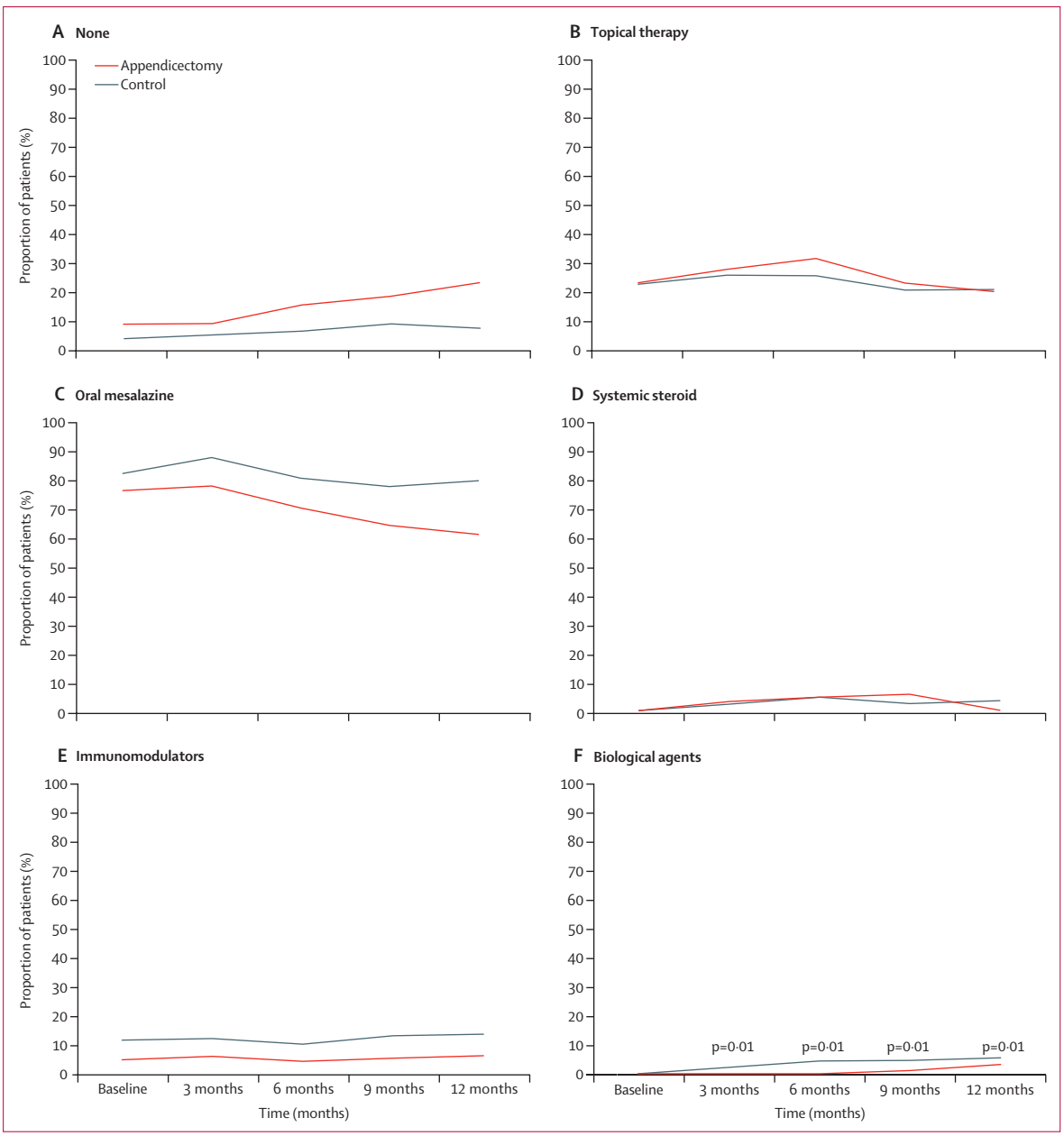

Figure 4: **Medication use**

(A) None. (B) Topical therapy, defined as rectal enemas or suppositories. (C) Oral mesalazine. (D) Systemic steroid, as oral corticosteroids (prednisone or equivalents or budesonide). (E) Immunomodulators (ie, azathioprine, methotrexate, thioguanine). (F) Biological agents, such as biological medication (anti-TNF, integrin antibody, or small molecules such as JAK inhibitors). In the generalised estimating equation, the baseline measurement was included as a fixed effect to adjust for initial differences between groups. Data for medication use were available for 97 patients in the appendicectomy group and 93 in the control group at 3 months; 89 and 90, respectively, at 6 months; 91 and 87, respectively, at 9 months; and 94 and 91, respectively, at 12 months.

Discussion

This randomised controlled trial showed that appendicectomy was superior to medical therapy alone in maintaining remission in patients with ulcerative colitis within 1 year. At 12 months, around a third of the patients in the appendicectomy group had a relapse compared with more than half of those in the control group. This significant relative risk reduction (RR 0·65 [95% CI 0·47–0·89]) suggests that appendicectomy might be a viable additional therapeutic option for maintaining remission in ulcerative colitis. Furthermore, patients who underwent appendicectomy were significantly more likely to maintain lower disease activity, reduce the initiation of biological agents, and improve health-related quality of life compared with patients who received standard medical therapy alone at 1 year.

The relapse rates in the trial were higher in both groups than initially expected, and several factors might have contributed to this difference. First, the protocol was amended to include patients on immunomodulators, who exhibit higher relapse rates[26] than the reported 37% in patients on oral mesalazine within 1 year.[27] Second, the efficacy–effectiveness gap, reflecting differences between outcomes in clinical trials and real-world practice, might also have had an effect on these relapse rates. This pragmatic trial more closely resembles real-world practice, by maintaining standard medical therapy at the discretion of the treating gastroenterologist in both groups, rather than enforcing standardised medication. This approach, combined with the potential issue of non-adherence to maintenance therapy, a known risk factor for relapse,[28,29] might consequently explain the higher relapse rates observed.

Previous studies on the role of appendicectomy in ulcerative colitis have suggested a potential beneficial effect on the disease course, but were limited by their observational, uncontrolled designs.[11,12] The current randomised controlled trial provides more solid evidence confirming these preliminary observations, and supports the theory that the appendix has an immunomodulatory role in ulcerative colitis.[9,10] The appendix is known to be a reservoir for commensal gut bacteria and gut-associated lymphoid tissue, both having an important role in the gastrointestinal tract's immune response. In ulcerative colitis, the dysregulated immune system leads to chronic colonic inflammation. One possible mechanism is that the appendix contributes to the maintenance and activation of immune cells, especially CD4 T helper cells, that drive the inflammatory process. By removing the appendix, these immune cells might be diminished, thereby reducing the inflammatory mucosal activation and leading to a reduced relapse rate. Nevertheless, this trial primarily focused on clinical outcomes, and did not evaluate the appendix's immunomodulatory mechanism, so no further causal conclusions can be drawn. Further studies are needed to elucidate the immunological mechanisms of the appendix in ulcerative colitis and ongoing follow-up of this trial will inform longer term outcomes. Further research should also focus on identifying patients who are most likely to benefit.

The appendicectomy group not only had lower relapse rates but also showed favourable trends in medication use. Biological agents were initiated less frequently in the appendicectomy group than in the control group, with the largest difference observed at 6 months (0·0% *vs* 4·4%, respectively). By 12 months, however, this difference had narrowed (3·2% *vs* 5·5%), suggesting that appendicectomy may delay the need for biologic therapy. If this trend were to persist beyond 12 months, even a modest reduction in biologic use could be clinically and economically meaningful. These findings should be interpreted with caution, as these patient numbers are small.[30] Pillai and colleagues reported a 10% annual increase in health-care costs for ulcerative colitis, primarily driven by the increased use of biological agents.[31] Another advantage of a surgical procedure as therapeutic intervention is that non-adherence is not a factor, making it a more attractive alternative to medication or maintenance medication for a subset of patients.

Moreover, the appendicectomy group showed a beneficial effect on some health-related quality-of-life outcomes. This might be a result of the lower relapse rates in this group, as active colitis is associated with an impaired health-related quality of life.[4–6] The difference was primarily observed regarding bowel symptoms, although the difference between the groups in the IBDQ change from baseline to 12 months did not meet the calculated minimum clinically important difference. The lack of significant differences in EQ-5D-3L utility and EORTC QLQ-C30 scores between the groups might be due to lower sensitivity and weaker correlation of these measures with disease relapse compared with the total IBDQ score. Given the nature of the EQ-5D-3L questions, patients experiencing relapse are more likely to report worse scores in the dimensions of usual activities, pain or discomfort and anxiety or depression, but not in mobility or self-care.

Limitations of this trial were the absence of a sham-surgery control group to determine the contribution of the placebo effect, which might have biased some of the health-related quality-of-life read outs, and the long duration of the trial, which might compromise the external validity. Nonetheless, this pragmatic trial was done across 21 international sites, enhancing its external validity. Participation bias might have been introduced, as it is likely that only a subset of patients who were in remission were willing to participate in a randomised surgical trial to undergo an additional appendicectomy. With the publication of beneficial results of appendicectomy trials, patient self-preference patterns might have been influenced. Finally, in this pragmatic trial, not all patients underwent follow-up endoscopy to objectively determine the relapse rate. Since a per-protocol analysis was not prespecified in the statistical analysis plan, these data are not presented here. However, the incidences of relapse were similar between both groups, and a similar difference between the groups was observed (appendix p 17).

In conclusion, appendicectomy is a viable and safe strategy for reducing the relapse rate in patients with ulcerative colitis compared with standard medical therapy at 1 year, offering a potential addition to standard medical therapies.

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A detailed list of trial sites and investigators are in the appendix (p 4).

Contributors

WAB, JPYB, CJB, GRD'H, EJE, ODF, THI, MK, LM, SP, TDP, CYP, and BS contributed to the conceptualisation of the study. WAB, JPYB, GRD'H, MGWD, EJE, ODF, KH, LH, THI, MK, LM, SP, CYP, SS, BS, MES, and EV curated the data. MGWD and EV did the formal analysis. CJB and TDP provided funding acquisition. YIZA, NA, EA, WAB, JDWvdB, HB, MAB, MB, JPYB, SRB, CJB, ECJC, RC, RMPHC, RJD, ACTMD, GRD'H, GD, PvD, MD, EJE, JPE, ODF, SCMF, MFG, JG, CEG, LH, RH, THI, JJ, MK, LM, RCM-H, GHHM, GM, GAN, SP, EGJMP, TDP, CYP, TR, IR, SS, JPS, TCJS, JS, SMS, BS, MES, PCFS, EV, MSV, BCV, RW, JKW, MEW, DW, NY, and EPMvdZ conducted the investigation. WAB, CJB, GRD'H, MGWD, EJE, ODF, KH, THI, MK, LM, SP, TDP, CYP, and BS contributed to the study's methodology. YIZA, NA, EA, WAB, JDWvdB, HB, MAB, MB, JPYB, SRB, CJB, ECJC, RC, RMPHC, RJD, ACTMD, GRD'H, GD, PvD, MD, EJE, JPE, ODF, SCMF, MFG, JG, CEG, LH, RH, THI, JJ, MK, LM, RCM-H, GHHM, GM, GAN, SP, EGJMP, TDP, CYP, TR, IR, SS, JPS, TCJS, JS, SMS, BS, MES, PCFS, EV, BCV, RW, DW, NY, and EPMvdZ carried out project administration. MGWD and KH developed the software. WAB, JPYB, CJB, GRD'H, EJE, ODF, THI, MK, LM, SP, TDP, CYP, BS, and MEW provided the resources. WAB, JPYB, CJB, GRD'H, MGWD, MD, ODF, RH, THI, MK, SP, TDP, CYP, and BS supervised the project. WAB, JDWvdB, HB, MAB, MB, JPYB, SRB, CJB, ECJC, RC, RMPHC, RJD, ACTMD, GRD'H, MGWD, GD, PvD, EJE, JPE, SCMF, MFG, JG, CEG, KH, RH, THI, JJ, MK, LM, RCM-H, GHHM, GM, GAN, SP, EGJMP, TDP, CYP, TR, IR, JPS, TCJS, JS, SMS, PCFS, EV, BCV, RW, DW, NY, and EPMvdZ were responsible for validation of the data. EV was responsible for visualisation and writing of the original draft. YIZA, NA, WAB, JDWvdB, HB, MAB, MB, JPYB, SRB, CJB, ECJC, RC, RMPHC, RJD, ACTMD, GRD'H, MGWD, GD, PvD, MD, EJE, JPE, ODF, SCMF, MFG, JG, CEG, KH, LH, RH, THI, JJ, MK, LM, RCM-H, GHHM, GM, GAN, SP, EGJMP, TDP, CYP, TR, IR, SS, JPS, TCJS, JS, SMS, BS, MES, PCFS, MSV, BCV, RW, JKW, MEW, DW, NY, and EPMvdZ reviewed and edited of the manuscript. All authors contributed substantially to the interpretation of data for the work, reviewed the manuscript critically for important intellectual content, approved the final version of the manuscript to be published, and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. EV, CJB, MGWD, and TDP had directly accessed and verified the underlying data reported in the manuscript.

Declaration of interests

NA reports receiving consulting fees from Pfizer; presentation fees from Pfizer, Lilly, Takeda, and AbbVie; and travel support from Tillotts Pharma. WAB reports received speaker fees from Applied Medical and Johnson & Johnson. JPYB reports receiving funding from the National Institute for Health and Social Care Research (NIHR) Efficacy and Mechanism Evaluation (EME) programme for the conduct of the ACCURE-UK 2 study, the UK part of the ACCURE trial. CJB reports receiving funding from Nuts-Ohra (FNO 1202–008), the Netherlands part of the ACCURE trial; and received speakers fees from Takeda, Janssen, and Tillotts Pharma. RC reports receiving speaker fees from

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Data sharing

Data collected for this study, including deidentified individual participant data, will be made available to others upon reasonable request. These data are available after publication of primary and secondary analysis with no specified end date. Access to the data will be granted to researchers who provide a methodologically sound proposal. Proposals should be directed to EV or CJB. To gain access, data requestors will be required to sign a data sharing agreement, and the data will be provided after the proposal is approval and the data sharing agreement is signed. The trial protocol and statistical analysis plan are available in the appendix (pp 18–86).

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