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

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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 fill 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,1,2 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,
not least because of rehospitalisation due to recurrent ischaemia.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{10–12} Furthermore, when invasive management is performed, percutaneous coronary intervention (PCI) is less likely in prior CABG patients,\textsuperscript{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,\textsuperscript{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,\textsuperscript{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,\textsuperscript{16} particularly when the intervention disrupts standard care. Enrolment of elderly patients may be challenging, sometimes leading to premature trial discontinuation.\textsuperscript{17–19}

We hypothesised that the clinical characteristics, treatments 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,\textsuperscript{20} and results of the main trial have been published.\textsuperscript{21}

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.
Table 1  Baseline clinical characteristics of the trial and registry participants

| Characteristics                              | Statistic | All  | Trial | Registry | P value |
|----------------------------------------------|-----------|------|-------|----------|---------|
|                                              |           | N=133| N=60  | N=73     |         |
| 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/m²)            | N (%)     | 37 (28)| 22 (37)| 15 (21)  | 0.05    |
| Presentation type*                           | N (%)     | 90 (68)| 41 (68)| 49 (67)  | 1.00    |
| Non-ST segment elevation MI                  | 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    |
| Valvular 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    | Median (IQR)| 0.674 (0.447–0.866)| 0.748 (0.514–0.899)| 0.658 (0.437–0.817)| 0.11 |
| Dimensions 5 Levels score                    |           |      |       |          |         |
| 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    |
| O-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§ | N (%)     | 4 (3)  | 2 (3)  | 2 (3)    | 0.83    |
| 1                                            | N (%)     | 11 (8) | 6 (10) | 5 (7)    |         |
| 2                                            | N (%)     | 26 (20)| 10 (17)| 16 (22)  |         |
| 3                                            | N (%)     | 90 (69)| 41 (69)| 49 (68)  |         |
| New York Heart Association functional class  |           |      |       |          |         |

Continued
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 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 enzyme; AF, atrial fibrillation; HF, heart failure; MI, myocardial infarction.
Outcomes

Primary outcome
Defined as post-randomisation 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),
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 (21 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±16g/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).

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 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   |
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 outcome.
## 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-SD-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-SD-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-SD-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.
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. 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.

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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.

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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.
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 \( \geq 25\% \) 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

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

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

Ethics

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

Trial management

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

Supplemental Figure 1.
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
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survive.
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