



Deposited via The University of Sheffield.

White Rose Research Online URL for this paper:

<https://eprints.whiterose.ac.uk/id/eprint/164696/>

Version: Published Version

Article:

Lee, M.J., Hawkins, D.J., Bradburn, M.J. et al. (2021) Atrial fibrillation after resection: a PROGRESS III study. *Colorectal Disease*, 23 (1). pp. 307-315. ISSN: 1462-8910

<https://doi.org/10.1111/codi.15314>

Reuse

This article is distributed under the terms of the Creative Commons Attribution (CC BY) licence. This licence allows you to distribute, remix, tweak, and build upon the work, even commercially, as long as you credit the authors for the original work. More information and the full terms of the licence here:

<https://creativecommons.org/licenses/>

Takedown

If you consider content in White Rose Research Online to be in breach of UK law, please notify us by emailing eprints@whiterose.ac.uk including the URL of the record and the reason for the withdrawal request.



European Colorectal Congress

29 November – 2 December 2020, St.Gallen, Switzerland

Sunday, 29 November 2020

MASTERCLASS

Introduction & course objectives

Michel Adamina, Winterthur, CH

Myths and facts about oral antibiotics, bowel preparation, and timing of iv antibiotics to reduce surgical site infection

Frédéric Ris, Geneva, CH

Management of colorectal GIST – all you should know from diagnosis to handling recurrences

Paris Tekkis, London, UK

Do and don't in taTME surgery – a decade of experience explained

Roel Hompes, Amsterdam, NL

What your pathologist can do for you: from standard margins recommendations to molecular pathology, liquid biopsies, and the microbiome

Phil Quirke, Leeds, UK

Prehabilitation, patient blood management, frailty index – welcome addition or resource wasting

Des Winter, Dublin, IE

Selective use of neoadjuvant and adjuvant radiotherapy for rectal cancer

Chris Cunningham, Oxford, UK

Handling large rectal adenoma and malignant polyps

Willem Bemelman, Amsterdam, NL

All techniques to avoid staple line intersections in colorectal surgery

Antonino Spinelli, Milano, IT

Management of pelvic sepsis after colorectal / coloanal anastomosis and oncological outcomes of the GRECCAR 5 trial

Quentin Denost, Bordeaux, FR

Best practices in colostomy construction and repair of parastomal hernia

Eva Angenete, Göteborg, SE

The EBSQ Coloproctology Examination

Michel Adamina, Winterthur, CH

Wrap-up

Michel Adamina, Winterthur, CH

Sunday, 29 November 2020

COURSE OF PROCTOLOGY

Introduction & course objectives

Bruno Roche, Geneva, CH

Complex pelvic fistula revisited: established wisdom and innovative approaches

Alexander Herold, Mannheim, DE

Obstretical trauma: assessment, timing and options to repair

Patrick Hohlfeld, Lausanne, FR

The painful bottom – Proctalgia beyond the classical abscess, fissures, and hemorrhoids

Bruno Roche, Geneva, CH

Sexually transmitted diseases in proctology

Karel Skala, Geneva, CH

Anorectal trauma and foreign bodies

Richard Cohen, London, UK

Pilonidal sinus – strategies and outcomes

Frédéric Ris, Geneva, CH

Fecal incontinence: investigations and conservative treatment

Beatrice Salvioli, Milano, IT

Fecal incontinence: neuromodulation and interventional options

Joan Robert-Yap, Geneva, CH

The pelvic floor revealed: transperineal / transvaginal / transanal repairs explained

Bruno Roche, Geneva, CH

The pelvic floor revealed: investigations and pelvic floor therapy

Jacqueline de Jong, Bern, CH

Obstructed defecation and IBS: investigations, differential diagnosis, and treatment strategies

Daniel Pohl, Zurich, CH

Obstructed defecation: surgical options

André d'Hoore, Leuven, BE

Wrap-up

Alexander Herold, Mannheim, DE

Monday, 30 November 2020

SCIENTIFIC PROGRAMME

Opening and welcome

Jochen Lange, St. Gallen, CH

Is cancer an infectious disease: role of the microbiome

Philip Quirke, Leeds, UK

Ethical considerations in crisis – lessons from Covid-19

Omar Faiz, London, UK

SATELLITE SYMPOSIUM Medtronic

Prophylactic mesh in colorectal surgery

René H. Fortelny, Wien, AT

Lars Pahlman lecture: Extending the limits of liver surgery

Markus Büchler, Heidelberg, DE

Multimodal approaches to colorectal liver metastases

Mohammed Abu Hilal
Brescia, IT

SATELLITE SYMPOSIUM Ethicon

Urogenital dysfunction in patients treated for rectal cancer – what do we know and what can we do?

Eva Angenete, Göteborg, SE

Hemorrhoids – new options and time-tested solutions

Alexander Herold,
Mannheim, DE

Anal pain and emergency proctology: what every surgeon should know & do

Richard Cohen, London, UK

All you need to know about anorectal fistula

Bruno Roche, Genève, CH

Strategies and outcomes for obstructive cancers of the colon and rectum

Willem Bemelman,
Amsterdam, NL

Tuesday, 1 December 2020

BREAKFAST SYMPOSIUM Karl Storz

Lessons learned along the robotic learning curve: a video guide for colorectal surgeons

Jim Khan, Portsmouth, UK



EAES presidential lecture: Strategies for lifelong learning and implementation of new technologies

Andrea Pietrabissa, Pavia, IT

SATELLITE SYMPOSIUM Intuitive

A journey in global surgery – why getting out of the comfort zone

Raffaele Rosso, Lugano, CH

Enhanced recovery pathways reloaded – a practical guide to success

Roberto Persiani, Roma, IT

Cancer at the extremes of age: are there any differences in handling youngsters and seniors

Des Winter, Dublin, IE

Management pearls for early rectal cancer

Roel Hompes, Amsterdam, NL

Ventral rectopexy: indications, tricks of the trade, and long-term results

Chris Cunningham, Oxford, UK

SATELLITE SYMPOSIUM BBraun

Total neoadjuvant therapy for colon and rectum cancers

Ronan O'Connell, Dublin, IE

Randomized trial evaluating chemotherapy followed by pelvic reirradiation vs chemotherapy alone as preoperative treatment for locally recurrent rectal cancer (GRECCAR 15)

Quentin Denost, Bordeaux, FR

Timeline of surgery following neoadjuvant radiotherapy – balancing morbidity and efficacy

Torbjörn Holm, Stockholm, SE

Poster award

Michel Adamina, Winterthur, CH

Wednesday, 2 December

Place and outcome of total colectomy in the surgical armamentarium

Neil Mortensen, Oxford, UK

Kono S anastomosis and over the valve stricturoplasties: hope for better outcomes

André D'Hoore, Leuven, BE

New drugs, old fears: state of the art management of IBD patients

Gerhard Rogler, Zurich, CH

SATELLITE SYMPOSIUM Takeda

Do resection of the mesentery in Crohn's & appendectomy in ulcerative colitis alter the course of disease

Christianne Buskens,
Amsterdam, NL

The septic abdomen: getting out of misery and closing the case

Marja Boermeester,
Amsterdam, NL

Management strategies for patients with advanced colorectal cancers

Paris Tekkis, London, UK

Anastomotic leak in colorectal surgery: insights, perspectives, and practical strategies

Antonino Spinelli, Milano, IT

Closing words

Michel Adamina, Winterthur, CH

The publication of this advertisement does not constitute endorsement by the society, publisher, or Editors, and is unrelated to the content that follows

Information & Registration

www.colorectalsurgery.eu

Atrial fibrillation after resection: a PROGRESS III study

M. J. Lee*[†] , D. J. Hawkins*, M. J. Bradburn[‡], J. Lee[§], S. R. Brown*  and M. J. Wilson[¶]

*General Surgery, Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, UK, [†]Department of Oncology and Metabolism, The Medical School, University of Sheffield, Sheffield, UK, [‡]Clinical Trials Research Unit, University of Sheffield, Sheffield, UK, [§]Department of Cardiology, Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, UK, and [¶]School of Health and Related Research, Sheffield, UK

Received 3 May 2020; accepted 5 August 2020; Accepted Article online 14 August 2020

Abstract

Aim Atrial fibrillation (AF) is a common cardiac arrhythmia, and is associated with worsening quality of life and complications such as stroke. Previous work showed that 8% of patients develop new-onset AF following colonic resection and highlighted factors that might predict the development of postoperative AF. The development of a new arrhythmia may have a negative effect on longer-term quality of life as well as cancer survivorship. The aim of this study is to accurately quantify the incidence of AF following colorectal cancer surgery and to validate a model to predict its development.

Method The Atrial Fibrillation After Resection (AFAR) study will recruit 720 patients aged 65 or over undergoing resection of colorectal cancer with curative intent. The primary outcome is development of AF within 90 days of surgery. Assessment of cardiac rhythm will be performed using 24-h Holter monitors at baseline, 30 and 90 days after surgery. An electrocardiogram

(ECG) will be performed on the day of discharge. Baseline descriptors including model variables and quality of life will be recorded using EQ-5D-5L. The occurrence of complications and other key surgical outcomes will be recorded. An additional blood test for N-terminal pro B-type natriuretic peptide (NT-proBNP) will be performed prior to surgery. Statistical analysis will validate a previously derived model and will test the incremental value of added variables such as NT-proBNP. Finally, an exploratory analysis will assess whether changes in ECG measures between baseline and postoperative ECG can predict subsequent new-onset AF.

Conclusion This study will provide data that may allow us to stratify the risk of developing AF following colorectal cancer surgery. This may inform screening or prophylactic approaches.

Keywords Colorectal cancer, atrial fibrillation, stratification

Introduction

Atrial fibrillation (AF) is a common condition characterized by chaotic electrical cardiac activity resulting in loss of atrial contraction. This affects filling of the ventricles and can impair cardiac function, leading to symptoms such as shortness of breath and dizziness. Blood stasis allows clots to form within the atria, increasing the risk of systemic embolism and stroke. It has an estimated prevalence of 3.7–4.2% in those aged 60–70 years and of 10–17% in those aged 80 years or older [1].

Following abdominal surgery, AF occurs in approximately 12–15% of patients [2]. This can be associated with a complication of surgery, such as an ‘anastomotic leakage’ or pelvic collection, or with other cardiovascular or respiratory complications. However, some patients develop AF without an obvious underlying complication. Clinically significant new-onset AF is associated with a longer hospital length of stay [3], and increased risk of stroke within 30 days (OR 3.51, 95% CI 1.45–8.52) [4]. Perioperative AF is also associated with an increased risk of stroke, myocardial infarction and death at 1 year [1]. A large number of colorectal cancer resections are carried out in those over 65 years of age [5]. As the surgical population ages this number will inevitably increase, with a commensurate elevation in AF disease burden.

AF can be paroxysmal (intermittent) or persistent. This presents a challenge when attempting to secure a

Correspondence to: Matthew Lee, Department of Oncology and Metabolism, The Medical School, University of Sheffield, Sheffield, S10 2RX, UK.
E-mail: m.j.lee@sheffield.ac.uk

 @wannabehawkeye

Clinical trials registry number: clinicaltrials.gov NCT04037319.

First patient recruited 17 January 2020.

diagnosis. Investigation with a single electrocardiogram (ECG) may capture just a few seconds of cardiac rhythm when AF is not present, resulting in a patient being falsely reassured. Ambulatory monitoring, such as with a Holter monitor, assesses cardiac rhythm over a longer period, typically 24 h, providing greater opportunity to detect paroxysmal AF. Many patients with AF are asymptomatic, and up to 50% of cases may be undiagnosed [6]. Current evidence suggests that asymptomatic AF may still carry significant risk for mortality and morbidity [7]. Paroxysmal AF often goes undetected, and therefore untreated, unlike persistent AF.

The majority of evidence regarding postoperative AF is related to cardiac and thoracic surgery. This includes a number of trials evaluating prophylactic beta-blockers and amiodarone for the prevention and treatment of AF [4,8]. A recent Cochrane review has shown that the benefit of prophylactic beta-blockade in noncardiac surgery is doubtful at best [2]. The aetiology of AF after cardiac surgery and abdominal visceral surgery differs, with the former being directly related to surgical manipulation of the heart and pulmonary vessels. The causes of new AF after noncardiac surgery are more complex and are related to the response to the systemic insult of surgery and factors that render the myocardium intrinsically vulnerable. Proposed mechanisms for the development of postoperative AF are multifactorial. The event of surgery, or complications such as anastomotic leakage, can cause systemic inflammation, which sensitizes the pacemaker cells. This may be augmented by increased sympathetic tone in response to surgery as well as to pain. There may be changes in myocardial electrical function due to altered oxygen delivery, intraoperative variation in blood pressure and fluid administration. These might cause AF alone, or may have effects augmented in a susceptible atrial substrate stimulated by a number of factors to cause arrhythmia [9,10]. This information is summarized in Fig. 1.

Our previous work investigated the incidence of new AF following gastrointestinal surgery using seven patient features available from routinely collected hospital data [3] and summarized in Table 1. That study found that 6.5% of patients undergoing a colorectal resection developed AF within 30 days of surgery, rising to 8.1% by 90 days. Multivariable analysis found that increasing age (OR 1.03, 95% CI 1.01–1.06), hypertension (OR 1.73, 95% CI 1.19–2.51), congestive cardiac failure (OR 3.04, 95% CI 1.88–4.92) and peripheral vascular disease (OR 2.29, 95% CI 1.39–3.37) were associated with the development of postoperative AF, yielding an area under the curve (AUROC) of 0.733. This study had limitations as it is likely that the

underlying population only underwent assessment for AF when symptomatic, and a proportion may have had asymptomatic AF. In terms of prognostic research this equates to a PROGRESS II stage study as it identifies factors which might be linked to outcome [4]. A PROGRESS III study would test the proposed model robustly in the target population [5].

If the incidence of postoperative AF is high in the postresection population, a large number of patients could potentially benefit from an accurate prognostic model for its occurrence. The identification of high-risk populations might allow the introduction of cost-effective screening strategies and research into mitigation procedures. It would also better aid the consent and counselling of patients undergoing major colorectal cancer surgery.

The aim of this study is to accurately define the rate of AF within 90 days of surgery for colorectal cancer, and to test whether we can identify those at highest risk of developing postoperative AF.

Method

This protocol has been prepared with reference to the SPIRIT guidelines. The study has been registered on the clinicaltrials.gov database (NCT04037319) and is funded by the NIHR RfPB Programme (PB-PG-1217-20015).

The study has a prospective cohort design. It will take place at clinical sites within the UK which offer elective surgery for colorectal cancer.

Eligibility criteria

Patients aged 65 years or older who are undergoing elective surgery for colorectal cancer with curative intent and who are without a diagnosis of AF are eligible. Surgery can include laparoscopic, open or robotic approaches, and includes right/left hemicolectomy, subtotal colectomy, anterior resection and abdominoperineal excision. Formation of stoma or anastomosis does not affect eligibility. It does not include those undergoing pelvic exenteration, excision of locally recurrent rectal cancer, surgery for anal cancer or those undergoing cytoreductive type procedures. Those with preexisting AF (either persistent or paroxysmal), who have a life expectancy of less than 12 months or who are unable to provide informed consent will not be eligible to participate.

Additional investigations

Cardiac rhythm will be assessed using two tools. The first is a standard 12-lead ECG. The second is a 24-h

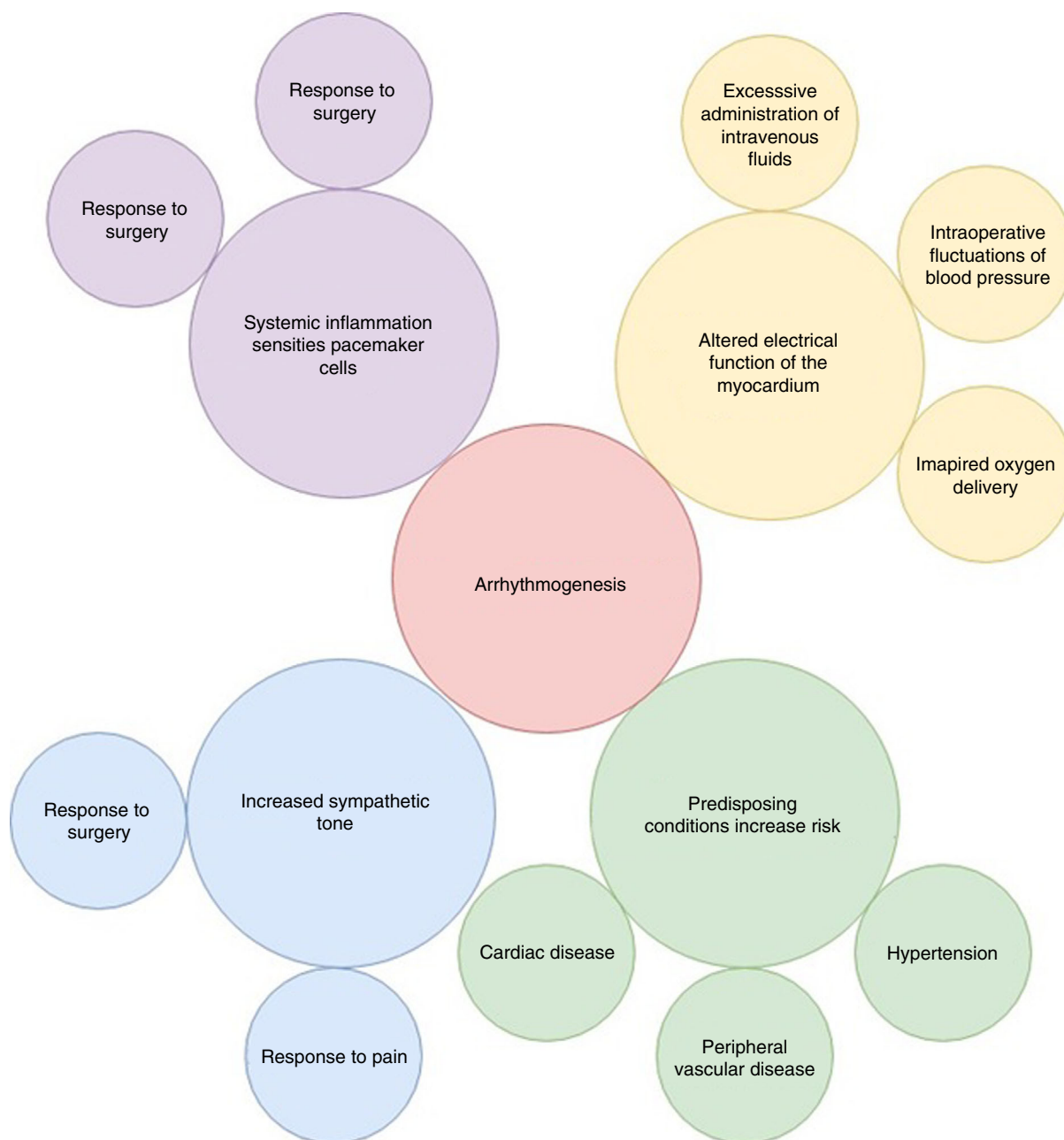


Figure 1 Factors associated with the development of postoperative atrial fibrillation.

rhythm recording using a standard three-lead Holter monitor for ambulatory (i.e. at home) recording of rhythm.

Outcomes

The primary outcome is the occurrence of new-onset AF within 90 days following colorectal cancer surgery.

AF is defined as ≥ 30 s of AF identified on a 24-h cardiac rhythm tape or on an ECG.

Secondary outcomes include:

- 1 estimation of the proportion of patients with prevalent AF undergoing surgery for CRC;
- 2 description of the baseline characteristics of patients who develop postoperative AF;
- 3 description of the characteristics of ECGs associated with subsequent AF;

Table 1 Factors in the original model.

	Odds ratio	95% CI
Age (years)	1.03	1.01–1.06
Male sex	1.23	0.86–1.76
Prior stroke	1.83	0.82–4.08
Congestive cardiac failure	3.04	1.88–4.92
Hypertension	1.73	1.19–2.51
Diabetes mellitus	0.73	0.46–1.16
Vascular disease	2.29	1.39–3.77

Area under the receiver-operator curve = 0.733.

- 4 use of data to test the performance of a predictive model to identify the highest risk strata;
- 5 measurement of the quality of life in patients with and without AF after surgery for colorectal cancer.

Participant timeline

In order to identify AF, each participant will undergo five discrete assessments of cardiac rhythm. Prior to recruitment a routine ECG will be reviewed for evidence of AF. Providing this does not show AF, the participant may enter into the study. He or she will undergo a further 24-h rhythm (Holter monitor) assessment prior to surgery. Preoperatively, one additional blood test (Nt-Pro BNP) will be taken to inform the risk model. Surgery and perioperative care will be performed as normal with no deviations from usual care. As part of routine care, any AF which develops during surgery will be noted. Formal reassessment of rhythm will be undertaken by ECG on the day of discharge, and two further periods of 24-h monitoring at 30 and 90 days following surgery (± 7 days).

Sample size

We aim to recruit 720 participants undergoing elective colorectal cancer resection. This allows for a 5% withdrawal/dropout rate and assumes an incidence of AF of around 15%. Withdrawals will comprise patients who are identified as having preoperative AF on 24-h tape following initial consent; participants who die following surgery without a diagnosis of AF having been made will also be excluded from analysis. With an expected 15% incidence of AF the remaining number of patients (around $n = 684$ individuals) fulfils the recommendation by Collins *et al.* [6] that a minimum of 100 events are needed to validate an existing prognostic model, and also meets the recommended 10 events per covariate rule for developing new prognostic models. The

sample size will also allow the postoperative incidence of AF to be estimated within a standard error of < 1.5%.

Recruitment

Patients will be recruited from 15 NHS sites in the UK over an 18-month recruitment period. They will be identified through colorectal cancer multidisciplinary team meetings when surgery is the proposed treatment for their colorectal cancer. Potential participants should be approached following the clinic where surgery is discussed and screened for eligibility. Patients can be approached by the local principal investigator (PI) or delegated team members with the appropriate good clinical practice (GCP) training. The patient will be given a written information sheet to consider (see Appendix S1) and allowed at least 24 h to consider participation. Patients willing to take part in the study will then provide written consent. This is anticipated to take place at preoperative assessment appointments or other regular clinical contacts prior to the day of surgery. Recruitment must be completed to allow time for a 24-h Holter recording to be analysed prior to surgery. The patient's GP and consultant will be informed of their participation in the study.

A patient can withdraw from the study at any point, without giving reasons. The data collected up to the point of withdrawal will be retained. The date of withdrawal will be documented in the database and the recruitment log updated. If patients withdraw from the study their normal routine care will continue. Participants will be withdrawn if AF is detected before the operation.

Data collection methods

A summary of data collection points is shown in Table 2. A pseudonymized scan of the ECG will be uploaded to the research database. It is expected that local services will review all their own ECGs; however, the first ECG from each site will be reviewed centrally for monitoring purposes. The remaining ECGs will undergo central assessment following completion of the study.

The following data will be collected prior to operation (defined as entry into the anaesthetic room): demographic data, including gender, age, ethnicity, height, weight, body mass index, smoking status, and disease characteristics, including tumour location, radiology staging, evidence of metastatic spread, Dukes classification, co-morbidities, concurrent medications with cardiac effects, EQ-5D-5L quality of life questionnaire and blood test for N-terminal pro B-type

Table 2 Summary of data collection points.

Test	Preop. assessment/ prescreening	Baseline –21 days to day 0	Preop. (–14 days to day 0)	Operation (day 0)	Discharge	Day 30 postop. ± 7 days	Day 90 postop. ± 7 days
ECG (if AF is detected, the patient is not included in the study)	x				x		
Consent		x					
GP and consultant informed of patient participation		x					
Demographics		x					
EQ-5D-5L		x				x	x
Blood tests: NT-proBNP (K, Mg, Ca if available)		x					
24 h cardiac rhythm			x			x	x
Echo (if available)		x					
CPET (if available)		x					
Operation details				X			
Any surgical complications					x		
Health service use							x

AF, atrial fibrillation; CPET, cardiopulmonary exercise test; ECG, electrocardiogram; GP, general practitioner; NT-proBNP, N-terminal pro b-type natriuretic peptide.

natriuretic peptide (NT-proBNP). The blood test can be taken at any time between listing for surgery up to the morning of the operation.

Results of blood tests for serum potassium, magnesium and calcium will be captured only if performed as part of routine care. Equally, if cardiopulmonary exercise testing or echocardiogram are performed preoperatively as routine care a pseudonymized copy of the report will be uploaded to the database.

A 24-h recording of cardiac rhythm will be undertaken prior to surgery to confirm the absence of AF. This can be completed (i.e. the 24-h recording ends) at any time prior to the patient's operation. The results will be analysed by local services and the pseudonymized scanned summary report uploaded to the research database. If AF is reported, the patient will not be withdrawn from the study.

The following information will be collected at operation: operative approach, operation description, anaesthesia modalities (i.e. inhalational general anaesthetic, spinal/epidural anaesthesia), American Society of Anesthesiologists status, duration of operation, occurrence of intra-operative AF identified by the anaesthetist. If AF is detected during the operation, the patient is not withdrawn from the study.

The following information will be collected at discharge: ECG test with assessment for AF, occurrence of AF prior to discharge and associated treatment and length of hospital stay. Key complications occurring up

to the point of discharge will be identified from clinical notes using predefined definitions. These include: in-hospital mortality, urinary tract infection, development of pneumonia, development of cardiac complications, deep-vein thrombosis, delirium, surgical site infection, fascial dehiscence, anastomotic leakage, radiological drainage, re-operation and unplanned escalation of care. Appendix S2 in the online Supporting Information gives a summary of definitions.

Follow-up at 30 and 90 days includes repeated 24-h Holter monitoring (interpreted locally) and administration of the EQ-5D-5L score. At day 90, a brief questionnaire will be administered about the use of health services for cardiac complaints. Patients who do not attend their 90-day follow-up visit will be 'lost to follow-up', and should be recorded on the recruitment log. Routine follow-up for colorectal cancer will be undertaken as per local guidance.

Data management

Data will be collected and stored online through a secure server running the Research Electronic Data Capture (REDCap) web application [7]. REDCap allows collaborators to enter and store data in a secure system. All transmission and web storage by this system is encrypted using 'SSL' and compliant with HIPAA-Security Guidelines the United States. System users will be allocated to a data access group for their hospital.

This allows them to create and edit records entered by their own team but not those from other hospitals. Collaborators will be required to set passwords which include letters, numbers and special characters. Passwords will be changed every 30 days. The REDCap servers are encrypted and are hosted in a secure building at the University of Sheffield, and undergo regular back-up. The sponsor (Sheffield Teaching Hospitals NHS Foundation Trust, STH) and University of Sheffield are joint data controllers. The study team at the University of Sheffield will have access to the data for statistical analysis at the end of the study.

Data from this study will be securely retained on University of Sheffield servers for up to 15 years after the study has ended and will not be sent outside the UK. Sites will be responsible for archiving the source data, case report forms and other essential documents at their own site for a period of up to 15 years.

Statistical methods

Analyses will be undertaken in accordance with the TRIPOD statement [8]. The number and percentage of patients screened, the number eligible, the number ineligible due to prevalent AF and the number consenting to study will be reported. The incidence of postoperative AF at 30- and 90-day follow-up will be presented along with 95% CIs. The first stage will be to validate the previously derived model for predicting 30- and 90-day AF on the basis of routinely collected risk factors. Factors included in the model were age, sex, cardiovascular comorbidities and diabetes. These are shown in Table 1.

The original model will be fitted to the prospectively collected data. We will firstly apply the original coefficients (Table 1) to the new data set and assess the AUROC, and thereafter re-estimate coefficients for the same covariates by logistic regression. The difference between the two AUROCs will indicate the degree of shrinkage (or overfitting) and thereby the stability of the original model. Thereafter the incremental value of the additional factors (e.g. ECG parameters, NT-proBNP) will be assessed. If several potential candidate covariates are identified a least absolute shrinkage and selection operator (LASSO) analysis will be performed to avoid overfitting. Finally, an exploratory analysis will assess whether changes in ECG measures between baseline and postoperative ECG can predict subsequent new onset AF. The functional form of continuous predictors in relation to outcome will be assessed using lowess smoothing and fractional polynomials. The stability of the models will be assessed using bootstrap methods with visual calibration methods. The performance of the competing models will be evaluated by calculating the

AUROC together with the sensitivity, specificity and positive and negative predictive values for various cut-off points of the risk score to assess whether individual predictions may be made with adequate specificity without compromising sensitivity. The EQ-5D-5L questionnaire will be used to derive health utility using UK reference populations. Changes in the quality of life index will be calculated and compared between groups with postoperative AF and no postoperative AF, and also between those with symptomatic AF and those with asymptomatic AF. If a viable prognostic model is identified, further modelling will be undertaken to assess the cost-effectiveness of implementing a risk-based screening programme for postsurgical AF using these data.

Analysis population and missing data

Analyses will include all participants with the exception of (1) patients with AF detected on preoperative investigations and (2) participants who die without a diagnosis of AF. Participants who do not complete their 30- and 90-day Holter assessments will be included in the primary analysis using incidence of AF recorded in their clinical notes. A sensitivity analysis will exclude participants who do not complete their 90-day assessment. EQ-5D-5L data will only be included if all items contain a response.

Data monitoring

The first ECG from each site will be monitored by the sponsor. Data monitoring will be undertaken periodically by the steering and management groups. This will serve two purposes: (1) to identify missing data and initiate action to remedy this and (2) to identify potentially outlying/erroneous data and initiate action to remedy this. Data issues relating to either of the above criteria will be identified and actioned by the management group. A log of queries and outcomes will be maintained and presented to the steering group.

The sponsor will ensure that research ethics committee approval and health research authority (HRA) approval are in place. The study will be registered with the local R&D office at each NHS site and it is the responsibility of each site to ensure that recruitment does not commence until local confirmation of capacity and capability has been given. Each site will be responsible for setting up and maintaining an investigator site file. Sites will all conduct the study to good clinical practice (GCP) standards. The PIs at each site and delegated team members taking part in the consent process will be required to have GCP training.

The study will not be monitored at individual sites; however, a site initiation teleconference will be conducted before each site opens covering the research background, study visits, CRF completion and database training. The sponsor will retain a site initiation visit attendance log and delegation log from each participating site. Any protocol deviations and violations should be reported to the sponsor's site.

In addition, the study is overseen by a steering group who are independent of the study. This includes an intensivist, a colorectal surgeon, a cardiologist and an expert in prognostic factor research.

Harms

This is an observational study; we therefore do not anticipate any serious adverse events relating directly to participation in this study. It is possible that patients may experience a local inflammatory reaction to the monitor pads. This should be recorded using the adverse event form. Any serious unexpected serious adverse reactions related to the study will be reported to the chief investigator and sponsor within 24 h of occurrence. Reports will be reviewed by the steering group and appropriate action taken. This may range from no action to modification of the study protocol.

Auditing

The first ECG from each site will be monitored by the sponsor. Data monitoring will be undertaken periodically by the steering and management groups. This will serve two purposes: (1) to identify missing data and initiate action to remedy this and (2) to identify potentially outlying/erroneous data and initiate action to remedy this. Data issues relating to either of the above criteria will be identified and actioned by the management group.

Ethical approval

Ethical review and approval has been conducted by East Midlands NHS Research Ethics Committee (ref. 19/EM/0257). HRA approval was secured prior to the commencement of the study (IRAS ID 261310). The study is registered on the clinicaltrials.gov website.

It is the responsibility of each participating NHS site to ensure that recruitment does not commence until local confirmation of capacity and capability has been given.

Amendments to the study will be reviewed and approved by the ethics committee and HRA and disseminated to participating sites as appropriate.

Public and patient involvement

Improvement of outcomes following surgery in the older patient has been identified by the James Lind Alliance as a research priority. A focus group was conducted prior to commencement of the study with people aged 65 and older who had undergone surgery for colorectal cancer. They confirmed the acceptability of the additional monitoring, and the importance of the study. All indicated they would participate if offered the opportunity.

The study management group included a lay member, who has had to withdraw. A replacement is being sought, along with a lay member with experience of AF. They will be involved in all project management group meetings, advise on patient-facing materials and advise the team on how to share findings with patients.

Protocol amendments

Protocol amendments will be approved by the HRA, and communicated to all PIs and research and development teams by a member of the project management group.

Confidentiality

All data will be handled in accordance with GDPR 2018 principles. The database will contain pseudonymized study data, patients' NHS numbers and consent forms for monitoring purposes. Patients will be required to provide consent for this. NHS numbers will be collected for a follow-on data linkage study to look at longer-term patient outcomes. Data will be held securely, and will be accessible only by members of the research team. The dataset will be limited to those data that are necessary for each function and will not include NHS numbers for analysis. Only the administrator is able to access these.

Access to data

Anonymized data may be shared with appropriately accredited researchers who have relevant questions that do not conflict with the primary aims of the study. Data will only be shared if appropriate ethical approvals and data transfer agreements are in place.

Ancillary and posttrial care

Should AF be detected, the patient will be informed and directed to an appropriate local service (cardiology outpatients, older persons' surgical services, or general practitioner).

If a participant develops AF prior to discharge from hospital, they will be managed as per local policies. For example, if a patient develops AF they will be contacted by the study team upon receipt of their Holter report. Enquiries will be made about symptoms. If the participant is unwell, they will be directed to attend their local emergency department. If they are well, then they will be directed to contact their GP (who will receive a copy of the result), or will be directed to their local older persons clinic or cardiology outpatients, depending on local policies.

Dissemination policy

Anonymized results will be published in peer review journals and at appropriate medical forums including national and international conferences and NHS meetings. Findings will be shared with academic health science networks and National Institute for Health and Care Excellence clinical exemplar repositories. Under no circumstances will individual patients be identified.

Authorship

The study management group will be headline authors for this study. Site (associate) PIs and up to three other team members will be eligible for collaborative authorship, assuming completion of recruitment and follow-up of participants as agreed.

Discussion

This study will be the first to screen for AF in patients who have undergone colorectal cancer surgery. Early detection (and treatment) of postoperative AF could bring benefits to patients and the health system. AF is not just a result of complications of surgery such as anastomotic leakage: our previous work showed it could be diagnosed weeks to months after surgery [3]. This temporal relationship suggests that complications alone do not drive the development of AF.

It is generally considered that interventions to prevent stroke are cost-effective due to the costs of providing long-term care following a cerebrovascular event [9]. Other screening interventions such as smartphone-based community ECGs have also been found to be cost-effective for stroke prevention [10]. It is clear that investment of time and resources into performing a potentially curative resection only for the patient to suffer a stroke is undesirable. Beyond stroke, AF is associated with a worse quality of life. As cancer outcomes improve, we look towards quality of survival and the avoidance of late effects of cancer treatment [11]. In

this context, AF might be considered such a 'late effect'. With the results of this study, we may be able to stratify those at the highest risk of developing AF. This would allow interventions such as screening to be delivered in a high-risk population for maximum yield. This might prevent or delay episodes of hospitalization for AF or cardiac failure. There is a quality of life benefit associated with this. Identification of a high-risk stratum would also provide a useful sub-population upon which to trial prophylactic interventions. Indeed, the inclusion of a heterogeneous population in previous prophylaxis trials might explain why the effects are inconsistent.

The study has been designed to estimate the incidence of postoperative AF in the colorectal cancer cohort and to validate a model to stratify patients by risk. Whilst previous work looked at all gastrointestinal patients, the present study will be limited this to those undergoing colorectal cancer surgery. This will provide a relatively stable surgical insult, and in this context we can more accurately assess the role of patient factors. The study team have selected 24-h Holter monitors at three points to monitor for AF. These time points were based upon earlier work which showed that rates of new AF plateaued at around 90 days after surgery [3]. Whilst tools such as implantable monitors are available [12], our public and patient involvement exercise told us that an additional invasive procedure around the time of cancer surgery would be unwelcome. As a noninvasive investigation, Holter monitors were considered acceptable. Other types of monitors would also have cost implications, at least doubling the funding required to deliver this study.

This study began recruiting in January 2020 and has recruited three patients per month at open sites. Challenges have been met during set-up in relation to the excess treatment costs related to the performance of Holter monitors as well as the availability of testing. The research team have purchased a limited number of Holter monitors to aid sites in this regard. At the time of writing, the study has been halted temporarily due to the COVID-19 pandemic. The patient population under study is at high risk and advised to isolate. It would be ethically difficult to justify asking patients to attend hospital for additional tests (Holter monitoring) when it is not part of their cancer treatment. An extension to recruitment has been secured to allow the remaining recruitment period to continue once pandemic research restrictions are lifted.

Conflicts of interest

The authors have no conflicts of interest to declare.

Funding

This study is funded by the NIHR Research for Patient Benefit (ref. PB-PG-1217-20015). The views expressed are those of the author(s) and not necessarily those of the NHS the NIHR or the Department of Health.

Sponsor: Sheffield Teaching Hospitals NHS Foundation Trust (STH20223).

References

- 1 Conen D, Alonso-Coello P, Douketis J *et al.* Risk of stroke and other adverse outcomes in patients with perioperative atrial fibrillation 1 year after non-cardiac surgery. *Eur Heart J* 2020; **1**: 645–51.
- 2 Domanovits H, Schlager O, Wildner B. Perioperative beta-blockers for preventing surgery-related mortality and morbidity in adults undergoing non-cardiac surgery. *Cochrane Database Syst Rev* 2019; **9**: CD013438.
- 3 Heywood EG, Drake TM, Bradburn M, Lee J, Wilson MJ, Lee MJ. Atrial fibrillation after gastrointestinal surgery: incidence and associated risk factors. *J Surg Res* 2019; **238**: 23–8.
- 4 Riley RD, Hayden JA, Steyerberg EW *et al.* Prognosis Research Strategy (PROGRESS) 2: prognostic factor research. *PLoS Med* 2013; **5**: e1001380.
- 5 Steyerberg EW, Moons KGM, van der Windt DA *et al.* Prognosis Research Strategy (PROGRESS) 3: prognostic model research. *PLoS Med* 2013; **5**: e1001381.
- 6 Collins GS, Ogundimu EO, Altman DG. Sample size considerations for the external validation of a multivariable prognostic model: a resampling study. *Stat Med* 2016; **30**: 214–26.
- 7 Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)—a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform* 2009; **42**: 377–81.
- 8 Collins GS, Reitsma JB, Altman DG, Moons KGM. Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): the TRIPOD statement. *Br J Surg* 2015; **102**: 148–58.
- 9 Ebrahim S. Cost-effectiveness of stroke prevention. *Br Med Bull* 2000; **56**: 557–70.
- 10 Lowres N, Neubeck L, Salkeld G *et al.* Feasibility and cost-effectiveness of stroke prevention through community screening for atrial fibrillation using iPhone ECG in pharmacies. *Thromb Haemost* 2014; **111**: 1167–76.
- 11 Kline RM, Arora NK, Bradley CJ *et al.* Long-term survivorship care after cancer treatment - summary of a 2017 National Cancer Policy Forum Workshop. *J Natl Cancer Inst* 2018; **1**: 1300–10.
- 12 Reiffel JA, Verma A, Kowey PR *et al.* Incidence of previously undiagnosed atrial fibrillation using insertable cardiac monitors in a high-risk population: the REVEAL AF study. *JAMA Cardiol* 2017; **1**: 1120–7.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Sample participant information sheet.

Appendix S2. Definitions of complications.