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Dual ACS

Duration of Dual Anti-Platelet Therapy in
Acute Coronary Syndrome
The DUAL-ACS Trial

**Statistical Analysis Plan**

# CONFIDENTIAL

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# Table of Contents

# List of Abbreviations for SAP and programming

| Abbreviation | Full name |
|---|---|
| ACS | Acute coronary syndrome |
| CABG | Coronary artery bypass grafting |
| CHD | Coronary heart disease |
| CHF | Congestive heart failure |
| CI | Confidence interval |
| CIF | Cumulative incidence function |
| ECTU | Edinburgh clinical trials unit |
| GFR | Glomerular filtration rate |
| HDL | High density lipoprotein |
| ICA | Invasive coronary angiogram |
| IHD | Ischaemic heart disease |
| IPD | Individual participant data |
| IQR | Interquartile range |
| ITT | Intention to treat |
| LDL | Low density lipoprotein |
| MI | Myocardial infarction |
| NZ | New Zealand |
| PBPP | Public benefit and privacy panel |
| PCI | Percutaneous coronary intervention |
| RMST | Restricted mean survival time |
| SD | Standard deviation |
| SOP | Standard operating procedure |
| TCL | Total cholesterol |
| TRE | Trusted research environment |
| TRI | Triglycerides |
| UK | United Kingdom |

# 1. Introduction

This document details the criteria to be used for the definitions of the analysis populations and the statistical methodology for analysis of the Dual-ACS trial, a prospective multicentre national open-label randomised controlled trial comparing the duration of dual antiplatelet therapy. The aim is to randomise 18,318 patients with type I myocardial infarction (MI) to 12 or 3 months of dual antiplatelet therapy in a 1:1 ratio. Randomisation is by permuted-blocks with a level of stratification for each of the following groups of patients:

(i) conservative non-invasive strategy (invasive coronary angiography is not planned),
(ii) invasive coronary angiography is planned but has not yet occurred,
(iii) an invasive coronary angiogram has been performed and the patient has been referred or undergone coronary artery bypass grafting (CABG) surgery,
(iv) an invasive coronary angiogram has been performed and the patient has had at least one drug eluting stent implanted,
(v) an invasive coronary angiogram has been performed and the patient has had only bare metal stents implanted,
(vi) an invasive coronary angiogram has been performed and the patient is to receive medical management only.

Recruitment in the United Kingdom (UK) was halted after 4,576 patients because the funder felt the trial was no longer deliverable due to the challenging environment of the COVID-19 pandemic. The statistical analysis will include the patients recruited in the UK and as many international patients who have completed 15 months follow-up at the time of analysis.

This document has been compiled according to the Edinburgh Clinical Trials Unit (ECTU) standard operating procedure (SOP) "ECTU_SOP_ST_04 Statistical Analysis Plans v7.0" and has been written based on information contained in the study protocol version 6.0, dated 22nd July 2022.

# 2. Statistical Methods section from the protocol

*"For the primary outcome (all-cause mortality) we will compare time-to-event in a Cox regression model, stratifying by country and centre to account for clustering of participants, and adjusting for cardiac history (stratification factor in randomisation). For secondary outcomes of non-cardiovascular mortality and bleeding death, we will similarly estimate cause-specific hazard ratios, censoring for competing causes of death. All analyses will be by intention-to-treat.*

*It is highly likely that baseline characteristics will have a major influence on the overall clinical benefits and risks [Steg et al, 2011]. We will explore efficacy and safety outcomes in the 4 pre-specified and stratified cohorts nested within the trial: (i) medically managed, (ii) percutaneous*

*coronary intervention with bare metal stent, (iii) percutaneous coronary intervention with drug-eluting stent, and (iv) coronary artery bypass graft surgery.*

*In a sensitivity analysis, we will consider a two-stage individual participant data (IPD) meta-analysis where the IPD from each country are analysed separately then combined by an appropriate fixed-effect or random effects meta-analysis model [Burke et al, 2017].*

*The statistical methods will be documented in full in a detailed statistical analysis plan. The methods used will take into account the early stopping of the trial, and the limited numbers of events that will be available for analysis. A composite outcome of non-fatal bleeding and all-cause mortality will be explored."*

## 3. Overall Statistical Principles

All analyses will be based on the intention to treat (ITT) principle as far as possible. Patients will be analysed according to their allocation intervention, irrespective of whether the patient's actual management complied with the allocated intervention.

In general terms, categorical data will be presented using counts and percentages, whilst continuous variables will be presented using the mean, median, standard deviation (SD), minimum, maximum, inter quartile range (IQR) and number of patients with an observation (n).

All applicable statistical tests will be 2-sided and presented with 95% (2-sided) confidence intervals (CIs) and a 5% significance level.

Where there is missing data for an outcome variable, in the first instance, those records will be removed from any formal statistical analysis relating to that outcome variable, unless otherwise specified. A sensitivity analysis using imputation of missing values will be considered only if the proportion of cases with missing values is sufficiently large. In tabulations, numbers of missing observations will be provided, but percentages will not include them.

Distributional assumptions underlying the statistical analyses will be assessed by visual inspection of residual plots. Normality will be examined by normal probability plots. If the distributional assumptions for the parametric approach are not satisfied, further data transformation (to alleviate substantial skewness (i.e. log-transformation) or to stabilise the variance), or other suitable methods will be considered. This will be documented in the statistical results report together with the reasoning supporting the action taken, if applicable.

All analyses and data manipulations will be performed using the latest available version of SAS software within the Trusted Research Environment (TRE).

# 4. List of Analyses

## 4.1 ITT analysis population

The ITT analysis population will include patients who have been randomised into the Dual ACS trial in the UK and New Zealand (NZ) and for whom outcome data are available. Those who subsequently became ineligible after a diagnosis other than Type 1 myocardial infarction (MI) and withdrawn from the trial will be excluded[1].

## 4.2 Recruitment and retention

Numbers required to complete a CONSORT flow diagram will be provided. The statistical report will tabulate the number of patients consented, randomised, adherent and completed follow-up overall and by treatment group. The number of patients discontinued early from the study will be summarised by reason for withdrawal and treatment.

## 4.3 Baseline data

No formal statistical testing will be performed comparing characteristics at baseline. The following will be presented and summarised by treatment group and overall:

- Cardiac history (covariate used for stratifying at randomisation)
    - (i) conservative non-invasive strategy (invasive coronary angiography is not planned)
    - (ii) invasive coronary angiography is planned but has not yet occurred*
    - (iii) an invasive coronary angiogram has been performed and the patient has been referred or undergone CABG surgery
    - (iv) an invasive coronary angiogram has been performed and the patient has had at least one drug eluting stent implanted
    - (v) an invasive coronary angiogram has been performed and the patient has had only bare metal stents implanted
    - (vi) an invasive coronary angiogram has been performed and the patient is to receive medical management only

  *Where possible, it will be summarised which group the participants belong to following their angiogram based on definitions in appendix A.
- Gender and age at randomisation
- Time from date of MI to randomisation
- Derived from data linkage from the participant's electronic health records (appendix B).
    - Index of multiple deprivation
    - Ethnicity
    - Smoking history

[1] The protocol refers to "If there is no substantial heterogeneity in outcome between these two groups, then they can be included in the analysis and further increase the power". Due to recruitment being halted early and the small numbers in these groups, this will be explored in subgroup analyses only and all participants will be included in the ITT analysis population.

- Hypertension
- Diabetes Mellitus
- Hyperlipidaemia
- Ischaemic heart disease
- Myocardial infarction
- Percutaneous coronary intervention
- Coronary artery bypass grafting
- Heart failure
- Ischaemic stroke
- Haemorrhagic stroke
- Chronic kidney disease
- Medications
    - Aspirin
    - Clopidogrel
    - Prasugrel
    - Ticagrelor
    - Lipid lowering therapy
    - Beta-blocker
    - Angiotensin converting enzyme inhibitor or angiotensin receptor blockers
    - Oral anticoagulants

A further descriptive summary will explore any association between the COVID-19 pandemic and UK participant characteristics. The baseline characteristics summary will be stratified by date of lockdown for UK participants: randomisations occurring up to and including 23 March 2020 and those occurring after 23 March 2020.

### 4.4 Adherence to allocated treatment duration

Adherence data will be summarised, where available.

The average duration of antiplatelet therapy with be summarised descriptively overall and by treatment group.

Adherence will be defined as follows:

- Allocated to 3 months:
  A record of prescription of 90% or greater for the first 3 months and 10% or less for months 4-12.
- Allocated to 12 months
  A record of prescription of 90% or greater for the first 12 months and 10% or less for months 13-15.

Adherence will be reported descriptively overall and by treatment group.
Note the first month's prescription will be made in hospital and there will be no record of it on routinely collected prescribing data. Therefore participants will be assumed to be adherent for the first month following their date of MI.

### 4.5 Primary outcome analysis

The primary outcome event is all-cause mortality (appendix C). This will be analysed as time to first outcome event during follow-up from date of the index myocardial infarction. Follow-up will be censored at 15 months from date of index MI[2]. The number and proportion of participants with an event will be summarised overall and by treatment group.

The primary analysis will compare the time to event outcome between groups using a Cox regression model, stratifying by country[3] to account for clustering of participants, and adjusting for cardiac history as a fixed effect (stratification factor in randomisation). The primary result will be presented as an adjusted hazard ratio with its corresponding 95% CI and p-value.

To aid interpretation, the restricted mean survival time (RMST)[1] at 15 months and the difference between groups will be estimated.

Results from a Cox regression model stratifying by country only, will also be presented to support the findings of the principal analyses.

The standard Kaplan-Meier estimate of survival of the two groups will be presented separately for each country. Event rates and absolute difference at 15 months will be estimated from the Kaplan-Meier analysis.

The proportional hazards assumption will be assessed graphically and by including a non-proportional treatment effect in the model. If there is strong evidence of violation of this assumption and the number of events is sufficient to assess the assumption adequately, a flexible parametric model will be fitted (assigning 3 degrees of freedom to the baseline distribution) including a time-dependent treatment effect (1 degrees of freedom). The time-dependent hazard ratio and 95% CI will be presented graphically over time. The RMST at 15 months and the difference between groups will be estimated. The sensitivity of the results to the degree of flexibility in the baseline distribution and the time-dependent treatment effect will be explored. Under non-proportional hazards, the primary analysis will be the logistic regression specified in section 4.5.1.

#### 4.5.1 Secondary analyses

The comparison between the groups is considering differing lengths of the same treatment; this inherently causes the potential violation of the proportional hazards' assumption. Therefore, in a secondary analysis of the primary outcome all-cause mortality at 15 months from date of MI will be compared between groups using a logistic regression model stratifying by country and adjusting for cardiac history. Results will be presented as an adjusted odds ratio with corresponding 95% CI and p-value.

[2] Note that we will not censor at date of withdrawal, as we will not have outcome data collected up to the point of withdrawal and therefore withdrawn participants will be excluded from the analysis.
[3] The protocol refers to stratifying by centre but due recruitment being halted early and the potential for small number of outcome events per centre, the analysis will only adjust for country and the effect of centre will be explored in a sensitivity analysis.

### 4.5.2 Sensitivity analyses

Two-stage individual participant data (IPD) meta-analysis

In a sensitivity analysis, we will consider a two-stage individual participant data (IPD) meta-analysis[2]. The first stage will analyse the IPD from each country separately as per the analysis model described above in section 4.5. In the second stage, we will combine the individual estimates using a fixed effect inverse-weighted meta-analysis model of adjusted log hazard ratios. The results will be presented as adjusted HRs with 95% confidence intervals for each study and the pooled estimate. A random effects (DerSimonian and Laird method) model will also be estimated to check the robustness of the findings (irrespective of the degree of heterogeneity).

Landmark analysis

Both randomised groups receive the same treatment for the first 3 months and therefore would expect, apart from random chance, to observe no difference in outcomes. In a second sensitivity analysis, we will therefore perform a landmark analysis including only those participants who have survived at 3 months from date of MI. The analysis will be performed as per the analysis model described above in section 4.5

Adjusting for centre

In a third sensitivity analysis, the analysis model specified in section 4.5 will also include stratifying by centre to determine the robustness of the results. In the event of issues with model fitting, this will be performed for Scottish participants only which comprise most randomised participants.

### 4.5.3 Subgroup analysis

A priori sub-groups for the primary outcome will be explored as follows:

i. medically managed (including conservative non-invasive strategy)
ii. percutaneous coronary intervention with bare metal stent
iii. percutaneous coronary intervention with drug-eluting stent
iv. coronary artery bypass graft surgery.

If the number of events is sufficient, these analyses will be performed by including an interaction term between treatment group and the covariate in the Cox proportional hazards regression model described in Section 4.5 above. Otherwise, no formal analyses will be undertaken and summaries only of primary outcome events will be presented for each of the subgroups, split by treatment group.

In the event of problems due to small numbers in the subgroups, the groups will be combined as follows: any stent (combining bare metal and drug-eluting stents); and any intervention (combining bare metal and drug-eluting stents and coronary artery bypass graft surgery).

The subgroup analysis will be performed with and without those with a cardiac history of 'invasive coronary angiography is planned but has not yet occurred'. They will be included in the group to which they belong following their angiogram based on definitions in appendix A.

#### 4.5.4 Assessing the impact of COVID-19

The impact of COVID-19 is expected to be minimal due to the study design. Study-related procedures encompass a single 30-minute contact with the patient who is already in a hospital ward or attending an out-patient facility. All follow up is through routinely collected health record data and the drugs are prescribed as part of standard of care. The primary outcome of all-cause mortality is objective and should not be influenced by lockdown restrictions.

An exploratory analysis will summarise descriptively the primary outcome by treatment group and stratified by the date of the lockdown for UK participants: randomisations occurring up to and including 23 March 2020 versus those occurring after 23 March 2020.

### 4.6 Secondary outcomes

The interpretation of trial findings for secondary outcomes will focus on the effect size and 95% CI. No formal adjustment will be made to significance levels to allow for multiplicity.

For each of the following secondary outcomes (appendix C), events are defined as the time to first outcome event during follow-up from date of the index myocardial infarction. Follow-up will be censored at competing causes of death or 15 months from date of MI, whichever occurs first.

Efficacy

- Cardiovascular death and non-fatal myocardial infarction
- Cardiovascular mortality (cardiac and non-cardiac)
- Myocardial infarction (fatal and non-fatal)
- Stent thrombosis
- Coronary revascularisation
- Thrombotic stroke

Safety

- Non-cardiovascular death (including fatal bleeding) and major non-fatal bleeding
- Non-cardiovascular death (including fatal bleeding)
- Major fatal and non-fatal bleeding
- Hospitalisation for bleeding
- Intracranial haemorrhage
- Gastrointestinal bleeding

The analysis will follow that specified for the primary outcome in section 4.5. The number and proportions of participants with an event for individual components of the secondary outcomes will also be reported alongside the composite.

#### 4.6.1 Sensitivity analyses

Competing risk of death

To take into account the possibility of a competing risk of death, a Fine and Gray[3] proportional sub-distribution hazards regression model will be used to take into account the competing risk of death to provide reassurance about the robustness of the analysis. The effect of the randomised intervention will be presented by the sub-distribution hazard ratio and 95% confidence interval. The cumulative incidence function (CIF) obtained from the Fine-Gray model will be plotted separately for each intervention; the median time to event and its 95% CI will be reported by intervention group. The absolute risk difference (and its 95% CI) will also be reported at the median time to event.

Diagnostic position

The analysis of secondary safety outcomes, will consider the occurrence of an event if the diagnostic codes, as defined in Appendix C, occur in any diagnostic position.

### 4.7 Other outcomes

The following binary (yes/no) outcomes[4] (appendix C) will be summarised descriptively, where available.

- Blood Transfusion
- Iron therapy

### 4.8 Additional outcomes

We will explore the composite outcome of non-fatal bleeding and all-cause mortality. This will be analysed using the same approach as for the primary outcome in section 4.5. The number and proportions of participants with an event for the individual components of the outcome will be reported alongside the composite.

### 4.9 Extended follow-up

The analyses of the primary and secondary outcomes will be repeated censoring at the date of last available follow-up.

[4] The Haemoglobin outcome in the protocol will not be analysed, as the data is not nationally linked.

## 5. Validation and QC

The following will be done by a second statistician:

1. The code will be checked and run to ensure results are as stated
2. Check of data fidelity from raw data to SAS data files (random selection)
3. Check treatment allocation consistent between UK and NZ datasets
4. Check of ICD10/OPCS4 (or equivalents codes) in SMR01 (or equivalent datasets) map to the study SAP
5. The statistical report will be read and sense-checked.

## 6. Data sharing

Data will be stored inside a Trusted Research Environment (TRE) managed by AIMES on behalf of ECTU for 12 years. Access to the data needs to be approved, there are no data sharing agreements, protocols or contracts in place or planned.

## 7. References

1. Royston, P. and M.K. Parmar, *The use of restricted mean survival time to estimate the treatment effect in randomized clinical trials when the proportional hazards assumption is in doubt.* Stat Med, 2011. **30**(19): p. 2409-21.
2. Burke, D.L., J. Ensor, and R.D. Riley, *Meta-analysis using individual participant data: one-stage and two-stage approaches, and why they may differ.* Statistics in Medicine, 2017. **36**(5): p. 855-875.
3. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of competing risks in survival analysis. J Am Stat Assoc. 1999; 94:496–509. https://doi.org/10.2307/2670170

**Appendix A**

Operation code identified following date of MI in ANY position. It will be assumed those with none of the following codes recorded will be classed as medically managed.

Data sources: Scotland: SMR00/SMR01 England: Hospital Episode Statistics

| Code | Procedure | Cardiac history group |
|---|---|---|
| **OPCS4 K75.1** | Percutaneous transluminal balloon angioplasty and insertion of 1–2 drug-eluting stents into coronary artery | **Coronary angioplasty with drug eluting stent** |
| **OPCS4 K75.2** | Percutaneous transluminal balloon angioplasty and insertion of 3 , more drug-eluting stents into coronary artery | |
| **OPCS4 K75.3** | Percutaneous transluminal balloon angioplasty and insertion of 1–2 stents into coronary artery (stent not specified) | **Coronary angioplasty – stent type not specified** |
| **OPCS4 K75.4** | Percutaneous transluminal balloon angioplasty and insertion of 3 , more stents into coronary artery (stent not specified) | |
| **OPCS4 K75.3** , **K75.4, Y14.1** , **Y14.2** , **Y14.3** | Percutaneous transluminal balloon angioplasty and insertion of stent (other than drug-eluting stent). | **Coronary angioplasty with bare metal stent** |

| Code | Procedure | Cardiac history group |
|---|---|---|
| **OPCS4 K40** | Saphenous vein graft of coronary artery | **Coronary artery bypass graft surgery** |
| **OPCS4 K41** | Other autograft replacement of coronary artery | |
| **OPCS4 K42** | Allograft replacement of coronary artery | |
| **OPCS4 K43** | Prosthetic replacement of coronary artery | |
| **OPCS4 K44** | Other replacement of coronary artery | |
| **OPCS4 K45** | Connection of thoracic artery to coronary artery | |
| **OPCS4 K46** | Other bypass of coronary artery | |
| **OPCS4 K48** | Other open operation on coronary artery | |

**Appendix B**

Baseline characteristics defined as follows using the following codes in ANY position in the 10 years prior to the date of index MI (or date of admission for index MI). If code is not identified in any admissions then they will be assumed to not have the variable of interest.

Data sources
Scotland: SMR00 / SMR01 / Prescribing Information System / SCI-Diabetes
England: Hospital Episode Statistics / Medicines dispensed in Primary Care (NHSBSA data)

| **Variable** | ***Code (ICD-10 , OPCS4)*** |
|---|---|
| IMD | Index of Multiple Deprivation |
| Ethnicity | Ethnicity |
| **Cardiovascular risk factors** | |
| Smoking history | Z87.891x (including Z812 / Z720/T652/F17x) |
| Hypertension | Previously prescribed AntiHypertensiveTherapy<br><br>Approved drug names: ATENOLOL, ATENOLOL WITH NIFEDIPIN, BISOPROLOL FUMARATE, CARVEDILOL, LABETALOL HYDROCHL, AMLODIPINE AND VALSARTAN, CANDESARTAN CILEXETIL, CAPTOPRIL, CO-ZIDOCAPT, ENALAPRIL MALEATE, ENALAPRIL MALEATE WITH, EPROSARTAN MESILATE, FOSINOPRIL, IRBESARTAN, IRBESARTAN AND HYDROCHL, LISINOPRIL, LISINOPRIL AND HYDROCHL, LOSARTAN POTASSIUM, LOSARTAN WITH HYDROCHL, OLMESARTAN MEDOXOMIL, PERINDOPRIL, PERINDOPRIL WITH AMLODI, PERINDOPRIL WITH INDAPA, QUINAPRIL, QUINAPRIL HYDROCHL, RAMIPRIL, TELMISARTAN, TELMISARTAN AND HYDROCH, TRANDOLAPRIL, VALSARTAN, VALSARTAN AND HYDROCHL, AMLODIPINE, FELODIPINE, LERCANIDIPINE, DOXAZOSIN, BENDROFLUMETHIAZIDE. |
| Diabetes Mellitus | E10x, E11x, E12x, E13x, E14x, |

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|---|---|
| | Previously prescribed AntiHyperglycaemics<br><br>Approved drug names: METF,MIN, REPAGLINIDE, PIOGLITAZONE, ROSIGLITAZONE, SITAGLIPTIN, SAXAGLIPTIN, VILDAGLIPTIN, ALOGLIPTIN, LINAGLIPTIN, GLIPIZIDE, DAPAGLIFLOZIN, EMPAGLIFLOZIN, CANAGLIFLOZIN, GLIBENCLAMIDE, REPAGLINIDE, TOLBUTAMIDE, EXENATIDE, LIRAGLUTIDE, SEMAGLUTIDE, INSULIN |
| Hyperlipidaemia | Previously prescribed LipidLoweringTherapy<br><br>Approved drug names: ATORVASTATIN, BEZAFIBRATE, CIPROFIBRATE, EZETIMIBE, EZETIMIBE AND SIMVASTATIN, FENOFIBRATE, FLUVASTATIN, GEMFIBROZIL, PRAVASTATIN, ROSUVASTATIN, SIMVASTATIN |
| **Other medical history** | |
| Ischaemic heart disease | I20x, I21x, I22x, I23x, I24x, I25x, |
| Myocardial infarction | I21x, I22x, |
| Percutaneous coronary intervention | Z98.61x<br><br>OPCS4 codes:<br><br>K50x, K75x, K49x |
| Coronary artery bypass grafting | Z95.1x,<br><br>OPCS4 codes<br><br>K40x, K41x, K42x, K43x, K44x, K45x, K46x, K47x, K48x |
| Heart failure | I50x |

| | |
|---|---|
| Ischaemic stroke | I63x |
| Haemorrhagic stroke | I60x, I61x, I62x |
| Chronic kidney disease | N18x, N19x |
| **Medications at presentation** | |
| Aspirin | Previously prescribed Aspirin<br>Approved drug names: ASPIRIN |
| Clopidogrel | Previously prescribed Clopidogrel<br>Approved drug names: Clopidogrel |
| Prasugrel | Previously prescribed Prasugrel<br>Approved drug names: Prasugrel |
| Ticagrel | Previously prescribed Ticagrel,<br>Approved drug names: Ticagrel, |
| Lipid lowering therapy | Previously prescribed LipidLoweringTherapy<br>Approved drug names: ATORVASTATIN, BEZAFIBRATE, CIPROFIBRATE, EZETIMIBE, EZETIMIBE AND SIMVASTAT, FENOFIBRATE, FLUVASTATIN, GEMFIBROZIL, PRAVASTATIN, ROSUVASTATIN, SIMVASTATIN |
| Beta-blocker | Previously prescribed BetaBlocker<br>Approved drug names: ACEBUTOLOL, ATENOLOL, ATENOLOL WITH NIFEDIPIN, BISOPROLOL FUMARATE, CARVEDILOL, CELIPROLOL HYDROCHL, CO-TENIDONE, LABETALOL HYDROCHL, METOPROLOL TARTRATE, NADOLOL, NEBIVOLOL, OXPRENOLOL HYDROCHL, PINDOLOL, PROPRANOLOL HYDROCHL, TIMOLOL MALEATE |

| | |
|---|---|
| Angiotensin converting enzyme inhibitor , angiotensin receptor blockers | Previously prescribed ACEInhibitorARB<br><br>Approved drug names: AMLODIPINE AND VALSARTAN, CANDESARTAN CILEXETIL, CAPTOPRIL, CO-ZIDOCAPT, ENALAPRIL MALEATE, ENALAPRIL MALEATE WITH, EPROSARTAN MESILATE, FOSINOPRIL, IRBESARTAN, IRBESARTAN AND HYDROCHL, LISINOPRIL, LISINOPRIL AND HYDROCHL, LOSARTAN POTASSIUM, LOSARTAN WITH HYDROCHL, OLMESARTAN MEDOXOMIL, PERINDOPRIL, PERINDOPRIL WITH AMLODI, PERINDOPRIL WITH INDAPA, QUINAPRIL, QUINAPRIL HYDROCHL, RAMIPRIL, TELMISARTAN, TELMISARTAN AND HYDROCH, TRANDOLAPRIL, VALSARTAN, VALSARTAN AND HYDROCHL |
| oral anticoagulants | Previously prescribed OralAnticoagulant<br><br>Approved drug names: ACENOCOUMAROL, APIXABAN, DABIGATRAN ETEXILATE, PHENINDIONE, RIVAROXABAN, WARFARIN SODIUM, EDOXABAN |

**Appendix C**

Outcomes defined used the following codes and positions specified below following the date of index MI unless otherwise specified. If the code is not identified in any admissions/deaths then they will be assumed to not have the outcome of interest.

Data sources
Scotland: SMR00 / SMR01 / NRS Deaths / Prescribing Information System / Scottish Blood Transfusion Database
England: Hospital Episode Statistics / Civil Registrations of Death / Medicines dispensed in Primary Care (NHSBSA data)

| ***Outcome*** | ***Code (ICD-10 , OPCS4)*** |
|---|---|
| ***All-cause mortality*** | Any record of death. |
| **Non-cardiovascular death (including fatal bleeding) and major non-fatal bleeding** | Death due to a non-cardiovascular cause<br><br>Primary position for cause of death<br><br>Ax, Bx, Cx, Dx Ex, Fx , Gx , Hx , Jx, Kx , Lx , Mx , Nx , Ox , Px , Qx , Rx , Sx , Tx , Ux , Vx , Xx , Yx , Zx.<br><br>OR<br><br>Hospitalisation for bleeding<br><br>Primary or first secondary position<br><br>I60x, I61x, I62x, S06.4x, S06.5x, S06.6x, K92.0x, K92.1x, K 92.2x, I85.0x, I98.3x, K22.6x, K25.0x, K25.2x, K25.4x, K25.6x, K26.0x, K26.2x, K26.4x, K26.6x, K27.0x, K27.2x, K27.4x, K27.6x, K28.0x, K28.2x, K28.4x, K28.6x, K29.0x, K62.5x, K66.1x, R58x, I23.0x, I31.2x, I69.0x, I69.1x, I69.2x, H21x, H35.6x, H31.3x, H43.1x, H44.8x, H45.0x, R04.0x, R04.1x, R04.2x, R04.8x, R04.9x, T81.0x, D62x, N83.7x, N93.8x , N93.9x, O03.1x, O03.6x, O04.1x, O04.6x, O05.1x, O05.6x, O06.1x, O06.6x, O20.8x, O20.9x, O46x , O67x, O07.1x, O07.6x, O08.1x, O71.7x , O72.0x , O72.1x , O72.2x , O90.2x , P26.1x , R31x , M25.0x.<br><br>OR |

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| | Primary procedure position (OPSC4)<br><br>E05x , E058x , E059x , F162x , D041x , E203x , F365x , G523x , H212x , H531x , K681x , P093x , P271x , T301x, Y221x , T032x , Y221x , T032x , Y321x , V032x , A052x , A053x , A054x , A103x , A401x , A411x |
| **Non-cardiovascular death (including fatal bleeding)** | Primary cause of death<br><br>Ax , Bx , Cx , Dx , Ex , Fx , Gx , Hx , Jx , Kx , Lx , Mx , Nx , Ox , Px , Qx , Rx , Sx , Tx , Ux , Vx , Xx , Yx , Zx |
| **Major fatal and non-fatal bleeding** | Hospitalisation for bleeding<br><br>Primary or first secondary position<br><br>I60x, I61x, I62x, S06.4x, S06.5x, S06.6x, K92.0x, K92.1x, K 92.2x, I85.0x, I98.3x, K22.6x, K25.0x, K25.2x, K25.4x, K25.6x, K26.0x, K26.2x, K26.4x, K26.6x, K27.0x, K27.2x, K27.4x, K27.6x, K28.0x, K28.2x, K28.4x, K28.6x, K29.0x, K62.5x, K66.1x, R58x, I23.0x, I31.2x, I69.0x, I69.1x, I69.2x, H21x, H35.6x, H31.3x, H43.1x, H44.8x, H45.0x, R04.0x, R04.1x, R04.2x, R04.8x, R04.9x, T81.0x, D62x, N83.7x, N93.8x , N93.9x, O03.1x, O03.6x, O04.1x, O04.6x, O05.1x, O05.6x, O06.1x, O06.6x, O20.8x, O20.9x, O46x , O67x, O07.1x, O07.6x, O08.1x, O71.7x , O72.0x , O72.1x , O72.2x , O90.2x , P26.1x , R31x , M25.0x.<br><br>OR<br><br>Primary procedure position (OPCS4)<br><br>E05x , E058x , E059x , F162x , D041x , E203x , F365x , G523x , H212x , H531x , K681x , P093x , P271x , T301x, Y221x , T032x , Y221x , T032x , Y321x , V032x , A052x , A053x , A054x , A103x , A401x , A411x<br><br>OR<br><br>Death due to bleeding<br><br>Primary cause of death |

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| | I60x, I61x, I62x, S06.4x, S06.5x, S06.6x, K92.0x, K92.1x, K 92.2x, I85.0x, I98.3x, K22.6x, K25.0x, K25.2x, K25.4x, K25.6x, K26.0x, K26.2x, K26.4x, K26.6x, K27.0x, K27.2x, K27.4x, K27.6x, K28.0x, K28.2x, K28.4x, K28.6x, K29.0x, K62.5x, K66.1x, R58x, I23.0x, I31.2x, I69.0x, I69.1x, I69.2x, H21x, H35.6x, H31.3x, H43.1x, H44.8x, H45.0x, R04.0x, R04.1x, R04.2x, R04.8x, R04.9x, T81.0x, D62x, N83.7x, N93.8x , N93.9x, O03.1x, O03.6x, O04.1x, O04.6x, O05.1x, O05.6x, O06.1x, O06.6x, O20.8x, O20.9x, O46x , O67x, O07.1x, O07.6x, O08.1x, O71.7x , O72.0x , O72.1x , O72.2x , O90.2x , P26.1x , R31x , M25.0x. |
| **Hospitalisation for bleeding** | Hospitalisation for bleeding<br><br>Primary or first secondary position<br><br>I60x, I61x, I62x, S06.4x, S06.5x, S06.6x, K92.0x, K92.1x, K 92.2x, I85.0x, I98.3x, K22.6x, K25.0x, K25.2x, K25.4x, K25.6x, K26.0x, K26.2x, K26.4x, K26.6x, K27.0x, K27.2x, K27.4x, K27.6x, K28.0x, K28.2x, K28.4x, K28.6x, K29.0x, K62.5x, K66.1x, R58x, I23.0x, I31.2x, I69.0x, I69.1x, I69.2x, H21x, H35.6x, H31.3x, H43.1x, H44.8x, H45.0x, R04.0x, R04.1x, R04.2x, R04.8x, R04.9x, T81.0x, D62x, N83.7x, N93.8x , N93.9x, O03.1x, O03.6x, O04.1x, O04.6x, O05.1x, O05.6x, O06.1x, O06.6x, O20.8x, O20.9x, O46x , O67x, O07.1x, O07.6x, O08.1x, O71.7x , O72.0x , O72.1x , O72.2x , O90.2x , P26.1x , R31x , M25.0x.<br><br>OR<br><br>Primary procedure position (OPCS4)<br><br>E05x , E058x , E059x , F162x , D041x , E203x , F365x , G523x , H212x , H531x , K681x , P093x , P271x , T301x, Y221x , T032x , Y221x , T032x , Y321x , V032x , A052x , A053x , A054x , A103x , A401x , A411x |
| **Intracranial haemorrhage** | Intracranial haemorrhage event<br><br>Primary or first secondary position<br><br>I60x , I61x , I62x , S06.5x , S06.6x. |

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| | OR<br><br>Death due to intracranial haemorrhage<br><br>Primary cause of death<br><br>I60x , I61x , I62x , S06.5x , S06.6x. |
| **Gastrointestinal bleeding** | Gastrointestinal bleeding event<br><br>Primary or first secondary position<br><br>K92.0x , K92.1x , K 92.2x , I85.0x , I98.3x, K22.6x , K25.0x , K25.2x , K25.4x , K25.6x , K26.0x , K26.2x , K26.4x , K26.6x , K27.0x , K27.2x , K27.4x , K27.6x, K28.0x , K28.2x , K28.4x , K28.6x , K29.0x , K62.5x , K55.2x , K66.1x.<br><br>OR<br><br>Death due to Gastrointestinal bleeding<br><br>Primary cause of death<br><br>K92.0x , K92.1x , K 92.2x , I85.0x , I98.3x, K22.6x , K25.0x , K25.2x , K25.4x , K25.6x , K26.0x , K26.2x , K26.4x , K26.6x , K27.0x , K27.2x , K27.4x , K27.6x, K28.0x , K28.2x , K28.4x , K28.6x , K29.0x , K62.5x , K55.2x , K66.1x. |
| **Cardiovascular mortality and non-fatal myocardial infarction** | Death due to a cardiovascular cause<br><br>Primary cause of death<br><br>Ix<br><br>OR<br><br>Myocardial infarction after the Index Admission Discharge Date |

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| | Primary or first secondary position<br><br>I21x, I22x |
| **Cardiovascular mortality (cardiac and non-cardiac)** | Death due to a cardiovascular cause<br><br>Primary cause of death<br><br>Ix |
| **Myocardial infarction (fatal and non- fatal)** | Myocardial infarction after the Index Admission Discharge Date<br><br>Primary or first secondary position<br><br>I21x, I22x<br><br>OR<br><br>Death due to myocardial infarction<br><br>Primary cause of death<br><br>I21x, I22x |
| **Stent thrombosis** | Stent thrombosis<br><br>Primary or first secondary position<br><br>T82.8x |
| **Coronary revascularisation** | Coronary revascularisation after the Index Admission Discharge Date<br><br>Primary procedure position (OPCS4) |

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| | K40x, K41x, K42x, K43x, K44x, K45x, K46x, K47x, K48x, K49x, K50x, K75x. |
| **Thrombotic stroke** | Ischaemic stroke<br><br>Primary or first secondary position<br><br>I63x<br><br>OR<br><br>Death due to ischaemic stroke<br><br>Primary cause of death<br><br>I63x |
| **Blood transfusion** | Any record of transfusion |
| **Iron therapy** | Prescribed Iron Therapy<br><br>Approved drug names: FERROUS SULPHATE, FERROUS FUMARATE, FERROUS GLUCONATE, FERRIC MALTOL, FERROUS CALCIUM CITRATE, FERROUS GLYCINE SULFATE, IRON CARBOXYMALTOSE, SODIUM FEREDETATE, IRON CARBOXYMALTOSE, IRON DEXTRAN, IRON SUCROSE, VENOFER, FERINJECT |