openheart

Invasive versus medically managed acute coronary syndromes with prior bypass (CABG-ACS): insights into the registry versus randomised trial populations

Matthew M Y Lee ,[1,2,3,4,5] Mark C Petrie ,[1,2,3] Paul Rocchiccioli ,[2,3] Joanne Simpson,[1,2] Colette E Jackson,[1,2,4] David S Corcoran ,[1,2] Kenneth Mangion ,[1,2] Ammani Brown,[4] Pio Cialdella,[2] Novalia P Sidik,[1,2] Margaret B McEntegart,[1,2,4] Aadil Shaukat,[2,3] Alan P Rae,[1,3] Stuart H M Hood,[1,2,5] Eileen E Peat,[2,5] Iain N Findlay,[5] Clare L Murphy,[5] Alistair J Cormack,[5] Nikolay B Bukov,[6] Kanarath P Balachandran,[6] Ian Ford ,[7] Olivia Wu ,[8] Alex McConnachie ,[7] Sarah J E Barry ,[9] Colin Berry ,[1,2,4] On behalf of the CABG-ACS Investigators

► Additional material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/openhrt-2020-001453).

To cite: Lee MMY, Petrie MC, Rocchiccioli P, *et al*. Invasive versus medically managed acute coronary syndromes with prior bypass (CABG-ACS): insights into the registry versus randomised trial populations. *Open Heart* 2021;**8**:e001453. doi:10.1136/openhrt-2020-001453

Received 17 September 2020
Revised 23 November 2020
Accepted 22 January 2021

For numbered affiliations see end of article.

Correspondence to
Professor Colin Berry, British Heart Foundation Glasgow Cardiovascular Research Centre, Institute of Cardiovascular and Medical Sciences, Glasgow G12 8TA, United Kingdom; colin.berry@glasgow.ac.uk

ABSTRACT

Background Coronary artery bypass graft (CABG) patients are under-represented in acute coronary syndrome (ACS) trials. We compared characteristics and outcomes for patients who did and did not participate in a randomised trial of invasive versus non-invasive management (CABG-ACS).

Methods ACS patients with prior CABG in four hospitals were randomised to invasive or non-invasive management. Non-randomised patients entered a registry. Primary efficacy (composite of all-cause mortality, rehospitalisation for refractory ischaemia/angina, myocardial infarction (MI), heart failure) and safety outcomes (composite of bleeding, stroke, procedure-related MI, worsening renal function) were independently adjudicated.

Results Of 217 patients screened, 84 (39%) screenfailed, of whom 24 (29%) did not consent and 60 (71%) were ineligible. Of 133 (61%) eligible, 60 (mean±SD age, 71±9 years, 72% male) entered the trial and 73 (age, 72±10 years, 73% male) entered a registry (preferences: physician (79%), patient (38%), both (21%)).
Compared with trial participants, registry patients had more valve disease, lower haemoglobin, worse New York Heart Association class and higher frailty.
At baseline, invasive management was performed in 52% and 49% trial and registry patients, respectively, of whom 32% and 36% had percutaneous coronary intervention at baseline, respectively (p=0.800). After 2 years follow-up (694 (median, IQR 558–841) days), primary efficacy (43% trial vs 49% registry (HR 1.14, 95% CI 0.69 to 1.89)) and safety outcomes (28% trial vs 22% registry (HR 0.74, 95% CI 0.37 to 1.46)) were similar. EuroQol was lower in registry patients at 1 year.

Conclusions Compared with trial participants, registry participants had excess morbidity, but longer-term outcomes were similar.

Trial registration number NCT01895751.

Key questions

What is already known about this subject?

► Pivotal clinical trials of invasive management versus non-invasive medical management in acute coronary syndromes (ACS) excluded patients with prior coronary artery bypass graft (CABG).

What does this study add?

► The CABG-ACS trial and registry provides novel, contemporary insights into an understudied subgroup of ACS patients with a substantial health burden.

How might this impact on clinical practice?

► The CABG-ACS pilot trial and registry fills in an evidence gap on the natural history and optimal treatment strategy for this comparatively large subgroup of patients. Furthermore, the CABG-ACS trial and registry may be helpful in the design of clinical trials in this patient group.

INTRODUCTION

Coronary artery bypass graft (CABG) surgery is standard of care for patients with obstructive coronary artery disease. However, occlusive disease of saphenous vein grafts is common within 10 years of surgery,[1–3] meaning patients with prior CABG have a progressive longer-term risk of recurrent ischaemia, including angina and myocardial infarction (MI), heart failure (HF) and death. Given the large number of CABG recipients living globally, and their health complexities, including increasing age and multimorbidity, this represents an increasing healthcare challenge globally,

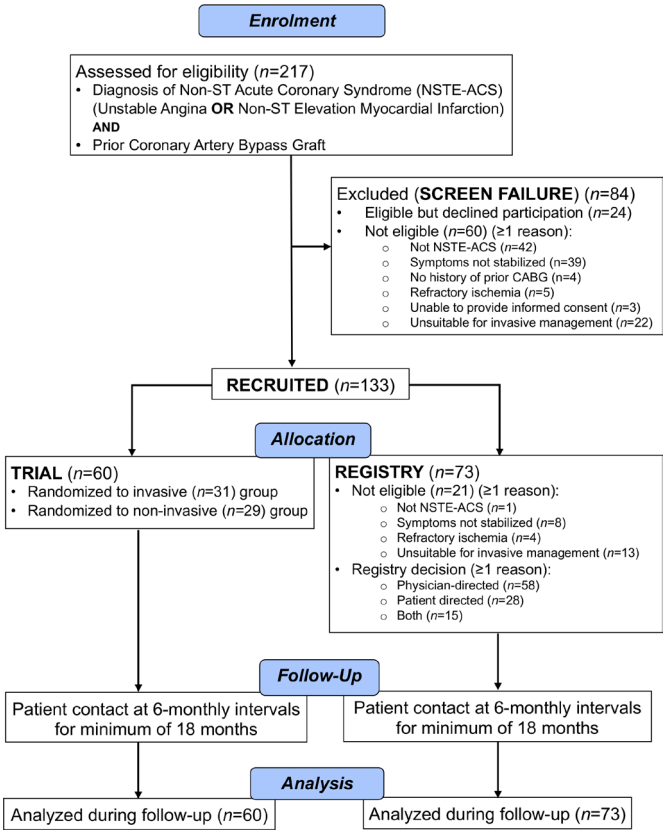


Figure 1 CONSORT diagram in CABG-ACS. CABG, coronary artery bypass graft; CONSORT, Consolidated Standards of Reporting Trials; NSTE-ACS, non-ST segment elevation acute coronary syndrome.

not least because of rehospitalisation due to recurrent ischaemia.[4 5] Chest pain is the most common reason for hospital admission in the UK and about 1 in 10–15 patients admitted to hospital with an acute non-ST segment elevation acute coronary syndrome (NSTE-ACS) have a prior CABG.[6]

Pivotal clinical trials comparing routine invasive management vs conservative non-invasive management in unstable coronary syndromes excluded patients with prior CABG (online supplemental table 1). Current guidelines recommend a routine early invasive strategy in higher risk NSTE-ACS patients.[7–9] However, invasive management is performed less often in NSTE-ACS patients with prior CABG, probably because the risk:benefit balance is considered to be less favourable in these patients compared with those without prior CABG.[10–12] Furthermore, when invasive management is performed, percutaneous coronary intervention (PCI) is less likely in prior CABG patients,[11–13] implying a lower likelihood of benefit with a routine invasive strategy. Real-world evidence implies clinical practice departs from the results of systematic reviews and guidelines,[14 15] indicating physician and patient preferences for treatment options may be relevant. Overall, evidence is lacking to inform the validity of current guideline recommendations,[7–9] in NSTE-ACS patients with prior CABG. This important subgroup of ACS patients remains comparatively understudied. Enrolment into randomised trials can be challenging,[16] particularly when the intervention disrupts standard care. Enrolment of elderly patients may be challenging, sometimes leading to premature trial discontinuation.[17–19]

We hypothesised that the clinical characteristics, treatment and health outcomes would differ between participants enrolled in a randomised controlled trial of routine invasive versus routine non-invasive management in NSTE-ACS patients with prior CABG, and participants enrolled in the registry due to physician and/or patient preference. We aimed to prospectively gather information on the trial and registry participants in order to gain contemporary information on the natural history and reasons for trial participation or not.

METHODS

We undertook a randomised controlled trial of routine invasive management vs routine conservative management in NSTE-ACS patients with prior CABG. Concurrently, patients who were ineligible for randomisation and who gave informed consent were entered into an observational registry. The study design,[20] and results of the main trial have been published.[21]

Study population

Inclusion criteria were: (1) unstable angina or non-ST segment elevation MI; (2) stabilised symptoms without recurrent chest pain or intravenous therapy for 12 hours and (3) prior CABG.

Exclusion criteria were: (1) refractory ischaemia (ie, recurrent angina with minimal exertion or at rest (ie, Canadian Cardiovascular Society (CCS) class III or IV) not controlled by medical therapy); (2) cardiogenic shock; (3) lack of informed consent and (4) unsuitable for invasive management.

Randomisation

Patients fulfilling inclusion criteria without any exclusion criteria who consented to participate in the randomised trial were enrolled (figure 1). Randomisation was performed by the Trials Unit interactive voice recognition system to one of two groups: initial medical management or initial invasive management (online supplemental methods).

Registry

Information was prospectively recorded in a registry for acute NSTE-ACS and prior CABG patients who were not randomised but consented to participate in the registry. Reasons for non-participation in the randomised trial were prospectively recorded: exclusion criteria present, unsuitability for either invasive or non-invasive management, physician preference, patient preference or a combination of these factors. Baseline and follow-up clinical information were obtained similarly to the trial patients.

Table 1 Baseline clinical characteristics of the trial and registry participants

Characteristics	Statistic	All N=133	Trial N=60	Registry N=73	P value
Clinical					
Age, years	Mean±SD	71±10	71±9	72±10	0.46
Female sex	N (%)	37 (28)	17 (28)	20 (27)	1.00
Obese (body mass index >30 kg/m^2)	N (%)	37 (28)	22 (37)	15 (21)	0.05
Presentation type*					
Non-ST segment elevation MI	N (%)	90 (68)	41 (68)	49 (67)	1.00
Unstable angina	N (%)	43 (32)	19 (32)	24 (33)	1.00
Medical history					
Diabetes mellitus†	N (%)	50 (38)	21 (35)	29 (40)	0.60
Previous MI	N (%)	91 (68)	41 (68)	50 (68)	1.00
Cardiac arrhythmia	N (%)	47 (36)	19 (32)	28 (39)	0.37
Treated hypertension	N (%)	88 (66)	42 (70)	46 (63)	0.46
Renal impairment	N (%)	38 (29)	13 (22)	25 (34)	0.13
Peripheral vascular disease	N (%)	32 (24)	16 (27)	16 (22)	0.55
Cerebrovascular disease	N (%)	30 (23)	13 (22)	17 (23)	0.84
Congestive HF	N (%)	44 (33)	14 (23)	30 (41)	0.04
Anaemia	N (%)	20 (15)	5 (8)	15 (21)	0.05
Valve disease	N (%)	43 (32)	12 (20)	31 (42)	0.01
Pacemaker	N (%)	11 (8)	5 (8)	6 (8)	1.00
History of smoking					
Current	N (%)	27 (20)	12 (20)	15 (21)	0.35
Former (>3 months)	N (%)	80 (60)	33 (55)	47 (64)	
Never	N (%)	26 (20)	15 (25)	11 (15)	
Serum creatinine, µmol/L	Median (IQR)	86 (71–114)	84 (68–101)	89 (73–131)	0.11
Haemoglobin, g/L	Mean±SD	131±18	135±16	127±18	0.01
Charlson Comorbidity Index	Median (IQR)	5 (3–7)	4 (3–6)	5 (3–7)	0.28
Health-related quality of life, EuroQol 5 Dimensions 5 Levels score	Median (IQR)	0.674 (0.447–0.866)	0.748 (0.514–0.899)	0.658 (0.437–0.817)	0.11
ECG abnormalities at initial presentation					
ST-segment depression	N (%)	67 (50)	28 (47)	39 (53)	0.49
ST-segment elevation	N (%)	27 (20)	11 (18)	16 (22)	0.67
T-wave inversion	N (%)	89 (67)	38 (63)	51 (70)	0.46
Q-waves	N (%)	42 (32)	15 (25)	27 (37)	0.19
Left bundle branch block	N (%)	11 (8)	5 (8)	6 (8)	1.00
AF or flutter	N (%)	23 (17)	9 (15)	14 (19)	0.65
New ischaemic ECG changes‡	N (%)	66 (50)	30 (50)	36 (50)	1.00
Canadian Cardiovascular Society angina class§					
1	N (%)	4 (3)	2 (3)	2 (3)	0.83
2	N (%)	11 (8)	6 (10)	5 (7)	
3	N (%)	26 (20)	10 (17)	16 (22)	
4	N (%)	90 (69)	41 (69)	49 (68)	
New York Heart Association functional class					

Continued

Table 1 Continued

Characteristics	Statistic	All N=133	Trial N=60	Registry N=73	P value
I	N (%)	47 (35)	30 (50)	17 (23)	0.01
II	N (%)	47 (35)	18 (30)	29 (40)	
III	N (%)	28 (21)	8 (13)	20 (27)	
IV	N (%)	11 (8)	4 (7)	7 (10)	
Coronary artery bypass grafts					
Left internal mammary artery	N (%)	109 (82)	50 (83)	59 (81)	0.82
No/unknown	N (%)	24 (18)	10 (17)	14 (19)	
Saphenous vein graft					
0	N (%)	10 (8)	3 (5)	7 (10)	0.74
1	N (%)	37 (29)	17 (29)	20 (29)	
2	N (%)	54 (43)	25 (43)	29 (43)	
≥3	N (%)	25 (20)	13 (22)	12 (18)	
Frailty index					
Fit or well (1,2,3)	N (%)	60 (45)	35 (58)	25 (34)	0.03
Vulnerable (4) or mildly frail (5)	N (%)	42 (32)	14 (23)	28 (38)	
Moderately frail (6)	N (%)	29 (22)	10 (17)	19 (26)	
Severely frail (7)	N (%)	2 (2)	1 (2)	1 (1)	
Medication prior to hospital admission					
Aspirin	N (%)	113 (85)	52 (87)	61 (84)	0.81
Statin	N (%)	113 (85)	55 (92)	58 (79)	0.06
Beta-blocker	N (%)	94 (71)	42 (70)	52 (71)	1.00
Calcium channel blocker	N (%)	133 (100)	60 (100)	73 (100)	1.00
Isosorbide mononitrate	N (%)	50 (38)	20 (33)	30 (41)	0.38
Nicorandil	N (%)	47 (35)	22 (37)	25 (34)	0.86
ACE inhibitor	N (%)	101 (76)	50 (83)	51 (70)	0.10
Insulin	N (%)	20 (15)	10 (17)	10 (14)	0.64
Oral antidiabetic therapy	N (%)	28 (21)	10 (17)	18 (25)	0.29
Antidepressant therapy	N (%)	24 (18)	13 (22)	11 (15)	0.37
Diuretic	N (%)	52 (39)	18 (30)	34 (47)	0.07

Note that where there are missing values, the percentages are calculated out of the number of patients with data. Cardiac arrhythmia (2 missing from registry). New ischaemic ECG changes (1 missing from registry). Canadian Cardiovascular Society angina class (1 missing from trial, 1 missing from registry). Saphenous vein graft (2 missing from trial, 5 missing from registry). Mean ± SD or median (IQR) for normal and non-normally distributed data, respectively.
*During the index hospitalisation, all patients in the randomised trial group had a type 1 MI, while seven patients in the registry group did not have a type 1 MI but had a type 2 MI (2 AF, 1 AF+HF, 1 severe aortic stenosis+HF, 1 anaemia, 1 AF+acute kidney injury, 1 HF+respiratory tract infection).
†Diabetes mellitus was defined as a history of diet-controlled or treated diabetes.
‡Any previous episode with new ischaemic ECG changes.
§The highest Canadian Cardiovascular Society value of any previous episode for each patient.
ACE, Angiotensin-converting enyzme; AF, atrial fibrillation; HF, heart failure; MI, myocardial infarction.

Follow-Up

Follow-up (via telephone contact, clinic visits, letter) with completion of quality of life assessments (EuroQol Visual Analogue Scale (EQ-VAS) and EuroQol 5 Dimensions 5 Levels (EQ-5D-5L)) was maintained 6 monthly until ≥18 months follow-up was reached for the final recruited patient (online supplemental methods).

Clinical event committee

An independent clinical event committee reviewed the primary efficacy and safety endpoints (online supplemental methods).

Table 2 Reasons for changing medical therapy during the index hospitalisation

Reason	All N=133 (%)	Trial N=60 (%)	Registry N=73 (%)	P value
Recurrent angina	47 (35)	13 (22)	34 (47)	0.003
Standard optimisation of secondary prevention therapy	103 (77)	54 (90)	49 (67)	0.002
Intolerance of therapy without adverse reaction	8 (6)	2 (3)	6 (8)	0.293
Adverse drug reaction	10 (8)	2 (3)	8 (11)	0.113
Other	7 (5)	3 (5)	4 (5)	1.000

Outcomes

Primary outcome

Defined as postrandomisation rate of major adverse events (coprimary composite outcome), including one composite outcome for efficacy and one composite outcome for safety.

Primary efficacy outcome

Defined as all-cause mortality, rehospitalisation for refractory ischaemia/angina, MI or hospitalisation for HF. The endpoints were assessed during the study until the final randomised patient had completed 18 months follow-up.

Primary safety outcome

Defined as bleeding (Bleeding Academic Research Consortium (BARC) types 2–4),[22] stroke, procedure-related MI (type 4a, universal definition), worsening renal function or haemodialysis during the index hospitalisation.

Secondary outcomes

1. Quality of life.
2. CCS angina class.
3. Hospitalisation for refractory ischaemia and/or angina.
4. Repeat invasive management during follow-up.
5. Freedom from coronary and/or bypass graft intervention.

Definitions of adverse events

Refractory ischaemia, death, procedure-related MI, stroke, major bleeding and worsening renal function are defined in online supplemental methods.

RESULTS

Two hundred and seventeen patients with prior CABG and an unplanned hospitalisation for a suspected NSTE-ACS were screened (figure 1).

Eighty-four (39%) participants were identified during screening but were deemed ineligible for progressing into the trial or registry, of whom 24 (29%) did not consent and 60 (71%) consented but were ineligible (≥1 reason): 42 (70%) not confirmed NSTE-ACS, 39 (65%) not stabilised symptoms, 4 (7%) no prior CABG, 5 (8%) refractory ischaemia, 3 (5%) unable to provide informed consent and 22 (37%) unsuitable for invasive management.

Of 133 (61%) eligible patients who consented to either the trial or registry, 60 patients (mean±SD age, 71±9 years, 43 (72%) male) were randomised and 73 (mean±SD age, 72±10 years, 53 (73%) male) entered the registry. The decision for entering the registry included physician preference (58 (79%)), patient preference (28 (38%)) or both (15 (21%)).

Baseline characteristics

The characteristics of the trial and registry participants are described (table 1). Compared with trial participants, registry patients were twice as likely to have valve disease (31 (42%) vs 12 (20%); p=0.01), a lower haemoglobin (mean±SD 127±18 vs 135±16 g/L; p=0.01), worse New York Heart Association class (37% vs 20% in class III or IV; p=0.01) and higher frailty index (27% vs 18% moderately or severely frail and 38% vs 23% mildly frail; p=0.03). Fifty (83%) trial and 59 (81%) registry patients participants had a previous left internal mammary artery graft (p=0.82). Baseline EQ-VAS, EQ-5D-5L and medications were similar.

In-hospital clinical course and invasive management

More than twice as many patients in the registry versus the trial had a medication change for recurrent angina. Approximately three-quarters of registry patients had medication changes for standard optimisation of secondary prevention therapy compared with trial patients (table 2).

At baseline, invasive management (coronary angiography±PCI) was undertaken in 31 (52%) and 36 (49%) patients in the trial and registry groups, respectively, increasing during follow-up to 46 (77%) and 40 (55%), respectively (table 3). Of those who had invasive management at baseline and follow-up, PCI was performed in 10 (22%) and 13 (33%) of trial and registry patients at baseline, increasing to 21 (46%) and 18 (45%) patients during follow-up, respectively (table 3). For baseline procedures, the British Cardiovascular Intervention Society-1 Jeopardy Score was similar between trial (4±4) and registry (5±3; p=0.19) patients (table 3). At baseline and follow-up, compared with trial patients, registry patients had more urgent inpatient invasive procedures (39 (75%) vs 27 (47%)) and fewer outpatient invasive procedures (13 (25%) vs 30 (53%); p=0.004) (table 3). The culprit lesion was uncertain in 27 (47%) and 21 (40%) of procedures in the trial and registry groups, respectively (table 3).

Table 3 Invasive management (coronary angiography±PCI) in trial and registry patients at baseline (index admission) and follow-up (≥18 months)

Patients with procedures at baseline and follow-up	Trial N=46 (%)	Registry N=40 (%)	P value
Patients with one procedure	37 (80.4)	32 (80.0)	0.084
Patients with two procedures	8 (17.4)	4 (10.0)	
Patients with three procedures	0 (0)	4 (10.0)	
Patients with four procedures	1 (2.2)	0 (0)	
Patients with PCI at baseline	10 (21.7)	13 (32.5)	0.331
Patients with PCI at baseline and follow-up	21 (45.7)	18 (45.0)	1.000
Days from enrolment to patient's first procedure	22.5 (6.5-64.75)	1.5 (0-7.25)	<0.001
<30 days	25 (54.3)	36 (90.0)	<0.001
30–59 days	9 (19.6)	0 (0)	
≥60 days	12 (26.1)	4 (10.0)	
Procedures at baseline	**Trial n=31**	**Registry n=36**	**P-value**
BCIS Jeopardy Score (pre-PCI) at baseline*	4.3±3.7	5.4±3.1	0.189
PCI at baseline	10 (32.3)	13 (36.1)	0.800
BCIS Jeopardy Score (post-PCI) at baseline	2.4±2.5	4.0±3.4	0.220
Procedures at baseline and follow-up	**Trial n=57**	**Registry n=52**	**P-value**
Urgent in-patient procedure	27 (47.4)	39 (75.0)	0.004
Outpatient procedure	30 (52.6)	13 (25.0)	
Hospitalisation†	28 (49.1)	41 (78.8)	0.002
Complications related to angiogram‡	1 (1.8)	6 (11.5)	0.052
Culprit vessel uncertain	27 (47.4)	21 (40.4)	0.563
Culprit vessel identified	30 (52.6)	31 (59.6)	
Graft only	17 (56.7)	15 (48.4)	0.611
Native artery only	12 (40.0)	15 (48.4)	0.609
Both graft and native artery	1 (3.3)	1 (3.2)	1.000
Multiple culprit lesions	3 (10.0)	2 (6.5)	0.671
PCI at baseline and follow-up	24 (42.1)	25 (48.1)	0.567
Thrombus aspiration	1 (4.2)	0 (0)	0.490
Rotational atherectomy	4 (16.7)	0 (0)	0.050
Intravascular ultrasound	2 (8.3)	3 (12.0)	1.000
Distal protection device	3 (12.5)	2 (8.0)	0.667

Mean±SD and median (IQR) for non-normally distributed data.
*BCIS Jeopardy score not available in one registry patient because of poor-quality angiogram and limited data for right coronary artery (only still frame and not a run).
†Admission to hospital including at least one overnight stay.
‡Complications in trial (N=1) was worsening renal function after angiography; complications in registry (N=6) were side branch abrupt closure, main branch distal embolisation into filter, no reflow, dissection post-angioplasty (+haematoma > 5 cm in same patient), pulmonary oedema on angiography table, side branch new/worsened thrombus.
BCIS, British Cardiovascular Intervention Society; PCI, percutaneous coronary intervention.

Adoption of adjunctive techniques, for example, rotational atherectomy was low (table 3).

Health outcomes

During a median of 694 (IQR 558–841) days follow-up, the primary efficacy outcome occurred in 26 (43%) and 36 (49%) trial and registry participants, respectively (HR 1.14, 95% CI 0.69 to 1.89) (table 4). The primary safety outcome occurred in 17 (28%) and 16 (22%) trial and registry participants, respectively (HR 0.74, 95% CI 0.37 to 1.46). The observed proportion of registry patients experiencing the efficacy outcome was slightly higher than in the trial group, whereas the opposite occurred for the safety

Table 4 Primary and secondary outcomes over follow-up period (≥18 months; median 694 (IQR 558–841) days)

Outcome	Trial N=60	Registry N=73	HR (registry vs trial) (95% CI)
Primary efficacy outcome			
Composite of all-cause mortality, rehospitalisation for refractory ischaemia/angina, MI and HF	26 (43%)	36 (49%)	1.14 (0.69 to 1.89)
Primary safety outcome			
Composite of bleeding (BARC≥2), stroke, procedure-related MI and worsening renal function during the index hospitalisation	17 (28%)	16 (22%)	0.74 (0.37 to 1.46)
Experienced both primary efficacy and safety outcomes	10 (17%)	8 (11%)	0.64 (0.25 to 1.63)
Experienced either primary efficacy or safety outcomes	33 (55%)	44 (60%)	1.05 (0.67 to 1.65)
Components of primary efficacy outcome			
All-cause mortality	8 (13%)	17 (23%)	
Cardiovascular death	2 (3%)	10 (14%)	
Non-cardiovascular death	4 (7%)	5 (7%)	
Unknown cause of death	2 (3%)	2 (3%)	
Rehospitalisation for refractory ischaemia/angina	0 (0%)	0 (0%)	
Non-fatal MI	22 (37%)	18 (25%)	
HF	7 (12%)	11 (15%)	
Primary efficacy outcome at 12 months			
Composite of all-cause mortality, rehospitalisation for refractory ischaemia/angina, MI and HF at 12 months	20 (33%)	23 (32%)	
All-cause mortality at 12 months	5 (8%)	9 (12%)	
Components of primary safety outcome			
Bleeding (BARC 2–4)	11 (18%)	10 (14%)	
Stroke	0 (0%)	2 (3%)	
Procedure-related MI	0 (0%)	0 (0%)	
Worsening renal function during the index hospitalisation	8 (13%)	5 (7%)	
Primary safety outcome at 12 months			
Composite of bleeding (BARC≥2), stroke, procedure-related MI and worsening renal function during the index hospitalisation at 12 months	12 (20%)	14 (19%)	
Other secondary outcomes			
Total number of SAE	170	117	
Number of patients with a SAE	40 (67%)	49 (67%)	
Number of SAEs per patient, median (IQR)	1(0, 2)	1(0, 2)	
Number of patients experiencing			
Rehospitalisation	39 (65%)	47 (64%)	
Invasive management (coronary angiography)	46 (77%)	40 (55%)	
PCI	21 (35%)	18 (25%)	
Redo CABG	0 (-)	1 (1%)	
Coronary revascularisation (PCI or CABG)	21 (35%)	18 (25%)	
Quality of life and angina			
EQ-VAS health status, 6 months, median (IQR)	75 (60-80)	50 (40-75)	
EQ-5D-5L score, 6 months, median (IQR)	0.82 (0.53-0.94)	0.61 (0.29-0.82)	
CCS angina class, 6 months, median (IQR)	3.0 (1.0-3.0)	3.0 (2.0-4.0)	
EQ-VAS health status, 12 months, median (IQR)	70 (50-80)	58 (40-75)	
EQ-5D-5L score, 12 months, median (IQR)	0.82 (0.62-0.95)	0.78 (0.50-0.89)	
CCS angina class, 12 months, median (IQR)	3.0 (3.0-4.0)	3.0 (2.0-4.0)	

HRs and corresponding 95% CI from an unadjusted Cox model are given for the time from study entry to occurrence of primary outcomes only, comparing the registry to the trial group. Median (IQRs) are used for non-normally distributed data. Follow-up period was over median 694 (IQR 558–841) days.
BARC, Bleeding Academic Research Consortium; CABG, coronary artery bypass graft; CCS, Canadian Cardiovascular Society; EQ-5D-5L, EuroQol 5 Dimensions 5 Levels; EQ-VAS, EuroQol Visual Analogue Scale; HF, heart failure; MI, myocardial infarction; PCI, percutaneous coronary intervention; SAE, serious adverse event.

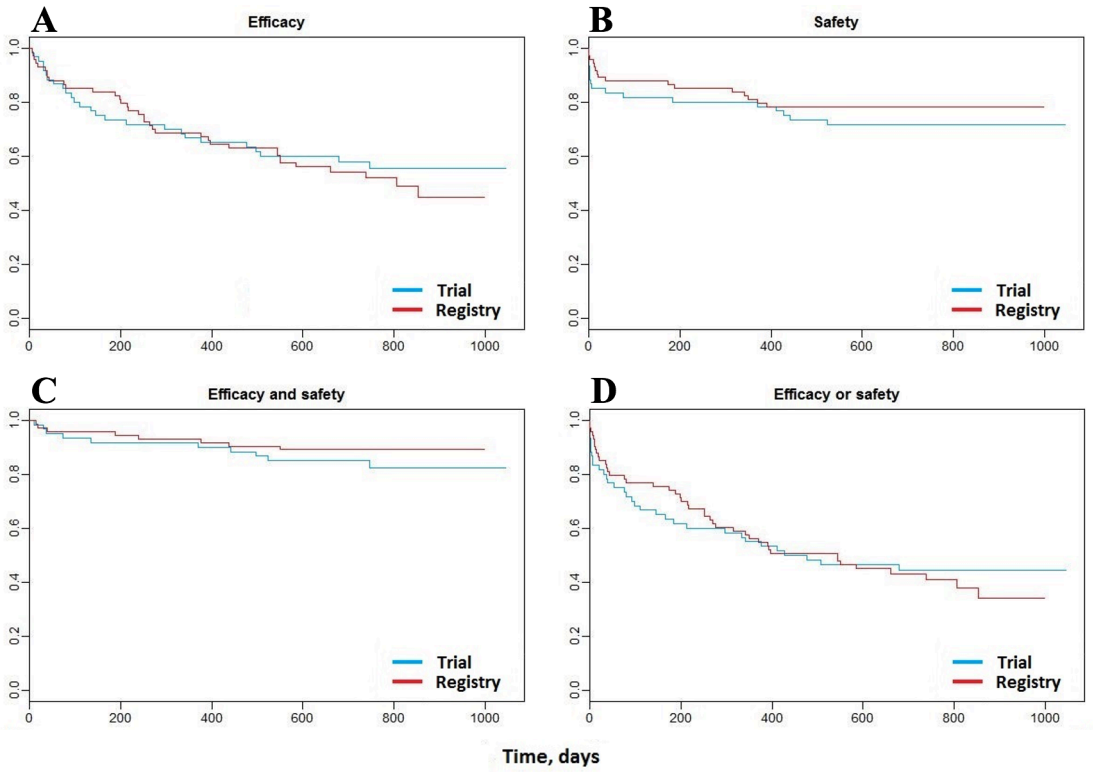


Figure 2 Kaplan-Meier survival curves: during a median of 694 (IQR 558–841) days follow-up: (A) The primary efficacy outcome occurred in 26 (43%) and 36 (49%) of trial and registry participants, respectively, HR 1.14, 95% CI 0.69 to 1.89. (B) The primary safety outcome occurred in 17 (28%) and 16 (22%) of trial and registry participants, respectively, HR 0.74, 95% CI 0.37 to 1.46. (C) The primary efficacy and safety outcome occurred in 10 (17%) and 8 (11%) of trial and registry participants, respectively, HR 0.64, 95% CI 0.25 to 1.63. (D) The primary efficacy or safety outcome occurred in 33 (55%) and 44 (60%) of trial and registry participants, respectively, HR 1.05, 95% CI 0.67 to 1.65.

outcome. When considered together (efficacy or safety), the rates were very similar between the groups. There was a lower proportion in the registry group experiencing both outcomes, but these events were very small in number.

Kaplan-Meier survival curves (figure 2) reveal that health outcomes in the trial and registry groups were similar during follow-up. Compared with the trial group, all-cause mortality and cardiovascular death occurred more often in the registry group, but non-fatal MI and worsening renal function during the index hospitalisation occurred less often (table 4). Two-thirds of patients in both groups experienced a serious adverse event (table 4). Redo CABG occurred in only one registry patient and in none of the trial participants (table 4).

Health status

Compared to the trial group, the median EQ-VAS health status in the registry group was 25 points lower (worse) at 6 months, and 12 points lower at 12 months (table 4).

Angina

The CCS angina class was similar between the groups at 6 months (median (IQR) trial 3 (1-3) vs registry 3 (2-4)) and 12 months (median (IQR) trial 3 (3-4) vs registry 3 (2-4)) (table 4).

DISCUSSION

The main findings of our study are, compared with the trial group, in the registry group: (1) multimorbidity, functional limitation, frailty and impaired health status were more pronounced; (2) changes to medication were more often made because of recurrent angina but less often made for standard optimisation of secondary prevention; (3) in invasively managed patients, the extent of jeopardised myocardium was similarly high and the culprit lesion was identified in half, and revascularisation by PCI was performed on one third; (4) health-related quality of life was lower at baseline, 6 and 12 months and (5) there was a fourfold increased risk of cardiovascular death, although power was limited. Overall, our study provides novel, contemporary insights into an understudied subgroup of ACS patients with a substantial health burden.

Our registry-based trial provided a framework for information to be prospectively gathered on patients who may have been eligible for randomisation but were not, including the reasons for not being randomised. Registry participation reflected physician and/or patient preferences for one form of treatment over another.[16] These beliefs substantially limited enrolment into the randomised trial. This finding has implications for the design and funding of future trials in this population. Moreover, the finding in the comparison of the

randomised trial groups that health outcomes were not different with invasive management versus conservative management supports the notion that enrolment rates could be increased by education of physicians and patients.[21] Our trial results broadly reflect equipoise between the randomised strategies which should enhance confidence to support enrolment into a future randomised trial.

Compared with trial participation, registry participation was associated with a fourfold higher likelihood of cardiovascular death, with the caveat that event rates were very low for this outcome. This prognostic association may be partly explained by the greater burden of cardiovascular health problems at baseline, including HF and valve disease. Compared with trial patients, registry patients had more medication changes for recurrent angina—this may be partly explained by some registry patients having symptoms which were not stabilised and/or refractory ischaemia (both reasons for exclusion from the randomised trial) (figure 1). However, up-titration of medical therapy for secondary prevention occurred less often in the registry group, implying less intensive management, less scope for therapy improvements or both. The results highlight the substantial levels of morbidity, polypharmacy and adverse health outcomes in this group. The clinical course of two participants is illustrated (online supplemental figures 1 and 2).

Advances in interventional management

In our trial, invasive management was selected in 36 (49%) of registry participants at baseline, but PCI was performed in only 13 (36%) of these patients. The lower PCI rate in our population may be explained by the complex nature of native vessel and graft disease, lack of a clear culprit (in almost half), and, arguably, lack of definitive evidence in support of the benefits of PCI in this population.

PCI continues to evolve with technical advances potentially leading to improvements in safety and procedural success (online supplemental discussion).

Feasibility of a future substantive trial in patients with an NSTE-ACS and prior CABG

About one in 10–15 NSTE-ACS patients have a prior CABG (online supplemental table 1).[6] This proportion is likely to remain stable in the coming years reflecting revascularisation practices in the past decade and increasing longevity. Many participants in this study were elderly, frail and multimorbid. Screening and obtaining informed consent were time-consuming for research staff. Medical decisions during urgent care may happen out-with office hours when research staff availability was limited. Medical information was commonly lacking at the time of hospitalisation, for example, graft history, limited recall by patients. These considerations present logistical barriers to enrolling patients into a randomised trial.

High event rates in patients with an NSTE-ACS and prior CABG

Almost half of the participants in both groups experienced a primary efficacy outcome event (table 4). In contemporary trials involving NSTE-ACS patients, the 12-month major adverse cardiac event (MACE) rate is usually 8%–10%, which is very much lower than observed in this study's patients. The proportion of affected patients increased substantially during longer-term follow-up beyond 12 months. Again, this progressive accrual of adverse cardiac events over time contrasts with other trials in NSTE-ACS patients in which cardiac events may plateau over time. The older age and universal presence of multi-morbidity probably explain the differences in prognosis between NSTE-ACS patients with versus without prior CABG. Considering future trials in NSTE-ACS patients with prior CABG, there are considerable logistical challenges to enrolment but, however, the event rate implies that the sample size may be lower than for other populations in which primary outcome event rates are expectedly lower.

Limitations

Our pilot trial was not powered to assess for between-group differences in the rates of the serious adverse events contributing to the prespecified efficacy and safety outcomes. The sample size was small, with resultant wide confidence intervals. Both groups included patients that were managed differently (PCI vs medical therapy), thereby confounding between-group comparisons.

CONCLUSION AND POTENTIAL VALUE OF RESULTS

Since clinical trials usually excluded patients with prior CABG, practice guidelines are not evidence based with respect to this group. In real-world practice, clinicians lack relevant information to inform decision making. Our trial and registry may be helpful in the design of clinical trials in this patient group.

Author affiliations
[1]Institute of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow, UK
[2]West of Scotland Heart and Lung Centre, Golden Jubilee National Hospital, Clydebank, UK
[3]Cardiology, Glasgow Royal Infirmary, Glasgow, UK
[4]Cardiology, Western Infirmary, Glasgow, UK
[5]Cardiology, Royal Alexandra Hospital, Paisley, UK
[6]Cardiology, Royal Blackburn Hospital, Blackburn, UK
[7]Robertson Centre for Biostatistics, University of Glasgow, Glasgow, UK
[8]Health Economics and Health Technology Assessment, University of Glasgow, Glasgow, UK
[9]Department of Mathematics and Statistics, University of Strathclyde, Glasgow, UK

Twitter Kenneth Mangion @kenneth_mangion and Colin Berry @ColinBerryMD

Contributors All authors meet all four ICMJE criteria for authorship. MMYL and AB coordinated study, enrolled patients, collected clinical data; MMYL also coordinated Clinical Event Committee. MCP, PR, JS and CEJ: clinical Event Committee. APR, CB, INFi and KPB: local principal investigators. MBM, AS, SHMH, EEP, CLM, AJC and NBB: enrolled patients, collected clinical data. DSC and KM: collected clinical data. PC, NPS: angiographic analyses for BCIS-1 Jeopardy Score. OW: study design and health economics. IFo, AM and SJEB: biostatistics. CB: chief investigator.

Funding CB has received research support from the British Heart Foundation (PG/17/2532884, FS/17/26/32744, and RE/18/6134217) and the Medical Research Council (MR/S005714/1). KM and NS were supported by BHF Clinical Training Fellowships (FS/15/54/31639; FS/17/26/32744). This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests CB is employed by the University of Glasgow, which holds consultancy and/or research agreements with companies that have commercial interests in the diagnosis and treatment of ischaemic heart disease, including Abbott Vascular, AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, HeartFlow, Menarini Farmaceutica, Opsens, Philips and Siemens Healthcare. There are no other relevant personal disclosures.

Patient consent for publication Not required.

Ethics approval The study was reviewed and approved by the West of Scotland National Health Service Research Ethics Service (Reference 11-WS-0116).

Provenance and peer review Not commissioned; internally peer reviewed.

Data availability statement The data that support the findings of this study are available from the corresponding author on reasonable request.

ORCID iDs
Matthew M Y Lee http://orcid.org/0000-0001-9213-2067
Mark C Petrie http://orcid.org/0000-0003-1350-1544
Paul Rocchiccioli http://orcid.org/0000-0003-1350-1544
David S Corcoran http://orcid.org/0000-0001-5047-0885
Kenneth Mangion http://orcid.org/0000-0002-3505-7440
Ian Ford http://orcid.org/000-0001-5927-1823
Olivia Wu http://orcid.org/0000-0002-0570-6016
Alex McConnachie http://orcid.org/0000-0002-7262-7000
Sarah J E Barry http://orcid.org/0000-0003-3039-8729
Colin Berry http://orcid.org/0000-0002-4547-8636

REFERENCES

1 Campbell PG, Teo KSL, Worthley SG, *et al*. Non-Invasive assessment of saphenous vein graft patency in asymptomatic patients. *Br J Radiol* 2009;82:291–5.
2 Tatoulis J, Buxton BF, Fuller JA. Patencies of 2127 arterial to coronary conduits over 15 years. *Ann Thorac Surg* 2004;77:93–101.
3 Cao C, Ang SC, Wolak K, *et al*. A meta-analysis of randomized controlled trials on mid-term angiographic outcomes for radial artery versus saphenous vein in coronary artery bypass graft surgery. *Ann Cardiothorac Surg* 2013;2:401–7.
4 National Institute for Cardiovascular Outcomes Research (NICOR), Healthcare Quality Improvement Partnership (HQIP). National Adult Cardiac Surgery Audit: 2019 summary report, 2019. Available: https://www.hqip.org.uk/a-z-of-nca/heart-cardiac-surgery-audit-ncap/ [Accessed 17 Sep 2020].
5 Bhatnagar P, Wickramasinghe K, Williams J, *et al*. The epidemiology of cardiovascular disease in the UK 2014. *Heart* 2015;101:1182–9.
6 Shoaib A, Kinnaird T, Curzen N, *et al*. Outcomes following percutaneous coronary intervention in Non-ST-Segment-Elevation myocardial infarction patients with coronary artery bypass grafts. *Circ Cardiovasc Interv* 2018;11:e006824.
7 Windecker S, Kolh P, *et al*, Authors/Task Force members. 2014 ESC/EACTS guidelines on myocardial revascularization: the Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic surgery (EACTS). Developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). *Eur Heart J* 2014;35:2541–619.
8 Hamm CW, Bassand JP, Agewall S, *et al*. ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: the task force for the management of acute coronary syndromes (ACS) in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J* 2011;32:2999–3054.
9 National Institute for Health and Care Excellence (NICE). Unstable angina and NSTEMI: early management. Clinical guideline 94, 2010. Available: https://www.nice.org.uk/guidance/cg94 [Accessed 17 Sep 2020].
10 Kim MS, Wang TY, Ou FS, *et al*. Association of prior coronary artery bypass graft surgery with quality of care of patients with non-ST-segment elevation myocardial infarction: a report from the National Cardiovascular Data Registry Acute Coronary Treatment and Intervention Outcomes Network Registry-Get With the Guidelines. *Am Heart J* 2010;160:951–7.
11 Elbarasi E, Goodman SG, Yan RT, *et al*. Management patterns of non-ST segment elevation acute coronary syndromes in relation to prior coronary revascularization. *Am Heart J* 2010;159:40–6.
12 Al-Aqeedi R, Asaad N, Al-Qahtani A, *et al*. Acute coronary syndrome in patients with prior coronary artery bypass surgery: observations from a 20-year registry in a Middle-Eastern country. *PLoS One* 2012;7:e40571.
13 Nikolsky E, McLaurin BT, Cox DA, *et al*. Outcomes of patients with prior coronary artery bypass grafting and acute coronary syndromes: analysis from the ACUITY (Acute Catheterization and Urgent Intervention Triage Strategy) trial. *JACC Cardiovasc Interv* 2012;5:919–26.
14 Fanning JP, Nyong J, Scott IA, *et al*. Routine invasive strategies versus selective invasive strategies for unstable angina and non-ST elevation myocardial infarction in the stent era. *Cochrane Database Syst Rev* 2016:CD004815.
15 Asrar Ul Haq M, Rudd N, Mian M, *et al*. Predictors and outcomes of early coronary angiography in patients with prior coronary artery bypass surgery presenting with non-ST elevation myocardial infarction. *Open Heart* 2014;1:e000059.
16 Feit F, Brooks MM, Sopko G, *et al*. Long-term clinical outcome in the Bypass Angioplasty Revascularization Investigation Registry: comparison with the randomized trial. BARI Investigators. *Circulation* 2000;101:2795–802.
17 Sanchis J, Núñez E, Barrabés JA, *et al*. Randomized comparison between the invasive and conservative strategies in comorbid elderly patients with non-ST elevation myocardial infarction. *Eur J Intern Med* 2016;35:89–94.
18 de Belder A. Revascularisation or medical therapy in elderly patients with acute anginal syndromes (RINCAL), 2014. Available: https://clinicaltrials.gov/ct2/show/NCT02086019 [Accessed 17 Sep 2020].
19 Godfrey R, de Belder A. 162 recruitment for clinical trials for elderly patients – insights from the XIMA and RINCAL trials. *Heart* 2019;105:A135.
20 Lee MMY, Petrie MC, Rocchiccioli P, *et al*. Non-invasive versus invasive management in patients with prior coronary artery bypass surgery with a non-ST segment elevation acute coronary syndrome: study design of the pilot randomised controlled trial and registry (CABG-ACS). *Open Heart* 2016;3:e000371.
21 Lee MMY, Petrie MC, Rocchiccioli P, *et al*. Invasive versus medical management in patients with prior coronary artery bypass surgery with a non-ST segment elevation acute coronary syndrome. *Circ Cardiovasc Interv* 2019;12:e007830.
22 Mehran R, Rao SV, Bhatt DL, *et al*. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. *Circulation* 2011;123:2736–47.

SUPPLEMENTAL MATERIAL

Supplemental Methods

Setting

Study participants were enrolled in two large urban hospitals and two regional district general hospitals in the National Health Service (NHS) in the United Kingdom (UK). The hospitals differed in geography, availability of catheter laboratory facilities on-site (or not), and hospital type (academic vs. regional). Royal Blackburn Hospital was the only hospital with an on-site cardiac catheterisation laboratory. In the other hospitals, patients were triaged for invasive management by referral and transferred to the regional cardiothoracic centre (Golden Jubilee National Hospital).

Screening

The clinical research team on each site screened for patients aged ≥18 years, of either sex, admitted during unscheduled emergency care with a suspected acute non-ST segment elevation acute coronary syndrome and prior coronary artery bypass graft (CABG). Screening took place in the acute medical and cardiology wards during the course of routine healthcare. Patients eligible for either invasive (with coronary and graft angiography) or non-invasive management were invited to participate. Eligible patients were given an information sheet prior to participation. All randomised and registry patients provided written informed consent as soon as feasible after hospital admission and prior to referral for coronary angiography. Each patient was given a site and study number and entered into a screening log which only contained de-identified information. Patients who did not consent were included in the 'screen failure' log.

Lee MMY, *et al. Open Heart* 2021; 8:e001453. doi: 10.1136/openhrt-2020-001453

The community health index (CHI) or NHS number was recorded to enable electronic record linkage.

Randomisation

Randomisation was stratified by centre, using randomised permuted blocks of length 4 and 6, with block lengths chosen at random.

Non-invasive group

Participants who had been randomised to the non-invasive group could be referred for invasive management if any pre-specified criteria were met (**Supplemental Methods**).

Invasive group

Invasive management was performed early (i.e. ≤72 hours wherever possible) after hospital admission. Invasive management included native coronary and bypass graft angiography and coronary and/or graft revascularisation with percutaneous coronary intervention (PCI) and/or CABG, as clinically appropriate.

Optimal medical therapy

Optimal medical therapy was intended for all of the participants. Guidance on up-titration of medical therapy was provided in an investigator guideline. Medical therapy included dual anti-platelet, anti-thrombotic, and anti-ischaemic therapies as per local protocols and international guidelines.[1,2]

Non-invasive group

Study participants who had been randomised to the non-invasive group could be referred for invasive management if one of the following pre-specified criteria are met: 1) recurrent or

refractory (class III or IV) angina with documented ischaemic electrocardiogram (ECG) changes whilst on "optimal" anti-ischaemic therapy, 2) new ST-segment elevation in two contiguous leads without Q waves or T wave inversion greater than 3 mm or development of haemodynamic instability, or 3) a deterioration in heart failure (HF) status (consistent with Killip class 3 or 4) that the attending clinician judges to be ischaemia-related based on the presence of symptoms, ECG changes and cardiac biomarker elevation.

Follow-up and outcome collection

Clinical research nurses and clinicians who were independent of the study teams and aware of the group allocations supported enrolment and follow-up assessments on all sites. They prospectively gathered information on screening, recruitment, randomisation (to medical therapy or invasive management), crossover rates, and serious adverse events in patients with prior coronary artery bypass graft and a recent non-ST segment elevation acute coronary syndrome.

Data will be held for up to 20 years to enable long-term follow-up analyses. Following randomisation, clinical assessments involved gathering information from standard-of-care clinical reviews (end of hospitalisation, 30-42 days and 1 year) and also from clinical contacts recorded in the patients' medical records. In West of Scotland hospitals, a single system of electronic patient records is used for all hospital attendances and correspondence with primary care.

Serious adverse events during the index admission and follow-up were evaluated from review of patient records obtained during usual care, and electronic health databases, using the CHI and NHS number. All outcomes were prospectively entered into an electronic Case Report Form.

Clinical Event Committee

The Clinical Event Committee (CEC) reviewed cases of interest to determine if they meet the criteria defined in the pre-specified charter. Causality assessments were not made by the CEC. The CEC was blinded to all information relating to the randomisation group. The CEC included 4 cardiovascular physicians who have expertise in the diagnosis and treatment of cardiovascular disorders and in the medical aspects of clinical trials. The CEC had a Chairman (M.C.P.) and coordinator (M.M.Y.L.) to assist with preparation of de-identified source clinical data, reports and communication with the Trials Unit. The CEC followed a pre-determined adjudication charter.

Definitions of adverse events

Refractory ischaemia

Recurrent ischaemic symptoms lasting more than 5 minutes, whilst on optimal medical therapy (at least 2 anti-anginal treatments) with documented characteristic ECG changes indicative of ischaemia and requiring an additional intervention. An additional intervention was defined as reperfusion therapy for myocardial infarction (MI), cardiac catheterisation, and insertion of intra-aortic balloon pump or revascularisation procedure (percutaneous coronary intervention or coronary artery bypass graft surgery) within 48 hours of the onset of this episode. This definition is in line with the Timing of Intervention in Acute Coronary Syndromes (TIMACS) trial.[3]

Death

All-cause, sudden cardiac death, death due to MI, death due to HF, death due to stroke, death due to extra-axial haemorrhage, death due to cardiovascular operation, death due to other

cardiovascular cause (e.g. infective endocarditis), presumed cardiovascular death (undetermined cause of death), non-cardiovascular death.[4]

Procedure-related MI

According to the Universal Definition of MI (Type 4b).[5] A post-procedure ECG was used to diagnose Q-wave vs. non-Q-wave MI.

Stroke

Defined as the presence of a new focal neurologic deficit thought to be vascular in origin, with signs or symptoms lasting more than 24 hours;[3] subdural haemorrhage.

Major bleeding

Defined according to the Bleeding Academic Research Consortium criteria.[6]

Worsening renal function

Defined as deterioration in estimated Glomerular Filtration Rate ≥ 25% of baseline during the index admission.

Crossover

A crossover between groups was defined as a change of treatment strategy from invasive to non-invasive management, or vice versa. In addition, we pre-defined crossover as occurring within 30 days after randomisation.

Sample Size

Since CABG-ACS was an exploratory pilot trial, no sample size calculation was performed. The sample size was n=60 based on the number of participants projected to be enrolled in 4 hospitals within a 12–18 month period. We chose this number across different secondary care settings to

be broadly representative of the diversity in UK hospitals. The sample size was selected to enable the feasibility of randomisation, and the reasons for not being randomised were prospectively recorded. The trial was designed but not powered to assess for between-group differences in the rates of the serious adverse events contributing to the prespecified efficacy and safety outcomes.

Data management and biostatistics

The Robertson Centre for Biostatistics acted as an independent coordinating centre for data management and statistical analyses. The Centre is registered with a Clinical Trials Unit (National Institute for Health Research Registration number: 16). The Chief Investigator (Professor Berry) had full access to all the data in the study and takes responsibility for its integrity and the data analysis.

Patient confidentiality

Patients were assigned an identification code at the time of recruitment.

Statistical analysis

Baseline data

Baseline characteristics were summarised using mean (standard deviation (SD)) or median (interquartile range (IQR) for skewed data) for continuous variables, and count (%) for categorical variables. Baseline characteristics for randomised vs. registry participants were compared using t-tests, Mann-Whitney tests and chi-squared tests (or Fisher's exact tests) as appropriate.

126 **Efficacy and safety outcomes**

127 Numbers of events and numbers (%) of patients with adverse events were summarised. The
128 proportion of patients with adverse events was compared between the registry and trial groups
129 with a chi-squared test. Kaplan-Meier curves were produced for time to occurrence of the
130 primary efficacy and safety outcomes. The hazard ratios (HR) of the primary outcomes,
131 comparing the registry to trial group, were calculated with corresponding 95% confidence
132 interval (CI) from a Cox model. Secondary outcomes were presented as descriptive statistics
133 only, since this was a pilot trial with insufficient power for statistical testing of these outcomes.

134 **Ethics**

135 Potential benefits to participants include avoidance of harmful invasive management and
136 avoidance of longer-term stent failure. No additional interventions were proposed nor were
137 procedures withdrawn that would be needed on clinical grounds. While the intention-to-treat in
138 each group was either with non-invasive or invasive management, all treatment options remained
139 available according to patient and physician preference i.e. patients initially randomised to
140 medical therapy could have undergone invasive management and vice versa.

141 **Trial management**

142 A Trial Management Group including the researchers and Local Principal Investigator on each of
143 the 4 sites coordinated the study's activities on a day-to-day basis. The NHS Sponsor monitored
144 the trial. Since the trial was a pilot, there was no Independent Data and Safety Monitoring
145 Committee.

Supplemental Discussion

Pivotal trials excluded patients with prior CABG, limiting the applicability of practice guidelines that recommend invasive management in non-ST segment elevation acute coronary syndrome (NSTE-ACS) with prior CABG.[1,2,7] Our results provide real-world insights into the baseline characteristics, treatment and outcomes of patients who were ineligible for randomisation but provided informed consent for registry participation. Commonly, this information is not gathered in clinical trials due to resource implications and logistics. Bypass Angioplasty Revascularization Investigation (BARI) was a trial of percutaneous transluminal coronary angioplasty (PTCA) versus CABG.[8] BARI included a registry of eligible patients who were not randomised based on physician and/or patient preference.[8] The main reason for not being randomised was physician and patient preference for PTCA. In BARI, the physicians selected PTCA rather than CABG for 65% of registry patients who underwent revascularisation without compromising long-term survival either in the overall population or in patients with treated diabetes. This result is in contrast to the randomised trial where patients with treated diabetes who underwent CABG gained a survival advantage compared to those patients with treated diabetes who had PTCA.

We also gathered information on the selection process for trial participation, providing insights into the reasons for this decision. Within the registry, invasive management was substantially the preferred strategy by physicians and cardiologists. However, the proportions of patients treated by PCI in the registry group and the invasive group in the randomised trial were similarly low. A registry can disclose information on patient subsets in whom an intervention may have differential effects (harm or benefit).

Registry patients who were selected for invasive management may have been identified by clinicians as being potentially amenable to gaining symptomatic or prognostic benefit from revascularisation. Conversely, registry patients who were selected for medical management may have been judged as having little to gain and at risk of harm from invasive management and with non-modifiable chronic health impairment.

Advances in interventional management

In recent years, radial artery access has become the standard approach for invasive management rather than femoral artery access. The left radial artery can provide arterial access in patients with a left internal mammary graft. However, Complete High risk Indicated Patient (CHIP) procedures may require simultaneous left and right coronary artery access which necessitates vascular access via the femoral artery. Overall, our results support the safety of invasive management in selected NSTE-ACS patients with prior CABG.

Advances in CHIP procedures lead to new possibilities for revascularisation in patients with complex disease.[9] Specialist techniques have developed with ‘antegrade’ and ‘retrograde’ approaches to recanalize chronic totally occluded (CTO) coronary arteries such that CTO PCI in native vessel CTOs has become increasingly feasible.[9] However, CTO PCI procedures are complex, require advanced skills, only undertaken by a minority of interventional cardiologists, and are usually pre-planned on an elective basis. Equipment can be expensive. Some of these techniques evolved very recently and so were not routinely implemented in the invasively managed patients. Whether CHIP procedures would increase revascularisation rates, comparable safety, and improvements in prognosis merit prospective evaluation in a substantive multicentre trial.[9]

Abbreviations: Acronyms of trials

FRISC II = FRagmin and Fast Revascularisation during InStability in Coronary artery disease

ICTUS = Invasive versus Conservative Treatment in Unstable Coronary Syndromes

ISAR-COOL = Intracoronary Stenting with Antithrombotic Regimen Cooling-Off

LIPSIA-NSTEMI = The Leipzig Immediate versus early and late PercutaneouS coronary Intervention triAl in NSTEMI

MATE = Medicine versus Angiography in Thrombolytic Exclusion

MOSCA = coMOrbilidades en el Síndrome Coronario Agudo

OASIS-5 = Fifth Organization to Assess Strategies in Ischemic Syndromes

RINCAL = Revascularisation or Medical Therapy in Elderly Patients with Acute Anginal Syndromes

RITA 3 = Randomized Intervention Trial of unstable Angina

TACTICS-TIMI 18 = Treat Angina with Aggrastat and Determine Cost of Therapy with an Invasive or Conservative Strategy – Thrombolysis in Myocardial Infarction 18

TIMACS = Timing of Intervention in Acute Coronary Syndromes

TIMI IIIB = Thrombolysis in Myocardial Ischemia

TRUCS = Treatment of Refractory Unstable angina in geographically isolated areas without Cardiac Surgery

VANQWISH = Veterans Affairs Non-Q-Wave Infarction Strategies in Hospital

VINO = Value of first day angiography/angioplasty In evolving Non-ST segment elevation myocardial infarction: an Open multicenter randomized trial

Supplemental Tables

Supplemental Table 1. Trials of patients with non-ST elevation acute coronary syndromes.

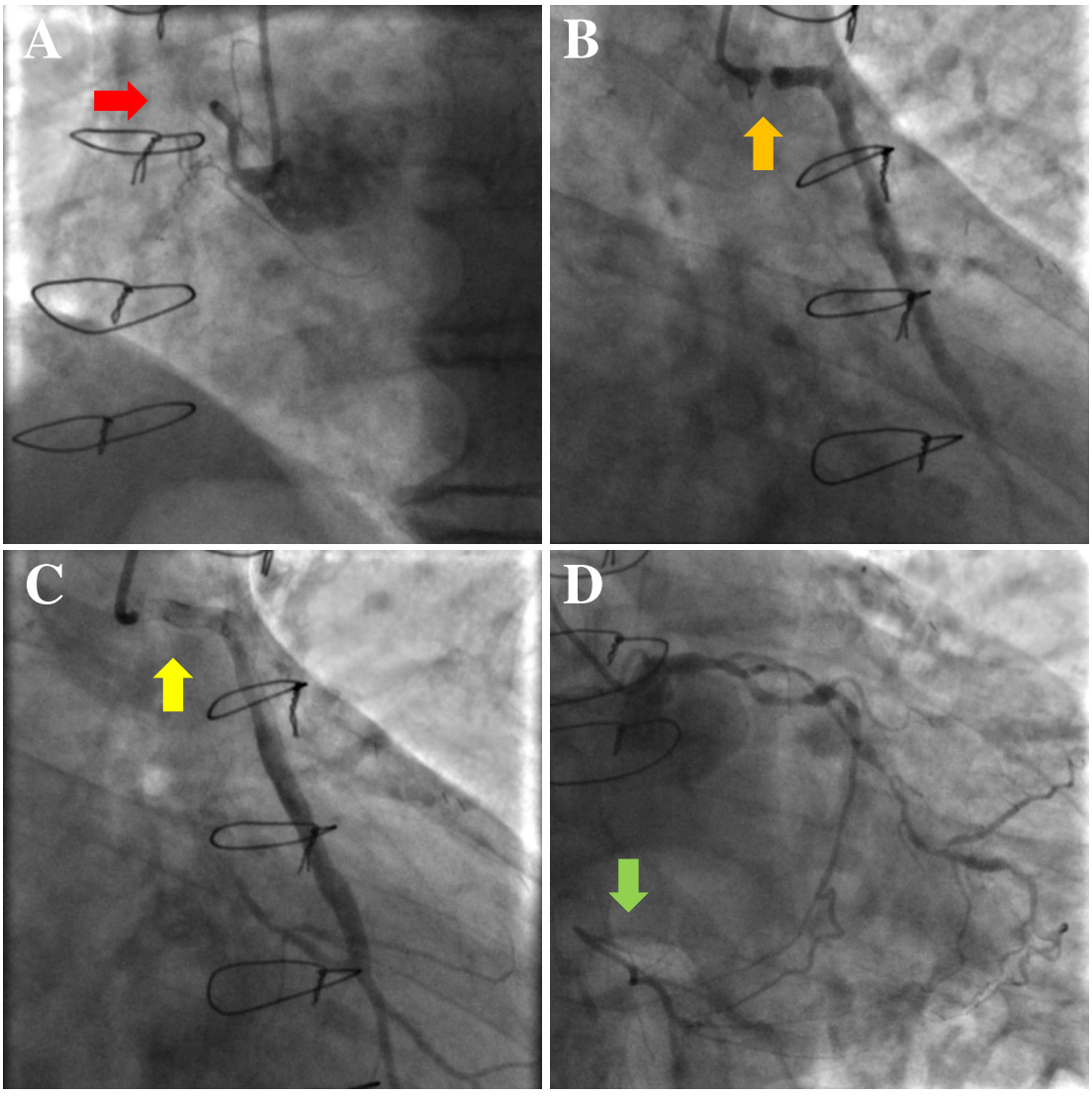
Trials which included patients with prior coronary artery bypass grafting (CABG)			
Trial	**Year published**	**N**	**N (%) with prior CABG**
VANQWISH[10]	1998	920	156 (17.0%) (CABG >3 months before randomisation)
MATE[11]	1998	201	19 (9.5%)
TRUCS[12]	2000	148	18 (12.2%)
TACTICS-TIMI 18[13]	2001	2220	484 (21.8%) (CABG >6 months before randomisation)
ISAR-COOL[14]	2003	410	48 (11.7%)
ICTUS[15]	2005	1200	105 (8.8%)
OASIS-5[16]	2009	20078	1643 (8.2%)
Italian Elderly ACS[17]	2012	313	29 (9.3%)
LIPSIA-NSTEMI[18]	2012	600	41 (6.8%)
CABG-ACS pilot[19,20]	2016	60	60 (100.0%)
After Eighty study[21]	2016	457	76 (16.6%)
MOSCA[22]	2016	106	14 (13.2%)

Trials which excluded patients with prior CABG

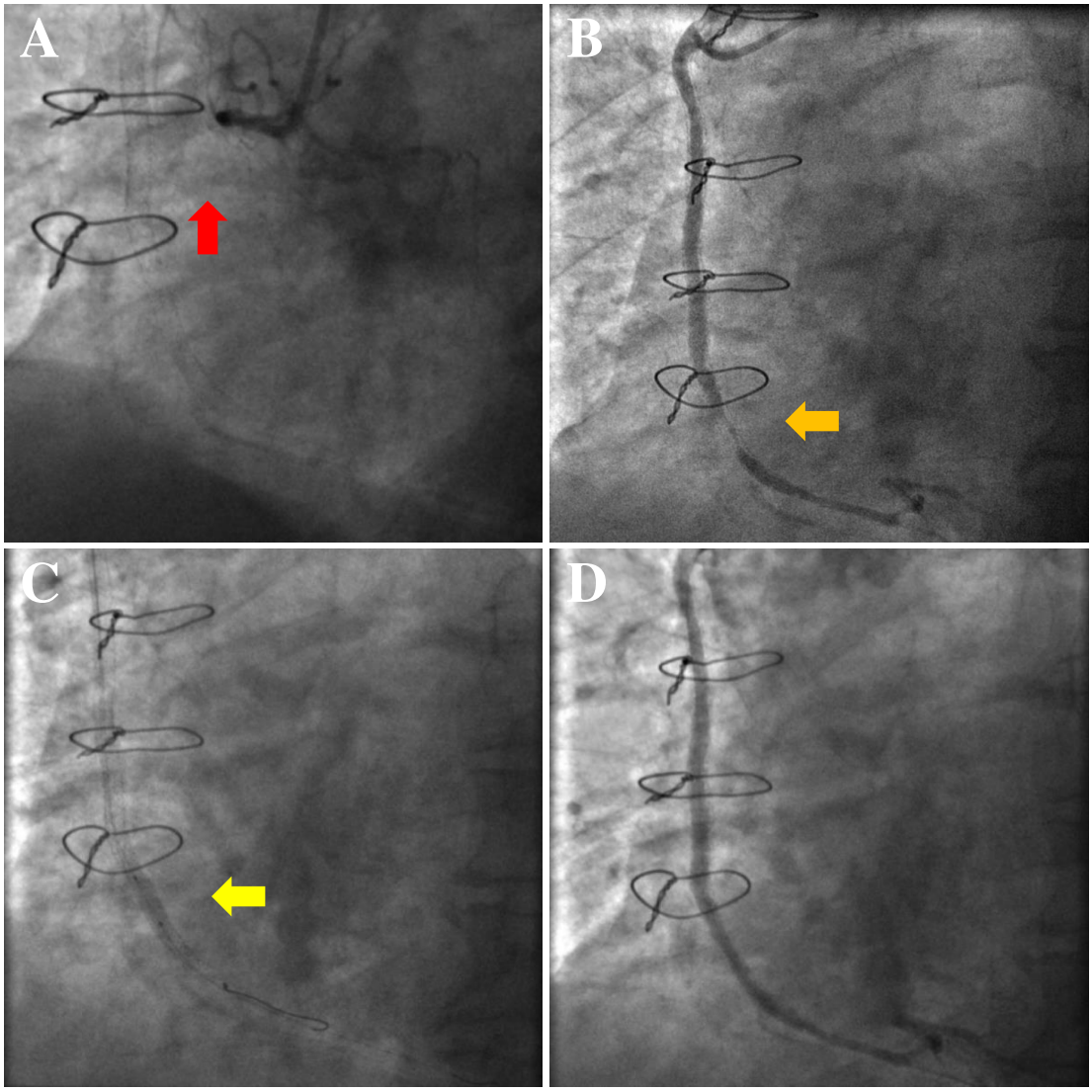
Trial	**Year published**	**N**	**Exclusion**
TIMI IIIB[23]	1994	1473	CABG at any time
FRISC-II[24]	1999	2457	Previous open-heart surgery
VINO[25]	2002	131	CABG less than 6 months
RITA 3[26]	2002	1810	CABG at any time

213 **Supplemental Figures**

214 **Supplemental Figure 1.**



215 **Supplemental Figure 2.**



Supplemental Figure Legends

Supplemental Figure 1:

Clinical case example: This 72-year-old male in the registry had an inpatient coronary angiogram at baseline which showed a (A) blocked right coronary artery (red arrow) and a (B) tight stenosis in his saphenous vein graft supplying the obtuse marginal artery (orange arrow). He underwent (C) successful percutaneous coronary intervention to this saphenous vein graft (yellow arrow), thereby restoring flow to his (D) right coronary artery (green arrow) which was collateralised by his circumflex artery. This case highlights a diseased culprit vessel supplying collaterals to another territory that is not supplied by another patent saphenous vein graft or native artery. This participant experienced serious adverse events during follow-up including bleeding (Bleeding Academic Research Consortium type 2) and heart failure hospitalisation.

Supplemental Figure 2:

Clinical case example: This 63-year-old male with a history of previous coronary artery bypass grafting and multiple coronary stents for intractable angina, was admitted with a non-ST elevation acute coronary syndrome and was recruited to the CABG-ACS registry due to physician preference for invasive management. Urgent inpatient coronary angiography revealed a (A) occluded native right coronary artery (red arrow) and (B) diseased saphenous vein graft-right coronary artery (orange arrow). (C and D) Percutaneous coronary intervention to his saphenous vein graft-right posterior descending artery (yellow) was unsuccessful (plain old balloon angioplasty only, no stents). Following multi-disciplinary team discussion, he subsequently underwent redo coronary artery bypass grafting (long saphenous vein to posterior

238 descending artery) but unfortunately after a protracted post-operative recovery period, he did not
239 survive.

Supplemental References

1 Windecker S, Kolh P, Alfonso F, *et al.* 2014 ESC/EACTS Guidelines on myocardial revascularization: The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J* 2014;**35**:2541–619. doi:10.1093/eurheartj/ehu278

2 Hamm CW, Bassand JP, Agewall S, *et al.* ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J* 2011;**32**:2999–3054. doi:10.1093/eurheartj/ehr236

3 Mehta SR, Granger CB, Boden WE, *et al.* Early versus delayed invasive intervention in acute coronary syndromes. *N Engl J Med* 2009;**360**:2165–75. doi:10.1056/NEJMoa0807986

4 Cutlip DE, Windecker S, Mehran R, *et al.* Clinical end points in coronary stent trials: a case for standardized definitions. *Circulation* 2007;**115**:2344–51. doi:10.1161/CIRCULATIONAHA.106.685313

5 Thygesen K, Alpert JS, Jaffe AS, *et al.* Third Universal Definition of Myocardial Infarction. *J Am Coll Cardiol* 2012;**60**:1581–98. doi:10.1016/j.jacc.2012.08.001

6 Mehran R, Rao S V., Bhatt DL, *et al.* Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. *Circulation* 2011;**123**:2736–47. doi:10.1161/CIRCULATIONAHA.110.009449

7 NICE. Unstable angina and NSTEMI: early management. Clinical guideline 94. March 2010 (Updated November 2013). https://www.nice.org.uk/guidance/cg94 (accessed 17 Sep 2020).

8 Feit F, Brooks MM, Sopko G, *et al.* Long-term clinical outcome in the Bypass

Angioplasty Revascularization Investigation Registry: comparison with the randomized trial. BARI Investigators. *Circulation* 2000;**101**:2795–802. doi:10.1161/01.CIR.101.24.2795

9 Smith EJ, Strange JW, Hanratty CG, *et al.* Percutaneous intervention for chronic total occlusion: integrating strategies to address an unmet need. *Heart* 2013;**99**:1471–4. doi:10.1136/heartjnl-2013-304521

10 Boden WE, O'Rourke RA, Crawford MH, *et al.* Outcomes in patients with acute non-Q-wave myocardial infarction randomly assigned to an invasive as compared with a conservative management strategy. Veterans Affairs Non-Q-Wave Infarction Strategies in Hospital (VANQWISH) Trial Investigators. *N Engl J Med* 1998;**338**:1785–92. doi:10.1056/NEJM199806183382501

11 McCullough PA, O'Neill WW, Graham M, *et al.* A prospective randomized trial of triage angiography in acute coronary syndromes ineligible for thrombolytic therapy: Results of the medicine versus angiography in thrombolytic exclusion (MATE) trial. *J Am Coll Cardiol* 1998;**32**:596–605. doi:10.1016/S0735-1097(98)00284-8

12 Michalis LK, Stroumbis CS, Pappas K, *et al.* Treatment of Refractory Unstable angina in geographically isolated areas without Cardiac Surgery. Invasive versus conservative strategy (TRUCS Study). *Eur Heart J* 2000;**21**:1954–9. doi:10.1053/euhj.2000.2397

13 Cannon CP, Weintraub WS, Demopoulos LA, *et al.* Comparison of Early Invasive and Conservative Strategies in Patients with Unstable Coronary Syndromes Treated with the Glycoprotein IIb/IIIa Inhibitor Tirofiban. *N Engl J Med* 2001;**344**:1879–87. doi:10.1056/NEJM200106213442501

14 Neumann FJ, Kastrati A, Pogatsa-Murray G, *et al.* Evaluation of Prolonged Antithrombotic Pretreatment ("Cooling-Off" Strategy) Before Intervention in Patients

With Unstable Coronary Syndromes: A Randomized Controlled Trial. *JAMA* 2003;**290**:1593–9. doi:10.1001/jama.290.12.1593

15 de Winter RJ, Windhausen F, Cornel JH, *et al.* Early Invasive versus Selectively Invasive Management for Acute Coronary Syndromes. *N Engl J Med* 2005;**353**:1095–104. doi:10.1056/nejmoa044259

16 Jolly SS, Faxon DP, Fox KAA, *et al.* Efficacy and safety of fondaparinux versus enoxaparin in patients with acute coronary syndromes treated with glycoprotein IIb/IIIa inhibitors or thienopyridines: results from the OASIS 5 (Fifth Organization to Assess Strategies in Ischemic Syndromes) trial. *J Am Coll Cardiol* 2009;**54**:468–76. doi:10.1016/j.jacc.2009.03.062

17 Savonitto S, Cavallini C, Petronio AS, *et al.* Early Aggressive Versus Initially Conservative Treatment in Elderly Patients With Non–ST-Segment Elevation Acute Coronary Syndrome: A Randomized Controlled Trial. *JACC Cardiovasc Interv* 2012;**5**:906–16. doi:10.1016/j.jcin.2012.06.008

18 Thiele H, Rach J, Klein N, *et al.* Optimal timing of invasive angiography in stable non-ST-elevation myocardial infarction: The Leipzig Immediate versus early and late PercutaneouS coronary Intervention triAl in NSTEMI (LIPSIA-NSTEMI Trial). *Eur Heart J* 2012;**33**:2035–43. doi:10.1093/eurheartj/ehr418

19 Lee MMY, Petrie MC, Rocchiccioli P, *et al.* Non-invasive versus invasive management in patients with prior coronary artery bypass surgery with a non-ST segment elevation acute coronary syndrome: study design of the pilot randomised controlled trial and registry (CABG-ACS). *Open Heart* 2016;**3**:e000371. doi:10.1136/openhrt-2015-000371

20 Lee MMY, Petrie MC, Rocchiccioli P, *et al.* Invasive Versus Medical Management in Patients With Prior Coronary Artery Bypass Surgery With a Non-ST Segment Elevation

Acute Coronary Syndrome: A Pilot Randomized Controlled Trial. *Circ Cardiovasc Interv* 2019;**12**:e007830. doi:10.1161/CIRCINTERVENTIONS.119.007830

21 Tegn N, Abdelnoor M, Aaberge L, *et al.* Invasive versus conservative strategy in patients aged 80 years or older with non-ST-elevation myocardial infarction or unstable angina pectoris (After Eighty study): an open-label randomised controlled trial. *Lancet* 2016;**387**:1057–65. doi:10.1016/S0140-6736(15)01166-6

22 Sanchis J, Núñez E, Barrabés JA, *et al.* Randomized comparison between the invasive and conservative strategies in comorbid elderly patients with non-ST elevation myocardial infarction. *Eur J Intern Med* 2016;**35**:89–94. doi:10.1016/j.ejim.2016.07.003

23 The TIMI IIIB Investigators. Effects of tissue plasminogen activator and a comparison of early invasive and conservative strategies in unstable angina and non-Q-wave myocardial infarction. Results of the TIMI IIIB Trial. Thrombolysis in Myocardial Ischemia. *Circulation* 1994;**89**:1545–56. doi:10.1016/S0196-0644(94)70199-7

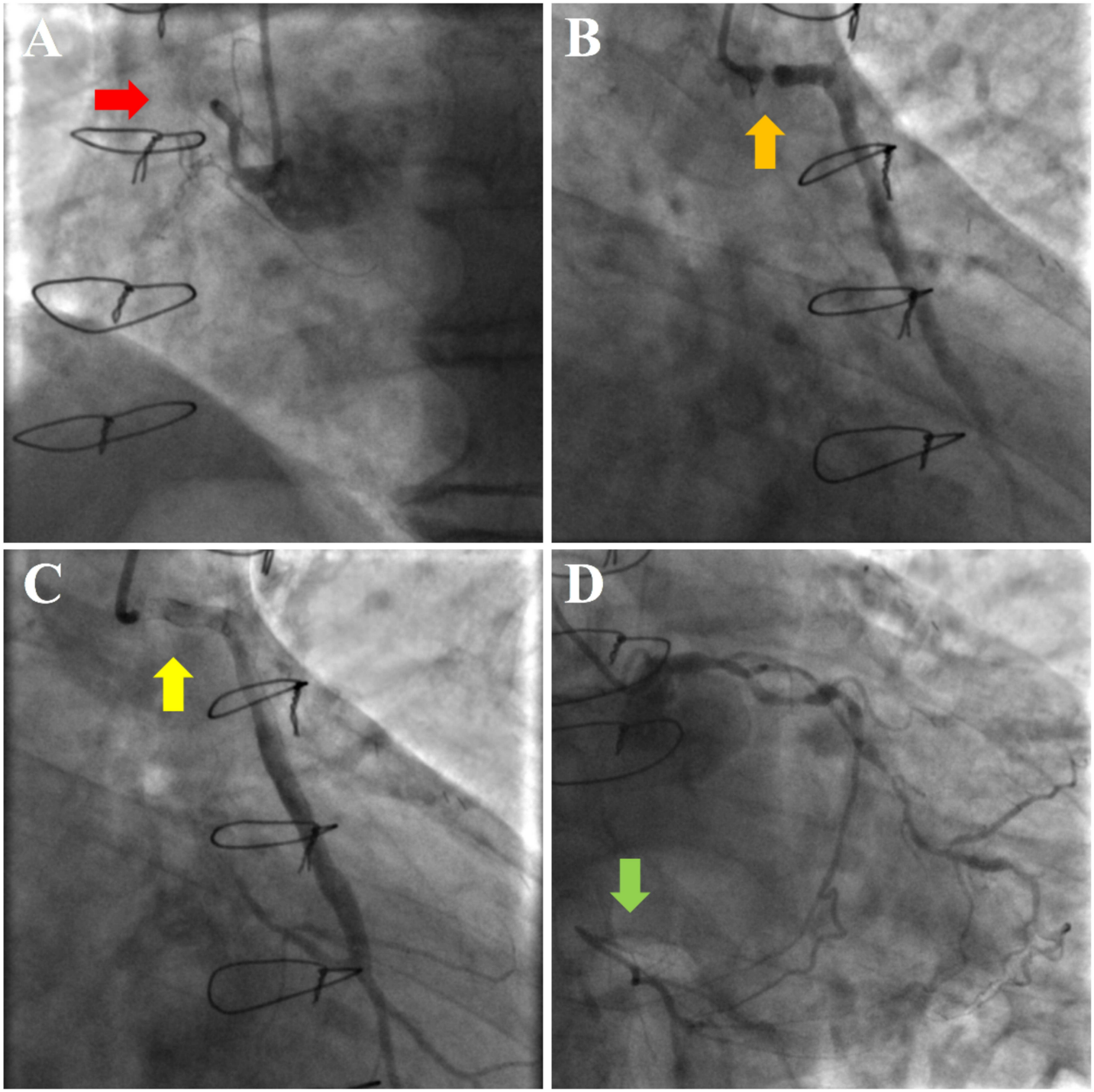
24 FRagmin and Fast Revascularisation during InStability in Coronary artery disease (FRISC II) Investigators. Invasive compared with non-invasive treatment in unstable coronary-artery disease: FRISC II prospective randomised multicentre study. *Lancet* 1999;**354**:708–15.

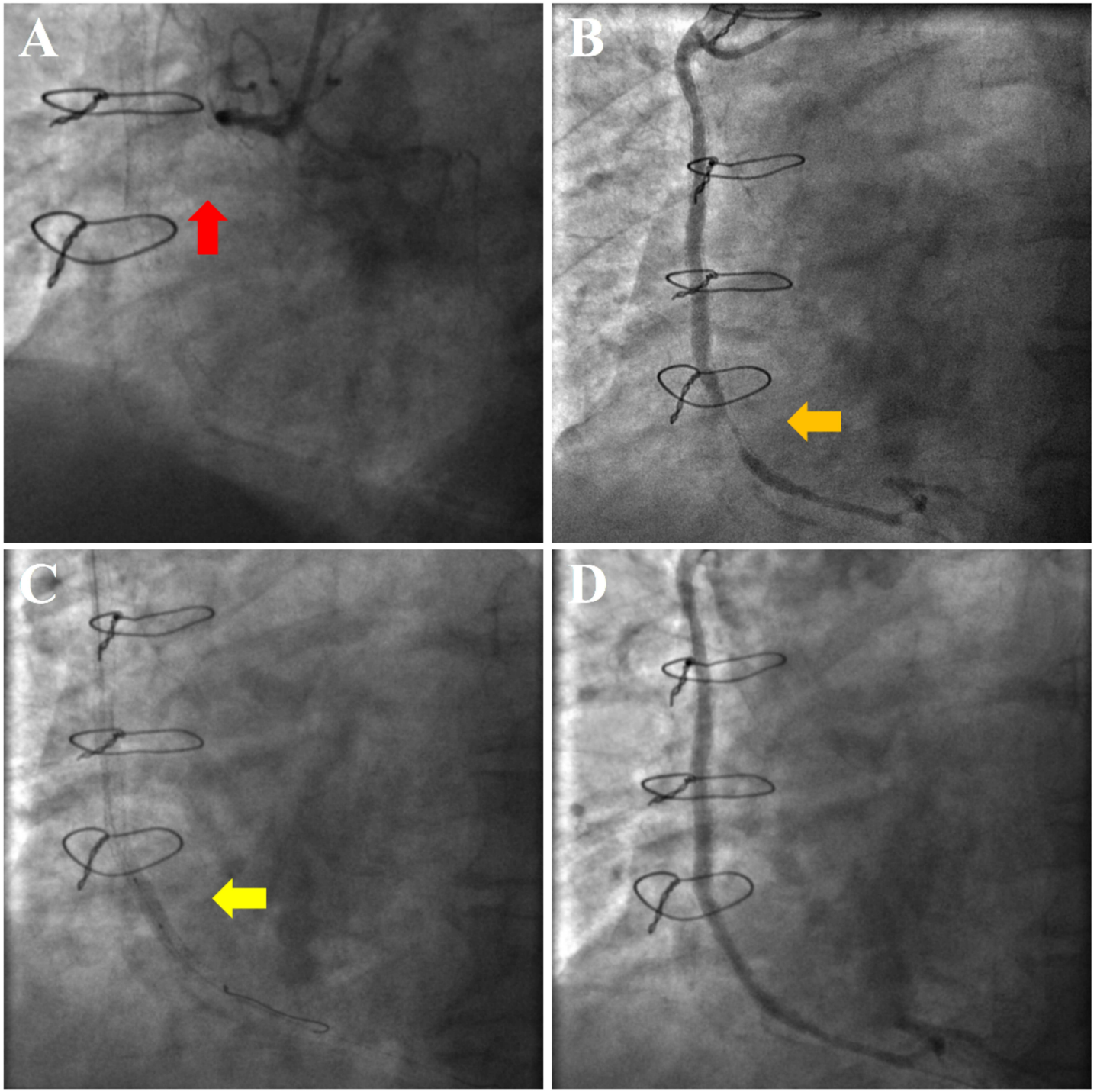
25 Spacek R, Widimský P, Straka Z, *et al.* Value of first day angiography/angioplasty In evolving Non-ST segment elevation myocardial infarction: an Open multicenter randomized trial: The VINO study. *Eur Heart J* 2002;**23**:230–8. doi:10.1053/euhj.2001.2735

26 Fox KAA, Poole-Wilson PA, Henderson RA, *et al.* Interventional versus conservative treatment for patients with unstable angina or non-ST-elevation myocardial infarction: the British Heart Foundation RITA 3 randomised trial. Randomized Intervention Trial of

335 unstable Angina. *Lancet* 2002;**360**:743–51. doi:10.1016/S0140-6736(02)09894-X

336


A
B
C
D


A
B
C
D