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A Study to Improve Cardiovascular Outcomes in High Risk Older PatieNts (ICON1) with Acute Coronary Syndrome: Study Design and Protocol of a Prospective Observational Study

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Running title: Study design of ICON1

ABSTRACT

Introduction: The ICON1 study (a study to **I**mprove **C**ardiovascular **O**utcomes in high risk older patie**N**ts with acute coronary syndrome) is a prospective observational study of older patients (≥75 years old) with non-ST elevation acute coronary syndrome managed by contemporary treatment (pharmacological and invasive). The aim of the study is to determine the predictors of poor cardiovascular outcomes in this age group and to generate a risk prediction tool.

Methods and Analysis: Participants are recruited from two tertiary hospitals in the United Kingdom. Baseline evaluation includes frailty, co-morbidity, cognition and quality of life measures, inflammatory status assessed by a biomarker panel including microRNAs, senescence assessed by telomere length and telomerase activity, cardiovascular status assessed by arterial stiffness, endothelial function, carotid intima media thickness and left ventricular systolic and diastolic function, and coronary plaque assessed by virtual histology intravascular ultrasound and optical coherence tomography. Patients are followed up at 30 days and at one year for primary outcome measures of death, myocardial infarction, stroke, revascularisation, bleeding and re-hospitalisation.

Ethics and Dissemination: The study has been approved by the regional ethics committee (REC 12/NE/016). Findings of the study will be presented in scientific sessions and will be published in peer reviewed journals.

Study registration: United Kingdom Clinical Research Network ID: 12742; ClinicalTrials.gov ID: NCT01933581.

Keywords: Study design, acute coronary syndrome, older patients

Abbreviations

ACS	Acute Coronary Syndrome
ADMA	Asymmetric Dimethyl Arginine
BARC	Bleeding Academic Research Consortium
CA	Coronary Angiography
CABG	Coronary Artery Bypass Graft
CCS	Canadian Cardiovascular Society
CIMT	Carotid Intima-Media Thickness
CVD	Cardiovascular Disease
DHA	Docosahexaenoic acid
EEM	External Elastic Membrane
EPA	Eicosapentaenoic acid
hsCRP	high sensitive C-Reactive Protein
IHD	Ischemic Heart Disease
IL-6	Interleukin-6
$LpPLA_2$	Lipoprotein-associated Phospholipase A2
MINAP	Myocardial Infarction National Audit Project
MoCA	Montreal Cognitive Assessment
MPO	Myeloperoxidase
NT-proBNP	N-terminal prohormone of brain natriuretic peptide
OCT	Optical Coherence Tomography
PAT	Peripheral Arterial Tonometry
PWV	Pulse Wave Velocity
NSTEMI	Non ST Elevation Myocardial Infarction
NYHA	New York Heart Association
PCI	Percutaneous Coronary Intervention
STEMI	ST Elevation Myocardial Infarction
TCFA	Thin Capped Fibroatheroma
TNF-α	Tumor Necrosis Factor-alpha
VH-IVUS	Virtual Histology Intravascular Ultrasound

INTRODUCTION

In the general population, ischaemic heart disease (IHD) is the leading cause of death worldwide.[1] Mortality due to IHD increases steeply among those aged >70 years of age.[2] In 2010 in the United Kingdom (UK), more than twice as many individuals >75 years of age (n=55,028) died from IHD, compared to younger individuals <75 years (n=25,540).[3] According to the Myocardial Ischaemia National Audit Project (MINAP) Database annual public report 2012-13, there were 80,974 admissions with a final diagnosis of myocardial infarction (MI). Of these, 60% had non ST elevation myocardial infarction (NSTEMI). Of the patients with NSTEMI, 59% were >70 years of age (26% were aged 70-79 years, 26% were 80-89 years and 7% were ≥90 years).[4] Mortality benefit from advances in the management of acute coronary syndrome (ACS) has largely been realised in patients <65 years old.[2] There has been an increase in IHD burden in older patients, who are at risk of poorer outcomes due to frailty and co-morbidity.[5]

There is a paucity of evidence from clinical trials and studies to inform the management of ACS in older patients. More than half of all randomised controlled trials for acute coronary syndrome failed to enrol participants >75 years of age and, even in those that did, only 9% were >75 years of age.[6] Evidence-based recommendations from trials do not account for age-related differences in physiology, disease and co-morbidities, which may alter the risk-benefit profile of cardiovascular treatments and interventions. The age mismatch between trial and community populations begins at 75 years and widens with age.[7] Furthermore, older people that are included in trials have lower than expected rates of traditional cardiovascular risk factors, fewer co-morbidities and better renal function than the community population.[8] Risks and benefits derived from trials cannot always be

extrapolated to older patients in daily clinical practice due to the differences between the patient groups and their baseline characteristics.[9]

In the ageing population, there is increasing evidence for the association of cardiovascular disease (CVD) and frailty.[10] Depending on the frailty scale used and the population studied, almost half of patients with CVD can be identified as frail.[11] There is an increased risk of mortality and major adverse cardiovascular events in frail patients with CVD, especially those undergoing invasive procedures or suffering from coronary artery disease and heart failure.[11] In patients >75 years, frailty was strongly and independently associated with in-hospital mortality (Odds Ratio [OR] 4.6; 95% Confidence Interval [CI] 1.3-16.8) and one-month mortality (OR 4.7; 95% CI, 1.7-13.0).[12] At one year, there was a significant increase in mortality among frail patients compared with non-frail patients (Hazard Ratio 4.3, 95% CI 2.4-7.8).[13] Similarly, in >65 year old patients, frailty was associated with increased long-term mortality and myocardial infarction (MI) among patients undergoing percutaneous coronary intervention (PCI).[14]

No studies to evaluate predictors of poor outcomes, or to develop strategies to improve outcomes following ACS, have been performed in older patients undergoing an invasive treatment strategy. The ACS and PCI risk models that are currently available were mainly derived from patients <65 years, and hence cannot be applied to the increasing proportion of older (>75 years) patients with ACS managed by contemporary treatment.[15] The goal of ICON1 (**I**mprove **C**ardiovascular **O**utcomes in High Risk Older Patie**N**ts with Acute Coronary Syndrome) is to determine the predictors of adverse outcomes (death, MI, stroke, repeat revascularisation, bleeding and rehospitalisation for any reason) at one month and at one year following invasive management of non ST elevation acute coronary

syndrome (NSTEACS) in older patients, and to develop an integrated risk score to predict adverse outcomes at one-year that will inform clinical decision making. In addition, the impact of contemporary NSTEACS management on the quality of life will be assessed.

HYPOTHESIS

Frailty and co-morbid status in older patients are associated with worse outcomes following invasive treatment for NSTEACS.

TRIAL DESIGN

The study has been designed as a multicentre prospective observational study of patients aged ≥75 years undergoing invasive management (coronary angiography with a view to revascularisation) for NSTEACS.

METHODS

Study Setting

This ongoing multicentre observational study is being conducted in two tertiary cardiac care hospitals in the North-East of England. The Freeman Hospital, in Newcastle upon Tyne, is a tertiary cardiac centre with a catchment population of 2 million. Approximately 3,000 PCI procedures are performed each year. The James Cook University Hospital, in Middlesbrough, performs approximately 1,750 PCI procedures every year. The study participants are recruited from patients referred to these hospitals from the neighbouring district general hospitals for invasive treatment of NSTEACS. Patients are transferred the day before or on the day of procedure to the tertiary hospitals. Prospective ICON1 patients are identified from an electronic

referral system and, on arrival to the tertiary hospitals, are approached for recruitment into the study. The study team explains the study to the patient and a patient information sheet is provided. If the patient agrees to participate in the study, written informed consent is obtained. All patients screened for the study are entered in a screening log, with details regarding the patients consented, declined, and consented but not recruited (due to alternative diagnosis following coronary angiography). The inclusion and exclusion criteria are displayed in **Table 1**. Recruitment to the study commenced in October 2012 with the 1-year follow-up is projected to reach completion in December 2016.

Treatment Protocol

Contemporary treatment of NSTEACS, as felt appropriate by the treating interventional cardiologist, is offered to the patient.[16] According to standard practice, patients are revascularised by PCI or coronary artery bypass graft (CABG) surgery. Patients may also be managed medically, if deemed not appropriate for either of the revascularisation strategies at the discretion of the operating cardiologist.

Data Collection

Data are collected on standardised case report forms by members of the research team. The data collected include demographics, baseline characteristics, and details of coronary angiography and or PCI. Peri-procedural complications and in-hospital complications are recorded. Further data are collected on the cardiovascular status, Canadian Cardiovascular Society (CCS) angina grade, New York Heart Association (NYHA) dyspnoea grade, frailty category, functional health status, quality of life and cognitive status. These are listed in **Table 2**. The

assessments and techniques used for the above data collection are discussed in the following sections. The study flow chart is displayed in **Figure 1**.

Frailty and Co-Morbidity Assessments

Frailty is assessed by Fried Frailty Index, derived from Cardiovascular Health Study[17] and Rockwood Frailty Index, derived from Canadian Study of Health and Aging.[18] The Fried Frailty Index is based on assessing 5 criteria, comprising subjective answers provided by the patient (regarding weight loss, physical energy, physical activity) and objective assessment (hand grip strength). A score of 0 is categorised as robust, 1 or 2 as intermediate or pre-frail and 3 or more as frail. The Rockwood Frailty Index is based on assessment by the researcher into categories 1 to 7, from very fit to severely frail, depending on functional status and independence/dependence on others for activities of daily living.

In addition, the Charlson Comorbidity Index,[19] a method of predicting mortality based on a weighted index of the number and seriousness of co-morbid conditions, is evaluated for each patient. Charlson Comorbidity Index has been demonstrated to be an appropriate indicator of in-hospital and one-year outcomes in the setting of ACS.[20]

Functional Status and Quality of Life Measures

The Short Form-36 Standard (SF-36® Standard) health survey is completed by each patient prior to discharge from the hospital and at one-year follow-up in order to assess functional health and quality of life. The responses will be used to obtain physical component summary and mental component summary scores.[21] In

addition, the EQ-5D™-3L questionnaire is used to assess health outcome of each patient at discharge and one-year follow-up.[22, 23]

Cognitive Status Assessment

Atherosclerosis is associated with increased risk of cognitive impairment in older patients.[24] To assess the cognitive status of patients during admission, the Montreal Cognitive Assessment (MoCA©)[25] test is utilised. The MoCA has been shown to have high sensitivity in screening patients with known CVD for mild cognitive impairment, even in a non-memory clinic setting.[26] This test is repeated at one-year follow-up.

Biomarker Sampling

Blood samples are collected at the time of coronary angiography (CA) and/or PCI for analysis of biomarker analysis. Serum for biomarkers is stored for analysis in batches. Peripheral blood mononuclear cells are separated by centrifugation techniques for storage at -80°C for analysis of telomeres and telomerase activity. High-sensitivity C-reactive protein (hsCRP), parathyroid hormone and total vitamin D are analysed. Full blood count, renal function, blood glucose, cholesterol and high-sensitivity cardiac troponin T (hsTnT) levels are measured in patients as part of routine care.

Inflammation plays a central role in acute thrombotic complications of unstable atherosclerotic coronary plaque. Increased levels of markers of inflammation predict CV outcomes following ACS. Inflammatory markers including myeloperoxidase (MPO),[27] hsCRP[28] and soluble CD40 ligand[29] have been associated with ACS and have been shown to predict outcome. Patients with ACS

have decreased levels of anti-inflammatory omega-3 fatty acids (eicosapentaenoic acid [EPA] and docosahexaenoic acid [DHA]).[30] Increased lipoprotein-associated phospholipase A_2 ($LpPLA_2$) activity has been associated with increased cardiovascular event rates.[31, 32] An elevated level of asymmetric dimethyl arginine (ADMA) is a strong and independent predictor of adverse outcomes following ACS.[33] Interleukin-6 (IL-6) levels in the serum were increased in patients with ACS.[34] IL-6 expressed in atherosclerotic plaques may increase plaque instability.[35] Elevated IL-6 was a predictor of 6 and 12-month mortality in patients with unstable coronary artery disease.[36] Tumor Necrosis Factor-alpha (TNF-α) is a pro-inflammatory cytokine associated with myocardial dysfunction and remodelling following ACS.[37] In patients with recent MI, increased levels of TNF-α were associated with adverse cardiovascular outcomes (recurrent MI and cardiac death).[38] Vitamin D deficiency has been associated with elevated CAD burden and worse cardiovascular outcomes.[39] These biomarkers will be analysed in this group of ≥75 year old patients to enable determination of predictors of adverse CV outcomes at 1-year. Telomere shortening has been associated with ageing and senescence, and shorter leukocyte telomeres are associated with increased cardiovascular risk and mortality.[40] Shorter leucocyte telomere length predicted high-risk plaque morphology on virtual histology intravascular ultrasound (VH-IVUS).[41] Whether shorter telomere length is a predictor of adverse events among older patients undergoing PCI is not known and will be evaluated in this study.

MicroRNA Analysis

MicroRNAs (miRNAs) are small non-coding RNAs that post transcriptionally inhibit gene expression.[42] In the last few years, miRNAs have emerged as key tools

for the understanding of IHD pathophysiology, with great potential to be used as new biomarkers and therapeutic targets. MicroRNAs seem to possess ideal characteristics to be used as disease biomarkers, as they are detectable in biofluids in a reproducible and stable fashion, even after years of sample storage and freeze-thaw cycles.[43] In the blood, circulating miRNAs are found mainly within extracellular vesicles, such as exosomes, microvesicles, and apoptotic bodies[44] and to a lesser extent, associated with HDL-cholesterol particles[45, 46] or Argonaute-2 protein[47]. Several studies have demonstrated elevated or decreased levels of specific circulating miRNAs in patients with ACS[48-51]. However, few have addressed their prognostic value with regards to major cardiovascular events[52] or death[53], especially amongst older cohorts of patients presenting with NSTEACS.

The levels of nine circulating miRNAs, known to be differentially expressed in patients with ACS (miR-21-5p, miR-126-5p, miR-132-3p, miR-133a-3p, miR-142-3p, miR-150-5p, miR-208-3p, miR-223-3p, and miR-320a), will be quantified by reverse transcription quantitative polymerase chain reaction, in serum and circulating microvesicles (isolated from an additional 200μL of serum) from 100 participants, and correlated with clinical variables with a view to assess their value as a prognostic biomarkers in older patients with NSTEACS.

Invasive Coronary Artery Imaging

Post-mortem studies have identified that vulnerable plaques, with specific morphological characteristics, are implicated in the pathophysiology of ACS. These plaques, which are prone to erosion and rupture, have inflamed fibrous caps, rich in macrophages, overlying a lipid pool.[54] Burke et al examined the hearts of 113 men that had died suddenly, and found that 95% of ruptured plaques had fibrous caps

<65μm thick (mean thickness 23±19μm) with an infiltrate of macrophages.[55] ICON1 aims to identify whether the increased mortality in the older population with ACS is due to an increased prevalence of these vulnerable thin-capped fibroatheroma (TCFAs). Following diagnostic coronary angiography, patients undergo VH IVUS imaging and optical coherence tomography (OCT) imaging in all three coronary arteries prior to PCI, where feasible, and VH IVUS imaging post-PCI in the culprit vessel at the discretion of the operating cardiologist.

Virtual Histology Intravascular Ultrasound

Grayscale IVUS image uses only the amplitude of the reflected ultrasound wave. VH IVUS utilises spectral analysis of the frequency and power of the reflected wave to generate a more accurate reflection of the tissue subtypes present within the vessel wall.[56] This can then be used to differentiate plaque components (fibrous, fibro-fatty, dense calcium and necrotic core) and identify high-risk vulnerable plaques. Although VH IVUS lacks the resolution to identify the thin fibrous cap of the TCFA, it is well placed to accurately identify the necrotic core of these plaques.[56] A 20MHz, phased-array Eagle Eye Platinum™ catheter is mounted on an R-100 pullback device and connected to either an integrated S5i system or mobile S5 tower. Image acquisition is performed at a pullback speed of 0.5mm/s and is ECG-gated to ensure one frame is acquired per cardiac cycle. The maximum length of all three coronary arteries is imaged, where feasible.[57] The data is anonymised and transferred to DVD for offline data analysis. The operator is blinded to this data.

VH IVUS data analysis is performed using Medis (Leiden, Netherlands) QIvus software. Contours are drawn manually around the external elastic membrane (EEM) and lumen of the vessel for each grayscale IVUS frame, taking care to exclude any

ring-down artefact or previously stented segments. The software then calculates several parameters such as minimum lumen area and diameter, percent stenosis, and absolute volume and percentage of each plaque component. The image reader can also calculate the remodelling index[58] and classify the lesion type from this data. Lesion classification in ICON1 is based on previously published recommendations for tissue characterisation by radiofrequency data analysis (**Figure 2**).[57]

Optical Coherence Tomography

OCT generates an image analogous to IVUS using a low coherence, near-infrared (wavelength 1.3μm) light source, instead of sound.[59] A bloodless field inside the coronary artery is vital, as red blood cells strongly backscatter the near-infrared light. This is obtained by using a flush of contrast during image acquisition. OCT has a greater resolution than IVUS (20-40μm vs. 100-200μm) and is thus able to delineate the thin fibrous cap present in a TCFA. However, its poorer penetration (1-2.5mm) can limit its capacity to identify deep lipid pools and quantify plaque volume.[60, 61]

OCT images are obtained using a Dragonfly catheter (St Jude Medical, Minnesota, USA) connected to the Ilumien™ PCI Optimization System. Just before image acquisition, a short flush of iso-osmolar contrast is administered to ensure the guide catheter is well engaged with the coronary artery and the catheter is clear of blood. The system is calibrated and OCT pullback is initiated with a further flush of iso-osmolar contrast (10ml in the right coronary artery, 15ml in the left coronary artery). OCT images are obtained in 54mm segments at a pullback rate of 20mm/s in all three coronary arteries, where feasible. Data is transferred anonymously to a DVD for offline analysis; the operator is blinded to this data during the procedure.

OCT data is analysed using the Medis QIvus software. Contours are drawn around the lumen to generate data on the minimum lumen area and diameter. The whole vessel is then analysed to identify plaque subtypes. An atherosclerotic lesion is seen on OCT as a mass lesion within the arterial wall, with focal intimal thickening or loss of the normal vessel architecture[62]. Fibrous plaque is homogenous and highly backscattering, calcified plaques are signal-poor areas with sharply delineated borders, and lipid pools are signal-poor regions with poorly defined borders and a fast OCT signal drop-off.[62] Using side branches and areas of calcification as landmarks, it is possible to compare the accuracy of lesion subtypes identified by VH IVUS and OCT.

NON-INVASIVE ASSESSMENT OF CARDIOVASCULAR STATUS

Arterial Stiffness

Arterial stiffness is now increasingly recognized as a surrogate endpoint for the assessment of CVD status.[63] Arterial stiffness can lead to angina in the presence of even minor coronary artery disease and to the development of diastolic dysfunction, the commonest form of heart failure in the elderly.[64] Arterial stiffness is determined by carotid-femoral pulse wave velocity (PWV) which is a simple, non-invasive, robust and reproducible investigation method that can be performed at the bedside.[63] In older patients, arterial stiffness assessed by increased PWV is associated with poor cardiovascular outcomes.[65] In the ICON1 study, carotid-femoral PWV is assessed by the Vicorder device (Skidmore Medical Limited, Bristol, UK). In addition brachio-femoral PWV, pulse wave analysis (includes pulse pressure, augmentation pressure and augmentation index) and ankle brachial pressure index are also assessed.

Endothelial Function

Endothelial dysfunction is considered one of the earliest markers of atherosclerosis,[66] contributing to lesion development and its later clinical manifestations.[67, 68] Endothelial dysfunction is associated with increased risk of cardiovascular events and has been proposed as a marker of poor CV outcomes.[69-71] Peripheral arterial tonometry (PAT) by finger plethysmography (EndoPAT™; Itamar Medical, Caesarea, Israel) is a novel method of measuring the peripheral vasodilator response.[72, 73] Hyperaemic response measured by PAT signal amplitude gives a measure of nitric oxide-mediated endothelial function.[74, 75] In patients with low-risk findings during stress testing and/or the absence of new obstructive lesions on angiography, lower natural logarithmic-scaled reactive hyperaemia index (<0.40) is associated with increased cardiovascular death over six years.[76] In the ICON1 study, endothelial function is measured by EndoPAT™. PAT signals are recorded from the index fingers with pneumatic probes at baseline, during cuff occlusion and during hyperaemia. A measure of endothelial function is calculated from the ratio of PAT signal amplitude at baseline and post-occlusion. Reactive hyperaemia index data from the study will be used in the prediction of adverse CV outcomes, and will be incorporated in the risk model.

Carotid Intima Medial Thickness

Carotid Intima Media Thickness (CIMT) is a significant predictor of incident adverse cardiovascular events.[77, 78] Increased CIMT was associated with severity of coronary atherosclerosis in ACS.[79] CIMT and its association with predicting CV events in older NSTEACS patients are not known. In a meta-analysis, addition of carotid intimal media thickness (CIMT) to Framingham risk score in general

population did not improve 10-year prediction of first MI or stroke.[80] However CIMT and arterial stiffness together increases the cardiovascular risk in patients with known vascular disease or cardiovascular risk factors.[81] In the ICON1 study, CIMT is assessed using a Vivid I GE machine, with a vascular probe. CIMT measurement is obtained via semi-automated software, which uses an edge detection technique. CIMT values will be analysed for prediction of adverse outcomes and will be incorporated in the risk model.

Transthoracic Echocardiogram

In hospitalised elderly patients with known cardiovascular disease, left ventricular diastolic dysfunction was similar in prevalence to systolic dysfunction and was associated with similar cardiovascular and all-cause mortality.[82] Transthoracic echocardiography will be performed using Vivid I GE echo machine, according to the British Society of Echocardiography guidelines, to assess systolic function, diastolic function and valvular heart disease.[83] Systolic and diastolic function will be analysed for prediction of adverse CV outcomes.

Follow-up

One-month outcomes are recorded using general practitioner summary documents, obtained from the patients' general practitioner. Patients are followed-up in a study outpatient clinic at one year. During this follow-up visit, repeat blood samples for biomarker analysis are collected. In addition, NYHA class, CCS angina class, SF-36, EQ-5D™ and MoCA® assessments are completed. Frailty status is re-assessed using Fried and Rockwood Frailty Criteria.

Primary Outcome Measures

Primary outcome measures are death, myocardial infarction, stroke, repeat revascularisation and BARC (Bleeding Academic Research Consortium)-defined bleeding at one-year and rehospitalisation for any reason[84,85].

Sample Size

For the primary outcome, Hsieh and Lavori's method was used to calculate the power for testing the association of the risk score with adverse outcomes, based on 300 subjects with type I error rate 0.05 [86]. From previous studies, the mortality rate in similar cohorts at 1-year is approximately 2-5%. Estimates of the standard deviation and hazard ratio of the risk score are unknown. Assumption was made on the hazard ratios being an increment of one standard deviation of the risk score. **Figure 3** shows the plot of powers versus hazard ratios for the sample size of 300 patients and 1-year mortality rates.

STATISTICAL METHODS

Risk Factor Selection

Cox proportional hazards regression analysis will be performed to estimate hazard ratios of the risk factors and associated p-values for the primary outcome. Multiple logistic regression analysis will be performed to estimate odds ratios of the risk factors and associated p-values for the secondary outcome. The bootstrap method will be used to avoid over-fitting the data. One thousand bootstrap samples will be used. Backward selection with a p-value <0.05 for statistical significance will be used to remove variables in each sample. Variables selected ≥800 times (80%) in the overall sample will be included in the final model.

Risk Score Construction

To construct the risk score, risk factors identified through the multivariable model will be assigned a weight. Weights are the estimated regression coefficients from the Cox proportional hazards regression or logistic regression model. The risk score is thus the weighted average of the identified risk factors. Another Cox proportional hazards regression or logistic regression model will be applied to detect the association of the proposed risk score to the outcomes.

Risk Score Evaluation

Harrell's C-index will be used to assess the discriminatory capacity of the integrated risk score, for primary and secondary outcomes. The Jackknife method will be used to estimate the standard error of the estimated Harrell's C-index[87] or area under the curve (AUC). The difference between model-predicted and observed event rates (goodness-of-fit) will be evaluated with the Hosmer-Lemeshow test (p-value >0.10 will be considered to indicate lack of deviation between the model and observed event rates). Reclassification calibration measures (e.g. net reclassification improvement [NRI], and integrated discrimination improvement [IDI]) will be used to evaluate the improvement of new predictors (relative to existing predictors) on the agreement between observed outcomes and predictions.[88] Cross-validation technique will be used to assess how the results of statistical analysis generalize to an independent dataset.[89] Finally, a prediction nomogram[90] will be developed to facilitate calculating the risk scores and the corresponding survival probability at 1 year.

Ethics

The study has been approved by the regional ethics committee (REC 12/NE/016). The study is conducted in accordance with the Declaration of Helsinki (64th World Medical Association General Assembly, Fortaleza, Brazil, October 2013).[91]

CONCLUSION

ICON1 study will identify predictors of poor cardiovascular outcomes among older (≥75 years) patients presenting with NSTEACS managed by contemporary pharmacotherapy and invasive revascularisation strategy. Based on clinical characteristics, frailty status, co-morbidities and cardiovascular status, an integrated risk stratification tool to help decision-making in the management of older patients will be developed.

Author Contributions:

VK Conceived the study and carries overall responsibility for the full study and the study protocol.

DN Responsible for the biomarker sub-study

HS Contributed to the invasive sub-study

JB Overall critical review and revision of the manuscript

MV Contributed to the non-invasive sub-study and the initial draft of this manuscript

GF Provided expert input into the design of the protocol and critical review of the manuscript

WQ Responsible for the statistical aspect of the study and the design of the study

Conflict of interest: None of the authors have any conflict of interest

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References

1. Murray CJ, Lopez AD. Mortality by cause for eight regions of the world: Global Burden of Disease Study. Lancet 1997;349(9061):1269-76.
2. Finegold JA, Asaria P, Francis DP. Mortality from ischaemic heart disease by country, region, and age: statistics from World Health Organisation and United Nations. International journal of cardiology 2013;168(2):934-45.
3. Townsend N, Wickramasinghe K, Bhatnagar P, Smolina K, Nichols M, Leal J, et al. Coronary heart disease statistics 2012 edition. London: British Heart Foundation; 2012.
4. Gavalova L WC. Myocardial Ischaemia National Audit Project Annual Public Report April 2012-March 2013. London: National Institute for Cardiovascular Outcomes Research; 2013.
5. Veerasamy M, Edwards R, Ford G, Kirkwood T, Newton J, Jones D, et al. Acute Coronary Syndrome among Older Patients: A Review. Cardiol Rev 2014.
6. Lee PY, Alexander KP, Hammill BG, Pasquali SK, Peterson ED. Representation of elderly persons and women in published randomized trials of acute coronary syndromes. JAMA 2001;286(6):708-13.
7. Alexander KP, Newby LK, Cannon CP, Armstrong PW, Gibler WB, Rich MW, et al. Acute coronary care in the elderly, part I: Non-ST-segment-elevation acute coronary syndromes: a scientific statement for healthcare professionals from the American Heart Association Council on Clinical Cardiology: in collaboration with the Society of Geriatric Cardiology. Circulation 2007;115(19):2549-69.
8. Kandzari DE, Roe MT, Chen AY, Lytle BL, Pollack CV, Jr., Harrington RA, et al. Influence of clinical trial enrollment on the quality of care and outcomes for patients with non-ST-segment elevation acute coronary syndromes. American heart journal 2005;149(3):474-81.
9. Tinetti ME, Bogardus ST, Jr., Agostini JV. Potential pitfalls of disease-specific guidelines for patients with multiple conditions. The New England journal of medicine 2004;351(27):2870-4.
10. Afilalo J, Karunananthan S, Eisenberg MJ, Alexander KP, Bergman H. Role of frailty in patients with cardiovascular disease. Am J Cardiol 2009;103(11):1616-21.
11. Afilalo J. Frailty in Patients with Cardiovascular Disease: Why, When, and How to Measure. Curr Cardiovasc Risk Rep 2011;5(5):467-472.
12. Ekerstad N, Swahn E, Janzon M, Alfredsson J, Lofmark R, Lindenberger M, et al. Frailty Is Independently Associated With Short-Term Outcomes for Elderly Patients With Non-ST-Segment Elevation Myocardial Infarction. Circulation 2011;124(22):2397-404.
13. Ekerstad N, Swahn E, Janzon M, Alfredsson J, Lofmark R, Lindenberger M, et al. Frailty is independently associated with 1-year mortality for elderly patients with non-ST-segment elevation myocardial infarction. Eur J Prev Cardiol 2013.
14. Singh M, Rihal CS, Lennon RJ, Spertus JA, Nair KS, Roger VL. Influence of frailty and health status on outcomes in patients with coronary disease undergoing percutaneous revascularization. Circ Cardiovasc Qual Outcomes 2011;4(5):496-502.
15. Bawamia B, Mehran R, Qiu W, Kunadian V. Risk scores in acute coronary syndrome and percutaneous coronary intervention: a review. Am Heart J 2013;165(4):441-50.
16. Hamm CW, Bassand JP, Agewall S, Bax J, Boersma E, Bueno H, et al. ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: The Task Force for the management of acute coronary syndromes (ACS) in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). European heart journal 2011;32(23):2999-3054.
17. Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, et al. Frailty in older adults: evidence for a phenotype. The journals of gerontology Series A, Biological sciences and medical sciences 2001;56(3):M146-56.

18. Rockwood K, Song X, MacKnight C, Bergman H, Hogan DB, McDowell I, et al. A global clinical measure of fitness and frailty in elderly people. CMAJ 2005;173(5):489-95.
19. E CM. A new method of classifying prognostic comorbidity in longitudinal studies: Development and validation. Journal of Chronic Diseases 1987;40(5):373-383.
20. Radovanovic D, Seifert B, Urban P, Eberli FR, Rickli H, Bertel O, et al. Validity of Charlson Comorbidity Index in patients hospitalised with acute coronary syndrome. Insights from the nationwide AMIS Plus registry 2002-2012. Heart 2014;100(4):288-94.
21. Ware JE, Jr., Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Medical care 1992;30(6):473-83.
22. Group TE. EuroQol-a new facility for the measurement of health-related quality of life. Health Policy 1990;16(3):199-208.
23. R B. EuroQol: the current state of play. Health Policy 1996;37(1):53-72.
24. van Oijen M, de Jong FJ, Witteman JC, Hofman A, Koudstaal PJ, Breteler MM. Atherosclerosis and risk for dementia. Annals of neurology 2007;61(5):403-10.
25. Nasreddine ZS, Phillips NA, Bedirian V, Charbonneau S, Whitehead V, Collin I, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. Journal of the American Geriatrics Society 2005;53(4):695-9.
26. McLennan SN, Mathias JL, Brennan LC, Stewart S. Validity of the montreal cognitive assessment (MoCA) as a screening test for mild cognitive impairment (MCI) in a cardiovascular population. Journal of geriatric psychiatry and neurology 2011;24(1):33-8.
27. Baldus S, Heeschen C, Meinertz T, Zeiher AM, Eiserich JP, Munzel T, et al. Myeloperoxidase serum levels predict risk in patients with acute coronary syndromes. Circulation 2003;108(12):1440-5.
28. Zairis MN, Adamopoulou EN, Manousakis SJ, Lyras AG, Bibis GP, Ampartzidou OS, et al. The impact of hs C-reactive protein and other inflammatory biomarkers on long-term cardiovascular mortality in patients with acute coronary syndromes. Atherosclerosis 2007;194(2):397-402.
29. Varo N, de Lemos JA, Libby P, Morrow DA, Murphy SA, Nuzzo R, et al. Soluble CD40L: risk prediction after acute coronary syndromes. Circulation 2003;108(9):1049-52.
30. Block RC, Harris WS, Reid KJ, Sands SA, Spertus JA. EPA and DHA in blood cell membranes from acute coronary syndrome patients and controls. Atherosclerosis 2008;197(2):821-8.
31. Lp PLASC, Ballantyne C, Cushman M, Psaty B, Furberg C, Khaw KT, et al. Collaborative meta-analysis of individual participant data from observational studies of Lp-PLA2 and cardiovascular diseases. European journal of cardiovascular prevention and rehabilitation : official journal of the European Society of Cardiology, Working Groups on Epidemiology & Prevention and Cardiac Rehabilitation and Exercise Physiology 2007;14(1):3-11.
32. Lp PLASC, Thompson A, Gao P, Orfei L, Watson S, Di Angelantonio E, et al. Lipoprotein-associated phospholipase A(2) and risk of coronary disease, stroke, and mortality: collaborative analysis of 32 prospective studies. Lancet 2010;375(9725):1536-44.
33. Cavusoglu E, Ruwende C, Chopra V, Yanamadala S, Eng C, Pinsky DJ, et al. Relationship of baseline plasma ADMA levels to cardiovascular outcomes at 2 years in men with acute coronary syndrome referred for coronary angiography. Coronary artery disease 2009;20(2):112-7.
34. Biasucci LM, Vitelli A, Liuzzo G, Altamura S, Caligiuri G, Monaco C, et al. Elevated levels of interleukin-6 in unstable angina. Circulation 1996;94(5):874-7.
35. Schieffer B, Schieffer E, Hilfiker-Kleiner D, Hilfiker A, Kovanen PT, Kaartinen M, et al. Expression of angiotensin II and interleukin 6 in human coronary atherosclerotic

plaques: potential implications for inflammation and plaque instability. Circulation 2000;101(12):1372-8.

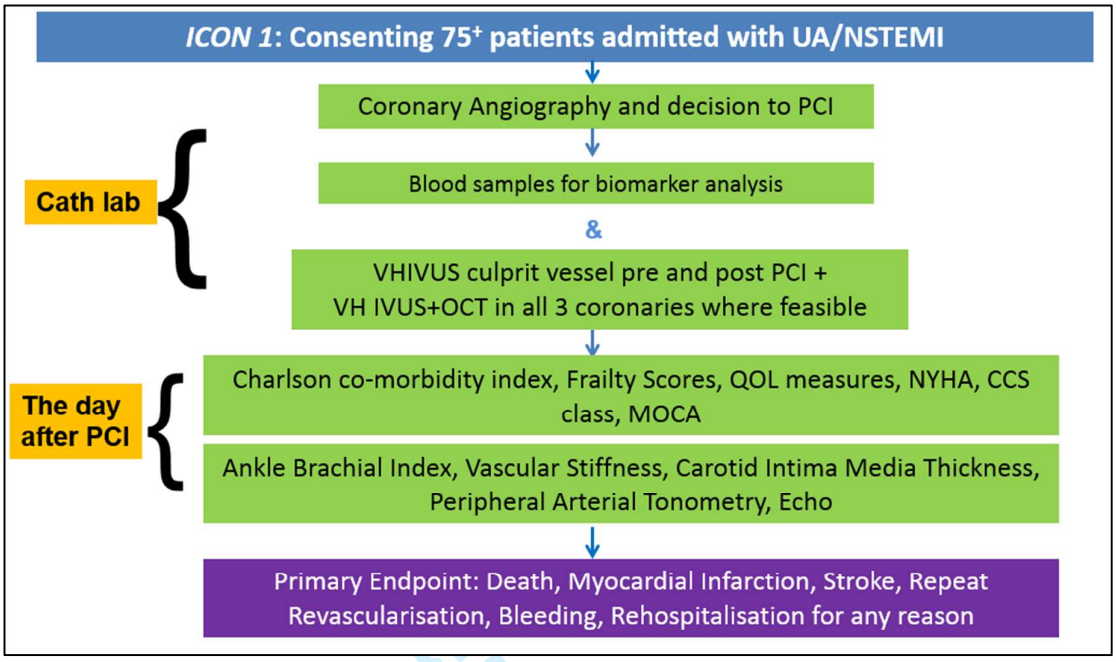
36. Lindmark E, Diderholm E, Wallentin L, Siegbahn A. Relationship between interleukin 6 and mortality in patients with unstable coronary artery disease: effects of an early invasive or noninvasive strategy. JAMA : the journal of the American Medical Association 2001;286(17):2107-13.
37. Nian M, Lee P, Khaper N, Liu P. Inflammatory cytokines and postmyocardial infarction remodeling. Circulation research 2004;94(12):1543-53.
38. Ridker PM, Rifai N, Pfeffer M, Sacks F, Lepage S, Braunwald E. Elevation of tumor necrosis factor-alpha and increased risk of recurrent coronary events after myocardial infarction. Circulation 2000;101(18):2149-53.
39. Kunadian V, Ford GA, Bawamia B, Qiu W, Manson JE. Vitamin D deficiency and coronary artery disease: a review of the evidence. American heart journal 2014;167(3):283-91.
40. Perez-Rivera JA, Pabon-Osuna P, Cieza-Borrella C, Martin-Herrero F, Gonzalez-Porras JR, Gonzalez-Sarmiento R. Prognostic value of telomere length in acute coronary syndrome. Mechanisms of ageing and development 2012;133(11-12):695-7.
41. Calvert PA, Liew TV, Gorenne I, Clarke M, Costopoulos C, Obaid DR, et al. Leukocyte telomere length is associated with high-risk plaques on virtual histology intravascular ultrasound and increased proinflammatory activity. Arteriosclerosis, thrombosis, and vascular biology 2011;31(9):2157-64.
42. Berezikov E. Evolution of microRNA diversity and regulation in animals. Nature reviews Genetics 2011;12(12):846-60.
43. Moldovan L, Batte KE, Trgovcich J, Wisler J, Marsh CB, Piper M. Methodological challenges in utilizing miRNAs as circulating biomarkers. Journal of cellular and molecular medicine 2014;18(3):371-90.
44. Valadi H, Ekstrom K, Bossios A, Sjostrand M, Lee JJ, Lotvall JO. Exosome-mediated transfer of mRNAs and microRNAs is a novel mechanism of genetic exchange between cells. Nature cell biology 2007;9(6):654-9.
45. Vickers KC, Palmisano BT, Shoucri BM, Shamburek RD, Remaley AT. MicroRNAs are transported in plasma and delivered to recipient cells by high-density lipoproteins. Nature cell biology 2011;13(4):423-33.
46. Wagner J, Riwanto M, Besler C, Knau A, Fichtlscherer S, Roxe T, et al. Characterization of levels and cellular transfer of circulating lipoprotein-bound microRNAs. Arteriosclerosis, thrombosis, and vascular biology 2013;33(6):1392-400.
47. Turchinovich A, Burwinkel B. Distinct AGO1 and AGO2 associated miRNA profiles in human cells and blood plasma. RNA biology 2012;9(8):1066-75.
48. D'Alessandra Y, Devanna P, Limana F, Straino S, Di Carlo A, Brambilla PG, et al. Circulating microRNAs are new and sensitive biomarkers of myocardial infarction. European heart journal 2010;31(22):2765-73.
49. Wang GK, Zhu JQ, Zhang JT, Li Q, Li Y, He J, et al. Circulating microRNA: a novel potential biomarker for early diagnosis of acute myocardial infarction in humans. European heart journal 2010;31(6):659-66.
50. De Rosa S, Fichtlscherer S, Lehmann R, Assmus B, Dimmeler S, Zeiher AM. Transcoronary concentration gradients of circulating microRNAs. Circulation 2011;124(18):1936-44.
51. Devaux Y, Vausort M, McCann GP, Zangrando J, Kelly D, Razvi N, et al. MicroRNA-150: a novel marker of left ventricular remodeling after acute myocardial infarction. Circulation Cardiovascular genetics 2013;6(3):290-8.
52. Eitel I, Adams V, Dieterich P, Fuernau G, de Waha S, Desch S, et al. Relation of circulating MicroRNA-133a concentrations with myocardial damage and clinical prognosis in ST-elevation myocardial infarction. American heart journal 2012;164(5):706-14.

53. Widera C, Gupta SK, Lorenzen JM, Bang C, Bauersachs J, Bethmann K, et al. Diagnostic and prognostic impact of six circulating microRNAs in acute coronary syndrome. Journal of molecular and cellular cardiology 2011;51(5):872-5.
54. Farb A, Burke AP, Tang AL, Liang TY, Mannan P, Smialek J, et al. Coronary plaque erosion without rupture into a lipid core. A frequent cause of coronary thrombosis in sudden coronary death. Circulation 1996;93(7):1354-63.
55. Burke AP, Farb A, Malcom GT, Liang YH, Smialek J, Virmani R. Coronary risk factors and plaque morphology in men with coronary disease who died suddenly. N Engl J Med 1997;336(18):1276-82.
56. Nair A, Kuban BD, Tuzcu EM, Schoenhagen P, Nissen SE, Vince DG. Coronary plaque classification with intravascular ultrasound radiofrequency data analysis. Circulation 2002;106(17):2200-6.
57. Garcia-Garcia HM, Mintz GS, Lerman A, Vince DG, Margolis MP, van Es GA, et al. Tissue characterisation using intravascular radiofrequency data analysis: recommendations for acquisition, analysis, interpretation and reporting. EuroIntervention 2009;5(2):177-89.
58. Mintz GS, Kent KM, Pichard AD, Satler LF, Popma JJ, Leon MB. Contribution of inadequate arterial remodeling to the development of focal coronary artery stenoses. An intravascular ultrasound study. Circulation 1997;95(7):1791-8.
59. Huang D, Swanson EA, Lin CP, Schuman JS, Stinson WG, Chang W, et al. Optical coherence tomography. Science 1991;254(5035):1178-81.
60. Sinclair H, Bourantas C, Bagnall A, Mintz GS, Kunadian V. OCT for the identification of vulnerable plaque in acute coronary syndrome. JACC Cardiovascular imaging 2015;8(2):198-209.
61. Prati F, Guagliumi G, Mintz GS, Costa M, Regar E, Akasaka T, et al. Expert review document part 2: methodology, terminology and clinical applications of optical coherence tomography for the assessment of interventional procedures. European heart journal 2010;33(20):2513-20.
62. Tearney GJ, Regar E, Akasaka T, Adriaenssens T, Barlis P, Bezerra HG, et al. Consensus standards for acquisition, measurement, and reporting of intravascular optical coherence tomography studies: a report from the International Working Group for Intravascular Optical Coherence Tomography Standardization and Validation. Journal of the American College of Cardiology 2012;59(12):1058-72.
63. Laurent S, Cockcroft J, Van Bortel L, Boutouyrie P, Giannattasio C, Hayoz D, et al. Expert consensus document on arterial stiffness: methodological issues and clinical applications. European heart journal 2006;27(21):2588-605.
64. Weber T, Auer J, O'Rourke MF, Punzengruber C, Kvas E, Eber B. Prolonged mechanical systole and increased arterial wave reflections in diastolic dysfunction. Heart 2006;92(11):1616-22.
65. Veerasamy M, Ford GA, Neely D, Bagnall A, Macgowan G, Das R, et al. Association of Aging, Arterial Stiffness and Cardiovascular Disease: A Review. Cardiol Rev 2014.
66. Luscher TF, Barton M. Biology of the endothelium. Clinical cardiology 1997;20(11 Suppl 2):II-3-10.
67. Veerasamy M, Bagnall A, Neely D, Allen J, Sinclair H, Kunadian V. Endothelial dysfunction and coronary artery disease: a state of the art review. Cardiology in review 2015;23(3):119-29.
68. Ross R. The pathogenesis of atherosclerosis: a perspective for the 1990s. Nature 1993;362(6423):801-9.
69. Halcox JP, Schenke WH, Zalos G, Mincemoyer R, Prasad A, Waclawiw MA, et al. Prognostic value of coronary vascular endothelial dysfunction. Circulation 2002;106(6):653-8.
70. Schachinger V, Britten MB, Zeiher AM. Prognostic impact of coronary vasodilator dysfunction on adverse long-term outcome of coronary heart disease. Circulation 2000;101(16):1899-906.

71. Suwaidi JA, Hamasaki S, Higano ST, Nishimura RA, Holmes DR, Jr., Lerman A. Long-term follow-up of patients with mild coronary artery disease and endothelial dysfunction. Circulation 2000;101(9):948-54.
72. Kuvin JT, Patel AR, Sliney KA, Pandian NG, Sheffy J, Schnall RP, et al. Assessment of peripheral vascular endothelial function with finger arterial pulse wave amplitude. American heart journal 2003;146(1):168-74.
73. Lavie P, Schnall RP, Sheffy J, Shlitner A. Peripheral vasoconstriction during REM sleep detected by a new plethysmographic method. Nature medicine 2000;6(6):606.
74. Nohria A, Gerhard-Herman M, Creager MA, Hurley S, Mitra D, Ganz P. Role of nitric oxide in the regulation of digital pulse volume amplitude in humans. Journal of applied physiology 2006;101(2):545-8.
75. Noon JP, Haynes WG, Webb DJ, Shore AC. Local inhibition of nitric oxide generation in man reduces blood flow in finger pulp but not in hand dorsum skin. The Journal of physiology 1996;490 (Pt 2):501-8.
76. Rubinshtein R, Kuvin JT, Soffler M, Lennon RJ, Lavi S, Nelson RE, et al. Assessment of endothelial function by non-invasive peripheral arterial tonometry predicts late cardiovascular adverse events. European heart journal 2010;31(9):1142-8.
77. Lorenz MW, Markus HS, Bots ML, Rosvall M, Sitzer M. Prediction of clinical cardiovascular events with carotid intima-media thickness: a systematic review and meta-analysis. Circulation 2007;115(4):459-67.
78. Carpenter M, Sinclair H, Kunadian V. Carotid Intimal Media Thickness and its Utility as a Predictor of Cardiovascular Disease: A Review of Evidence. Cardiology in review 2015.
79. Kalay N, Yarlioglues M, Ardic I, Duran M, Kaya MG, Inanc T, et al. The assessment of atherosclerosis on vascular structures in patients with acute coronary syndrome. Clinical and investigative medicine Medecine clinique et experimentale 2010;33(1):E36-43.
80. Den Ruijter HM, Peters SA, Anderson TJ, Britton AR, Dekker JM, Eijkemans MJ, et al. Common carotid intima-media thickness measurements in cardiovascular risk prediction: a meta-analysis. JAMA 2012;308(8):796-803.
81. Simons PC, Algra A, Bots ML, Grobbee DE, van der Graaf Y. Common carotid intima-media thickness and arterial stiffness: indicators of cardiovascular risk in high-risk patients. The SMART Study (Second Manifestations of ARTerial disease). Circulation 1999;100(9):951-7.
82. Zhang Y, Safar ME, Iaria P, Agnoletti D, Protogerou AD, Blacher J. Prevalence and prognosis of left ventricular diastolic dysfunction in the elderly: The PROTEGER Study. American heart journal 2010;160(3):471-8.
83. Gill Wharton RS, Jane Allen, Hollie Brewerton, Richard Jones, Prathap Kanagala, Guy Lloyd, Navroz Masani, Thomas Mathew, David Oxborough, Bushra Rana, Julie Sandoval, Richard Wheeler. A Minimum Dataset for a Standard Transthoracic Echocardiogram From the British Society of Echocardiography Education Committee. In; 2012.
84. Thygesen K, Alpert JS, White HD, Joint ESCAAHAWHFTFftRoMI. Universal definition of myocardial infarction. European heart journal 2007;28(20):2525-38.
85. Mehran R, Rao SV, Bhatt DL, Gibson CM, Caixeta A, Eikelboom J, et al. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. Circulation 2011;123(23):2736-47.
86. Hsieh FY, Lavori PW. Sample-size calculations for the Cox proportional hazards regression model with nonbinary covariates. Control Clin Trials 2000;21(6):552-60.
87. Harrell FE, Jr., Lee KL, Pollock BG. Regression models in clinical studies: determining relationships between predictors and response. Journal of the National Cancer Institute 1988;80(15):1198-202.

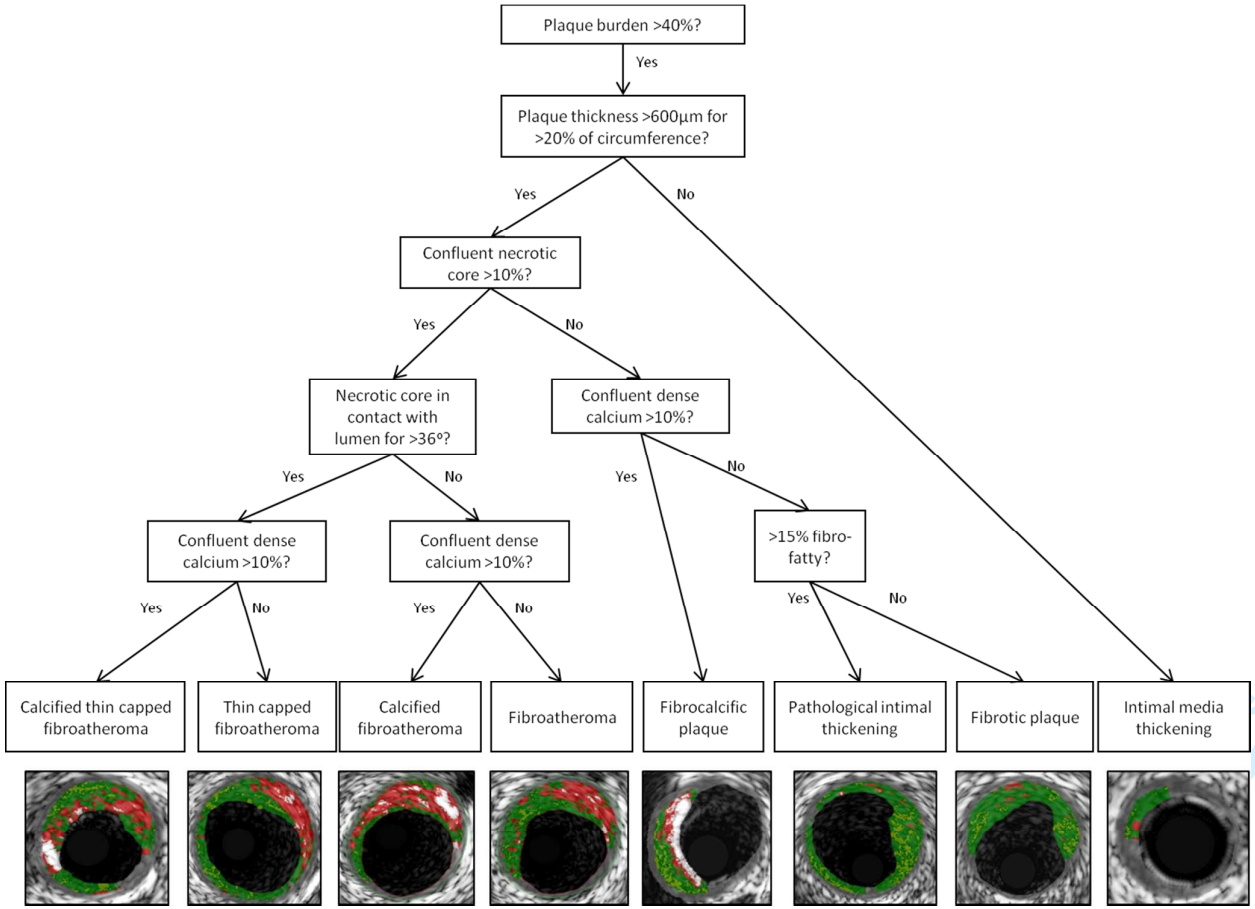
88. Cook NR, Ridker PM. Advances in measuring the effect of individual predictors of cardiovascular risk: the role of reclassification measures. Annals of internal medicine 2009;150(11):795-802.
89. Picard RR, Cook RD. Cross-Validation of Regression-Models. J Am Stat Assoc 1984;79(387):575-583.
90. Iasonos A, Schrag D, Raj GV, Panageas KS. How to build and interpret a nomogram for cancer prognosis. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2008;26(8):1364-70.
91. World Medical A. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. JAMA 2013;310(20):2191-4.

Figure 1. ICON1 Study flow chart



UA- Unstable angina; NSTEMI - Non-ST-elevation acute coronary syndrome, PCI - percutaneous coronary intervention, VH-IVUS - virtual histology - intravascular ultrasound, OCT - optical coherence tomography, NYHA - New York Heart Association, CCS - Canadian Cardiovascular Society, MoCA - Montreal Cognitive Assessment

Figure 2. Decision tree for lesion classification on VH-IVUS with image examples



Adapted from Garcia-Garcia HM, Mintz GS, Lerman A, et al. Eurointervention. 2009;5(2):177-89

Figure 3. Study power

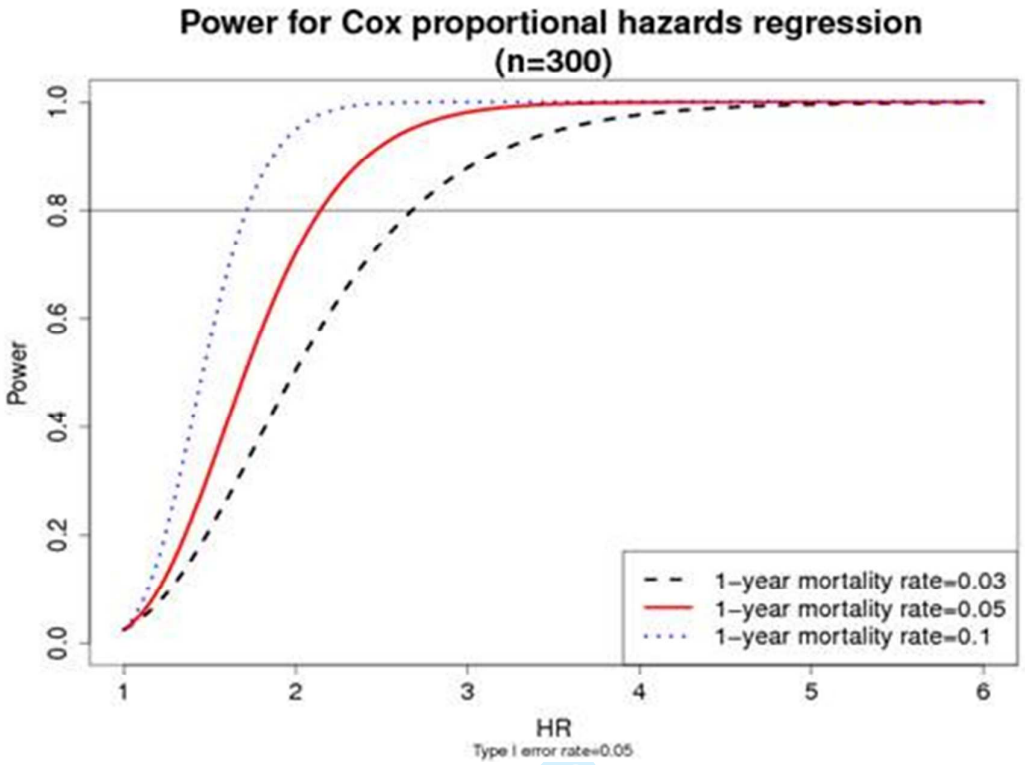


Table 1. Inclusion and exclusion criteria

Inclusion Criteria
≥ 75 years old
Non ST Elevation Acute Coronary Syndrome
Planned for CA or PCI
Exclusion Criteria
Cardiogenic shock
Primary Arrhythmias
Significant valvular heart disease
Malignancy with life expectancy <1 year
Active Infection
Urinary Tract Infection
Pneumonia
Sepsis
Alternative diagnosis after CA (excluded after consent)
Pulmonary embolism
Takotsubo cardiomyopathy
Myocarditis
Coronary vasospasm
Unable to consent
Known Dementia
Language barrier
Visual impairment
Lack of capacity

CA - coronary angiogram, PCI - percutaneous coronary intervention

Table 2. ICON1 Study Assessments

Biomarkers
High sensitive C-reactive protein
Vitamin D
Myeloperoxidase
Asymmetric dimethyl arginine
Eicosapentaenoic acid
Docosahexaenoic acid
Soluble p selectin
Cluster Differentiation 40
Lipoprotein-associated phospholipase A_2
Interleukin-6
Tumor Necrosis Factor-alpha
N-terminal prohormone Brain Natriuretic Peptide
MicroRNAs (miR-21-5p, miR-126-5p, miR-132-3p, miR-133a-3p, miR-142-3p, miR-150-5p, miR-208-3p, miR-223-3p, and miR-320a)
Peripheral Blood Mononuclear Cells
Telomere length
Telomerase activity
Intracoronary Imaging
Virtual Histology Intravascular Ultrasound
Optical Coherence Tomography
Cardiovascular Status
Arterial Stiffness
Peripheral Arterial Tonometry
Carotid Intima Media Thickness
Trans-thoracic Echocardiogram
Cardiac Symptoms
New York Heart Association Dyspnoea
Canadian Cardiovascular Society Angina
Frailty Assessment
Fried Frailty Index
Rockwood Frailty Index
Quality of Life
SF-36, Euro Qol - 5D (EQ-5D™)
Cognitive Status
Montreal Cognitive Assessment (MoCA©) *
Co-morbidity
Charlson Co-morbidity Index

MiR - micro RNA, MoCa - Montreal Cognitive Assessment, Qol - quality of life.
** Permission to use MoCA test obtained from MoCA© team (on behalf of Dr Ziad Nasreddine)*

Appendices

Appendix 1: Fried Frailty Index derived from Cardiovascular Health Study

Criterion	Frailty Status
Shrinking	**Frailty cut point:** **Baseline:** Self reported unintentional weight loss ≥10lb in previous year **Follow-up:** Unintentional weight loss ≥5% of previous year's body weight *OR* BMI <18.5kg/m^2
Physical endurance/energy	*Geriatric Depression Scale:* 1. *Do you feel full of energy?* 2. *During the last 4 weeks how often you rested in bed during day?* Response options: Every day, every week, once, not at all. **Frailty cut point:** No to 1 and every day or every week to 2.
Low physical activity	*Frequency of mildly energetic, moderately energetic and very energetic physical activity.* Response options: ≥3 times per week, 1-2 times per week, 1-3 times per month, hardly ever/never **Frailty cut point:** Hardly ever/never for very energetic physical activity AND for moderately energetic physical activity.
Weakness	Hand grip strength in Kg: GRIP-D hand held dynamometer, dominant hand, average of 3 measures. **Frailty cut point:** **Grip strength:** lowest 20% (by gender, body mass index) *Men* BMI ≤24 ≤29 BMI 24.1–26 ≤30 BMI 26.1–28 ≤30 BMI >28 ≤32 *Women* BMI ≤23 ≤17 BMI 23.1–26 ≤17.3 BMI 26.1–29 ≤18 BMI >29 ≤21
Slow walking speed	Walking time in seconds (usual pace) over 15 feet **Frailty cut point:** Slowest 20%, stratified by gender and median standing height. *Men* Height ≤173 cm ≥7 seconds Height >173 cm ≥6 seconds *Women* Height ≤159 cm ≥7 seconds Height >159 cm ≥6 seconds *OR* Time to complete "timed up and go test" (TUG) **Frailty cut point:** TUG time ≥19 seconds

Frail: ≥3 criteria present; **Intermediate or Pre-Frail:**1 or 2 criteria present; **Robust :** 0 criteria present

Adapted from Fried et al, Cardiovascular Health Study Collaborative Research G. Frailty in older adults: Evidence for a phenotype. The Journals of Gerontology. Series A, Biological sciences and medical sciences. 2001;56:M146-156.

Appendix 2: Rockwood Frailty Index derived from Canadian Study of Health and Aging

1	Very fit – robust, active, energetic, well motivated and fit; these people commonly exercise regularly and are in the most fit group for their age
2	Well – without active disease, but less fit than people in category 1.
3	Well, with treated co-morbid disease – disease symptoms are well controlled compared with those in category 4
4	Apparently vulnerable – although not frankly dependent, these people commonly complain of being “slowed up” or have disease symptoms.
5	Mildly frail – with limited dependence on others for instrumental activities of daily living
6	Moderately frail – help is needed with both instrumental and non-instrumental activities of daily living
7	Severely frail – completely dependent on others for the activities of daily living, or terminally ill.

Adapted from Rockwood et al, A global clinical measure of fitness and frailty in elderly people. Canadian Medical Association Journal 2005;173:489-495

Appendix 3: Definitions of outcome measures

Outcome	Definition
Death	Death from any cause Classified as cardiovascular or non-cardiovascular
Myocardial Infarction*	Defined as below
Type 1	Spontaneous myocardial infarction related to ischaemia due to a primary coronary event such as plaque erosion and/or rupture, fissuring, or dissection
Type 2	Myocardial infarction secondary to ischaemia due to either increased oxygen demand or decreased supply, e.g. coronary artery spasm, coronary embolism, anaemia, arrhythmias, hypertension, or hypotension
Type 3	Sudden unexpected cardiac death, including cardiac arrest, often with symptoms suggestive of myocardial ischaemia, accompanied by presumably new ST elevation, or new LBBB, or evidence of fresh thrombus in a coronary artery by angiography and/or at autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood
Type 4a	Myocardial infarction associated with PCI
Type 4b	Myocardial infarction associated with stent thrombosis as documented by angiography or at autopsy
Type 5	Myocardial infarction associated with CABG
Revascularisation	PCI to lesions not identified previously. CABG for new symptoms or complications of PCI Target lesion or target vessel revascularisation
Target Lesion Revascularisation	Re-interventions inside the implanted stent or within 5 mm proximally or distally
Target Vessel Revascularisation	Re-interventions in the same vessel by PCI or by CABG
Stroke	Stroke is 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. It is strongly recommended (but not required) that an imaging procedure such as CT scan or MRI be performed. Stroke will be further classified as ischaemic, haemorrhagic or type uncertain.
Heart Failure	Heart failure will be defined as a hospital admission with any of the following symptoms and signs: worsening breathlessness, fatigue, fluid overload, pulmonary oedema, elevated venous pressure and elevated NT-prohormone Brain Natriuretic Peptide. Confirmation of heart failure according to local expert judgement and evidence of impaired left ventricular function will be required for the event to be classified as heart failure.
Rehospitalisation	Repeat hospitalisation for any reason during follow up period
Adverse Event	Any untoward medical occurrence
Serious Adverse Event	Any untoward medical occurrence that: Results in death and is life-threatening. The term "life-threatening" in the definition of "serious adverse event" refers to an event that 1. Requires hospitalisation or prolongation of existing inpatient's hospitalisation; 2. Results in persistent or significant disability or incapacity.

PCI-Percutaneous Coronary Intervention, CABG-Coronary Artery Bypass Graft, CT-Computerised Tomography, MRI-Magnetic Resonance Imaging

** Adapted from Thygesan et al, Universal definition of myocardial infarction, European Heart Journal (2007) 28, 2525–2538*

Appendix 4: Bleeding Academic Research Consortium (BARC) definition for bleeding

Type 0	No 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. May include episodes leading to self-discontinuation of medical therapy by the patient without consulting a healthcare professional.
Type 2	Any overt, actionable sign of haemorrhage (e.g. more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for Type 3, 4 or 5 but does meet at least one of the following criteria: (1) requiring non-surgical, medical intervention by a healthcare professional, (2) leading to hospitalization or increased level of care, or (3) prompting evaluation.
Type 3a	Overt bleeding plus haemoglobin drop of 3 to <5g/dl* (provided haemoglobin drop is due to bleed) Any transfusion with overt bleeding
Type 3b	Overt bleeding plus haemoglobin drop ≥5g/dl* (provided haemoglobin drop is due to bleed) Cardiac tamponade Bleeding requiring surgical intervention for control (excluding dental/ nasal/ skin/ haemorrhoid) Bleeding requiring intravenous vasoactive agents
Type 3c	Intracranial haemorrhage (does not include micro-bleeds or haemorrhagic transformation, does include intraspinal) Subcategories confirmed by autopsy or imaging or lumbar puncture Intraocular bleed compromising vision
Type 4:	CABG-related bleeding Perioperative intracranial bleeding within 48 hours Reoperation following closure of sternotomy for the purpose of controlling bleeding Transfusion of ≥5 units of whole blood or packed red blood cells within a 48-hour period† Chest tube output ≥ 2 litres within a 24-hour period 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'.
Type 5a	Probable fatal bleeding; no autopsy or imaging confirmation, but clinically suspicious
Type 5b	Definite fatal bleeding; overt bleeding or autopsy or imaging confirmation

**Corrected for transfusion (1 U packed red blood cells or 1 U whole blood1 g/dL haemoglobin).*
†Cell saver products are not counted.

Adapted from Mehran et al, Standardized bleeding definitions for cardiovascular clinical trials: A consensus report from the bleeding academic research consortium. Circulation. 2011;123:2736-2747

BMJ Open

A Study to Improve Cardiovascular Outcomes in High Risk Older PatieNts (ICON1) with Acute Coronary Syndrome: Study Design and Protocol of a Prospective Observational Study

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A Study to Improve Cardiovascular Outcomes in High Risk Older PatieNts (ICON-1) with Acute Coronary Syndrome: Study Design and Protocol of a Prospective Observational Study

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Running title: Study design of ICON1

ABSTRACT

Introduction: The ICON-1 study (a study to **I**mprove **C**ardiovascular **O**utcomes in high risk older patie**N**ts with acute coronary syndrome) is a prospective observational study of older patients (≥75 years old) with non-ST elevation acute coronary syndrome managed by contemporary treatment (pharmacological and invasive). The aim of the study is to determine the predictors of poor cardiovascular outcomes in this age group and to generate a risk prediction tool.

Methods and Analysis: Participants are recruited from two tertiary hospitals in the United Kingdom. Baseline evaluation includes frailty, co-morbidity, cognition and quality of life measures, inflammatory status assessed by a biomarker panel including microRNAs, senescence assessed by telomere length and telomerase activity, cardiovascular status assessed by arterial stiffness, endothelial function, carotid intima media thickness and left ventricular systolic and diastolic function, and coronary plaque assessed by virtual histology intravascular ultrasound and optical coherence tomography. Patients are followed up at 30 days and at one year for primary outcome measures of death, myocardial infarction, stroke, unplanned revascularisation, bleeding and re-hospitalisation.

Ethics and Dissemination: The study has been approved by the regional ethics committee (REC 12/NE/016). Findings of the study will be presented in scientific sessions and will be published in peer reviewed journals.

Study registration: United Kingdom Clinical Research Network ID: 12742; ClinicalTrials.gov ID: NCT01933581.

Keywords: Study design, acute coronary syndrome, older patients

Article Summary

Strengths and Limitations of this Study

- Older patients with non-ST-elevation acute coronary syndrome represent a high-risk population, understudied in contemporary cardiovascular research.
- This prospective cohort study is designed and powered to identify risk factors for adverse outcomes, at 30-days and 1-year, in patients aged ≥ 75-years-old, undergoing invasive management of non-ST elevation acute coronary syndrome.
- This study will evaluate the role of frailty, using a well-defined frailty index, and invasive imaging modalities (including optical coherence tomography and virtual histology intravascular ultrasound) as determinants of clinical outcome and quality of life in this age group.
- Limitations include: (i) the non-randomised character of this study, which is not able to derive definitive insights regarding the causality of factors associated with clinical outcomes, and (ii) that intracoronary imaging will be performed in only a subset of patients recruited, owing to anatomical contraindications and patient wishes.
- The results of this study will enable improved risk stratification for older patients presenting with non-ST-elevation ACS, and will have implications for the design of future clinical trials in this high-risk population.

Abbreviations

ACS	Acute Coronary Syndrome
ADMA	Asymmetric Dimethyl Arginine
BARC	Bleeding Academic Research Consortium
CA	Coronary Angiography
CABG	Coronary Artery Bypass Graft
CCS	Canadian Cardiovascular Society
CIMT	Carotid Intima-Media Thickness
CVD	Cardiovascular Disease
DHA	Docosahexaenoic acid
EEM	External Elastic Membrane
EPA	Eicosapentaenoic acid
hsCRP	high sensitive C-Reactive Protein
IHD	Ischemic Heart Disease
IL-6	Interleukin-6
$LpPLA_2$	Lipoprotein-associated Phospholipase A2
MINAP	Myocardial Infarction National Audit Project
MoCA	Montreal Cognitive Assessment
MPO	Myeloperoxidase
NT-proBNP	N-terminal prohormone of brain natriuretic peptide
OCT	Optical Coherence Tomography
PAT	Peripheral Arterial Tonometry
PWV	Pulse Wave Velocity
NSTEMI	Non ST Elevation Myocardial Infarction
NYHA	New York Heart Association
PCI	Percutaneous Coronary Intervention
STEMI	ST Elevation Myocardial Infarction
TCFA	Thin Capped Fibroatheroma
TNF-α	Tumor Necrosis Factor-alpha
VH-IVUS	Virtual Histology Intravascular Ultrasound

INTRODUCTION

In the general population, ischaemic heart disease (IHD) is the leading cause of death worldwide.[1] Mortality due to IHD increases steeply among those aged >70 years of age.[2] In 2010 in the United Kingdom (UK), more than twice as many individuals >75 years of age (n=55,028) died from IHD, compared to younger individuals <75 years (n=25,540).[3] According to the Myocardial Ischaemia National Audit Project (MINAP) Database annual public report 2012-13, there were 80,974 admissions with a final diagnosis of myocardial infarction (MI). Of these, 60% had non ST elevation myocardial infarction (NSTEMI). Of the patients with NSTEMI, 59% were >70 years of age (26% were aged 70-79 years, 26% were 80-89 years and 7% were ≥90 years).[4] Mortality benefit from advances in the management of acute coronary syndrome (ACS) has largely been realised in patients <65 years old.[2] There has been an increase in IHD burden in older patients, who are at risk of poorer outcomes due to frailty and co-morbidity.[5]

Until recent years, there has persisted a paucity of evidence from clinical trials and studies to inform the management of ACS in older patients. More than half of all randomised controlled trials for acute coronary syndrome failed to enrol participants >75 years of age and, even in those that did, only 9% were >75 years of age.[6] ***Notable studies, recruiting patients >75 years of age, have been reported in recent years, in the context of both invasive and non-invasive management of ST-elevation MI and non-ST-elevation ACS.***[7-10] Evidence-based recommendations from trials do not account for age-related differences in physiology, disease and co-morbidities, which may alter the risk-benefit profile of cardiovascular treatments and interventions. The age mismatch between trial and community populations begins at 75 years and widens with age.[11] Furthermore, older people that are included in trials have lower than expected rates of traditional cardiovascular risk factors, fewer co-morbidities and better renal function than the community population.[12] Risks and benefits derived from trials cannot always be extrapolated to older patients in daily clinical practice due to the differences between the patient groups and their baseline characteristics.[13]

In the ageing population, there is increasing evidence for the association of cardiovascular disease (CVD) and frailty.[14] Depending on the frailty scale used and the population studied, almost half of patients with CVD can be identified as frail.[15] There is an increased risk of mortality and major adverse cardiovascular events in frail patients with CVD, especially those undergoing invasive procedures or suffering from coronary artery disease and heart failure.[15] In patients >75 years, frailty

was strongly and independently associated with in-hospital mortality (Odds Ratio [OR] 4.6; 95% Confidence Interval [CI] 1.3-16.8) and one-month mortality (OR 4.7; 95% CI, 1.7-13.0).[16] At one year, there was a significant increase in mortality among frail patients compared with non-frail patients (Hazard Ratio 4.3, 95% CI 2.4-7.8).[17] Similarly, in >65 year old patients, frailty was associated with increased long-term mortality and myocardial infarction (MI) among patients undergoing percutaneous coronary intervention (PCI).[18]

No studies to evaluate predictors of poor outcomes, or to develop strategies to improve outcomes following ACS, have been performed in older patients undergoing an invasive treatment strategy. The ACS and PCI risk models that are currently available were mainly derived from patients <65 years, and hence cannot be applied to the increasing proportion of older (>75 years) patients with ACS managed by contemporary treatment.[19] The goal of ICON1 (**I**mprove **C**ardiovascular **O**utcomes in High Risk Older Patie**N**ts with Acute Coronary Syndrome) is to determine the predictors of adverse outcomes (death, MI, stroke, repeat, unplanned revascularisation, bleeding and rehospitalisation for any reason) at one month and at one year following invasive management of non ST elevation acute coronary syndrome (NSTEACS) in older patients, and to develop an integrated risk score to predict adverse outcomes at one-year that will inform clinical decision making. In addition, the impact of contemporary NSTEACS management on the quality of life will be assessed.

HYPOTHESIS

Frailty and co-morbid status in older patients are associated with worse outcomes following invasive treatment for NSTEACS.

TRIAL DESIGN

The study has been designed as a multicentre prospective observational study of patients aged ≥75 years undergoing invasive management (coronary angiography with a view to revascularisation) for NSTEACS.

METHODS

Study Setting

This ongoing multicentre observational study is being conducted in two tertiary cardiac care hospitals in the North-East of England. The Freeman Hospital, in Newcastle upon Tyne, is a tertiary cardiac centre with a catchment population of 2 million. Approximately 3,000 PCI procedures are performed each year. The James Cook University Hospital, in Middlesbrough, performs approximately 1,750 PCI procedures every year. ***The study participants are recruited from patients referred to these hospitals from the neighbouring district general hospitals for invasive treatment of NSTEACS. Patients are diagnosed on the basis of clinical symptoms, electrocardiography criteria and high-sensitivity troponin testing, in line with guidelines[20 21] transferred the day before or on the day of procedure to the tertiary hospitals.*** Prospective ICON1 patients are identified from an electronic referral system and, on arrival to the tertiary hospitals, are approached for recruitment into the study. The study team explains the study to the patient and a patient information sheet is provided. If the patient agrees to participate in the study, written informed consent is obtained. All patients screened for the study are entered in a screening log, with details regarding the patients consented, declined, and consented but not recruited (due to alternative diagnosis following coronary angiography). The inclusion and exclusion criteria are displayed in **Table 1**. Recruitment to the study commenced in October 2012 with the 1-year follow-up is projected to reach completion in December 2016.

Treatment Protocol

During the course of the study, patients were treated according to contemporary evidenced-based guidelines, as directed by an interventional cardiologist, at the time of study enrolment.[20 21] According to standard practice, patients are revascularised by PCI or coronary artery bypass graft (CABG) surgery. Patients may also be managed medically, if deemed not appropriate for either of the revascularisation strategies at the discretion of the operating cardiologist.

Data Collection

Data are collected on standardised case report forms by members of the research team. The data collected include demographics, baseline characteristics, and details of coronary angiography and or PCI. Peri-procedural complications and in-hospital complications are recorded. Further data are collected on the cardiovascular status, Canadian Cardiovascular Society (CCS) angina grade,

New York Heart Association (NYHA) dyspnoea grade, frailty category, functional health status, quality of life and cognitive status. These are listed in **Table 2**. The assessments and techniques used for the above data collection are discussed in the following sections. The study flow chart is displayed in **Figure 1**. All questionnaires were administered verbally, in person, by a trained, clinical researcher. Appropriate training was provided to researchers, ensuring that these scripted questionnaires were performed, and results recorded, in unbiased fashion.

Frailty and Co-Morbidity Assessments

Frailty is assessed by Fried Frailty Index, derived from Cardiovascular Health Study[22] and Rockwood Frailty Index, derived from Canadian Study of Health and Aging.[23] The Fried Frailty Index is based on assessing 5 criteria, comprising subjective answers provided by the patient (regarding weight loss, physical energy, physical activity) and objective assessment (hand grip strength). A score of 0 is categorised as robust, 1 or 2 as intermediate or pre-frail and 3 or more as frail. The Rockwood Frailty Index is based on assessment by the researcher into categories 1 to 7, from very fit to severely frail, depending on functional status and independence/dependence on others for activities of daily living.

In addition, the Charlson Comorbidity Index,[24] a method of predicting mortality based on a weighted index of the number and seriousness of co-morbid conditions, is evaluated for each patient. Charlson Comorbidity Index has been demonstrated to be an appropriate indicator of in-hospital and one-year outcomes in the setting of ACS.[25]

Functional Status and Quality of Life Measures

The Short Form-36 Standard (SF-36® Standard) health survey is completed by each patient prior to discharge from the hospital and at one-year follow-up in order to assess functional health and quality of life. The responses will be used to obtain physical component summary and mental component summary scores.[26] In addition, the EQ-5D™-3L questionnaire is used to assess health outcome of each patient at discharge and one-year follow-up.[27 28]

Cognitive Status Assessment

Atherosclerosis is associated with increased risk of cognitive impairment in older patients.[29] To assess the cognitive status of patients during admission, the Montreal Cognitive Assessment (MoCA©)[30] test is utilised. The MoCA has been shown to have high sensitivity in screening patients with known CVD for mild cognitive impairment, even in a non-memory clinic setting.[31] This test is repeated at one-year follow-up.

Biomarker Sampling

Blood samples are collected at the time of coronary angiography (CA) and/or PCI for analysis of biomarker analysis. Serum for biomarkers is stored for analysis in batches. Peripheral blood mononuclear cells are separated by centrifugation techniques for storage at -80°C for analysis of telomeres and telomerase activity. High-sensitivity C-reactive protein (hsCRP), parathyroid hormone and total vitamin D are analysed. Full blood count, renal function, blood glucose, cholesterol and high-sensitivity cardiac troponin T (hsTnT) levels are measured in patients as part of routine care.

Inflammation plays a central role in acute thrombotic complications of unstable atherosclerotic coronary plaque. Increased levels of markers of inflammation predict CV outcomes following ACS. Inflammatory markers including myeloperoxidase (MPO),[32] hsCRP[33] and soluble CD40 ligand[34] have been associated with ACS and have been shown to predict outcome. Patients with ACS have decreased levels of anti-inflammatory omega-3 fatty acids (eicosapentaenoic acid [EPA] and docosahexaenoic acid [DHA]).[35] Increased lipoprotein-associated phospholipase A_2 ($LpPLA_2$) activity has been associated with increased cardiovascular event rates.[36 37] An elevated level of asymmetric dimethyl arginine (ADMA) is a strong and independent predictor of adverse outcomes following ACS.[38] Interleukin-6 (IL-6) levels in the serum were increased in patients with ACS.[39] IL-6 expressed in atherosclerotic plaques may increase plaque instability.[40] Elevated IL-6 was a predictor of 6 and 12-month mortality in patients with unstable coronary artery disease.[41] Tumor Necrosis Factor-alpha (TNF-α) is a pro-inflammatory cytokine associated with myocardial dysfunction and remodelling following ACS.[42] In patients with recent MI, increased levels of TNF-α were associated with adverse cardiovascular outcomes (recurrent MI and cardiac death).[43] Vitamin D deficiency has been associated with elevated CAD burden and worse cardiovascular outcomes.[44] These biomarkers will be analysed in this group of ≥75 year old patients to enable determination of predictors of adverse CV outcomes at 1-year. Telomere shortening has been associated with ageing and senescence, and

shorter leukocyte telomeres are associated with increased cardiovascular risk and mortality.[45] Shorter leucocyte telomere length predicted high-risk plaque morphology on virtual histology intravascular ultrasound (VH-IVUS).[46] Whether shorter telomere length is a predictor of adverse events among older patients undergoing PCI is not known and will be evaluated in this study.

MicroRNA Analysis

MicroRNAs (miRNAs) are small non-coding RNAs that post transcriptionally inhibit gene expression.[47] In the last few years, miRNAs have emerged as key tools for the understanding of IHD pathophysiology, with great potential to be used as new biomarkers and therapeutic targets. MicroRNAs seem to possess ideal characteristics to be used as disease biomarkers, as they are detectable in biofluids in a reproducible and stable fashion, even after years of sample storage and freeze-thaw cycles.[48] In the blood, circulating miRNAs are found mainly within extracellular vesicles, such as exosomes, microvesicles, and apoptotic bodies[49] and to a lesser extent, associated with HDL-cholesterol particles[50 51] or Argonaute-2 protein[52]. Several studies have demonstrated elevated or decreased levels of specific circulating miRNAs in patients with ACS[53-56]. However, few have addressed their prognostic value with regards to major cardiovascular events[57] or death[58], especially amongst older cohorts of patients presenting with NSTEACS.

The levels of nine circulating miRNAs, known to be differentially expressed in patients with ACS (miR-21-5p, miR-126-5p, miR-132-3p, miR-133a-3p, miR-142-3p, miR-150-5p, miR-208-3p, miR-223-3p, and miR-320a), will be quantified by reverse transcription quantitative polymerase chain reaction, in serum and circulating microvesicles (isolated from an additional 200μL of serum) from 100 participants, and correlated with clinical variables with a view to assess their value as a prognostic biomarkers in older patients with NSTEACS.

Invasive Coronary Artery Imaging

Post-mortem studies have identified that vulnerable plaques, with specific morphological characteristics, are implicated in the pathophysiology of ACS. These plaques, which are prone to erosion and rupture, have inflamed fibrous caps, rich in macrophages, overlying a lipid pool.[59] Burke et al examined the hearts of 113 men that had died suddenly, and found that 95% of ruptured plaques

had fibrous caps <65μm thick (mean thickness 23±19μm) with an infiltrate of macrophages.[60] ICON1 aims to identify whether the increased mortality in the older population with ACS is due to an increased prevalence of these vulnerable thin-capped fibroatheroma (TCFAs). ***Following diagnostic coronary angiography, patients undergo VH IVUS imaging and optical coherence tomography (OCT) imaging in all three coronary arteries prior to PCI, where feasible and not contraindicated, and VH IVUS imaging post-PCI in the culprit vessel at the discretion of the operating cardiologist.***

Virtual Histology Intravascular Ultrasound

Grayscale IVUS image uses only the amplitude of the reflected ultrasound wave. VH IVUS utilises spectral analysis of the frequency and power of the reflected wave to generate a more accurate reflection of the tissue subtypes present within the vessel wall.[61] This can then be used to differentiate plaque components (fibrous, fibro-fatty, dense calcium and necrotic core) and identify high-risk vulnerable plaques. Although VH IVUS lacks the resolution to identify the thin fibrous cap of the TCFA, it is well placed to accurately identify the necrotic core of these plaques.[61] A 20MHz, phased-array Eagle Eye Platinum™ catheter is mounted on an R-100 pullback device and connected to either an integrated S5i system or mobile S5 tower. Image acquisition is performed at a pullback speed of 0.5mm/s and is ECG-gated to ensure one frame is acquired per cardiac cycle. The maximum length of all three coronary arteries is imaged, where feasible and not contraindicated.[62] The data is anonymised and transferred to DVD for offline data analysis. The operator is blinded to this data.

VH IVUS data analysis is performed using Medis (Leiden, Netherlands) QIvus software. Contours are drawn manually around the external elastic membrane (EEM) and lumen of the vessel for each grayscale IVUS frame, taking care to exclude any ring-down artefact or previously stented segments. The software then calculates several parameters such as minimum lumen area and diameter, percent stenosis, and absolute volume and percentage of each plaque component. The image reader can also calculate the remodelling index[63] and classify the lesion type from this data. Lesion classification in ICON1 is based on previously published recommendations for tissue characterisation by radiofrequency data analysis (**Figure 2**).[62]

Optical Coherence Tomography

OCT generates an image analogous to IVUS using a low coherence, near-infrared (wavelength 1.3μm) light source, instead of sound.[64] A bloodless field inside the coronary artery is vital, as red blood cells strongly backscatter the near-infrared light. This is obtained by using a flush of contrast during image acquisition. OCT has a greater resolution than IVUS (20-40μm vs. 100-200μm) and is thus able to delineate the thin fibrous cap present in a TCFA. However, its poorer penetration (1-2.5mm) can limit its capacity to identify deep lipid pools and quantify plaque volume.[65 66]

OCT images are obtained using a Dragonfly catheter (St Jude Medical, Minnesota, USA) connected to the Ilumien™ PCI Optimization System. Just before image acquisition, a short flush of iso-osmolar contrast is administered to ensure the guide catheter is well engaged with the coronary artery and the catheter is clear of blood. The system is calibrated and OCT pullback is initiated with a further flush of iso-osmolar contrast (10ml in the right coronary artery, 15ml in the left coronary artery). OCT images are obtained in 54mm segments at a pullback rate of 20mm/s in all three coronary arteries, where feasible. Data is transferred anonymously to a DVD for offline analysis; the operator is blinded to this data during the procedure.

OCT data is analysed using the Medis QIvus software. Contours are drawn around the lumen to generate data on the minimum lumen area and diameter. The whole vessel is then analysed to identify plaque subtypes. An atherosclerotic lesion is seen on OCT as a mass lesion within the arterial wall, with focal intimal thickening or loss of the normal vessel architecture[67]. Fibrous plaque is homogenous and highly backscattering, calcified plaques are signal-poor areas with sharply delineated borders, and lipid pools are signal-poor regions with poorly defined borders and a fast OCT signal drop-off.[67] Using side branches and areas of calcification as landmarks, it is possible to compare the accuracy of lesion subtypes identified by VH IVUS and OCT.

NON-INVASIVE ASSESSMENT OF CARDIOVASCULAR STATUS

Arterial Stiffness

Arterial stiffness is now increasingly recognized as a surrogate endpoint for the assessment of CVD status.[68] Arterial stiffness can lead to angina in the presence of even minor coronary artery disease and to the development of diastolic dysfunction, the commonest form of heart failure in the elderly.[69] Arterial stiffness is determined by carotid-femoral pulse wave velocity (PWV) which is a

simple, non-invasive, robust and reproducible investigation method that can be performed at the bedside.[68] In older patients, arterial stiffness assessed by increased PWV is associated with poor cardiovascular outcomes.[70] In the ICON1 study, carotid-femoral PWV is assessed by the Vicorder device (Skidmore Medical Limited, Bristol, UK). In addition brachio-femoral PWV, pulse wave analysis (includes pulse pressure, augmentation pressure and augmentation index) and ankle brachial pressure index are also assessed.

Endothelial Function

Endothelial dysfunction is considered one of the earliest markers of atherosclerosis,[71] contributing to lesion development and its later clinical manifestations.[72 73] Endothelial dysfunction is associated with increased risk of cardiovascular events and has been proposed as a marker of poor CV outcomes.[74-76] Peripheral arterial tonometry (PAT) by finger plethysmography (EndoPAT™; Itamar Medical, Caesarea, Israel) is a novel method of measuring the peripheral vasodilator response.[77 78] Hyperaemic response measured by PAT signal amplitude gives a measure of nitric oxide-mediated endothelial function.[79 80] In patients with low-risk findings during stress testing and/or the absence of new obstructive lesions on angiography, lower natural logarithmic-scaled reactive hyperaemia index (<0.40) is associated with increased cardiovascular death over six years.[81] In the ICON1 study, endothelial function is measured by EndoPAT™. PAT signals are recorded from the index fingers with pneumatic probes at baseline, during cuff occlusion and during hyperaemia. A measure of endothelial function is calculated from the ratio of PAT signal amplitude at baseline and post-occlusion. Reactive hyperaemia index data from the study will be used in the prediction of adverse CV outcomes, and will be incorporated in the risk model.

Carotid Intima Medial Thickness

Carotid Intima Media Thickness (CIMT) is a significant predictor of incident adverse cardiovascular events.[82 83] Increased CIMT was associated with severity of coronary atherosclerosis in ACS.[84] CIMT and its association with predicting CV events in older NSTEACS patients are not known. In a meta-analysis, addition of carotid intimal media thickness (CIMT) to Framingham risk score in general population did not improve 10-year prediction of first MI or stroke.[85] However CIMT and arterial stiffness together increases the cardiovascular risk in patients with known vascular

disease or cardiovascular risk factors.[86] In the ICON1 study, CIMT is assessed using a Vivid I GE machine, with a vascular probe. CIMT measurement is obtained via semi-automated software, which uses an edge detection technique. CIMT values will be analysed for prediction of adverse outcomes and will be incorporated in the risk model.

Transthoracic Echocardiogram

In hospitalised elderly patients with known cardiovascular disease, left ventricular diastolic dysfunction was similar in prevalence to systolic dysfunction and was associated with similar cardiovascular and all-cause mortality.[87] Transthoracic echocardiography will be performed using Vivid I GE echo machine, according to the British Society of Echocardiography guidelines, to assess systolic function, diastolic function and valvular heart disease.[88] Systolic and diastolic function will be analysed for prediction of adverse CV outcomes.

Follow-up

One-month outcomes are recorded using general practitioner summary documents, obtained from the patients' general practitioner. Patients are followed-up in a study outpatient clinic at one year. During this follow-up visit, repeat blood samples for biomarker analysis are collected. In addition, NYHA class, CCS angina class, SF-36, EQ-5D™ and MoCA® assessments are completed. Frailty status is re-assessed using Fried and Rockwood Frailty Criteria.

Primary Outcome Measures

The primary outcome measure is a composite of death, myocardial infarction, stroke, repeat, unplanned revascularisation and BARC (Bleeding Academic Research Consortium)-defined bleeding (type 2 or greater) at one year.[89,90] We also intend to analyse one-year mortality as an independent outcome measure. All-cause hospitalisation comprises a secondary outcome measure.

Sample Size

For the primary outcome, Hsieh and Lavori's method was used to calculate the power for testing the association of the risk score with adverse outcomes, based on 300 subjects with type I

error rate 0.05.[91] ***From national-level registry data, the one-year mortality rate for NSTEMI in all patients undergoing invasive strategy is approximately 2-5%.***[92] Estimates of the standard deviation and hazard ratio of the risk score are unknown. Assumption was made on the hazard ratios being an increment of one standard deviation of the risk score. **Figure 3** shows the plot of powers versus hazard ratios for the sample size of 300 patients and 1-year mortality rates.

STATISTICAL METHODS

Risk Factor Selection

Cox proportional hazards regression analysis will be performed to estimate hazard ratios of the risk factors and associated p-values for the primary outcome. Multiple logistic regression analysis will be performed to estimate odds ratios of the risk factors and associated p-values for the secondary outcome. ***The bootstrap method will be used to avoid over-fitting the data. One thousand bootstrapping will be performed. For each bootstrapping, we will sample with replacement 300 patients from the original 300 patients.*** Backward selection with a p-value <0.05 for statistical significance will be used to remove variables in each sample. Variables selected ≥800 times (80%) in the overall sample will be included in the final model. All missing values will be reported and appropriate statistical methods will be utilized to handle missing values.

Risk Score Construction

To construct the risk score, risk factors identified through the multivariable model will be assigned a weight. Weights are the estimated regression coefficients from the Cox proportional hazards regression or logistic regression model. The risk score is thus the weighted average of the identified risk factors. Another Cox proportional hazards regression or logistic regression model will be applied to detect the association of the proposed risk score to the outcomes.

Risk Score Evaluation

Harrell's C-index will be used to assess the discriminatory capacity of the integrated risk score, for primary and secondary outcomes. The Jackknife method will be used to estimate the standard error of the estimated Harrell's C-index[93] or area under the curve (AUC). The difference between model-predicted and observed event rates (goodness-of-fit) will be evaluated with the

Hosmer-Lemeshow test (p-value >0.10 will be considered to indicate lack of deviation between the model and observed event rates). Reclassification calibration measures (e.g. net reclassification improvement [NRI], and integrated discrimination improvement [IDI]) will be used to evaluate the improvement of new predictors (relative to existing predictors) on the agreement between observed outcomes and predictions.[94] Cross-validation technique will be used to assess how the results of statistical analysis generalize to an independent dataset.[95] Finally, a prediction nomogram[96] will be developed to facilitate calculating the risk scores and the corresponding survival probability at 1 year.

Ethics

The study has been approved by the regional ethics committee (REC 12/NE/016). The study is conducted in accordance with the Declaration of Helsinki (64th World Medical Association General Assembly, Fortaleza, Brazil, October 2013).[97]

CONCLUSION

ICON1 study will identify predictors of poor cardiovascular outcomes among older (≥75 years) patients presenting with NSTEACS managed by contemporary pharmacotherapy and invasive revascularisation strategy. Based on clinical characteristics, frailty status, co-morbidities and cardiovascular status, an integrated risk stratification tool to help decision-making in the management of older patients will be developed. The variables that we hypothesise may be relevant to such a model would be either (i) routinely collected in clinical practice as part of current evidence-based practice, or (ii) should not be unduly burdensome to collect, during routine clinical assessment.

Author Contributions:

VK Conceived the study and carries overall responsibility for the full study and the study protocol.

DN Responsible for the biomarker sub-study

HS Contributed to the invasive sub-study

JAB Overall critical review and revision of the manuscript

MV Contributed to the non-invasive sub-study and the initial draft of this manuscript

GF Provided expert input into the design of the protocol and critical review of the manuscript

WQ Responsible for the statistical aspect of the study and the design of the study

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References

1. Murray CJ, Lopez AD. Mortality by cause for eight regions of the world: Global Burden of Disease Study. Lancet 1997;**349**(9061):1269-76.
2. Finegold JA, Asaria P, Francis DP. Mortality from ischaemic heart disease by country, region, and age: statistics from World Health Organisation and United Nations. Int J Cardiol 2013;**168**(2):934-45.
3. Townsend N, Wickramasinghe K, Bhatnagar P, et al. Coronary heart disease statistics 2012 edition. London: British Heart Foundation, 2012.
4. Gavalova L WC. Myocardial Ischaemia National Audit Project Annual Public Report April 2012-March 2013. London: National Institute for Cardiovascular Outcomes Research, 2013.
5. Veerasamy M, Edwards R, Ford G, et al. Acute coronary syndrome among older patients: a review. Cardiol Rev 2015;**23**(1):26-32.
6. Lee PY, Alexander KP, Hammill BG, et al. Representation of elderly persons and women in published randomized trials of acute coronary syndromes. JAMA 2001;**286**(6):708-13.
7. Bueno H, Betriu A, Heras M, et al. Primary angioplasty vs. fibrinolysis in very old patients with acute myocardial infarction: TRIANA (TRatamiento del Infarto Agudo de miocardio eN Ancianos) randomized trial and pooled analysis with previous studies. Eur Heart J 2011;**32**(1):51-60.
8. Savonitto S, Cavallini C, Petronio AS, et al. Early aggressive versus initially conservative treatment in elderly patients with non-ST-segment elevation acute coronary syndrome: a randomized controlled trial. JACC Cardiovasc Interv 2012;**5**(9):906-16.
9. Tegn N, Abdelnoor M, Aaberge L, et al. Invasive versus conservative strategy in patients aged 80 years or older with non-ST-elevation myocardial infarction or unstable angina pectoris (After Eighty study): an open-label randomised controlled trial. Lancet 2016;**387**(10023):1057-65.
10. Roe MT, Goodman SG, Ohman EM, et al. Elderly patients with acute coronary syndromes managed without revascularization: insights into the safety of long-term dual antiplatelet therapy with reduced-dose prasugrel versus standard-dose clopidogrel. Circulation 2013;**128**(8):823-33.
11. Alexander KP, Newby LK, Cannon CP, et al. Acute coronary care in the elderly, part I: Non-ST-segment-elevation acute coronary syndromes: a scientific statement for healthcare professionals from the American Heart Association Council on Clinical Cardiology: in collaboration with the Society of Geriatric Cardiology. Circulation 2007;**115**(19):2549-69.
12. Kandzari DE, Roe MT, Chen AY, et al. Influence of clinical trial enrollment on the quality of care and outcomes for patients with non-ST-segment elevation acute coronary syndromes. Am Heart J 2005;**149**(3):474-81.
13. Tinetti ME, Bogardus ST, Jr., Agostini JV. Potential pitfalls of disease-specific guidelines for patients with multiple conditions. N Engl J Med 2004;**351**(27):2870-4.
14. Afilalo J, Karunananthan S, Eisenberg MJ, et al. Role of frailty in patients with cardiovascular disease. Am J Cardiol 2009;**103**(11):1616-21.
15. Afilalo J. Frailty in Patients with Cardiovascular Disease: Why, When, and How to Measure. Curr Cardiovasc Risk Rep 2011;**5**(5):467-72.
16. Ekerstad N, Swahn E, Janzon M, et al. Frailty is independently associated with short-term outcomes for elderly patients with non-ST-segment elevation myocardial infarction. Circulation 2011;**124**(22):2397-404.
17. Ekerstad N, Swahn E, Janzon M, et al. Frailty is independently associated with 1-year mortality for elderly patients with non-ST-segment elevation myocardial infarction. Eur J Prev Cardiol 2013.
18. Singh M, Rihal CS, Lennon RJ, et al. Influence of frailty and health status on outcomes in patients with coronary disease undergoing percutaneous revascularization. Circ Cardiovasc Qual Outcomes 2011;**4**(5):496-502.
19. Bawamia B, Mehran R, Qiu W, et al. Risk scores in acute coronary syndrome and percutaneous coronary intervention: a review. Am Heart J 2013;**165**(4):441-50.
20. Hamm CW, Bassand JP, Agewall S, et al. ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: The Task Force for the management of acute coronary syndromes (ACS) in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J 2011;**32**(23):2999-3054.

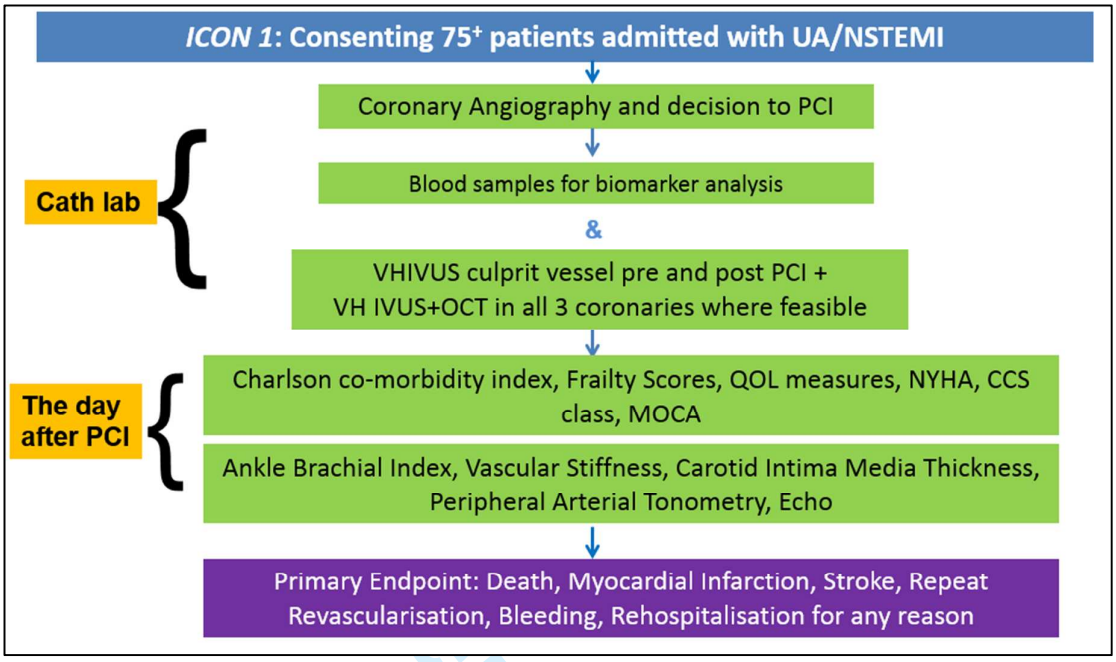
21. Roffi M, Patrono C, Collet JP, et al. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). Eur Heart J 2016;**37**(3):267-315.
22. Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci 2001;**56**(3):M146-56.
23. Rockwood K, Song X, MacKnight C, et al. A global clinical measure of fitness and frailty in elderly people. CMAJ 2005;**173**(5):489-95.
24. Charlson ME, Pompei P, Ales KL, et al. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987;**40**(5):373-83.
25. Radovanovic D, Seifert B, Urban P, et al. Validity of Charlson Comorbidity Index in patients hospitalised with acute coronary syndrome. Insights from the nationwide AMIS Plus registry 2002-2012. Heart 2014;**100**(4):288-94.
26. Ware JE, Jr., Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care 1992;**30**(6):473-83.
27. EuroQOL Group. EuroQol--a new facility for the measurement of health-related quality of life. Health Policy 1990;**16**(3):199-208.
28. Brooks R. EuroQol: the current state of play. Health Policy 1996;**37**(1):53-72.
29. van Oijen M, de Jong FJ, Witteman JC, et al. Atherosclerosis and risk for dementia. Ann Neurol 2007;**61**(5):403-10.
30. Nasreddine ZS, Phillips NA, Bedirian V, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. J Am Geriatr Soc 2005;**53**(4):695-9.
31. McLennan SN, Mathias JL, Brennan LC, et al. Validity of the montreal cognitive assessment (MoCA) as a screening test for mild cognitive impairment (MCI) in a cardiovascular population. J Geriatr Psychiatry Neurol 2011;**24**(1):33-8.
32. Baldus S, Heeschen C, Meinertz T, et al. Myeloperoxidase serum levels predict risk in patients with acute coronary syndromes. Circulation 2003;**108**(12):1440-5.
33. Zairis MN, Adamopoulou EN, Manousakis SJ, et al. The impact of hs C-reactive protein and other inflammatory biomarkers on long-term cardiovascular mortality in patients with acute coronary syndromes. Atherosclerosis 2007;**194**(2):397-402.
34. Varo N, de Lemos JA, Libby P, et al. Soluble CD40L: risk prediction after acute coronary syndromes. Circulation 2003;**108**(9):1049-52.
35. Block RC, Harris WS, Reid KJ, et al. EPA and DHA in blood cell membranes from acute coronary syndrome patients and controls. Atherosclerosis 2008;**197**(2):821-8.
36. Ballantyne C, Cushman M, Psaty B, et al. Collaborative meta-analysis of individual participant data from observational studies of Lp-PLA2 and cardiovascular diseases. Eur J Cardiovasc Prev Rehabil 2007;**14**(1):3-11.
37. Thompson A, Gao P, Orfei L, et al. Lipoprotein-associated phospholipase A(2) and risk of coronary disease, stroke, and mortality: collaborative analysis of 32 prospective studies. Lancet 2010;**375**(9725):1536-44.
38. Cavusoglu E, Ruwende C, Chopra V, et al. Relationship of baseline plasma ADMA levels to cardiovascular outcomes at 2 years in men with acute coronary syndrome referred for coronary angiography. Coron Artery Dis 2009;**20**(2):112-7.
39. Biasucci LM, Vitelli A, Liuzzo G, et al. Elevated levels of interleukin-6 in unstable angina. Circulation 1996;**94**(5):874-7.
40. Schieffer B, Schieffer E, Hilfiker-Kleiner D, et al. Expression of angiotensin II and interleukin 6 in human coronary atherosclerotic plaques: potential implications for inflammation and plaque instability. Circulation 2000;**101**(12):1372-8.
41. Lindmark E, Diderholm E, Wallentin L, et al. Relationship between interleukin 6 and mortality in patients with unstable coronary artery disease: effects of an early invasive or noninvasive strategy. JAMA 2001;**286**(17):2107-13.
42. Nian M, Lee P, Khaper N, et al. Inflammatory cytokines and postmyocardial infarction remodeling. Circ Res 2004;**94**(12):1543-53.
43. Ridker PM, Rifai N, Pfeffer M, et al. Elevation of tumor necrosis factor-alpha and increased risk of recurrent coronary events after myocardial infarction. Circulation 2000;**101**(18):2149-53.
44. Kunadian V, Ford GA, Bawamia B, et al. Vitamin D deficiency and coronary artery disease: a review of the evidence. Am Heart J 2014;**167**(3):283-91.

45. Perez-Rivera JA, Pabon-Osuna P, Cieza-Borrella C, et al. Prognostic value of telomere length in acute coronary syndrome. Mech Ageing Dev 2012;**133**(11-12):695-7.
46. Calvert PA, Liew TV, Gorenne I, et al. Leukocyte telomere length is associated with high-risk plaques on virtual histology intravascular ultrasound and increased proinflammatory activity. Arterioscler Thromb Vasc Biol 2011;**31**(9):2157-64.
47. Berezikov E. Evolution of microRNA diversity and regulation in animals. Nat Rev Genet 2011;**12**(12):846-60.
48. Moldovan L, Batte KE, Trgovcich J, et al. Methodological challenges in utilizing miRNAs as circulating biomarkers. J Cell Mol Med 2014;**18**(3):371-90.
49. Valadi H, Ekstrom K, Bossios A, et al. Exosome-mediated transfer of mRNAs and microRNAs is a novel mechanism of genetic exchange between cells. Nat Cell Biol 2007;**9**(6):654-9.
50. Vickers KC, Palmisano BT, Shoucri BM, et al. MicroRNAs are transported in plasma and delivered to recipient cells by high-density lipoproteins. Nat Cell Biol 2011;**13**(4):423-33.
51. Wagner J, Riwanto M, Besler C, et al. Characterization of levels and cellular transfer of circulating lipoprotein-bound microRNAs. Arterioscler Thromb Vasc Biol 2013;**33**(6):1392-400.
52. Turchinovich A, Burwinkel B. Distinct AGO1 and AGO2 associated miRNA profiles in human cells and blood plasma. RNA Biol 2012;**9**(8):1066-75.
53. D'Alessandra Y, Devanna P, Limana F, et al. Circulating microRNAs are new and sensitive biomarkers of myocardial infarction. Eur Heart J 2010;**31**(22):2765-73.
54. Wang GK, Zhu JQ, Zhang JT, et al. Circulating microRNA: a novel potential biomarker for early diagnosis of acute myocardial infarction in humans. Eur Heart J 2010;**31**(6):659-66.
55. De Rosa S, Fichtlscherer S, Lehmann R, et al. Transcoronary concentration gradients of circulating microRNAs. Circulation 2011;**124**(18):1936-44.
56. Devaux Y, Vausort M, McCann GP, et al. MicroRNA-150: a novel marker of left ventricular remodeling after acute myocardial infarction. Circ Cardiovasc Genet 2013;**6**(3):290-8.
57. Eitel I, Adams V, Dieterich P, et al. Relation of circulating MicroRNA-133a concentrations with myocardial damage and clinical prognosis in ST-elevation myocardial infarction. Am Heart J 2012;**164**(5):706-14.
58. Widera C, Gupta SK, Lorenzen JM, et al. Diagnostic and prognostic impact of six circulating microRNAs in acute coronary syndrome. J Mol Cell Cardiol 2011;**51**(5):872-5.
59. Farb A, Burke AP, Tang AL, et al. Coronary plaque erosion without rupture into a lipid core. A frequent cause of coronary thrombosis in sudden coronary death. Circulation 1996;**93**(7):1354-63.
60. Burke AP, Farb A, Malcom GT, et al. Coronary risk factors and plaque morphology in men with coronary disease who died suddenly. N Engl J Med 1997;**336**(18):1276-82.
61. Nair A, Kuban BD, Tuzcu EM, et al. Coronary plaque classification with intravascular ultrasound radiofrequency data analysis. Circulation 2002;**106**(17):2200-6.
62. Garcia-Garcia HM, Mintz GS, Lerman A, et al. Tissue characterisation using intravascular radiofrequency data analysis: recommendations for acquisition, analysis, interpretation and reporting. EuroIntervention 2009;**5**(2):177-89.
63. Mintz GS, Kent KM, Pichard AD, et al. Contribution of inadequate arterial remodeling to the development of focal coronary artery stenoses. An intravascular ultrasound study. Circulation 1997;**95**(7):1791-8.
64. Huang D, Swanson EA, Lin CP, et al. Optical coherence tomography. Science 1991;**254**(5035):1178-81.
65. Sinclair H, Bourantas C, Bagnall A, et al. OCT for the identification of vulnerable plaque in acute coronary syndrome. JACC Cardiovasc Imaging 2015;**8**(2):198-209.
66. Prati F, Guagliumi G, Mintz GS, et al. Expert review document part 2: methodology, terminology and clinical applications of optical coherence tomography for the assessment of interventional procedures. Eur Heart J 2010;**33**(20):2513-20.
67. Tearney GJ, Regar E, Akasaka T, et al. Consensus standards for acquisition, measurement, and reporting of intravascular optical coherence tomography studies: a report from the International Working Group for Intravascular Optical Coherence Tomography Standardization and Validation. J Am Coll Cardiol 2012;**59**(12):1058-72.
68. Laurent S, Cockcroft J, Van Bortel L, et al. Expert consensus document on arterial stiffness: methodological issues and clinical applications. Eur Heart J 2006;**27**(21):2588-605.

69. Weber T, Auer J, O'Rourke MF, et al. Prolonged mechanical systole and increased arterial wave reflections in diastolic dysfunction. Heart 2006;**92**(11):1616-22.
70. Veerasamy M, Ford GA, Neely D, et al. Association of Aging, Arterial Stiffness and Cardiovascular Disease: A Review. Cardiol Rev 2014.
71. Luscher TF, Barton M. Biology of the endothelium. Clin Cardiol 1997;**20**(11 Suppl 2):II-3-10.
72. Veerasamy M, Bagnall A, Neely D, et al. Endothelial dysfunction and coronary artery disease: a state of the art review. Cardiol Rev 2015;**23**(3):119-29.
73. Ross R. The pathogenesis of atherosclerosis: a perspective for the 1990s. Nature 1993;**362**(6423):801-9.
74. Halcox JP, Schenke WH, Zalos G, et al. Prognostic value of coronary vascular endothelial dysfunction. Circulation 2002;**106**(6):653-8.
75. Schachinger V, Britten MB, Zeiher AM. Prognostic impact of coronary vasodilator dysfunction on adverse long-term outcome of coronary heart disease. Circulation 2000;**101**(16):1899-906.
76. Suwaidi JA, Hamasaki S, Higano ST, et al. Long-term follow-up of patients with mild coronary artery disease and endothelial dysfunction. Circulation 2000;**101**(9):948-54.
77. Kuvin JT, Patel AR, Sliney KA, et al. Assessment of peripheral vascular endothelial function with finger arterial pulse wave amplitude. Am Heart J 2003;**146**(1):168-74.
78. Lavie P, Schnall RP, Sheffy J, et al. Peripheral vasoconstriction during REM sleep detected by a new plethysmographic method. Nat Med 2000;**6**(6):606.
79. Nohria A, Gerhard-Herman M, Creager MA, et al. Role of nitric oxide in the regulation of digital pulse volume amplitude in humans. J Appl Physiol 2006;**101**(2):545-8.
80. Noon JP, Haynes WG, Webb DJ, et al. Local inhibition of nitric oxide generation in man reduces blood flow in finger pulp but not in hand dorsum skin. J Physiol 1996;**490 (Pt 2)**:501-8.
81. Rubinshtein R, Kuvin JT, Soffler M, et al. Assessment of endothelial function by non-invasive peripheral arterial tonometry predicts late cardiovascular adverse events. Eur Heart J 2010;**31**(9):1142-8.
82. Lorenz MW, Markus HS, Bots ML, et al. Prediction of clinical cardiovascular events with carotid intima-media thickness: a systematic review and meta-analysis. Circulation 2007;**115**(4):459-67.
83. Carpenter M, Sinclair H, Kunadian V. Carotid Intimal Media Thickness and its Utility as a Predictor of Cardiovascular Disease: A Review of Evidence. Cardiol Rev 2015.
84. Kalay N, Yarlioglues M, Ardic I, et al. The assessment of atherosclerosis on vascular structures in patients with acute coronary syndrome. Clin Invest Med 2010;**33**(1):E36-43.
85. Den Ruijter HM, Peters SA, Anderson TJ, et al. Common carotid intima-media thickness measurements in cardiovascular risk prediction: a meta-analysis. JAMA 2012;**308**(8):796-803.
86. Simons PC, Algra A, Bots ML, et al. Common carotid intima-media thickness and arterial stiffness: indicators of cardiovascular risk in high-risk patients. The SMART Study (Second Manifestations of ARTerial disease). Circulation 1999;**100**(9):951-7.
87. Zhang Y, Safar ME, Iaria P, et al. Prevalence and prognosis of left ventricular diastolic dysfunction in the elderly: The PROTEGER Study. Am Heart J 2010;**160**(3):471-8.
88. Wharton G, Steeds R, Allen J, et al. A minimum dataset for a standard adult transthoracic echocardiogram: a guideline protocol from the British Society of Echocardiography. Echo Res Pract 2015;**2**(1):G9-g24.
89. Thygesen K, Alpert JS, White HD, et al. Universal definition of myocardial infarction. Eur Heart J 2007;**28**(20):2525-38.
90. Mehran R, Rao SV, Bhatt DL, et al. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. Circulation 2011;**123**(23):2736-47.
91. Hsieh FY, Lavori PW. Sample-size calculations for the Cox proportional hazards regression model with nonbinary covariates. Control Clin Trials 2000;**21**(6):552-60.
92. British Cardiovascular Intervention Society. *BCIS Audit Return 2011*. London, United Kingdom: British Cardiovascular Intervention Society, 2011.
93. Harrell FE, Jr., Lee KL, Pollock BG. Regression models in clinical studies: determining relationships between predictors and response. J Natl Cancer Inst 1988;**80**(15):1198-202.

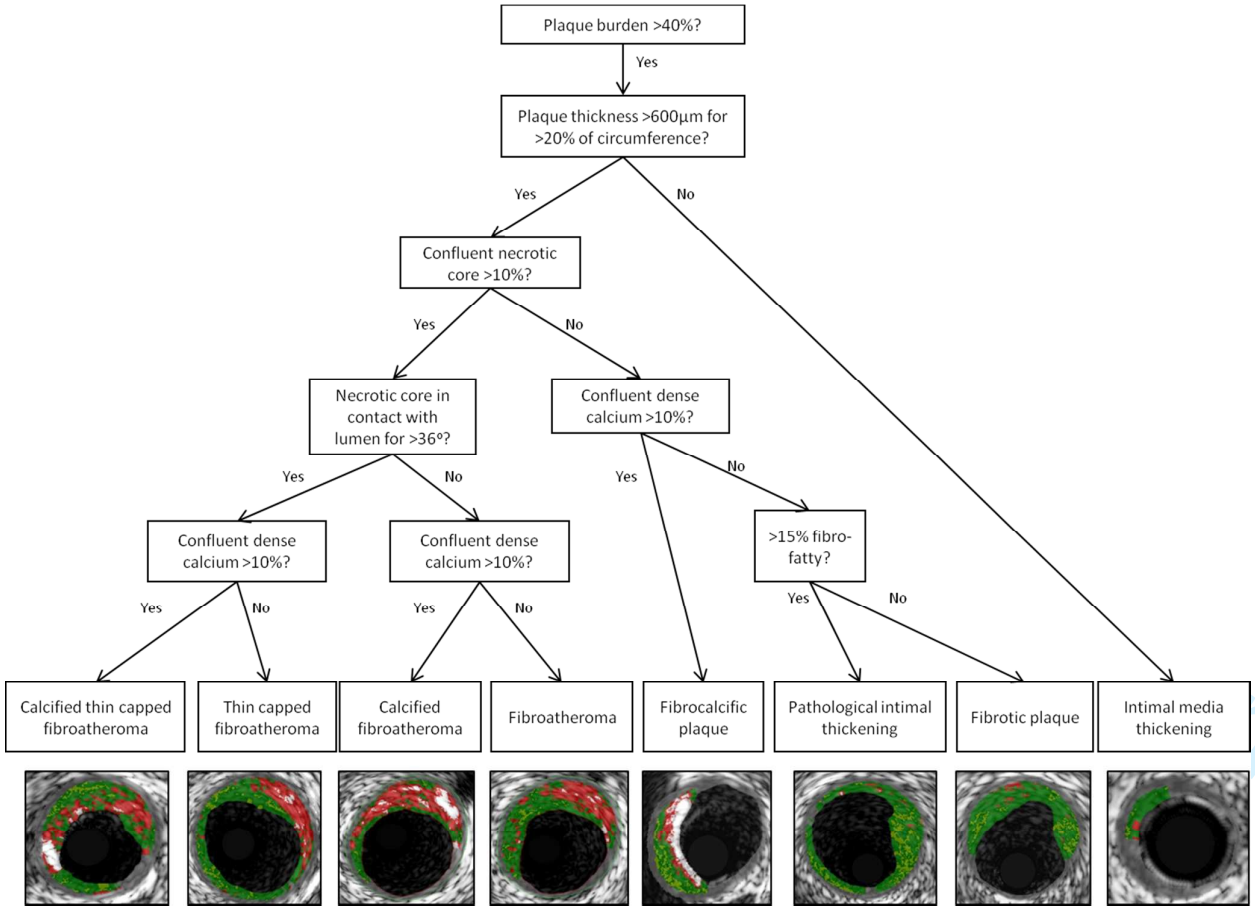
94. Cook NR, Ridker PM. Advances in measuring the effect of individual predictors of cardiovascular risk: the role of reclassification measures. Ann Intern Med 2009;**150**(11):795-802.
95. Picard RR, Cook RD. Cross-Validation of Regression-Models. Journal of the American Statistical Association 1984;**79**(387):575-83.
96. Iasonos A, Schrag D, Raj GV, et al. How to build and interpret a nomogram for cancer prognosis. J Clin Oncol 2008;**26**(8):1364-70.
97. World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. Jama 2013;**310**(20):2191-4.

Figure 1. ICON1 Study flow chart



UA- Unstable angina; NSTEMI - Non-ST-elevation acute coronary syndrome, PCI - percutaneous coronary intervention, VH-IVUS - virtual histology - intravascular ultrasound, OCT - optical coherence tomography, NYHA - New York Heart Association, CCS - Canadian Cardiovascular Society, MoCA - Montreal Cognitive Assessment

Figure 2. Decision tree for lesion classification on VH-IVUS with image examples



Adapted from Garcia-Garcia HM, Mintz GS, Lerman A, et al. Eurointervention. 2009;5(2):177-89

Figure 3. Study power

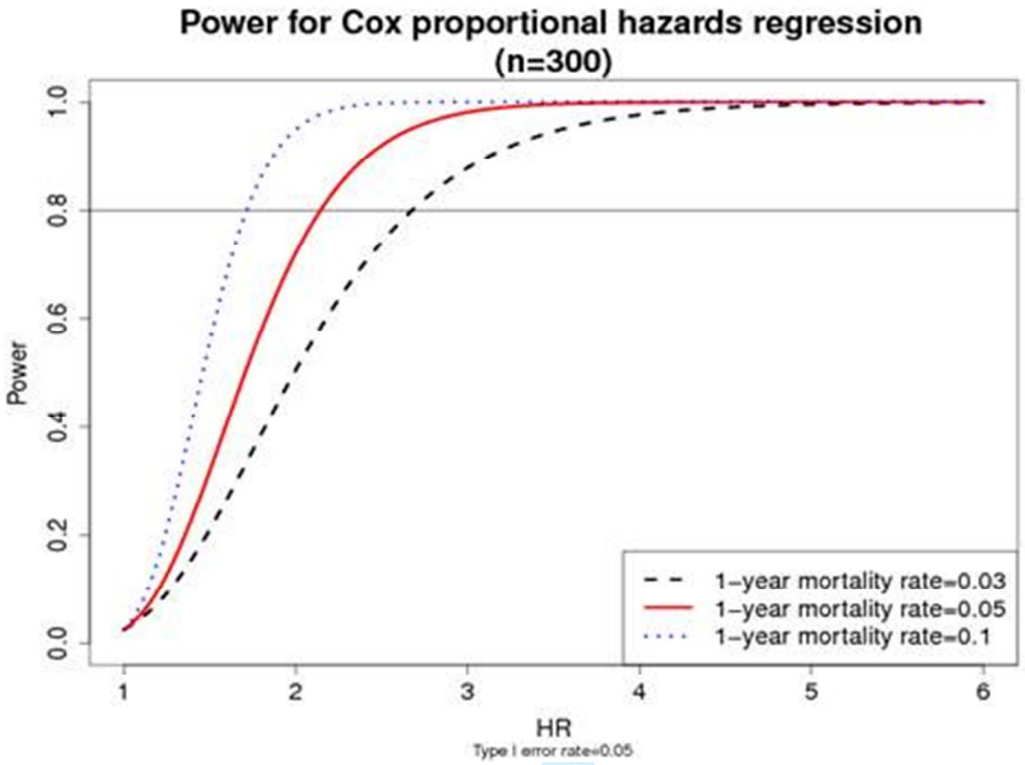


Table 1. Inclusion and exclusion criteria

Inclusion Criteria
≥ 75 years old
Non ST Elevation Acute Coronary Syndrome
Planned for CA or PCI
Exclusion Criteria
Cardiogenic shock
Primary Arrhythmias
Significant valvular heart disease
Malignancy with life expectancy <1 year
Active Infection
Urinary Tract Infection
Pneumonia
Sepsis
Alternative diagnosis after CA (excluded after consent)
Pulmonary embolism
Takotsubo cardiomyopathy
Myocarditis
Coronary vasospasm
Unable to consent
Known Dementia
Language barrier
Visual impairment
Lack of capacity

CA - coronary angiogram, PCI - percutaneous coronary intervention

Table 2. ICON1 Study Assessments

Biomarkers
High sensitive C-reactive protein
Vitamin D
Myeloperoxidase
Asymmetric dimethyl arginine
Eicosapentaenoic acid
Docosahexaenoic acid
Soluble p selectin
Cluster Differentiation 40
Lipoprotein-associated phospholipase A_2
Interleukin-6
Tumor Necrosis Factor-alpha
N-terminal prohormone Brain Natriuretic Peptide
MicroRNAs (miR-21-5p, miR-126-5p, miR-132-3p, miR-133a-3p, miR-142-3p, miR-150-5p, miR-208-3p, miR-223-3p, and miR-320a)
Peripheral Blood Mononuclear Cells
Telomere length
Telomerase activity
Intracoronary Imaging
Virtual Histology Intravascular Ultrasound
Optical Coherence Tomography
Cardiovascular Status
Arterial Stiffness
Peripheral Arterial Tonometry
Carotid Intima Media Thickness
Trans-thoracic Echocardiogram
Cardiac Symptoms
New York Heart Association Dyspnoea
Canadian Cardiovascular Society Angina
Frailty Assessment
Fried Frailty Index
Rockwood Frailty Index
Quality of Life
SF-36, Euro Qol - 5D (EQ-5D™)
Cognitive Status
Montreal Cognitive Assessment (MoCA©) *
Co-morbidity
Charlson Co-morbidity Index

MiR - micro RNA, MoCa - Montreal Cognitive Assessment, Qol - quality of life.
** Permission to use MoCA test obtained from MoCA© team (on behalf of Dr Ziad Nasreddine)*

Appendices

Appendix 1: Fried Frailty Index derived from Cardiovascular Health Study

Criterion	Frailty Status
Shrinking	**Frailty cut point:** **Baseline:** Self reported unintentional weight loss ≥10lb in previous year **Follow-up:** Unintentional weight loss ≥5% of previous year's body weight *OR* BMI <18.5kg/m^2
Physical endurance/energy	*Geriatric Depression Scale:* 1. *Do you feel full of energy?* 2. *During the last 4 weeks how often you rested in bed during day?* Response options: Every day, every week, once, not at all. **Frailty cut point:** No to 1 and every day or every week to 2.
Low physical activity	*Frequency of mildly energetic, moderately energetic and very energetic physical activity.* Response options: ≥3 times per week, 1-2 times per week, 1-3 times per month, hardly ever/never **Frailty cut point:** Hardly ever/never for very energetic physical activity AND for moderately energetic physical activity.
Weakness	Hand grip strength in Kg: GRIP-D hand held dynamometer, dominant hand, average of 3 measures. **Frailty cut point:** **Grip strength:** lowest 20% (by gender, body mass index) *Men* BMI ≤24 ≤29 BMI 24.1–26 ≤30 BMI 26.1–28 ≤30 BMI >28 ≤32 *Women* BMI ≤23 ≤17 BMI 23.1–26 ≤17.3 BMI 26.1–29 ≤18 BMI >29 ≤21
Slow walking speed	Walking time in seconds (usual pace) over 15 feet **Frailty cut point:** Slowest 20%, stratified by gender and median standing height. *Men* Height ≤173 cm ≥7 seconds Height >173 cm ≥6 seconds *Women* Height ≤159 cm ≥7 seconds Height >159 cm ≥6 seconds *OR* Time to complete "timed up and go test" (TUG) **Frailty cut point:** TUG time ≥19 seconds

Frail: ≥3 criteria present; **Intermediate or Pre-Frail:**1 or 2 criteria present; **Robust :** 0 criteria present

Adapted from Fried et al, Cardiovascular Health Study Collaborative Research G. Frailty in older adults: Evidence for a phenotype. The Journals of Gerontology. Series A, Biological sciences and medical sciences. 2001;56:M146-156.

Appendix 2: Rockwood Frailty Index derived from Canadian Study of Health and Aging

1	Very fit – robust, active, energetic, well motivated and fit; these people commonly exercise regularly and are in the most fit group for their age
2	Well – without active disease, but less fit than people in category 1.
3	Well, with treated co-morbid disease – disease symptoms are well controlled compared with those in category 4
4	Apparently vulnerable – although not frankly dependent, these people commonly complain of being "slowed up" or have disease symptoms.
5	Mildly frail – with limited dependence on others for instrumental activities of daily living
6	Moderately frail – help is needed with both instrumental and non-instrumental activities of daily living
7	Severely frail – completely dependent on others for the activities of daily living, or terminally ill.

Adapted from Rockwood et al, A global clinical measure of fitness and frailty in elderly people. Canadian Medical Association Journal 2005;173:489-495

Appendix 3: Definitions of outcome measures

Outcome	Definition
Death	Death from any cause Classified as cardiovascular or non-cardiovascular
Myocardial Infarction*	Defined as below
Type 1	Spontaneous myocardial infarction related to ischaemia due to a primary coronary event such as plaque erosion and/or rupture, fissuring, or dissection
Type 2	Myocardial infarction secondary to ischaemia due to either increased oxygen demand or decreased supply, e.g. coronary artery spasm, coronary embolism, anaemia, arrhythmias, hypertension, or hypotension
Type 3	Sudden unexpected cardiac death, including cardiac arrest, often with symptoms suggestive of myocardial ischaemia, accompanied by presumably new ST elevation, or new LBBB, or evidence of fresh thrombus in a coronary artery by angiography and/or at autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood
Type 4a	Myocardial infarction associated with PCI
Type 4b	Myocardial infarction associated with stent thrombosis as documented by angiography or at autopsy
Type 5	Myocardial infarction associated with CABG
Revascularisation	PCI to lesions not identified previously. CABG for new symptoms or complications of PCI Target lesion or target vessel revascularisation
Target Lesion Revascularisation	Re-interventions inside the implanted stent or within 5 mm proximally or distally
Target Vessel Revascularisation	Re-interventions in the same vessel by PCI or by CABG
Stroke	Stroke is 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. It is strongly recommended (but not required) that an imaging procedure such as CT scan or MRI be performed. Stroke will be further classified as ischaemic, haemorrhagic or type uncertain.
Heart Failure	Heart failure will be defined as a hospital admission with any of the following symptoms and signs: worsening breathlessness, fatigue, fluid overload, pulmonary oedema, elevated venous pressure and elevated NT-prohormone Brain Natriuretic Peptide. Confirmation of heart failure according to local expert judgement and evidence of impaired left ventricular function will be required for the event to be classified as heart failure.
Rehospitalisation	Repeat hospitalisation for any reason during follow up period
Adverse Event	Any untoward medical occurrence
Serious Adverse Event	Any untoward medical occurrence that: Results in death and is life-threatening. The term "life-threatening" in the definition of "serious adverse event" refers to an event that 1. Requires hospitalisation or prolongation of existing inpatient's hospitalisation; 2. Results in persistent or significant disability or incapacity.

PCI-Percutaneous Coronary Intervention, CABG-Coronary Artery Bypass Graft, CT-Computerised Tomography, MRI-Magnetic Resonance Imaging

** Adapted from Thygesan et al, Universal definition of myocardial infarction, European Heart Journal (2007) 28, 2525–2538*

Appendix 4: Bleeding Academic Research Consortium (BARC) definition for bleeding

Type 0	No 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. May include episodes leading to self-discontinuation of medical therapy by the patient without consulting a healthcare professional.
Type 2	Any overt, actionable sign of haemorrhage (e.g. more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for Type 3, 4 or 5 but does meet at least one of the following criteria: (1) requiring non-surgical, medical intervention by a healthcare professional, (2) leading to hospitalization or increased level of care, or (3) prompting evaluation.
Type 3a	Overt bleeding plus haemoglobin drop of 3 to <5g/dl* (provided haemoglobin drop is due to bleed) Any transfusion with overt bleeding
Type 3b	Overt bleeding plus haemoglobin drop ≥5g/dl* (provided haemoglobin drop is due to bleed) Cardiac tamponade Bleeding requiring surgical intervention for control (excluding dental/ nasal/ skin/ haemorrhoid) Bleeding requiring intravenous vasoactive agents
Type 3c	Intracranial haemorrhage (does not include micro-bleeds or haemorrhagic transformation, does include intraspinal) Subcategories confirmed by autopsy or imaging or lumbar puncture Intraocular bleed compromising vision
Type 4:	CABG-related bleeding Perioperative intracranial bleeding within 48 hours Reoperation following closure of sternotomy for the purpose of controlling bleeding Transfusion of ≥5 units of whole blood or packed red blood cells within a 48-hour period† Chest tube output ≥ 2 litres within a 24-hour period 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'.
Type 5a	Probable fatal bleeding; no autopsy or imaging confirmation, but clinically suspicious
Type 5b	Definite fatal bleeding; overt bleeding or autopsy or imaging confirmation

**Corrected for transfusion (1 U packed red blood cells or 1 U whole blood1 g/dL haemoglobin).*
†Cell saver products are not counted.

Adapted from Mehran et al, Standardized bleeding definitions for cardiovascular clinical trials: A consensus report from the bleeding academic research consortium. Circulation. 2011;123:2736-2747

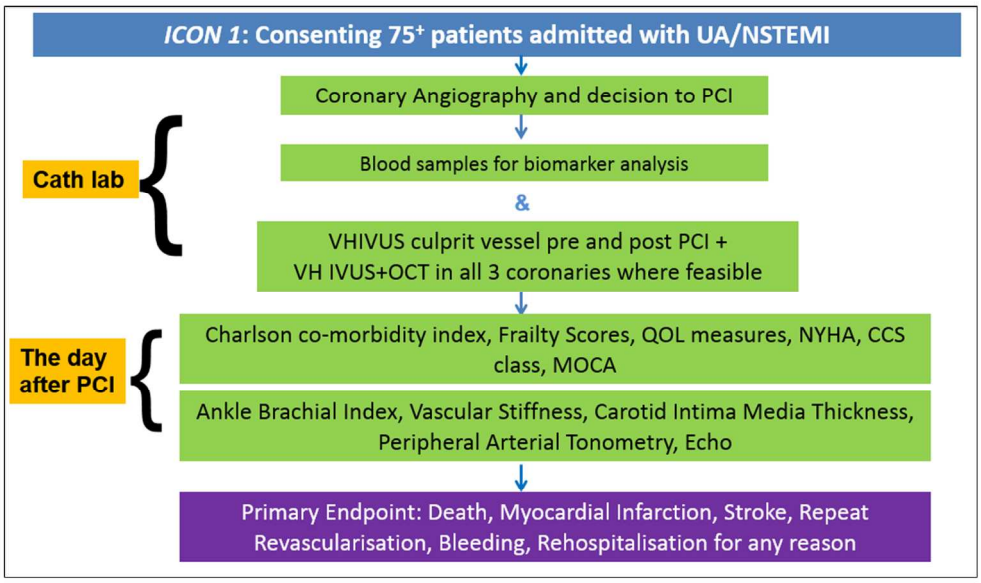


Figure 1. ICON1 Study flow chart \r\nUA- Unstable angina; NSTEMI - Non-ST-elevation acute coronary syndrome, PCI - percutaneous coronary intervention, VH-IVUS - virtual histology - intravascular ultrasound, OCT - optical coherence tomography, NYHA - New York Heart Association, CCS - Canadian Cardiovascular Society, MoCA - Montreal Cognitive Assessment.

Figure 1

254x150mm (300 x 300 DPI)

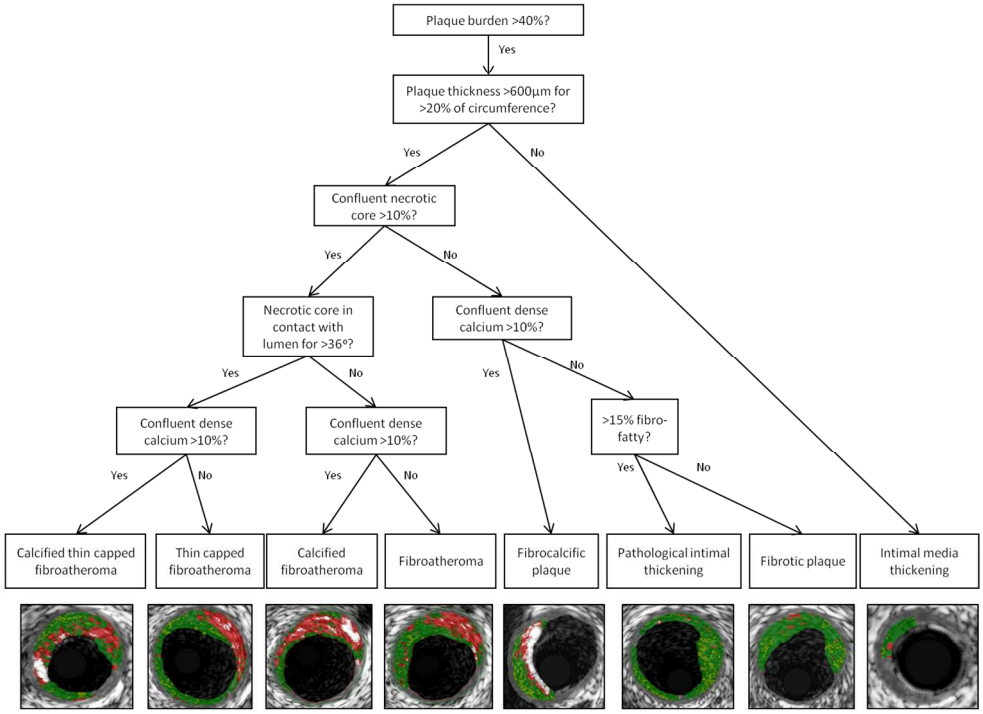


Figure 2. Decision tree for lesion classification on VH-IVUS with image examples\r\nAdapted from Garcia-Garcia HM, Mintz GS, Lerman A, et al. Eurointervention. 2009;5(2):177-89.
Figure 2
508x384mm (300 x 300 DPI)

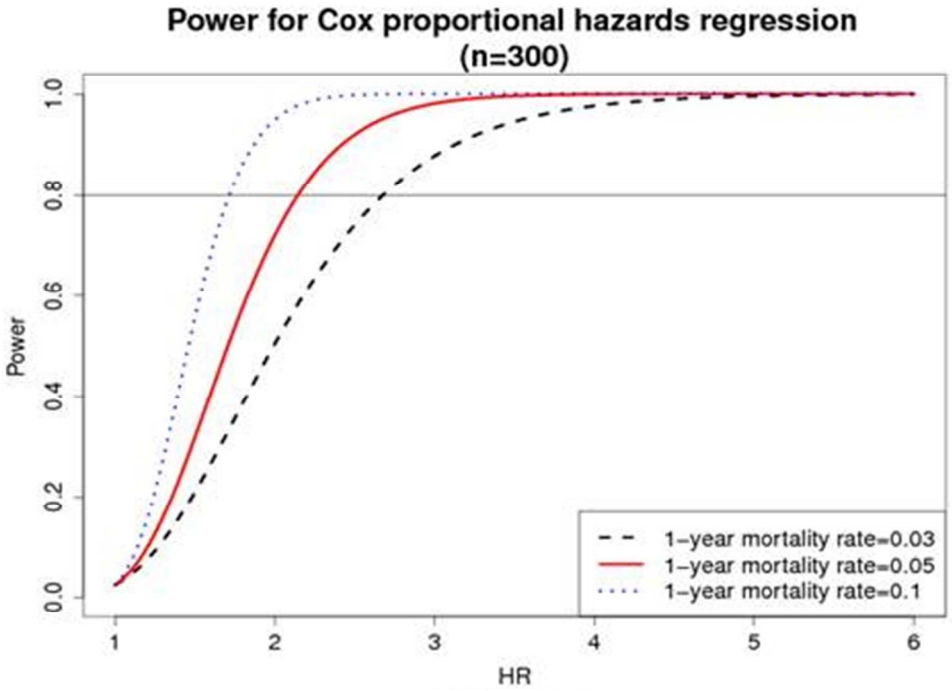


Figure 3. Study power\r\nA plot of power versus hazard ratios for sample size, n = 300 patients and 1-year mortality rates.
Figure 3
254x190mm (300 x 300 DPI)

Appendix 1: Fried Frailty Index derived from Cardiovascular Health Study

Criterion	Frailty Status
Shrinking	**Frailty cut point:** **Baseline:** Self reported unintentional weight loss ≥10lb in previous year **Follow-up:** Unintentional weight loss ≥5% of previous year's body weight *OR* BMI <18.5kg/m^2
Physical endurance/energy	*Geriatric Depression Scale:* 1. *Do you feel full of energy?* 2. *During the last 4 weeks how often you rested in bed during day?* Response options: Every day, every week, once, not at all. **Frailty cut point:** No to 1 and every day or every week to 2.
Low physical activity	*Frequency of mildly energetic, moderately energetic and very energetic physical activity.* Response options: ≥3 times per week, 1-2 times per week, 1-3 times per month, hardly ever/never **Frailty cut point:** Hardly ever/never for very energetic physical activity AND for moderately energetic physical activity.
Weakness	Hand grip strength in Kg: GRIP-D hand held dynamometer, dominant hand, average of 3 measures. **Frailty cut point:** **Grip strength:** lowest 20% (by gender, body mass index) *Men* BMI ≤24 ≤29 BMI 24.1–26 ≤30 BMI 26.1–28 ≤30 BMI >28 ≤32 *Women* BMI ≤23 ≤17 BMI 23.1–26 ≤17.3 BMI 26.1–29 ≤18 BMI >29 ≤21
Slow walking speed	Walking time in seconds (usual pace) over 15 feet **Frailty cut point:** Slowest 20%, stratified by gender and median standing height. *Men* Height ≤173 cm ≥7 seconds Height >173 cm ≥6 seconds *Women* Height ≤159 cm ≥7 seconds Height >159 cm ≥6 seconds *OR* Time to complete "timed up and go test" (TUG) **Frailty cut point:** TUG time ≥19 seconds

Frail: ≥3 criteria present; **Intermediate or Pre-Frail:**1 or 2 criteria present; **Robust :** 0 criteria present

Adapted from Fried et al, Cardiovascular Health Study Collaborative Research G. Frailty in older adults: Evidence for a phenotype. The Journals of Gerontology. Series A, Biological sciences and medical sciences. 2001;56:M146-156.

Appendix 2: Rockwood Frailty Index derived from Canadian Study of Health and Aging

1	Very fit – robust, active, energetic, well-motivated and fit; these people commonly exercise regularly and are in the most fit group for their age
2	Well – without active disease, but less fit than people in category 1.
3	Well, with treated co-morbid disease – disease symptoms are well controlled compared with those in category 4
4	Apparently vulnerable – although not frankly dependent, these people commonly complain of being "slowed up" or have disease symptoms.
5	Mildly frail – with limited dependence on others for instrumental activities of daily living
6	Moderately frail – help is needed with both instrumental and non-instrumental activities of daily living
7	Severely frail – completely dependent on others for the activities of daily living, or terminally ill.

Adapted from Rockwood et al, A global clinical measure of fitness and frailty in elderly people. Canadian Medical Association Journal 2005;173:489-495

Appendix 3: Definitions of outcome measures

Outcome	Definition
Death	Death from any cause Classified as cardiovascular or non-cardiovascular
Myocardial Infarction*	Defined as below
Type 1	Spontaneous myocardial infarction related to ischaemia due to a primary coronary event such as plaque erosion and/or rupture, fissuring, or dissection
Type 2	Myocardial infarction secondary to ischaemia due to either increased oxygen demand or decreased supply, e.g. coronary artery spasm, coronary embolism, anaemia, arrhythmias, hypertension, or hypotension
Type 3	Sudden unexpected cardiac death, including cardiac arrest, often with symptoms suggestive of myocardial ischaemia, accompanied by presumably new ST elevation, or new LBBB, or evidence of fresh thrombus in a coronary artery by angiography and/or at autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood
Type 4a	Myocardial infarction associated with PCI
Type 4b	Myocardial infarction associated with stent thrombosis as documented by angiography or at autopsy
Type 5	Myocardial infarction associated with CABG
Revascularisation	PCI to lesions not identified previously. CABG for new symptoms or complications of PCI Target lesion or target vessel revascularisation
Target Lesion Revascularisation	Re-interventions inside the implanted stent or within 5 mm proximally or distally
Target Vessel Revascularisation	Re-interventions in the same vessel by PCI or by CABG
Stroke	Stroke is 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. It is strongly recommended (but not required) that an imaging procedure such as CT scan or MRI be performed. Stroke will be further classified as ischaemic, haemorrhagic or type uncertain.

Heart Failure	Heart failure will be defined as a hospital admission with any of the following symptoms and signs: worsening breathlessness, fatigue, fluid overload, pulmonary oedema, elevated venous pressure and elevated NT-prohormone Brain Natriuretic Peptide. Confirmation of heart failure according to local expert judgement and evidence of impaired left ventricular function will be required for the event to be classified as heart failure.
Rehospitalisation	Repeat hospitalisation for any reason during follow up period
Adverse Event	Any untoward medical occurrence
Serious Adverse Event	Any untoward medical occurrence that: Results in death and is life-threatening. The term "life-threatening" in the definition of "serious adverse event" refers to an event that 1. Requires hospitalisation or prolongation of existing inpatient's hospitalisation; 2. Results in persistent or significant disability or incapacity.

PCI-Percutaneous Coronary Intervention, CABG-Coronary Artery Bypass Graft, CT-Computerised Tomography, MRI-Magnetic Resonance Imaging

** Adapted from Thygesan et al, Universal definition of myocardial infarction, European Heart Journal (2007) 28, 2525–2538*

Appendix 4: Bleeding Academic Research Consortium (BARC) definition for bleeding

Type 0	No 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. May include episodes leading to self-discontinuation of medical therapy by the patient without consulting a healthcare professional.
Type 2	Any overt, actionable sign of haemorrhage (e.g. more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for Type 3, 4 or 5 but does meet at least one of the following criteria: (1) requiring non-surgical, medical intervention by a healthcare professional, (2) leading to hospitalization or increased level of care, or (3) prompting evaluation.
Type 3a	Overt bleeding plus haemoglobin drop of 3 to <5g/dl* (provided haemoglobin drop is due to bleed) Any transfusion with overt bleeding
Type 3b	Overt bleeding plus haemoglobin drop ≥5g/dl* (provided haemoglobin drop is due to bleed) Cardiac tamponade Bleeding requiring surgical intervention for control (excluding dental/ nasal/ skin/ haemorrhoid) Bleeding requiring intravenous vasoactive agents
Type 3c	Intracranial haemorrhage (does not include micro-bleeds or haemorrhagic transformation, does include intraspinal) Subcategories confirmed by autopsy or imaging or lumbar puncture Intraocular bleed compromising vision
Type 4:	CABG-related bleeding Perioperative intracranial bleeding within 48 hours Reoperation following closure of sternotomy for the purpose of controlling bleeding Transfusion of ≥5 units of whole blood or packed red blood cells within a 48-hour period† Chest tube output ≥ 2 litres within a 24-hour period 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'.
Type 5a	Probable fatal bleeding; no autopsy or imaging confirmation, but clinically suspicious
Type 5b	Definite fatal bleeding; overt bleeding or autopsy or imaging confirmation

**Corrected for transfusion (1 U packed red blood cells or 1 U whole blood1 g/dL haemoglobin).*
†Cell saver products are not counted.

Adapted from Mehran et al, Standardized bleeding definitions for cardiovascular clinical trials: A consensus report from the bleeding academic research consortium. Circulation. 2011;123:2736-2747