Supplementary data

Supplementary Appendix 1. Original RINCAL trial protocol

Revascularisation or medIcal therapy iN elderly patients with aCute anginAL syndromes: the RINCAL trial.

Protocol ID: BN-AdB-RINCAL-2013

Version 9.0

April 2019

Funder:

Medtronic Clinical Research Institute

Chief Investigator:

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Sussex Cardiac Centre
Brighton
UK

Sponsor:

Brighton and Sussex University Hospitals NHS Trust
Brighton, UK

Protocol Finalisation Signature Page

Revascularisation or medIcal therapy iN elderly patients with aCute anginAL syndromes

Rec no.	13/LO/1082
Chief Investigator	Adam de Belder MD Sussex Cardiac Centre Brighton UK Tel: 01273 696955

The trial will be conducted in accordance with good clinical practice. All key personnel involved in the trial will have completed GCP training.

The trial will be carried out in accordance with the protocol.

We will permit access to source data and trial related documents by regulatory bodies and the sponsor, for regulatory monitoring and audits.

The signature below constitutes the approval of this protocol and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements.

Chief Investigator: Dr Adam de Belder

Signed_____ Date_____

On behalf of Sponsor:

Signed_____ Date_____

Protocol Acceptance Signature Page

Revascularisation or medIcal therapy iN elderly patients with aCute anginAL syndromes

Rec no.	13/LO/1082
Chief Investigator	Adam de Belder MD Sussex Cardiac Centre Brighton UK Tel: 01273 696955

I agree to conduct the study in accordance with the current protocol.

Principal Investigator's Name (print) _____

Principal Investigators Signature _____ Date _____

Title of Study	**R**evascularisation or med**I**cal therapy i**N** elderly patients with a**C**ute angin**AL** syndromes The **RINCAL** trial
Protocol Date	14th October 2015
Planned Study Period	12-18 months recruitment
Study Design	**Multi-centre, randomised, prospective**
Number of Subjects	750
Number of Centres	20
Objectives	To determine whether an invasive strategy is superior to a conservative strategy in NSTEMI patients aged ≥80 years
Endpoints	**Primary**: Primary endpoint – Composite at 1 year of: • Death • Non-fatal myocardial infarction **Secondary:** • Time to death/non-fatal MI • Unplanned revascularisation • Permanent Stroke • Major bleeding • Deterioration of renal function during hospital admission • Angina symptoms (3 months and 1 year) • Stent thrombosis at 1 year • Drug compliance (6 months and 1 year)

	• All cause mortality at 2,3 and 4 years • Hospital readmission for ACS/STEMI • In-hospital major complications **Procedural:** • Procedure success • Procedure MACE • In-hospital complications • Procedural cost

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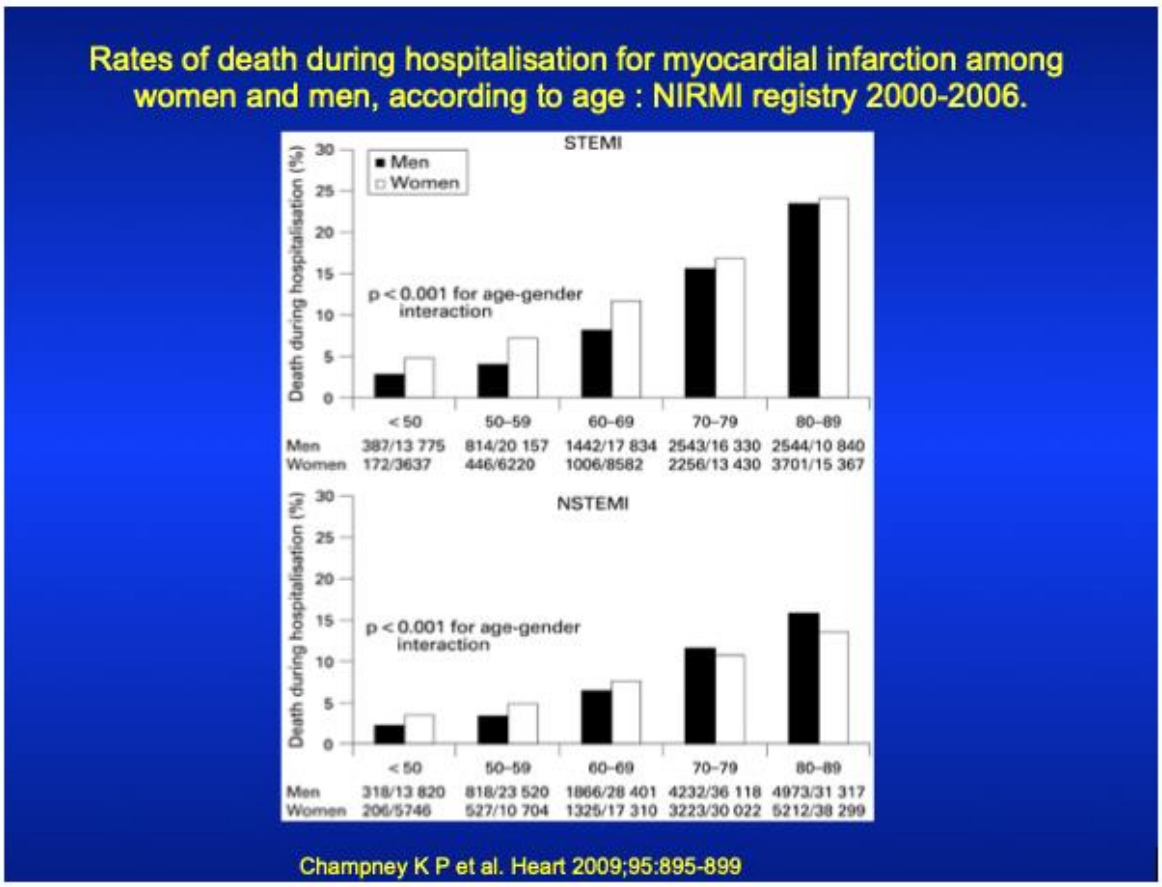
Background and rationale

Non ST elevation myocardial infarction (NSTEMI) in octogenarian patients has a significant impact on mortality. Data from the NIRMI registry demonstrates a significant age-related mortality relationship.

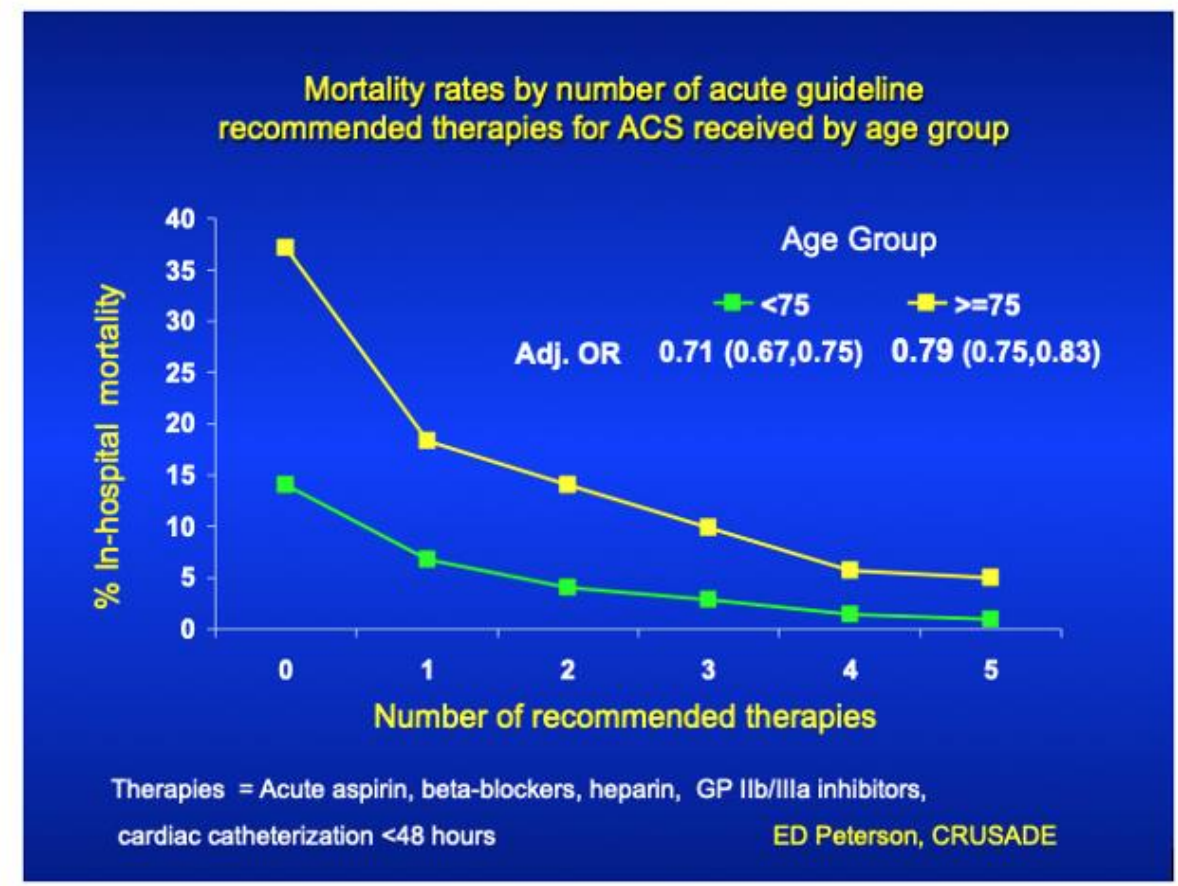


Despite rapid advances in technological and pharmacological improvements in recent years, inspection of the BCIS 2010 database shows 1 year mortality of approximately 14% at 1 year i.e. for those patients treated by stenting. It should be remembered that this does not include patients who have not had an angiogram, or even those who have had an angiogram and did not undergo stenting or a CABG.

The current management of elderly patients (octogenarians) with NSTEMI is variable. Many physicians take the view that initial medical therapy with a non-invasive conservative approach is the best model, and reserving invasive

investigations for those patients with on-going symptoms despite appropriate medical therapy.

Best medical therapy has not always been used, for fear of side effects relating to treatment hampering the intended benefits. Despite this, there is some evidence to suggest better outcomes with comprehensive 'traditional' NSTEMI treatment. Based on this data, as much as is feasible in this trial, we intend to deliver medical treatment to our patients.



The trials that have investigated a conservative vs. invasive approach in younger patients (FRISC-II, RITA III) have favoured an invasive approach, which has now become standard practice. There remains a concern among physicians attending these patients that the elderly cohort has significant issues that prevent them from benefitting from an invasive-guided approach.

In the recent ESC guidelines the following comments are made about elderly patients:

Elderly Patients

Recommendations

Class I

1. Decisions on management should reflect considerations of general health, co morbidities, cognitive status, and life expectancy. (Level of Evidence: C)

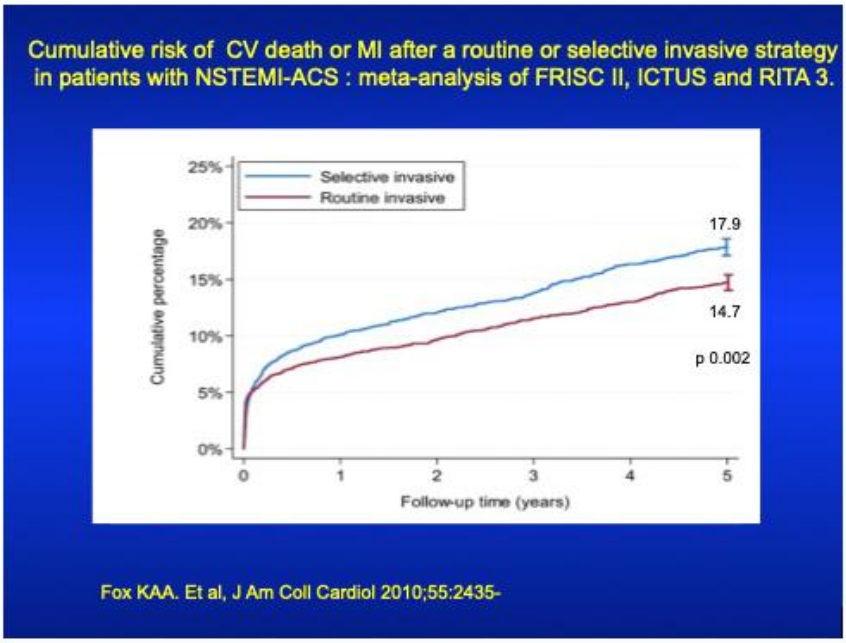
2. Attention should be paid to altered pharmacokinetics and sensitivity to hypotensive drugs. (Level of Evidence: B)

3. Intensive medical and interventional management of ACS may be undertaken but with close observation for adverse effects of these therapies. (Level of Evidence: B)

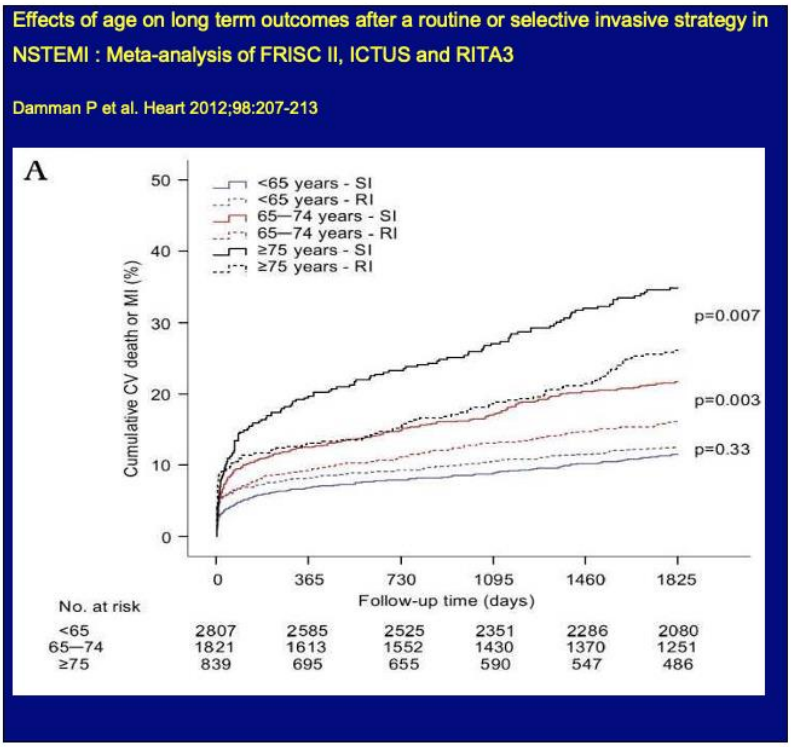
The reason for this general caution is the lack of prospectively collected data on this age group. Yet, the evidence that does exist from several major interventional trials demonstrated a benefit for older patients.

A collaborative meta-analysis of several more recently published PCI trials (FRISC-II, TACTICS, RITA-3, VINO, and MATE) suggested that, in contemporary strategies used in trials published after 1999, the majority of benefit was gained from an invasive strategy in the elderly and in patients with positive troponins or cardiac biomarkers. These trials indicated that compared with younger patients, the elderly gain important absolute benefits from an early invasive strategy but at a cost of increased bleeding.

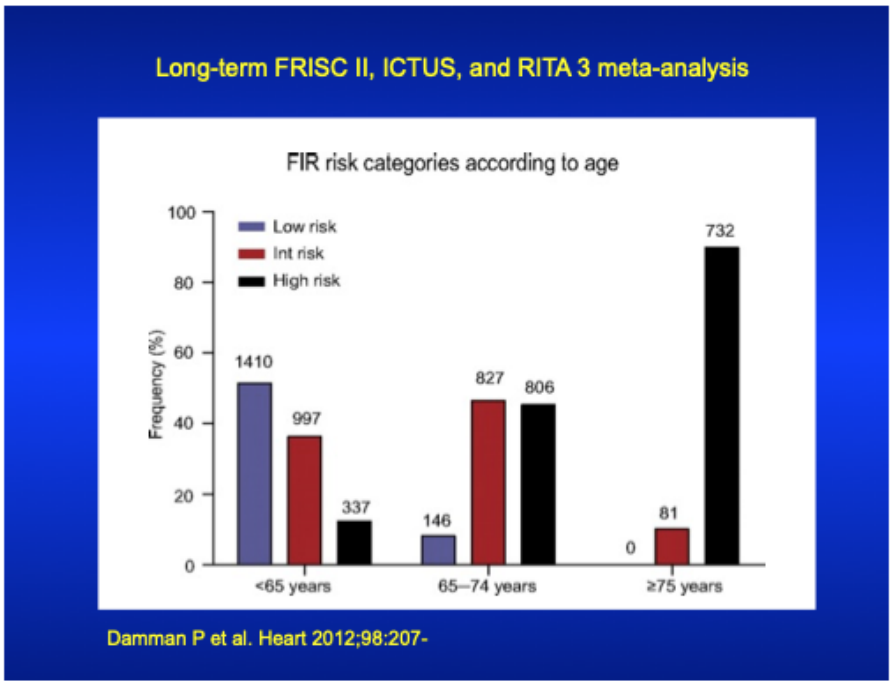
Recent publications have dissected further differences in some of these trials. The figure below outlines the all-comer results from 3 trials comparing an invasive and conservative strategy for the management of NSTEMI.



Breakdown of this data into age groups provides data that supports a benefit from the invasive approach:



If the patients are categorised by risk the elderly patients carry the largest slice:



More contemporary studies have confirmed this advantage, including TACTICS-TIMI 18. Among patients older than 75 years of age, the early invasive strategy conferred an absolute reduction of 10.8 percentage points (to 10.8% from 21.6%; p= 0.016) and a relative reduction of 56% in death or MI at 6 months; however, benefits came with an increased risk of major bleeding events (16.6% vs. 6.5%; p= 0.009).

There have been a number of registries that have reported on outcomes in this age group and, similarly, retrospective analyses have been reported that show differing outcomes.

All of these data point towards a significant benefit from an invasive approach in the octogenarian cohort, but there remains a need for a significant large prospective randomised trial comparing medical treatment vs. invasive strategy in this age group.

Currently there is no evidence available to indicate whether an invasive or conservative approach is superior for the treatment of octogenarian patients with

NSTEMI. Meta-analysis suggests a benefit in the invasive strategy in NSTEMI up to 80 years. These findings need to be evaluated in the ≥80 age group in an appropriately powered randomised trial. Historically there is a lack of consensus in treatment strategies in this patient population; RINCAL has been developed to extend the evidence base to help clinicians deliver the best possible treatment to their ≥80 patients with NSTEMI.

Objectives

Hypothesis

For octogenarian patients with NSTEMI an invasive-guided strategy will prove superior to a conservative strategy with respect to a combined endpoint of all cause mortality, or repeat non-fatal myocardial infarction at 1 year.

Trial Design

A multicentre randomised comparison of conservative strategy and invasive-guided strategy in the treatment of octogenarian patients presenting with non-ST elevation myocardial infarction

Trial Setting

Up to 20 sites in the UK

Eligibility Criteria

Inclusion Criteria

AGE ≥80

Current NSTEMI – characteristic chest pain accompanied by

- Typical ischaemic ECG changes
- A troponin rise.

Suitable for conservative or invasive strategy

Exclusion Criteria

Acute STEMI

Cardiogenic shock

Lack of suitability for whatever clinical reason to be randomised (Any condition in the opinion of the Investigator would make it unsafe or unsuitable for the patient to participate in the study)

Platelet count $\leq 50 \times 10^9/mm^3$

Patient life expectancy < 1 year

Known allergies to Clopidogrel (or equivalent anti-platelet drug being used in study participants), aspirin, heparin, contrast or stent drug elutant

Recent major GI haemorrhage (within 3 months)

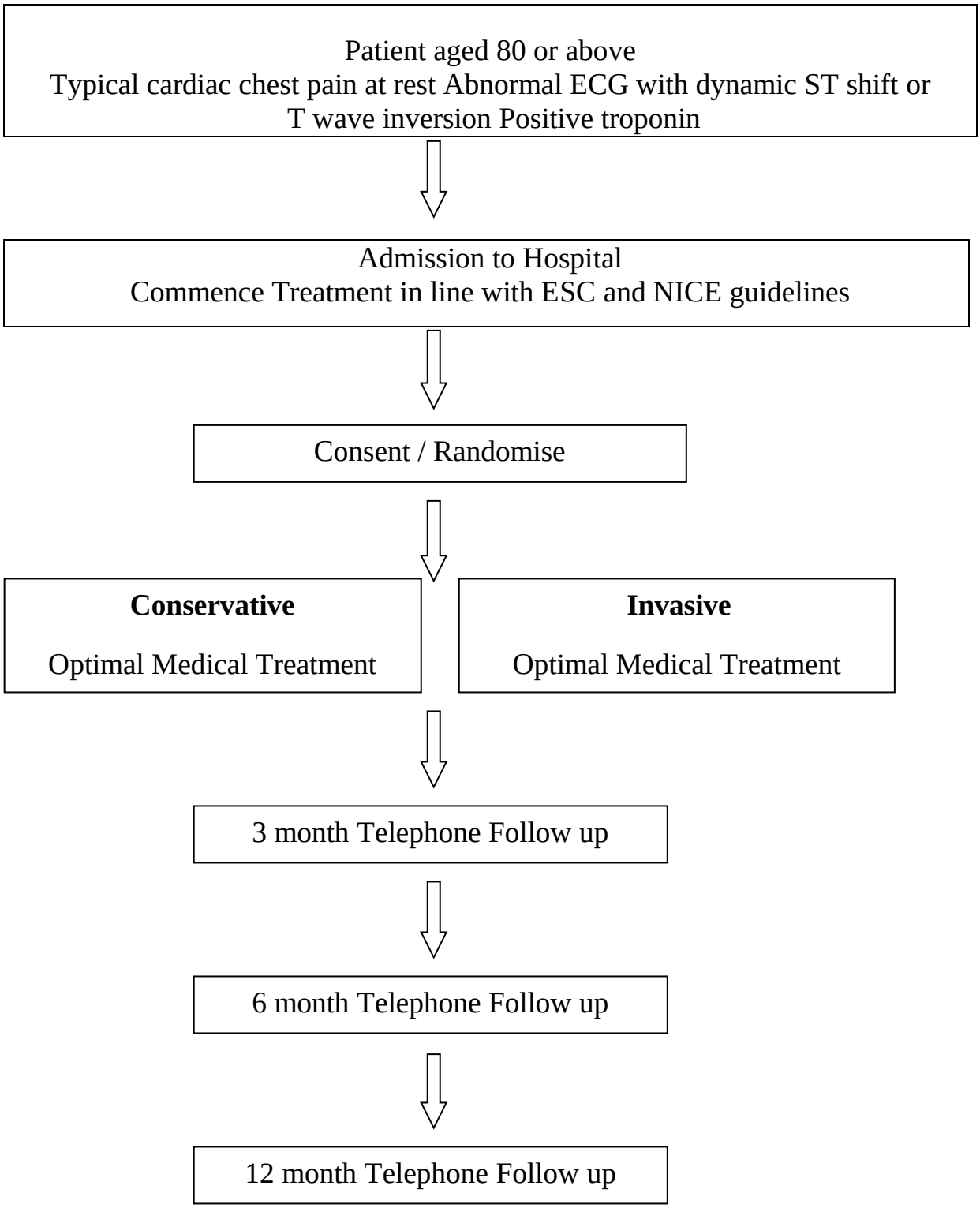
Any previous cerebral bleeding episode

Participation in another investigational drug or device study

Patient unable to give consent

Clinical decision precluding the use of stents

Trial Flow Chart



Optimal Medical Treatment (OMT)

Early Treatment

Antiplatelet agents

Aspirin (loading dose)

P2Y12 receptor antagonists (loading dose) e.g.

- Clopidogrel
- Prasugrel
- Ticagrelor

Glycoprotein IIb/IIIa receptor inhibitors (with extreme caution in this age group) e.g.

Abciximab

Eptifibatide

Tirofiban

Antithrombotic

Fondaparinux

Direct thrombin inhibitors (bivalirudin)

Anti-ischaemic agents

Beta-blockers

Nitrates

Calcium channel blockers

Secondary Treatment (titrate to target dose)

Dual antiplatelet Therapy

Beta-blockers

ACE (Angiotensin-Converting-Enzyme) inhibitors/ **ARBs** (Angiotensin Receptor Blockers)

Statin (HMG-CoA reductase inhibitors)

Eplerenone

Conservative Arm

There are two stages in the 'medical' treatment of NSTEMI. The first aim is to settle the acute situation with appropriate pharmacological treatment. All patients will receive LMWH, aspirin, clopidogrel (or equivalent), a beta blocker (Bisoprolol or equivalent) and a statin (Simvastatin or equivalent). For on-going symptoms of angina a GTN infusion should be started.

For younger patients, IIb/IIIa glycoprotein inhibitors would be used, and they can be administered within the protocol of this trial, but we suggest these drugs are used with caution in view of the risk of bleeding associated with their use in this age group. The type of IIb/IIIa glycoprotein inhibitor is at the discretion of the physician.

Once the episode of NSTEMI has settled, the plan is to optimise long term medical treatment in order to reduce potential for future ischaemic events. Ideally, if patients are able to tolerate them, they should be discharged on aspirin, clopidogrel (or equivalent) to be taken for at least 6 months, a beta blocker (Bisoprolol or equivalent), an ACE inhibitor (Ramipril, the highest dose tolerated, or equivalent), and a statin (Simvastatin or equivalent)

Crossover to Invasive Arm

If patients have episodes of on-going angina at rest despite initial measures, a GTN infusion must be started, and consideration be given to a glycoprotein IIb/IIIa infusion (if bleeding risk is thought to be low). If despite these measures

angina continues with ECG changes, then crossover to an invasive strategy can be considered.

Invasive Arm

Revascularisation

Percutaneous coronary intervention (PCI) or Coronary Artery Bypass Graft (CABG)

Prior to revascularisation all patients will undergo an assessment of angina status, angina medication, ECG and troponin measurement.

IF PCI STRATEGY IS CHOSEN

Medication

Pre PCI

Aspirin should be continued at 75mg dose if the patient is already established on it. If not a loading dose of 300mg should be given on the morning of the procedure, preferably 3 hours beforehand, and a daily dose of aspirin 75mg continued thereafter.

Clopidogrel 75mg (or equivalent) daily should be continued if the patient is established on this medication. If not, clopidogrel 600mg (or equivalent) should be given on the morning of the study at least 3 hours before the procedure. Clopidogrel (or equivalent) will be continued for 6 months after the stenting procedure.

Patients taking Warfarin

Many elderly patients meet the criteria for taking long term warfarin, usually to prevent cerebral embolism with atrial fibrillation. TAKING WARFARIN IS NOT A CONTRAINDICATION TO JOINING THE TRIAL. The physician must weigh up the odds about whether or not a course of clopidogrel (or equivalent) and aspirin in addition to warfarin is appropriate. It may be a decision is made to keep the INR at 1.5-2.0 whilst taking the combined antiplatelet therapy. If the risk is considered too great by the physician then the patient must not be enrolled.

PCI procedure

It is encouraged to perform lesion preparation before stent deployment. This will usually be with balloon inflation, but other strategies such as cutting balloon or rotablation can be used. There are no limitations to the number of stents to be used.

For bifurcation lesions a simple strategy is encouraged, with stenting of the main conduit, with maintenance of flow in the side-branch. If stenting of the side-branch is required, then any technique with which the operator has experience can be used. The coronary anatomy in most of these patients will be complex and it is likely that drug-eluting stent technology will be used to reduce the risk of recurrent ischaemia.

All procedures should have unfractionated heparin 70 iu/kg at the start of the procedure. 45 minutes into the procedure an ACT should be checked and further boluses of heparin delivered to maintain an ACT of >200 seconds.

The use of IIb/IIIa inhibitors is at the discretion of the operator, but any decision about their use must consider the risk of increased bleeding in this age group.

Post PCI

Aspirin 75mg daily indefinitely

Patients with DES –clopidogrel 75mg (or suitable equivalent) daily for 6 months

Patients with BMS – clopidogrel 75mg (or suitable equivalent) daily for 6 months

Proton pump inhibitors should be given if there is prior history of indigestion or prior GI bleed, or if the clinician feels it is appropriate.

Discontinuation of the antiplatelet regime is strongly discouraged.

CABG

Following angiography, the physician may consider CABG to be the most appropriate form of revascularisation. These matters should be considered at a multidisciplinary meeting, where the patient characteristics and angiographic details are discussed. It may be decided that incomplete revascularisation of the culprit lesion by PCI will have the least morbidity and mortality risk. If surgery is agreed, then it should be performed within 6 weeks of the angiogram. If the LAD is to be revascularised, then every consideration should be given to using a LIMA graft.

Post CABG, the patients should receive aspirin, beta blockers, ACEi and statin in appropriate doses.

Periprocedural Assessment

Troponin will be measured at the start of the procedure in all patients, and again 16-22 hours following the PCI, or as near to discharge as possible if sooner.

Endpoints

Primary endpoint

Composite at 1 year of:

- Death
- Non-fatal myocardial infarction

Secondary endpoints

- Time to death/non-fatal MI
- Unplanned revascularisation
- Permanent Stroke
- Major bleeding (BARC definition 3B or above) in-hospital and 1 year
- Deterioration of renal function during hospital admission (requirement for renal replacement therapy, or rise in creatinine >25% from baseline value)
- Angina symptoms at 3 months and 1 year
- Stent thrombosis at 1 year

- Drug compliance at 6 months and 1 year
- All-cause mortality at 2, 3 and 4 years
- Hospital readmission for ACS/STEMI
- In-hospital major complications

Procedural:

- Procedure success
- Procedure MACE
- In-hospital complications
- Procedural cost

Participant Timeline

Time and Event Schedule

Event	Screen	Procedure	16-22 hours	3 months	6 months	12 months
Informed Consent	X					
Inclusion/Exclusion	X					
AMT	X			X	X	X
Physical Exam	X					
Medical History	X			X	X	X
Angina History	X			X	X	X
ECG	X		X			
Troponin	X		X			
Medication History	X	X		X	X	X
Adverse Event		X		X	X	X
PCI or CABG		X				

Follow Up

Patients will be contacted at 3, 6 and 12 months post randomisation and thereafter as clinically indicated. Follow-up will be undertaken by a designated research nurse and/or research registrar. The 3 month, 6 month and 1 year assessment can be made by telephone.

At 3 months

Assessment of cardiac signs and symptoms

Assessment of SAE and endpoints

Record of current medications

Abbreviated Mental Test

Any abnormalities might trigger further investigations as appropriate

At 6 months

Assessment of cardiac signs and symptoms

Assessment of SAE and endpoints

Record of current medications

Abbreviated Mental Test

Any abnormalities might trigger further investigations as appropriate

At 1 year

Assessment of cardiac signs and symptoms

Assessment of SAE and endpoints

Record of current medications

Abbreviated Mental Test

If significant abnormalities are detected, further investigation may be required with either non-invasive testing and/or a further angiogram.

If a follow-up angiogram is performed within 1 year of the original PCI and further revascularisation is decided upon (CABG or re-PCI), this will count as completion of the primary endpoint of TVF, irrespective of whether the revascularisation procedure lies within the 1 year time frame of the study.

Long term mortality tracking will be performed using the UK national mortality tracking system at 2, 3 and 4 years

Sample Size

The expected death/nonfatal MI rate for the group of patients treated with a conservative strategy would be 38% at 1 year, based on published data. We estimate the expected death/nonfatal MI for the invasive strategy group to be 28%. Using this estimate a sample size of 712 patients would achieve 80% power for 5% significance. To allow for 5% of patients lost to follow-up, it is proposed that 750 patients will be recruited.

Recruitment

All patients aged 80 or above presenting on the date of their NSTEMI will be considered for the trial. A total of 750 patients will be enrolled in the study at 20 UK sites. Each site is expected to enrol 2-3 patients per month.

Randomisation

Patients who fulfil inclusion criteria and consent to the study will be randomised on a 1:1 basis electronically using the Dendrite clinical systems electronic data capture.

Data Collection and Management

Participant data will be recorded in a limited access secure electronic CRF system. The clinical database will reside on a production server hosted by Dendrite. All changes made to the clinical data will be captured in an electronic audit trail and available for review by BSUH or its representative. The associated software and database have been designed to meet regulatory compliance for deployment as part of a validated system compliant with laws and regulations applicable to the conduct of clinical studies pertaining to the use of electronic records and signatures. Database backups are performed regularly.

The site Investigator team will maintain in original format all essential study documents and source documentation that support the data collected on the study participants in compliance with ICH/GCP guidelines. The site Investigator team will take measures to ensure that these essential documents are not accidentally damaged or destroyed.

Prior to database export, the data will be checked, cleaned and locked. Export will be to a .csv (or similar) file for import to Stata version 15.1 or higher.

Statistical Methods

Participant flow through the trial will be depicted in a CONSORT flow chart, according to the CONSORT Statement 2010.

Available cases will be analysed in the group to which they were randomised.

Comparability of treatment groups will be checked descriptively. Patient characteristics and outcomes will be summarised by group using descriptive statistics. Categorical outcomes will be summarised using frequencies and percentages, continuous outcomes using medians and interquartile ranges.

Kaplan-Meier curves will be plotted for time death/MI.

The primary analysis will be conducted using logistic regression with fixed effects for invasive versus non-invasive treatment and centre. Other pre-randomisation variables prognostic of the composite endpoint death/MI may be included; these will be agreed and written into an analysis plan which will be signed off prior to final analysis. We will report the odds ratio for invasive vs. non-invasive treatment and its 95% confidence interval, together with the p-value. Time to the primary endpoint will be a secondary outcome. A Cox proportional hazards model will be fitted with fixed effects as described above and the proportional hazards assumption checked. If this assumption is not satisfied, we will introduce time by covariate interactions. We will report the hazard ratio for invasive vs. non-invasive treatment, with its 95% confidence interval and p-value.

Other secondary outcomes (as appropriate) will be analysed using logistic regression models with fixed effects as described above.

All analysis will be conducted in Stata version 15.1 or higher.

Stopping Rules

One interim analysis is planned for the primary endpoint. It is expected that the interim analysis will be performed at the 1/3rd recruitment stage of the study. The interim analysis for stopping the trial early for positive efficacy will use an alpha-spending function. The Lan-DeMets method will be used to specify p-values for the interim analysis of efficacy that are allowed. This method allows for changing the time of an interim analysis, adding interim analyses, or dropping analyses under certain circumstances.

This method requires an alpha spending function to generate interim p-value cut-off levels for significance testing. The boundary chosen is the O'Brien-Fleming boundary. This is a boundary that is conservative for early time points, and most of the alpha-spending is at the final analysis. The p-value criteria at the interim and final analyses preserves overall alpha for the primary endpoint at 0.05 (2-sided).

At the request of the DSMC and Chief Investigator the trial has stopped recruiting patients as of the 24th September 2018.

The primary reason for stopping recruitment early is slow recruitment to the trial. We have thus far recruited 252 patients to the trial. Recruitment commenced on 16th May 2014. The original target sample size was 750 with a planned end to the trial of 1st June 2019. It would be futile to continue the trial on the current recruitment trajectory. The last patient recruited to the trial will have 1-year follow up on 24th September 2019 and all sites will be informed of the amendment and closure

The Research Governance and Quality Assurance Group of Brighton and Sussex University Hospitals NHS Trust have approved this request for a substantial amendment to the trial protocol on the 20th March 2019.

Adverse Events

Participants in the study are elderly and have presented acutely with a NSTEMI, undergoing major heart surgery. In such a population many AEs and/or SAEs are expected to occur.

This is an endpoint driven study and all primary and secondary endpoints need to be reported to the sponsor as soon as the investigator is aware of their occurrence who will then notify the study's safety committee. However, as these events are expected, they do not need to be reported as SAEs. The Chief Investigator (CI) is responsible for reporting related and unexpected SAE to the relevant Research Ethics Committee (REC) and the sponsor for the study. They are also responsible for ensuring all investigators are promptly notified of any findings that may impact participant safety.

The PI/CI will assess each AE for causality, seriousness and expectedness and for reporting unexpected and related SAEs to the CI and sponsor immediately.

The Sponsor will be responsible for creating and maintaining a database of reported unexpected and related SAEs and tracking their outcome.

Data Monitoring

A Data and Safety Monitoring Committee (DSMC) will be convened to look at the data from an ethical standpoint, the safety, rights and well being of the trial participants being paramount. The members of the DMC have the experience and expertise and are independent of the trials: Professor Adrian Banning (independent expert), Dr Angela Hoye (independent expert) and Derek Robinson (statistician).

The role of the DSMC will be to determine if additional interim analyses of the trial data should be undertaken, review reports from the clinical events adjudication committee. To consider the data from interim analyses, plus any

additional safety issues for the trial and relevant information from other sources. To report to the Trial Steering Committee (TSC) to recommend on the continuation of the trial and to consider any requests for release of interim trial data.

Trial Steering Committee

The role of the Trial Steering Committee (TSC) is to provide overall supervision of the trial. In particular, the progress of the trial to maximise the chances of completing the trial within the agreed time scale, adherence to the protocol, patient safety and consideration of new information.

- Monitor and supervise the progress of the trial
- Review relevant information from other sources
- Consider the recommendations of the DSMC
- Inform the regulatory boards of the progress of the trial
- To advise on publicity and presentation of all aspects of the trial

Dr Adam de Belder

Dr David Hildick-Smith

Dr Simon Redwood

Dr Peter O'Kane

Dr Juliet Wright (Consultant for Stroke and Elderly Care Medicine)

Clinical Events Committee

The Clinical Events Committee (CEC) is an independent committee to review the information obtained on endpoints reported in the trial to determine whether the endpoints meet protocol-specified criteria.

Dr Mark de Belder

Dr Andrew Sutton

Ethics

The UK Chief Investigator (CI) will obtain approval for the trial from the main research ethics committee (REC). The CI will also facilitate the trial through the NIHR CRN portfolio and study-wide governance reviews. The CI will advise the REC of the process of the trial, submit yearly reports and the end of study report.

The Principal Investigator at each UK site will be responsible for obtaining trust approval prior to commencing the trial.

Amendments

The CI will submit to REC any amendments to the protocol, the PI will gain trust approval for the amendment prior to implementing the amendment.

Informed Consent

Signed informed consent will be obtained by a member of the research team before any trial specific procedures. Participates and researchers must personally sign and date the REC approved consent form prior to enrolment.

Confidentiality

All patient data will be anonymised by the site research team. Each patient entering the study will be given a case specific number. This number replaces the use of any personal identifiable data. Data transferred onto the electronic case report form (e-CRF) will require only the case specific number. This should ensure that there is no risk to patient confidentiality.

The local sites will retain a list of case specific study numbers, for their patients, this list will not leave the local site.

Declaration of Interests

The trial is supported by an unrestricted grant from Medtronic Cardiovascular. The Author declares that there is no conflict of interest.

Publication Policy

The investigators are committed to the publication and widespread dissemination of the results of the Study. It is agreed that the recommendation of any party concerning manuscripts or text shall be taken into consideration in the final preparation of scientific documents for publication and presentation. All proposed publications and presentations resulting from or relating to the study must be submitted to the steering committee for review and approval prior to submission for publication or presentation.

It is intended that the Principal Investigators from the highest-recruiting centres will be invited to participate fully in the preparation and authorship of the main manuscripts resulting from this study.

Appendices

Appendix A: References for the original trial protocol

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Appendix B: Definitions

Definition of Death

The cause of death will be adjudicated as being due to cardiovascular causes, non cardiovascular causes, or undetermined causes.

- Cardiovascular Death includes sudden cardiac death, death due to acute myocardial infarction, death due to heart failure or cardiogenic shock, death due to stroke or death due to other cardiovascular causes
- Non-Cardiovascular Death is defined as any death not covered by cardiac death or vascular death.
- Undetermined cause of death refers to a death not attributable to one of the above categories of cardiovascular death or to a non-cardiovascular cause.

N.B. For this trial all deaths with undetermined causes will be included in the cardiovascular category.

Myocardial Infarction

The ESC/ACC definition of myocardial infarction will be applied, including the special circumstances of same admission myocardial re-infarction, or myocardial infarction peri-PCI.

Either one of the following criteria satisfies the diagnosis for an acute, evolving or recent MI:

- Typical rise and gradual fall of troponin with at least one of the following:

- ischemic symptoms
- development of pathologic Q waves on ECG
- ECG changes indicative of ischemia (ST segment elevation or depression) or
- coronary artery intervention (e.g., coronary angioplasty)
- pathologic findings of an acute MI

Biochemical marker evidence of MI:

- Troponin T or I: Maximal concentration greater than the MI decision limit on ≥ 1 occasion (reference values must be determined in each laboratory by studies using specific assays with appropriate quality control). Acceptable imprecision at the 99th percentile for each assay should be defined as ≤10%. Each individual laboratory should confirm the range of reference values in their specific settings.

Special circumstances

- For patients who die and for whom no cardiac markers were obtained, the presence of new ST-segment elevation and new chest pain would meet criteria for MI.

Target vessel failure

This incorporates both target vessel inadequacy and target vessel revascularisation

Target vessel inadequacy

Shall be deemed to have occurred if flow in any vessel or side-branch is <TIMI 3 after appropriate vasodilators have been given (where a further angiogram has been carried out for clinical purposes).

Target vessel revascularisation

Shall be deemed to have occurred at follow-up if any coronary vessel requires or undergoes attempted repeat revascularisation with either balloon angioplasty, stenting, or coronary artery bypass grafting.

Deterioration of renal function during hospital admission

Worsening renal function is an absolute increase in serum creatinine of ≥ 0.3mg/dl (26.5 umol/l) at any time during hospitalization compared to the value obtained at admission

Stroke

A stroke is a loss of neurological function caused by an ischaemic or haemorrhagic event with residual symptoms at least 24 hours after onset or leading to death

Bleeding (BARC definition)

Type 0: no evidence of bleeding.

Type 1: bleeding that is not actionable and does not cause the patient to seek unscheduled performance of studies, hospitalization, or treatment by a healthcare professional. Examples include, but are not limited to, bruising, haematoma, nosebleeds, or haemorrhoidal bleeding for which the patient does not seek medical attention. Type 1 bleeding may include episodes that lead to discontinuation of medications by the patient because of bleeding without visiting a healthcare provider.

Type 2: any clinically overt sign of haemorrhage (e.g., more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that is actionable but does not meet criteria for type 3, type 4 (CABG-related), or type 5 (fatal bleeding) BARC bleeding. The bleeding must

require diagnostic studies, hospitalization, or treatment by a healthcare professional. In particular, the bleeding must meet at least one of the following criteria: First, it requires intervention, defined as a healthcare professional–guided medical treatment or percutaneous intervention to stop or treat bleeding, including temporarily or permanently discontinuing a medication or study drug. Examples include, but are not limited to, coiling, compression, use of reversal agents (e.g., vitamin K, protamine), local injections to reduce oozing, or a temporary/permanent cessation of antiplatelet, antithrombin, or fibrinolytic therapy. Second, the bleeding leads to hospitalization or an increased level of care, defined as leading to or prolonging hospitalization or transfer to a hospital unit capable of providing a higher level of care. Or third, the bleeding prompts evaluation, defined as leading to an unscheduled visit to a healthcare professional resulting in diagnostic testing (laboratory or imaging). Examples include, but are not limited to, haematocrit testing, haemoccult testing, endoscopy, colonoscopy, computed tomography scanning, or urinalysis. A visit or phone call to a healthcare professional during which neither testing nor treatment is undertaken does not constitute type 2 bleeding.

Type 3: clinical, laboratory, and/or imaging evidence of bleeding with specific healthcare provider responses, as listed below:

—Bleeding Academic Research Consortium type 3a bleeding

Any transfusion with overt bleeding

Overt bleeding plus haemoglobin drop ≥3 to <5 g/dL (provided haemoglobin drop is related to bleeding). Haemoglobin drop should be corrected for intercurrent transfusion in which 1U packed red blood cells or 1 U whole blood would be expected to increase haemoglobin by 1 g/dL.

—Bleeding Academic Research Consortium **type 3b** bleeding

Overt bleeding plus haemoglobin drop ≥5 g/dL (provided haemoglobin drop is related to bleed). Haemoglobin drop should be corrected for intercurrent transfusion in which 1 U packed red blood cells or 1 U whole blood would be expected to increase haemoglobin by 1 g/dL.

Cardiac tamponade

Bleeding requiring surgical intervention for control (excluding dental/nasal/skin/haemorrhoid)

Bleeding requiring intravenous vasoactive drugs

—Bleeding Academic Research Consortium **type 3c** bleeding

Intracranial haemorrhage (does not include microbleeds or haemorrhagic transformation; does include intraspinal); subcategories confirmed by autopsy, imaging, or lumbar puncture

Intraocular bleed compromising vision

Type 4: Coronary Artery Bypass Graft–related bleeding

Perioperative intracranial bleeding within 48 hours

Reoperation after closure of sternotomy for the purpose of controlling bleeding

Transfusion of ≥5 U whole blood or packed red blood cells within a 48-hour period (only allogenic transfusions are considered transfusions for CABG-related bleeds)

Chest tube output ≥2 L within a 24-hour period

Notes: If a CABG-related bleed is not adjudicated as at least a type 3 severity event, it will be classified as not a bleeding event. If a bleeding event occurs with a clear temporal relationship to CABG (i.e., within a 48-hour time frame)

but does not meet type 4 severity criteria, it will be classified as not a bleeding event.

Type 5: Fatal bleeding

Fatal bleeding is bleeding that directly causes death with no other explainable cause. BARC fatal bleeding is categorized as either definite or probable as follows:

Probable fatal bleeding (type 5a) is bleeding that is clinically suspicious as the cause of death, but the bleeding is not directly observed and there is no autopsy or confirmatory imaging.

Definite fatal bleeding (type 5b) is bleeding that is directly observed (by either clinical specimen [blood, emesis, stool, etc.] or imaging) or confirmed on autopsy.

The site of fatal bleeding is specified as intracranial, gastrointestinal, retroperitoneal, pulmonary, pericardial, genitourinary, or other.

Bleeding Academic Research Consortium fatal bleeding is meant to capture deaths that are directly due to bleeding with no other cause. The time interval from the bleeding event to the death should be considered with respect to likely causality, but there is no specific time limit proposed. Bleeding that is contributory but not directly causal to death is not classified as fatal bleeding but may be categorized as other forms of bleeding. Bleeding that leads to cessation of antithrombotic or other therapies may be contributory but again would not be classified as fatal bleeding. Bleeding associated with trauma or with surgery may be fatal, depending on whether it was determined to be directly causal or not.

Appendix C: Abbreviations

ACT	Activated Clotting Time
BCIS	British Cardiovascular Intervention Society
BMS	Bare Metal Stent
CABG	Coronary Artery Bypass Graft
CEC	Clinical Events Committee
CI	Chief Investigator
DES	Drug Eluting Stent
DMC	Data-Monitoring Committee
ECG	Electrocardiogram
ESC	European Society of Cardiology
GI	Gastrointestinal
GTN	Glyceryl trinitrate
LAD	Left Anterior Descending
LIMA	Left Internal Mammary Artery
MI	Myocardial Infarction
NICE	National Institute for health care Excellence
NIRMI	National Registry of Myocardial Infarction
NOACs	New Oral Anticoagulants
NSTEMI	Non ST Elevation Myocardial Infarction
OMT	Optimal Medical Treatment
PCI	Percutaneous Coronary Intervention
STEMI	ST Elevation Myocardial Infarction
TSC	Trial Steering Committee
TVF	Target Vessel Failure

Appendix D: Abbreviated Mental Test

Question	Score
What is your age? (1 point)	
What is the time to the nearest hour? (1 point)	
Give the patient an address, and ask him or her to repeat it at the end of the test. (1 point) e.g. 42 West Street	
What is the year? (1 point)	
What is the name of the hospital or number of the residence where the patient is situated? (1 point)	
Can the patient recognize two persons (the doctor, nurse, home help, etc.)? (1 point)	
What is your date of birth? (day and month sufficient) (1 point)	
In what year did World War 1 begin? (1 point) (other dates can be used, with a preference for dates some time in the past.)	
Name the present monarch/dictator/prime minister/president. (1 point) (Alternatively, the question "When did you come to [this country]? " has been suggested)	
Count backwards from 20 down to 1. (1 point)	

Appendix E: Sample of data to be collected

Date of birth

Sex

Ethnicity

Hospital

Angina status

NYHA class

Risk factors

- Smoking history
- FH premature IHD
- Hypertension
- Hypercholesterolaemia
- Peripheral vascular disease
- Body mass index
- Diabetes mellitus
- Renal impairment
- Previous cardiac history
- Myocardial infarction
- Previous PCI

Previous CABG

Congestive cardiac failure

LV function

Carotid endarterectomy/angioplasty

Peripheral bypass grafts/angioplasty

Physical examination

Height

Weight

BMI

BP

Pulses/bruits

ECG

Rhythm

LBBB

RBBB

Resting ST depression

T wave inversion

Q waves

Clinical presentation

Acute coronary syndrome (troponin+ve)

TIMI risk score

GRACE risk score

Strategy Randomised

Conservative vs. Invasive strategy

Medication preprocedure

Aspirin

Clopidogrel

Glycoprotein inhibitor

B-Blocker

Ca antagonist

Nicorandil

Nitrates

Angiogram

Vessels greater than 70% stenosed

LV function (<30%, 30-50%, >50%)

Vessels planned to be treated

Nature of lesion to be treated

Length of treatment site

Diameter of vessel site

ACC grade of vessel lesion (A,B,C)

Calcification (mild, moderate, severe)

In-stent restenosis

Chronic total occlusion – timing of occlusion

Procedural details

Approach – femoral/radial

French size

Heparin dose

Guide catheter

Planned strategy complete or incomplete revascularisation

No of diseased vessels

No of vessels planned for intervention

Type of Stent deployed

Successful outcome

Final result – successful, partial success, poor, failure to cross.

Angioplasty details overall

Final angiographic result in all vessels treated

Glycoprotein inhibitor use

Complications

No. of Balloons used

No. of Stents used

Procedure duration

Fluoroscopy time

Post revascularisation

Time to discharge (<24 hours, 24-48 hours, >48 hours)

Reasons for delayed discharge

Post PCI ECG

Troponin I at 16-22 hours

Complications (access site, revascularisation, MI, CABG)

Discharge medications

Coronary artery bypass surgery (CABG)

Time from randomisation to CABG (days)

EuroScore

No. of grafts

Type of graft

Bypass time

On or off bypass

Procedural time

Length of hospital stay

Major complications of surgery

Minor complications of surgery